INAHTA Briefs

INAHTA

International Network of
Agencies for Health
Technology Assessment

INAHTA Briefs Compilation

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INAHTA Briefs

The series, *INAHTA Briefs,* is a forum for member agencies to present brief and structured overviews of recently published reports. INAHTA Briefs are published regularly and are available free of charge at www.inahta.org. Information presented in the INAHTA Briefs is developed and submitted by the member agencies. This publication series would not be possible without the members' ongoing commitment and support.

The views expressed in each overview are those of the authors alone and do not necessarily reflect the position of INAHTA.

INAHTA asks readers to direct your personal medical and health questions to your family physician. Information found in INAHTA publications should not be used as a substitute for consulting with your doctor.

Please refer to the *INAHTA Health Technology Assessment (HTA) Glossary* on INAHTA's website for descriptions of the terms used.

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This is INAHTA

Many organizations throughout the world assess healthcare technology. There is an evident need to cooperate and share information from different cultures. The International Network of Agencies on Health Technology Assessment (INAHTA) serves this purpose.

INAHTA was established in 1993 and has now grown to 53 member agencies in 26 countries. The network includes members from North and Latin America, Europe and Australasia.

Aims:

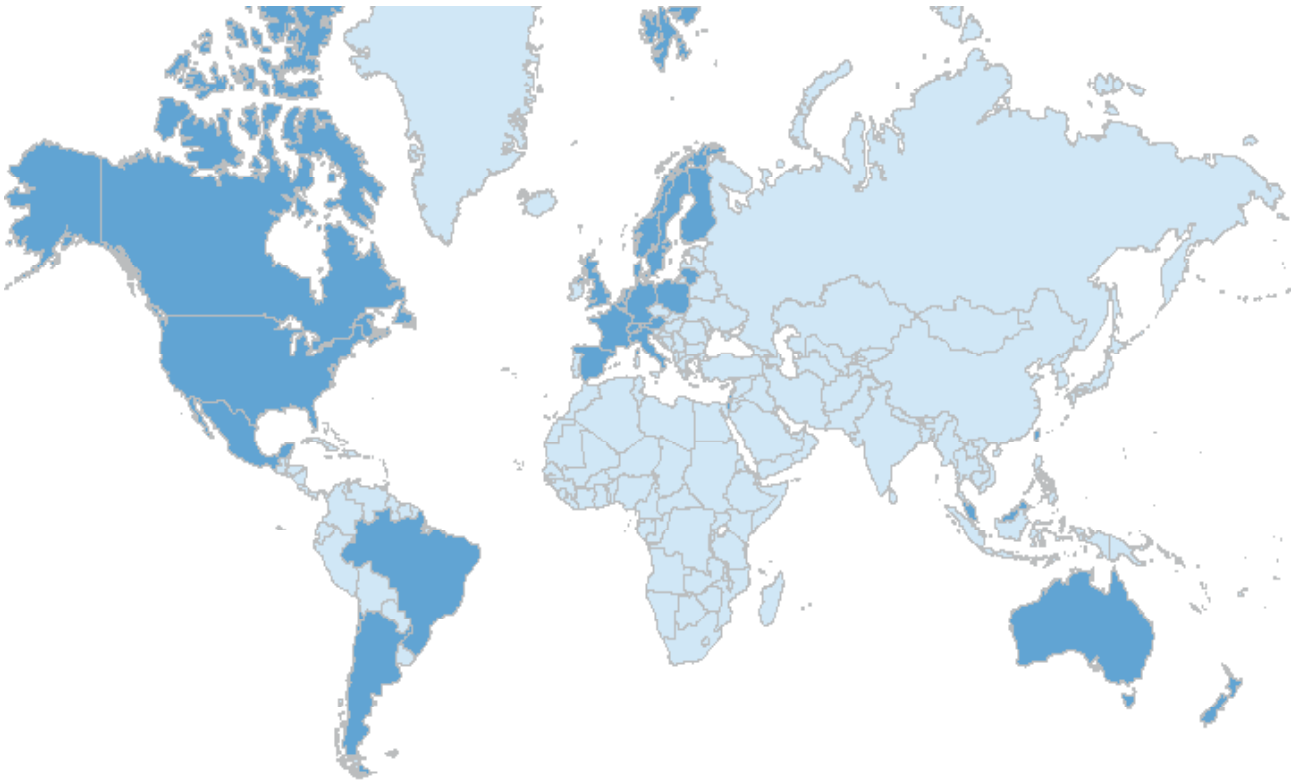
» To accelerate exchange and collaboration among HTA agencies

» To create a forum for the identification and pursuit of interests common to HTA agencies

» To promote information sharing and comparison among HTA agencies

» To create a forum for joint projects, developement of new guidelines and learning new metods

» To prevent unnecessary duplication of activities among agencies



Who can become a member?

Membership is open to any organization which fulfill the following criteria:

» Assesses technology in healthcare

» Is a non-profit organization

» Relates to a regional or national government

» Is funded at least 50% by public sources

» Provides members free access to reports

» Shares information within network

Activities of working groups:

» Solutions for improvement within the network

» Identifying processes of decision making

» Impact of HTAs

» Improvement of quality of HTA reports

» Education and Training programs

» Clarification of Ethical approaches in HTA

» Creating awareness of INAHTA

INAHTA Collaborating partners:

» HTAi – Memorandum of Understanding (MoU)

» WHO – Collaborating Centers, MoU

» HEN – technical member

» PAHO – collaborating partner

» EUnetHTA – collaborating partner

» EuroScan collaboration

» World Bank cooperation

» Industry – awareness, HTAi Policy Forum

INAHTA activities:

» HTA Database – Library of HTAs

» Annual Meetings – Networking opportunities

» Working groups – Joint projects

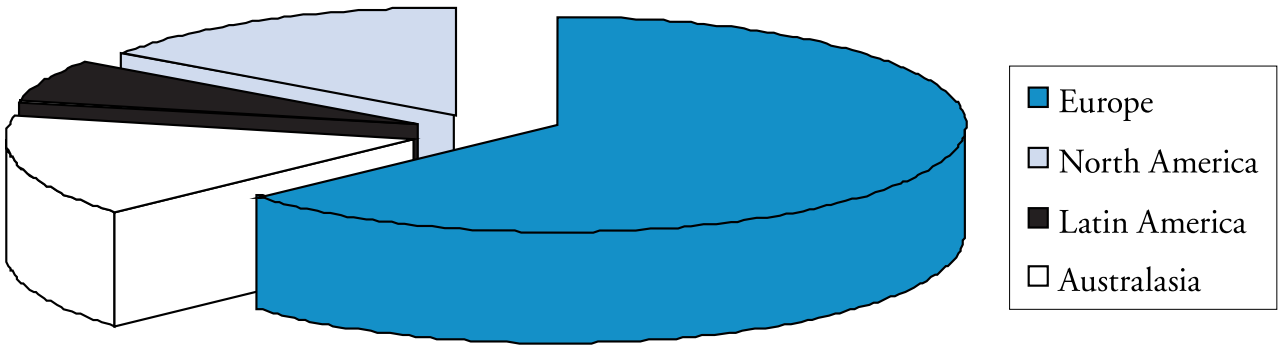
» Surveys – Sharing practices

» ListServ – Communication strategy

» E-learning courses – human resources

» Articles in Medical Journals

INAHTA – A Global Network:



Dissemination activities

INAHTA's key communication form is Internet. The INAHTA website and Members-only section provides the best source of regularly updated information about ongoing activities and member agencies.

Please visit **www.inahta.org**.

The Brief series is intended as a forum for member agencies to present overviews of recently published reports. Information in the INAHTA briefs is developed and submitted by the member, regularly published, and placed on the INAHTA website.

Joint projects involve the member agencies in collaborative efforts to evaluate medical technologies of mutual interest. The INAHTA/HTAi Working Group on Ethical Issues has recently published "Ethics manual".

The HTA Database contains information on healthcare technology assessments and is managed by INAHTA in collaboration with our UK member Centre for Reviews and Dissemination (CRD). New records are continually added, and INAHTA publications and on-going reviews are sent to CRD by the INAHTA Secretariat every six months. All titles of current projects and publications from INAHTA agencies are also available in Spanish.

Other means of dissemination include participation in international conferences, workshops, exhibitions, and educational activities and seminars. The INAHTA exhibition is presented yearly at the HTAi conference. INAHTA and most member agencies distribute reports and other information at the exhibition. There is also an opportunity to meet and exchange experience on HTA related issues with representatives from the INAHTA agencies during the Meet the Agencies initiative.

HTA Glossary gives the HTA community, both producers and users of assessment information, a common vocabulary for work in this field.

For more information, please visit www.inahta.org or contact the INAHTA Secretariat via e-mail: secretariat@inahta.org, tel +46 8 412 3200, or fax +46 8 411 3260.

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Title	**Portable Monitoring Devices for Diagnosis of Obstructive Sleep Apnea at Home: Review of Accuracy, Cost Effectiveness, Guidelines, and Coverage in Canada**
Agency	**CADTH, Canadian Agency for Drugs and Technologies in Health** Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada; Tel: +1 613 226 2553, Fax: +1 613 226 5392; publications@cadth.ca, www.cadth.ca
Reference	CADTH Technology Rapid Review, December 2009. ISBN 978-1-926680-30-9 (print), ISBN 978-1-926680-31-6 (online)

Aim

To review evidence on the accuracy and cost effectiveness of using portable monitoring devices to diagnose obstructive sleep apnea (OSA) at home and in the laboratory when compared with laboratory polysomnography (PSG).

Results and conclusions

Although laboratory PSG is the standard test used to diagnose OSA, the evidence shows that, among patients with a high pretest probability of moderate-to-severe OSA, portable monitoring devices can be used at home for diagnosis when access to laboratory sleep studies and sleep specialists is limited. Results obtained from using portable monitoring devices at home may be less accurate compared to portable monitoring conducted in a laboratory or with laboratory PSG. Some studies show no difference in short-term compliance and response to continuous positive airway pressure (CPAP) therapy when portable monitoring and CPAP autotitration at home are compared with laboratory-based PSG diagnosis and CPAP titration.

Recommendations

Not applicable.

Methods

The review included current guidelines, information on portable monitoring devices available in Canada, coverage of devices by private and public health plans in Canada, and the level of patient compliance with CPAP treatment when OSA is diagnosed.

Written by Ndegwa S, Clark M, and Argáez C, CADTH, Canada

Title **Dialectical Behavior Therapy in Adolescents for Suicide Prevention: Systematic Review of Clinical Effectiveness**

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Reference CADTH Technology Rapid Review, April 2009.
ISBN 978-1-926680-02-6 (print), ISBN 978-1-926680-03-3 (online)

Aim

To review the evidence on clinical effectiveness of dialectical behavior therapy (DBT) compared to treatment as usual (TAU) for preventing suicide in adolescents.

Conclusions and results

Dialectical behavior therapy (DBT) may be effective in treating suicidality in adolescents with or suspected of having bipolar disorder. However, more evidence is needed from higher quality studies to confirm these findings.

Recommendations

Not applicable.

Methods

Selected databases and relevant websites were searched for studies that assessed DBT in adolescents aged 18 years or younger. Database searches covered studies published between 2004 and January 2009 and included all study types. Those meeting the criteria for inclusion were reviewed. The report summarizes and discusses the results.

Further research/reviews required

Further research plus an evaluation of the long-term effectiveness of DBT on suicidal adolescents, and assessments of the cost effectiveness of DBT, would contribute to the decision-making process of treatment providers and policy makers.

Written by Mujoomdar M, Cimon K, and Nkansah E, CADTH, Canada

INAHTA Briefs

Issue 2010/018

Title **Dabigatran or Rivaroxaban Versus Other Anticoagulants for Thromboprophylaxis After Major Orthopedic Surgery: Systematic Review of Comparative Clinical-Effectiveness and Safety**

Agency **CADTH, Canadian Agency for Drugs and Technologies in Health**
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Reference CADTH Technology Rapid Review, May 2009. Amended Sept 2009.
ISBN 978-1-926680-06-4 (print), ISBN 978-1-926680-07-1 (online)

Aim

To determine the clinical effectiveness and safety of dabigatran or rivaroxaban compared to low-molecular-weight heparins (LMWH), unfractionated heparin, warfarin, or fondaparinux for thromboprophylaxis after elective total hip replacement, elective total knee replacement, or hip fracture surgery.

Conclusions and results

The evidence that dabigatran is at least as effective as enoxaparin for thromboprophylaxis after total hip replacement (THR) or total knee replacement (TKR) is conflicting. Three phase-3 trials evaluating rivaroxaban showed superior clinical effectiveness over enoxaparin in preventing venous thromboembolism (VTE) after THR or TKR. The Canadian Expert Drug Advisory Committee (CEDAC) recommended that rivaroxaban, but not dabigatran, be listed in publicly funded drug plans for prophylaxis of VTE after TKR or THR. No head-to-head trials compare rivaroxaban with dabigatran, or compare either drug to other anticoagulants. There is no evidence to support the use of dabigatran or rivaroxaban in patients undergoing hip fracture surgery.

Recommendations

Not applicable.

Methods

Published English-language reports of any study design, were identified by searching electronic databases between 1999 and April 17, 2009. The websites of regulatory, health technology assessment, and other related agencies were searched for additional reports. Searches were supplemented by hand searching bibliographies of relevant reports. Two reviewers selected articles for inclusion using pre-defined criteria.

Further research/reviews required

Although some efficacy and safety data for dabigatran and rivaroxaban are available, data from additional trials and postmarketing surveillance are needed to characterize the role of these anticoagulants for thromboprophylaxis among diverse patient populations after major orthopedic surgery.

Written by Ndegwa S, Moulton K, and Argáez C, CADTH, Canada

Title	**TomoTherapy, Gamma Knife, and CyberKnife Therapies for Patients with Tumors of the Lung, Central Nervous System, or Intra-abdomen: A Systematic Review of Clinical Effectiveness and Cost Effectiveness**
Agency	**CADTH, Canadian Agency for Drugs and Technologies in Health** Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada; Tel: +1 613 226 2553, Fax: +1 613 226 5392; publications@cadth.ca, www.cadth.ca
Reference	CADTH Technology Rapid Review, September 2009. ISBN 978-1-926680-14-9 (print), ISBN 978-1-926680-15-6 (online)

Aim

To examine the comparative clinical and cost effectiveness of TomoTherapy, GammaKnife, and CyberKnife therapies for patients with cancer of the lung, central nervous system, or intra-abdomen.

Conclusions and results

Evidence is insufficient to reliably estimate the comparative clinical effectiveness (benefit and harm), cost effectiveness, and impact on quality of life of TomoTherapy, Gamma Knife surgery (GKS), or CyberKnife surgery (CKS). The specific patient caseloads and sites requiring radiosurgery or radiotherapy may be factors to consider before purchasing.

Recommendations

Not applicable.

Methods

Literature published in English between 2004 and April 2009 that focused on tumors in the lung, central nervous system, or intra-abdomen and mentioned TomoTherapy, GKS, or CKS were selected from common bibliographic databases, the websites of relevant agencies and associations, and other specialized databases. Literature searches were limited to systematic reviews, health technology assessments, meta-analyses, randomized controlled trials, and economic studies. Clinical endpoints of interest were tumor control rates, overall survival rates, and adverse events. Health-related quality of life measures were collected, when available. Two independent reviewers selected articles for inclusion based on specific criteria, and disagreements were resolved by consensus. This report reviews and discusses the results.

Written by Boudreau R, Clark M, and Nkansah E, CADTH, Canada

Title **Computed Tomography for Pediatric Patients: Review of Clinical Effectiveness and Indications for Use**

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Reference CADTH Technology Rapid Review, September 2009.
ISBN 978-1-926680-18-7 (print), ISBN 978-1-926680-19-4 (online)

Aim

To assess the capability of computed tomography (CT) scanners with various numbers of slices to obtain acceptable images while minimizing radiation doses in diagnosing common pediatric indications, eg, head CT for trauma, chest CT, cardiac CT, and abdominal CT.

Conclusions and results

Most studies identified were either performed on adult populations, or the number of slices for the scanners was not specified, resulting in limited published evidence for answering the research question. Based on the limited data available, the image quality of 64-MSCT (multislice computed tomography) and 16-MSCT was found to be comparable, and the 64-slice scanner reduced radiation exposure by 26.3% compared to the 16-slice scanner. A lower tube voltage (80 kVp) reduced radiation dosage to patients without sacrificing image quality. The use of MSCT combined with automatic exposure control effectively reduced radiation exposure. A comparison between a 16-slice MSCT scanner and MRI showed that CT was not as sensitive as diffusion-weighted MRI (DW MRI) in detecting brain injuries in children.

Recommendations

Not applicable.

Methods

Literature published in English between 2004 and April 2009 comparing CT scanners with different numbers of slices, and MSCT with ultrasound or MRI were selected from common bibliographic databases and websites of relevant agencies and associations. Two independent reviewers selected articles for inclusion based on specific criteria, and disagreements were resolved by consensus. Searches were limited to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, and guidelines. This report presents and discusses the results.

Further research/reviews required

Well-designed clinical studies need to provide more rigorous evidence on the clinical effectiveness of using MSCT in the pediatric population. Also, clinical practice guidelines need to be developed on the use of MSCT in children.

Written by Chen S, Moulton K, and Spry C, CADTH, Canada

Title **Fecal Immunochemical Tests for Colorectal Cancer Screening: A Systematic Review of Accuracy and Compliance**

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Reference CADTH Technology Rapid Review.
ISBN 978-1-926680-16-3 (print), ISBN 978-1-926680-17-0 (online)

Aim

To review the evidence on diagnostic accuracy and patient compliance when using fecal immunochemical tests to screen for colorectal cancer.

Conclusions and results

Fecal immunochemical testing (FIT) may be an effective method to screen for colorectal cancer (CRC) and advanced adenomas, and may be more effective when compared with other screening tests, eg, the guaiac fecal occult blood test (gFOBT). In particular, the HemeSelect, FlexSure OBT, and OC-Sensor Micro FITs demonstrate improved diagnostic performance characteristics compared with gFOBT. All included studies that compared participation rates of FIT with other tests showed that FIT had higher completion rates than the other tests, including gFOBT.

Limitations of the included studies should be considered during decision making. Other things to consider when making decisions about the appropriateness of FIT as a screening tool for CRC include the type of FIT to be used, the associated costs, the appropriate hemoglobin cutoff level, and the capacity for follow-up using colonoscopy (CS) or flexible sigmoidoscopy (FS).

Recommendations

Not applicable.

Methods

Literature published in English between 2004 and April 2009 comparing fecal immunochemical tests (FIT) with guaiac fecal occult blood tests (gFOBT) was selected from bibliographic databases, the websites of relevant agencies and associations, and other specialized databases. Two independent reviewers selected articles for inclusion based on specific criteria and resolved disagreements by consensus. Outcomes of interest included sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) to detect advanced adenomas and colorectal cancer (CRC). This report reviews and discusses the results.

Further research/reviews required

To more accurately assess the impact of screening, more evidence is needed from studies that evaluate the sensitivity and specificity of these tests.

Written by Mujoomdar M, Cimon K, and Spry C, CADTH, Canada

Title **Endobronchial Ultrasound for Lung Cancer Diagnosis and Staging: A Review of the Clinical- and Cost-Effectiveness**

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Reference CADTH Technology Rapid Review, August 2009.
ISBN 978-1-926680-08-8 (print), ISBN 978-1-926680-09-5 (online)

Aim

To review the clinical and cost effectiveness of using endobronchial ultrasound (EBUS) in diagnosing and staging lung cancer.

Conclusions and results

Current evidence indicates that endobronchial ultrasound (EBUS) is an accurate and safe tool for lung cancer diagnosis and staging. The cost effectiveness of EBUS has not been formally evaluated, but findings from cost analyses showed that compared with transbronchial needle aspiration (TBNA), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) reduced the per patient staging cost by 24%. Minimal data compare EBUS to its current comparator, mediastinoscopy. Using Australian cost-analysis data, and assuming that the costs are similar in Canada, the use of EBUS-TBNA compared to conventional TBNA in Canada for NSCLC staging and diagnosing mediastinal masses could potentially save between 0.8 million and 1.3 million Canadian dollars (CAD) per year in the Canadian healthcare system.

Recommendations

No applicable.

Methods

Literature published in English between 2004 and April 2009 was selected from common bibliographic databases, the websites of relevant agencies and associations, and other specialized databases. Retrieval was not limited by study type. Quality of the HTA and meta-analysis were assessed using the Oxman and Guyatt criteria for the quality of systematic reviews, and economic study quality was assessed using Drummond's quality checklist.

Written by Ho C, Clark M, and Argáez C, CADTH, Canada

Title **Fecal Immunochemical Testing in Colorectal Cancer Screening of Average Risk Individuals: Economic Evaluation**

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Reference CADTH Technology Rapid Review, October 2009.
ISBN 978-1-926680-26-2 (print), ISBN 978-1-926680-27-9 (online)

Aim

To evaluate the economics of using fecal immunohistochemical testing (FIT) to screen for colorectal cancer (CRC) in average-risk individuals.

Conclusions and results

All CRC screening modalities are associated with improved clinical outcomes and higher costs compared with no screening. FIT seems superior to fecal occult blood testing (FOBT), particularly in detecting polyps. More study is warranted. Compared with no screening, mid-range FIT (FIT-mid) was associated with a cost per QALY of $4350, which was robust to sensitivity analysis. If jurisdictions implement screening programs using FIT, volume-based contracts could be used to achieve lower prices for the FIT assays. To optimize FIT test performance, programs could include the testing of 2 to 3 stool samples.

Recommendations

Not applicable.

Methods

Data from previous CADTH HTAs were used in an incremental cost-utility analysis to compare FIT and the most widely used CRC screening strategies (colonoscopy and FOBT) with no screening in average-risk patients. Modalities were rank ordered by cost, eliminating dominated strategies and strategies that were eliminated by extended dominance. The outcomes included costs, QALYs, number of cancers, number of cancer deaths, and the cost per QALY gained. Modeling was performed using Markov analysis and an annual cycle. Base-case analyses were performed using cohort simulation, with alternative modeling strategies (first-order Monte Carlo simulation) used to assess cancer rates and number of colonoscopies. Given the heterogeneity of available FIT tests, 3 independent scenarios were modeled to represent studies reporting: *lower* (FIT-low), *mid-range* (FIT-mid), and *high* test performance (FIT-high).

Further research/reviews required

FIT seems to be superior to FOBT screening, particularly in detecting polyps. More study is warranted.

Written by Heitman S, Au F, Hilsden R, and Manns B, CADTH, Canada

INAHTA Briefs

Issue 2010/024

Title **Radioimmunotherapies for Non-Hodgkin Lymphoma: Systematic Review of Clinical Effectiveness, Cost Effectiveness, and Guidelines**

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Reference CADTH Technology Rapid Review, October 2009.
ISBN 978-1-926680-22-4 (print), ISBN 978-1-926680-23-1 (online)

Aim

To review the clinical and cost effectiveness of using radioimmunotherapies in treating non-Hodgkin lymphoma, and to identify guidelines on their use.

Conclusions and results

The use of ^{131}I-tositumomab and ^{90}Y-ibritumomab may be treatment options for patients with refractory or relapsed non-Hodgkin lymphoma (NHL). Guidelines recommend the use of these drugs in patients with NHL that is refractory to chemotherapy. The cost-effectiveness information, which was not presented from a Canadian perspective, suggests that the use of ^{131}I-tositumomab may be a cost-effective option during third- or fourth-line NHL treatment, depending on a third-party payer's willingness to pay for a quality-adjusted life-year. The evidence suggests that the use of ^{131}I-tositumomab and ^{90}Y-ibritumomab be reserved for individuals with follicular NHL whose initial treatment fails to produce a response.

Recommendations

Not applicable.

Methods

Literature related to the use of radioimmunotherapies in non-Hodgkin lymphoma (NHL) published in English between 2004 and June 2009 was selected from bibliographic databases, websites of relevant agencies and associations, and other specialized databases. Searches were limited to systematic reviews, health technology assessments, meta-analyses, randomized controlled trials, observational studies, economic studies, and guidelines. Clinical outcomes of interest included symptom improvement, remission induction, overall survival, progression-free survival, relapse-free survival, and quality of life. Guidelines of interest were those including information related to dosage, frequency and method of administration, and patient selection. Two independent reviewers selected articles for inclusion based on specific criteria, and disagreements were resolved by consensus. This report reviews and discusses the results.

Written by Pohar R, Clark M, and Nkansah E, CADTH, Canada

Title **Recombinant Activated Factor VII in Treatment of Hemorrhage Unrelated to Hemophilia: A Systematic Review and Economic Evaluation**

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Reference CADTH Technology Report, Issue 118, April 2009.
ISBN 978-1-926680-04-0 (print), ISBN 978-1-926680-05-7 (online)

Aim

To assess the implications of adopting rFVIIa in managing uncontrolled bleeding in individuals without hemophilia or other inherited bleeding disorders in the following off-label indications: treatment of bleeding associated with blunt or penetrating trauma; surgery unrelated to trauma; gastrointestinal bleeding; and intracerebral hemorrhage (ICH).

Conclusions and results

Based on the available evidence, we found no clearly demonstrated benefit or harm from using rFVIIa relative to usual care in uncontrolled bleeding due to blunt or penetrating trauma, surgery that is unrelated to trauma, gastrointestinal bleeding, or ICH in individuals without hemophilia, inherited platelet disorders, or other coagulopathies. Dose-response relationships in the safety and efficacy of rFVIIa were inconsistent. Economic impact was uncertain due to the weakness of current clinical efficacy data. Potential cost effectiveness can only be confirmed by future research.

Recommendations

Not Applicable.

Methods

A systematic review of clinical and economic literature was performed along with an economic evaluation and budget impact analysis. The economic evaluation focused on the routine use of rFVIIa compared to standard care without rFVIIa, from the perspective of the publicly funded healthcare system. The budget impact of using rFVIIa for blunt trauma was viewed from the perspective of the Canadian Blood Services.

Further research/reviews required

The potential cost effectiveness of rFVIIa in severe blunt trauma can only be confirmed by further research.

Written by Pohar SL, Tsakonas E, Murphy G, Anderson D, and Carney D, CADTH, Canada

Title **Erythropoiesis-Stimulating Agents for Anemia of Cancer or of Chemotherapy: Systematic Review and Economic Evaluation**

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Reference CADTH Technology Report, Issue 119 , May 2009.
ISBN 978-1-897465-98-1 (print), ISBN 978-1-897465-99-8 (online)

Aim

To assess the clinical efficacy, clinical harm, and economic implications of using erythropoiesis-stimulating agents (ESA) in adult patients with anemia due to cancer or chemotherapy.

Conclusions and results

The use of erythropoiesis-stimulating agents (ESAs) by patients with cancer led to clinically meaningful improvements in quality of life (QoL) and decreased the risk of blood transfusions. However, ESA use led to an increased risk in all-cause mortality, a significantly increased risk in serious adverse events, and cost-utility ratios exceeding commonly accepted standards for economic attractiveness. These considerations raise potential safety concerns.

Recommendations

Not applicable.

Methods

A systematic review and analysis of clinical literature was used to determine clinical benefits and assess the impact of ESAs in managing cancer-related anemia. Information from the literature review provided data for modeling the trade-off of healthcare resources for effectiveness, focusing on the use of ESAs versus no ESAs.

Further research/reviews required

We found no evidence to show that the risks or benefits of ESA therapy differed among patients who did or did not meet recently revised criteria for their use in patients with cancer. These findings suggest that existing practice guidelines should be reassessed and that further review by regulatory authorities may be advisable.

Written by Tonelli M, Lloyd A, Lee H, Wiebe N, Hemmelgarn B, Reiman T, Manns B, Reaume MN, and Klarenbach S, CADTH, Canada

Title **Technologies to Reduce Errors in Dispensing and Administration of Medication in Hospitals: Clinical and Economic Analyses**

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Reference CADTH Technology Report, Issue 121, August 2009.
ISBN 978-1-926680-12-5 (print), ISBN 978-1-926680-13-2 (online)

Aim

To assess the clinical and economic impact of adopting technologies designed to facilitate medication dispensing and administration in hospitals.

Conclusions and results

Limited quality data from available literature indicates the potential to reduce medication errors in some hospital settings. Findings indicate that the use of bar coding for medication dispensing and administration systems, and the simultaneous use of technologies and ward-based automatic dispensing devices, could reduce the risk of medication errors in hospitals. The evidence is insufficient to reliably estimate the impact of implementing pharmacy-based automatic dispensing devices, or predict how automation affects the rate of adverse drug events, near misses, morbidity, and mortality. Ward-based automated dispensing devices in medical-surgical patient care units can reduce costs and error rates. Reliable estimates of the economic impact of other technologies were not possible due to lack of evidence.

Recommendations

Not applicable.

Methods

We systematically reviewed the clinical and economic literature to assess the impact of automated technologies on medication errors. Mathematical modeling was used to compare the cost effectiveness of manual (with medication cassettes) to unprofiled and profiled ward-based automated drug distribution systems.

Further research/reviews required

More research is needed to better evaluate the effect of technologies and the association between their use and a reduction in adverse drug events.

Written by Perras C, Jacobs P, Boucher M, Murphy G, Hope J, Lefebvre P, McGill S, Morrison A, CADTH, Canada

Title **Anti-TNF-alpha Drugs for Refractory Inflammatory Bowel Disease: Clinical- and Cost-Effectiveness Analyses**

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Reference CADTH Technology Report, Issue 120, July 2009.
ISBN 978-1-897465-90-5 (print), ISBN 978-1-897465-91-2 (online)

Aim

To evaluate the comparative clinical effectiveness of anti-TNF-*alpha* drugs in patients with Chron's disease (CD) or ulcerative colitis (UC) with an inadequate response to conventional therapy and to determine the economic value of anti-TNF-*a* drugs compared with that of conventional therapy and surgical interventions.

Conclusions and results

Infliximab and adalimumab are superior to placebo in inducing and maintaining clinical remission and in reducing the rates of surgery and hospitalization in refractory CD. Infliximab provides higher response and remission rates in patients with UC compared to placebo. The evidence suggests that etanercept has no clinically important effect in treating CD. Compared to usual care, anti-TNF-a drugs are unlikely to be cost effective in Crohn's disease unless society is willing to pay more than $208 000 for a healthy year of life (QALY). In ulcerative colitis, a strategy based on 5 mg/kg of infliximab and adalimumab is unlikely to be a cost effective compared to usual care unless society is willing to pay more than $370 000 for a QALY. Higher doses of infliximab will cost more and result in less health benefit.

Recommendations

Not applicable.

Methods

A systematic review and an economic evaluation were performed to examine the clinical and cost effectiveness of anti-TNF-*a* agents compared to conventional therapy. Comparative effectiveness was assessed by systematically reviewing clinical studies. A tradeoff of health for healthcare resources was estimated using a mathematical model populated with information from the literature review and relevant Canadian sources.

Further research/reviews required

The clinical review found a paucity of trials on the use of etanercept by patients with inflammatory bowel disease (IBD) and on adalimumab for refractory UC. More long-term trials on anti-TNF-*a* drugs and head-to-head trials comparing the effectiveness of anti-TNF-a drugs in treating IBD could advance our knowledge. More RCT evidence would be appropriate given the large remission rates reported in some induction trials.

Written by Assasi N, Blackhouse G, Xie F, Gaebel K, Marshall J, Irvine EJ, Giacomini M, Robertson D, Campbell K, Hopkins R, and Goeree R., CADTH, Canada

INAHTA Briefs

Issue 2010/029

Title **Rapid Testing for Group B Streptococcus During Labor: A Test Accuracy Study with Evaluation of Acceptability and Cost-Effectiveness**

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Reference Volume 13.42. ISSN 1366-5278. www.hta.ac.uk/project/1388.asp

Aim

To determine the: *accuracy* (sensitivity, specificity, predictive values) of polymerase chain reaction (PCR) and optical immunoassay (OIA) technologies as rapid tests for maternal vaginal and rectal group B streptococcus (GBS) colonization at the onset of labor, using selective enrichment culture as the reference standard; *acceptability* of rapid testing for GBS colonization among pregnant women of different social and ethnic groups; and *cost and cost effectiveness* of rapid intrapartum testing for maternal GBS colonization to prevent early onset (EO) GBS disease, and compared this with other strategies for screening and prevention.

Conclusions and results

In all combinations of index and reference tests PCR was significantly more accurate than OIA in detecting maternal GBS colonisation. Combined vaginal or rectal swab index tests were more sensitive than either test considered individually (combined swab sensitivity for PCR 84% (95% CI 79%-88%); vaginal swab 58% (52%-64%); rectal swab 71% (66%-76%)). The highest sensitivity for PCR came at the cost of lower specificity (combined specificity 87% (95% CI 85%-89%); vaginal swab 92% (90%-94%); rectal swab 92% (90%-93%)). The sensitivity and specificity of rapid tests varied according to presence or absence of maternal risk factors, but not consistently. PCR results were determinants of neonatal GBS colonization, but maternal risk factors were not. Overall, the acceptability for rapid testing among participants was high, and no evidence showed that screening had raised anxiety. Vaginal swabs were more acceptable than rectal swabs.

Modeling analysis revealed that the most cost-effective strategy was to provide routine intrapartum antibiotic prophylaxis (IAP) to all women without prior screening. Since this was deemed unlikely to be acceptable to most women and midwives, the analysis was repeated without this strategy. Here, the most cost-effective screening was based on culture testing at 35 to 37 weeks' gestation, with antibiotics provided to all women who screened positive (assuming all women in premature labor received IAP). The results were sensitive to very small increases in costs and changes in other assumptions.

Recommendations

Although PCR performed better than OIA, neither rapid test was sufficiently accurate or cost effective to recommend in routine clinical practice. Rectal swabbing was less acceptable and the technologies need to be further refined for point-of-care use. The most cost-effective approach to reducing EO GBS disease is likely to be IAP for all women without prior testing. If this strategy is discarded on grounds of acceptability, IAP directed by screening at 35 to 37 weeks' gestation, with IAP to all premature laboring women, becomes cost effective. At present, it would be premature to suggest the implementation of either strategy.

Methods

See Executive Summary link at www.hta.ac.uk/project/1388.asp.

Further research/reviews required

The relative effectiveness, feasibility, and acceptability to women of screening by enriched culture and provision of routine IAP should be explored. Further refinements in rapid tests would be required to improve accuracy and make point-of-care testing practicable and cheaper, but would require further evaluation and comparison with existing strategies.

Written by Jane Daniels, University of Birmingham, NETSCC, United Kingdom

Title **Screening to Prevent Spontaneous Preterm Birth: Systematic Reviews of Accuracy and Effectiveness Literature with Economic Modeling**

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Reference Volume 13.43. ISSN 1366-5278. www.hta.ac.uk/project/1486.asp

Aim

To systematically review evidence on tests intended to identify women with singleton pregnancy at risk of spontaneous preterm birth, and interventions that prevent or delay birth, to allow institution of treatments to improve neonatal outcome.

Conclusions and results

The overall aim was to identify areas where evidence is strong enough to generate recommendations for clinical practice, or otherwise key areas and research questions requiring further primary research. This project intended to meet the following objectives: 1) To determine, among asymptomatic women with singleton gestation in early pregnancy (before 23 completed weeks of gestation): a) the accuracy of various tests for predicting the risk of spontaneous preterm birth; and b) the effectiveness of various interventions for preventing spontaneous preterm birth. 2) To determine, among women with a viable singleton pregnancy (after 23 completed weeks of gestation), symptomatic of threatened preterm labor with intact amniotic membrane and before advance cervical dilatation: a) the accuracy of various tests in predicting the risk of imminent preterm birth; and b) the effectiveness of various antenatal interventions to delay preterm birth to allow institution of interventions for improving outcome of the premature neonate. 3) To determine the cost effectiveness of testing (in both population) and consequent prevention and treatment strategies using decision-analytic modeling. The output from these reviews was used in economic modeling to determine the most efficient management strategies.

Overall, the studies available were generally of poorer quality either in methods or in reporting. A few accurate tests were identified in predicting spontaneous preterm birth in asymptomatic women at early gestation: ultrasonographic cervical length measurement, cervicovaginal fetal fibronectin screening, uterine contraction monitoring with a home uterine monitoring device, and amniotic fluid C-reactive protein measurement. While for women symptomatic with threatened preterm labor (and a viable fetus): absence of fetal breathing movements, cervical length and funneling, amniotic fluid interleukin 6, serum C-reactive protein (for predicting birth within 2–7 days of testing); and matrix metalloproteases-9, amniotic fluid interleukin 6, cervico-vaginal fetal fibronectin, cervico-vaginal beta-hcg and cervicovaginal interleukin 8 (for predicting spontaneous preterm birth before 34 or 37 weeks' gestation). Progestational agent, periodontal therapy and fish oil appeared promising as preventative interventions in asymptomatic women.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1486.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1486.asp.

Further research/reviews required

See Executive Summary link at www.hta.ac.uk/project/1486.asp.

Written by Dr Khalid Khan, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/031

Title **A Randomized Controlled Trial of the Use of Aciclovir and/or Prednisolone for the Early Treatment of Bell's Palsy: The BELLS Study**

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Reference Volume 13.47. ISSN 1366-5278. www.hta.ac.uk/project/1375.asp

Aim

1) To describe the resolution of neurological deficit and cosmetic, psychological, and functional recovery in each of four patient groups: those treated with prednisolone, aciclovir, both, or neither; 2) to determine which group of patients has the greatest reduction in neurological disability scores on the House-Brackmann grading system at 3 and 9 months after randomization; 3) to compare self-reported health status (including assessments of pain) at 3 and 9 months after randomization; and 4) to compare the incremental cost per neurological deficit resolved (case cured) and incremental cost per QALY in the study groups.

Conclusions and results

Of 496 completed patients, 357 had recovered at 3 months. A further 80 had recovered at 9 months, leaving 59 with a residual facial nerve deficit. No significant prednisolone-aciclovir interaction was found at 3 months or at 9 months (p=0.32, p=0.72 respectively). There were significant differences in complete recovery at 3 months between the prednisolone comparison groups (83.0% for prednisolone, 63.6% for no prednisolone, a difference of +19.4% (95% CI: +11.7% to +27.1%, p<0.001). The number needed to treat (NNT) to achieve one additional complete recovery was 6 (95% CI: 4 to 9). No significant difference was found between the aciclovir comparison groups (71.2% for aciclovir and 75.7% for no aciclovir, a difference of –4.5% (95% CI: –12.4% to +3.3%, p=0.30, adjusted 0.50). Nine-month assessments of patients recovered were: 94.4% for prednisolone compared with 81.6% for no prednisolone, a difference of +12.8% (95% CI: +7.2% to +18.4%, p<0.001); the NNT is 8 (95% CI: 6 to 14). Proportions recovered at 9 months are 85.4% for aciclovir and 90.8% for no aciclovir, a difference of –5.3% (95% CI: –11.0% to +0.3%, p=0.07, adjusted 0.10). We found no significant differences in our secondary measures apart from HUI3 at 9 months in those treated with prednisolone. The mean cost of prednisolone was 232 pounds sterling (GBP) and the mean cost of no prednisolone was GBP 248. Prednisolone was more effective in terms of cure and provided on average slightly more QALYs (0.718 versus 0.717). A probabilistic analysis suggested that prednisolone was likely (70%) to be considered cost effective at a GBP 20 000 or GBP 30 000 cost per QALY threshold. Aciclovir was, on average, more costly than no aciclovir (GBP 253 versus GBP 246) and likely to be no more effective in terms of cure and QALYs (0.717 versus 0.718). It was unlikely (15%) to be considered cost effective at a GBP 20 000 or GBP 30 000 cost per QALY threshold.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1375.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1375.asp.

Further research/reviews required

See Executive Summary link at www.hta.ac.uk/project/1375.asp.

Written by Professor Frank Sullivan, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/032

Title **ARTISTIC: A Randomized Trial of Human Papillomavirus (HPV) Testing in Primary Cervical Screening**

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Reference Volume 13.51. ISSN 1366-5278. www.hta.ac.uk/project/1162.asp

Aim

To determine if human papillomavirus (HPV) testing adds significant sensitivity to liquid-based cytology (LEC) in primary cervical screening.

Conclusions and results

Round 2 involved 14 230 women (58.1%) who had been screened in round 1. There was no statistical difference in the detection of CIN3+ between the concealed and revealed arms in either round 1, round 2, or rounds 1 and 2 combined. In round 1, there were 313 CIN 3+ (233 revealed versus 80 concealed; p=0.81) and in round 2 there were only 31 CIN3+ (19 revealed versus 12 concealed; p=0.08) among women who were cytology -ve and HPV +ve in round 1. There was a statistically significant lower rate of CIN2+ (but not CIN3+) in the revealed arm in round 2 (p=0.036). Only 10 CIN3+ lesions were detected in round 1 as a direct consequence of adjunctive HPV testing. The prevalence of high-risk types was age-dependent: 27.9% in women aged 25 through 29 years compared with 6.5% aged 50 through 64 years. The prevalence of HPV 16 and/or 18 in borderline, mild, moderate, and severe dyskaryosis was 10.0%, 22.0%, 46.8%, and 62.4% respectively. Viral persistence rates decline from over 80% at 6 months to 20% to 25% over 48 months. Mean (SD) costs per woman in round 1 were 72 pounds sterling (GBP) (GBP 175) for the revealed arm and GBP 56 (GBP 178) for the concealed arm (p<0.001). As costs were age-dependent, an age adjustment based on the age profile for the national screening program reduced the mean costs to GBP 65 and GBP 52 respectively. The incremental cost-effectiveness ratio for detecting an additional CIN3+ by the addition of HPV testing to LBC screening in round 1 was GBP 38 771. The experiences of revealed women in round 1 informed the development of alternative screening policies with simplified management protocols. An age-adjusted mean cost for LBC primary screening with HPV triage was GBP 39 compared with GBP 48 for HPV primary screening with LBC triage, the main influence on the costs being the rates of referral for colposcopy. HPV testing did not appear to cause significant psychosocial distress.

Recommendations

HPV testing did not add significantly to the effectiveness or cost effectiveness of LBC in this study. An unexpectedly low number of CIN 3+ lesions in round 2 suggested a marked increase in sensitivity compared to conventional cytology. No significant adverse psychosocial effects were detected. It would not be cost effective to screen with cytology and HPV combined, but HPV testing either as a triage or as an initial test triaged by cytology appears to be cheaper than the current use of cytology without HPV testing.

Methods

See Executive Summary link at www.hta.ac.uk/project/1162.asp.

Further research/reviews required

The low incidence of CIN 3+ in the ARTISTIC cohort needs to be confirmed in a subsequent screening round of women previously screened with LBC. Confirmation from other UK laboratories would suggest that LBC can achieve greater sensitivity in the quality assured setting of the NBS. The ARTISTIC trial continues to follow women while maintaining the randomized concealment of HPV testing results. This will allow evaluation of the type-specific risk of developing cytological abnormalities in HPV-positive women with negative baseline cytology, which will be important in developing screening protocols for the post-vaccination era when the case for initial HPV testing with cytology triage will be stronger. Such an approach would require an effective and cost effective means of managing HPV-positive/cytology-negative women.

Written by Professor Henry Kitchener, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/033

Title **Randomized Preference Trial of Medical Versus Surgical Termination of Pregnancy less than 14 Weeks' Gestation (TOPS)**

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Reference Volume 13.53. ISSN 1366-5278. www.hta.ac.uk/project/1441.asp

Aim

1) To compare the acceptability, efficacy, and costs of medical versus surgical termination of pregnancy at less than 14 weeks' gestation. 2) To understand women's decision-making processes and experiences when accessing the abortion service and taking part in the trial.

Conclusions and results

Of women in the preference arms, 54% chose medical termination of pregnancy (MTOP). When questioned 2 weeks after the procedure, more women having surgical termination of pregnancy (STOP) would chose the same method again in the future: adjusted difference 24.9% in the randomized arm and 15.9% in the preference arm. Acceptability of MTOP declined with gestational age. Differences in acceptability persisted at 3 months. No differences were found in the mean maximum amount women were willing to pay for their preferred method either before abortion (preference arms) or after (preference and randomized arms). No differences in anxiety or depression were found between women having MTOP and STOP. Women randomized to MTOP had higher scores on the intrusion subscale of the IES at 2 weeks and both intrusion and avoidance subscales at 3 months. There was no difference in IES scores in the preference arms. Overall satisfaction with care and median semantic differential scores were higher with STOP; women experienced STOP as milder, more agreeable, faster, and safer. In MTOP, women had more symptoms, reported higher mean pain scores during admission, and had more nausea and diarrhea after discharge. Around 90% of women had returned to work and normal activity by 2 weeks (this was not influenced by abortion method). Rates of unplanned or emergency admissions and overall complications were higher after MTOP than STOP.

The overall cost of STOP was greater than MTOP (GBP 498 versus GBP 287), but MTOP was more cost effective (based on successful completion of TOP on the day of admission). Three key service attributes were identified in the DCE; provision of counseling, delay to the procedure, and need for overnight stay. The desire for quick access to abortion was confirmed in the qualitative substudy.

Recommendations

Negative experiences of care and lower acceptability were greater with MTOP than with STOP. Acceptability of MTOP declined with gestational age. MTOP was less costly than STOP, but less effective. Most women choosing MTOP were satisfied with their care and found the procedure acceptable, suggesting a patient-centered abortion service should offer the choice of medical or surgical abortion up to 14 weeks' gestation.

Methods

Participants with no preference were randomized using a purpose-designed computer system, while those with a preference were assigned to their method of choice. MTOP was carried out with mifepristone 200 mg orally and misoprostol 800 µg vaginally followed as necessary by repeated doses of misoprostol 400 µg vaginally or orally. STOP was carried out by vacuum aspiration under general anesthesia after cervical priming with misoprostol 400 µg. Participants were interviewed 2 weeks after the procedure, but could contribute outcome data by telephone, fax, or Internet. Participants were sent a questionnaire at 3 months after the procedure.

Further research/reviews required

Further studies need to explore the barriers to offering women the choice of TOP method. Studies also need to determine the acceptability and effectiveness of; a) MTOP and manual vacuum aspiration in pregnancies below 9 weeks' gestation and b) MTOP and STOP after 14 weeks' gestation.

Written by Professor Stephen Robson, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/034

Title **VenUS II: A Randomized Controlled Trial of Larval Therapy in the Management of Leg Ulcers**

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Reference Volume 13.55. ISSN 1366-5278. www.hta.ac.uk/project/1339.asp

Aim

To compare the clinical and cost effectiveness of larval therapy with a standard debridement technique (hydrogel) in treating sloughy and/or necrotic venous leg ulcers.

Conclusions and results

Between July 2004 and May 2007 the trial recruited 267 people aged 20 to 94 years at trial entry. Female participants outnumbered male participants. The nurse classified most ulcers as having an area exceeding 5cm2. To test the difference over time of Kaplan-Meier curves for the 3 treatment arms, the log rank test was used to compare the distribution of the cumulative times to healing. The difference in the distribution of cumulative healing between the individuals in the 3 arms was not statistically significant at the 5% level. We then adjusted for stratification and prespecified prognostic factors (center, baseline ulcer area, ulcer duration and ulcer type). We found no difference in healing rates between the loose and bagged larvae arms in this model. Results for larvae (loose and bagged pooled) compared with hydrogel showed no evidence of a difference between arms in time to healing. The same analytical steps were used to investigate time to debridement. Larvae-treated ulcers debrided significantly more rapidly than hydrogel-treated ulcers, but the difference in time to debridement between loose and bagged larvae was not significant (Cox proportional hazards model). The adjusted analysis reported the hazard of debriding at any time for those in loose and bagged larvae groups as approximately twice that of the hydrogel group. No differences in health-related quality of life or bacteriology were observed between trial arms. Larval therapy was associated with significantly more ulcer-related pain than hydrogel. Our base case economic evaluation showed large decision uncertainty associated with the cost effectiveness of larval therapy when compared with hydrogel, with a 50% probability of the larval therapy being cost effective. Hence, our findings suggest that larval therapy could be as effective and costly as hydrogel therapy.

Recommendations

Compared to hydrogel therapy, larval therapy significantly reduced the time to debridement of sloughy and/or necrotic, chronic venous leg ulcers. However, larval therapy did not significantly increase the rate of ulcer healing. Regarding cost effectiveness, it was impossible to distinguish between larval therapy and hydrogel.

Methods

A pragmatic, 3-armed, randomized controlled trial with an economic evaluation recruited participants from community, district-nurse-led services, community leg-ulcer clinics, and hospital outpatient leg-ulcer clinics in a range of urban and rural settings.

Further research/reviews required

Further research is required to investigate the association of debridement and healing and ulcer microbiology and healing. The importance of debridement as a clinical outcome for patients and nurses should also be investigated. Exploration of the impact of informative censoring on cost effectiveness, ie, using multistate models to estimate the transition probabilities of different events of interest (debridement, healing, amputation, and/or death) should be conducted.

Written by Professor Nicky Cullum, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/035

Title **A Prospective Randomized Controlled Trial and Economic Modeling of Antimicrobial Silver Dressings Versus Non-Adherent Control Dressings for Venous Leg Ulcers: The VULCAN Trial**

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Reference Volume 13.56. ISSN 1366-5278. www.hta.ac.uk/project/1380.asp

Aim

To examine whether antimicrobial silver-donating dressings were more effective than simple nonadherent dressings beneath compression bandaging in treating venous ulcers.

Conclusions and results

No significant differences (p>0.05) were found between the group that had silver-donating antimicrobial dressings and the group with the control dressing for the primary outcome measure of proportion of ulcers healed at 12 weeks (59.6% for silver and 56.7% for control dressings). The overall median time to healing was not significantly different between the two groups (p=0.408). Mean utility valuations for both the EQ-5D and SF-6D showed no statistically significant differences between the groups at 1, 3, 6, or 12 months. Compared to the control group, the antimicrobial group had an incremental cost of 97.85 pounds sterling (GBP) and an incremental QALY gain of 0.0002 giving an incremental cost-effectiveness ratio (ICER) for the antimicrobial dressings of 489.250 GBP. Cost-effectiveness modeling of the results of the RCT showed, for the base case model, that only included variables that were predictive of healing antimicrobial dressings were not cost effective. Sensitivity analysis where dressing type was forced into the model, and where a small benefit in utility was assumed to occur at the point of healing, resulted in a small average incremental benefit for the antimicrobial dressings. However, this was not sufficient to justify the additional cost, and there remained a high probability that the treatment was not cost effective.

Recommendations

This study found no significant difference in either primary or secondary endpoints between the use of antimicrobial silver dressings and the control group of low adherent dressings. The cost analysis showed a significantly higher cost for those treated with antimicrobial dressings. Cost-effectiveness modeling showed antimicrobial dressings to be dominated by inert dressings: no difference was found in clinical outcomes, and antimicrobial dressings were associated with higher cost.

Methods

See Executive Summary link at www.hta.ac.uk/project/1380.asp.

Further research/reviews required

1) Development of a disease-specific, quality-of-life measure for venous ulcer patients that can be used in economic evaluations. 2) Research to ensure clear descriptions of epidemiology, treatment methods, and experiences of staff engaged in compression bandaging. 3) Research into new treatments for leg ulcers, including mathematical modeling to establish the potential value of further clinical trials and to assist in appropriate trial design prior to undertaking large and potentially expensive clinical trials. 4) Research on problems of ulcers that fail to heal after 12 weeks of compression, and whether antimicrobial dressings might have advantages in patients who are unable to tolerate compression. 5) Clarification of whether the diagnosis of "infection" in leg ulcers might be relevant to the use of antimicrobials. 6) Studies on how clinicians make decisions regarding dressing type, particularly the influence of sales representatives as sources of evidence and guidance.

Written by Professor Jonathan Michaels, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/036

Title **Colour Vision Testing for Diabetic Retinopathy: A Systematic Review of Diagnostic Accuracy and Economic Evaluation**

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Reference Volume 13.60. ISSN 1366-5278. www.hta.ac.uk/project/1665.asp

Aim

1) To determine the diagnostic performance of color vision testing (CVT) options to identify and/or monitor the progression of diabetic retinopathy (DR) and identify patient preferences related to incorporating CVT in the retinopathy screening program. 2) To determine what tests are currently used to detect and manage DR, and views on future research priorities. 3) To review previous economic studies of DR screening with CVT and develop a cost-effectiveness model to evaluate the potential efficiency of incorporating CVT into the current DR screening program.

Conclusions and results

Of the 25 studies reporting on CVT, 18 presented 2x2 diagnostic accuracy data. The quality of studies and reporting was generally poor. Automated or computerized CVTs reported variable sensitivities (63%-97%) and specificities (71-95%). One study reported good diagnostic accuracy estimates for combined computerized CVT and retinal photography in detecting sight-threatening DR, but this single study included few cases of retinopathy. Results for other types of CVTs (pseudoisochromatic plates, anomaloscopes, and color arrangement tests) were heterogeneous, but largely inadequate for DR screening; most performed little better than chance, having Youden indices (sensitivity + specificity – 100%) close to zero. We found no studies that addressed patient preferences relating to color vision screening for DR. Retinal photography is universally employed as the primary method for retinal screening by centers responding to a survey of current practice (none used CVT). The most frequently cited preference for future research was the use of ocular coherence tomography (OCT) to detect clinically significant macular edema. Our search of the economic evaluation literature revealed no studies describing the cost and effects of any type of CVT. The results of the economic evaluation suggested that adding CVT to the current national screening program could be cost effective if it adequately increases sensitivity and is relatively inexpensive. The base case analysis, based on one small diagnostic accuracy study, indicated that the cost per QALY gained is 3337 pounds sterling (GBP) and GBP 6674 for type 1 and type 2, diabetes respectively. However, there is scant evidence on the diagnostic accuracy of combining CVT with retinal photography.

Recommendations

Not all color vision tests have been evaluated, and those that have were generally not considered in the context of retinal photography-based screening. The data are insufficient on any predictive/protective value of CVT. There is a lack of primary studies evaluating the efficiency of including CVT in DR screening. Evidence is insufficient to support the use of CVT alone as a screening method for retinopathy in patients with diabetes.

Methods

See Executive Summary link at www.hta.ac.uk/project/1665.asp.

Further research/reviews required

Survey respondents did not identify CVT as a research priority; around a third of respondents considered OCT to be a research priority. Any study to resolve outstanding uncertainties would have to evaluate the addition of CVT to retinal photography and be: prospective; generalizable to a screening population; independent of test developers; designed to account for lens yellowing, iris color, macular pigment density, and other clinical factors; and comply with STARD reporting guidelines.

Written by Mrs Marie Elaine Westwood, NETSCC, United Kingdom

Title Contamination in Trials of Educational Interventions

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Reference Volume 11.43. ISSN 1366-5278. www.hta.ac.uk/project/1570.asp

Aim

To consider the effects of contamination on the magnitude and statistical significance (or precision) of the estimated effect of an educational intervention; to investigate the mechanisms of contamination; and to consider how contamination can be avoided.

Conclusions and results

The probability, nature, and process of contamination should be considered when designing and analyzing controlled trials of educational interventions in health. Cluster randomization may or may not be appropriate and should not be uncritically assumed to be a solution. Complier Average Causal Effect models are an appropriate way to adjust for contamination, if it can be measured. When conducting such trials, it is a priority to report the extent, nature, and effects of contamination.

Although few relevant studies quantified contamination, experts largely agreed on where contamination was more or less likely. Simulation of contamination processes showed that with various combinations of timing, intensity, and baseline dependence of contamination, cluster randomized trials might produce biases greater than, or similar to, those of individually randomized trials. Complier Average Causal Effect analyses produced results that were less biased than intention-to-treat or per-protocol analyses. They also showed that individually randomized trials would, in most situations, be more powerful than cluster randomized trials despite contamination.

Recommendations

Since few studies reported on whether contamination occurred, the literature search uncovered little evidence that contamination is actually a problem in trials of educational interventions in health. However, there is consensus on the types of situations where contamination is more or less likely. If it is likely, then cluster randomization may reduce contamination unless entire clusters are contaminated. CACE analysis may reduce bias if contamination is measured. A priority in future trials of educational interventions in health would be to report the extent, nature, and effects of contamination.

Methods

An exploratory search for literature published up to May 2005 was conducted via major electronic databases. The results of trials included in previous relevant systematic reviews were then analyzed to see whether studies that avoided contamination resulted in larger effect estimates than those that did not. Expert opinions were elicited about factors more or less likely to lead to contamination. We simulated contamination processes to compare contamination biases between cluster and individually randomized trials. Statistical adjustment was made for contamination using Complier Average Causal Effect analytic methods, using published and simulated data. The bias and power of cluster and individually randomized trials were compared, as were Complier Average Causal Effect, intention-to-treat, and per-protocol methods of analysis.

Further research/reviews required

See Executive Summary link at www.hta.ac.uk/project/1570.asp.

Written by Professor Max Bachmann, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/038

Title **Multi-Centre Randomized Controlled Trial Examining the Cost-Effectiveness of Contrast-Enhanced High Field Magnetic Resonance Imaging in Women Scheduled for Wide Local Excision (COMICE)**

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Reference Volume 14.01. ISSN 1366-5278. www.hta.ac.uk/project/1216.asp

Aim

To determine if adding magnetic resonance (MR) imaging of the breast to current patient evaluation by triple assessment (clinical, radiological [x-ray mammography and breast ultrasound] and pathological [fine needle aspiration cytology/core biopsy]) would; a) help localize tumors in the breast and reduce the reoperation rate in women with primary tumors scheduled for wide local excision (WLE) and b) be economically worthwhile from the perspective of the NHS.

Conclusions and results

In total, 1623 patients were randomized between Dec 2001 and Jan 2007 (816 MR imaging, 807 no MR imaging). No differences in reoperation rates were found between the two groups of patients (MR imaging patients 18.75%, no MR imaging patients 19.33%, difference=0.58%, 95% confidence interval (CI) [-3.24%, 4.40%]). Adding MR imaging to conventional triple assessment alone was not found to be statistically significantly associated with reduced reoperation (odds ratio=0.96, 95% CI=[0.75, 1.24], p=0.7691). Sixteen patients in the MR imaging arm (2.0%) underwent a pathologically avoidable mastectomy at initial surgery, as did two patients in the no MR imaging arm (0.2%) that received an MR scan.

Overall, the best agreement between all imaging modalities and histopathology, with respect to tumor size and extent of disease, was found in patients who were over 50 years of age, had ductal tumors NST, and were node negative. Considering the effectiveness of imaging, the sensitivity and positive predictive values of MR imaging (as regards determining patient management) were 50.0% (95% CI [42.65, 57.35]) and 61.8% (95% CI [53.87, 69.74]) respectively. In the MR imaging arm, of the 58 patients undergoing a mastectomy 16 (27.6%) were classed as being pathologically avoidable. Weighted kappa statistics ranged from 0.3803 for ultrasound to 0.4767 for MR imaging, when assessing agreement between imaging methods and pathology. No significant differences were identified between the groups in the proportion of patients receiving chemotherapy, radiotherapy, or additional adjuvant therapies (p=0.3699, p=0.7439, p=0.5591). None of the 25 patients with MR-only detected <5mm lesions had a clinically significant lesion evident at their 12-month repeat MR scan. Of the 66 patients with MR-only detected ≥5mm biopsy negative lesions, only 3 had potentially clinically significant lesions at their 12-month repeat MR scan (based on overall lesion score as these lesions were not biopsied). Kaplan Meier estimates of the local recurrence-free interval rate were 99.87% (95% CI [99.05%, 99.98%]) for patients randomized to MR imaging, compared to 99.73% (95% CI [98.93%, 99.93%]) for patients randomized to no MR imaging. We found no differences in QoL between the two groups of patients (measured by FACT-B). It proved possible to develop a reliable and acceptable nonscheduled standardized interview (NSSI) for use in this patient population. Satisfaction and reassurance levels were high in patients randomized to receive MR imaging, despite reported levels of distress secondary to the procedure.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1216.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1216.asp.

Further research/reviews required

The introduction of 3T MR systems offers significant improvements in signal-to-noise and fat suppression compared to 1.5T systems. See Executive Summary link at www.hta.ac.uk/project/1216.asp.

Written by Professor Lindsay Wilson Turnbull, NETSCC, United Kingdom

Title **Effectiveness and Cost Effectiveness of Arthroscopic Lavage in the Treatment of Osteoarthritis of the Knee: A Mixed Methods Study of the Feasibility of Conducting a Surgical Placebo-Controlled Trial (The KORAL Study)**

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Reference Volume 14.05. ISSN 1366-5278. www.hta.ac.uk/project/1448.asp

Aim

To ascertain the acceptability of a randomized controlled trial comparing arthroscopic lavage with a placebo-surgical procedure in managing osteoarthritis of the knee; and to assess the practical feasibility (via a formal, pilot study) of mounting such a multicenter placebo-controlled trial.

Conclusions and results

Stakeholder groups generally accepted the need to learn more about the effectiveness of arthroscopic lavage. However, opinions varied within all groups about *how* researchers should approach this and whether or not it would be acceptable to use placebo surgery. Health professional groups tended to be split between those who were strongly opposed to including a placebo surgery arm (on the grounds that it could lead to potential harm in individuals who could expect no personal benefit) and those who were more in favor (on the grounds that the potential benefit outweighed the perceived small risks to relatively few people in a placebo surgery trial arm). For prospective trial participants who had osteoarthritis of the knee, the acceptability of the trial reflected more their personal reasons for or against participating. The majority in this group said they would consider taking part. As well as expressing a desire to help others through participation, they tended to downplay any potential risk of harm from their participation while emphasizing the potential to gain some form of personal benefit. Given the nature of the proposed design, the health professionals and MREC chairs recognized that particular attention should be paid to the informed consent process when attempting to recruit participants. The pilot study showed that, in principle, a placebo-controlled trial could be conducted and that patients were willing to participate in a trial involving a placebo-surgical arm. Further, it was possible to undertake placebo surgery successfully and to blind patients to their allocation (although once patients knew their allocation, some patients allocated to surgery withdrew due to their concern about the possibility of undergoing placebo surgery). The experience of the pilot showed, however, that despite full MREC approval the study required major discussion and negotiation before local clinical approvals could be obtained. The fact that ethics approval had been granted did not mean that clinicians would automatically accept that the process was ethical. Recent national trend data show a slow, continuing decline in the utilization of arthroscopic lavage.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1448.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1448.asp.

Further research/reviews required

Researchers need to investigate: the impact of different terminology referring to placebos (eg, placebo, sham, dummy) on understanding the role and function of a placebo; the usefulness of formal decision aids in facilitating participant consent in the context of a placebo-controlled trial; and the impact of individual versus collective ethics in conducting placebo-controlled trials.

Written by Professor Marion K Campbell, NETSCC, United Kingdom

Title **Follow-up in Gynecological Cancer Patients**

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Reference 2009; 11(2). ISBN 978-87-7676-919-2.
www.sst.dk/publ/Publ2009/MTV/Ktrlforl_gynaek_kraeftpat/MTV_kontrolforloeb_net_final.pdf (Danish; English summary)

Aim

To assess the follow-up provided for women who have completed treatment for endometrial or ovarian cancer to:

- assess the effects of follow-up
- improve the follow-up.

Conclusions and results

The systematic review of the literature does not document that follow-up enhances the probability of surviving the disease. The report notes that scientific literature is insufficient in addressing the follow-up of endometrial and ovarian cancer, and the quality-of-life studies are not unequivocal. Many women perceive that follow-up gives a sense of security, but they also experience nervousness before every consultation. The analysis points out the opportunity for organizing more differentiated follow-up, adjusted to the individual's risk for relapse and the individual's need for security.

Based on the results of this report, it is appropriate to question whether follow-up has become a natural extension of treatment, ie, part of the course of cancer that has become a traditional and established part of the treatment culture in Denmark. However, this does not change the viewpoint that follow-up is an intervention, and that healthcare interventions must be evidence based to be justified (even though follow-up is used to identify suitable patients for scientific studies). In a system with limited resources, debate on priorities is a positive sign.

Recommendations

This report focuses objectively on follow-up of women with endometrial and ovarian cancer. It is hoped that the report can support a scientific debate on priorities, leading to the benefit of following up cancer patients in a manner that outweighs the efforts necessary to provide this care.

Methods

Systematic literature searches were conducted on all aspects of the assessment to investigate questions related to assessing health technology. The literature found via the searches was critically assessed, and studies considered to be of sufficiently high quality were included as a basis for conclusions. Further data were collected to supplement the literature searches. Focus group interviews were conducted as part of analyzing the patients, and the organizational analysis included a questionnaire survey of relevant hospital departments and interviews of key people. The economic analysis is based on the primary data collection and registry analysis.

Further research/reviews required

Investigating whether follow-up of patients with cancer influences their rehabilitation would be important. This health technology assessment focused on the key clinical content of follow-up. Given the limited resources and timeframe of the project, it does not include assessment of rehabilitation.

Written by Diana Reerman, DACEHTA, Denmark

Title	**Postoperative Pain Treatment at Home with an Elastomeric Pump**
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Reference	2008; 8(2). ISBN 978-87-7676-688-7. www.sst.dk/Udgivelser/2008/Postoperative%20pain%20treatment%20at%20home%20with%20a%20elastomeric%20pump%20-%20a%20Health%20Technology%20Assessment%20Summery.aspx

Aim

To determine whether it is appropriate to introduce a new analgesic method after foot surgery.

Conclusions and results

In patients with moderate to severe postoperative pain lasting 3 to 4 days, conventional oral painkillers do not provide sufficient analgesia. The standard postoperative pain treatment regime for these patients has been a blockade of the sciatic nerve in the popliteal fossa as a single-shot injection (block method). The problem with this regime is that the duration of analgesia is too short. Hence, a new method was introduced (block+pump), where the effect of the blockade is prolonged through continuous infusion of a local anesthetic by using a perineural catheter and elastomeric pump.

The scientific literature and our own studies provide a basis for concluding that the block+pump method is more effective than block alone. A high success rate (95%-98%) is reported when experienced practitioners perform the procedure. It will be possible to further improve effectiveness by applying new methods.

Recommendations

Based on the present economic analysis, no definitive recommendations can be made on whether a block, or block+pump should be used. It has been shown that block+pump treatment minimizes the loss in quality of life, but it is also more expensive than treating pain by the block method alone.

Methods

This report is based on a literature study and the results of our own studies. Due to the lack of randomized controlled trials and organizational studies, the project group decided to supplement the literature study with results from concurrent clinical studies at the anesthesia clinic, Frederiksberg Hospital.

Written by Camilla Palmhøj Nielsen, DACEHTA, Denmark

Title **Home Visits to Patients with Severe COPD**

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http://www.sst.dk/Udgivelser/2009/Home%20visits%20to%20patients%20with%20servere%20COPD%20-%20a%20health%20tecnology%20assessment%20summary.aspx

Aim

To determine the effectiveness of home visits to patients with severe chronic obstructive pulmonary disease (COPD).

Conclusions and results

Overall, the results show that home visits have several positive consequences and can be considered a good service. Nevertheless, stronger evidence is needed, especially concerning the economic aspects. Hospitals offering home visits carry out check-ups on a large number of patients, including severely ill patients that would normally require horizontal transport. This is one of the main reasons for arranging home visits to check oxygen consumption. The technology for oxygen-related home visits is available and applicable as a relevant service to COPD patients and other patient groups. The results of 4 subanalyses suggest that general developments in establishing advanced services are especially relevant in this case. The hospital-based approach (reported in all cases) is attributed to the need of hospital management to maintain an overview of oxygen consumption and the patient's situation. This suggests improved communications and greater coordination of services between the parties involved in planning different types of care for this patient group. Hence, the technology involved in arranging home visits represents the beginning of a sound trend towards "shared care" between the specialized hospital-based service, the oxygen suppliers, the home nursing system, and the general practitioner.

Recommendations

There is a need to further strengthen services for patients with chronic diseases. Organizationally, the development of home visit arrangements suggests that further interpretation and adaptation of the organization and delivery of this function is recommended.

Methods

Primary data were collected, which involved keeping records of oxygen consumption check-ups during a 4-month period at three hospitals offering home visits and two hospitals not offering home visits. During this 4-month period, 783 patients connected with the hospitals received home visits and 439 patients did not.

Further research/reviews required

Overall, this study suggests that home visits are a good service. The evolution of treatment and management of patients with severe COPD needs to be evidence based, which would require more extensive studies of sufficient strength to demonstrate statistically significant results.

Written by Mirja Elisabeth Kløjgaard, DACEHTA, Denmark

Title **A Randomized 2 × 2 Trial of Community versus Hospital Pulmonary Rehabilitation for Chronic Obstructive Pulmonary Disease Followed by Telephone or Conventional Follow-Up**

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Reference Volume 14.06. ISBN 1366-5278. www.hta.ac.uk/project/1316.asp

Aim

To determine: 1) whether community provision of pulmonary rehabilitation for people with chronic obstructive pulmonary disease (COPD) is more likely to confer benefit compared to hospital provision in both the short and long term; and 2) whether regular encouraging telephone calls prolong the benefit gained.

Conclusions and results

Pulmonary rehabilitation (PR) is known to help improve walking distance and health-related quality of life (HRQoL). It is usually provided in a secondary care setting. In the UK, interest is increasing to provide PR in a community setting.

Mean attendance at rehabilitation sessions was 80% for the community group and 83% for the hospital. Immediately post-intervention there was an increase in endurance shuttle walking time that did not differ significantly between groups. All HRQoL scores (Eq5D, CRQ total, and SF6D) improved significantly after treatment in either site, but no significant difference was found between sites, eg, SF-6D mean difference (adjusted for baseline) between hospital and community 0.01, p=0.37, CI –0.02 to 0.04. After 18 months of follow-up there was no significant difference in improvement in endurance shuttle time for hospital versus community, after adjustment for baseline walk, follow-up visit, and factorial design. No difference was found in effects on health status outcomes.

Telephone encouragement had no effect on exercise capacity, but the disease-specific CRQ total and mastery differed significantly. Emotion approaches significance. Fatigue and dyspnea are unchanged. This was not apparent for the generic SF36 or EQ5D. Post hoc analysis showed significant differences in the post-rehabilitation endurance shuttle walking distance of subjects treated by each of three rehabilitation teams when corrected for baseline distance walked. Preliminary economic analysis shows a trend for increased efficacy over 18 months in the hospital group, but lower cost in the community group, resulting in community rehabilitation being most likely to have beneficial cost-effectiveness ratios. Telephone follow-up might be cost effective in the community group.

Major exclusions were candidates for long-term oxygen therapy, or people with unstable cardiac disease. Outcome was assessed by physiological measurements and both generic and disease-specific assessments of HRQoL. All effects were fully costed in terms of their health economic effects.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1316.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1316.asp.

Further research/reviews required

This study excluded patients needing long-term oxygen therapy. Further research is required to ensure that results can be generalized to this group and that they can be safely rehabilitated in a community setting. We noted a significant dropout between patients' initial agreement and consent to rehabilitation, and their attendance for pre-rehabilitation assessment. See Executive Summary link at www.hta.ac.uk/project/1316.asp.

Written by Ms Judith Waterhouse, United Kingdom

INAHTA Briefs

Issue 2010/044

Title **Dissemination and Publication of Research Findings: An Updated Review of Related Biases**

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Reference Volume 14.08. ISBN 1366-5278. www.hta.ac.uk/project/1627.asp

Aim

To update a 2000 HTA monograph on publication bias by synthesizing findings from previously and newly indentified studies.

Conclusions and results

The objectives were: to identify and appraise empirical studies on publication and related biases published since 1998; to assess the usefulness and limitations of available methods to deal with publication and related biases; and to examine measures taken in a random sample of published systematic reviews to prevent, reduce, and detect different types of dissemination bias.

The updated review confirmed findings from the previous HTA report that studies with significant or positive results are more likely to be published than those with nonsignificant or negative results. The existence of outcome reporting bias has been demonstrated by recently published empirical studies. Studies with significant results tend, on average, to be published earlier than studies with nonsignificant results, although new evidence is less clear than was suggested in the previous review. New empirical evidence suggested that published studies tend to report a greater treatment effect than those of grey literature. Exclusion of non-English language studies appears to result in a particularly high risk of bias in some areas of research, eg, complementary and alternative medicine. Consequences of publication and related biases are different for different types of research studies. The most important consequences of dissemination bias include avoidable suffering of patients and waste of limited resources. This updated review identified only a couple of new cases that indicate the detrimental impact of publication and related biases. Publication bias is often due to investigators' failure to write up and submit. The interests of research sponsors, particularly industry's commercial interests, can restrict the dissemination of the research findings. The compulsory policy of trial registration adopted by the International Committee of Medical Journals in 2004 may be the most influential initiative to promote prospective registration of clinical trials. The impact of dissemination bias may be reduced by systematic searching for grey literature or unpublished studies. All statistical methods, simple or complex, for assessing or adjusted for publication bias in systematic reviews are often based on certain assumptions that can be difficult to justify. The available statistical methods may be useful for the purpose of sensitivity analyses. See Executive Summary link at www.hta.ac.uk/project/1627.asp.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1627.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1627.asp.

Further research/reviews required

1) Further research is needed to strengthen the development of prospective registration of clinical trials and to initiate prospective registration of basic research and observational studies. 2) Evidence is lacking on the impact of publication bias on health decision making and the outcomes of patient management. 3) There is a lack of methods that can be used to qualitatively assess the risk of publication bias in systematic reviews. 4) Many available statistical methods to test publication bias have never, or rarely, been used in systematic reviews. Further research should focus on the practical application of these statistical methods.

Written by Dr Fujian Song, United Kingdom

INAHTA Briefs

Issue 2010/045

The Relevance of the Neonatal Urine Screening for Inborn Errors of Metabolism Performed in Québec

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Aim

To assess the scientific relevance of screening for 18 diseases that has been detected in at least one child in Québec since 1973 under the Québec Newborn Urine Screening Program (QNUSP), to weigh its benefits and drawbacks, and to evaluate the efficacy and efficiency of screening techniques.

Conclusions and results

The lack of relevant evidence to address screening criteria for rare diseases makes it difficult to determine the full range of inborn errors of metabolism (IEMs) that should be screened for. Only those tested for under the QNUSP were examined. For these diseases, mass neonatal screening using tandem mass spectrometry (MS/MS) on blood samples seems more effective than multiplex thin-layer chromatography (TLC) on urine samples for: urea cycle disorders, triple H syndrome, methylmalonic aciduria, propionic aciduria, 3-methylcrotonylglycinuria I, and glutaric aciduria I. Cystathioninuria, hypersarcosinemia, hyperhistidinemia, and Hartnup disorder, generally benign conditions, should not be screened for. The debatable benefits of early screening for cystinuria, dicarboxylicamino aciduria, Fanconi-Bickel syndrome, prolidase deficiency, and pyroglutamic aciduria remain unresolved because of a lack of evidence. Waiting until the 21st day of life to obtain a urine sample (presently the case) can considerably affect screening performance. Hence, performing MS/MS on blood samples during the first few days of life appears to be more advantageous. MS/MS has an excellent level of diagnostic accuracy and is a quantitative method that is easier to standardize than the semi-quantitative TLC method, which depends on the interpreter's expertise. The relevance of adding other IEMs for neonatal screening should be assessed in a planned manner based on available scientific evidence.

Methods

A list of 14 screening criteria based on UK National Screening Committee criteria, and used for a report on neonatal blood screening done at the *Institut national de santé publique du Québec* to determine screening relevance, served as a basis for this assessment. Sources of information for evaluating clinical relevance included specialized manuals, recent literature reviews, and evidence based assessment reports from 1995 to August 2008. A systematic review (SR) of the literature with no time limit was carried out for neonatal urine screening by TLC. Primary study quality was assessed using the QUADAS checklist. SR of economic studies published since 1975 on urine screening with TLC was carried out, and the SR from a previous AETMIS report on MS/MS was updated. A SR updating the previous reports on ethical, psychosocial and organizational issues related to TLC and urine screening programs was carried out with no backward time limit, up to August 2008. Interviews with pediatricians were conducted to better understand specific issues related to clinical and organizational aspects of the program.

Further research/reviews required

The performance and viability of the QNUSP should be evaluated with regard to metabolite transport disorders that cannot be detected by blood sampling: cystinuria, Fanconi-Bickel syndrome, and dicarboxylicamino aciduria. Screening methods for these renal disorders should be reviewed, although the relevance of such screening remains controversial due to a lack of evidence on efficacy.

Written by Jolianne Renaud and Pierre Dagenais, AETMIS, Canada

Title **Telemedicine and Radiation Oncology: State of the Evidence**

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Aim

To examine telemedicine applications in radiation oncology and their potential modes of operation.

Conclusions and results

Two major findings emerge from the literature consulted on radiation therapy. First, cancer incidence is increasing in the industrialized world, including Canada and Québec, and the need for treatment, specifically radiotherapy, will continue to increase as a result. Second, oncology centers are generally concentrated in large cities, while treatment needs are geographically dispersed over a vast area. This situation leads to suboptimal delivery of radiotherapy services. Although strong steps have been taken over the past few years, the dispersion of Québec's population over a large territory still imposes major burdens and inconvenience on patients who live in remote areas. In this context, telemedicine can be viewed as a possible solution. Finally, the literature review shows that the main application of telemedicine in radiation oncology is remote treatment planning. It can assist in networking various centers and decentralizing radiotherapy services by providing satellite centers with access to expertise not available on-site. However, the success of such an initiative depends on implementing a stringent quality assurance process.

Methods

A scientific literature review was undertaken for the purpose of preparing this technical note.

Further research/reviews required

The literature barely addressed the medico-legal liability issues raised by remote treatment planning and simulation and the economic issues surrounding this therapeutic modality. These issues will require further study.

Written by Khalil Moqadem and Gilles Pineau, AETMIS, Canada

Title **Initial Staging of Esophageal Cancer: Systematic Review of the Performance of Diagnostic Methods**

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Aim

To systematically review the literature on the performance of diagnostic methods used for clinically staging esophageal cancer.

Conclusions and results

Most of the studies reviewed were characterized by poor methodological quality, small sample sizes, and little evidence regarding certain technologies. The many methodological limitations of the studies we examined did not enable us to draw any firm conclusions. Taking these limitations into account, AETMIS has drawn several conclusions that are consistent with several existing practice guidelines. A combination of techniques must be used for optimal clinical staging of esophageal cancer. A diagnostic test sequence for clinical staging is proposed: 1) start with a computed tomography (CT) scan of the neck, thorax, and abdomen to determine the presence of any distant metastases; 2) if no distant metastases are present, use endoscopic ultrasound (EUS) to evaluate locoregional invasion and celiac lymph nodes and EUS fine-needle aspiration (FNA) if the tumor does not obstruct the needle. If a stenosing tumor is present, the optimal approach is not known, but dilatation is indicated, except in the case of severe stenosis, and should be carried out in centers possessing considerable expertise; 3) add positron emission tomography to computed tomography (PET-CT) in the cancer staging process if the patient is deemed eligible for curative treatment after a CT scan and EUS; 4) use magnetic resonance imaging (MRI) if CT cannot be performed; 5) perform minimally invasive surgical procedures in certain situations, eg, laparoscopy, to evaluate abdominal metastases when the cancer is located in the gastroesophageal junction.

Methods

A systematic review of the scientific literature focused on the performance of diagnostic tests used in clinical staging of cancer of the esophagus and gastroesophageal junction not associated with stomach cancer. The review of primary studies covered January 1999 to December 2007 in the MEDLINE (PubMed) and Cochrane Library databases. A literature watch for systematic reviews and guidelines continued until July 2008.

Further research/reviews required

Primary studies of better methodological quality are required, eg, prospective studies featuring a blinding interpretation between diagnostic test outcomes and histopathological analysis findings. Moreover, additional studies comparing PET-CT to other diagnostic tests, eg, EUS-FNA and CT, for initial staging are also necessary. More studies need to compare MRI to other modalities in staging esophageal cancer.

Written by Julie Tranchemontagne, AETMIS, Canada

Title **Sentinel Lymph Node Biopsy in Breast Cancer Treatment: Technical Aspects**

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Aim

To systematically review the validity of current evidence on the technical aspects of sentinel node biopsy in breast cancer treatment.

Conclusions and results

Sentinel node biopsy is a proven technique in terms of feasibility and diagnostic accuracy. In experienced hands, it generally yields high identification rates (around 95%) and has a low risk of false negatives (around 5%). However, certain technical aspects influence these performance measures: 1) The use of radioisotope alone is better than the use of blue dye alone. Combining the two tracers achieves the best identification rates and the lowest risk of false-negative findings; 2) The different types of dyes or radioactive colloids do not substantially modify the results of sentinel node biopsy; 3) Superficial injection of the tracer offers better success rates than intraparenchymal injection in identifying sentinel nodes; 4) The time from radioisotope injection to surgery is not meaningful if the dose is increased for injection administered the day before the procedure; 5) Preoperative lymphoscintigraphy appears not to improve either sentinel node identification rates or the sensitivity of sentinel node biopsy in detecting axillary lymphatic invasion; 6) Immunohistochemistry combined with standard histological examination achieves highly variable results and does not seem to reduce the risk of false negatives in sentinel node biopsy; 7) Despite low sensitivity for detecting micrometastases, intraoperative examination of sentinel nodes by imprint cytology or frozen section offers the possibility of immediate axillary dissection in the event of positive intraoperative findings; 8) Surgeon experience affects sentinel node identification rates, but has a lesser impact on the risk of false negatives. The learning curve seems short: high performance levels may be achieved with as few as 20 biopsies under the supervision of a qualified surgeon, where sentinel node identification rates may subsequently serve as a performance indicator.

Methods

A systematic literature review focused on the feasibility and diagnostic accuracy of sentinel node biopsy, with two main study parameters: sentinel node identification rate and risk of false negatives (1 - negative predictive value). Methods also included analysis of the false-negative risk (with study patients who underwent axillary dissection) and assessment of the following technical aspects of sentinel lymph node biopsy: type of tracer, type of radioactive colloid, type of dye, tracer injection site, time from injection to surgery, use of preoperative lymphoscintigraphy or not, histological examination method, and intraoperative examination. The role of the learning curve for this technique was also evaluated.

Further research/reviews required

The prognostic value of micrometastases detected solely through immunohistochemistry should be investigated.

Written by Cathy Gosselin, AETMIS, Canada

Title	**Telepathology: Guidelines and Technical Standards, Literature Review**
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Aim

To perform a thorough literature review of technology standards and guidelines that could contribute to the ongoing implementation of a telepathology technological platform for the province of Québec.

Conclusions and results

Telepathology is the practice of remote anatomical pathology between two or more distant facilities using a microscope (or a slide scanner), a telecommunications medium, and a workstation for the consulting pathologist. Its aim is to provide pathology services at a distance when an on-site pathologist is unavailable. Two types of telepathology are: static telepathology (involves capturing, digitizing, and transmitting images of a gross or microscopic specimen to a consulting pathologist), and dynamic telepathology (involves real-time transmitting and viewing of histological images from a microscope located at a distant facility). Both types have their advantages, drawbacks, and applications and are useful in diagnosis, obtaining a second medical opinion, or teletraining.

Our analysis shows:

1. A virtual slide is the best solution to most problems associated with distance and the lack of pathologists at remote hospitals, and it constitutes the best compromise.

2. In spite of its promising advantages, dynamic telepathology is not often used.

3. The main technological issue concerns difficult interoperability between the various components, eg, microscope, camera, personal computer, and digitizer.

4. The most important technical issues involve data security and archiving, especially when dealing with secure networks and intranets.

5. Organizationally, adequate training of all telepathology personnel (new user-pathologists, pathology technicians, surgeons, etc.) in virtual environments is a critical prerequisite, along with medical accreditation, confidentiality, payment of fees, professional liability, and other unresolved medicolegal problems. In addition, standardizing the digital-image generation process among various teams is crucial to minimize the risk of error.

6. The ethical, legal, and economic issues associated with telepathology should be examined to facilitate the deployment of technology.

Methods

We reviewed the literature published between Jan. 1997 and Dec. 2007. Databases queried included Medline (via PubMed), Database of Abstracts of Reviews of Effects (DARE), National Health Service Economic Evaluation Database (NHS-EED), Telemedicine Information Exchange (TIE), The Cochrane Library, and the International Network of Agencies for Health Technology Assessment (INAHTA). We surveyed trade journals and consulted article references, Web sites, and pamphlets from virtual microscopy and telepathology equipment suppliers. The literature watch ended in July 2008.

Further research/reviews required

On-site tests will be required in the future. No such tests have been conducted because telepathology technologies did not exist in Québec at the time of publishing. Discussions regarding the legal aspects of possible options for static telepathology archiving are also required.

Written by Khalil Moqadem and Gilles Pineau, AETMIS, Canada

INAHTA Briefs

Issue 2010/050

Title **Surveillance of Cirrhosis for Hepatocellular Carcinoma: Systematic Review and Economic Analysis**

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Reference Volume 11.34. ISSN 1366-5278. www.hta.ac.uk/project/1494.asp

Aim

To evaluate the effectiveness, cost effectiveness, and cost utility of surveillance of patients with cirrhosis (alcoholic liver disease [ALD], hepatitis B [HBV], and C virus [HCV]) using periodic serum alpha-fetoprotein (AFP) testing and/or liver ultrasound examination to detect hepatocellular carcinoma (HCC), followed by treatment with liver transplantation or resection, where appropriate.

Conclusions and results

No studies were identified that met the criteria of the systematic review. Based on the assumptions used in the model, the most effective surveillance strategy uses a combination of AFP testing and ultrasound at 6-month intervals. Compared with no surveillance, this strategy is estimated to more than triple the number of people with operable HCC tumors at time of diagnosis, and almost halves the number of deaths from HCC. On all effectiveness measures and at both testing frequencies, AFP- and ultrasound-led surveillance strategies are similar. This may be because test sensitivity varied according to tumor size, which means that AFP testing is capable of identifying many more small tumors than ultrasound. The best available evidence suggests that AFP tests will detect approximately six times as many small tumors as ultrasound. Increasing the frequency of either test to 6-month intervals is more effective than performing combined testing on an annual basis. The undiscounted lifetime cost of the surveillance strategies, including all care and treatment costs, ranges from 40 300 pounds sterling (GBP) (annual AFP triage) to GBP 42 900 (6-month AFP and ultrasound). The equivalent discounted costs are GBP 28 400 and GBP 30 400. Only a small proportion of these total costs results from the cost of the screening tests. However, screening test costs, and the cost of liver transplants and caring for people post-transplant, accounted for most of the incremental cost differences between alternative surveillance strategies. The results suggest that different surveillance strategies may provide the best value for money in patient groups of different cirrhosis etiologies. Surveillance in people with HBV-related cirrhosis for HCC provides the best value for money, while surveillance in people with ALD-related cirrhosis provides the poorest value for money. In people with HBV-related cirrhosis, at an assumed maximum willingness to pay (WTP) for a quality-adjusted life-year (QALY) of GBP 30 000, both the deterministic and probabilistic cost-utility analyses suggest the optimal surveillance strategy would be 6-month surveillance with the combination of AFP testing and ultrasound. See Executive Summary link at www.hta.ac.uk/project/1494.asp.

Recommendations

In a mixed etiology cohort, the most effective surveillance strategy is to screen each. This may be largely due to the younger age at diagnosis of cirrhosis in patients with HBV. This raises the possibility of further subgroups of ALD and HCV patients diagnosed with cirrhosis at a younger age, in which more intensive surveillance might provide value for money. *Implications for policy:* The results show that surveillance strategies for HCC are effective and can often be considered cost effective in patients with cirrhosis. We believe that the implementation of formal surveillance programs should be considered where they do not currently exist. See Executive Summary link at www.hta.ac.uk/project/1494.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1494.asp.

Further research/reviews required

See Executive Summary link at www.hta.ac.uk/project/1494.asp.

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INAHTA Briefs

Issue 2010/051

Title **A Review and Critique of Modeling in Prioritizing and Designing Screening Programs**

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Reference Volume 11.52. ISBN 1366-5278. www.hta.ac.uk/project/1567.asp

Aim

To undertake a structured review and critical appraisal of methods for model-based, cost-utility analysis of screening programs. Informed by the review, study aims include development of guidelines and an assessment checklist of good practice in screening models.

Conclusions and results

Few relevant methodological studies were identified, and no studies reporting direct empirical comparisons on the relative merits of alternative methodologies. Hence, the defined guidelines and assessment checklist are based on theoretical interpretations of the impact of alternative approaches to different components of the modeling process when applied to the cost-utility analysis of screening programs. The review identified many alternative modeling methods that had been applied in cost-utility analyses of screening programs, including some relatively new approaches that had not been widely disseminated. The natural history modeling approach was identified as the preferred general method of evaluation for screening programs. Alternative modeling approaches were generally used only to extrapolate the observed effects of screening and were unsuitable for evaluating unobserved screening options.

State transition models have generally been used to represent disease natural histories, though individual sampling models are more prevalent than in treatment intervention evaluations. Structural aspects that were not well handled by screening models include post-diagnosis disease progression and screening uptake. Calibration is common and important in screening models, and models are fitted to observed data describing outputs of the model to populate unobserved input parameters. In most cases, calibration was limited to identifying best fitting parameter values. See Executive Summary link at www.hta.ac.uk/project/1567.asp.

Recommendations

The review of methods for the model-based, cost-utility analysis of screening programs identified the natural history modeling approach as the preferred general method of evaluation for screening programs. More complex model structures may incorporate important additional aspects of the disease natural history, although any benefits should outweigh the consequences of additional unobservable input parameters and increased complexity in implementing the model. Preferred approaches to handling post-diagnosis disease progression and screening uptake would incorporate treatment models representing current treatment patterns, while available evidence might inform links between screening uptake rates and disease incidence or progression. Model calibration should predict output parameters for many input parameter sets, with the accuracy of each set's predictions represented as a weight. The main analysis of the model then samples many input parameter sets according to the weights attached, from which mean values and probability distributions of cost-effectiveness can be derived. Further research should address methods with the potential to improve accuracy in screening models and to respond to the needs of model users.

Methods

Literature searches identified applied and methodological studies of economic evaluations of healthcare screening programs. In addition, applied screening models in antenatal screening and 3 broad disease areas (cancer, cardiovascular disease, and diabetes) were reviewed. See Executive Summary link at www.hta.ac.uk/project/1567.asp.

Further research/reviews required

More complex mathematical modeling approaches have great potential as alternatives or adjuncts to state-based modeling techniques in evaluating the cost utility of screening programs. See Executive Summary link at www.hta.ac.uk/project/1567.asp.

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INAHTA Briefs

Issue 2010/052

Title **Stapled Haemorrhoidectomy (Haemorrhoidopexy) for the Treatment of Haemorrhoids: A Systematic Review and Economic Evaluation**

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Reference Volume 12.08. ISSN 1366-5278. www.hta.ac.uk/project/1544.asp

Aim

To determine the safety, clinical effectiveness, and cost effectiveness of circular stapled hemorrhoidopexy (SH) compared to conventional excisional hemorrhoidectomy (CEH) in treating hemorrhoids.

Conclusions and results

The review included 27 RCTs (n=2279; 1137 SH; 1142 CEH). All had some methodological flaws; only two reported recruiting patients with second, third, and fourth degree hemorrhoids, and only 37% reported using an appropriate method of randomization and/or allocation concealment. Compared to CEH, SH was associated with less pain in the immediate postoperative period, shorter operating times, a more rapid return to normal activity, and fewer unhealed wounds at 6 weeks, but a higher rate of residual prolapse, and prolapse and reintervention for prolapse, in the longer term (1 year and beyond). SH and CEH did not differ in the incidence of postoperative complications, bleeding, pain after the 21st postoperative day, or reinterventions for pain. Given the paucity of long-term data, the absolute and relative rates of recurrence and reintervention for both techniques remain uncertain.

Economic assessment showed similar costs and QALYs for CEH and SH; the average difference in costs between the procedures was 19 pounds sterling (GBP) and the difference in QALY was -0.001 favoring CEH over 3 years. The superior quality of life due to less pain after SH was offset by the higher rate of symptoms over the follow-up period. The additional cost of the staple gun is likely to be offset by savings in operating time and hospital stay. Some training may be required to use the staple gun, but this is not expected to have major resource implications. The results were particularly sensitive to the valuation of utility in the early postoperative period. Probabilistic sensitivity analysis showed that, at a threshold ICER of between GBP 20 000 and GBP 30 000 per QALY, SH had a 45% probability of being cost effective.

Recommendations

Given the clinical evidence and results of the economic analysis, the choice between SH and CEH should be based primarily on the patient's priorities and preferences (reduced pain and rapid return to normal activities in the short-term, versus reduced risk of recurrence in the longer-term) and the surgeon's preference. See Executive Summary link at www.hta.ac.uk/project/1544.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1544.asp.

Further research/reviews required

An adequately powered, good-quality RCT is required, comparing SH with CEH, recruiting patients with second, third and fourth degree hemorrhoids, and having a minimum follow-up of 5 years to ensure adequate evaluation of reintervention rates. The effectiveness of SH in patients with fourth degree hemorrhoids and patients with co-morbid conditions should be evaluated. All treatments for hemorrhoids (conservative, nonsurgical, and surgical) need to be reviewed, including a comparison of reintervention rates. Other areas for research are utilities of patients up to 6 months postoperatively, the trade-offs of patients for short-term pain versus long-term outcomes, and the ability of SH to reduce hospital stays in a real practice setting. See Executive Summary link at www.hta.ac.uk/project/1544.asp.

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INAHTA Briefs

Issue 2010/053

Title **Cessation of Attention Deficit Hyperactivity Disorder Drugs in the Young (CADDY) – A Pharmacoepidemiological and Qualitative Study**

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Reference Volume 13.50. ISSN 1366-5278. www.hta.ac.uk/project/1513.asp

Aim

To review current practices in treating adolescents and young adults with attention deficit hyperactivity disorder (ADHD).

Conclusions and results

Objectives: 1) To estimate the prevalence of ADHD treatments in the target population. 2) To describe the demographic and clinical details of patients in the target population who received ADHD pharmacotherapy. 3) To estimate the percent of patients in the target group who stopped ADHD pharmacotherapy. 4) To search the literature for and assess the feasibility of using appropriate quality-of-life measures in this patient population. 5) To identify the reasons for and factors related to cessation of ADHD pharmacotherapy (and effects on symptoms). 6) To interview clinicians to obtain their perceptions of the process and outcome of cessation of ADHD pharmacotherapy (and effects on symptoms).

Part 1: 983 patients (896 males, 91%) received 18 371 prescriptions during the study period. The overall prevalence of prescribing (males and females aged 15-21), increased 87.4% over the study period, from 0.26 per 1000 patients in 1999 to 2.07 per 1000 patients in 2006. The largest increase in prevalence occurred in younger patients, but the increase became less evident as patients grew older.

Treatment Cessation: Survival analysis was conducted on 845 patients who entered the analysis aged 15 between 1999 and 2006. The Kaplan Meier plot estimate of the survival function showed that when patients were 16 years of age (ie, 1 year after entering the study) 83% remained on treatment. At age 17, only 54% remained on treatment. This fell to 36% at age 18, 24% at age 19, 22% at age 20, and 17% at age 21. Of the covariates tested, gender and the year of study entry were significant in predicting treatment cessation. Regarding gender, the Cox model suggested no difference in the hazards before 6 months. However, after 6 months the hazard of a female stopping treatment was 63% less than a male. The model also suggested that the patients aged 15 years between 2004 and 2006 at inclusion were 40% less likely to stop treatment compared to patients aged 15 years between 1999 and 2003. See Executive Summary link at www.hta.ac.uk/project/1513.asp.

Recommendations

This study raises the possibility that treatment may be prematurely stopped by or for some adolescents and young adults with ADHD, and that overall the fall in treatment prevalence may be out of step with the numbers of people who still require treatment as young adults. The evidence base on the outcomes of cessation of treatment in ADHD patients is scarce. Hence, guidelines may help patients, clinicians, and families decide on an appropriate cessation strategy. Further research would be necessary to develop these guidelines.

Methods

See Executive Summary link at www.hta.ac.uk/project/1513.asp.

Further research/reviews required

An RCT would be appropriate to determine the outcomes of patients who stop treatment compared to those who do not. Such a study, if sufficiently powered, might be able to detect factors that predict which patients are more likely to have favorable outcomes.

Written by Professor Ian Wong, The School of Pharmacy, University of London, United Kingdom

INAHTA Briefs

Issue 2010/054

Title **Randomized Controlled Trial of the use of Three Dressing Preparations in the Management of Chronic Ulceration of the Foot in Diabetes**

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Reference Volume 13.54. ISSN 1366-5278. www.hta.ac.uk/project/1357.asp

Aim

To compare the use of three dressing products in managing chronic foot ulcers.

Conclusions and results

The study included 317 people with diabetes and had five objectives: 1) To test whether a modern dressing product (Aquacel®) is more clinically effective than traditional dressings (Inadine®, N-A®) in treating diabetes-related foot ulcers. 2) To investigate changes in condition and reoccurrence associated with each dressing during the study. 3) To determine the relative cost effectiveness of the three dressings. 4) To assess patients' health-related quality of life (HRQoL), physical and social functioning, and pain associated with each of the dressings. 5) To investigate the self-care contributions by patients and carers.

1) We found no difference in the effectiveness of the three dressing products studied and no difference in the cumulative incidence of adverse or serious adverse events. 2) We confirmed that a greater proportion of smaller ulcers (<1cm2) would heal within the specified time of 24 weeks: 47.7% versus 36.1%. In the 114 for whom data were available, ulcers recurred in 13 (11.4%) within 3 months. At 3-month follow-up, 47% of 232 participants who completed the study had an active ulcer. 3) The only statistically significant difference was in the costs associated with providing dressings. The professional time involved in dressing changes was similar. Further research needs to assess the relationship between unhealed ulcers and the risk of amputation. Given that the effectiveness of dressing types does not differ, the additional cost of Aquacel® does not appear to be justified. 4) We found no difference between dressing groups in terms of HRQoL, although differences were found between those with healed and with unhealed ulcers using the Cardiff Wound Impact Schedule (CWIS). The overall prevalence of pain in unhealed ulcers did not differ between the three groups. 5) We found that 51% of participants had at least one dressing changed by themselves or their carer. Almost 70% of all dressing changes were undertaken by nonprofessionals. See Executive Summary link at www.hta.ac.uk/project/1357.asp.

Recommendations

We found no evidence to suggest that any dressing product was more effective, more acceptable, or safer than any other. Further research needs to establish the cost implications of ulcers failing to heal. In the absence of clear evidence of benefit, preference should be given to cheaper, more traditional products in routine clinical practice.

Methods

See Executive Summary link at www.hta.ac.uk/project/1357.asp.

Further research/reviews required

The effectiveness of all dressing products being promoted for chronic foot ulcers in diabetes should be compared with products like those used in this study. The study provides a benchmark for comparisons. The methods used here may be adapted to determine the effectiveness of dressing products for specific types of chronic ulcers. Patients and their carers perform most dressing changes, which has implications in economic evaluations that assume that professionals change all dressings.

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INAHTA Briefs

Issue 2010/055

Title **The Clinical Effectiveness of Diabetes Education Models for Type 2 Diabetes: A Systematic Review**

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Reference Volume 12.09. ISSN 1366-5278. www.hta.ac.uk/project/1550.asp

Aim

To examine the clinical effectiveness of patient education models for adults with type 2 diabetes.

Conclusions and results

The evidence suggests that education delivered by a team of educators, with some reinforcement at additional points of contact, may provide the best opportunity for improvements in patient outcomes. Educators need to have adequate time and resources to fulfill the needs of any structured educational program. Educational programs need to be clearly described from the outset. The evidence indicates it is unclear what resources would need to be directed at the educators themselves to ensure that they can deliver programs successfully. Including the studies identified in the previous systematic review, 13 published studies addressed education on multiple aspects of diabetes self-management and 8 studies addressed education focused on a particular aspect of self-management. The quality of reporting and methodology of the studies varied. Studies of multicomponent educational interventions yielded mixed results. Some trials reported significant improvements in measures of diabetic control, but others did not. Positive effects may be attributable to longer-term interventions of shorter duration between the end of the intervention and the follow-up evaluation. There may also be an effect of having a multiprofessional team deliver the educational program. Studies of focused educational interventions did not yield consistent results. Some effects were shown on measures of diabetic control in studies that focused on diet or exercise alone. Although the effects shown were generally small, those that were present appeared to be relatively long lasting. This update does not substantially alter the conclusions of the previous systematic review; for each outcome, a similar proportion of studies demonstrated significant effects of education.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1550.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1550.asp.

Further research/reviews required

Any future research should consider patient education within the context of overall diabetes care and, as such, should follow guidelines for the development and evaluation of complex interventions. Good-quality, longer-term studies would be desirable, but these would require careful consideration of the nature of any control group. To ensure the success and cost effectiveness of educational programs, information is needed to clarify the sensitivity of diabetes education programs in relation to the performance of the diabetes educators.

Written by Dr Emma Loveman, SHTAC, University of Southampton, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/056

Title **Cyclooxygenase-2 Selective Non-Steroidal Anti-Inflammatory Drugs (Etodolac, Meloxicam, Celecoxib, Rofecoxib, Etoricoxib, Valdecoxib and Lumiracoxib) for Osteoarthritis and Rheumatoid Arthritis: A Systematic Review and Economic Evaluation**

Agency **NETSCC, HTA, NIHR Evaluation and Trials Coordinating Centre**
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Reference Volume 12.11. ISSN 1366-5278. www.hta.ac.uk/project/1383.asp

Aim

To review the clinical and cost effectiveness of cyclooxygenase-2 (COX-2) selective nonsteroidal antiinflammatory drugs (NSAIDs) for osteoarthritis (OA) and rheumatoid arthritis (RA).

Conclusions and results

The COX-2 selective NSAIDs examined in this report (ie, etodolac, meloxicam, celecoxib, rofecoxib, valdecoxib, etoricoxib, and lumiracoxib) were found to be similar to nonselective NSAIDs for the symptomatic relief of RA and OA and to provide superior gastrointestinal (GI) tolerability (most evidence is in patients with OA). Although COX-2 selective NSAIDs offer protection against serious GI events compared to nonselective NSAIDs, the amount of evidence for this protective effect varied considerably across individual drugs. The volume of trial evidence with regard to cardiovascular safety also varied substantially between COX-2 selective NSAIDs. Increased risk of myocardial infarction (MI) compared to nonselective NSAIDs was observed among those drugs with greater volume of evidence in terms of exposure in patient-years. Subgroup analyses of clinical and complicated upper GI events and MI events related to aspirin use, steroid use, prior GI history, and *Helicobacter pylori* status were based on relatively small numbers and were inconclusive. Economic modeling shows a wide range of possible costs per quality-adjusted life year (QALY) gained in patients with OA and RA. Costs per QALY varied if individual drugs were used *in standard-* or *high-risk* patients, the choice of nonselective NSAID comparator, and whether NSAID was combined with a proton pump inhibitor (PPI). When the model was run using ibuprofen or diclofenac combined with a PPI as the comparator, the results changed substantially, with the COX-2 selective NSAIDs looking generally unattractive from a cost-effectiveness standpoint. See Executive Summary link at www.hta.ac.uk/project/1383.asp.

Recommendations

This report summarizes the best available evidence and discusses its implications, but does not make recommendations about policy or clinical care.

Methods

Systematic reviews of randomized controlled trials and a model-based economic evaluation were undertaken. Electronic databases were searched up to November 2003. Industry submissions to the National Institute for Health and Clinical Excellence in 2003 were also reviewed. Meta-analyses were undertaken for each COX-2 selective NSAID compared with placebo and nonselective NSAIDs.

Further research/reviews required

With reduced costs of PPIs, future primary research needs to compare the effectiveness and cost effectiveness of COX-2 selective NSAIDs relative to nonselective NSAIDs with a PPI. Direct comparisons of different COX-2 selective NSAIDs, using equivalent doses that compare GI and MI risk are needed. Pragmatic studies that include a wider range of people, including the older age groups with a greater burden of arthritis, are also necessary to inform clinical practice.

Written by Dr Yen-Fu Chen, University of Birmingham, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/057

Title **Ranibizumab and Pegaptanib for the Treatment of Age-Related Macular Degeneration: A Systematic Review and Economic Evaluation**

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Reference Volume 12.16. ISSN 1366-5278. www.hta.ac.uk/project/1528.asp

Aim

To assess the clinical and cost effectiveness of ranibizumab and pegaptanib for subfoveal choroidal neovascularization (CNV) associated with wet age-related macular degeneration (AMD).

Conclusions and results

Patients with AMD of any lesion type benefit from treatment with pegaptanib or ranibizumab on measures of visual acuity when compared with sham injection and/or photodynamic therapy (PDT). Patients who continued treatment with either drug appeared to maintain benefits after 2 years of follow-up. When comparing pegaptanib and ranibizumab, the evidence was less clear due to the lack of direct comparison through head-to-head trials and the lack of opportunity for indirect statistical comparison due to heterogeneity. Cost-effectiveness analysis showed that the two drugs offered additional benefit over the comparators of usual care and PDT, but at increased cost. The VISION study reported a combined analysis of two randomized controlled trials (RCTs) of pegaptanib [0.3 mg (licensed dose), 1.0 mg and 3.0 mg] versus sham injection in patients with all lesion types. Three published RCTs (MARINA, ANCHOR, FOCUS) and an unpublished RCT (PIER) of ranibizumab were identified. Significantly more patients lost less than 15 letters of visual acuity at 12 months with pegaptanib or ranibizumab than sham injection or, in the case of ranibizumab, PDT. The proportion of patients gaining 15 letters or more was statistically significantly greater with pegaptanib for doses of 0.3 and 1.0 mg but not for 3.0 mg, and for ranibizumab compared with sham injection or PDT. This was also statistically significant for 0.5 mg ranibizumab plus PDT compared with PDT plus sham injection. Pegaptanib patients lost statistically significantly fewer letters after 12 months of treatment than the sham group. In MARINA and ANCHOR trials, ranibizumab patients gained letters of visual acuity at 12 months, whereas patients with sham injection or PDT lost about 10 letters ($p < 0.001$). Adverse events were common for both pegaptanib and ranibizumab, but most were mild to moderate. Drug costs for 1 year of treatment were estimated as 4626 pounds sterling (GBP) for pegaptanib and GBP 9134 for ranibizumab. Non-drug costs accounted for an additional GBP 2614 for pegaptanib and GBP 3120 for ranibizumab. Further costs are associated with the management of injection-related adverse events, from GBP 1200 to GBP 2100. For pegaptanib compared with usual care, the incremental cost-effectiveness ratio (ICER) ranged from GBP 163 603 for the 2-year model to GBP 30 986 for the 10-year model. Similarly, the ICERs for ranibizumab for patients with minimally classic and occult non-classic lesions, compared with usual care, ranged from GBP 152 464 for the 2-year model to GBP 25 098 for the 10-year model. See Executive Summary link at www.hta.ac.uk/project/1528.asp.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1528.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1528.asp.

Further research/reviews required

1) Trials to compare pegaptanib with ranibizumab and bevacizumab, and the role of verteporfin PDT in combination with these drugs. 2) A study to assess adverse events outside the proposed RCTs. 3) Studies to determine the optimal dosing regimes of these drugs and the benefits of re-treatment after initial treatment. 4) Research into health-state utilities and their relationship with visual acuity and contrast sensitivity, the relationship between duration of vision loss and the quality of life, and functional impact of vision loss. See Executive Summary link at www.hta.ac.uk/project/1528.asp.

Written by Dr Jill Colquitt, University of Southampton, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/058

Title **The Effectiveness and Cost Effectiveness of Behavioral Interventions for the Prevention of Sexually Transmitted Infections in Young People Aged 13–19: A Systematic Review and Economic Evaluation**

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Reference Volume 14.07. ISSN 1366-5278. www.hta.ac.uk/project/1666.asp

Aim

To assess the effectiveness and cost effectiveness of behavioral interventions to prevent sexually transmitted infections (STIs) in young people.

Conclusions and results

A descriptive map of 136 studies meeting the inclusion criteria was produced. The results illustrated the predominance of North American trials of educational interventions in schools. Discussion with the project's advisory group enabled the prioritization of a policy-relevant subset of studies for systematic review. For inclusion, studies had to: 1) be a randomized controlled trial (RCT); 2) evaluate a behavioral intervention including factual information on STIs and skills development for negotiation of safer sex; 3) be delivered in a school; and 4) report a sexual behavioral outcome. In total, 15 RCTs met the inclusion criteria for systematic review. Most were conducted in the US, with only two in the UK. Of the 15 RCTs, 12 were judged to be methodologically sound and were included in the analysis of effectiveness. Few statistically significant differences were found between behavioral interventions and the comparators in terms of sexual behavior outcomes. A meta-analysis of condom use showed no overall statistically significant difference between study groups. However, significant differences favored the behavioral intervention for improving knowledge and some types of self-efficacy. None of the studies reported infection rates. Nine of the 12 methodologically sound RCTs conducted a process evaluation. Analysis of process evaluation data found that interventions were not always implemented as intended. Variation in implementation was affected by whether or not there was a supportive school culture, flexible school administration, and enthusiasm and expertise from teachers and peers in delivering interactive sexual health sessions, eg, role plays. Secondly, not all young people found the interventions as engaging or as acceptable as they might have done. Provider qualities (enthusiasm, credibility, and expertise in content and in managing classrooms) influenced whether or not young people found the interventions acceptable and engaging. In a cohort of 1000 boys and 1000 girls aged 15 years, the economic model estimated that the behavioral interventions would avert 2 STI cases and save 0.35 QALY. The incremental cost effectiveness of the teacher-led and peer-led interventions was 20 223 pounds sterling (GBP) and GBP 80 782 per QALY gained respectively (compared to standard, non-skills-based, sex education). See Executive Summary link at www.hta.ac.uk/project/1666.asp.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1666.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1666.asp.

Further research/reviews required

Further research could include long-term follow-up to assess the adoption and maintenance of safer sexual behavior into adulthood and evaluation of the impact of booster sessions. All trials should involve rigorous process evaluation to assess factors contributing to success or failure, and economic evaluation to assess cost effectiveness. Other markers of risk reduction (eg, STI testing) should be measured. Data are needed for economic evaluation of the group aged <16 years.

Written by Dr Jonathan Shepherd, SHTAC, University of Southampton, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/059

Title **Comparison of Case Note Review Methods for Evaluating Quality and Safety in Health Care**

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Reference Volume 14.10. ISSN 1366-5278. www.hta.ac.uk/project/1575.asp

Aim

1) To determine which of two methods of case note review – holistic (implicit) or criterion-based (explicit) – provides the most useful and reliable information for quality and safety of care. 2) To explore the process–outcome relationship between holistic and criterion-based quality-of-care measures and hospital-level outcome indicators.

Conclusions and results

Using the holistic approach, 3 staff groups appeared to interpret case notes differently when they reviewed the same record. When doctors and nonclinical audit staff reviewed the same clinical record, the groups' assessments of quality of care did not differ significantly. The 3 staff groups performed reasonably well when using criterion-based review, although the quality and type of information provided by doctors was of greater value. Hence, when measuring quality of care from case notes, consideration needs to be given to the method of review, the type of staff undertaking the review, and the methods of analysis available to the review team. Review can be enhanced using a combination of both criterion-based and structured holistic methods with textual commentary. Variations in quality of care can best be identified from a combination of holistic scale scores and textual data review. Overall, 1473 holistic and 1389 criterion-based reviews were undertaken in the first part of the study. When the same staff-type reviewer pairs/groups reviewed the same record, holistic scale score interrater reliability was moderate within each of the 3 staff groups (intraclass correlation coefficient [ICC] 0.46–0.52), and interrater reliability for criterion-based scores was moderate to good (ICC 0.61–0.88). When different staff-type pairs/groups reviewed the same record, agreement between the reviewer pairs/groups was weak to moderate for overall care (ICC 0.24–0.43). Comparison of holistic review and criterion-based scores of case notes reviewed by doctors and nonclinical audit staff showed a reasonable level of agreement (p-values for difference 0.406 and 0.223, respectively), although results from all 3 staff types showed no overall level of agreement (p-value for difference 0.057). Detailed qualitative analysis of the textual data indicated that the 3 staff types tended to provide different forms of commentary on quality of care, although the groups showed some overlap. In the process–outcome study, the criterion-based scores for all hospitals were generally high, whereas interhospital variation was greater between the holistic review overall scale scores. Textual commentary on the quality of care verified the holistic scale scores. Differences among hospitals in the relationship between mortality and quality of care were not statistically significant.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1575.asp.

Methods

In the first part of the study, retrospective multiple reviews of 684 case notes were undertaken using both holistic (implicit) and criterion-based (explicit) review methods. Quality-of-care measures included evidence based review criteria and a quality-of-care rating scale. Textual commentary on the quality of care was provided as a component of holistic review. Data were collected in 9 randomly selected acute hospitals in England, by hospital staff trained in case note review. These local review teams comprised combinations of 3 staff types: doctors (n=16), specialist nurses (n=10) and clinically trained audit staff (n=3) (n=13 in total), and nonclinical audit staff (n=9).

Further research/reviews required

See Executive Summary link at www.hta.ac.uk/project/1575.asp.

Written by Professor Allen Hutchinson, University of Sheffield, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/060

Title **A Summary of the Evidence for use of Acupuncture from Systematic Reviews and Meta-Analyses**

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Reference VA Technology Assessment Program Report, Final Report, May 2007.
www4.va.gov/VATAP/docs/Acupuncture2007tagm.pdf

Aim

To summarize the best available evidence of the safety and efficacy of acupuncture to inform the scope of practice in VA (Veteran Affairs).

Conclusions and results

Literature searches for acupuncture identified 488 unique references published since 1990 including 121 meta-analyses, 170 Cochrane Library systematic reviews, 87 other published systematic reviews, and 17 guidelines. The Technology Assessment Program (TAP) identified the three most recent and comprehensive reports that catalogued evidence of the efficacy and safety of acupuncture over a wide range of indications. These reports served as the basis for the review. While acupuncture appears to be a safe procedure based on these results, the results highlight the overall poor quality of studies and reporting in the evidence base.

Recommendations

No acupuncture procedure warranted either a Level A or Level D recommendation. Indications that received a Level B recommendation (sufficient, strong, and consistent evidence of positive effect) were for relief of acute dental pain associated with tooth extraction and treatment of postoperative- and chemotherapy-related nausea and vomiting. A Level C recommendation (evidence is trending positive, but insufficient) was issued for the short-term relief of osteoarthritis, knee pain, and chronic low back pain, migraine and idiopathic headache, menstrual cramps, tennis elbow, and fibromyalgia. The evidence was inconclusive (Level I) for acupuncture use in carpal tunnel syndrome, addiction, stroke rehabilitation, and asthma.

Methods

The VA Technology Assessment Program (TAP) carried out scoping searches of the general CAM literature and detailed searches of acupuncture. Detailed literature searches were performed between September 2006 and February 2007 in the following databases: MEDLINE, SCI-Search, EMBASE, Current Contents, and BIOSIS. The Cochrane Database of Systematic Reviews was searched separately. A quality filter was applied to identify the highest quality evidence from clinical trials, RCTs, guidelines, systematic reviews, and meta-analyses. US Preventive Services Task Force classification for grading the strength of policy recommendations based on scientific evidence was applied.

Further research/reviews required

Additional monitoring of the literature is needed to identify new, high-quality evidence of the effectiveness of acupuncture.

Written by Elizabeth Adams, VATAP, USA

Title **Systematic Reviews for Amyotrophic Lateral Sclerosis**

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Reference VA Technology Assessment Program Report, Brief Overview, June 2009.
www4.va.gov/VATAP/docs/ALS2009tagm.pdf

Aim

To summarize the literature on amyotrophic lateral sclerosis (ALS) in support of the National Task Group's development of an integrated system of care for veterans with ALS.

Conclusions and results

The Technology Assessment Program (TAP) found no systematic reviews addressing the diagnosis of ALS. Out of 150 articles, TAP included 18 independent systematic reviews of treatment interventions, 3 related publications, and 8 Cochrane protocols. Published literature on ALS is lacking in both quantity and quality. Much of the focus in ALS research remains on the pathology of ALS and possibly distinct forms of the disease. No INAHTA members have organized systems of care specific to ALS, and VA (Veterans Affairs) cannot make specific conclusions based on the literature.

Recommendations

Due to the lack of treatment options and the lack of research on the efficacy of those treatments, VA cannot make specific recommendations for patients with ALS. However, VA did develop a research agenda for further studies of ALS.

Methods

TAP identified available systematic reviews on ALS by searching MEDLINE and the Cochrane Library using the terms "amyotrophic lateral sclerosis" and "Lou Gherig's disease." TAP also sought information on the organization of ALS care from other INAHTA members.

Further research/reviews required

Further studies of diagnostic tools are needed on: ALS and other motor neuron diseases; the benefits of clinics and their impact on patient quality of life; treatments for ALS and their efficacy; and the economic impacts of treatment.

Written by Karen Flynn, VATAP, USA

Title **Regionalization of Surgical Services**

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Reference VA Technology Assessment Program Brief Overview, April, 2009.
www4.va.gov/VATAP/docs/RegionalizationSurgery2010tagm.pdf

Aim

To review the structures, processes, and effects of model programs for rural surgery and procedural practice within the US and in healthcare systems of other developed nations.

Conclusions and results

The review focused on the following questions:

1) What changes in surgical quality and access are attained by regionalization of services to high-volume providers?
2) What do we know about the etiology of the volume/experience effects?

Seventy-two relevant articles/citations were abstracted in the report's appendix. The literature supports a volume or experience effect for a wide range of complex surgical procedures. However, the trade-offs in access or patient satisfaction are unclear.

Recommendations

Evidence is not available to make a recommendation on the regionalization of surgical services.

Methods

MEDLINE via PubMed and Dialog, EMBASE, Cochrane, and the HTA databases of INAHTA were searched for articles published from 2000 to February, 2009. Specific search terms were surgical quality, rural surgery, access, regionalization, and hospital or procedure volume. All searches were limited to adult human patients and English language publications.

Further research/reviews required

Additional research is needed to determine the factors responsible for the volume-outcome relationship and if those processes can be identified and employed in low-volume hospitals.

Written by Karen Flynn, VATAP, USA

Title **Bibliography: Robotic Surgery — Update 2006**

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Reference VA Technology Assessment Program Report. Bibliography: Robotic Surgery —Update 2006. www4.va.gov/VATAP/docs/RoboticSurgery2006ttm.pdf

Aim

To update the 2004 bibliography of FDA-approved robotic surgical devices and compare the use of these robotic-assisted surgical devices with existing surgical procedures.

Conclusions and results

Twenty-six articles met the inclusion criteria for this review: 4 health technology assessments (HTAs) and 22 primary articles. Thirteen indications for using robotic-assisted endoscopic procedures were identified, of which radical prostatectomy was the most widely studied. Small randomized controlled trials (RCTs) or pseudo-RCTs provided limited evidence on adrenalectomy, cholecystectomy, Nissen fundoplication, and gastric bypass. From these analyses, no clear advantages of robotically-assisted techniques versus either standard laparoscopic procedures or open procedures can be concluded. Limitations on clinical use are: high initial investment and operating costs; substantial training requirements; and lack of strong evidence from well-designed clinical trials that would help determine the effectiveness and cost effectiveness of robotic-assisted surgical devices compared to current practices.

Recommendations

Although the evidence does not confer clear advantages to using robotically assisted surgical procedures, Veterans Affairs (VA) may have other reasons to evaluate certain applications. These include the prevalence of disease or condition or the ability to address staffing shortages in the surgical theater in a safe and cost-effective manner. In this regard, the robotically assisted laparoscopic applications with the best evidence of offering safe and cost-effective alternatives to current practices for prevalent health conditions in VA are radical prostatectomy, Nissen fundoplication, and cholecystectomy.

Methods

The VA Technology Assessment Program searched the FDA databases, databases covering the FDA and device industries (PROMT, Health Devices Alerts, DIOGENES, FDA News, ESPICOM), MEDLINE, EMBASE, Current Contents, Science Citation Index, and BIOSIS databases from 2002 through September 2006. The review included studies published in English that reported primary data with at least 12 consecutive, live, human subjects, or high-quality evidence reviews or HTAs.

Further research/reviews required

Additional monitoring of the literature is needed to identify new studies and evidence of effectiveness and cost effectiveness relative to current practices for robotically assisted devices.

Written by Elizabeth Adams, VATAP, USA

Title **Brief Overview: Benzocaine-Associated Methemoglobinemia in Dental Patients**

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Reference VA Technology Assessment Program Report, February 2006.
www4.va.gov/VATAP/docs/BenzocainMetheoglobinemiaDentalpatients2006tagm.pdf

Aim

To survey the literature on the existence and strength of an association between methemoglobinemia and the use of topical benzocaine in dentistry.

Conclusions and results

The searches yielded 39 citations, of which 9 were retrieved and 7 ultimately abstracted as directly relevant to the review. The 7 citations included 2 substantial case series and 2 case-control studies. The Technology Assessment Program (TAP) concluded that methemoglobinemia is an uncommon event that also can be associated with nitrates. Nitrates are ubiquitous environmental chemicals for which an association of methemoglobinemia with exposure has been more rigorously researched. An association between methemoglobinemia and topical benzocaine as used in dentistry is insufficiently proven for it to be the basis of major clinical policy or formulary change in Veterans Affairs (VA). Although the FDA is aware of adverse events apparently related to benzocaine sprays, it is not planning action to remove the drugs from the market.

Recommendations

The Office of the Assistant Under Secretary of Health for Dentistry recommended that topical benzocaine gel as used in dentistry be omitted from restrictions on benzocaine spray within the Veterans Health Administration (VHA).

Methods

TAP searched MEDLINE and EMBASE from 1951 and 1974, respectively, to February 2006 using search terms for topical benzocaine, adverse reactions, complications, methemo-globinemia, dental, epidemiology, and specific study types such as case-control or cohort, the latter two for the added part of TAP's charge. TAP retrieved full-text articles for any English-language citations apparently relevant to a clinical dental setting (oral administration of topical benzocaine), published in dental journals, or contributing to the evidence for an association, along with relevant citations in the reference lists from initially retrieved articles. TAP applied an analytic framework that documented the existence and strength of an association between exposure and disease.

Written by Karen Flynn, VATAP, USA

Title **Short Report: Temporal Artery Thermometry in the Post-Operative Setting**

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Reference VA Technology Assessment Program Short Report, December 2006.
www4.va.gov/VATAP/docs/TemporalArteryThermometryPostOperative2006tminm.pdf

Aim

To provide a rapid, qualitative systematic review of the best available evidence of the clinical utility of temporal artery thermometry (TAT) to inform development of new quality measures in Veterans Affairs' (VA) postoperative patient care.

Conclusions and results

The searches yielded 85 citations, including 11 studies comparing TAT to another thermometry device. The best available evidence consists of two preliminary studies with conflicting results that compare the diagnostic accuracy of TAT to pulmonary artery catheter measurement in mixed adult inpatient populations. No HTA reports or systematic reviews on this topic were identified. The review found a lack of conclusive evidence supporting the clinical use of TAT as an instrument for measuring core temperature in adult inpatient populations, including those in the postoperative setting.

Recommendations

Given the paucity of the current evidence base, this device cannot be recommended for routine use in VA postoperative patients at this time.

Methods

TAP searched MEDLINE, PUBMED, EMBASE, the Cochrane Library, and Current Contents from 1990 to April 2006 for temporal artery thermometry, body temperature, arterial temperature, and infrared thermometry. The FDA Center for Devices and Radiological Health and manufacturer Web pages were searched for information relating to regulation and clinical use of TAT. VATAP queried its INAHTA colleagues via its electronic listserv on April 26, 2006 for completed HTA reports or ongoing reviews on the subject. Inclusion criteria were full-text studies of the clinical use of TAT in adults in the postoperative setting, with emphasis on diagnostic performance. Excluded from the review were studies published in languages other than English, of pediatric patients, or of devices not commercially available in the US. For quality appraisal of included studies, VATAP applied the Standards for Reporting of Diagnostic Accuracy framework.

Further research/reviews required

Several investigators having institutional experience with newer thermometry devices such as TAT have called for improved study quality and quality monitoring of new products in the appropriate clinical setting, involving a range of suitable patients to confirm safe use and clinical value before adopting the method more widely.

Written by Elizabeth Adams, VATAP, USA

Title **Visual Field Testing in VA Compensation and Pension Examinations**

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Reference VA Technology Assessment Program Short Report March, 2003 Number 6.
www4.va.gov/VATAP/docs/VisualFieldTestingVAExaminations2003t90m.pdf

Aim

To determine the effectiveness of the Goldmann perimeter and Humphrey Field Analyzer and their role in assessing disability or handicap.

Conclusions and results

The review included 91 full-text articles, 2 of which compared the Goldmann and Humphrey perimeters for visual field defects in glaucoma. Both studies found the automated Humphrey perimeter identified visual field defects earlier in the disease compared to the manual Goldmann perimeter. Tracking the literature from the 1970s to the present suggests that automated perimeters are replacing manual perimeters. This is not related to the functionality of either perimeter. The literature suggests complementary roles for each perimeter since each measures different proportions of the entire volume of the normal visual field. For this reason, the location within the field that is of interest in a particular patient should guide the selection of the perimeter. Since anatomy-based visual field testing assesses impairment and not disability or handicap, functional visual field indices, eg, the Esterman function index, can be used with either manual or automated perimeters.

Recommendations

Evidence on the effectiveness of the Goldmann perimeter and Humphrey Field Analyzer suggest a complementary role for each perimeter, depending on the location of the visual field of interest. The AMA recommends the use of functional residual field indices such as the Esterman function index to assess visual field disability.

Methods

Comprehensive literature searches were conducted using Dialog OneSearches of MEDLINE, EMBASE, Current Contents, Biosis, and SciSearch from 1980 to February 2002. Search strategies aimed to retrieve full-text articles on perimetry (Goldmann and Humphrey) and diagnosis of visual field defects.

Citations were also obtained from colleague agencies in the INAHTA community.

Further research/reviews required

Additional studies are required to determine the use of visual field testing in evaluating visual disability. The report discusses areas for additional research.

Written by Karen Flynn, VATAP, USA

Title **Appropriate use of Insulin Pump—Real-Time Continuous Glucose Monitoring Systems in the Veteran Population**

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Reference VA Technology Assessment Program Brief Overview, July 20, 2006.
www4.va.gov/VATAP/docs/InsulinPump2008tagm.pdf

Aim

To evaluate the use of insulin pumps – real-time continuous blood glucose monitoring devices in managing Veterans Affairs' (VA) patients with type 1 diabetes.

Conclusions and results

Literature searches resulted in 183 citations, of which 34 were retrieved and 8 citations met criteria for inclusion in this report. The results suggest comparable safety and efficacy of the insulin pump and multiple daily injections in adults with insulin-treated, uncontrolled, diabetes who are adequately trained and supported by a specialized team. Results also suggest insulin pumps may improve lifestyle and quality of life based on convenience, flexibility, and ease of use. However, existing evidence has not shown significant improvements in controlling diabetes or improvements in quality of life using indicators from which we can derive reliable cost-effectiveness estimates of the available treatment options.

Recommendations

No firm conclusions or recommendations can be made regarding the appropriate use of insulin pump – real-time continuous glucose monitoring systems to manage VA patients with diabetes.

Methods

In June 2006, comprehensive literature searches of the peer-reviewed published literature were conducted using the Cochrane Library, MEDLINE, EMBASE, and Current Contents databases, and the HTA database, using word phrases and thesaurus terms describing continuous blood glucose monitoring and insulin infusion pumps. The American Diabetes Association annual meeting abstracts were hand searched for 2006. US government sources, Medtronic Minimed, FDA, and patent applications for data supporting FDA approval were also searched.

Further research/reviews required

Additional studies using large populations are needed to determine the impact of CGMS on managing patients with diabetes.

Written by Elizabeth Adams, VATAP, USA

Title **A Systematic Review of Clinical Predictors of Outcomes in Adults with Recent Lower Limb Amputation**

Agency **VATAP, VA Technology Assessment Program**

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Reference VA Technology Assessment Program Short Report, February, 2005. www4.va.gov/VATAP/docs/ClinicalPredictorsAdultsOutcomesLowerLimbAmputation2005tm.pdf

Aim

To identify clinical predictors of outcomes in adult patients with major lower limb amputation that may help direct healthcare resources toward individuals who are most likely to benefit from specific rehabilitative interventions.

Conclusions and results

Predictors of poor outcome were advancing age, poor compliance, phantom limb pain, and comorbid conditions. Predictors of positive outcome included the patient's general condition, preamputation functional capability, the patient's socioeconomic situation, the amputation level and covering of the stump, and the absence of stump pain. These predictors need to be confirmed and assessed in VA patients to determine the most suitable outcomes to use for veterans with major lower limb amputation.

Recommendations

Promising predictors of outcomes were identified for further study. Additional research is needed to confirm these predictors and determine which predictors are most useful in clinical practice.

Methods

A qualitative systematic review was undertaken. Comprehensive searches were conducted in MEDLINE, EMBASE, Current Contents, Science Citation Index on Dialog, and the Cochrane Library from 1990 to February 2004. The bibliographic search strategy included terms for lower limb/extremity amputation and combined them with terms for rehabilitation, prognosis, recovery of function, quality of life, activities of daily living, treatment outcome, and analytic methods. These searches yielded 581 references of which 128 were identified as potentially relevant. Seven studies met the inclusion criteria for clearly described, original, research published in English that used multivariable analysis to derive predictive factors in adult patients with lower extremity amputation.

Further research/reviews required

Additional longitudinal studies are needed to derive a comprehensive set of clinical predictors suitable for the veteran population. These predictors will be used to improve the quality of rehabilitation care for lower limb amputees.

Written by Elizabeth Adams, VATAP, USA

Title **Antibiotic Therapy in Hospital, Oral versus Intravenous Treatment**

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Reference Report number 2, 2010, ISBN 978-82-8121-324-1.
www.kunnskapssenteret.no/Publikasjoner/8448.cms

Aim

To determine if efficacy differs between oral and intravenous antibiotic treatment of infectious diseases in large and important groups of patients.

Conclusions and results

The documentation provides no basis for determining whether a difference exists in the efficacy and side effects of oral versus intravenous administration of antibiotics. This does not mean that there are no differences in the administration route, but that the results are too uncertain to draw conclusions.

We included 6 systematic reviews that evaluated the effect of oral versus intravenous administration of antibiotics for pneumonia, urinary tract infection, osteomyelitis, spontaneous bacterial peritonitis, and febrile neutropenia in cancer patients. In addition, we included 10 randomized controlled trials. On the whole, we found no significant differences between oral and intravenous administration of antibiotics. The quality of this documentation is low, and the estimates are therefore uncertain.

Methods

We based this systematic review on a search for other systematic reviews in relevant bibliographic databases. For pneumonia and urinary tract infections, we also searched for randomized controlled trials. We compiled, analyzed, and graded the quality of the documentation and summarized the results for 6 main outcomes; total mortality, cure rates, treatment failure, readmissions, length of stay in hospital, and serious side effects.

Further research/reviews required

The report reveals a lack of high-quality documentation addressing oral versus intravenous antibiotic use. We need more and better research on large patient groups. Since the use of antibiotics and resistance conditions in Norway still differ somewhat from countries outside the Nordic region, studies carried out in Norway or Scandinavia are needed.

Written by Ingvil Sæterdal, NOKC, Norway

Title **Reuse of Single-Use Medical Devices**

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Reference ETMIS 2009 5 (2), Printed French edition 978-2-550-55099-0, English summary (PDF) 978-2-550-55100-3. www.aetmis.gouv.qc.ca/site/en_publications2009.phtml

Aim

To re-examine the clinical, economic, legal, and ethical issues surrounding the reuse of single-use medical devices (SUDs) in view of recommendations issued in Québec and Canada.

Results and conclusions

AETMIS considers that the conclusions of studies on the safety and efficacy of reused SUDs cannot be generalized to these devices as a whole. While the reuse of single-use hemodialysis membranes is considered safe and effective, the conclusions that can be drawn about other types of SUDs are limited by the small number of scientific studies and by the poor quality, low level of evidence, and in vitro nature of these studies. The reuse of electrophysiological catheters, orthopedic external fixator components, and sphincterotomes may be safe if properly reprocessed, but evidence remains insufficient to justify reusing them in clinical practice. Reused percutaneous transluminal coronary angioplasty (PTCA) catheters and laparoscopy instruments can be safe and effective if strict reprocessing and inspection protocols are followed. The studies on reused biopsy forceps show that they may not be safe after being reprocessed. The economic benefits of reusing SUDs vary according to the type of device and how often it is reused. Moreover, most of the very few economic studies are incomplete. Although Québec has no specific law or regulation directly governing this practice, healthcare institutions are liable for injury potentially caused by reprocessed SUDs. Given the conclusions drawn, the general position adopted by Canadian organizations, and the considerable requirements associated with reprocessing, hospitals and other healthcare facilities in Québec should stop in-house reprocessing of critical or semicritical SUDs until the requirements can be met for ensuring this practice complies with the highest recognized standards of quality. Hospitals wishing to reuse these devices should subcontract reprocessing to a third-party reprocessor certified by a regulatory authority and qualified to supply a final product that meets the standards and requirements applicable to all SUD manufacturers, and should ensure that they meet the applicable requirements.

Methods

A scientific literature review was undertaken to assess currently available evidence on the efficacy and safety of reusing reprocessed SUDs. Nineteen types of critical or semicritical devices were covered, and the conclusions drawn from assessments by the Conseil d'évaluation des technologies de la santé (CETS), New Zealand Health Technology Assessment (NZHTA) and the Canadian Agency for Drugs and Technologies in Health (CADTH) were taken into consideration.

Further research/reviews required

More in vivo studies on the safety and efficacy of reused SUDs are needed, specifically clinical studies on reprocessing methods and the effects of reusing SUDs in the Québec healthcare system. More studies on economic aspects of reusing SUDs are also required.

Written by Geneviève Martin, Lorraine Caron, and Alexandra Obadia, AETMIS, Canada

Title **Comparative Analysis of Bedpan Processing Equipment**

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Reference ETMIS 2009 5 (4), Printed French edition 978-2-550-54865-1, English summary (PDF) 978-2-550-54864-4. www.aetmis.gouv.qc.ca/site/en_publications2009.phtml

Aim

To assess the use of bedpan washers for reusable bedpans compared to macerators for disposable bedpans, examining their effectiveness, safety, and organizational, economic, and environmental factors.

Results and conclusions

Bedpan processing methods in Québec healthcare facilities are not uniform. Decisions regarding the most suitable method, based on eliminating sources of risk, are left to each facility's infection prevention and control team in conjunction with facility management and other medical and professional staff. Basic principles should be followed in regard to 1) infection prevention, 2) infection control, 3) workplace layout, and 4) preventive measure follow-up.

1) Manual bedpan cleaning must be proscribed; the use of automated bedpan washers or macerators for processing bedpans is recommended if it adheres to stringent infection prevention procedures; reusable bedpans must be disinfected after each use; piling up soiled bedpans on counters must be avoided; and disposable bedpan supports must be transferred to a centralized sterilization area for disinfection in a washer-disinfector after patient discharge. 2) Sterilization of reusable bedpans between patients must be considered; if the use of bedpan washers is adopted, a backup option must be planned and the use of hygienic bags for all patients should be considered in some circumstances. 3) Bedpan washers and macerators must be installed in dirty utility rooms located a reasonable distance away from patients' rooms; dirty utility rooms must be large enough to house the reprocessing equipment and to allow supplies to be properly stored; installation of modular bedpan-washer units or macerators in the washrooms of isolation rooms should be considered. 4) Staff must be properly trained and consistently comply with procedures for human waste management, bedpan reprocessing and equipment operation; preventive maintenance and verification of the equipment's operational parameters must be monitored on a regular and ongoing basis. Finally, analysis of the literature revealed that both types of bedpan processing equipment have benefits and drawbacks. The data helped identify the issues specific to each type of equipment, without determining the best choice for hospitals. Although consultation with professionals in the field shed light on several relevant aspects, it did not help establish a consensus guideline. Several variables influence that choice: bedpan use requirements, risk of infection and outbreaks, staff availability, the possibility of redesigning infrastructures, geographic area, and budgets.

Methods

An exhaustive narrative review of selected articles and grey literature was performed.

Written by Christine Lobè, AETMIS, Canada

Title **Comparative Analysis of Pasteurization and Thermal Disinfection in a Washer-Disinfector: Anesthesia and Respiratory Devices**

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Reference ETMIS 2009 5 (7), Printed French edition 978-2-550-56959-6, English summary (PDF) 978-2-550-56958-9. ww.aetmis.gouv.qc.ca/site/en_publications2009.phtml

Aim

To determine the extent to which the thermal disinfection cycle in a washer-disinfector is equivalent to pasteurization for reprocessing anesthesia and respiratory devices; to present the economic implications of using these two methods.

Results and conclusions

This comparative assessment gauges the effectiveness of both processes, describes the standards prevailing in Canada and abroad regarding the two methods, and provides an acquisition and operating cost scenario for related equipment.

Studies show that thermal disinfection in a washer-disinfector that complies with ISO 15883 or CSA-Z15883 requirements, and that fits the description provided in CSA-Z314.8-08, is equivalent to conventional pasteurization. Both procedures are effective for disinfecting and reprocessing anesthesia and respiratory devices because they destroy vegetative bacteria, mycobacteria, fungi, and viruses, but not spores. Economic analysis shows that the annual operating costs of a washer-disinfector are equivalent to those of a pasteurizer. However, the multipurpose nature of a washer-disinfector yields a non-negligible benefit, both financially and organizationally.

Methods

A MEDLINE search covering January 1980 to April 2008 and updated in May 2009 identified relevant studies on pasteurization and thermal disinfection in a washer-disinfector. Standards, recommended practices, and guidelines addressing the reprocessing or disinfection of anesthesia and respiratory devices were also examined. The studies analyzed were performed under experimental conditions. Some of these studies date back several years and do not necessarily reflect current technological advances. Nevertheless, the parameters tested in these studies met the requirements set out in CSA-Z314.8-08 for pasteurization and those in ISO 15883 for disinfection in a washer-disinfector.

Written by Christine Lobè, AETMIS, Canada

INAHTA Briefs

Issue 2010/073

Title **Curative Treatment for Esophageal Cancer: Systematic Review of Neoadjuvant Therapy and Chemoradiotherapy Alone**

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Reference ETMIS 2009 5 (9), Printed French edition 978-2-550-57294-7, English summary (PDF) 978-2-550-57293-0. www.aetmis.gouv.qc.ca/site/en_publications2009.phtml

Aim

To systematically review the relative efficacy of neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy, and chemoradiotherapy without surgery in curative treatment of cancer of the esophagus and gastroesophageal junction.

Conclusions and results

The results of this review are intended to serve as the basis for a clinical practice guideline to be developed by the *Comité de l'évolution des pratiques en oncologie* (CEPO).

Available data do not allow selecting the most effective therapeutic option among the treatments examined in this report. The choice of therapeutic management depends on the tumor's histological type and stage and on the patient's clinical status. It has been established that patients who respond well to neoadjuvant therapy have a better prognosis and better chances of survival. However, no criteria currently define the profile of patients likely to respond to neoadjuvant therapy; information that would enable health services to target them better.

Methods

We analyzed randomized controlled trials (RTCs), meta-analyses, and systematic reviews addressing solely the curative treatment of esophageal cancer and published until 2007, with regular updates until the end of 2008. When a good-quality meta-analysis was available, we presented its results with those of the included primary studies. Otherwise, we performed a meta-analysis of the outcomes of the primary studies on the topic. Six types of treatment modalities were covered: 1) neoadjuvant chemotherapy compared to surgery alone; 2) combined neoadjuvant chemotherapy and radiotherapy (chemoradiotherapy) compared to surgery alone; 3) chemoradiotherapy alone (without surgery) compared to surgery alone; 4) chemoradiotherapy alone (without surgery) compared to radiotherapy alone; 5) chemoradiotherapy alone compared to neoadjuvant chemoradiotherapy to determine the benefit added by surgery after chemoradiotherapy with curative intent; and (6) comparison of different modalities of radiotherapy combined with chemotherapy.

Further research/reviews required

Most of the primary RCTs had small sample sizes, were of poor methodological quality, and were heterogeneous in terms of surgical techniques, chemotherapy and radiotherapy protocols, and clinical characteristics of the patients and tumors (which were not always described). Hence, more studies are required.

Written by Faiza Boughrassa, AETMIS, Canada

Title **Applicability of Sentinel-Lymph-Node Detection and Biopsy in the Treatment of Vulval Cancer**

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Reference CT 2009/05. www.sergas.es/MostrarContidos_N3_T02.aspx?IdPaxina=60563&uri=http://www.sergas.es/docs/Avalia-t/CT2009_05_textocompleto.pdf&hifr=1250&seccion=0

Aim

To assess the percentage of sentinel-lymph-node detection in vulval cancer and the diagnostic accuracy of the test by determining its sensitivity and negative predictive value (NPV); to ascertain the adverse effects of this technology and long-term relapses of tumors.

Conclusions and results

In total, 29 studies were selected for the assessment. Of these, 19 studies (all observational) met the inclusion criteria and were included in the review. The sentinel lymph node was detected by dye in 81% and by Tc99-colloid and combined technique in 98% of patients. The percentage of false negatives observed was below 2%, while sensitivity values and NPV exceeded 95%. The lymph node recidivation rate of the disease was around 3%, and the specific survival rate at 3 years was 97%. The technique appeared to be safe, with few side effects.

The sentinel-lymph-node detection and false negative percentages, together with the sensitivity and negative predictive values, render this technique comparable to that of sentinel-lymph-node detection in breast cancer. Factors considered to be critical in implementing the technique include: multidisciplinary team, patient selection, primary tumor site, anatomopathological technique used, and learning curve. The recidivation rate is similar to that described with classic lymphadenectomy and displays fewer side effects, both short- and long-term.

Recommendations

Provided that it is performed by an experienced multidisciplinary team on appropriately selected patients, sentinel-lymph-node detection and biopsy technique would seem to be a reasonable alternative to complete inguinal lymphadenectomy in patients with stage I-II vulval cancer. When it comes to implementing the technique, a series of recommendations must be borne in mind with respect to the work team, patient selection, sentinel-lymph-node detection technique, surgical and anatomopathological techniques, and learning curve.

Methods

We searched the scientific literature published up to September 2009, stipulating no time limit and covering the following databases: MEDLINE; EMBASE; HTA (Health Technology Assessment); DARE (Database of Abstracts of Reviews of Effectiveness); NHSEED (National Health Service Economic Evaluation Database); Cochrane Library Plus; Clinical Trials Registry; and Health Services Research Projects in Progress (HSPROJ). From the papers yielded by the bibliographic search, we selected only those that met the selection criteria. Data were then extracted and the evidence summarized.

Further research/reviews required

Quality studies that are sufficiently statistically robust and homogeneous in terms of patients and techniques are needed to furnish definitive data on long-term tumor recidivation.

Written by Gerardo Atienza, AVALIA-T, Spain

Title **Detection of High Risk Human Papillomavirus E6 and E7 Oncogenes for Cervical Cancer Screening**

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Reference CT 2010/01. www.sergas.es/MostrarContidos_N3_T02.aspx?IdPaxina=60538&uri=http://www.sergas.es/docs/Avalia-t/CT2010_01_deteccion%20oncogenes.pdf&hifr=1250&seccion=0

Aim

To assess the effectiveness of various HPV E6 E7 mRNA detection methods in cervical cancer and for different clinical applications, ie, when used: 1) as the primary screening method; 2) for triage of women with inconclusive results or low-grade intraepithelial lesions; and 3) for triage of women with positive results in HPV DNA tests.

Conclusions and results

Results of the studies that assessed the effectiveness of primary screening showed that specificity for detection of CIN2+ lesions was higher with the PreTec HPV Proofer test than with any of the HPV DNA tests evaluated (Sp=89%-97% vs 67%-92%), but sensitivity was relatively low in some studies (64%-86% vs 93%-100%). For this reason, and because all of the studies retrieved were cross-sectional studies with methodological limitations, this technique cannot be considered for primary screening. Despite the potential interest of these tests in triage of women with inconclusive results, or low-grade intraepithelial lesions, or normal women with HPV (+) results, there is not sufficient evidence to establish whether these techniques amount to an improvement with respect to cytology and/or HPV DNA. Nearly all of the studies used the PreTec HPV Proofer test, and it is not known whether techniques that detect a greater number of genotypes, or do so quantitatively, yield better results. The only study that assessed HPV mRNA determination using the Aptima test displayed high sensitivity (S=92%, Sp=54%).

Recommendations

Clinical trials should be designed to assess the effectiveness of HPV mRNA detection tests versus other cervical cancer screening strategies in different clinical applications.

Methods

We conducted a bibliographic search for papers published in the principal bibliographic databases, eg, MEDLINE (PubMed), EMBASE (Ovid), and Web of Knowledge (WoK), and in specific databases focusing on systematic reviews and ongoing research projects. Papers were selected in accordance with pre-established selection criteria, and quality was assessed using the QUADAS tool.

Further research/reviews required

Yes.

Written by Leonor Varela, AVALIA-T, Spain

INAHTA Briefs

Issue 2010/076

Title	**Rapid Review of Robotic-Assisted Surgery for Urological, Cardiac, and Gynaecological Procedures**
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Reference	Report number 75. ISBN 978-0-9806299-6-5. www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/ASERNIPSPublications/Rapid_Review_No_75.htm

Aim

To evaluate the safety and efficacy of robotic-assisted surgery compared to conventional surgery for common urological, cardiac, and gynecological procedures; and to summarize the experiences of Australian hospitals and surgeons using this technology and the views of jurisdictional health representatives and patient advocates.

Conclusions and results

This review included 44 studies (1 systematic review, 43 nonrandomized comparative studies). Despite shortcomings in the published evidence, robotic-assisted surgery is emerging as an alternative to conventional open or laparoscopic approaches for a range of urological, cardiac, and gynecological procedures. In reviewing the relevant comparative evidence published in the past 5 years, it seems that robotic-assisted surgery is at least as efficacious as conventional open or laparoscopic surgery, and appears to offer the advantages of decreased blood loss and transfusions with resultant decreases in length of hospital stay without increasing the rate of severe complications. To date, operative times for robotic-assisted approaches have generally been equal to or longer than conventional approaches, although it is likely they have been influenced by the experience of the surgical team and are amenable to improvement with increased experience. These findings from the published literature seem to echo the experiences of the Australian surgeons using this technology who were interviewed for this report.

Methods

Studies were identified by searching PubMed, EMBASE, the Cochrane Library, and the York (UK) Centre for Reviews and Dissemination (CRD) databases for studies published from January 1, 2004 to February 20, 2009. Studies considered eligible for critical appraisal and inclusion in the review were limited to English language systematic reviews of primary studies, randomized controlled trials (RCTs), and nonrandomized comparative studies that reported on the use of robotic-assisted surgery for urological, cardiac, and gynecological procedures compared to conventional surgical approaches. Data on the main outcomes of interest were reported narratively. Interviews were conducted with 7 surgeons from 6 of the 7 Australian hospitals using the da Vinci Surgical System, and with a theatre nurse experienced in the set-up and maintenance of the system, 2 jurisdictional health representatives from one Australian state and one territory, and 2 representatives from patient advocacy organizations.

Further research/reviews required

Many of the limitations in the published evidence used in this review would be overcome by the availability of concurrently-controlled trial evidence. While the undertaking of multicenter RCTs of robotic-assisted surgery is desirable, this may be difficult due to problems inherent in attempting to randomize patients who are actively seeking treatment with this technology, which at present is primarily available in private hospitals in Australia.

Written by Dr Prema Thavaneswaran, ASERNIP-S, Australia

Title **Biologics for Early Rheumatoid Arthritis**

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Reference Kornor H, Burger E, Harboe I, Klemp M. Biologics in early rheumatoid arthritis. Oslo: NOKC; 2010. Report no. 9. ISBN no. 978-82-8121-338-8.
www.kunnskapssenteret.no/Publikasjoner/9235.cms

Aim

To investigate the efficacy and safety of biologics compared to disease-modifying antirheumatic drugs (DMARDs) in patients with early (≤ 3 years) rheumatoid arthritis (RA).

Conclusions and results

We included 12 randomized controlled trials (RCTs) that examined the effect of biologics infliximab, adalimumab, etanercept, and abatacept. The results suggest that, compared with DMARDs alone, biologics in combination with DMARDs yield:

- more patients in remission
- neither more nor less serious adverse events
- more patients who achieve 50% improvement
- improved physical function
- less joint destruction

Due to methodological weaknesses in the included studies most results contain some degree of uncertainty.

Methods

We systematically searched for literature in EMBASE, MEDLINE (Ovid), and Cochrane Library. In addition, we searched the reference lists of relevant publications, searched for relevant websites, and contacted experts, affected companies, and the Norwegian Rheumatism Association. Two researchers independently reviewed abstracts and full-text publications for inclusion. We included RCTs) that studied the efficacy and safety of biologics (etanercept, infliximab, adalimumab, rituximab, tocilizumab, anakinra or abatacept), alone or in combination with DMARDs, in people with RA of a maximum duration of 3 years. Relevant RCTs should have one or more DMARDs as comparison, and outcomes should include disease progression, quality of life, employability, functioning, and safety. We included publications in all languages, provided that the abstract was in English or one of the Scandinavian languages.

The included studies were critically appraised before we extracted relevant data. Where possible and appropriate, we combined results in meta-analyses. We also assessed the overall quality of the documentation for each outcome. The final report has been subject to internal and external peer reviews.

Further research/reviews required

Future research should focus on very early RA, and perhaps include only people who have been recently diagnosed with the new ACR-/EULAR criteria. Moreover, an important future research task is to identify subgroups of early RA patients who would achieve remission with biologics as first-line treatment. Head-to-head studies that examine the relative effects of the various biological agents are also an imminent research need.

Written by Hege Kornør, NOKC, Norway

INAHTA Briefs

Issue 2010/078

Title **Safety of Gadolinium-Containing Contrast Agents for Magnetic Resonance Imaging in Patients with Renal Disease**

Agency **VATAP, VA Technology Assessment Program**
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Reference VA Technology Assessment Program Brief Overview, December 2006

Aim

To review the literature to determine the safety of using gadolinium-containing contrast agents for magnetic resonance imaging (MRI) in patients with renal disease.

Conclusions and results

The review resulted in 63 citations, of which 20 were selected for full-text retrieval. The searches did not identify case-control or cohort studies connecting gadolinium exposure to nephrogenic systemic fibrosis (NSF). One study examined the association of nephrogenic fibrosing dermopathy (NFD) with renal transplant.

Recommendations

Evidence is not available to make a recommendation on the use of gadolinium-containing contrast agents for MRI in patients with renal disease.

Methods

MEDLINE and EMBASE were searched from 1995 to November 2006 for specific terms (adverse reactions; complications; nephrogenic fibrosing dermopathy; gadolinium; epidemiology) and specific study types (case-control, cohort) for NFD and NSF. All searches were aimed at identifying articles studying an association between gadolinium exposure and NFD, or the safety of gadolinium-containing contrast agents in patients with renal disease. All full-text articles were retrieved.

Further research/reviews required

Discussed in detail in the report.

Written by Karen Flynn, VATAP, USA

Title **Health Risks of Cellular Phone Use**

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Reference VA Technology Assessment Program Brief Overview, December, 2009.
www4.va.gov/VATAP/docs/Cellphonemt2009.pdf

Aim

To determine if health risk is increased due to the use of cellular phones.

Conclusions and results

Reviews covered 170 primary studies of cell phone use from the 1990s to the present. To date, no definite link has been established between cell phone use and disease, nor has any risk been quantified. Due to the short history of cell phone use, more studies are needed to determine any long-term effects of using cell phones.

Recommendations

None.

Methods

The Technology Assessment Program (TAP) searched MEDLINE, the Cochrane Library, and INAHTA databases using the terms "mobile phone" and "risk", along with publication types (systematic review, meta-analysis) to identify reviews published in English from 2000 to 2009 that synthesized research in adult human patients.

Further research/reviews required

More long-term studies are needed, as there is concern that adverse affects of cell phone use may take over a decade to manifest. Results are awaited from the latest 13-country INTERPHONE study.

Written by Karen Flynn, VATAP, USA

Title **Proton Beam Therapy for Cancer**

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Reference VA Technology Assessment Program Brief Overview, April, 2010.
www4.va.gov/VATAP/docs/protontherapycancerupdate2010.pdf

Aim

To identify those cancer diagnoses for which proton therapy has been shown by rigorous research to be effective.

Conclusions and results

We examined and annotated 13 systematic reviews. At present, no studies have shown proton therapy to be unequivocally effective, or more effective, than its alternatives.

Recommendations

No recommendations regarding the use of proton beam therapy for cancer can be made at this time.

Methods

We searched MEDLINE, the databases of the INAHTA, and the Cochrane Library for systematic reviews, technology assessments, economic evaluations, and horizon scanning reports, for research in adult human subjects, printed in English between 1990 to April 2010. The terms "proton beam" and "proton therapy" were used, crossed with cancer.

Further research/reviews required

One Phase III randomized controlled trial, to be completed in February 2012, is investigating proton therapy versus other radiation for intermediate-risk prostate cancer. Future studies are needed to determine the effectiveness of proton beam therapy for cancer. In particular, decisions need to be made about which malignancies are amenable to and should require randomized trials, and which malignancies are sufficiently rare or difficult to treat by other means. Future studies should also consider the cost effectiveness of proton beam therapy.

Written by Karen Flynn, VATAP, USA

Title **A Systematic Review of Economic Evaluations for Tobacco Control Programs**

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Reference HSAC Report 2010; 3(17). ISBN 978-0-9864563-7-4 (Online), ISSN 1178-5748 (Online)

Aim

To systematically review economic evaluations of public health tobacco control programs.

Conclusions and results

Thirty-nine publications, describing 38 different studies, qualified for inclusion. They included economic evaluations on tobacco policy, taxation, mass media and telephone quit lines, games and monetary incentive programs, self-help and counselling interventions, school-based health promotion and education, and programs for pregnant women. Several factors limited our ability to draw head-to-head conclusions about the most effective and cost-effective public health tobacco control strategies. One such factor was variability in methodology in terms of whether studies attempted to quantify downstream health costs related to tobacco-related diseases. However, most of the included studies showed that public health tobacco control programs are highly cost effective.

Recommendations

Although the evidence clearly shows that tobacco use interventions are highly cost effective, more work is needed to rigorously evaluate price and tax increases, media campaigns, smoke-free air laws and workplace place interventions, quit lines, youth access enforcement, and school and community-based programs.

Methods

To identify relevant economic studies, we conducted a comprehensive literature search of medical and health technology assessment databases. Identified citations were scanned for relevance using a priori-defined inclusion and exclusion criteria based on the population and intervention. Studies that met the inclusion criteria were quality assessed using the quality appraisal checklist described in Drummond et al (1997). Information regarding study design, methods, and results were extracted into standardised data extraction forms.

Further research/reviews required

Further economic evaluations of tobacco control programs are encouraged.

Written by Dan Paech, HSAC, Australia

INAHTA Briefs

Issue 2010/082

Title **Sexual Exploitation of Children and Youth over the Internet: A Rapid Review of the Scientific Literature**

Agency **IHE, Institute of Health Economics**
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Reference April 2010 (English); ISBN 978-1-897443-68-2 (print); ISSN 978-1-897443-69-9 (online). www.ihe.ca/publications/library/

Aim

To synthesize evidence on the: 1) frequency, effects, and risk factors for sexual exploitation of children/youth over the Internet; 2) assessment tools for children/youth who have been sexually exploited via the Internet; 3) safety, efficacy/effectiveness, and economic, social, legal, and ethical aspects of prevention and therapeutic strategies.

Conclusions and results

Thirteen relevant studies were identified. Two main types of sexual exploitation were evaluated: Internet-initiated grooming for sexual abuse (online sexual solicitation) and Internet-based receipt of sexual images by children/youth (unwanted exposure to sexual material). Most victims of online sexual exploitation were aged 12.6 to 15.9 years (mean). Prevalence estimates varied widely and should be interpreted with caution. Four studies based on the self-report of children/youth from the general population found that 13% to 19% had experienced online sexual solicitation in the last year. One study found that 2% of all child sexual abuse cases reported to police related to online-initiated sexual solicitation, although a study of a highly selected population showed a rate of 26%. Three studies based on the self-report of children/youth from the general population found that 14% to 34% had been exposed to unwanted sexual material via the Internet. In another study, mental health professionals reported that 6% of their clients had received unwanted sexual material via the Internet.

Risk factors for exposure to online sexual solicitation include: being female over 14 years of age, engaging in high-risk behaviors online (eg, sending personal information to strangers), the presence of other problematic Internet experiences (eg, cyberbullying), high Internet use, and accessing the Internet via mobile devices or computers away from home. Individuals were more likely to be exposed to unwanted sexual material via the Internet if they were: male aged 13 to 17 years, used file sharing programs, frequently accessed chat rooms, engaged in online conversations with strangers, and accessed the Internet at computers away from home.

No studies reported on assessment tools or preventive or therapeutic strategies for children/youth that have been sexually exploited via the Internet. Various resources are available to educate children, youth, parents, educators, and law enforcement agents about the risks of online sexual exploitation. Most of these approaches focus on safe online practices, but their effectiveness has not been formally evaluated.

Methods

We searched sociological, criminal justice, psychological, educational, and biomedical electronic databases to identify relevant primary and secondary research published in English from Jan 2003 to Sept 2009. Government websites, scientific conference proceedings, and bibliographies of relevant studies were searched. One reviewer selected studies and extracted data. Data were synthesized qualitatively; the studies were not appraised for quality.

Further research/reviews required

Research is needed to develop strategies to assess and prevent online sexual exploitation and to evaluate treatment approaches in relation to efficacy, effectiveness, and safety. Government agencies and the new technology industries should be aware of the problem, have knowledge of its characteristics and consequences, and understand the inherent policy and practice implications.

Written by Maria Ospina, Christa Harstall, and Liz Dennet, IHE, Canada

INAHTA Briefs

Issue 2010/083

Title **Population Ultrasound Screening for Abdominal Aortic Aneurysms**

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Reference ETMIS 2010 6 (1). Printed French edition 978-2-550-57817-8, English summary (PDF) 978-2-550-567816-1. www.aetmis.gouv.qc.ca/site/en_publications2009.phtml

Aim

To assess the appropriateness and feasibility of an abdominal aortic aneurysm (AAA) screening program in Québec.

Conclusions and results

The evidence suggests that, theoretically, an AAA screening program would be effective (especially in men aged 65 to 74 years), assuming that criteria regarding the disease, screening test, treatment, and cost effectiveness are met. For women aged 65 years or older, the data are insufficient to clearly demonstrate those benefits. Even regarding men, the operation or actual effectiveness of such a program has not been demonstrated. No health authorities (with a recent exception in the UK) have decided to implement such a program, despite positive recommendations from HTA agencies. In Québec, the required epidemiological and organizational conditions for its implementation are not presently met. If this program were set up with a cohort of men aged 65 to 74 years and followed up for 41 months, it would yield approximately 100 preventable deaths per year. Presently, Québec has: a lack of family physicians and human and material resources required for ultrasound procedures; a need to optimize access to surgical resources; uncertainty about the eventual participation rate of the target population; and pressure to deal with other and more urgent health problems. However, this contextual analysis reveals several possible avenues for improvement. Accordingly, the MSSS (Department of Health and Social Services) and directly concerned professional organizations are invited to join in setting priorities and developing an action plan to improve the clinical and organizational aspects of managing people who present with AAA or associated risk factors, and to fully evaluate the real potential of a population screening program.

Methods

This report presents a systematic literature review of population screening for AAA, its acceptability and cost effectiveness, and potential organizational requirements in Québec. To retrieve primary studies, various strategies were used to search MEDLINE, the Cochrane Library, and other databases. Articles were selected according to predefined inclusion and exclusion criteria. A single researcher extracted the data. The appropriateness and feasibility of AAA screening was analyzed, using the UK National Screening Committee criteria. Contextual date were obtained through semistructured interviews with medical and administrative stakeholders in Québec's public health system. A modeling exercise, including a sensitivity analysis, was conducted to estimate the potential yield of an AAA screening program if one were to be implemented in Québec.

Further research/reviews required

Studies would need to examine screening efficacy in a group of women who have a family history of AAA combined with other risk factors (age, known cardiovascular disease, and history of smoking). Studies on the actual effectiveness of AAA screening (in the UK) would also be required.

Written by Brigitte Côté, Jean-Marie R. Lance, and Michel LeBrun, AETMIS, Canada

Title **Clinical Efficiency and Safety Profile of Selective Serotonin Reuptake Inhibitors**

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Reference ISBN 978-3-85159-130-9. Report is available in German.
www.goeg.at/de/BerichtDetail/SSRI

Aim

To systematically investigate a difference in clinical efficiency between selective serotonin reuptake inhibitors (SSRIs) and placebo in relation to the severity grade of disease; and to systematically review the safety profile of SSRI treatment in terms of adverse side effects.

Conclusions and results

No difference in clinical efficiency of SSRIs in comparison to placebo could be detected. Evidence for clinical efficiency of SSRIs in mild to moderate depression is scarce. Studies show a trend – that SSRIs are efficient in severe depression – but significance is missing. Adverse side effects of SSRI treatment include sexual dysfunction, elevated bleeding risk, suicidal behavior, and occurrence of serotonin-syndrome, SSRI-discontinuation syndrome, and syndrome of inappropriate antidiuretic hormone secretion.

Recommendations

Diagnostic assessment of patients with depression must be reevaluated, especially in general medical practice. Clinical efficiency of SSRIs should be further investigated in comparison to first-generation antidepressants and nonpharmaceutical therapeutic options. Also, helpful in therapeutic decision making would be a systematic assessment of potential differences in clinical efficiency, the safety profile of the SSRI subclasses accepted for use in Austria, and unconfined documentation of SSRI-associated adverse side effects.

Methods

This report is a rapid assessment. We searched the Cochrane Library and MEDLINE databases for reports, meta-analyses, and systematic reviews presented between 2005 and 2008. We also searched for new primary studies (Jan-Jul 2008). The literature was completed by hand searching relevant international websites and databases. All literature was critically appraised. Searches were limited to German and English language. An external expert reviewed the report.

Further research/reviews required

Long-term studies (with follow-up periods exceeding 8 months) with large patient numbers are required to enable definite recommendations regarding the clinical efficiency and safety profile of long-term treatment with SSRIs. In general, research on antidepressants should always take into account the potential presence of statistical bias, should verify the correctness of the study design, and should distinguish between statistical and clinical significance.

Written by Sophie Brunner-Ziegler and Mag. Johannes Zsifkovits, GmbH, Austria

INAHTA Briefs

Issue 2010/085

Title **Rapid Assessment: Professional Dental Hygiene - Effectiveness and Safety of Professional Dental Hygiene for Caries Prophylaxis and Periodontal Therapy**

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Reference ISBN 10 3-85159-138-0. www.goeg.at/de/BerichtDetail/Dentalhygiene

Aim

To determine: 1) the efficacy and safety of professional dental hygiene interventions in preventing and treating periodontal diseases, reducing inflammation and relieving pain, maintaining oral stability, and avoiding tooth loss; 2) the efficacy and safety of nonsurgical periodontal treatment compared to surgical periodontal treatment; and 3) if it makes a difference if dentists, dental hygienists, or dental assistants perform dental hygiene measures.

Conclusions and results

Two systematic reviews and one RCT met the inclusion criteria for professional dental hygiene as a preventive measure, but yielded weak evidence. The systematic reviews and meta-analyses included for professional dental hygiene as nonsurgical periodontal therapy and supportive periodontal care have a high risk of bias. Tentatively, scaling and root planing can stop progression in patients with periodontitis, according to one RCT. Outcomes were mainly surrogate parameters. Four publications assessed nonsurgical versus surgical periodontal treatment. They showed that both interventions are more effective the deeper the initial periodontal pockets, but nonsurgical treatment performs better with shallow to moderate initial pockets. Seven controlled trials compared the performance of different professionals carrying out dental hygiene interventions. Most of these studies focus on a specific intervention, and all have strong formal limitations.

Recommendations

Based on the available data, supragingival and subgingival mechanical plaque removal can be recommended as nonsurgical periodontal treatment and as long-term periodontal maintenance care as well as in secondary and tertiary prevention of periodontal disease. Recommendation should be based on an appropriate systematic periodontal inspection and a periodontal diagnosis to assess individual periodontal needs.

Methods

A systematic literature search in EMBASE, MEDLINE, DARE, NHS-EED, CDSR, and CCRCT yielded 431 hits. Selection involved a 2-step selection process according to the PICO questions, and was completed by hand searching. 18 publications were included to answer the 3 research questions. Only systematic reviews, meta analyses, and RCTs were used to assess the effectiveness and safety of professional dental hygiene as prophylaxis and as periodontal therapy vs. no therapy and vs. surgical periodontal therapy. Controlled trials were also included to assess the effectiveness and safety of dental hygiene interventions performed by different health care professionals.

Further research/reviews required

Given the lack of evidence on preventive effects of routine supragingival scaling and polishing in healthy populations, more evidence is needed to show which measure is most effective in order to prevent the high prevalence of periodontal diseases in Austria. Long-term studies on preventive effects and safety, with large samples and with different professional providers, could be conducted. The findings would be most relevant to the healthcare system and society in public health and health economic contexts.

Written by Elisabeth Breyer, Gesundheit Österreich GmbH, Austria

INAHTA Briefs

Issue 2010/086

Title **Additional Therapy for Young Children with Spastic Cerebral Palsy: A Randomized Controlled Trial**

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Reference Volume 11.16. ISSN 1366-5278. www.hta.ac.uk/project/983.asp

Aim

To investigate whether, in the short and medium term, additional support by: a) a physiotherapy assistant improved physical function in young children with spastic cerebral palsy; and b) a family support worker improved family functioning.

Conclusions and results

The findings support the current literature, which has reported no evidence that additional intervention (ie, physiotherapy assistant or family support worker) helped the motor or general development of young children with spastic cerebral palsy. No quantitative evidence showed that providing extra family support helped levels of parental stress and family needs. The implication is that providing extra physical therapy does not necessarily improve the motor function of a young child with cerebral palsy, and additional family support should not automatically be assumed to be beneficial. No significant association was found between the intensity of the local services and any outcome measure, other than a slight association with lowered family needs. Provision of local services was related to the severity of the child's impairments and not to family difficulties. A small group of families with complex family problems needed more service input. The cost of services varied widely. Researchers need to examine what the 'sufficient' levels of provision or therapy might be for which children and which families. A time series of different levels of input and outcomes would provide valuable information to practitioners. Future assessments of therapies of this type should adopt a similar multifaceted approach, which is likely to be more suitable than a simple RCT for evaluating clinical interventions where the effects are complex. The most appropriate outcome measures should be used, including assessment of information and emotional support provided to families. No evidence showed that additional physical therapy for 1 hour per week for 6 months by a physiotherapy assistant improved any child outcome measure in the short or medium term. Intervention by a family support worker did not have a clinically significant effect on parental stress or family needs. Over the 6-month period the total cost of services for each child ranged from 250 pounds sterling (GBP) to GBP 6750, with higher costs associated with children with more severe impairments. See Executive Summary link at www.hta.ac.uk/983.

Recommendations

See Executive Summary link at www.hta.ac.uk/983.

Methods

See Executive Summary link at www.hta.ac.uk/983.

Further research/reviews required

Research is needed to examine what the 'sufficient' levels of provision or therapy might be for which children and which families. Key issues are: 1) how the allocation of resources to individual children and families is decided; and 2) the variability among child development centers in relation to how families are assessed, the formulation of a family plan, referrals to other agencies, and interagency working. See Executive Summary link at www.hta.ac.uk/983.

Written by Professor Michael Weindling, University of Liverpool, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/087

Title **Recruitment to Randomized Trials: Strategies for Trial Enrolment and Participation Study. The STEPS Study**

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Reference Volume 11.48. ISSN 1366-5278. www.hta.ac.uk/project/1564.asp

Aim

To identify factors associated with good and poor recruitment to multicenter trials.

Conclusions and results

While not producing sufficiently definitive results to make strong recommendations, this work suggests that future trials should consider the different needs at different phases in the life of trials and place greater emphasis on *conduct* (the process of actually doing trials). This implies learning lessons from successful trialists and trial managers, with better training for issues relating to trial conduct. The complexity of large trials means that unanticipated difficulties are highly likely at some time in every trial. The reference model developed in this project needs to be further considered in other similar and different trials to assess its robustness. These and other strategies aimed at increasing recruitment and making trials more successful need to be formally evaluated for their effectiveness in a range of trials. In the 114 trials found in our epidemiological review, less than one-third recruited their original target within the time originally specified, and around one-third had extensions. Factors observed more often in trials that recruited successfully were: having a dedicated trial manager, being a cancer or drug trial, and having interventions only available inside the trial. The most commonly reported strategies to improve recruitment were newsletters and mailshots, but it was not possible to assess whether they were causally linked to changes in recruitment. The analyses of the case studies suggested that successful trials were those addressing clinically important questions at a timely point. See Executive Summary link at www.hta.ac.uk/project/1564.asp.

Recommendations

The work here suggests that people undertaking trials ought to think about the different needs at different phases in the life of trials, and place greater emphasis on *conduct* (the process of actually doing trials). This implies learning lessons from successful trialists and trial managers, with better training for issues relating to trial conduct. The complexity of large trials means that unanticipated difficulties are highly likely at some time in every trial. Our research suggested that successful trials were those flexible and robust enough to adapt to unexpected issues. Arguably, the trialists should also expect agility from funders within a proactive approach to monitoring ongoing trials.

Methods

See Executive Summary link at www.hta.ac.uk/project/1564.asp.

Further research/reviews required

Three important areas for further research arise. First, an extension of our review of case studies to trials with different recruitment patterns (including 'failures') may help clarify whether the patterns seen in the 'exemplar' trials differ, or are similar. Second, our reference model was based around a single large trial with the unusual feature that patients were mainly unconscious. Before use as an audit tool for diagnosing and/or addressing management factors, the reference model needs to be considered in other similar and different trials to assess its robustness. Finally, these and other strategies aimed at increasing recruitment and making trials more successful need to be formally evaluated for their effectiveness in a range of trials.

Written by Professor Marion Campbell, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/088

Title **A Randomized Controlled Trial of Cognitive Behavior Therapy in Adolescents with Major Depression Treated by Selective Serotonin Reuptake Inhibitors. The ADAPT Trial**

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Reference Volume 12.14. ISSN 1366-5278. www.hta.ac.uk/project/1123.asp

Aim

To determine if in the short term – in depressed adolescents attending routine NHS Child and Adolescent Mental Health Services (CAMHS) and receiving ongoing active clinical care – treatment with selective serotonin reuptake inhibitors (SSRIs) plus cognitive behavior therapy (CBT) results in better healthcare outcomes in comparison to SSRI alone.

Conclusions and results

For moderately to severely depressed adolescents who do not respond to a brief initial intervention (BII), the addition of CBT to fluoxetine plus routine clinical care does not improve outcome or confer protective effects against adverse events and is not cost effective. SSRIs (mostly fluoxetine) are unlikely to have harmful adverse effects. Further research should focus on evaluating the efficacy of specific psychological treatments against BII, determining the characteristics of patients with severe depression who do not respond to fluoxetine, relapse prevention in severe depression, and improving tools for determining treatment responders and nonresponders. Of the 208 patients randomized, 200 (96%) completed the trial to the primary endpoint at 12 weeks. At 28-week follow-up, 174 (84%) participants were reevaluated. Overall, 193 (93%) participants had been assessed at one or more time points. Clinical characteristics indicated that the trial was conducted on a severely depressed group. Recovery was significant at all time points in both arms. The findings showed no difference in treatment effectiveness for SSRI+CBT over SSRI for the primary or secondary outcome measures at any time point. This lack of difference held when baseline and treatment characteristics were taken into account (age, sex, severity, comorbid characteristics, quality and quantity of CBT treatment, number of clinic attendances). See Executive Summary link at www.hta.ac.uk/project/1123.asp.

Recommendations

The findings are broadly consistent with the National Institute for Health and Clinical Excellence guidelines on the treatment of moderate to severe depression. Modification is advised for those presenting with moderate (6-8 symptoms) to severe (>8 symptoms) depressions and in those with either overt suicidal risk and/or high levels of personal impairment. In such cases, the time allowed for response to psychosocial interventions should not exceed 2 to 4 weeks, after which fluoxetine should be prescribed.

Methods

See Executive Summary link at www.hta.ac.uk/project/1123.asp.

Further research/reviews required

Evaluate the efficacy of specific psychological treatments compared to brief psychological intervention. The current findings provide anecdotal information for the putative effectiveness of BII for some cases of depression. BII can most likely be delivered by all routine CAMHS services. It is not clear if BII would be as safe and effective as CBT, family, or interpersonal psychotherapy for adolescents with moderate depressions.

Written by Professor Ian Goodyer, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/089

Title **The Use of Irinotecan, Oxaliplatin and Raltitrexed for the Treatment of Advanced Colorectal Cancer: Systematic Review and Economic Evaluation (Review of NICE Guidance No. 33)**

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Reference Volume 12.15. ISSN 1366-5278. www.hta.ac.uk/project/1432.asp

Aim

To evaluate 3 technologies for managing advanced colorectal cancer: 1) first-line irinotecan combination (with 5-fluorouracil [5-FU]) or second-line monotherapy; 2) first- or second-line oxaliplatin combination (again, with 5-FU); and 3) raltitrexed, where 5-FU is inappropriate.

To examine the role of irinotecan and oxaliplatin in reducing the extent of incurable disease before curative surgery (downstaging).

Conclusions and results

Treatment with 3 active therapies appears most clinically effective and cost effective. NHS routine data could be used to validate downstaging findings, and a meta-analysis using individual patient-level data is suggested to validate the optimal treatment sequence. We found 17 trials of varying methodological quality. Compared to 5-FU, first-line irinotecan improved overall survival (OS) by 2 to 4 months ($p = 0.0007$), progression-free survival (PFS) by 2 to 3 months ($p < 0.00001$), and response rates ($p = 0.001$). It offered a different toxicity profile and no quality of life (QoL) advantage. However, second-line irinotecan compared with 5-FU improved OS by 2 months ($p = 0.035$) and PFS by 1 month ($p = 0.03$), and provided a better partial response rate, but with more toxicities and no QoL advantage. Compared to second-line best supportive care, irinotecan improved OS by 2 months ($p = 0.0001$), had a different toxicity profile, and maintained baseline QoL longer, but with no overall difference. Adding oxaliplatin to second-line 5-FU is associated with a borderline significant improvement in overall survival ($p = 0.07$), a significantly higher response rate (<0.0001), and more serious toxicities. There is no evidence of a significant difference in QoL. Schedules with treatment breaks may not reduce clinical effectiveness, but reduce toxicity. The addition of oxaliplatin to second-line 5-FU also saw no improvement in OS ($p = 0.07$), better PFS (by 2.1 months, $p = 0.0001$), an 8.9% higher response rate ($p = 0.0001$), more toxicities, and no QoL advantage. There was no significant difference in OS or PFS between first-line irinotecan and oxaliplatin combinations except when 5-FU was delivered by bolus injection, when oxaliplatin provided better OS ($p = 0.032$) and response rates ($p = 0.032$), but not PFS ($p = 0.169$). The regimens had different toxicity profiles and neither conferred a QoL advantage. When compared to 5-FU, raltitrexed is associated with no significant difference in overall or progression-free survival; no significant difference in response rates; more vomiting and nausea, but less diarrhea and mucositis; no significant difference in, or worse, QoL. Raltitrexed treatment was cut short in 2 of 4 trials due to excess toxic deaths. 5-FU followed by irinotecan was inferior to any other sequence. First-line irinotecan/5-FU combination improved OS and PFS, although further unplanned therapy exaggerated the OS effect size. See Executive Summary link at www.hta.ac.uk/project/1432.asp.

Recommendations

Treatment with 3 active therapies appears to be most clinically effective and cost effective.

Methods

Searches in 10 electronic bibliographic databases identified studies of the effectiveness and economics of the methods. Studies that evaluated any of the indications outlined above were included. Two reviewers independently extracted data and assessed generic components of methodological quality. Survival outcomes were meta-analyzed.

Further research/reviews required

Collection of routine data from within the NHS would help validate the downstaging of people with liver metastasis. A meta-analysis using individual patient-level data is suggested to validate the optimal treatment sequence and to provide a baseline against which future treatment sequences could be compared.

Written by Mr Paul Tappenden, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/090

Title **Systematic Review of the Clinical Effectiveness and Cost Effectiveness of 64-Slice or Higher Computed Tomography Angiography as an Alternative to Invasive Coronary Angiography in the Investigation of Coronary Artery Disease**

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Reference Volume 12.17. ISSN 1366-5278. www.hta.ac.uk/project/1545.asp

Aim

To assess the clinical and cost effectiveness, in different patient groups, of using 64-slice or higher computed tomography (CT) angiography instead of invasive coronary angiography (CA) in diagnosing suspected coronary artery disease (CAD) and assessing people with known CAD.

Conclusions and results

The main value of 64-slice CT may be to rule out significant CAD. Avoiding unnecessary CA through the use of 64-slice CT appears likely to save costs in the diagnostic pathway. However, 64-slice CT is unlikely to replace CA in assessing revascularization of patients, particularly as angiography and angioplasty are often done on the same occasion. The diagnostic accuracy and prognostic studies enrolled over 2500 and 1700 people, respectively. Overall quality of the studies was reasonably good. In the pooled estimates, 64-slice CT angiography was highly sensitive for patient-based detection of significant CAD (defined as 50% or more stenosis), while across studies the negative predictive value (NPV) was very high (median 100%, range 86% to 100%). In segment-level analysis compared with patient-based detection, sensitivity was lower and specificity higher, while across studies the median NPV was similar (99%, range 95% to 100%, versus 100%, range 86% to 100%). See Executive Summary link at www.hta.ac.uk/project/1545.asp.

Recommendations

The proportion of CA that could be replaced by 64-slice CT is uncertain. Reduction in CA would occur mainly at the diagnostic end of the pathway, in both elective assessment of chest pain of possibly anginal origin, and assessment of suspected acute coronary syndromes in some patients with normal or equivocal ECGs and negative troponin tests. In emergency situations, some hospital admissions might be avoided. However, to do so, 64-slice CT would need to be readily available, ideally on a 24-hour basis, which is unlikely to be the case in most hospitals. Some perfusion studies could also be replaced by 64-slice CT angiography. One issue is whether to acquire 64-slice CT systems, or wait until 256-slice systems become available. Evidence on 256-slice CT is sparse. However, it is unlikely that performance would be inferior, and if cost differences between 64- and 256-slice machines were small, it could be argued that the NHS should bypass 64-slice machines in favor of 256-slice ones. At some point the extra data might not provide additional clinical benefit, but it is not yet clear when that point will be reached.

Methods

See Executive Summary link at www.hta.ac.uk/project/1545.asp.

Further research/reviews required

Further research is required on the marginal advantages and costs of 256-slice CT versus 64-slice CT, the usefulness of 64-slice CT in people with suspected acute coronary syndrome, the potential of multislice CT to examine plaque morphology, the role of CT in identifying patients suitable for coronary artery bypass grafting, and the concerns raised about the use and repetitive use of 64-slice or higher CT angiography in younger individuals or women of childbearing age. See Executive Summary link at www.hta.ac.uk/project/1545.asp.

Written by Mr Graham Mowatt, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/091

Structural Neuroimaging in Psychosis: A Systematic Review and Economic Evaluation

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Reference Volume 12.18. ISSN 1366-5278. www.hta.ac.uk/project/1594.asp

Aim

To establish the clinical and cost effectiveness of structural neuroimaging, ie, magnetic resonance imaging (MRI) or computed tomography (CT), for all patients with psychosis (particularly a first episode of psychosis) relative to the current UK practice of selective screening only when clinically indicated by symptoms or signs of a space-occupying brain lesion.

Conclusions and results

Evidence to date suggests that structural neuroimaging screening of all patients presenting with psychotic symptoms would yield little to affect clinical management beyond the information provided by a full clinical history and neurological examination. From an economic perspective, the outcome is unclear. Neuroimaging for all could be either cost-incurring or cost-saving for MRI or CT, depending on the assumptions used. The results would depend on assumptions around the prevalence of structural lesions causing psychosis, but results must be interpreted with caution since evidence is sparse. The systematic review included 24 studies of a diagnostic, before-after type of design evaluating the clinical benefits of CT, structural MRI, or combinations in treatment-naïve, first-episode, or unspecified psychotic patients, including one study in schizophrenia patients resistant to treatment. Also included was a review of published case reports of misidentification syndromes. Almost all evidence concerned patients aged below 65 years. In most studies, structural neuroimaging identified little to influence patient management that was not suspected based on a medical history and/or physical examination. See Executive Summary link at www.hta.ac.uk/project/1594.asp.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1594.asp.

Methods

A systematic review included studies (any study design) reporting the additional diagnostic benefit of structural MRI, CT, or combinations of these in patients with psychosis. The comparator was any current standard practice of diagnostic workup without structural neuroimaging. Only studies reporting clinically relevant outcomes were included. MEDLINE, EMBASE, the Cochrane Library, PsycINFO, and CINAHL were searched from inception to November 2006. Inclusion, quality assessment, and data extraction were undertaken in duplicate. There were no language restrictions. Studies were assessed qualitatively only. Economic assessment consisted of a systematic review of economic evaluations and development of a threshold analysis to predict the gain in quality-adjusted life-years (QALYs) required to make neuroimaging cost effective at commonly accepted threshold levels (20 000 pounds sterling [GBP] and GBP 30 000 per QALY). Sensitivity analyses addressed several parameters including prevalence of psychosis. Full economic modeling was not possible due to lack of clinical evidence.

Further research/reviews required

The main research priorities are to monitor current NHS use of structural neuroimaging in psychosis in patients aged below 65 years to identify clinical triggers and subsequent outcomes. In addition, well-executed, diagnostic before-after studies on representative populations are required to determine the clinical utility of structural neuroimaging in this patient group. Research is also needed to determine whether the most appropriate structural imaging modality in psychosis should be CT or MRI.

Written by Dr Catherine Meads, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/092

Title **Systematic Review and Economic Analysis of the Comparative Effectiveness of Different Inhaled Corticosteroids and Their Usage with Long Acting Beta2 Agonists for the Treatment of Chronic Asthma in Children under the Age of 12 Years**

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Reference Volume 12.20. ISSN 1366-5278. www.hta.ac.uk/project/1524.asp

Aim

To assess the clinical and cost effectiveness of inhaled corticosteroids (ICS) alone, beclometasone dipropionate (BDP), budesonide (BUD), fluticasone propionate (FP), and ICS used in combination with a long-acting beta2 agonist (LABA), salmeterol (SAL), or formoterol fumarate (FF) in treating chronic asthma in children aged under 12 years.

Conclusions and results

Limited evidence indicates no consistent significant differences in effectiveness between the 3 ICS licensed for use in children at either low or high dose. BDP CFC-propelled products are often the cheapest ICS available at both low and high dose, and may remain so even when CFC-propelled products are excluded. Exclusion of CFC-propelled products increases the mean annual cost of all budesonide (BUD) and BDP, while the overall cost differences between the comparators diminish. Very limited evidence on the efficacy and safety of ICS and LABAs in children suggests no significant clinical differences in effects between using a combination inhaler versus the same drugs in separate inhalers. In the absence of any evidence concerning the effectiveness of ICS at higher dose with ICS and LABA, a cost-consequence analysis gives mixed results. Potentially, costs can be saved by using combination inhalers compared to separate inhalers. At present prices, the BUD/FF combination is more expensive than those containing FP/SAL, and no clinically significant differences are shown between them. A direct head-to-head trial comparing the two combination therapies of FP/SAL and BUD/FF is warranted. It is important to assess whether the addition of a LABA to a lower dose of ICS could potentially be as effective as an increased dose of ICS alone, but also be steroid sparing. Long-term adverse events associated with using ICS need to be systematically assessed. Future trials of treatment for chronic asthma in children should aim to standardize outcome measures. See Executive Summary link at www.hta.ac.uk/project/1524.asp.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1524.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1524.asp.

Further research/reviews required

A scoping review is needed to assess the requirements for additional primary research on the clinical effectiveness of treatment for asthma in children aged under 5 years. Such a review could include all treatment options (pharmacological and nonpharmacological) for asthma. No trial evidence is currently available to inform the relative effectiveness of the two combination inhalers of FP/SAL and BUD/FF in a pediatric population. The current assessment found no significant differences in effectiveness of FP/SAL when the drugs were delivered via a single inhaler or concurrently in two separate inhalers. However, as ease of treatment regimen may affect concordance, a direct head-to-head trial comparing the two combination therapies of FP/SAL and BUD/FF is warranted.

Written by Ms Caroline Main, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/093

Title **Ezetimibe for the Treatment of Hypercholesterolemia: A Systematic Review and Economic Evaluation**

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Reference Volume 12.21. ISSN 1366-5278. www.hta.ac.uk/project/1529.asp

Aim

To review the clinical and cost effectiveness of ezetimibe as a combination therapy or monotherapy in treating primary (heterozygous familial and nonfamilial) hypercholesterolemia in the UK.

Conclusions and results

Evidence from short-term, randomized controlled trials (RCT) demonstrates that ezetimibe is effective in reducing low-density lipoprotein cholesterol (LDL-c) when administered as monotherapy or in combination with a statin. However, when used as a monotherapy, ezetimibe's LDL-c lowering ability was less than that of statins alone. The cost effectiveness of ezetimibe is uncertain, but the economic model suggests that ezetimibe could be cost effective in treating individuals with high baseline LDL-c values, patients with diabetes, and individuals with heterozygous familial hypercholesterolemia. No published clinical outcome trials (>12 weeks) examining the cardiovascular benefit of ezetimibe were identified. In the absence of clinical endpoint data from trials, 13 (5 were multi-arm) phase III multicenter RCTs (of varying methodological quality) of short-term duration (12-48 weeks) with surrogate endpoint data (eg, LDL-c and total cholesterol [Total-c]) were included. For patients not adequately controlled with a statin alone, a meta-analysis of 6 studies showed that a fixed-dose combination of ezetimibe and statin treatment was associated with a statistically significant reduction in LDL-c and Total-c compared with statin alone (p<0.00001). Four studies that titrated the statin doses to LDL-c targets generally showed that the co-administration of ezetimibe and statin was significantly more effective in reducing plasma LDL-c concentrations than statin monotherapy (p<0.05 for all studies). For patients where a statin was considered inappropriate, a meta-analysis of 7 studies demonstrated that ezetimibe monotherapy significantly reduced LDL-c levels compared with placebo (p<0.00001). There were no statistically significant differences in LDL-c-lowering effects across subgroups. Ezetimibe therapy (either combined with a statin or monotherapy) appeared to be well tolerated compared to statin monotherapy or placebo, respectively. No ezetimibe studies reported data on health-related quality of life. Economic results varied widely depending on the treatment strategies evaluated. When comparing ezetimibe monotherapy with no treatment in individuals with baseline LDL-c values of 3.0-4.0 mmol/l, the results ranged from 21 000 pounds sterling (GBP) to GBP 50 000 per quality-adjusted life-year (QALY). Results for individuals with baseline LDL-c values over 5.0 mmol/l were below GBP 30 000 per QALY. When comparing the costs and benefits of adding ezetimibe to ongoing statin treatment compared with maintaining statin treatment at the current dose, most results were above values generally considered to be cost effective (GBP 19 000 to 48 000 per QALY). See Executive Summary link at www.hta.ac.uk/project/1529.asp.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1529.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1529.asp.

Further research/reviews required

1) Long-term studies reporting clinical outcome data, direct comparisons with other lipid-lowering treatments, and data from patients who are truly intolerant of statins. 2) Lifetime adherence to combination therapies in relatively healthy younger and asymptomatic patients with no history of CVD. 3) Establish if reductions in lipids to predetermined targets provide additional reductions in cardiovascular events.

Written by Mr Abdullah Pandor, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/094

Title **A Prospective Randomized Comparison of Minor Surgery in Primary & Secondary Care. The Mistic Trial**

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Reference Volume 12.23. ISSN 1366-5278. www.hta.ac.uk/project/1100.asp

Aim

To determine if GPs and hospital doctors are equally competent to perform various elective minor surgical procedures, in terms of safety, quality, and cost of care.

Conclusions and results

Using surgical quality as the primary outcome, the quality of minor surgery in general practice is not as high as that carried out in hospital, although the difference is not large. Patients are more satisfied if their procedure is performed in primary care, largely because of convenience. However, there are clear deficiencies in GPs' ability to recognize malignant lesions, and there may be differences in completeness of excision when compared with hospital doctors. Patient safety is of paramount importance, and this study does not demonstrate that minor surgery carried out in primary care is safe as it is currently practiced. Several alternative models for providing minor surgery are worthy of consideration, including ones based in primary care that require all excised tissue to be sent for histological examination, or that require further training of GPs. This study's findings suggest that a hospital-based service is more cost effective. It must be concluded that it is unsafe to leave minor surgery in the hands of doctors who have never been trained to do it. The 568 patients recruited (284 primary care, 284 hospitals) were randomized by 82 GPs. In total, 637 skin procedures plus 17 ingrowing toenail procedures were performed (313 primary care, 341 hospitals) by 65 GPs and 60 hospital doctors. Surgical quality was assessed for 273 (87%) primary care and 316 (93%) hospital lesions. Mean visual analogue scale score in hospital was significantly higher than that in primary care (mean difference=5.46 on 100-point scale; 95% CI 0.925 to 9.99), but the clinical importance of the difference was uncertain. Hospital doctors were better at achieving complete excision of malignancies, with a difference that approached statistical significance (7/16 GP versus 15/20 hospital, X^2=3.65, p=0.056). The proportion of patients with postoperative complications was similar in both groups. The mean cost for hospital-based minor surgery was 1222.24 pounds sterling (GBP) and for primary care GBP 449.74. Using postoperative complications as an outcome, both effectiveness and costs of the alternative interventions are uncertain. Using completeness of excision of malignancy as an outcome, hospital minor surgery becomes more cost effective. See Executive Summary link at www.hta.ac.uk/project/1100.asp.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1100.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1100.asp.

Further research/reviews required

Further work is required to determine GPs' management of various skin conditions (eg, potentially life-threatening malignancies), rather than just their recognition of them. Further economic modeling is required to look at the potential costs of training sufficient numbers of GPs and GPs with special interests to meet the demand for minor surgery safely in primary care, and of the alternative of transferring minor surgery to the hospital sector. Different models of provision need thorough testing before widespread introduction.

Written by Dr Steve George, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/095

Title **A Review and Critical Appraisal of Measures of Therapist-Patient Interactions in Mental Health Settings**

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Reference Volume 12.24. ISSN 1366-5278. www.hta.ac.uk/project/1556.asp

Aim

To assemble and appraise literature on tests and measures of therapist-patient interactions; make recommendations for practice, training, and research; and establish benchmarks for standardization, acceptability, and routine use of such measures.

Conclusions and results

The findings indicate that therapist-patient interaction can be measured using a wide range of instruments of varying value. However, care should be taken to ensure that the measure is suitable for the context in which it is to be used. This work suggests that specific research networks for developing therapist-patient measures should be established, that research activity should prioritize investment in increasing the evidence base of existing measures rather than attempting to develop new ones, and that research should focus on improving these existing measures in terms of acceptability and feasibility. The contextual map included the various concepts and domains that had been used in the context of the literature on therapist-patient interactions, and was used to guide the successive stages of the review. Three developmental processes were identified as necessary to provide an effective therapeutic relationship: establishing a relationship, developing a relationship, and maintaining a relationship. Eighty-three therapist-patient measures having basic information on reliability and validity were identified for critical appraisal. The areas of the conceptual map that received most coverage were framework, therapist and patient engagement, roles, therapeutic techniques, and threats to the relationship. These areas relate to the 3 key developmental processes outlined above. Of the 83 measures matching the content domain, 43 met the minimum standard. In total, 30 measures displayed adequate responsiveness or precision. None of the 43 measures that met the minimum standard was fully addressed in terms of acceptability and feasibility evidence. Most of these measures described 3 or fewer components. Of the 83 measures matching the content domain, none met an industry standard.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1556.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1556.asp.

Further research/reviews required

1) Specific research networks for the development of therapist-patient measures should be established. 2) Research activity should prioritize investments to increase the evidence base of existing measures rather than attempting to develop new ones. Where research effort and time are invested in new measures this should be done strategically in a fashion that will serve national policy needs. See Executive Summary link at www.hta.ac.uk/project/1556.asp.

Written by Professor Michael Barkham, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/096

Title **A Systematic Review of the Clinical Effectiveness and Cost Effectiveness and Economic Modeling of Minimal Incision Total Hip Replacement Approaches in the Management of Arthritic Disease of the Hip**

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Reference Volume 12.26. ISSN 1366-5278. www.hta.ac.uk/project/1598.asp

Aim

To assess the clinical and cost effectiveness of minimal incision approaches to total hip replacement (THR) for arthritis of the hip.

Conclusions and results

Compared to standard THR, minimal incision THR has small perioperative advantages in terms of blood loss and operation time. It may offer a shorter hospital stay and quicker recovery. It appears to have a procedure cost similar to standard THR, but evidence on its longer term performance is limited. Further long-term follow-up data on costs and outcomes, including analysis of subgroups of interest to the NHS, would strengthen the current economic evaluation.

Nine randomized controlled trials (RCTs), 17 non-randomized comparative studies, 6 case series, and 1 registry were useful in comparing single mini-incision THR with standard THR. One RCT compared two mini-incision THR with standard THR, and 2 RCTs, 5 nonrandomized comparative studies, and 2 case series compared two mini-incision with single mini-incision THR. The RCTs were of moderate quality. Most had fewer than 200 patients and follow-up less than 1 year. The single mini-incision THR may have some perioperative advantages, eg, blood loss and shorter operative time, of uncertain practical significance. It may also offer a shorter recovery period and greater patient satisfaction. Evidence on long-term outcomes is too limited to be useful. Lack of data prevented subgroup analysis. With respect to the two-incision approach, the data suggested shorter recovery compared to single-incision THR, but conclusions must be treated with caution. Two economic evaluations were identified, but added little value to the evidence base owing to their limited quality. In the economic model, the costs to the health service, per patient, of single mini-incision THR depended on assumptions made, but were similar at 1 year (7060 pounds sterling [GBP] versus GBP 7350 for standard THR). For a 40-year time horizon the costs were GBP 11 618 for mini-incision and GBP 11 899 for standard THR. The mean QALYs at 1 year were 0.677 for standard THR and 0.695 for mini-incision THR. For both the 1- and 40-year analyses, mini-incision THR was less costly and provided slightly more QALYs. See Executive Summary link at www.hta.ac.uk/project/1598.asp.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1598.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1598.asp.

Further research/reviews required

Data on long-term outcomes of single mini-incision or two mini-incision THR are needed. The sparse effectiveness data limit subsequent economic analysis. Further long-term follow-up data on costs and outcomes including analysis of subgroups of interest to the NHS would strengthen the economic evaluation, as would data on costs of long-term events and management, such as failure. In relation to utilities, short-term differences in recovery are required, in addition to long-term differences in outcomes that depend on both subsequent failures and differences in quality of life, caused by long-term implications of different degrees of dissection. If a large RCT addressing long-term effectiveness is conducted, a full economic evaluation should be incorporated as an integral part of the study from design to dissemination. Further careful work would be required to explore the value of such a large RCT more formally.

Written by Professor Luke Vale, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/097

Title **Time to Full Publication of Studies of Anti-Cancer Medicines for Breast Cancer, and the Potential for Publication Bias: A Short Systematic Review**

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Reference Volume 12.32. ISSN 1366-5278. www.hta.ac.uk/project/1675.asp

Aim

To identify the expected delay between publication of conference abstracts and full publication of results from trials of new anticancer agents for breast cancer and to identify apparent biases in publication and reporting.

Conclusions and results

The review included 6 anticancer treatments for breast cancer. Interventions for early breast cancer were docetaxel, paclitaxel, and trastuzumab. Interventions for advanced or metastatic breast cancer were gemcitabine, lapatinib, and bevacizumab. Of the 18 included RCTs, only 4 publications (from 3 RCTs) reported the same outcomes in both an abstract and a full publication. Time between the abstract and full publication was 5 months in two cases, 7 months in one case, and 19 months in one case (overall mean delay=9 months). Eleven trials were identified where the data presented in an abstract or conference proceeding had not been fully published. The duration between publication of the abstracts and the end of August 2007 varied from 3 months to 38 months (mean delay 16.5 months). The longest delays in publication were for trials investigating gemcitabine (38 months) or bevacizumab (33 months). Observational analysis of the published and unpublished trials did not indicate any particular biases in terms of whether positive results were more likely to be fully published than nonsignificant ones. A limitation of this review is the small number of studies included. With a larger sample, investigation into the effect of publication delay on decision-making might be feasible.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1675.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1675.asp.

Further research/reviews required

Future research should include extension of this work to other anticancer drugs and investigation into the reasons for the lengthy delays to full publication noted for some trials.

Written by Dr Emma Loveman, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/098

Title **Curative Catheter Ablation in Atrial Fibrillation and Typical Atrial Flutter: Systematic Review and Economic Evaluation**

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Reference Volume 12.34. ISSN 1366-5278. www.hta.ac.uk/project/1539.asp

Aim

To determine the safety and clinical and cost effectiveness of radio frequency catheter ablation (RCFA) in curative treatment of atrial fibrillation (AF) and typical atrial flutter.

Conclusions and results

RFCA is a relatively safe and efficacious procedure in treating AF and typical atrial flutter. Some randomized evidence suggests that RFCA is superior to antiarrhythmic drugs (AADs) in patients with drug-refractory paroxysmal AF in terms of freedom from arrhythmia at 12 months. RFCA appears to be cost effective if the observed benefits in quality of life are assumed to continue over a patient's lifetime. Uncertainties remain around longer-term effects of the intervention, and the extent to which published effectiveness findings can be generalized to 'typical' UK practice.

Any planned multicenter RCTs comparing RFCA against best medical therapy for treating AF and/or atrial flutter should be conducted among 'nonpioneering' centers using the techniques and equipment typically employed in UK practice and should measure relevant outcomes. We retrieved 4858 studies for the review of clinical effectiveness. Of these, 8 controlled studies and 53 case series of AF were included. Two controlled studies and 23 case series of typical atrial flutter were included. For atrial fibrillation, freedom from arrhythmia at 12 months in case series ranged from 28% to 85.3%, with a weighted mean of 76%. Three RCTs suggested that RFCA is more effective than long-term AAD therapy in patients with drug-refractory paroxysmal AF. Single RCTs also suggested superiority of RFCA over electrical cardioversion followed by long-term AAD therapy and of RFCA plus AAD therapy over AAD maintenance therapy alone in drug-refractory patients. The available RCTs provided insufficient evidence to determine the effectiveness of RFCA beyond 12 months, or in patients with persistent or permanent AF. Adverse events and complications were generally rare. Mortality rates were low in both RCTs and case series. Cardiac tamponade and pulmonary vein stenosis were the complications most frequently recorded. For atrial flutter, freedom from arrhythmia at 12 months in case series ranged from 85% to 92%, with a weighted mean of 88%. Neither of the atrial flutter RCTs reported freedom from arrhythmia at 12 months. See Executive Summary link at www.hta.ac.uk/project/1539.asp.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1539.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1539.asp.

Further research/reviews required

All catheter ablation procedures for treating AF or atrial flutter in the UK should be recorded prospectively and centrally. A Central Cardiac Audit Database already exists, but measures to increase compliance in recording RFCA procedures may be needed. This would be of particular value in establishing the long-term benefits of RFCA and the true incidence and impact of any complications. Collecting appropriate quality of life data in any such registry would be of value to future clinical- and cost-effectiveness research. Any planned multicenter RCTs comparing RFCA to best medical therapy for treating AF and/or atrial flutter should be conducted among 'non-pioneering' centers using the techniques and equipment typically employed in UK practice, and they should measure relevant outcomes.

Written by Mr Mark Rodgers, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/099

Title **Immunoprophylaxis Against Respiratory Syncytial Virus (RSV) with Palivizumab in Children – A Systematic Review and Economic Evaluation**

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Reference Volume 12.36. ISSN 1366-5278. www.hta.ac.uk/project/1596.asp

Aim

To systematically review the effectiveness and cost effectiveness of palivizumab in preventing respiratory syncytial virus (RSV) in children and examine prognostic factors to determine whether subgroups can be identified with important differences in cost effectiveness.

Conclusions and results

Prophylaxis with palivizumab is clinically effective in reducing the risk of serious lower respiratory tract infection (LRTI) caused by RSV infection and requiring hospitalization in high-risk children. But if used unselectively in the licensed population, the incremental cost-effectiveness ratio (ICER) is double that considered to represent good value for money in the UK. Future research should initially focus on systematically reviewing the major uncertainties for patient subgroups with chronic lung disease (CLD) and coronary heart disease (CHD) and then on primary research to address the important uncertainties that remain. Two randomized controlled trials (RCTs) were identified. Prophylaxis with palivizumab for preterm infants without CLD or children with CLD resulted in a 55% reduction in RSV hospital admission: 4.8% (48/1002) in the palivizumab group and 10.6% (53/500) in the no prophylaxis group (p = 0.0004). Prophylaxis with palivizumab was associated with a 45% reduction in hospitalization rate RSV among children with CHD. Hospitalization rates for RSV were 5.3% (34/639) in the palivizumab group and 9.7% (63/648) in the no prophylaxis group (p = 0.003). Of existing economic evaluations, 3 systematic reviews and 18 primary studies were identified. All systematic reviews concluded that the potential costs of palivizumab were far in excess of any potential savings achieved by decreasing hospital admission rates, and that the use of palivizumab was unlikely to be cost effective in all children for whom it is recommended, but that its continued use for particularly high-risk children may be justified. The ICERs of the primary studies varied 17-fold for life-years gained (LYG), from GBP 25 800/LYG to GBP 404 900/LYG, and several hundred-fold for quality-adjusted life-years (QALYs), from GBP 3200/QALY to GBP 1 489 700/QALY for preterm infants without CLD or children with CLD. For children with CHD, the ICER varied from GBP 5300/LYG to GBP 7900/LYG and from GBP 7500/QALY to GBP 68 700/QALY. An analysis of what led to the discrepant ICERs showed that the assumed mortality rate for RSV infection was the most important driver. The BrumEE shows that prophylaxis with palivizumab may be cost effective (based on a threshold of GBP 30 000/QALY, but the threshold for decision-makers may vary, particularly for this type of patient group) for children with CLD when the children have two or more additional risk factors. Our economic evaluation is limited by the quality and quantity of the primary data available and the pragmatic rather than systematic methods used to identify parameter values.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1596.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1596.asp.

Further research/reviews required

See Executive Summary link at www.hta.ac.uk/project/1596.asp.

Written by Dr Catherine Meads, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/100

Title **Thrombophilia Testing in People with Venous Thromboembolism: Systematic Review and Cost-Effectiveness Analysis**

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Reference Volume 13.02. ISSN 1366-5278. www.hta.ac.uk/project/1552.asp

Aim

To assess whether thrombophilia testing following a venous thrombotic event is clinically and cost effective in managing thrombosis compared to no testing for thrombophilia.

Conclusions and results

In terms of determining the duration of anticoagulation management, scenarios were found in which the cost per QALY of thrombophilia testing was below 20 000 pounds sterling (GBP). However, these results are subject to great uncertainty, largely due to lack of knowledge about the increased risk of recurrence with each type of thrombophilia. Results are influenced by the fact that men have a greater risk of recurrence than women and by the fact that the frequency of adverse events associated with warfarin treatment increases with age. Further research, eg, on the likely sensitivity and specificity of the tests for specific types of thrombophilia, is needed to reduce the uncertainty associated with these results. Studies comparing patients with a venous thromboembolic event (VTE) tested for thrombophilia against those whose risk assessment was based on personal and family history of thrombosis would also be beneficial. No clinical studies were identified that met the inclusion criteria for the systematic review. Further literature searches and clinical opinion were therefore used to inform the cost-effectiveness analysis. Thrombophilia testing in patients with pulmonary embolism (PE) had an estimated mean cost per quality-adjusted life-year (QALY) of below GBP 20 000 regardless of sex or age. In patients with a previous deep vein thrombosis (DVT), thrombophilia testing had an estimated mean cost per QALY of below GBP 20 000 in men aged 69 years or less and in women aged 49 years or less. The estimated duration of warfarin treatment (lifelong, 20 years, 10 years, or no extended treatment) that was most cost effective is presented for each age, sex, initial VTE, and type of thrombophilia.

Recommendations

No clinical studies were identified that met the inclusion criteria for the review. Our mathematical model estimates that undertaking thrombophilia testing on patients with PE has a mean cost per QALY below GBP 20 000 regardless of sex or age, although these values are uncertain. In patients with a previous DVT, thrombophilia testing has an estimated mean cost per QALY below GBP 20 000 in men aged 69 years or less and in women aged 49 years or less, but again the values are uncertain.

Methods A comprehensive search was undertaken to systematically identify literature on clinical and cost effectiveness that compared thrombophilia testing of patients with thrombosis with no testing, and the resulting long-term anticoagulation management and outcomes. A discrete event simulation model was constructed that assessed the cost effectiveness of changing the standard 3-month duration of warfarin treatment to 10 years, 20 years, or lifelong. The model was run for both sexes, using hypothetical cohorts of patients assumed to be 30, 40, 50, 60, and 70 years of age. Separate analyses were conducted for patients in whom the initial VTE was a DVT and for those in whom the initial VTE was a PE.

Further research/reviews required

See Executive Summary link at www.hta.ac.uk/project/1552.asp.

Written by Dr Emma Simpson, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/101

Title **Surgical Procedures and Non-Surgical Devices for the Management of Non-Apnoeic Snoring: A Systematic Review of Clinical Effects and Associated Treatment Costs**

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Reference Volume 13.03. ISSN 1366-5278. www.hta.ac.uk/project/1671.asp

Aim

To review the evidence on the clinical effects and associated treatment costs of surgical procedures and nonsurgical devices in managing nonapneic snoring.

Conclusions and results

This study highlighted the paucity and poor quality of the evidence available on the effects of both surgical procedures and nonsurgical devices in managing primary snoring. Hence, any conclusions to be drawn from the results are tentative. No procedure was clearly the least-cost option. The systematic review included 27 studies (3 randomized controlled trials, 2 controlled clinical trials, and 22 pre-post studies) reported in 30 publications assessing uvulopalatopharyngoplasty (UP3) versus laser-assisted uvulopalatoplasty (LAUP), UP3 alone, LAUP alone, palatal stiffening techniques (Pillar implants and injection snoreplasty), radiofrequency ablation (RFA) of the soft palate or tongue base, continuous positive airway pressure (CPAP) devices, and mandibular advancement splints (MAS). Studies were generally of low methodological quality with small sample sizes. In total, 1191 patients were included. Both UP3 and LAUP reduced the number of snores per hour and produced a modest reduction in snoring loudness. UP3 was effective in reducing several subjectively reported snoring indices, but results on objective measures were equivocal. Limited evidence indicates that subjectively assessed snoring is improved after LAUP; no objective measures were assessed. RFA was associated with a reduction in partner-assessed snoring intensity; evidence for an objective reduction in snoring sound levels was mixed. Pillar implants were moderately effective at reducing partner-rated snoring intensity, but had no effect on objective snoring indices. Use of CPAP reduced the number of snores per hour; no subjective measures were evaluated. Use of MAS improved objective snoring outcomes, including the maximal snoring sound volume, the mean snoring sound volume, and the percentage of time spent in loud snoring; no subjective measures were evaluated. The cost for UP3 ranges from approximately 1230 pounds sterling (GBP) to approximately GBP 1550. For LAUP the cost varies from GBP 790 to GBP 2070 depending on the number of stages of the procedure. Treatment costs associated with the use of Pillar implants range from GBP 1110 to GBP 1160. The approximate annual treatment costs associated with using a CPAP machine and MAS are GBP 220 and GBP 130 respectively.

Recommendations

No consistent significant differences appear in effects between UP3 compared with LAUP on snoring levels. UP3, LAUP, RFA of the soft palate, and Pillar implants are associated with a significant reduction in patient- or bed partner-reported snoring levels. However, the rate of relapse on subjectively assessed outcomes is variable and ranges from approximately 6% to 24%, depending on the procedure and the length of postoperative follow-up. There is no strong evidence that subjectively assessed snoring outcomes are associated with objective reductions in snoring sound levels. Very limited evidence on CPAP and MAS shows that both devices are associated with a significant reduction in objective snoring sound parameters, which if realized may translate into a significant reduction in bed partner-assessed snoring intensity. In terms of UP3, LAUP, and Pillar implants, no procedure is clearly the least-cost option based on the crude and limited analysis conducted. For use of CPAP or MAS, use of MAS appears cheaper than use of a CPAP machine.

Methods

See Executive Summary link at www.hta.ac.uk/project/1671.asp.

Further research/reviews required

See Executive Summary link at www.hta.ac.uk/project/1671.asp.

Written by Ms Caroline Main, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/102

Title **Clinical Effectiveness and Cost-Effectiveness of Continuous Subcutaneous Infusion for Diabetes: Systematic Review and Economic Evaluation**

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Reference Volume 14.11. ISSN 1366-5278. www.hta.ac.uk/project/1622.asp

Aim

To examine the clinical and cost effectiveness of using continuous subcutaneous insulin infusion (CSII) to treat diabetes; to update the previous assessment; and to take account of developments in alternative therapies, in particular the long-acting analogue insulins.

Conclusions and results

Based on the totality of evidence, using observational studies to supplement the limited data from randomized trials against best multiple daily injection (MDI), CSII provides some advantages over MDI in type 1 diabetes mellitus (T1DM) for both children and adults. However, no evidence indicated that CSII is better than analogue-based MDI in type 2 diabetes mellitus (T2DM) or in pregnancy. Further trials with larger numbers and longer durations comparing CSII and optimized MDI in adults, adolescents, and children are needed. In addition, a trial should compare CSII versus MDI with similar provision of structured education in both arms. A trial is also needed for pregnant women with pre-existing diabetes, to investigate using CSII to the best effect. The 74 studies used for analysis included 8 randomized controlled trials (RCTs) of CSII versus analogue-based MDI in either T1DM or T2DM, 8 new (since the last NICE appraisal) RCTs of CSII versus NPH-based MDI in T1DM, 48 observational studies of CSII, 6 studies of CSII in pregnancy, and 4 systematic reviews. The following benefits of CSII were highlighted: better control of blood glucose levels, as reflected by glycated hemoglobin (HbA1c) levels, with the size of improvement depending on the level before starting CSII; reduction in swings in blood glucose levels, and in problems due to the dawn phenomenon; fewer problems with hypoglycemic episodes; reduction in insulin dose per day, (partly off-setting the cost of CSII); improved quality of life, including reduced chronic fear of severe hypoglycemia; more flexibility of lifestyle (no need to eat at fixed intervals), more freedom of lifestyle and easier participation in social and physical activity; and benefits for the patients' family. The submission from INPUT emphasized the quality of life gains from CSII, as well as improved control and fewer hypoglycemic episodes. Also, there was a marked discrepancy between the improvement in social quality of life reported by successful pump users, and the lack of convincing health-related quality of life gains reported in the trials. With regard to economic evaluation, the main cost of CSII is for consumables, eg, tubing and cannulas, and is about 1800 to 2000 pounds sterling (GBP) per year. The cost of the pump, assuming 4-year life, adds another GBP 430 to GBP 720 per annum. The extra cost compared with analogue-based MDI averages GBP 1700.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1622.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1622.asp.

Further research/reviews required

1) The need for adequate trials of CSII against analogue-based MDI has not been met. We need further trials with larger numbers and longer durations, comparing CSII and optimized MDI in adults, adolescents, and children. Duration is important because maximum benefit from CSII might not be obtained for many months. Conversely, we need to know if initial benefits in HbA1c level are sustained. 2) A trial of CSII versus MDI is needed with similar provision of structured education in both arms. Without such trials, we cannot be sure whether the benefits observed with CSII are due to the CSII itself, or to better self-management of diabetes resulting from increased patient education. See Executive Summary link at www.hta.ac.uk/project/1622.asp.

Written by Dr Ewen Cummins, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/103

Title **Self-Monitoring of Blood Glucose in Type 2 Diabetes: Systematic Review**

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Reference Volume 14.12. ISSN 1366-5278. www.hta.ac.uk/project/1870.asp

Aim

To examine whether or not self-monitoring of blood glucose (SMBG) is worthwhile, in terms of glycemic control, hypoglycemia, quality of life (QoL), and cost per quality-adjusted life year (QALY), in people with type 2 diabetes mellitus (T2DM) who were not treated with insulin, or who were on basal insulin in combination with oral agents.

Conclusions and results

The evidence suggested that SMBG is of limited clinical effectiveness in improving glycemic control in people with T2DM on oral agents, or diet alone, and is unlikely to be cost effective. SMBG may lead to improved glycemic control only in the context of appropriate education – both for patients and healthcare professionals – on how to respond to the data in terms of lifestyle and treatment adjustment. Also, SMBG may be more effective if patients are able to self-adjust drug treatment.

The review identified 30 RCTs. Ten trials comparing SMBG with no SMBG showed a statistically significant reduction in HbA1c of 0.21%, which may not be considered clinically significant. A similar, though not statistically significant, difference was shown where SMBG with education was compared to SMBG without education or feedback. RCTs showed no consistent effect on hypoglycemic episodes and no impact on medication changes. Review of cost-effectiveness studies showed that costs of SMBG per annum vary considerably (10 to 259 pounds sterling, GBP). Although some studies assert that SMBG may lead to savings in healthcare costs, which could offset the costs of testing, the best analysis to date (Diabetes Glycemic Education and Monitoring, DiGEM) concluded that SMBG was not cost effective. Qualitative studies revealed a lack of education in how to interpret and use the data from SMBG, and that failure to act on the results was common.

Recommendations

In the authors' opinion, at a time when funds are scarce, the case for investing in blood glucose monitoring in T2DM, in patients who are not treated with insulin, is not proven.

Methods

Methods included a review of systematic reviews published since 1996, systematic review and meta-analyses of randomized controlled trials (RCTs) identified from the reviews and from searches for more recent trials, and review of qualitative and economic studies. See Executive Summary link at www.hta.ac.uk/project/1870.asp.

Further research required

Further research is required on the type of education and feedback that are most helpful, characteristics of patients benefiting most from SMBG, and optimum timing and frequency of SMBG. See Executive Summary link at www.hta.ac.uk/project/1870.asp.

Written by Professor Norman Waugh, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/104

Title **North of England and Scotland Study of Tonsillectomy and Adeno-Tonsillectomy in Children (NESSTAC): A Pragmatic Randomized Controlled Trial with a Parallel Non-Randomized Preference Study**

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Reference Volume 14.13. ISSN 1366-5278. www.hta.ac.uk/project/1212.asp

Aim

To examine the clinical and cost effectiveness of tonsillectomy/adenotonsillectomy in children aged 4 to 15 years with recurring sore throat in comparison to standard nonsurgical management.

Conclusions and results

Children and parents exhibited strong preferences for surgical management of recurring sore throat. Recurring sore throat in all children improved over time, but trial participants randomized to surgical management tended to experience better outcomes than those randomized to medical management.

Of the 1546 children assessed for eligibility, 817 were excluded (531 not meeting inclusion criteria, 286 refused) and 729 enrolled to the trial (268) or cohort study (461). The mean (standard deviation) episode of sore throats per month was: *Year 1* – cohort medical 0.59 (0.44), cohort surgical 0.71 (0.50), trial medical 0.64 (0.49), trial surgical 0.50 (0.43); *Year 2* – cohort medical 0.38 (0.34), cohort surgical 0.19 (0.36), trial medical 0.33 (0.43), trial surgical 0.13 (0.21). During both years of follow-up, children randomized to surgical management were less likely to record episodes of sore throat than those randomized to medical management; the incidence rate ratios in years 1 and 2 were 0.70 (95% confidence interval [CI] 0.61 to 0.80) and 0.54 (95% CI 0.42 to 0.70) respectively. The incremental cost-effectiveness ratio was estimated at 261 pounds sterling (GBP) per sore throat avoided (95% CI GBP 161 to GBP 586). Parents' mean willingness to pay for the successful treatment of their child's recurring sore throat was GBP 8059 (median GBP 5000). The estimated incremental cost per quality-adjusted life year (QALY) ranged from GBP 3129 to GBP 6904 per QALY gained.

Recommendations

The limitations of the study, due to poor response at follow-up, support the continuing careful use of "watchful waiting" and medical management in primary and secondary care (in line with current clinical guidelines) until clear-cut evidence of clinical and cost effectiveness is available.

Methods

See Executive Summary link at www.hta.ac.uk/project/1212.asp.

Further research/reviews required

1) As treated analysis

2) Methodological research of alternative methods of data collection

3) Larger sample completing utility/willingness-to-pay studies.

Written by Dr Catherine Lock, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/105

Title **Randomized Control Trials for Policy Interventions: A Review of Reviews and Meta-Regression**

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Reference Volume 14.16. ISSN 1366-5278. www.hta.ac.uk/project/1572.asp

Aim

To determine whether randomized controlled trials (RCTs) lead to the same effect size and variance as nonrandomized studies (NRSs) of similar policy interventions, and whether these findings can be explained by other factors associated with the interventions or their evaluation.

Conclusions and results

Prior methodological reviews and meta-analyses of reviews comparing effects from RCTs and nonrandomized controlled trials (nRCTs) suggested that effect sizes from RCTs and nRCTs may differ in some circumstances, and these differences may be associated with factors confounded with design. Resampling studies offered no evidence that the absence of randomization directly influences the effect size of policy interventions in a systematic way. At the level of individual studies, nonrandomized trials may lead to different effect sizes, but this is unpredictable. Many of the examples reviewed and the new analyses in the current study reveal that randomization is associated with changes in effect sizes of policy interventions in field trials. Despite extensive analysis, we have identified no consistent explanations for these differences.

Recommendations

1) Policy evaluations should adopt randomized designs whenever possible. 2) Policy evaluations should also adopt other standard procedures for minimizing bias and conducting high-quality assessment of effects of intervention, particularly blinded allocation of either individuals or groups and the avoidance of small sample sizes. 3) Clear descriptions should be included in systematic reviews of how judgments of equivalence (or otherwise) have been reached when comparing the effects found in randomized and nonrandomized studies of policy interventions.

Methods

This study employed four approaches: 1) Resampling studies: comparing controlled trials that are identical in all respects other than the use of randomization by "breaking" the randomization in a trial to create smaller nonrandomized trials and smaller randomized trials by resampling randomized and nonrandomized comparisons from the data. 2) Replication studies: comparing randomized and nonrandomized arms of controlled trials mounted simultaneously in the field. 3) Investigating comparable field studies: controlled trials drawn from systematic reviews that include both randomized and nonrandomized studies. 4) Meta-epidemiology: investigating associations between randomization and effect size using a pool of more diverse randomized and nonrandomized studies in broadly similar areas. These more diverse studies can be drawn from across reviews addressing different questions, or from broad sections of literature. See Executive Summary link at www.hta.ac.uk/project/1572.asp.

Further research/reviews required

1) Feasibility studies of randomizing geographical areas, communities, and regions should be carried out to evaluate policy interventions in a range of sectors, implemented within interventions, communities, and across regions. 2) Feasibility studies of blinded allocation should be carried out for policy interventions in a range of sectors, implemented within interventions, communities, and across regions. 3) Research is required into the reasons for choosing randomization, or not, particularly in the presence and absence of an explicit collective plan of action.

Written by Professor Sandy Oliver, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/106

Title	**Prevention of Infection After Knee Arthroplasty**
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Reference	HTA report volume 104. ISSN 1864-9645.
	http://portal.dimdi.de/de/hta/hta_berichte/hta264_bericht_de.pdf

Aim

To address questions regarding the medical effectiveness, cost effectiveness, and ethical, social, and legal aspects related to using interventions to prevent infections after knee arthroplasty.

Conclusions and results

A systematic literature search yielded 1030 hits. Ten publications were included in the analysis, based on predefined inclusion and exclusion criteria. The report does not find high-level evidence for the effectiveness of different hygiene interventions. Most of the unspecific interventions are recommended on the basis of results from nonrandomized controlled trials, from studies for other clinical indications and/or clinically nonrelevant endpoints, or on the basis of expert opinion. A high level of evidence on the effectiveness of intravenous prophylaxis with antibiotics in knee arthroplasty is also missing. The recommendations use evidence on the intravenous antibiotic prophylaxis transferred from RCT in hip arthroplasty to the arthroplasty of all joints, including knee replacement. Moreover, no evidence is found for differences in the effectiveness between various antibiotics in knee arthroplasty. The report finds strong hints for the effectiveness of antibiotics in cement in addition to intravenous prophylaxis. However, evidence of the effectiveness may be accepted only for operating rooms without clean-air measures. The cost effectiveness of different interventions to prevent infections in knee arthroplasty remains unclear. There are no signs for concern regarding any ethical, social, and/or legal consequences in using interventions to prevent infections in knee arthroplasty.

Recommendations

Based on the analysis, no proposals can be made to change the recommendations of the Robert Koch Institute with respect to hygiene interventions and intravenous antibiotic prophylaxis. Also, no recommendations to select a particular antibiotic can be derived from the analyzed data. The use of antibiotics in cement, in addition to intravenous prophylaxis, may be generally recommended.

Methods

A systematic literature search was conducted in MEDLINE, EMBASE, SciSearch, etc in June 2009 and completed by a hand search. The analysis includes publications that describe and/or evaluate clinical data from randomized controlled trials (RCTs) systematic reviews of RCTs, registers of endoprostheses, or databases on interventions to prevent infections after knee arthroplasty. The literature search also aimed to identify health economic studies and publications dealing explicitly with ethical, social, or legal aspects in using interventions to prevent infections after knee arthroplasty. The synthesis of information from different publications has been performed qualitatively.

Written by Vitali Gorenoi, Matthias P Schönermark, and Anja Hagen, DAHTA, Germany

INAHTA Briefs

Issue 2010/107

Title **Comparison of Tools for Assessing the Methodological Quality of Primary and Secondary Studies in Health Technology Assessment Reports**

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Reference HTA report volume 102. ISSN 1864-9645.
http://portal.dimdi.de/de/hta/hta_berichte/hta260_bericht_de.pdf

Aim

To compare and evaluate quality assessment tools (QAT) that are available to assess the quality of interventional studies or studies in the field of health economics with respect to formal and content criteria.

Conclusions and results

The report identifies 8 systematic methodological reviews and 147 QAT (15 for systematic reviews, 80 for randomized trials, 30 for observational studies, 17 for diagnostic studies, and 22 for health economic studies). Existing tools for assessing study quality can be classified into scales, checklists, and component ratings. The tools vary considerably as regards their content, performance, and quality of operationalization. Some tools include not only items of internal validity, but also items of quality concerning reporting and external validity. No tool covers all elements or domains. Design-specific generic tools are presented, which cover most of the content criteria. Evaluation of QAT by using content criteria is difficult due to the absence of scientific consensus on the necessary elements of internal validity, and not all of the generally accepted elements are based on empirical evidence. Comparing QAT based on content neglects the operationalization of the respective parameters, for which quality and precision are important for transparency, reproducibility, correct assessment, and interrater reliability. QAT, which mix items on the quality of reporting and internal validity, should be avoided. Mixing the reporting quality and internal validity can lead to misinterpretation of study quality, if elements of the reporting quality are used as a surrogate for assessing methodological quality.

Recommendations

Quality assessment of studies is a mandatory part of systematic reviews and must be documented transparently. Different design-specific QAT are available that can be selected according to their substantive coverage of the elements of internal validity. There is consensus that scales should not be used for quality assessments, or should be used without quantitative assessment. In general, the higher the scope for subjective assessments, the lower the agreement between the reviewers. To minimize subjectivity in an evaluation, tools with a detailed and precise operationalization of the items are preferable. Where necessary, the instructions can be adjusted to ensure that all reviewers are clear on how to score study quality. In health economic studies, tools should be developed and complemented with instructions that define the appropriateness of the criteria.

Methods

A systematic search of relevant databases from 1988 onward was supplemented by screening the references of HTA reports by the German Agency for Health Technology Assessment (DAHTA) and an Internet search. Two independent reviewers selected relevant literature, extracted data, and assessed quality. The substantive elements of the QAT were extracted using a modified criteria list consisting of items and domains specific to randomized trials, observational studies, diagnostic studies, systematic reviews, and health economic studies. Based on the number of covered items and domains, more and less comprehensive QAT have been distinguished.

Further research/reviews required

Further research is needed to identify study characteristics that influence the internal validity of studies, especially observational studies.

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INAHTA Briefs

Issue 2010/108

Title **Invasive Home Mechanical Ventilation, Mainly Focused on Neuromuscular Disorders**

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Reference HTA report volume 103. ISSN 1864-9645.
http://portal.dimdi.de/de/hta/hta_berichte/hta268_bericht_de.pdf

Aim

To assess medical, social, economic, and ethical aspects of invasive home mechanical ventilation for patients with chronic respiratory insufficiency due to neuromuscular diseases.

Conclusions and results

Analysis of the literature shows that invasive mechanical ventilation may improve symptoms of hypoventilation. An increase in life expectancy is likely, but for ethical reasons it is not confirmed by premium-quality studies. Complications (eg, pneumonia) are rare. A study regarding the pneumonia ratio reports 1.89 pneumoniae/1000 ventilator days in the first 500 days of invasive ventilation. This is a frequent reason for rehospitalization of patients, but the prognosis is favorable. Mobile home ventilators differ regrettably in their technical performance. Some studies compare the economic aspects of in-hospital ventilation to outpatient ventilation. The included studies report a 62% to 74% reduction for in-home care via an ambulatory nursing service, in comparison to the costs that accumulate in the intensive care unit of a hospital. Higher expenses arise due to the necessary equipment and the high cost of time for highly qualified staff in the partial 24-hour care of affected patients. However, none of the studies applies to the German provisionary conditions. The results of quality-of-life studies are mostly qualitative. Caregivers of ventilated patients report positive as well as negative ratings. From a legal standpoint the code of social law (*Sozialgesetzbuch V*) regulates the financing of home ventilation, especially invasive mechanical ventilation, requiring specialized technical nursing. The absorption of costs is distributed among different insurance carriers. Hence, the necessity to enforce a claim of cost absorption often arises in exercising the basic right of free choice of location.

Recommendations

For a so-called "participative decision" – made by the patient after intense counseling – early and honest patient education on the pros and cons of invasive mechanical ventilation is needed. Not only long-term survival, but also quality of life and individual, social, and religious aspects must be considered.

Methods

Fixed criteria were used to view and select literature found through a systematic literature search of 31 relevant databases in 2008. The analysis included randomized controlled studies, systematic reviews, health technology assessment (HTA) reports, clinical studies of >10 patients, health economic evaluations, primary studies with particular cost analyses, and quality-of-life studies related to the research questions. See Executive Summary link at http://portal.dimdi.de/de/hta/hta_berichte/hta268_summary_en.pdf.

Further research/reviews required

The literature does not address differences in quality of life associated with the type of outpatient care. A registry of home ventilation and research to ascertain valid data are necessary to improve outpatient structures. Specific German data is needed in the future to adequately depict the national concepts of provision and reimbursement.

Written by Jens Geiseler and Ortrud Karg, DAHTA, Germany

INAHTA Briefs

Issue 2010/109

Title	**Decision-Analytic Modeling Study to Evaluate the Long-Term Effectiveness and Cost Effectiveness of HPV-Based Primary Cervical Cancer Screening in Germany**
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Reference	HTA report volume 98. ISSN 1864-9645. http://portal.dimdi.de/de/hta/hta_berichte/hta265_bericht_de.pdf

Aim

To perform a decision analysis to systematically evaluate the long-term effectiveness and cost effectiveness of HPV-based primary cervical cancer (CC) screening in the German healthcare context.

Conclusions and results

Human papillomavirus (HPV)-based screening was more effective than cytology alone, with 71% to 97% (depending on screening intervals) reduction in CC compared to 53% to 80% for cytology. The incremental cost-effectiveness ratios (ICER) ranged between 2600 euros (EUR)/LYG (cytology, 5-year interval) and EUR 155 500/LYG (annual HPV-testing age 30 years, cytology 20 to 29 years). Annual cytology, the recommended screening strategy in Germany, was dominated by other strategies. Increasing the starting age to 25 years had no relevant loss in effectiveness, but resulted in lower costs. Considering long-term effectiveness and cost effectiveness, biennial HPV testing at age 30 years preceded by biennial cytology at age 25 to 29 years could be an optimal screening strategy (ICER: EUR 23 400/LYG). With increased screening adherence (>75%), or a substantial reduction in HPV incidence in the population (>70%), a longer screening interval (and with low adherence a shorter interval) would be more cost effective. In a scenario analysis with data for test accuracy from a German study (increased relative sensitivity for HPV testing compared to cytology) HPV-based screening in screening intervals of 1, 2, or 3 years were more effective than annual cytology.

Recommendations

- HPV-based primary screening for CC is more effective than cytology when considering long-term outcomes, eg, life expectancy and reduction in cervical cancer risk and mortality.
- Introducing HPV-based primary screening in Germany could extend the screening interval to 2 years for women of average risk.
- For women who undergo regular screening, the interval could be extended to >2 years. The same applies if the relative sensitivity increase with HPV testing is higher.
- For women with average risk, the starting age of screening can be increased to 25 years without a relevant loss in effectiveness.
- Screening at short intervals is recommended in populations with low screening adherence.
- An optimal screening strategy in Germany would be biennial HPV testing in women aged 30 years and older proceeded by biennial cytology between ages 25 and 29 years.

Methods

A Markov model simulating the natural history of CC was developed and validated for the German context. Different screening intervals and strategies were evaluated, eg, cytology alone, HPV testing alone, or combined with cytology or cytology triage for HPV-positive women. German clinical, epidemiological, and economic data were used. Test accuracy data were retrieved from international meta-analyses. Predicted outcomes were a reduction in CC cases and deaths, life expectancy, and discounted ICER. A healthcare system perspective and 3% annual discount rate were adopted. Extensive sensitivity analyses were performed to evaluate the robustness of results.

Further research/reviews required

Research is needed to acquire evidence-based information on adherence patterns, the impact of screening on quality of life and on decision-analytic evaluation of different integrated screening strategies in mixed vaccinated and unvaccinated populations, and systematic evaluation of different practice patterns in diagnostic work-up and treatment after initial screening results.

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INAHTA Briefs

Issue 2010/110

Title **Differential Diagnostics of the Burn-Out Syndrome**

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Reference HTA report volume 105. ISSN 1864-9645.
http://portal.dimdi.de/de/hta/hta_berichte/hta278_bericht_de.pdf

Aim

To answer the following questions: How is burnout diagnosed? Which criteria are relevant? How valid and reliable are the tools used? What kinds of disorders are relevant for a differential diagnosis of burnout? What is the economic effect of a differential diagnosis of burnout? Are there any negative effects of persons with burnout on patients or clients? Can stigmatization of burnout patients or clients be observed?

Conclusions and results

We identified 852 studies. After considering the inclusion and exclusion criteria, and after reviewing the full texts, 25 medical and 1 ethical study were included. No economic study met the criteria.

The key result of this report is that no standardized, general, and internationally valid procedure exists to obtain a burnout diagnosis. At present, it is up to the physician's discretion to diagnose burnout. The basic problem involves measuring a phenomenon that is not exactly defined. The current burnout measurements capture a 3-dimensional burnout construct. But the cutoff points do not conform to the standards of scientifically valid test construction. It is important to differentiate burnout from depression, alexithymia, feeling unwell, and the concept of prolonged exhaustion. An intermittent relation of the constructs is possible. Furthermore, burnout goes along with various ailments like sleeping disorders. Through a derogation of work performance it can have negative effects on significant others (eg, patients). No evidence shows stigmatization of persons with burnout. In most studies, the evidence is predominantly low (most studies are descriptive and explorative). Self-assessment tools are mainly used, primarily the Maslach Burnout Inventory (MBI). The studies seldom include objective data, eg, medical parameters, health status, sickness notes, or judgments by third persons. The sample construction is coincidental in the majority of cases, and response rates are often low. Almost no longitudinal studies are available. Results are insufficient regarding the stability and duration of related symptoms. Studies regularly neglect the ambiguity of the burnout diagnosis.

Methods

Health technology assessment, systematic review, social/ethical implications consideration, search of 36 data bases were the methods used.

Further research/reviews required

The authors conclude that: 1) further research (particularly high-quality studies) is needed to broaden the understanding of burnout syndrome; 2) a definition of burnout syndrome has to be found that goes beyond the published understanding of burnout and is based on common scientific consent; 3) a standardized, internationally accepted, and valid procedure for the differentiated diagnostic of burnout need to be found; 4) a third party assessment tool for diagnosing burnout needs to be developed; and 5) the economic effects and implications that burnout diagnostics have for the economy, health insurances, and patients need to be analyzed.

Written by Dr. Dieter Korczak, DAHTA, Germany

INAHTA Briefs

Issue 2010/111

Title **Virtual Colonoscopy: Meta-Analysis of Diagnostic Accuracy, Indications and Conditions of Use**

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Reference www.has-sante.fr/portail/jcms/c_923754/coloscopie-virtuelle-meta-analyse-des-performances-diagnostiques-indications-et-conditions-de-realisation

Aim

To perform a new meta-analysis (MA) on the diagnostic accuracy of virtual colonoscopy (VC) in detecting polyps and colorectal cancer.

Conclusions and results

The diagnostic accuracy of virtual colonoscopy (VC) compared to optical colonoscopy (OC) remains questionable for two main reasons. First, conflicting results have been reported repeatedly in original and large studies. Secondly, meta-analyses (MA) published at the time of our assessment could not be used for health technology assessment (HTA) as they included studies in which the mode of use of VC did not correspond to current international standards.

Twenty-four studies involving 7202 patients were included. MA showed highly heterogeneous results, requiring the use of a mixed model (Markov chain Monte Carlo method).

Whatever the lesion size, OC had significantly higher sensitivity and specificity than VC. Complications were infrequent for both. Subgroup analyses helped to define optimal technical characteristics of VC: complete colonic cleansing with fecal tagging, high spatial resolution imaging, and expert reading combining 2D and 3D methods. The French National Authority for Health (HAS) concluded that VC cannot replace OC, except in the case of incomplete optical colonoscopy, serious comorbidities, or patient refusal.

Methods

All studies (MEDLINE, EMBASE, Pascal, 2001-2009) comparing the diagnostic accuracy of VC in detecting colorectal polyps and cancer against OC as the gold standard were identified. Unlike previous MA, only studies that used a VC with systematic prone and supine acquisitions and with slice collimation not greater than 2.5 mm were included. Methodological quality of included studies was assessed using the *Quality Assessment of Diagnostic Accuracy Studies*.

Additionally, 14 experts representing 5 medical specialties (radiology, gastroenterology, oncology, pathology, and public health) were consulted. Conclusions were appraised by a specialized committee of HAS (*Commission d'Evaluation des Actes Professionnels)*.

Further research/reviews required

Further assessment should specify the attitude to be taken on discovery of polyps smaller than 6 mm. A medicoeconomic evaluation should also specify the place of VC in the event of OC refusal by a patient with a positive fecal test.

Written by Dominique Tessier-Vetzel, HAS, Frankrike

Title **Hyperbaric Oxygen Therapy for Traumatic Brain Injury and Post Traumatic Stress Disorder**

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Reference VA Technology Assessment Program Bibliography Update, January, 2010

Aim

To determine the published, peer-reviewed evidence on the clinical use of hyperbaric oxygen (HBO_2) in treating traumatic brain injury (TBI) and post traumatic stress disorder (PTSD) in veterans.

Conclusions and results

For TBI, 7 systematic review articles and 6 Phase I or II clinical trials were found. Five of the 6 clinical trials were in progress. The systematic review articles concluded that the clinical value of HBO_2 in treating TBI is unknown due to insufficient evidence; individual case studies have reported positive results with this treatment. For PTSD, only one case report was found. Hence, no conclusions could be drawn.

Recommendations

No recommendations can be made at this time. High-quality research is needed to determine the clinical efficacy of HBO_2 in treating TBI and PTSD.

Methods

Literature searches were conducted for articles (published in English) from the following databases: ClinicalTrials.gov, MEDLINE, EMBASE, INAHTA, Cochrane Library, and Dialog Information. Existing reports or reports in progress were obtained via email queries to the INAHTA listserv.

Further research/ reviews required

The US Department of Defense is conducting clinical trials addressing the need for randomized, double-blind, or controlled studies. Two clinical trials were scheduled for completion in 2010.

Written by Elizabeth Adams, VATAP, USA

Title **Mandatory Training – A Systematic Review of Research and Trends in Learning Organizations**

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Reference VA Technology Assessment Program Brief Overview, March, 2010

Aim

To determine: 1) the relative effectiveness of mandatory learning versus other strategies to improve organizational performance; 2) if the modality of learning matters; and 3) what the VHA can learn from other organizations.

Conclusions and results

Three systematic reviews and a primary study met the search criteria and are annotated in the report. None could provide solid conclusions due to poor study design, conflicting data, and understudied topics.

Recommendations

No evidence was available to make any recommendations.

Methods

The Technology Assessment Program (TAP) searched the literature across business, education, health care, social sciences, and biomedical domains from 1990 to February 2010. This included the Cochrane Library, Internet searches, and 17 Dialog® Information Services databases.

Further research/ reviews required

Mixed methodology research is needed to overcome traditional experimental approaches that control for the factors leading to the dissemination and implementation of complex learning strategies. Future research should also consider: organizational response to external mandates, any advantage between tacit or explicit transfer of knowledge, factors that motivate employees' engagement in self-directed learning, and the similarities and differences between private and public sector learning strategies.

Written by Elizabeth Adams, VATAP, USA

Title **Systematic Reviews for Nurse-Led Primary Care**

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Reference VA Technology Assessment Program Brief Overview, June, 2009

Aim

To seek support for expanding primary care capacity with nonphysician providers, eg, nurses.

Six reviews covering 150 studies met the report's inclusion criteria. The results indicate both nurses and physicians provide equivalent quality of care for patients. Patient satisfaction was higher with nurses. No conclusions could be drawn regarding a cost difference between care provided by nurses and physicians.

Recommendations

No specific recommendations were made for nurse-led primary care.

Methods

MEDLINE, Cochrane Library, and INAHTA databases were searched for articles published in English between 1990 and 2009.

Further research/reviews required

A randomized control clinical trial is in progress at the Catalan Institute of Health (Spain) researching nurse versus general practitioner care for patients requesting same-day consultation.

Written by Karen Flynn, VATAP, USA

INAHTA Briefs

Issue 2010/115

Title **Evaluation of Diagnostic Tests When There Is no Gold Standard. A Review of Methods**

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Reference Volume 11.50, ISSN 1366-5278. www.hta.ac.uk/project/1573.asp

Aim

To generate a classification of methods to evaluate medical tests in the absence of a gold standard.

Conclusions and results

Most methods try to impute, adjust, or construct a reference standard in an effort to obtain familiar diagnostic accuracy statistics, eg, sensitivity and specificity. In situations that deviate only marginally from the classical diagnostic accuracy paradigm, these are valuable methods. However, in situations where an acceptable reference standard does not exist, applying the concept of clinical test validation can provide a significant methodological advance. All methods summarized in this report need further development. Some methods, such as the construction of a reference standard using panel consensus methods and validation of tests outside the accuracy paradigm, are particularly promising, but are lacking in methodological research. These methods deserve particular attention in future research. Available methods were classified into 4 main groups. The first method group (impute or adjust for missing data on reference standard) pays careful attention to the pattern and fraction of missing values. The second group (correct imperfect reference standard) can be useful if there is reliable information about the degree of imperfection of the reference standard and about the correlation of the errors between the index test and the reference standard. The third method group (construct reference standard) combines multiple test results to construct a reference standard outcome including deterministic predefined rules, consensus procedures, and statistical modeling (latent class analysis). In the final group (validate index test results) the diagnostic test accuracy paradigm is abandoned and the research uses different methods to examine whether the results of an index test are meaningful in practice, eg, by relating index test results to other relevant clinical characteristics and future clinical events.

Recommendations

In situations where an acceptable reference standard does not exist, holding on to the accuracy paradigm is less fruitful. In these situations, applying the concept of clinical test validation can provide a significant methodological advance. Validating a test means that scientists and practitioners examine, using several different methods, whether the results of an index test are meaningful in practice. Validation will always be a gradual process. It will involve the scientific and clinical community defining a threshold, a point in the validation process, whereby the information gathered would be considered sufficient to allow clinical use of the test with confidence.

Methods

See Executive Summary link at www.hta.ac.uk/project/1573.asp.

Further research/reviews required

All methods summarized in this report need further development. Some methods, eg, construction of a reference standard using panel consensus methods and validation of tests outside the accuracy paradigm, are particularly promising, but are lacking in methodological research. These methods deserve particular attention in future research.

Written by Professor Khalid Khan, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/116

Title **The use of Economic Evaluations in NHS Decision-Making: A Review and Empirical Investigation**

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Reference Volume 12.07, ISSN 1366-5278. www.hta.ac.uk/project/1562.asp

Aim

To determine the extent to which health economic information is used in health policy decision-making in the UK, and to consider factors associated with the utilization of such research findings.

Conclusions and results

This study suggests that research is needed into structures, processes, and mechanisms by which technology coverage decisions can and should be made in healthcare. Further development of resource centers may be useful to provide independent published analyses to support local decision-makers. Improved methods of economic analyses and their presentation, which take account of the concerns of their users, are needed. Finally, the findings point to the need for further assessment of the feasibility and value of a formal process to clarify the objectives that we seek from investments in health care. The systematic review showed few previous systematic reviews of evidence in the area. At the local level in the NHS, it was exceptional for economic evaluation to inform technology coverage decisions. Local decision-making focused primarily on evidence of clinical benefit and cost implications. While information on implementation was frequently requested, cost-effectiveness information was rarely accessed. Several features of the decision-making environment appeared to militate against emphasis on cost-effectiveness analysis. Constraints on the capacity to generate access and interpret information led to a minor role for cost-effectiveness analysis in local decision-making. At the national UK policy level, economic analysis was found to be highly integrated into NICE's technology appraisal program. Attitudes toward economic evaluation varied between committee members with some significant disagreement, and extraneous factors diluted the economic analysis available to the committee. There was strong evidence of an ordinal approach to consideration of clinical and cost-effectiveness information. Some interviewees considered the key role of a cost-effectiveness analysis to be the provision of a framework for decision-making. Interviewees indicated that NICE makes use of some form of cost-effectiveness threshold, but expressed concern about its basis and its use in decision-making. Frustrations with the appraisal process were expressed. Committee members raised concerns about lack of understanding of the economic analysis, but felt that a single measure of benefit, eg, quality-adjusted life-years, was useful in comparing disparate health interventions and in providing a benchmark for later decisions.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1562.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1562.asp.

Further research/reviews required

Research is needed on: 1) healthcare organizational forms addressing the alternative structures, processes, and mechanisms by which technology coverage decisions can and should be made; 2) development of resource centers to provide information on high-quality independent published analyses and support decision-makers with local re-analysis and interpretation of findings; 3) development of improved methods of economic analysis that address concerns raised by practitioners and users of such analyses in this research; 4) design of more accessible forms of presentation of economic analyses; 5) feasibility and value derived from a formal discussion and deliberation process concerning the objectives that we seek from investments in healthcare.

Written by Professor Stirling Bryan, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/117

Title **Systematic Review and Economic Analysis of the Comparative Effectiveness of Different Inhaled Corticosteroids and Their Usage With Long-Acting Beta2 Agonists for the Treatment of Chronic Asthma in Adults and Children Aged 12 Years and Over**

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Reference Volume 12.19, ISSN 1366-5278. www.hta.ac.uk/project/1523.asp

Aim

To assess the clinical and cost effectiveness of inhaled corticosteroids (ICS) alone and ICS used in combination with a long-acting beta2 agonist (LABA) in treating chronic asthma in adults and children aged >12 years.

Conclusions and results

The evidence indicates few significant differences in effects between the 5 ICS licensed for use in adults and adolescents aged >12 years, at either low or high dose. On average, budesonide dipropionate (BDP) products currently tend to be the cheapest ICS and tend to remain so as the daily ICS dose increases. Evidence shows that adding a LABA to an ICS is potentially more clinically effective than doubling the dose of ICS alone, although consistent significant differences between the two treatment strategies are not observed for all outcome measures. Cost differences between combination therapies compared with ICS monotherapy are highly variable and depend on the dose required and the preparations used. In combining ICS/LABA there are potential cost savings from using combination inhalers versus separate inhalers, with few differences in effects. The only exception to this cost saving is with budesonide and formoterol fumarate (BUD & FF) at doses above 1200 µg/day, where separate inhalers can be equivalent to or cheaper than combination inhalers. Neither of the two combination inhalers fluticasone propionate and salmeterol (FP & SAL) or BUD & FF is consistently superior in terms of treatment effect. A comparison of costs associated with each combination therapy indicates that at low dose FP & SAL delivered via a pressurized metered-dose inhaler (pMDI) is currently the cheapest combination inhaler, but only marginally cheaper than BUD & FF delivered as a dry powder inhaler (DPI). At higher doses, both the FP & SAL combination inhalers (pMDI and DPI) are marginally cheaper than BUD & FF (DPI).

Recommendations

The evidence indicates few consistent significant differences in effects between the 5 ICS licensed for use in adults and adolescents aged >12 years, at either low or high dose. On average, BDP products currently tend to be the cheapest ICS available at starting doses and to remain so as the daily ICS dose required increases. Exclusion of chlorofluorocarbon-propelled (CFC) products may increase the mean annual cost of both BDP and BUD, but should have no effect on the cost of mometasone furoate (MF), FP, or ciclesonide (CIC), as all products for these drugs are CFC-free. See Executive Summary link at www.hta.ac.uk/project/1523.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1523.asp.

Further research/reviews required

Future trials in treating chronic asthma should standardize the definition and measurement of outcome measures, with a greater focus on patient-centered outcomes (eg, HRQoL and symptoms). To inform cost-utility and cost-effectiveness analyses from a UK NHS perspective, longitudinal studies need to comprehensively track the care pathways followed when people experience asthma exacerbations of different severity. See Executive Summary link at www.hta.ac.uk/project/1523.asp. Further research synthesis, quantifying the adverse effects of the different ICS, is required for treatment choices by patients and clinicians to be fully informed.

Written by Dr Jonathan Shepherd, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/118

Title **A Randomized Controlled Multicentre Trial of Treatments for Adolescent Anorexia Nervosa Including Assessment of Cost-Effectiveness and Patient Acceptability – The Toucan Trial**

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Reference Volume 14.15, ISSN 1366-5278. www.hta.ac.uk/project/1125.asp

Aim

To evaluate the clinical and cost effectiveness of inpatient vs outpatient treatment and general (routine) treatment in Child and Adolescent Mental Health Services (CAMHS) against specialist treatment for young people with anorexia nervosa; and to determine young people's and their carers' satisfaction with these treatments.

Conclusions and results

Poor adherence to randomization limits the assessment of the treatment effect of inpatient care. This study provides little support for lengthy inpatient psychiatric treatment on clinical or economic grounds. The findings are consistent with guidelines on treating anorexia nervosa, which suggest that outpatient treatments should be offered to the majority, with inpatient treatment offered in rare cases. Our findings lend little support to a stepped-care approach that offers inpatient care to outpatient nonresponders. Outpatient care, supported by brief (medical) inpatient management to correct acute complications may be preferable. Health economic analysis and user views both support NICE guidelines, which suggest that anorexia nervosa should be managed in specialist services. Comprehensive general CAMHS might, however, be well placed to manage milder cases. Research should focus on the specific components of outpatient psychological therapies. Although family-based treatments are well established, trials have not established their effectiveness compared to good-quality individual psychological therapies. The combination of individual and family approaches is untested. Research needs to establish which patients (if any) might respond to inpatient psychiatric treatment when unresponsive to outpatient care, the positive and negative components of it, and the optimum length of stay. Of the 167 patients randomized, 65% adhered to the allocated treatment. Adherence was lower for inpatient treatment (49%) than for general CAMHS (71%) or specialist outpatient treatment (77%) ($p = 0.013$). Every subject was traced at 1 and 2 years, with the main outcome measure completed (through contact with the subject, family members, or clinicians), by 94% at 1 year, 93% at 2 years, but only 47% at 5 years. A validated outcome category was assigned for 98% at 1 year, 96% at 2 years, and 60% at 5 years. All groups improved significantly at each time point, with the number achieving a good outcome being 19% at 1 year, 33% at 2 years, and 64% at 5 years. Analysis demonstrated no difference in treatment effectiveness of randomization to inpatient vs outpatient treatment, or specialist over generalist treatment at any time point when baseline characteristics were taken into account. Generalist CAMHS treatment was slightly more expensive over the first 2 years of the study, largely because greater numbers were subsequently admitted to hospital after the initial treatment phase.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1125.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1125.asp.

Further research/reviews required

Physical and psychological risk, parental anxiety, and social and educational withdrawal often result in inpatient admission. The opportunities for intensive psychological therapies, general support, refeeding, and respite from external stresses make specialist inpatient care a logical step. Satisfaction (particularly among parents) is good.

Written by Professor Simon Gowers, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/119

Title **Continuous Positive Airway Pressure Devices for the Treatment of Obstructive Sleep Apnoea-Hypopnoea Syndrome: A Systematic Review and Economic Analysis**

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Reference Volume 13.04, ISSN 1366-5278. www.hta.ac.uk/project/1592.asp

Aim

To determine the clinical effectiveness, safety, and cost effectiveness of continuous positive airway pressure (CPAP) devices in treating obstructive apnea/hypopnea syndrome (OSAHS), compared with the best supportive care, placebo, and dental devices.

Conclusions and results

CPAP is an effective and cost-effective treatment for OSAHS compared with conservative/usual care and placebo in populations with moderate to severe daytime sleepiness, and there may be benefits when the disease is mild. Dental devices may be a treatment option in moderate disease, but some uncertainty remains. The searches yielded 6325 citations, from which 48 relevant clinical effectiveness studies were identified, 29 of which provide data on daytime sleepiness. Most of the RCTs did not report using an adequate method of allocation concealment or an intention-to-treat analysis. Only the studies using a sham CPAP comparator were double blinded. The benefit with CPAP was statistically significant compared to control (placebo and conservative treatment/usual care) on the Epworth Sleepiness Scale (mean difference [MD] –2.7 points, 95% CI –3.45 to –1.96). Statistical heterogeneity was reduced when trials were subgrouped by severity of disease. CPAP showed a significant benefit when compared to usual care on the Maintenance of Wakefulness Test. There was no statistically significant difference between CPAP and dental devices (6 trials) in the impact on daytime sleepiness (ESS) among a population with moderate symptom severity at baseline (MD –0.9, 95% CI –2.1 to 0.4). A review of 5 studies evaluating the cost effectiveness of CPAP was undertaken. All cost-effectiveness studies had limitations. Hence, a new economic model was developed. It was found that, on average, CPAP was associated with higher costs and benefits than dental devices or conservative management. The incremental cost per QALY gained of CPAP was below 20 000 pounds sterling (GBP) in the base-case analysis and most alternative scenarios. CPAP had a high probability of being more cost effective than dental devices and conservative management at a cost-effectiveness threshold of GBP 20 000 per QALY gained.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1592.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1592.asp.

Further research/reviews required

1) The expected value of further information calculated in the York economic model indicates that further research to reduce uncertainty in the current evidence base would be potentially valuable. 2) Further investigation of the effectiveness of CPAP for populations with mild sleepiness is required. 3) Further trials comparing CPAP with dental devices may be useful. 4) Further investigation of the effect of CPAP on hypertension would be beneficial, particularly with respect to what populations might be expected to benefit, as would trials adequately powered to identify changes in cardio/cerebrovascular events

Written by Dr Catriona McDaid, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/120

Title **Use of Classical and Novel Biomarkers as Prognostic Risk Factors for Localized Prostate Cancer: A Systematic Review**

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Reference Volume 13.05, ISSN 1366-5278. www.hta.ac.uk/project/1614.asp

Aim

To provide an evidence-based perspective on the prognostic value of novel markers in localized prostate cancer; to identify the best prognostic model including the 3 classical markers; and to investigate whether models incorporating novel markers are better.

Conclusions and results

This review reveals poor quality and heterogeneity of studies, which render many of the results inconclusive. Only a small share of reported models are based on patient cohorts with a mean or median follow-up of at least 5 years, making long-term predictions unreliable. Prostate-specific antigen (PSA) velocity stood out in terms of the strength of evidence supporting its prognostic value and the relatively high hazard ratios. PSA velocity is of interest as a monitoring tool for active surveillance, but no consensus exists on its use or the threshold indicating the need for radical treatment. Of the 30 papers that met the inclusion criteria, 28 reported on prognostic novel markers and 5 on prognostic models. In total, 21 novel markers were identified from the 28 novel marker studies. Findings varied widely, the quality of the studies was generally poor, and some categories had a shortage of studies. The marker with the strongest evidence for its prognostic significance was PSA velocity (or doubling time). A particularly strong association was found between PSA velocity and prostate cancer death in both clinical and pathological models. In the clinical model, the hazard ratio for death from prostate cancer was 9.8 (95% CI 2.8–34.3, $p<0.001$) in men with an annual PSA velocity above 2ng/ml versus an annual PSA velocity of 2ng/ml or less; similarly, the hazard ratio was 12.8 (95% CI 3.7–43.7, $p<0.001$) in the pathological model. The quality of the prognostic model studies was adequate and overall better than the quality of the prognostic marker studies. All of the prognostic model studies dealt poorly with inclusion of established markers and consideration of the possible biases from study attrition. Given the models' heterogeneity, they are not comparable. Two models did not include a novel marker, and one of these included several demographic and comorbidity variables to predict all-cause mortality. Two models reported a measure of model performance, the *C*-statistic, but neither calculated it in an external data set. It was not possible to assess whether the models that included novel markers performed better than those without.

Recommendations

This review highlighted the poor quality of studies and the heterogeneity between studies, rendering the results of much of this research inconclusive. Hence, it is not possible to make recommendations for service provision. See Executive Summary link at www.hta.ac.uk/project/1614.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1614.asp.

Further research/reviews required

Conducting retrospective cohort studies in an organized and scientific manner would better enable identification of the most promising prognostic markers. Many of the studies appear ad hoc and poorly designed. Specific recommendations are: 1) Data could be collected prospectively for later retrospective studies. If this is combined with storage of biopsy and pathological material, new markers could be rapidly assessed with existing long-term follow-up data. 2) Larger patient cohorts are needed. For data to be combined from different centers, the parties need to agree on common definitions of PSA and clinical disease recurrence so that outcomes are not ambiguous. 3) Analysis and reporting of prognostic marker studies must be improved, following guidelines such as REMARK.

Written by Dr Paul Sutcliffe, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/121

Title **Systematic Review of the Clinical Effectiveness and Cost Effectiveness of Oesophageal Doppler Monitoring in Critically Ill and High Risk Surgical Patients**

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Reference Volume 13.07, ISSN 1366-5278. www.hta.ac.uk/project/1633.asp

Aim

To assess the clinical and cost effectiveness of oesophageal Doppler monitoring (ODM) compared with conventional clinical assessment and other methods of monitoring cardiovascular function.

Conclusions and results

More formal economic evaluation would allow better use of the available data. All identified studies were conducted in unconscious patients. However, further research is needed to evaluate new ODM probes that may be tolerated by awake patients. Given the paucity of the economic evidence base, any further primary research should include an economic evaluation, or should provide data suitable for use in an economic model. The AHRQ report contained 8 RCTs and was judged to be of high quality overall. Four comparisons were reported: ODM plus central venous pressure (CVP) monitoring plus conventional assessment (CA) vs CVP monitoring plus CA during surgery; ODM plus CA vs CVP monitoring plus CA during surgery; ODM plus CA vs CA during surgery; and ODM plus CVP monitoring plus CA vs CVP monitoring plus CA postoperatively. Five studies compared ODM plus CVP monitoring plus CA with CVP monitoring plus CA during surgery. There were fewer deaths (Peto odds ratio [OR] 0.13, 95% CI 0.02–0.96), fewer major complications (Peto OR 0.12, 95% CI 0.04–0.31), fewer total complications (fixed-effects OR 0.43, 95% CI 0.26–0.71) and shorter length of stay (pooled estimate not presented, 95% CI –2.21 to –0.57) in the ODM group. The results of the meta-analysis of mortality should be treated with caution owing to the low number of events and low overall number of patients in the combined totals. Three studies compared ODM plus CA with CA during surgery. There was no evidence of a difference in mortality (fixed-effects OR 0.81, 95% CI 0.23–2.77). Length of hospital stay was shorter in all three studies in the ODM group. Two studies compared ODM plus CVP monitoring plus CA vs CVP monitoring plus CA in critically ill patients. The patient groups were quite different (cardiac surgery and major trauma) and neither study, nor a meta-analysis, showed a statistically significant difference in mortality (fixed-effects OR 0.84, 95% CI 0.41–1.70). Fewer patients in the ODM group experienced complications (OR 0.49, 95% CI 0.30–0.81) and both studies reported a statistically significant shorter median length of hospital stay in that group. No economic evaluations that met the inclusion criteria were identified from the literature, so a series of balance sheets was constructed. The results show that ODM strategies are likely to be cost effective.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1633.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1633.asp.

Further research/reviews required

Although modest data are available, and consideration can be given to the balance of costs and benefits using the data from the balance sheets, more formal economic evaluation would be desirable to make better use of the data and to make valuations implicit in any decision more explicit. Furthermore, well-designed, multicenter RCTs are required among high-risk surgical patients to address the following question: Does ODM-guided fluid therapy plus conventional clinical assessment improve outcome with and without CVP monitoring compared with conventional clinical assessment with and without CVP monitoring? Newer ODM probes that may be tolerated by awake patients are now manufactured and further research is needed to evaluate these.

Written by Professor Luke Vale and team, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/122

Title **The Use of Surrogate Outcomes in Model-Based, Cost-Effectiveness Analyses: A Survey of UK Health Technology Assessment Reports**

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Reference Volume 13.08, ISSN 1366-5278. www.hta.ac.uk/project/1674.asp

Aim

To explore the use of surrogate outcomes in health technology assessment (HTA) and provide a basis to guide their future use, validation, and reporting.

Conclusions and results

This report focuses on the role of surrogate outcomes in cost-effectiveness models (CEMs) in UK HTA reports. In our survey of UK HTA reports, about 10% of the CEMs were explicitly based on surrogate outcomes. The strength of evidence for the surrogate-final outcome relationship, transparency of quantification, and exploration of uncertainty of this relationship varied considerably. In total, 35 out of 200 UK HTA reports published in 2005 and 2006 addressed an effectiveness/efficacy question and contained a CEM. Of these, 4 (~10%) based their CEM on a surrogate outcome. All 4 reports sourced treatment-related changes in surrogate outcomes through a systematic review of the literature. However, there was variability in the consistency and transparency by which these reports provided evidence of the validation for the surrogate-final outcome relationship. One of the reports undertook a systematic review to specifically seek the evidence base for the association between surrogate and final outcomes. This was the only report to provide level-1 surrogate-final outcome validation evidence, ie, RCT data showing a strong association between the change in surrogate outcome (biopsy confirmed acute rejection) and the change in final outcome (graft survival) at an individual patient level. This report met the JAMA criteria for acceptable evidence of a surrogate. Two reports provided level-2 evidence, ie, observational study data showing the relationship between the surrogate and final outcome, and one report provided level-3 evidence, ie, a review of disease natural history. None of the 4 reports achieved a sufficient score on the Outcomes Measures in Rheumatology Clinical Trials (OMERACT) biomarker and surrogate schema to be judged to have 'acceptable' evidence of a surrogate outcome.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1674.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1674.asp.

Further research/reviews required

1) Given both the UK focus and the relatively small number of HTA reports with a CEM explicitly based on surrogate outcomes identified, the generalizability of the findings may be limited. This supports a more extensive survey of the use of surrogate outcomes in HTA across international jurisdictions. Consideration should be given to the role of surrogate outcomes in both the clinical- and the cost-effectiveness components of these reports. Future empirical studies need to address situations in which HTA reports may combine both surrogate and final outcomes and the validity of using surrogates across technology classes. 2) The literature review in this report identified only two empirical studies designed to quantify the potential bias associated with using surrogate outcomes. Further empirical studies need to assess potential biases in using surrogate outcomes in HTA and cost-effectiveness analyses, eg, comparing the findings of cost-effectiveness analyses based on surrogate outcomes and cost-effectiveness analyses based on final outcomes. 3) Testing of the new OMERACT surrogate scoring schema and the development of similar tools. 4) Explore the transferability of the hierarchy of evidence framework for surrogate-final outcomes to the process of mapping disease-specific outcomes to health-related quality-of-life utility in CEM analyses.

Written by Professor Rod S Taylor, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/123

Title **Spinal Cord Stimulation for Chronic Pain of Neuropathic or Ischemic Origin: Systematic Review and Economic Evaluation**

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Reference Volume 13.17, ISSN 1366-5278. www.hta.ac.uk/project/1677.asp

Aim

To address the question: What is the clinical and cost effectiveness of spinal cord stimulation (SCS) in managing chronic neuropathic or ischemic pain?

Conclusions and results

The evidence suggested that SCS was effective in reducing the chronic neuropathic pain of failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS) type I. For ischemic pain, selection criteria developed for critical limb ischemia (CLI) and SCS may have clinical benefits for refractory angina, short-term. Further trials of other types of neuropathic pain or subgroups of ischemic pain may be useful. From approximately 6000 citations identified, 11 randomized controlled trials (RCTs) were included in the clinical effectiveness review: 3 of neuropathic pain and 8 of ischemic pain. Trials were available for the neuropathic conditions of FBSS and CRPS type I, and they suggested that SCS was more effective than conventional medical management (CMM) or reoperation in reducing pain. The ischemic pain trials had small sample sizes. Trial evidence failed to demonstrate that pain relief in CLI was better for SCS than for CMM. However, it suggested that SCS was effective in delaying refractory angina pain onset during exercise at short-term follow-up, although not more so than coronary artery bypass grafting (CABG) in patients eligible for that surgery. The results for the neuropathic pain model suggested that the cost-effectiveness estimates for SCS in patients with FBSS who responded inadequately to medical or surgical treatment were below 20 000 pounds sterling (GBP) per quality-adjusted life-year (QALY) gained. In patients with CRPS who responded inadequately to medical treatment, the incremental cost-effectiveness ratio (ICER) was GBP 25 095 per QALY gained. When the SCS device costs varied from GBP 5000 to GBP 15 000, the ICERs ranged from GBP 2563 per QALY to GBP 22 356 per QALY for FBSS when compared with CMM, and from GBP 2283 per QALY to GBP 19 624 per QALY for FBSS compared with reoperation. For CRPS, the ICERs ranged from GBP 9374 per QALY to GBP 66 646 per QALY. If device longevity and device average price were varied simultaneously, ICERs were below or close to GBP 30 000 per QALY when device longevity was 3 years, and below or close to GBP 20 000 per QALY when device longevity was 4 years. Sensitivity analyses varied the costs of CMM, device longevity, and average device cost, showing that ICERs for CRPS were higher. In the ischemic model, it was difficult to determine if SCS represented value for money when evidence was insufficient to demonstrate comparative efficacy. Threshold analysis suggested that the most favorable economic profiles for treatment with SCS were when compared to CABG in patients eligible for percutaneous coronary intervention (PCI), and in patients eligible for CABG and PCI. In these two cases, SCS dominated (it cost less and accrued more survival benefits) over CABG.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1677.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1677.asp.

Further research/reviews required

Clinical effectiveness was demonstrated for SCS over CMM in reducing pain for FBSS and CRPS type I. It is unclear whether this can be generalized to other forms of neuropathic pain. Evidence from small trials failed to demonstrate that pain relief in CLI was better for SCS than for CMM, and suggested that SCS was effective in delaying angina pain onset, short-term. Trials of other types of neuropathic pain, or subgroups of ischemic pain, may be useful.

Written by Dr Emma Simpson, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/124

Title **A Systematic Review of Presumed Consent Systems for Deceased Organ Donation**

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Reference Volume 13.26, ISSN 1366-5278. www.hta.ac.uk/project/1735.asp

Aim

To examine the impact of presumed consent legislation on organ donation and to review data on attitudes to presumed consent among the public, professionals, and other stakeholders.

Conclusions and results

Presumed consent alone is unlikely to explain the variation in organ donation rates between countries. A combination of legislation, availability of donors, transplantation system organization and infrastructure, wealth and investment in health care, and underlying public attitudes to and awareness of organ donation and transplantation, may all play a role (but the relative importance of each is unclear). Further reviews could investigate the factors likely to modify donor rates, eg, procedures for family involvement. The way in which families of a potential donor are approached is likely to be important, and a review of qualitative research examining the experience of relatives in this context would be useful. Over 2000 potentially relevant citations were identified, of which 13 studies met the inclusion criteria for the primary objective and 13 for the secondary objective. For the primary objective, 8 studies were between-country comparisons and 5 were before-and-after studies. Four of the between-country comparisons were of sufficient methodological quality to provide reliable results. In all 4 studies presumed consent law or practice was associated with increased rates of organ donation, ranging from an increase of 2.7 donors per million population (pmp) in one study to 6.14 donors per million in another, and an increase of between 20% and 30% in 2 other studies. Factors other than presumed consent that had an impact on organ donation rates were: mortality from road traffic accidents and cerebrovascular accident, the transplant capacity of a country, GDP per capita and health expenditure per capita, religion, education, public access to information, and a common law legal system. The 5 before-and-after studies represented 3 countries, all of which reported an increase in donation rates following the introduction of a presumed consent system. There was limited investigation of other changes taking place concurrently with the changes in legislation across this set of studies. Of the 13 studies addressing the secondary objective, 8 were surveys of the UK public, 4 were from other countries and 1 was an international survey of health professionals. The UK surveys varied in the level of support for presumed consent, with surveys conducted before 2000 reporting the lowest levels of support (28%-57%). The most recent survey by YouGov in 2007 reported that 64% of respondents supported a change to presumed consent.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1735.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1735.asp.

Further research/reviews required

When a change in legislation occurs it is important to evaluate and monitor the impact on donor rates and other factors, eg, registration to opt out. Further reviews could investigate the factors likely to modify donor rates, eg, procedures for family involvement. The information obtained could be used to determine a priori the factors to be investigated in any evaluation of a change in legislation. Concurrently, contextual information should be gathered, eg, transplant capacity and any ongoing media campaigns. As public views about presumed consent are crucial, future surveys should carefully consider the framing of questions and be designed to minimize the strong possibility of providing what is viewed as a socially acceptable answer.

Written by Dr Amanda Sowden, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/125

Title **Psychological Interventions for Postnatal Depression – Randomized Controlled Trial and Economic Evaluation (The Ponder Trial)**

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Reference Volume 13.30, ISSN 1366-5278. www.hta.ac.uk/project/1336.asp

Aim

Primary Aim - To estimate differences in outcomes (for postnatal women, infants, and family) attributed to training health visitors (HVs) in identifying depressive symptoms and delivering a psychological intervention based on either cognitive-behavioral principles or person-centered principles in primary care at the individual level for women at risk of postnatal depression (PND). *Secondary Aim* - To establish the relative cost effectiveness of the intervention from the NHS perspective, relative to usual care (control). *Cluster level objective* - To provide intervention cluster HVs with skills to identify depressive symptoms and provide effective psychological intervention. *Individual level objectives* - To identify:

1. Women at risk of PND by the presence of depressive symptoms at 6 weeks postnatally, using the Edinburgh Postnatal Depression Scale (EPDS).
2. Women eligible (identified by two EPDS scores ≥12.) for 8 psychological intervention sessions, 1 hour per week.
3. Differences in costs for use of services in the intervention group vs control.

Secondary objectives - To: 1) Monitor change in women's health at 6, 12, and 18 months postnatally; 2) Use the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) to assess the baseline severity of depression; 3) Examine outcomes in women's partners to 18 months; 4) Measure infant development at 18 months; and 5) Follow-up the cohort of all women who consented to take part in the study.

Conclusions and results

Of 418 at-risk women with a 6-week and 6-month EPDS score, 45.6% (67/147) in the control group vs 33.9% (93/271) in the intervention group had a 6-month EPDS score ≥12. The absolute difference of 11.7% (95% CI 0.4-22.9) was statistically significant (p=0.028 adjusted for covariates). The mean EPDS score (secondary outcome) was 11.3 (SD 5.8) for control group women and 9.2 (SD 5.4) for intervention group women. The mean difference was -2.1 (95% CI -3.4 to -0.8). This difference (p=0.002) remained statistically significant after adjusting for 6-week variables (p=0.001). There was also a significant difference in the SF-12 MCS, the SF-6D, the CORE-OM Total score, the STAI, and PSI, all favoring the intervention group. For all 2659 women followed up at 6 months postnatally, 11.7% intervention group women vs 16.4% control group women had an EPDS score ≥12 at 6 months (p=0.004). The mean EPDS score was 6.4 (SD 5.2) in the control group and 5.5 (SD 4.7) in the intervention group (p=0.001).

Recommendations

The statistically significant difference between the proportion of intervention group and control group at-risk women with a 6-month EPDS score ≥12 indicated that the improvement was probably attributable to the HV training intervention. The effect on the primary outcome arose despite the small number of psychological intervention sessions accepted. The 95% CI for the observed 11.7% difference was 0.4-22.9%. The true treatment effect may be less clinically important than a 15% difference. The economic evaluation found that the HV intervention was cost effective over the HV usual care.

Methods

See Executive Summary link at www.hta.ac.uk/project/1336.asp.

Further research/reviews required

See Executive Summary link at www.hta.ac.uk/project/1336.asp.

Written by Dr Jane Morrell, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/126

Title **The Effectiveness and Cost Effectiveness of Methods of Storing Donated Kidneys from Deceased Donors: A Systematic Review and Economic Evaluation**

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Reference Volume 13.38, ISSN 1366-5278. www.hta.ac.uk/project/1699.asp

Aim

To review the evidence for the effectiveness and cost effectiveness of storing kidneys from deceased donors prior to transplantation, using cold static storage solutions or pulsatile hypothermic machine perfusion.

Conclusions and results

The conclusions drawn in comparing machine perfusion with cold storage depend on which trial data are used in the model. Due to the lack of good research evidence for the superiority of ViaSpan vs Soltran, the cheaper (Soltran) may be preferable. In the absence of a cost-utility analysis, the results of our meta-analysis of the RCTs comparing ViaSpan with Celsior indicate that these cold storage solutions are equivalent. Further RCTs may be useful in studying comparators of interest to allow for appropriate analysis of subgroups and to determine whether either of the machines produces better outcomes. Additional research needs to: establish the strength and reliability of the presumed causal association between delayed graft function (DGF) and graft, and patient survival; investigate the utility of renal replacement therapy; determine what the additional cost, survival, and QALY impacts are of decreased or increased nonviable kidneys when discarded pre transplantation; and identify a reliable measure for predicting kidney viability from machine perfusion. Eleven studies were included: 3 full journal published RCTs, 2 ongoing RCTs, 1 cohort study, 3 full journal published retrospective record reviews, and 2 retrospective record reviews published as posters or abstracts only. For LifePort vs ViaSpan, no significant differences were found for DGF, primary nonfunction, acute rejection, duration of DGF, creatinine clearance or toxicity, patient survival, or graft survival at 6 months, but graft survival was better at 12 months post transplant with machine perfusion (LifePort=98%, ViaSpan=94%, p <0.03). For LifePort versus RM3, all outcomes favored RM3, although the results may be unreliable. For ViaSpan vs Soltran, there were no significant differences in graft survival for cold ischemic times up to 36 hours. For ViaSpan vs Celsior, no significant differences were found on any outcome measure. Regarding cost effectiveness, data from the MPT suggested that machine preservation was cheaper and generated more quality-adjusted life-years (QALYs), while the PPART study data suggested that cold storage was preferable on both counts. The less reliable deterministic outputs of the cohort study suggested that LifePort would be cheaper and would generate more QALYs than Soltran. Sensitivity analyses found that changes to the differential kidney storage costs between comparators have a low impact on overall net benefits; where differences in effectiveness exist, dialysis costs are important in determining overall net benefit; DGF levels become important only when differences in graft survival are apparent between patients experiencing immediate graft function (IGF) vs DGF; relative impact of differential changes to graft survival for patients experiencing IGF vs DGF depends on the relative proportion of patients experiencing each of these two outcomes.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1699.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1699.asp.

Further research/reviews required

There is a need for: 1) sufficiently large RCTs of comparators of interest to allow for appropriate analysis of subgroups; and 2) more research to establish the strength and reliability of the presumed causal association between DGF and graft and patient survival.

Written by Mrs Mary Bond, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/127

Title **The Effectiveness and Cost Effectiveness of Cochlear Implants for Severe to Profound Deafness in Children and Adults: A Systematic Review and Economic Model**

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Reference Volume 13.44, ISSN 1366-5278. www.hta.ac.uk/project/1593.asp

Aim

To investigate the clinical and cost effectiveness of providing: 1) a unilateral cochlear implant for severely to profoundly deaf people (using or not using hearing aids), and 2) a bilateral cochlear implant for severely to profoundly deaf people with a single cochlear implant (unilateral or unilateral plus hearing aid).

Conclusions and results

The clinical effectiveness review included 33 papers, of which only 2 were RCTs. They used 62 different outcome measures and overall were of moderate to poor quality. All studies in children comparing one cochlear implant with nontechnological support or an acoustic hearing aid reported gains on all outcome measures, some demonstrating greater gain from earlier implantation. The strongest evidence for an advantage of bilateral over unilateral implantation was for understanding speech in noisy conditions (mean improvement 13.2%, p <0.0001); those receiving a second implant earlier made greater gains. Comparison of bilateral with unilateral cochlear implants plus an acoustic hearing aid was compromised by small sample sizes and poor reporting, but benefits were seen with bilateral implants. Cochlear implants improved children's quality of life, and those who were implanted before attending school were more likely to do well academically and attend mainstream education than those implanted later. Adults derived greater benefit from cochlear implants than from nontechnological support in terms of speech perception. Increased age at implantation may reduce effectiveness, and a negative correlation exists between duration of deafness and effectiveness. Speech perception measures all showed benefits for cochlear implants over acoustic hearing aids (eg, mean increase in score of 37 points in noisy conditions [p <0.001] with BKB sentences); however, prelingually deafened adults benefited less than those postlingually deafened (mean change scores 20% versus 62%). For unilateral versus bilateral implantation, benefits in speech perception were significant in noisy conditions on all measures (eg, 76% for HINT sentences [p <0.0001]). Quality of life measured with generic and disease-specific instruments or by interview mostly showed significant gains or positive trends from cochlear implants.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1593.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1593.asp.

Further research/reviews required

1) Determination of the level of residual hearing remaining before it becomes cost ineffective to provide an implant rather than an acoustic hearing aid. 2) Definition of the earliest age at which the implantation of a congenitally deaf child is safe and effective. 3) Investigation of the utility gain for children from bilateral compared with unilateral implantation. 4) Studies in children and adults enabling mapping (ie, reliable prediction) from measures of speech perception and production and hearing to validate generic utility assessment instruments. 5) Studies on employment prospects in adults or children using cochlear implants compared to employment prospects in profoundly/severely deaf people. 6) Larger studies with longer follow-up, using standard measures for outcomes and quality of life impact, and recording full data on known covariates of postimplantation speech and quality of life outcomes.

Written by Mrs Mary Bond, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/128

Title **Vitamin K to Prevent Fractures in Older Women: A Systematic Review and Economic Evaluation**

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Reference Volume 13.45, ISSN 1366-5278. www.hta.ac.uk/project/1712.asp

Aim

To determine the clinical and cost effectiveness of vitamin K in preventing osteoporotic fractures in postmenopausal women.

Conclusions and results

It is uncertain whether vitamin K1 is more cost effective than alendronate (the current first-line treatment). Literature searches identified 1078 potentially relevant articles. Of these, 14 articles met the review inclusion criteria. The articles relate to 5 trials that compared vitamin K with a relevant comparator in postmenopausal women with osteoporosis or osteopenia. The double-blind ECKO trial compared 5 mg of phylloquinone (vitamin K1) with placebo in Canadian women with osteopenia but without osteoporosis. Four open-label trials used 45 mg of menatetrenone (vitamin K2) in Japanese women with osteoporosis; the comparators were no treatment, etidronate, or calcium. The methodological quality of the ECKO trial was good, but all 4 menatetrenone trials were poorly reported, and 3 were very small (n <100 in each group). Phylloquinone was associated with a statistically significant reduction in the risk of clinical fractures relative to placebo (relative risk 0.46, 95% confidence interval [CI] 0.22 to 0.99). These data were not reported by fracture site. The smaller menatetrenone trials found an association with a reduced risk of morphometric vertebral fractures relative to no treatment or calcium. The larger Osteoporosis Fracture (OF) study found no evidence of a reduction in vertebral fracture risk. The 3 smaller trials found no significant difference between treatment groups in nonvertebral fracture incidence. These data were not reported in the OF study. In the ECKO trial, phylloquinone was not associated with an increase in adverse events. In the menatetrenone trials, adverse event reporting was generally poor. In the OF study, menatetrenone was associated with a significantly higher incidence of skin and skin appendage lesions. Since we found no published economic evaluations of vitamin K, a mathematical model was constructed to estimate the cost effectiveness of vitamin K1. Comparators were alendronate, risedronate, and strontium ranelate. Vitamin K1 and alendronate were more cost effective than either risedronate or strontium ranelate. Base-case results favored vitamin K1, but relied on many assumptions, particularly on the efficacy of preventing hip and vertebral fractures. Calculation of the expected value of sampled information assumed an RCT of 5 years' duration comparing alendronate with vitamin K1.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1712.asp.

Methods

The scope of this assessment was to determine the clinical and cost effectiveness of vitamin K in preventing osteoporotic fractures in postmenopausal women compared to no intervention or specific drugs licensed in the UK for prevention or treatment of postmenopausal osteoporosis. Relevant outcome measures included incident vertebral and nonvertebral fractures, health-related quality of life, all-cause mortality, and adverse effects of treatment.

Further research/reviews required

Further research is required to resolve uncertainty over whether vitamin K1 is more cost effective than alendronate. Calculation of the expected value of sampled information shows that an RCT of 2000 women per arm would be a cost effective use of resources.

Written by Dr Matt Stevenson, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/129

Title **Endovascular Stents for Abdominal Aortic Aneurysms: A Systematic Review and Economic Model**

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Reference Volume 13.48, ISSN 1366-5278. www.hta.ac.uk/project/1678.asp

Aim

To determine the clinical and cost effectiveness of endovascular aneurysm repair (EVAR) of infrarenal abdominal aortic aneurysms (AAAs) in patients at varying levels of risk.

Conclusions and results

Open repair is more likely to be cost effective than EVAR on average in patients considered fit for open surgery. EVAR is likely to be more cost effective than open repair in a subgroup of patients at higher risk of operative mortality. These results are based on extrapolation of midterm results of clinical trials. Evidence does not currently support EVAR in the treatment of ruptured aneurysms. Follow-up of the UK trials should be undertaken, and the relative costs of procedures and devices should be investigated further. Six RCTs were included in the clinical effectiveness review. Thirty-four studies evaluated the role of patients' baseline characteristics in predicting risks of particular outcomes after EVAR. Most were based on data from the EUROSTAR registry relating to devices in current use. Compared with open repair, EVAR reduces operative mortality (odds ratio 0.35, 95% CI 0.19 to 0.63) and medium-term, aneurysm-related mortality (hazard ratio 0.49, 95% CI 0.29 to 0.83), but offers no significant difference in all-cause mortality. EVAR is associated with increased rates of complications and reinterventions, which are not offset by any increase in health-related quality of life. EVAR trial 2 comparing EVAR with nonsurgical management in patients unfit for open repair found no differences in mortality between groups. However, many patients randomized to nonsurgical management crossed over to receive surgical repair of their aneurysm. The cost-effectiveness systematic review identified 6 published decision models. Both models considered relevant for the decision in the UK concluded that EVAR was not cost effective on average compared with open repair at a threshold of 20 000 pounds sterling (GBP) per quality-adjusted life-year (QALY). Another model concluded that EVAR would be on average more cost effective than no surgical intervention in unfit patients at this threshold. The Medtronic model concluded that EVAR was more cost effective than open repair for fit patients at this threshold. The York economic evaluations found that EVAR is not cost effective compared with open repair on average at a threshold of GBP 30 000 per QALY, with the results very sensitive to model assumptions and the baseline risk of operative mortality. Exploratory analysis to evaluate management options in patients unsuitable for open surgery suggested that the cost effectiveness of EVAR might be sensitive to aneurysm size and patient's age at operation. Indicative modeling suggests that EVAR may be cost effective for small aneurysms in some patient groups. Ongoing RCTs will provide further evidence relating to these patients.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1678.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1678.asp.

Further research/reviews required

1) Follow-up of the UK trials (EVAR trial 1, EVAR trial 2) should be undertaken. 2) The relative procedure and device costs should be investigated further. 3) Opportunities for individual patient meta-analysis of all RCTs relating to EVAR should be sought. 4) Research is needed on the rates of late complications, reinterventions, and aneurysm-related mortality after EVAR, in particular those associated with the most recent generation of devices. 5) The optimal surveillance policy following EVAR should be investigated. 6) The extent to which the relative treatment effect of EVAR on operative mortality can be assumed constant across subgroups of patients should be investigated.

Written by Mr Duncan Chambers, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/130

Title **Antiviral Drugs for the Treatment of Influenza: A Systematic Review and Economic Evaluation**

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Reference Volume 13.58, ISSN 1366-5278. www.hta.ac.uk/project/1701.asp

Aim

To assess the effectiveness and cost effectiveness of antiviral drugs in treating seasonal influenza in healthy and at-risk individuals (eg, people with lung or heart diseases, diabetes, or other health problems).

Conclusions and results

The use of neuraminidase inhibitors to treat healthy people presenting with flu symptoms is unlikely to be the most appropriate course of action during a seasonal outbreak. The systematic review combined data from 29 trials of zanamivir (relenza) or oseltamivir (tamiflu). The trials varied in quality, with completeness of follow-up an issue in many, despite the shortness of duration (up to 28 days).

The review found that, compared to placebo, zanamivir or oseltamivir reduced the time to alleviation of influenza symptoms by approximately 0.5 to 1.0 day in otherwise healthy adults. For people considered 'at risk' of influenza-related complications, the time to alleviation of symptoms was generally reduced by up to 2.0 days with zanamivir, and less than 1.0 day with oseltamivir across populations. These reductions in symptoms are relatively small in the context of the overall length of symptoms for most patients. Where larger reductions in symptom duration were observed, data were limited, and there was considerable uncertainty about the results.

Insufficient data were available from which to draw conclusions regarding the potential of either zanamivir or oseltamivir to reduce the incidence of complications, eg, bronchitis or pneumonia.

Important variations appeared in the cost-effectiveness estimates, with more favorable estimates in the at-risk populations (eg, adults and children with comorbid conditions and the elderly) compared with otherwise healthy populations. Based on cost-effectiveness considerations in each of the separate at-risk populations considered, zanamivir appeared to be the optimal treatment. In contrast, oseltamivir was considered the optimal treatment in healthy populations (both adults and children). However, the overall differences between the two antivirals, in terms of the absolute estimates of both costs and outcomes, were minor across all populations.

Recommendations

Although the evidence for clinical effectiveness in healthy and at-risk populations is similar, and the data relating to complications is lacking in both groups, it is reasonable to recommend precautionary treatment to people at increased risk of suffering influenza-related complications. Even if active management of seasonal influenza in healthy adults was deemed a public health priority, recommending the use of antiviral drugs to treat healthy people presenting with symptoms is unlikely to be the most appropriate course of action.

Methods

See Executive Summary link at www.hta.ac.uk/project/1701.asp.

Further research/reviews required

See Executive Summary link at www.hta.ac.uk/project/1701.asp.

Written by Dr Jane Burch, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/131

Title **Systematic Review of the Effectiveness and Cost Effectiveness of Weight Management Schemes for the under Fives: A Short Report**

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Reference Volume 13.61, ISSN 1366-5278. www.hta.ac.uk/project/1891.asp

Aim

To search for, review, and synthesize studies of the effectiveness and cost effectiveness of weight management schemes for the "under fives".

Conclusions and results

We found no controlled trials addressing the issue of treating obesity, or evidence of cost-effectiveness studies, in the under-five population. Apart from the larger US trial, the interventions in 3 prevention studies showed no statistically significant differences in BMI and weight between the intervention and control groups. Firm conclusions are difficult to draw, based on only 3 dissimilar studies. Further research is needed, i.e. UK-based randomized controlled trials (RCTs) of weight management schemes aimed at preventing obesity in preschool children, combined with cost-effectiveness studies with long-term follow-up. One RCT was from the UK. It measured the effects of a physical activity intervention for children in nurseries combined with home-based health education for their parents; this was compared to usual care. The main outcome measure was body mass index (BMI); secondary measures were weight and physical activity. At 12-month follow-up, no statistically significant differences were found between the groups on any measure. However, a trend favoring the intervention was found for BMI and weight. Two RCTs were from the USA. The larger trial investigated the effects of a combined preschool and home intervention in African American and Latino communities. Nutrition education and physical activity programs targeted under fives in preschool. The home component consisted of related health education and homework for parents, who received a small financial reward on completion. Compared to the results at baseline, the 1- and 2-year results for the African American sites showed a significantly slower rate of increase in BMI for the intervention group than for the control group. However, in the Latino communities no such differences were found. The second US trial was a smaller home-based parental education program in Native American communities in the USA and Canada. The intervention consisted of a course for parents to improve diet and physical activity in their children.

Recommendations

Controlled trial evidence of weight management schemes and interventions aimed at preventing obesity in the under fives is scarce. Apart from the Hip-Hop Jr trial (African American sites), it is difficult to draw conclusions from the sparse evidence from prevention studies, since the interventions showed no statistically significant differences in BMI and weight between the intervention and control groups.

Methods

See Executive Summary link at www.hta.ac.uk/project/1891.asp.

Further research/reviews required

Further research is urgently needed, in particular: 1) well-designed, UK-based RCTs of weight management schemes aimed at preventing obesity, which combine with cost-effectiveness studies targeted at preschool children (under fives) with long-term follow-up (>12 months). 2) Well-designed UK-based RCTs of weight management schemes that address the issue of treating overweight and obesity in the under fives, which combine with cost-effectiveness studies targeted at preschool children (under fives) with long-term follow-up (>12 months).

Written by Mrs Mary Bond, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/132

Title **Bevacizumab, Sorafenib Tosylate and Sunitinib for Renal Cell Carcinoma: A Systematic Review and Economic Evaluation**

Agency **NETSCC, HTA, NIHR Evaluation and Trials Coordinating Centre**
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Reference Volume 14.02, ISSN 1366-5278. www.hta.ac.uk/project/1711.asp

Aim

To assess the clinical effectiveness and cost-effectiveness of bevacizumab, combined with interferon (IFN), sorafenib tosylate, sunitinib and temsirolimus in the treatment of people with advanced and/or metastatic renal cell carcinoma (RCC).

Conclusions and results

Treatment with bevacizumab plus IFN and sunitinib has clinically relevant and statistically significant advantages over treatment with IFN alone in patients with metastatic RCC. In people with three of six risk factors for poor prognosis, temsirolimus had clinically relevant advantages over treatment with IFN, and sorafenib tosylate was superior to best supportive care as second-line therapy. The frequency of adverse events associated with bevacizumab plus IFN, sunitinib and temsirolimus was comparable with that seen with IFN, although the adverse event profile is different. Treatment with sorafenib was associated with a significantly increased frequency of hypertension and hand–foot syndrome. Estimates from the PenTAG model suggested that none of the interventions would be considered cost-effective at a willingness-to-pay threshold of 30 000 pounds sterling (GBP) per QALY. A total of 888 titles and abstracts were retrieved in the clinical effectiveness review, including reports of eight clinical trials. Treatment with bevacizumab plus IFN or sunitinib had clinically relevant and statistically significant advantages over treatment with IFN alone, in terms of progression-free survival and tumor response, doubling median progression-free survival from approximately 5 months to 10 months. Temsirolimus had similar advantages over treatment with IFN in terms of progression-free and overall survival, increasing median overall survival from 7.3 to 10.9 months [hazard ratio (HR) 0.73; 95% confidence interval (CI) 0.58 to 0.92)], as did sorafenib in comparison with best supportive care in terms of overall survival, progression-free survival and tumor response, with a doubling of progression-free survival (HR 0.51; 95% CI 0.43 to 0.60). However, the last was associated with an increased frequency of hypertension and hand–foot skin reaction compared with placebo. No fully published economic evaluations of any of the interventions could be located. However, estimates from the PenTAG model suggested that none of the interventions would be considered cost-effective at a willingness-to-pay threshold of 30 000 GBP per quality-adjusted life-year (QALY). Estimates of cost per QALY ranged from 71 462 GBP for sunitinib to 171 301 GBP for bevacizumab plus IFN. Although there are many similarities in the methodology and structural assumptions employed by PenTAG and the manufacturers of the interventions, in all cases the cost-effectiveness estimates from the PenTAG model were higher than those presented in the manufacturers' submissions. Cost-effectiveness estimates were particularly sensitive to variations in the estimates of treatment effectiveness, drug pricing (including dose intensity data), and health-state utility input parameters.

Recommendations

For further details see Executive Summary link at www.hta.ac.uk/project/1711.asp.

Methods

For further details see Executive Summary link at www.hta.ac.uk/project/1711.asp.

Further research/reviews required

There are clear gaps in the evidence base needed to fully appraise the clinical effectiveness and cost-effectiveness of these four interventions in accordance with their marketing authorizations: More randomized clinical trials in the following areas would be useful: in patients unsuitable for treatment with IFN because of contraindications or who have been defined as having intermediate and poor prognosis and therefore unlikely to benefit from IFN; studies of sorafenib tosylate, sunitinib, bevacizumab plus IFN and best supportive care; and comparative trials of sunitinib and sorafenib as second-line therapy. For further details see Executive Summary link at www.hta.ac.uk/project/1711.asp.

Written by Professor Ken Stein, NETSCC, United Kingdom

Title **Methodology for Prevention and Management of Safety Incidents in Critical Care**

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Reference Serie de Cuadernos N°32.
www.redsalud.gov.cl/portal/url/item/82b5ac0d167304f5e040010110e017382.pdf

Aim

To systematize the risk management tools (described in the literature) for continuous improvement processes of care in health facilities so as to contribute to a culture of safety in care.

Conclusions and result

Clinical risk management and the systematization of safety of care are relatively new areas in the planning of health systems. The transfer of these techniques and technologies from the industrial sector is not yet reflected in research and results on methodological quality. Two different methodologies for retrospective or prospective analyses of critical events have been selected and recommended. Good quality evidence is not available to inform management practices.

Recommendations

The London Protocol is recommended for retrospective analysis of incidents. It contains elements of root cause analysis, but focuses on the organization as a whole. Incidents are viewed as more systemic and not as having a unique cause. Modal Analysis and Effects (FMEA) is recommended for prospective analysis. This technique places the emphasis on the prevention of errors that may occur, hypothetically, in the process of patient care.

Methods

The systematic search aimed to identify health technology assessment reports and systematic literature reviews that describe and evaluate implementation of the risk management techniques used in industry, and their subsequent application in the health field. Databases searched for 2007 through 2009 were: DARE, Cochrane Library, Tripdatabase, and LILACS.

Written by Luis Vera, Patricia Kraemer, ETESA, Chile

INAHTA Briefs

Issue 2010/134

Title **Axiom DRX 9000-True Non-Surgical Spinal Decompression System**

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Reference Technology Review Report, 007/09.
http://medicaldev.moh.gov.my/uploads/tr_2009/drx9000.pdf

Aim

To determine the safety, effectiveness, and cost effectiveness of a nonsurgical spinal decompression system.

Conclusions and results

Only limited evidence is available to warrant the routine use of the DRX9000 nonsurgical spinal decompression system. The retrieved evidence is inconclusive due to conflicting results from the randomized controlled trials in the systematic review and the low level of evidence from the phase II nonrandomized controlled trial and audit chart. This may be due, in part, to heterogeneous patient groups and the difficulties involved in properly blinding patients to the mechanical pulling mechanism. Scientifically more rigorous studies with better randomization, control groups, and standardized outcome measures are needed to overcome the limitations of past studies.

Recommendations

The evidence was insufficient to support safety and effectiveness. However, the potential for the DRX9000 nonsurgical decompression system looks promising. Further prospective clinical studies are needed to validate clinical and radiographic improvement in patients with chronic low back pain. In view of the above, the DRX9000 nonsurgical decompression system can be recommended only for research purposes.

Methods

A systematic review was conducted. PubMed, Ovid, and MEDLINE were searched using the following keywords: low back pain, mechanical or motorized traction, traction, treatment outcome, nonsurgical spinal decompression, Decompression Therapy System (DTS), DRX 9000, VAX-D, effectiveness, and adverse events either singly or in combination. The search was limited to human studies published from 2000 through 2008. In addition, the websites of HTA agencies and societies were searched, and the articles retrieved were cross-referencing according to the topic. Although 30 articles were retrieved from the search, only 4 studies (1 systematic review, 1 narrative review, 1 pilot study, and 1 retrospective chart audit) were included in this review.

Further research/reviews required

Further prospective clinical studies are needed to validate clinical and radiographic improvement in patients with chronic low back pain. To acquire better quality evidence, more clinical trials are warranted in this area.

Written by Noormah Mohd Darus, MaHTAS, Malaysia

INAHTA Briefs

Issue 2010/135

Title **Bevacizumab for 1. Age-related Macular Degeneration 2. Diabetic Retinopathy**

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Reference Health Technology Assessment Report, MOH/P/PAK/194.09(TR).
www.moh.gov.my/health_assesments/61

Aim

To undertake a systematic review of the effectiveness, safety, and cost effectiveness of bevacizumab in treating age-related macular degeneration (AMD) and diabetic retinopathy (DR).

Conclusions and results

The evidence suggests that bevacizumab is effective in treating AMD. However, the evidence was only of poor to fair quality, and the studies were of short duration. Fair evidence showed that bevacizumab was more effective compared to verteporfin photodynamic therapy for patients with minimally classic or occult choroidal neovascularization due to AMD.

Poor- to good-quality evidence was retrieved on the efficacy of bevacizumab for diabetic retinopathy. Good evidence showed that bevacizumab was more efficacious in patients with clinically significant diabetic macular edema compared to macular photocoagulation or combined therapy with intravitreal triamcinolone. Good evidence showed that bevacizumab treatment given after phacoemulsification and intraocular lens implantation reduced diabetic retinopathy progression. Fair evidence suggested that preoperative treatment with bevacizumab was beneficial for patients undergoing pars plana vitrectomy.

There was evidence to show that bevacizumab was more cost effective, compared to other treatment modalities, in managing AMD. There was no evidence on the cost effectiveness of bevacizumab for DR. Also, there was evidence to support the safety of bevacizumab in managing AMD and DR, but caution should be taken with high-risk patients.

Recommendations

Intraocular bevacizumab can be used selectively in patients with predominantly classic, minimally classic, or occult choroidal neovascularization due to AMD, and in patients with diabetic macular edema. However, caution needs to be taken in high-risk patients with a history of ischemic heart disease or thromboembolic events.

Methods

Electronic databases were searched for published literature addressing the use of intravitreal bevacizumab in treating AMD and DR. The databases searched included MEDLINE, PubMed, EBM Reviews-Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, HTA Databases, EBM Reviews-NHS Economic Evaluation Database, and DARE. Additional articles were identified from reviewing the bibliographies of retrieved articles and hand searching of journals. Further information was sought from unpublished reports. The search was limited to human studies. Quality of the papers was assessed using checklists from the Critical Appraisal Skills Programme (CASP), and evidence was graded according to US/Canadian Preventive Services Task Force Levels of Evidence.

Further research/reviews required

More clinical research is warranted for other indications, eg, proliferative diabetic retinopathy.

Written by Izzuna MMG, MaHTAS, Malaysia

INAHTA Briefs

Issue 2010/136

Title **Intraocular Lens (IOL) Implantation Hydrophilic Acrylic Versus Hydrophobic Acrylic**

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Reference Health Technology Assessment Report, MOH/P/PAK/193.09/ (TR).
www.moh.gov.my/health_assesments/59

Aim

To assess the safety of commonly used foldable IOLs (hydrophilic acrylic and hydrophobic acrylic IOL implants)

Conclusions and results

Poor- to fair-level evidence suggested that the incidence of IOL opacification affecting vision was reported only with hydrophilic acrylic IOL and not with hydrophobic acrylic IOL. IOL opacification of hydrophilic acrylic IOL was caused by deposition of calcium and phosphate on the IOL surface, or within the optic material, or both (on the surface and within the IOL material) depending on the designs of the hydrophilic acrylic IOL. The pathophysiology of the causes of such complications has not been fully described. Diabetic patients appeared to be affected more often and more severely by IOL opacification.

Recommendations

Based on the above review, we recommend the use of hydrophobic acrylic IOLs. Patients who had hydrophilic acrylic IOLs implantation need longer and more frequent follow-up, particularly in the presence of predisposing factors such as diabetes. In view of the absence of a Medical Device Act in Malaysia, an incident-reporting mechanism for IOL opacification, irrespective of materials and designs, needs to be established to provide more information on IOL opacification locally.

Methods

Electronic databases were searched, eg, MEDLINE, PubMed, EBM Reviews-Cochrane Database of Systematic Reviews, EBM Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-HTA databases, FDA website, and MHRA. No limitations were placed on the search. All relevant literature was appraised using the Critical Appraisal Skills Programme (CASP), and evidence was graded based on guidelines from US/Canadian Preventive Services Task Force. Nineteen full-text articles were included (6 cross-sectional studies, 6 case series, 5 case reports, 1 laboratory experimental study, and US FDA approval for premarketing of hydrophilic and hydrophobic IOLs). The search did not yield any health technology assessment reports, systematic reviews, or RCTs related to the safety of hydrophilic and hydrophobic IOLs.

Further research/reviews required

Incident reporting for IOL opacification irrespective of materials and designs.

Written by Dr Junainah Sabirin, MaHTAS, Malaysia

INAHTA Briefs

Issue 2010/137

Title **School Scoliosis Screening Program**

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Reference Health Technology Assessment Report, MOH/P/PAK/186.09 (TR).
www.moh.gov.my/health_assesments/58

Aim

To assess the effectiveness and economic implications of a school scoliosis screening program.

Conclusions and results

Females achieve adolescence 2 years before males and are afflicted with scoliosis 3 to 4 times more frequently than males. The prevalence of scoliosis was higher in girls compared to boys. Prevalence rates for girls were low at 6 to 10 years of age, but increased rapidly from 11 to 14 years of age.

Fair-level evidence suggested that a school scoliosis screening program was able to detect scoliosis at a younger age and with smaller Cobb angle, and could reduce the frequency of surgical treatment. The cost of screening a child ranged from 0.066 US dollars (USD) to USD 43.7 depending on how it was calculated. Evidence also showed that a school scoliosis screening program was cost-effective.

Fair-level evidence suggested that Adams forward-bending test, measurement of angle of trunk rotation using a scoliometer, measurement of rib hump height using humpometer, and Moire topography can be used as tests for scoliosis screening in schools. The tests are not time consuming. However, the Adams forward-bending test may result in high false negatives, which may lead to misdiagnosis, while the use of other screening tests such as scoliometer, Moire topography, and humpometer may lead to high false positives and will cause overreferrals. Few studies have suggested that cutoff limits for referrals, eg, asymmetry of two Moire fringes, a humpogram deformity = 10 mm, and 7° or 8° of scoliometer angle, would lead to a reduction in the number of referrals for radiographic examination.

Evidence showed that radiographic examination for scoliosis follow-up was safe. Proper training of the staff involved in screening is necessary, as is a good referral and follow-up system based on ethical and organizational considerations.

Recommendations

Based on the above review, screening for scoliosis in school children is recommended only for high-risk groups, eg, girls at 12 years or age (standard six). A combination of modalities of screening tests, eg, Adams forward-bending test and scoliometer with angle of trunk rotation of 7°, is recommended with the aim to reduce the number of referrals. Organizational issues, eg, training, manpower, good referral system, treatment, and funding need to be addressed at all levels.

Methods

We searched, eg, MEDLINE, PubMed, EBM Reviews-Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, HTA databases, EBM Reviews-NHS Economic Evaluation Database, EBM Full Text-Cochrane DSR, ACP Journal Club, and DARE. No limitations were placed on the search. Relevant literature was appraised using the Critical Appraisal Skills Programme (CASP), and evidence was graded according to US/Canadian Preventive Services Task Force, or hierarchy of evidence for test accuracy studies, CRD Report No. 4 (2nd Edition). One case control study, 1 before-and-after study, and 19 cross-sectional studies were included.

Further research/reviews required

Cost effectiveness of selective screening.

Written by Dr Junainah Sabirin, MaHTAS, Malaysia

INAHTA Briefs

Issue 2010/138

Title **Colon Hydrotherapy-An Update**

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Reference Technology Review Report, 012/2009.
http://medicaldev.moh.gov.my/uploads/tr_2009/colon.pdf

Aim

To assess the safety, effectiveness, and cost effectiveness of colon hydrotherapy for body detoxification, constipation, irritable bowel syndrome, and diverticulosis.

Conclusions and results

The search strategies yielded 2 articles on the U.S. Food and Drug Administration (FDA) premarket notifications for devices used in colon cleansing and 1 article issued by the Texas Attorney General. Seven articles (case series/case report/cross sectional studies) related to the adverse events of colon hydrotherapy. As for effectiveness, 1 technology review and 3 cross sectional studies were retrieved.

In the United States, the FDA approves treatments for patients only when medically indicated, eg, prior to undergoing radiologic or endoscopic examination.

There was poor level of evidence to suggest that commercial colonic hydrotherapy performed by individuals themselves or by alternative medicine practitioners may lead to adverse events such as colon or rectal perforations, abscess, perineal gangrene, abdominal pain, abdominal cramps, distended abdomen, rectal bleeding, outbreaks such as amoebiasis and death.

There was poor-level and insufficient evidence to suggest the effectiveness of colon hydrotherapy for constipation, irritable bowel syndrome, and fecal incontinence. There was no retrievable evidence on the cost effectiveness of colon hydrotherapy. Experienced and trained practitioners should perform colon hydrotherapy, and the practice should be regulated.

Recommndations

Based on the review, more high-quality clinical research is warranted for various application of this technology in different conditions, eg, constipation, irritable bowel syndrome, and fecal incontinence. Hence, commercial use of colon hydrotherapy when not medically indicated cannot be recommended until more high-quality evidence is available.

Methods

Electronic databases, including PubMed, Ovid MEDLINE from 1950 to May (2nd week) 2009, EBM Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Cochrane database of systematic reviews, EBM Reviews-HTA Databases, Horizon Scanning database (EuroScan, Australia and New Zealand Horizon Scanning, defra), FDA website, MHRA, and Google, were searched for published reports. No limits were placed on the search. Relevant articles were critically appraised using the Critical Appraisal Skills Programme (CASP) and were evidence graded using US / Canadian Preventive Services Task Force.

Further research/reviews required

More clinical research is warranted for various applications of this technology.

Written by Dr Junainah Sabirin, MaHTAS, Malaysia

Title **Parting Laser Perforator**

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Reference Technology Review Report, 011/2009.
http://medicaldev.moh.gov.my/uploads/tr_2009/parting%20laser.pdf

Aim

To assess the safety, effectiveness, and cost effectiveness of Biomed Parting Laser Perforator.

Conclusions and results

Limited evidence indicated that Biomed Parting Laser Perforator, Model: TZD-CX-100Y and other brands of laser skin perforators are safe. Limited evidence indicated an insignificant difference between laser skin perforators and stainless steel lancet as regards pain, convenience, and methods of preference.

No evidence was retrievable on the effectiveness of Biomed Parting Laser Perforator, Model: TZD –CX-100Y for collection of capillary blood samples. However, as regards other laser skin perforators, limited evidence showed that they are as effective as a stainless steel lancet for obtaining capillary blood in patients with diabetes. From the retrievable evidence, the results showed no significant difference between capillary blood obtained for glucose and hematocrit testing using the two methods. However, estimates of the potassium level in capillary blood obtained using laser skin perforator were not reliable. No evidence was retrievable on the cost effectiveness of Biomed Parting Laser Perforator, Model: TZD –CX-100Y or other brands of laser skin perforators.

Recommendations

Based on the review, more clinical research is warranted for this technology. Laser skin perforators do not seem to be superior compared to the conventional lancet in obtaining capillary blood. Hence, they cannot be recommended for routine use.

Methods

Electronic databases, including PubMed, MEDLINE from 1950 to 2009 (week 4), EBM Reviews-Cochrane Central Register of Controlled Trials, EBM Review-Cochrane database of systematic reviews, HTA Databases, Horizon Scanning database (EuroScan, Australia and New Zealand Horizon Scanning), FDA website, MHRA, and Google, were searched for published reports. Relevant articles were critically appraised and evidence graded using US/Canadian Preventive Services Task Force.

Further research/reviews required

More clinical research is warranted.

Written by Dr Junainah Sabirin, MaHTAS, Malaysia

Title MedicLaser +TinniTool®

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Reference Technology Review Report, 010/2009.
http://medicaldev.moh.gov.my/uploads/tr_2009/tinnitool.pdf

Aim

To determine the safety, effectiveness, and cost effectiveness of MedicLaser + TinniTool®.

Conclusions and results

The product is CE marked. However, there was no retrievable evidence on its clinical safety. This review includes only two studies (RCT), but a contradiction was found between the studies in analyzing the mean of delta Tinnitus Handicap Inventory scores in both the experimental group and the control group. Hence, the evidence on effectiveness was inconclusive. There was no retrievable evidence on cost effectiveness.

Recommendations

The device is not recommended for routine use. However, it can be considered for use as a research tool to produce more evidence on its clinical safety and effectiveness.

Methods

Electronic databases, which included MEDLINE, EMBASE, and Horizon Scanning were searched, as were the websites of the manufacturer, the European Commission's Medical Devices Sector, and the Food and Drug Administration. The Malaysian agency for devices was contacted for relevant regulatory affair certificates. Finally, a manual literature search was conducted via the manufacturer's list of literature. No limits were placed on the search. All published clinical trials were included. Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and evidence was graded using US/Canadian Preventive Services Task Force.

Further research/reviews required

More clinical trials are warranted.

Written by Dr Junainah Sabirin, MaHTAS, Malaysia

Title **Electrical Impedance Tomography (EIT) in Breast Cancer Screening**

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Reference Technology Review Report, 006/09.
http://medicaldev.moh.gov.my/uploads/tr_2009/eit_1.pdf

Aim

To assess the effectiveness, safety, and cost effectiveness of electrical impedance tomography in screening for breast cancer

Conclusions and results

Only one cross-sectional study and one Technology Review were retrieved for this review. The evidence was insufficient to support effectiveness, and no evidence was retrieved on the safety and cost effectiveness of electrical impedance tomography in screening for breast cancer.

Recommendations

Electrical impedance tomography is not recommended until more evidence becomes available to support its effectiveness, safety, and cost effectiveness in screening for breast cancer.

Methods

The literature searched of electronic databases included PubMed/MEDLINE, Cochrane, and INAHTA, and used the following search terms: "breast cancer", "electrical impedance tomography", and "electrical impedance mammography". In the PubMed/MEDLINE database, the search was limited to publications from the past 3 years, in humans, and in English. The retrieved papers were critically appraised and the evidence level was graded according to the US/Canadian Preventive Services Task Force.

Further research/reviews required

More clinical research is warranted on the device.

Written by Yusof MAM and Bakri R, MaHTAS, Malaysia

Title e-Membrane

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Reference Technology Review Report, 025/09.
http://medicaldev.moh.gov.my/uploads/tr_2009/e-membrane.pdf

Aim

To assess the safety, effectiveness, and cost effectiveness of e-membrane.

Conclusions and results

No retrievable scientific evidence was found on the safety, effectiveness, or cost effectiveness of using this technology as an application for filters, scaffolds for tissue engineering, protective clothing, reinforcement in composite materials, or sensors.

Recommendations

Based on the retrieved evidence, clinical research is warranted on safety and effectiveness of this technology.

Methods

The search of electronic databases included PubMed, Cochrane DSR, Journal @ Ovid full text, and CINAHL via OVID search engine. A general search was also conducted using Google. Although the distributor was contacted to provide any available scientific evidence, the representative failed to provide any reports by the time this report was written. No limitations were placed on the publication year or language.

Further research/reviews required

More clinical research is warranted.

Written by LT Sin, MaHTAS, Malaysia

Title	**Sinomarin**
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Reference	Technology Review Report, 009/09. http://medicaldev.moh.gov.my/uploads/tr_2009/Sinomarin.pdf

Aim

To assess the safety, effectiveness, and cost effectiveness of using Sinomarin® for nasal, ear cleansing, and post-operative irrigation.

Conclusions and results

Only three abstracts of clinical trials were retrieved that addressed the effectiveness of using Sinomarin® or hypertonic seawater solution for nasal cleansing and postoperative nasal irrigation. The results of the clinical trials were inconclusive.

The evidence was insufficient to show the effectiveness of using Sinomarin® for nasal cleansing and postoperative nasal irrigation. No retrievable evidence was available on the safety and cost effectiveness of the device. Likewise, there was no retrievable evidence to show the effectiveness and safety of using Sinomarin® for ear cleansing or postoperative ear irrigation.

Recommendations

Not recommended until more evidence is available.

Methods

Scientificelectronicdatabasessearchedwere:MEDLINE, PubMed, Cochrane Database of Systematic Reviews, INAHTA, Horizon Scanning, and the FDA website. We contacted (via email) the authors of the abstracts retrieved. Only studies on Sinomarin® or hypertonic seawater solution were selected for the review.

Further research/reviews required

None

Written by Haarathi Chandriah, MaHTAS, Malaysia

Title **StopBleed M.DOC™**

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Reference Technology Review Report, 008/09.
http://medicaldev.moh.gov.my/uploads/tr_2009/stopbleed.pdf

Aim

To determine the safety, effectiveness, and cost effectiveness of StopBleed M.DOC™ as a hemostatic agent.

Conclusions and results

StopBleed M.DOC™ is a product containing M.DOC or microdispersed oxidized cellulose, which is a hemostatic substance that stops bleeding from minor wounds, grazes, and nosebleeds. The StopBleed M.DOC™ product range consists of nasal plugs, spray, powder, plaster, and blotters. No evidence was retrieved on StopBleed M.DOC™ products. All information is based on summary articles provided by KAJ Biomedic (M) Sdn. Bhd. Only one abstract was retrieved on the mechanism of M.DOC as a hemostatic agent. Hence, there is insufficient evidence on safety and effectiveness and no retrievable evidence on the cost effectiveness of StopBleed M.DOC™ as a hemostatic agent.

Recommendations

Not recommended for use as a hemostatic agent.

Methods

Scientific electronic databases searched included: PubMed, Proquest, EBSCO Host, MEDLINE, CINAHL, Science Direct, Cochrane database of systematic reviews, HTA databases, Horizon scanning databases, and the FDA website.

Further research/reviews required

Research is required to determine effectiveness and safety of StopBleed M.DOC.

Written by Haarathi Chandriah, MaHTAS, Malaysia

Title AGT-1 Liquid Glove (AGT)

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Reference Technology Review Report, 001/2009.
http://medicaldev.moh.gov.my/uploads/tr_2009/agt.pdf

Aim

To determine the safety, efficacy, effectiveness, and cost of AGT-1 Liquid Glove as a disinfectant against microorganisms that cause nosocomial infections at hospitals.

Conclusions and results

Fair evidence on the safety aspect of AGT-1 Liquid Glove was described by experimental laboratory studies. A sufficient number of efficacy studies were conducted on AGT-1 Liquid Glove, but the level of evidence is low as the studies were mainly laboratory experiments. No evidence was retrieved to support the effectiveness of AGT-1 Liquid Glove.

Recommendations

AGT-1 Liquid can be recommended only for research purposes. Since the product is comparatively more expensive, the cost implications of using AGT-1 Liquid Glove must be considered against the alcohol-based disinfectants currently used in Ministry of Health hospitals.

Methods

This review was based on 3 published laboratory experiments, 5 research notes on laboratory experiments, 1 laboratory experiment on animals, and 3 reviews.

Further research/reviews required

A clinical trial to show the effectiveness of AGT-1 Liquid Glove is required.

Written by Mariammah K, MaHTA, Malaysia

INAHTA Briefs

Issue 2010/146

Title **Computerized Upper and Lower Extremity Evaluation and Exercise System Complete With Computer (E-Link)**

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Reference Technology Review Report, 003/09.
http://medicaldev.moh.gov.my/uploads/tr_2009/elink.pdf

Aim

To determine the safety, effectiveness, and cost effectiveness of Computerized Upper and Lower Extremity Evaluation And Exercise System Complete With Computer (E-Link) for disorders of upper and lower extremities.

Conclusions and results

No evidence was retrieved on the safety, effectiveness, or cost effectiveness of E-link.

Recommendations

Until more evidence can be obtained, E-link is not recommended for evaluation of disorders/injuries and exercise of upper and lower extremities.

Methods

The literature search included the following electronic databases: MEDLINE via Ovid, PubMed, Cochrane Library, and general databases such as Google and Yahoo. Key words included E-link OR "Computerized upper and lower extremity evaluation and exercise system", effectiveness OR efficacy, safety OR safe OR, "adverse effect*" OR "harm* effect*", "cost effectiveness" OR "cost analysis" OR econom*. No limitations were placed on the search.

Further research/reviews required

Further research is required.

Written by Izzuna MMG, MaHTAS, Malaysia

Title **High Focused Ultrasound (HIFU)-Albatherm® for Prostate Cancer**

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Reference Technology Review Report, 004/09.
http://medicaldev.moh.gov.my/uploads/tr_2009/hifu.pdf

Aim

To determine the safety, effectiveness, and cost effectiveness of high intensity focused ultrasound (HIFU) Albatherm® in treating prostate cancer.

Conclusions and results

The most common complications noted in studies of case series were stress urinary incontinence, urinary tract infection, urethral/bladder neck stenosis or strictures, and erectile dysfunction. The rate of these complications appears to have been reduced with Albatherm® because of technical improvements in the device.

No randomized trials are available on Albatherm® HIFU in the treatment of prostate cancer. All of the evidence on the effectiveness of primary treatment, or even salvage therapy, came from reports of case series or observational studies.

No evidence supports the cost effectiveness of HIFU in treating prostate cancer.

Recommendations

HIFU can be used in a research setting, but is not recommended for standard clinical practice.

Methods

The electronic database search for published reports included: PubMed, ProQuest, EBSCO Host, MEDLINE, CINAHL, Cochrane database of systematic reviews, HTA Databases, Horizon scanning databases (EUROSCAN), and the FDA website. Additional articles were identified by reviewing the bibliographies of retrieved articles.

The search strategy used the following terms, either alone or in various combinations: "high intensity focused ultrasound", HIFU, "prostate cancer", transrectal, therapeutic ultrasound, effective*, safe*, side effects, cost*.

All published articles (primary and secondary research) relating to the safety, effectiveness, and cost effectiveness of only the Albatherm® HIFU were reviewed.

Further research/reviews required

More research is warranted.

Written by Izzuna MMG, MaHTAS, Malaysia

Title **Shockwave Therapy System for Musculoskeletal Disorders**

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Reference Technology Review Report, 002/09.
http://medicaldev.moh.gov.my/uploads/tr_2009/shockwave.pdf

Aim

To determine the safety, effectiveness, and cost effectiveness of shock wave therapy systems in rehabilitating musculoskeletal disorders, specifically for elbow pain, shoulder calcific tendinitis, and heel pain.

Conclusions and results

The evidence was sufficiently strong to support the effectiveness of shock wave therapy in treating shoulder calcific tendinitis. Evidence also showed that extracorporeal shockwave therapy (ESWT) is more cost effective compared to surgery for shoulder calcific tendinitis. However, evidence remains inconclusive as regards the effectiveness of ESWT in treating lateral elbow pain. ESWT for heel pain appears to offer only marginal gains over placebo or other therapy. Evidence also showed that ESWT is a safe treatment. Minor side effects were reported with high-energy ESWT, but all of the side effects were self-limiting.

Recommendations

Shock wave therapy is recommended for treating shoulder calcific tendinitis. As for other clinical indications, more clinical research is warranted to establish its effectiveness. However, the limited scope of the evidence does not lend support towards purchasing shock wave therapy systems to treat just one specific condition for which conservative and surgical treatment options are already available locally.

Methods

The literature search of electronic databases included: MEDLINE, Cochrane Library, Science Direct, and general databases, eg, Google and Yahoo.

The search strategy used the following terms, either alone or in various combinations:

(shock wave therapy OR shockwave therapy OR extracorporeal shockwave therapy OR ESWT) AND (musculoskeletal disorders OR MSK OR musculoskeletal OR lateral epicondylitis OR tennis elbow OR plantar fasciitis OR heel pain OR shoulder calcific tendonitis OR shoulder calcific tendinitis). The search was limited to articles on humans. No language limitations were imposed on the search. A critical appraisal of all relevant literature was performed using Critical Appraisal Checklist Project (CASP) checklists, and the evidence was graded according to the US/Canadian Preventive Services Task Force Level of Evidence (2001).

Further research/reviews required

None.

Written by Izzuna MMG, MaHTAS, Malaysia

INAHTA Briefs

Issue 2010/149

Title **Systematic Review of the Clinical Effectiveness and Cost Effectiveness of Photodynamic Diagnosis and Urine Biomarkers (FISH, Immunocyt, NMP22) And Cytology for the Detection and Follow-Up of Bladder Cancer**

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Reference Volume 14.04. ISBN 1366-5278. www.hta.ac.uk/project/1713.asp

Aim

To assess the clinical and cost effectiveness of photodynamic diagnosis (PDD) compared to white light cystoscopy (WLC), urine biomarkers (fluorescence in situ hybridization [FISH], ImmunoCyt, NMP22), and cytology in detecting and following-up bladder cancer.

Conclusions and results

The advantages of PDD's higher sensitivity in detecting bladder cancer must be weighed against the disadvantages of a higher false-positive rate. Taking into account the assumptions in the model, strategies involving biomarkers and/or PDD provide additional benefits at a cost that society might be willing to pay. Strategies replacing WLC with PDD provide more life-years, but it is unclear whether they are worth the extra cost. In total, 27 studies reported PDD test performance. In pooled estimates (95% confidence interval [CI]) for patient-level analysis, PDD had higher sensitivity than WLC (92% [80% to 100%] versus 71% [49% to 93%]), but lower specificity (57% [36% to 79%] versus 72% [47% to 96%]). Similar results were found for biopsy-level analysis. The median sensitivities (range) of PDD and WLC for detecting lower risk, less aggressive tumors were similar for patient-level detection (92% [20% to 95%] versus 95% [8% to 100%]), but sensitivity was higher for PDD than for WLC in biopsy-level detection (96% [88% to 100%] versus 88% [74% to 100%]). For more aggressive, higher-risk tumors the median sensitivity of PDD for both patient-level (89% [6% to 100%]) and biopsy-level (99% [54% to 100%]) detection was higher than those of WLC (56% [0% to 100%] and 67% [0% to 100%] respectively). Four RCTs comparing PDD with WLC reported effectiveness outcomes. PDD use at transurethral resection of bladder tumor resulted in fewer residual tumors at check cystoscopy (relative risk, RR, 0.37 [95% CI 0.20 to 0.69]) and longer recurrence-free survival (RR 1.37 [95% CI 1.18 to 1.59]) compared with WLC. In 71 studies reporting the performance of biomarkers and cytology in detecting bladder cancer, sensitivity (95% CI) was highest for ImmunoCyt (84% [77% to 91%]) and lowest for cytology (44% [38% to 51%]), whereas specificity was highest for cytology (96% [94% to 98%]) and lowest for ImmunoCyt (75% [68% to 83%]). In the cost-effectiveness analysis, the most effective strategy in terms of true positive cases (44) and life-years (11.66) (flexible cystoscopy [CSC] and ImmunoCyt followed by PDD in initial diagnosis and CSC followed by WLC in follow-up) had an incremental cost per life-year over 270 000 pounds sterling (GBP). The least effective strategy (cytology followed by WLC in initial diagnosis [average cost over 20 years GBP 1403, average life expectancy 11.59]) was most likely to be considered cost-effective when society's willingness to pay was less than GBP 20 000 per life-year. No strategy was cost-effective more than 50% of the time, but 4 of the 8 strategies in the probabilistic sensitivity analysis (3 involving a biomarker or PDD) were each associated with a 20% chance of being considered cost effective. In sensitivity analyses, the results were most sensitive to the pretest probability of disease (5% in the base case).

Recommendations

See Executive Summary http://www.hta.ac.uk/project/1713.asp

Methods

See Executive Summary http://www.hta.ac.uk/project/1713.asp

Further research/reviews required

RCTs including economic evaluations comparing PDD with rigid WLC at TURBT, plus adjuvant immediate single-dose intravesical chemotherapy in patients with diagnosed bladder tumors at CSC.

Written by Mr Graham Mowatt, University of Aberdeen, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/150

Title **The Effectiveness and Cost Effectiveness of Biomarkers for the Prioritisation of Patients Awaiting Coronary Revascularization: A Systematic Review and Decision Model**

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Reference Volume 14.09. ISBN 1366-5278. www.hta.ac.uk/project/1515.asp

Aim

To determine the effectiveness and cost effectiveness of strategies based on conventional clinical information and novel circulating biomarkers for prioritizing patients with stable angina awaiting coronary artery bypass grafting (CABG).

Conclusions and results

Formally employing more information in prioritizing patients awaiting CABG appears to be a cost-effective approach and may improve health outcomes. The most robust results relate to a strategy employing a risk score using conventional clinical information along with a single biomarker (eGFR). The additional prognostic information via collecting the more costly novel circulating biomarker CRP, alone or in combination with other biomarkers, is unlikely to be cost effective in terms of waiting list prioritization. Our review included 390 reports of biomarker effects. The quality of study reports varied, with evidence of small study (publication) bias and incomplete adjustment for simple clinical information, eg, age, sex, smoking, diabetes, and obesity. The risk of cardiovascular events while on the waiting list for CABG was 3 per 10 000 patients per day within the first 90 days. Risk factors associated with an increased risk, and included in the basic risk equation, were: age, diabetes, heart failure, previous myocardial infarction, and involvement of the left main coronary artery or three-vessel disease. The optimal strategy in terms of cost effectiveness was a prioritization strategy employing biomarker information. Evaluating shorter maximum waiting times did not alter the conclusion that a prioritization strategy with a risk score using estimated glomerular filtration rate (eGFR) was cost effective. These results were robust to most alternative scenarios investigating other sources of uncertainty. However, the cost effectiveness of the strategy using a risk score with both eGFR and C-reactive protein (CRP) was potentially sensitive to the cost of the CRP test itself.

Recommendations

See Executive Summary www.hta.ac.uk/project/1515.asp

Methods

See Executive Summary www.hta.ac.uk/project/1515.asp

Further research/reviews required

1. To establish and develop a national register of coronary angiography in the UK, which would provide a platform for health technology appraisal and other outcomes-based research relevant to the NHS. Such a register should include details of angiographic findings, clinical details required for estimating risk equations, circulating biomarker information, and follow-up for events and revascularization. 2. To develop the decision-analytic framework by incorporating a more comprehensive range of biomarker strategies, and to reflect more formally the uncertainties in the various input sources estimates with probabilistic sensitivity analysis. To consider these in relation to a broader set of approaches to the overall management of stable disease, including a policy of shortening overall waiting times. 3. To consider the consequences of uncertainty in the model more formally using value of information analysis to target specific areas where further research appears most worthwhile. 4. To develop initiatives for improving the quality of biomarker prognosis research, for example by developing standards for reporting, and to foster collaborations that pool individual participant data sets.

Written by Professor Harry Hemingway, University College London, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/151

Title **Paracetamol and Selective and Non-Selective non-Steroidal anti-Inflammatory Drugs (Nsaids) for the Reduction of Morphine-Related Side Effects after Major Surgery: A Systematic Review**

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Reference Volume 14.17. ISSN 1366-5278. www.hta.ac.uk/project/1853.asp

Aim

To determine which class of non-opioid analgesics – paracetamol (acetaminophen), NSAIDs, or COX-2 inhibitors – is the most effective at reducing morphine consumption and associated adverse effects when used as part of multimodal analgesia following major surgery.

Conclusions and results

Compared to placebo, 24-hour morphine consumption decreased by 6.3 mg to 10.9 mg when paracetamol, NSAID, or COX-2 inhibitors were added to patient-controlled analgesia (PCA) morphine following surgery. Differences in effect between the 3 drug classes were small and unlikely to be of clinical significance. There does not appear to be a strong case to recommend routine addition of any of the 3 non-opioids to PCA morphine in the 24 hours immediately after surgery, or for favoring one drug class above the others.

Sixty relevant studies were identified. When paracetamol, NSAIDs, or COX-2 inhibitors were added to PCA morphine the reduction in morphine consumption was statistically significant: paracetamol (MD –6.34 mg; 95% CrI –9.02 to –3.65); NSAIDs (MD –10.18; 95% CrI –11.65 to –8.72); and COX-2 inhibitors (MD –10.92; 95% CrI –12.77 to –9.08). NSAIDs and COX-2 inhibitors were both significantly better than paracetamol, and there was no significant difference between NSAIDs and COX-2 inhibitors (MD –0.74; 95% CrI –3.03 to 1.56). There was a significant reduction in nausea and PONV with NSAIDs compared to placebo (OR 0.70; 95% CrI 0.53 to 0.88), but not for paracetamol or COX-2 inhibitors, nor for NSAIDs compared to paracetamol or COX-2 inhibitors.

Recommendations

See link www.hta.ac.uk/project/1853.asp.

Methods

See link www.hta.ac.uk/project/1853.asp.

Further research/reviews required

Given the overlap in the effects of the 3 analgesics, there does not appear to be a compelling case for a further trial. However, any future trials testing new analgesics in conjunction with postsurgical morphine should focus on morphine-related adverse effects, ensuring that the power calculation is based on key morphine-related adverse effects rather than on morphine consumption. Also, it would be valuable to explore whether taking baseline morphine consumption into account alters the results for morphine-related adverse effects.

Written by Dr Catriona McDaid, University of York, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/152

Title **The Clinical Effectiveness and Cost Effectiveness of Topotecan for Small Cell Lung Cancer: A Systematic Review and Economic Evaluation**

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Reference Volume 14.19. ISSN 1366-5278. www.hta.ac.uk/project/1754.asp

Aim

To assess the clinical and cost effectiveness of topotecan as second-line treatment for small cell lung cancer (SCLC).

Conclusions and results

Topotecan appeared to be better than best supportive care (BSC) alone in terms of improved survival, and was as effective as cyclophosphamide, Adriamycin (doxorubicin), and vincristine (CAV) and less favorable than intravenous (IV) amrubicin in terms of response. Oral topotecan and IV topotecan showed similar efficacy. Topotecan offers additional benefit over BSC, but at increased cost. Incremental cost-effectiveness ratios (ICERs) for IV topotecan, compared to BSC, were high and suggest it is unlikely to be a cost-effective option. The ICER for oral topotecan is at the upper extreme of the range that the NHS regards as cost effective. We identified 434 references, of which 5 were included in the clinical effectiveness review. In these trials, topotecan was compared with BSC, CAV, or amrubicin, or oral topotecan was compared with IV topotecan. No economic evaluations were identified. We found no statistically significant differences between groups when IV topotecan was compared with either CAV or oral topotecan for overall response rate (ORR). The response rate was significantly better in participants receiving IV amrubicin than in those receiving a low dose of IV topotecan (38% versus 13%, respectively, p = 0.039). We found a statistically significant benefit favoring oral topotecan compared with BSC (HR 0.61, 95% CI 0.43 to 0.87, p = 0.01). Drug acquisition costs for 4 cycles of treatment were estimated at 2550 pounds sterling (GBP) for oral topotecan and GBP 5979 for IV topotecan. Non-drug treatment costs accounted for an additional GBP 1097 for oral topotecan and GBP 4289 for IV topotecan. Total costs for the modeled time horizon of 5 years were GBP 4854 for BSC, GBP 11 048 for oral topotecan, and between GBP 16 914 and GBP 17 369 for IV topotecan (depending on assumptions regarding time progression). Life expectancy was 0.4735, 0.7984, and 0.7784 years for BSC, oral topotecan, and IV topotecan respectively. Total quality-adjusted life-years (QALYs) were 0.2247 and 0.4077 for BSC and oral topotecan respectively, resulting in an ICER of GBP 33 851 per QALY gained. Total QALYs for IV topotecan were between 0.3875 and 0.4157 (depending on assumptions regarding time progression) resulting in an ICER between GBP 74074 and GBP 65 507 per QALY gained.

Recommendations

See link www.hta.ac.uk/project/1754.asp.

Methods

See link www.hta.ac.uk/project/1754.asp.

Further research/reviews required

It is unlikely that any further RCTs of topotecan compared with BSC will be ethically acceptable, nor is it likely there will be a need for further comparisons with CAV therapy. Little can be gained from further study of the effectiveness of IV versus oral topotecan. However, when the ongoing RCTs of topotecan versus amrubicin report, it would be desirable to update the current review. Further research is required on the quality of life (QoL) of patients with relapsed SCLC, to identify the impact of disease progression on QoL. In patients receiving active treatment, further research is required on the impact of complete or partial response and the impact of treatment-related adverse events on QoL.

Written by Dr Emma Loveman, SHTAC, University of Southampton, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/153

Title **Weighting and Valuing Quality-Adjusted Life-Years Using Stated Preference Methods: Preliminary Results from the Social Value of a QALY Project**

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Reference Volume 14.27. ISSN 1366-5278. www.hta.ac.uk/project/1578.asp

Aim

To identify characteristics of beneficiaries of health care over which relative weights should be derived and to estimate relative weights to be attached to health gains according to characteristics of recipients of these gains (relativities study); and to assess the feasibility of estimating a willingness-to-pay (WTP)-based value of a quality-adjusted life-year (QALY) (valuation study).

Conclusions and results

Regarding relative weights, more research is required to explore methodological differences with respect to age and severity weighting. On valuation, particular issues concern the extent to which 'noise' and 'error' in people's responses might generate extreme and unreliable figures. Methods of aggregation and measures of central tendency were issues in both weighting and valuation procedures and require further exploration. In the relativities study, discrete choice results showed age and severity variables did not have a strong impact on respondents' choices over and above the health (QALY) gains presented. In contrast, a matching procedure showed age and severity impacts to be strong: depending on method of aggregation, gains to some groups were weighted 3 to 4 times more highly than gains to others. In the valuation study, combining WTP and SG results in different ways led to values of a QALY varying from being in the vicinity of the current National Institute for Health and Clinical Excellence (NICE) threshold to extremely high values.

Recommendations

The methodological nature of the research limits the implications for practice. Two main recommendations are: 1) On relativities: It might be premature to propose any particular set of QALY weights, but there is scope for further reconciliation and replication. However, it might equally be argued that there is no scope for reconciliation, and that we need to choose between the results in light of the caveats of the matching and discrete choice methods used. 2) On valuation: It was never the intention to conduct a representative survey using a definitive method. Hence, any future national sample survey should be preceded by further extensive qualitative research and cognitive testing to resolve the main questions identified in the present study.

Methods

See link www.hta.ac.uk/project/1578.asp.

Further research/reviews required

1) Findings from the relativities study indicate that more work is required in the short term to reconcile the results obtained. 2) In the longer term, with respect to relativities, further methodological research should attempt to account for deficiencies in the methods. 3) Building on the results of the methods devised in this study to derive relative weights, further replication of these results is required to address this important policy issue. 4) With respect to valuation, shorter-term work is required on issues of aggregation, combining WTP and SG values, and the appropriateness of different measures of central tendency. In the longer term, more qualitative and cognitive research is required around two issues in particular: (a) the problem of identifying health states to present to respondents which are 'minor enough' for people to be able to express their WTP, but not so minor that respondents will accept only minuscule risks of death when responding to SG-type questions; and (b) the extent to which 'noise' and 'error' in people's responses might generate extreme and unreliable figures.

Written by Professor Cam Donaldson, Glasgow Caledonian University, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/154

Title **The Impact of Communications About Swine Flu (Influenza A H1n1v) on Public Responses to the Outbreak: Results from 36 National Telephone Surveys in the UK**

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Reference Volume 14.34(3). ISSN 1366-5278. www.hta.ac.uk/project/2224.asp

Aim

To assess the association between levels of worry about the possibility of catching swine flu and the volume of media reporting; the role of psychological factors in predicting likely uptake of swine flu vaccine; and the role of media coverage and advertising in predicting other swine flu-related behaviors.

Conclusions and results

During the swine flu outbreak, uptake rates for protective behaviors and likely acceptance rates for vaccination were low. One reason might be the low level of public worry about catching swine flu. When levels of worry are generally low, acting to increase the volume of mass media and advertising coverage is likely to increase the perceived efficacy of recommended behaviors, which, in turn, is likely to increase their uptake. The percentage of 'very' or 'fairly' worried participants fluctuated between 9.6% and 32.9%. This figure was associated with the volume of media reporting, even after adjusting for the changing severity of the outbreak. However, this effect only occurred during the UK's first summer wave of swine flu. In total, 56.1% of respondents were very or fairly likely to accept the swine flu vaccine. The strongest predictors were being very worried about the possibility of oneself (adjusted odds ratio [aOR] 4.7, 95% confidence interval [CI] 3.2 to 7.0), or one's child (aOR 8.0, 95% CI 4.6 to 13.9) catching swine flu. Overall, 33.1% of participants reporting carrying tissues with them, 9.5% had bought sanitizing gel, 2.0% had avoided public transport, and 1.6% had sought medical advice. Exposure to media coverage or advertising about swine flu increased tissue carrying or buying of sanitizing hand gel and reduced avoidance of public transport or consultation with health services during early May 2009. Path analyses showed that media coverage and advertising had these differential effects because they raised the perceived efficacy of hygiene behaviors, but decreased the perceived efficacy of avoidance behaviors.

Recommendations

See link www.hta.ac.uk/project/2224.asp.

Methods

See link www.hta.ac.uk/project/2224.asp.

Further research/reviews required

1) While our results suggest that successfully communicating information about the efficacy of protective behaviors will increase the uptake of these behaviors, we are unable to specify the best techniques for providing information about efficacy. Additional research would help guide future communications campaigns. 2) Across all of the behavioral outcomes that we assessed, there was evidence that people from particular demographic groups were more inclined to engage in behavioral change. Our results showed that ethnicity, age, household size, health status, socioeconomic status, and gender all played a role in determining whether someone engaged in a given behavior or not. The complex mechanisms underlying these effects may have important implications for the ways to frame messages for these groups. Additional research to understand the reasons for and implications of these effects would be of value. 3) Since additional data from the surveys have become available (eg, potential outcome variables such as hand-washing data and actual vaccine uptake) we recommend further analysis of this data set. Similarly, the database would also allow a more detailed analysis of the content of media reporting to be used as a predictor of worry during the outbreak.

Written by Professor Susan Michie, University College London, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/155

The Impact of Illness and the Impact of School Closure on Social Contact Patterns

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Reference Volume 14.34(4). ISSN 1366-5278. www.hta.ac.uk/project/2224.asp

Aim

To describe and quantify the changes in: 1) social contact behavior experienced by individuals when they are ill with pandemic H1N1 influenza (swine flu) and 2) mixing patterns of school children that take place as a result of swine flu-related school closures.

Conclusions and results

Evidence from this study suggests that ill individuals make substantial changes to their social contact patterns. Changes were strongly linked to absence from work and the severity of the reported illness. Hence, epidemiological modelers should consider the implications of illness-related behavioral changes on model predictions. Future studies to measure the extent of behavioral change in a broader cross-section of infected cases could be valuable, along with more detailed studies of the social contact patterns of school children, focusing on differences between school terms and school holidays. For the patient study, approximately 3800 surveys were distributed by 31 antiviral distribution centre (ADCs). Overall, 317 responses to the initial survey were received, and 179 participants returned the follow-up survey. For all types of contact, except contacts made at home, there were highly significant differences in contact behavior. Individuals made substantially fewer contacts (approximately one third as many) when they were ill than when they were well. Analysis showed that returning to work was the most significant predictor of increased numbers of contacts. Also, the greater the change in the number of symptoms reported, the greater the change in the number of contacts. For the school study, approximately 1100 questionnaire packs were distributed and 134 responses were received, with 119 paired contact diaries. Pupils reported on average 18.5 contacts each day during term time and 9.2 during the half-term holiday – a reduction of over 50% and a highly significant change.

Recommendations

See link www.hta.ac.uk/project/2224.asp.

Methods

A self-completed questionnaire-based study was designed and carried out in the autumn/winter of 2009-2010. The study population was individuals who had been diagnosed with swine flu and who received a swine flu antiviral prescription from an ADC. The study aimed to quantify changes in participants' social contact behavior. The study consisted of two parts: the initial survey was designed to be filled in when participants were symptomatic with swine flu; the follow-up survey was designed to be filled in once they had recovered. Each part was returned by post in a prepaid envelope. Each part of the questionnaire had two sections. The first section collected information about the participant (age, sex, household size and composition), their health status (symptoms list, a measure of their current health, date of symptom onset, antiviral use), their behavior (work/school/college attendance, public transport use), and the impact of their illness on their activities (time off work, receiving care from others). This section also asked for participants' name and address so the follow-up survey could be sent to them. The second section was a contact diary in which participants were asked to list everyone they met over the course of a day. A meeting was defined as either talking face-to-face or skin-to-skin contact (eg, handshake, kiss, contact sports). Participants were asked for information about each person whom they reported meeting: 1) age (or age range), 2) gender, 3) whether there was skin-to-skin contact, 4) how long the encounter lasted, 5) the social setting in which the encounter occurred, and 6) how often they normally met this person.

Further research/reviews required

See link www.hta.ac.uk/project/2224.asp.

Written by Dr Ken Eames, London School of Hygiene and Tropical Medicine, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/156

Title **Vaccine Effectiveness in Pandemic Influenza Primary Care Reporting (VIPER): An Observational Study to Assess the Effectiveness of the Pandemic Influenza A (H1N1) V Vaccine**

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Reference Volume 14.34(5). ISSN 1366-5278. www.hta.ac.uk/project/2224.asp

Aim

To determine influenza A (H1N1)v vaccine effectiveness (VE) in the Scottish population at an early stage of the 2009-2010 H1N1v vaccination program, using a sentinel surveillance network of 41 general practices contributing to the Practice Team Information (PTI) network.

Conclusions and results

Evidence (swabs) from patients in the cohort who presented in general practice with influenza-like illness suggests that influenza A (H1N1)v vaccine in Scotland during 2009 was associated with a high degree of protection. Influenza A (H1N1)v immunization in primary healthcare settings appears to be effective and widely acceptable, and should continue to be the mainstay of disease prevention for at-risk patients. Further analysis encompassing the whole influenza season is required to cover more days of vaccination exposure and increase precision. At 25 December 2009, vaccine uptake estimates for the study population were 12.0% (95% CI 11.9 to 12.1). For patients in an at-risk group (n = 59 721), the uptake rate was 37.5% (95% CI 37.1 to 37.9). Among the 1492 patients swabbed, 467 were positive for H1N1, giving a positivity rate of 31.3% (95% confidence interval [CI] 29.0 to 33.7). Among those in a clinical risk group who were not vaccinated, 41.3% (95% CI 35.6 to 46.9) tested positive for influenza A (H1N1)v, a significant difference from the H1N1 positivity percentage among patients with no clinical risk ($p < 0.01$). Among those vaccinated and in a clinical risk group, only one patient (5%, 95% CI 0.3 to 23.6) tested after vaccination was positive for influenza A (H1N1)v. By comparing post-vaccination swabs in those who were vaccinated against swabs taken from those who remained unvaccinated, the VE was found to be 95.0% (95% CI 76.0 to 100.0). The study population had 2739 admissions to hospital, of which 1241 were emergency admissions; all 48 emergency hospitalizations for influenza and pneumonia occurred in unvaccinated patients. VE for single or combined endpoints of influenza and pneumonia hospitalization for all patients was estimated at 100.0% (95% CI ∞ to 100.0). There were 132 hospitalizations for cardiovascular-related conditions in the unvaccinated group versus 5 in the vaccinated group. The unvaccinated group had 193 hospitalizations versus 9 in those vaccinated in the group (ie, patients admitted for influenza, pneumonia, chronic obstructive pulmonary disease [COPD] and cardiovascular-related conditions). VE for cardiovascular-related conditions alone, or in individuals with influenza, pneumonia, COPD, and cardiovascular-related conditions, was 71.1% (95% CI 11.3 to 90.6) and 64.7% (95% CI 12.0 to 85.8) respectively.

Recommendations

See link www.hta.ac.uk/project/2224.asp.

Methods

Retrospective cohort study using record linkage. See link www.hta.ac.uk/project/2224.asp.

Further research/reviews required

To increase precision, further analysis encompassing the whole influenza season is required to encompass more days of vaccination exposure. To calculate and present meaningful results in pregnant women and under-5-year-olds, further study using a greater period of exposure is required. A future study that will repeat this data linkage and allow the calculation of longer-term VE (in reducing both morbidity and mortality) should be undertaken.

Written by Dr Colin Simpson, University of Edinburgh, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/157

Title **Intravenous Magnesium Sulphate and Sotalol for Prevention of Atrial Fibrillation after Coronary Artery Bypass Surgery: A Systematic Review and Economic Evaluation**

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Reference Volume 12.28. ISBN 1366-5278. www.hta.ac.uk/project/1659.asp

Aim

To assess the clinical and cost effectiveness of magnesium sulphate compared with sotalol, and to assess the clinical effectiveness of magnesium sulphate compared with placebo in preventing atrial fibrillation (AF) in patients who have had a coronary artery bypass graft (CABG).

Conclusions and results

Twenty-two papers met the inclusion criteria for the systematic review, reporting 15 trials which all compared magnesium sulphate with placebo or control. No randomized controlled trials (RCTs) were identified that specifically aimed to compare intravenous magnesium with sotalol as prophylaxis for AF in patients undergoing CABG. Included trials ranged from 15 to 176 patients randomized, and were conducted in Europe, the USA, and Canada. The standard of reporting was generally poor, with details of key methodological attributes difficult to elucidate. No trials were identified that specifically aimed to compare magnesium sulphate with sotalol. Of 1070 patients in the pooled magnesium group, 230 (21%) developed postoperative AF, compared with 307 of 1031 (30%) patients in the placebo or (control) group. Meta-analysis using a fixed-effects model generated a pooled odds ratio (OR) that was significantly less than 1.0 (OR = 0.65, 95% confidence interval [CI] 0.53 to 0.79, test for overall effect $p < 0.0001$), indicating that intravenous magnesium is effective in preventing postoperative AF, but with statistically significant heterogeneity ($I2 = 63.4\%$, $p = 0.0005$). AF was less likely to occur when a longer duration of prophylaxis was used, and the earlier that prophylaxis was started. However, this finding was associated with two RCTs that had more favorable results than the other trials. No clear relationship between dose and AF was observed; although a lower constant dose rate was associated with the lowest odds of AF. In the base-case analysis in the economic model, magnesium sulphate prophylaxis reduced the number of postoperative AF cases at a modest increase in cost. The results of the economic analysis are highly sensitive to variation in certain key parameters, including the baseline risk of AF following CABG, the effectiveness and cost of prophylaxis, and the resource consequences of postoperative AF. Prophylaxis is less likely to be cost effective if it requires changes in admission routines that result in longer preoperative stays than would be the case without prophylaxis.

Recommendations

No RCTs were identified that specifically aimed to compare intravenous magnesium with sotalol as prophylaxis for AF in patients undergoing CABG. Such a comparison does not appear to be clinically meaningful. Intravenous magnesium, compared with placebo or control, is effective in preventing postoperative AF, as confirmed by a statistically significant intervention effect based on pooled analysis of 15 RCTs.

Methods

For further details see link www.hta.ac.uk/project/1659.asp.

Further research/reviews required

Further research should investigate the relationship between dose, dose rate, duration of prophylaxis, timing of initiation of therapy, and patient characteristics, eg, degree of risk for AF. This will provide stronger evidence for the optimum delivery of intravenous magnesium in patients undergoing CABG.

Written by Dr Jonathan Shepherd, SHTAC, University of Southampton, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/158

Title **Routine Antenatal Anti-D Prophylaxis for Rhd-Negative Women: A Systematic Review and Economic Evaluation**

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Reference Volume 13.10. ISBN 1366-5278. www.hta.ac.uk/project/1670.asp

Aim

To assess the clinical and cost effectiveness of routine antenatal anti-D prophylaxis (RAADP) for Rhesus D (RhD)-negative women.

Conclusions and results

RAADP reduces the incidence of sensitization and hence of hemolytic disease of the newborn (HDN). Clinical effectiveness searches identified 670 potentially relevant articles, of which 12 (relating to 8 studies) were included in the review. With one exception, no additional studies were identified in comparison with the previous report, and some of the clinical effectiveness studies in the 2002 review had to be excluded since they did not use currently licensed doses. Hence, 8 studies comparing RAADP with no prophylaxis were identified in the clinical effectiveness review, and 9 (including the 2001 assessment report itself) in the cost-effectiveness review. The studies of clinical efficacy were generally of poor quality and did not provide a basis for differentiating between regimens of RAADP. The best indication of the likely efficacy of a program of RAADP comes from two nonrandomized community-based studies. Their pooled results suggest that such a program may reduce the sensitization rate from 0.95% (95% CI 0.18–1.71) to 0.35% (95% CI 0.29–0.40). This gives an odds ratio for the risk of sensitization of 0.37 (95% CI 0.21–0.65) and an absolute reduction in risk of sensitization in RhD-negative mothers at risk (ie, carrying a RhD-positive child) of 0.6%. The identified studies suggest that RAADP has minimal adverse effects. Of the 9 studies in the cost-effectiveness review, only 2 described a model that could be applicable to the NHS. The economic model modified from the 2002 appraisal suggests that the cost per quality-adjusted life-year (QALY) gained of RAADP given to RhD-negative primigravidae versus no treatment is between 9000 pounds sterling (GBP) and GBP 15 000, and for RAADP given to all RhD-negative women rather than to RhD-negative primigravidae only is between GBP 20 000 and GBP 35 000 depending on the regimen. Sensitivity analysis suggests that the results are reasonably robust to changes in the assumptions within the model.

Recommendations

All of the evidence indicates that RAADP reduces the incidence of sensitization and hence of HDN. The economic model suggests that RAADP given to all RhD-negative pregnant women is likely to be considered cost effective at a threshold of around GBP 30 000 per QALY gained. The total cost of providing RAADP to RhD-negative primigravidae in England and Wales is estimated to be around GBP 1.8 to 3.1 million per year, depending on the regimen of RAADP used (excluding WinRho). This takes into account the cost of RAADP and its administration, the cost of management of sensitization, and the cost savings associated with avoiding HDN. The additional cost of providing RAADP to all RhD-negative pregnant women in England and Wales is estimated to be around GBP 2.0 to 3.5 million.

Methods

See link www.hta.ac.uk/project/1670.asp.

Further research/reviews required

Studies need to compare the efficacy of the different RAADP regimens. Issues relating to compliance and safety may also influence the efficacy of the different regimens of RAADP, and hence further research would be useful in these areas.

Written by Mrs Hazel Squires (nee Pilgrim), SCHARR, University of Sheffield, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/159

Title **Amantadine, Oseltamivir and Zanamivir for the Prophylaxis of Influenza (Including a Review of Existing Guidance No. 67): A Systematic Review and Economic Evaluation**

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Reference Volume 13.11. ISBN 1366-5278. www.hta.ac.uk/project/1686.asp

Aim

To evaluate the clinical effectiveness and incremental cost effectiveness of amantadine, oseltamivir, and zanamivir for seasonal and postexposure prophylaxis of influenza.

Conclusions and results

All 3 interventions showed some efficacy for seasonal and postexposure prophylaxis. However, weaknesses and gaps in the clinical evidence base are directly relevant to the interpretation of the health economic model and rendered the use of advanced statistical analyses inappropriate. The clinical effectiveness review included 26 published references relating to 22 randomized controlled trials (RCTs) and 1 unpublished report (8, 6, and 9 RCTs were included for amantadine, oseltamivir, and zanamivir respectively). Study quality varied, and gaps in the evidence base limited the assessment of the clinical effectiveness of the interventions. For seasonal prophylaxis, limited evidence supported the efficacy of amantadine in preventing symptomatic, laboratory-confirmed influenza (SLCI) in healthy adults (relative risk [RR] 0.40, 95% confidence interval [CI] 0.08–2.03). Oseltamivir was effective in preventing SLCI, particularly when used in at-risk elderly (RR 0.08, 95% CI 0.01–0.63). The preventative efficacy of zanamivir was most notable in at-risk adults and adolescents (RR 0.17, 95% CI 0.07–0.44), and healthy and at-risk elderly (RR 0.20, 95% CI 0.02–1.72). For postexposure prophylaxis, data on amantadine use were again limited: in adolescents an RR of 0.10 (95% CI 0.03–0.34) was reported for the prevention of SLCI. Oseltamivir was effective in households of mixed composition (RR 0.19, 95% CI 0.08–0.45). The efficacy of zanamivir in postexposure prophylaxis in households was also reported (RR 0.21, 95% CI 0.13–0.33). Interventions appeared to be well tolerated. Limited evidence supported the effectiveness of the interventions in preventing complications and hospitalization and in minimizing length of illness and time to return to normal activities. No clinical effectiveness data were identified for health-related quality of life or mortality outcomes. With the exception of at-risk children, the incremental cost-utility of seasonal influenza prophylaxis is expected to range between 38 000 and 428 000 pounds sterling (GBP) per QALY gained (depending on subgroup). The cost-effectiveness ratios for oseltamivir and zanamivir as postexposure prophylaxis are expected to be below GBP 30 000 per QALY gained in healthy children, at-risk children, healthy elderly, and at-risk elderly individuals. Despite favorable clinical efficacy estimates, the incorporation of recent evidence of viral resistance to amantadine led to it being dominated in every economic comparison.

Recommendations

See link www.hta.ac.uk/project/1686.asp.

Methods

A systematic review was undertaken and an independent health economic model developed, based on clinical advice and a detailed review of existing cost-effectiveness models. The model draws on a broad spectrum of evidence relating to the costs and consequences of influenza and its prevention.

Further research/reviews required

1) Additional RCTs of influenza prophylaxis in subgroups for which data are currently lacking; 2) RCTs where follow-up extends beyond the duration of prophylaxis; 3) head-to-head RCTs that directly compare clinical effectiveness of interventions in different subgroups; 4) quality-of-life studies to inform future economic decision modeling; 5) further research on the incidence and management of influenza complications.

Written by Mr Paul Tappenden, SCHARR, University of Sheffield, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/160

Title **Improving the Evaluation of Therapeutic Interventions in Multiple Sclerosis: The Role of New Psychometric Methods**

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Reference Volume 13.12. ISBN 1366-5278. www.hta.ac.uk/project/1549.asp

Aim

To examine the added value of new psychometric methods (Rasch measurement and Item Response Theory) over traditional psychometric approaches by comparing and contrasting their psychometric evaluations of existing sets of rating scale data.

Conclusions and results

We concentrated on Rasch measurement (RM) rather than Item Response Theory (IRT) because we believe it is the more advantageous method for health measurement from conceptual, theoretical, and practical perspectives. Our intent is to provide an authoritative document that describes the principles of RM and the practice of Rasch analysis in a clear, detailed, nontechnical form that is accurate and accessible to clinicians and researchers. There is considerable added value in using Rasch analysis rather than traditional psychometric methods in health measurement. Both RM and IRT are conceptually and theoretically superior to traditional psychometric methods. Findings from the 5 studies show that Rasch analysis is empirically superior to traditional psychometric methods for evaluating rating scales, developing rating scales, analyzing rating scale data, understanding and measuring stability and change, and understanding the health constructs we seek to quantify.

Recommendations

The arguments and demonstrations in this monograph, both theoretical and empirical, illustrate that Rasch measurement is vastly superior to traditional psychometric methods. Although we have highlighted the value of Rasch measurement in the context of only a limited number of scales for people with multiple sclerosis (MS), we feel that it has much to offer all health measurement, state-of-the-art clinical trials, and individual patients treated by clinicians.

Methods

Chapters 1 through 3 of this monograph review the literature. Chapter 1 concerns the role of rating scales and the theory and practice of traditional psychometric methods. Chapter 2 outlines the impetus behind the new psychometric methods (IRT and RM), charts their development, and explains their similarities and differences. This chapter also provides the case underpinning the reasons why the rest of the monograph focuses on RM and not on IRT. Chapter 3 describes the theory behind RM, the development of the RM model, the properties of the model, and how it works in practice. Chapters 4 through 8 present five practical head-to-head comparisons of Rasch analysis and traditional psychometric methods based on data sets produced from a variety of settings. These demonstrations focus on two scales – the Rivermead Mobility Index and the Multiple Sclerosis Impact Scale (MSIS-29) – in large samples of people with MS.

Further research/reviews required

We recommend the following future research directions: (1) other researchers and clinicians reproduce our findings in a range of clinical populations; (2) detailed head-to-head comparisons of Rasch measurement and Item Response Theory; (3) determine further sample size requirements for adequate person and item estimations; and (4) explore the application of Rasch measurement to clinical practice in areas including prioritizing problems, facilitation of communication, screening potential problems, identifying preferences, monitoring changes or responses to treatment, training new staff, and clinical audit.

Written by Dr Jeremy Hobart, P, University of Plymouth, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/161

Title **Non-Occupational Post-Exposure Prophylaxis for HIV: A Systematic Review**

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Reference Volume 13.14. ISBN 1366-5278. www.hta.ac.uk/project/1716.asp

Aim

To review the evidence on the clinical effectiveness and cost effectiveness of nonoccupational postexposure prophylaxis (PEP) for HIV.

Conclusions and results

The limited evidence available does not enable conclusions about the clinical effectiveness of nonoccupational PEP for HIV. A review of cost effectiveness suggests that nonoccupational PEP may be cost effective, especially in certain population subgroups, but shortcomings in the cost-effectiveness studies mean that their results should be used with caution. One clinical effectiveness study meeting the inclusion criteria was identified (a cohort study of PEP in a high-risk HIV-negative homosexual male cohort in Brazil), but its quality was generally weak. Seroincidence in the cohort as a whole (2.9 per 100 person-years) was similar to that expected in this population (3.1 per 100 person-years, p>0.97), despite the seroconversion to HIV being 1/68 in the PEP group and 10/132 in the group not receiving PEP. High-risk sexual activities declined over time for both PEP and non-PEP users. Four economic evaluations met the inclusion criteria of the review, but their methodological quality was mixed. The studies are constrained by a lack of published data on the clinical effectiveness of PEP after nonoccupational exposure, with effectiveness data derived from one study of occupational PEP. Their generalizability to the UK is unclear. Results suggest that PEP following nonoccupational exposure to HIV was cost saving for men who have unprotected receptive anal intercourse with men, whether the source partner is known to be HIV positive or not; heterosexuals after unprotected receptive anal intercourse; and intravenous drug users, sharing needles with a known HIV-positive person. PEP following nonoccupational exposure to HIV was cost effective for all male-male intercourse and was possibly cost effective for intravenous drug users and high-risk women. Four additional studies yielded further information about adverse events associated with PEP after nonoccupational exposure to HIV. Most participants experienced adverse events, mainly nausea and fatigue. Rates were generally higher in participants receiving triple therapy than in participants receiving dual therapy. Completion of PEP therapy ranged from 24% to 78% of participants depending on therapy type. Toxicity was the main reason for discontinuing treatment.

Recommendations

It is not possible to draw conclusions on the clinical effectiveness of nonoccupational PEP for HIV because of the limited evidence in terms of quantity and quality of studies. One cohort study was identified that met the inclusion criteria for the systematic review. Four economic evaluations assessed cost effectiveness using evidence on the effectiveness of using PEP in an occupational setting. Results are consistent across studies and suggest that nonoccupational PEP may be cost-effective, especially in certain population subgroups.

Methods

See link www.hta.ac.uk/project/1716.asp.

Further research/reviews required

The most important research need is to establish the clinical effectiveness of nonoccupational PEP in the UK. Ongoing research in the NONOPEP project, an MRC-funded surveillance program of PEP for nonoccupational exposure to HIV, will address aspects of clinical effectiveness (seroconversion rates in people who take PEP compared with those who do not) and evaluate problems associated with taking antiretroviral medications. Data generated from this study can be assessed and used to inform future economic modeling of the cost effectiveness of nonoccupational PEP in the UK.

Written by Ms Jackie Bryant, SHTAC, University of Southampton, NETSCC, United Kingdom

Title **Complementary and Alternative Therapies for Post Traumatic Stress Disorder**

Agency **VATAP, VA Technology Assessment Program**
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Reference VA Technology Assessment Program Brief Overview, November 2009. www.va.gov/vatap

Aim

To systematically review the medical literature on the efficacy of complementary and alternative medicine (CAM) therapies for post traumatic stress disorder (PTSD).

Conclusions and results

Five articles met the inclusion criteria. Although promising results were seen using mantram repetition or acupuncture to treat PTSD, these studies were preliminary and not proven to be universal for all patients. Due to insufficient evidence, no conclusions regarding the benefit of complementary and alternative medicine therapies could be made.

Recommendations

The VA's PTSD patients should be aware that the benefits of complementary and alternative treatments are uncertain.

Methods

Using 29 CAM modalities combined with several combat terms, a literature search for articles published in English was conducted in the following databases: MEDLINE, EMBASE, and CurrentContents.

Further research/reviews required

Larger randomized controlled trials need to study the effect of complementary and alternative treatments in young Veterans with recent combat experience.

Written by Elizabeth Adams, MPH, VATAP. USA

INAHTA Briefs

Issue 2010/163

Title **Adefovir Dipivoxil and Pegylated Interferon Alpha for the Treatment of Chronic Hepatitis B: An Updated Systematic Review and Economic Evaluation**

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Reference Volume 13.35. ISBN 1366-5278. www.hta.ac.uk/project/1718.asp

Aim

To update and extend a 2006 report on the clinical and cost effectiveness of adefovir dipivoxil (ADV) and pegylated interferon alpha (PEG-a) in treating chronic hepatitis B (CHB).

Conclusions and results

Of the 8 randomized controlled trials (RCTs) included in the systematic review, 3 evaluated ADV, 4 evaluated PEG-a -2b, and 1 (from the original literature search) compared PEG-a -2b plus lamivudine (LAM) with PEG-a -2b monotherapy. No RCTs of PEG-a -2a were identified. One ADV trial showed a statistically significant difference between ADV and placebo in terms of ALT response and HBV DNA levels, favoring ADV. Following withdrawal of ADV, HBV DNA, and of ALT, response declined to levels similar to those observed in placebo patients. In the ADV versus ADV plus LAM trial in patients with LAM resistance, a statistically significant difference favored combination treatment. In the PEG-a trials, statistically significant differences favored PEG-a -2b plus LAM compared with either one of the drugs given as monotherapy. In the comparison between PEG-a -2b and IFN-a, and the comparison between different staggered regimens of the commencement of PEG-a -2b and LAM, there were no statistically significant differences between groups. Four full economic evaluations were identified in addition to one identified in the original report. Two assessed PEG-a -2a; the remainder assessed ADV. PEG-a -2a was associated with increased treatment costs and gains in quality-adjusted life expectancy. In a UK study, the incremental cost-effectiveness ratio (ICER) for PEG-a -2a was 10 444 pounds sterling (GBP) per QALY gained compared with LAM. The ICERs in our updated economic model were generally less favorable than those in the original assessment report. However, this primarily arises from a change in discounting practice. The sequential treatment strategy (interferon [pegylated or conventional] followed by LAM with ADV as salvage for patients who develop LAM resistance) identified as optimal in our original report remained optimal in the updated model. In a probabilistic sensitivity analysis, when compared with conventional interferon, PEG-a -2b had a probability of being cost-effective of 79% at a willingness-to-pay threshold of GBP 20 000 per QALY, and 86% at a willingness-to-pay threshold of GBP 30 000 per QALY.

Recommendations

Both ADV and PEG-a appear beneficial for patients with CHB in suppressing viral load, reducing liver damage-associated biochemical activity, inducing HBeAg seroconversion, and reducing liver fibrosis and necroinflammation. Overall, the evidence from RCTs suggests that the effects of long-term treatment with ADV are generally durable, with relatively low rates of resistance. Beneficial effects are lost once ADV is withdrawn. In LAM-resistant HBeAg-negative patients there were no significant differences between adding ADV to ongoing LAM or switching from LAM to ADV, except for viral resistance where the combination was more favorable. PEG-a -2b was associated with some benefit, relative to comparators. However, not all differences were statistically significant.

Methods

See link www.hta.ac.uk/project/1718.asp.

Further research/reviews required

Further research should assess the clinical and cost effectiveness of newer antiviral agents in relation to existing drugs, including the role of initiating treatment with combination therapy.

Written by Dr Jeremy Jones, SHTAC, University of Southampton, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/164

Title **The Clinical Effectiveness and Cost Effectiveness of Bariatric (Weight Loss) Surgery for Obesity: A Systematic Review and Economic Evaluation**

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Reference Volume 13.41. ISBN 1366-5278. www.hta.ac.uk/project/1742.asp

Aim

To assess the clinical and cost effectiveness of bariatric surgery for obesity.

Conclusions and results

Bariatric surgery, compared with nonsurgical interventions, appears to be clinically and cost effective for moderately to severely obese people. Uncertainties remain and further research needs to provide detailed data on patient quality of life (QoL), impact of surgeon experience on outcome, late complications leading to reoperation, duration of comorbidity remission, and resource use. Good-quality, randomized controlled trials (RCTs) will provide evidence on bariatric surgery for young people and for adults with class I or class II obesity. New research must report on the resolution and/or development of comorbidities, eg, Type 2 diabetes and hypertension, to assess the potential benefits of early intervention. Of 5386 references identified, 26 were included in the clinical effectiveness review (3 RCTs and 3 cohort studies compared surgery with nonsurgical interventions, and 20 RCTs compared different surgical procedures). Bariatric surgery was a more effective intervention for weight loss than nonsurgical options. In one large cohort study weight loss was still apparent 10 years after surgery, whereas patients receiving conventional treatment had gained weight. Some measures of QoL improved after surgery, but not others. After surgery, statistically fewer people had metabolic syndrome, and remission of Type 2 diabetes was higher than in nonsurgical groups. In a large cohort study, the incidence of 3 out of 6 comorbidities assessed 10 years after surgery was significantly reduced compared with conventional therapy. Gastric bypass (GBP) was more effective for weight loss than vertical banded gastroplasty (VBG) and adjustable gastric banding (AGB). Laparoscopic isolated sleeve gastrectomy (LISG) was more effective than AGB in one study. GBP and banded GBP led to similar weight loss and results for GBP versus LISG and VBG versus AGB were equivocal. All comparisons of open versus laparoscopic surgeries found similar weight losses in each group. Comorbidities after surgery improved in all groups, but with no significant differences between different surgical interventions. Adverse event reporting varied; mortality ranged from 0% to 10%. Adverse events from conventional therapy included intolerance to medication, acute cholecystitis, and gastrointestinal problems. Major adverse events following surgery included anastomosis leakage, pneumonia, pulmonary embolism, band slippage, and band erosion. Although bariatric surgery was cost effective compared to nonsurgical treatment in the reviewed published estimates of cost effectiveness, these estimates are likely to be unreliable and not generalizable due to methodological shortcomings and the modeling assumptions. Hence, a new economic model was developed. Surgical management was more costly than nonsurgical management in the 3 patient populations analyzed, but gave improved outcomes. For morbid obesity, incremental cost-effectiveness ratios (ICERs) (base case) ranged between 2000 pounds sterling (GBP) and GBP 4000 per QALY gained. They remained within the range regarded as cost effective by the NHS when assumptions for deterministic sensitivity analysis were changed. For BMI ≥30 and <40, ICERs were GBP 18 930 at 2 years and GBP 1397 at 20 years, and for BMI ≥30 and <35, ICERs were GBP 60 754 at 2 years and GBP 12 763 at 20 years.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1742.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1742.asp.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1742.asp.

Written by Dr Joanna Picot, SHTAC, University of Southampton, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/165

Title **Clinical and Cost Effectiveness of Epoprostenol, Iloprost, Bosentan, Sitaxentan and Sildenafil for the Treatment of Pulmonary Arterial Hypertension within Their Licensed Indications: A Systematic Review and Economic Evaluation**

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Reference Volume 13.49. ISBN 1366-5278. www.hta.ac.uk/project/1621.asp

Aim

To investigate the clinical and cost effectiveness of epoprostenol, iloprost, bosentan, sitaxentan, and sildenafil in treating adults with pulmonary arterial hypertension (PAH) within their licensed indications.

Conclusions and results

All 5 technologies, when added to supportive treatment and used at licensed dose(s), were more effective than supportive treatment alone in randomized controlled trials (RCTs) that included patients of mixed functional class (FC) and types of PAH. Current evidence does not allow adequate comparisons between the technologies nor for the use of combinations of the technologies. Independent economic evaluation suggests that bosentan, sitaxentan, and sildenafil may be cost effective by standard thresholds and that iloprost and epoprostenol may not be. The use of the most cost-effective treatment would reduce costs for the NHS. This assessment included 20 RCTs, mostly comparing one of the technologies added to supportive treatment with supportive treatment alone. Four published economic evaluations were identified. None produced results generalizable to the NHS. There was no consensus in the industry submissions on the most appropriate model structure for technology assessment. Improvement in 6-minute walk distance (6MWD) was seen with intravenous epoprostenol in primary pulmonary hypertension (PPH) patients with mixed FC compared with supportive care (58 meters; 95% CI 6-110). For bosentan compared with supportive care, the pooled result for improvement in 6MWD for FCIII patients with mixed PAH was 59 meters (95% CI 20-99). For inhaled iloprost, sitaxentan, and sildenafil no stratified data for improvement in 6MWD were available. The odds ratio (OR) for FC deterioration at 12 weeks was 0.40 (95% CI 0.13-1.20) for intravenous epoprostenol compared with supportive care. The corresponding values for inhaled iloprost (FCIII PPH patients; licensed indication), bosentan, sitaxentan (FCIII patients with mixed PAH; licensed indication), and sildenafil (FCIII patients with mixed PAH; licensed indication) were 0.29 (95% CI 0.07-1.18), 0.21 (95% CI 0.03-1.76), 0.18 (95% CI 0.02-1.64) and [Commercial-in-confidence information has been removed] respectively.

Recommendations

This report summarizes the best available evidence and discusses its implications, but does not include recommendations about policy or clinical care.

Methods

Systematic reviews of RCTs and economic literature, along with a model-based economic evaluation, were carried out. Electronic databases were searched up to February 2007. Industry submissions to the National Institute for Health and Clinical Excellence were reviewed.

Further research/reviews required

Long-term, double-blind RCTs of sufficient sample size need to directly compare bosentan, sitaxentan, and sildenafil, and evaluate outcomes including survival, quality of life, maintenance on treatment, and impact on the use of resources for NHS and personal social services. Possible differences in treatment effects between subcategories of PAH and between patients of different FC at baseline should be investigated within and across these trials. More RCTs need to evaluate combinations of the technologies versus monotherapy, and studies investigating the feasibilities of replacing an ongoing treatment that failed to provide adequate control of the disease with a new treatment rather than adding the new treatment to the existing treatment.

Written by Dr Yen-Fu Chen, University of Birmingham, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/166

Title **The Clinical Effectiveness of Glucosamine and Chondroitin Supplements in Slowing or Arresting Progression of Osteoarthritis of the Knee: A Systematic Review and Economic Evaluation**

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Reference Volume 13.52. ISBN 1366-5278. www.hta.ac.uk/project/1717.asp

Aim

To assess the clinical and cost effectiveness of glucosamine sulphate/hydrochloride and chondroitin sulphate in modifying the progression of osteoarthritis (OA) of the knee.

Conclusions and results

There was evidence that glucosamine sulphate shows some clinical effectiveness in treating OA of the knee and evidence to support the potential clinical impact of glucosamine sulphate. The value of information analysis identified 3 research priorities: quality of life (QoL), structural outcomes, and knee arthroplasty. The biological mechanism of glucosamine sulphate and chondroitin remains uncertain, and the proposal that the active substance may be sulphate should be explored further. Five systematic reviews and one clinical guideline met the inclusion criteria. They reported inconsistent conclusions with only modest effects on reported pain and function. A reduction in joint space narrowing was more consistently observed, but the effect size was small and the clinical significance uncertain. A separate review of 8 primary trials of >12 months' duration showed evidence of statistically significant improvements in joint space loss, pain, and function for glucosamine sulphate, but the clinical importance of these differences was unclear. Two studies of glucosamine sulphate showed a reduced need for knee arthroplasty from 14.5% to 6.3% at 8 years' follow-up. For glucosamine, chondroitin, and combination therapy, less evidence supported a clinical effect. Cost-effectiveness modeling was restricted to glucosamine sulphate. Over a lifetime horizon the incremental cost per quality-adjusted life-year (QALY) gain for adding glucosamine sulphate to current care was estimated to be 21 335 pounds sterling (GBP). Deterministic sensitivity analysis suggested that the cost effectiveness of glucosamine sulphate therapy depended particularly on the magnitude of the QoL gain, the change in knee arthroplasty probability with therapy, and the discount rate. At a cost per QALY gained threshold of GBP 20 000, the likelihood that glucosamine sulphate would be more cost effective than current care is 0.43, while at a threshold of GBP 30 000, the probability rises to 0.73. Probabilistic sensitivity analysis showed that estimates were imprecise and subject to a degree of decision uncertainty. Value of information analysis demonstrated the need for further research. Several biologically plausible mechanisms of action for glucosamine sulphate and chondroitin were proposed.

Recommendations

No trial data came from the UK, and in the absence of good UK data about the current referral practice, management, and surgical rate, caution should be exercised in generalizing these data to UK health care. Cost effectiveness was not conclusively demonstrated, with substantial uncertainty related to the magnitude and duration of QoL gain following treatment. There was evidence from biological studies to support the potential clinical impact of glucosamine sulphate. For other agents, the evidence base was less consistent (chondroitin) or absent (glucosamine hydrochloride).

Methods

See Executive Summary link www.hta.ac.uk/project/1717.asp.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1717.asp.

Written by Dr Corri Black, University of Aberdeen, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/167

Title **Sensitivity Analysis in Economic Evaluation: An Audit of NICE Current Practice and a Review of Its Use and Value in Decision-Making**

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Reference Volume 13.29. ISBN 1366-5278. www.hta.ac.uk/project/1673.asp

Aim

To determine how we define good practice in sensitivity analysis in general and probabilistic sensitivity analysis (PSA) in particular, and to what extent it has been adhered to in the independent economic evaluations undertaken for the National Institute for Health and Clinical Excellence (NICE); to establish what policy impact sensitivity analysis has in the context of NICE, and policy-makers' views on sensitivity analysis and uncertainty, and what use is made of sensitivity analysis in policy decision making.

Conclusions and results

The review and the policy impact assessment focused exclusively on documentary evidence, excluding other sources that might have revealed further insights on this issue. Some cost-effectiveness work, especially around the sensitivity analysis components, represents a challenge in making it accessible to those making decisions. This speaks to the training agenda for those sitting on such decision-making bodies, and to the importance of clear presentation of analyses by the academic community. Practice in relation to univariate sensitivity analysis is highly variable, with considerable lack of clarity in relation to the methods used and the basis of the ranges employed. In relation to PSA, there is a high level of variability in the form of distribution used for similar parameters, and the justification for such choices is rarely given. Virtually all analyses failed to consider correlations within the PSA, and this is an area of concern. Uncertainty is considered explicitly in the process of arriving at a decision by the NICE Technology Appraisal Committee, and a correlation between high levels of uncertainty and negative decisions was indicated. The findings suggest considerable value in deterministic sensitivity analysis. Such analyses highlight which model parameters are critical to driving a decision. Strong support was expressed for PSA, principally because indicates the parameter uncertainty around the incremental cost-effectiveness ratio.

Recommendations

Both deterministic and probabilistic sensitivity analyses should be used to address parameter uncertainty. For methodological and structural uncertainties, repeated analyses should be run using different models in which uncertainties regarding model structure exist, or different methods in which there are uncertainties. In the process of conducting and implementing sensitivity analyses, good practice would involve a clear and full justification of the choice of included variables, along with an explanation of the information source used to specify the ranges. Threshold analysis should be supported, especially where the value of a particular parameter is indeterminate, but a rationale for, and definition of, the threshold applied should be provided. Regarding PSA, distributions should be placed around all important model parameters, and any excluded parameters must be justified. The distributional assumption for each variable should be justified and should relate to the nature of the variable. The distribution should be consistent with any logical bounds on parameter values given its nature. There might be value in clearer methodology guidelines on which distributions are appropriate for which parameters. Where correlation between variables is expected, joint distributions should be used, and independence should not be assumed.

Methods

See Executive Summary link www.hta.ac.uk/project/1673.asp.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1673.asp.

Written by Professor Stirling Bryan, University of British Columbia, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/168

Title **Communication of Carrier Status Information Following Universal Newborn Screening for Sickle Cell Disorders and Cystic Fibrosis: Qualitative Study of Experience and Practice**

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Reference Volume 13.57. ISBN 1366-5278. www.hta.ac.uk/project/1510.asp

Aim

To describe and explore current practice, methods, and experience of communicating carrier status information following newborn screening for cystic fibrosis (CF) and sickle cell (SC) disorders, to inform practice and further research.

Conclusions and results

Methods of communicating newborn carrier results vary across England. Parents' needs for timely and appropriate information may not be met. Respondents' experiences suggest a need for greater recognition of communication with individuals across a screening pathway, rather than as a discrete event. Methods for, and respondents' experiences of, communication of carrier results varied considerably within and between regions, and within and between SC and CF contexts. Approaches ranged from letter or telephone call, to in-person communication in a clinic or at home, with health professionals (eg, in hemoglobinopathy, CF, screening) or from community and primary care (eg, health visitors with SC carrier results). Health professionals identified pros and cons of different methods, preferring opportunity for face-to-face communication with parents where possible, particularly for CF carrier results. They were concerned by regional variations in protocols, the lack of availability of translated information on SC carrier results, and the feasibility of sustaining more specialist involvement at current levels, particularly for SC carriers. Parents were often poorly prepared for the possibility of a newborn carrier result. Some had felt overloaded by screening information received during pregnancy or prior to newborn screening, or found this information failed to meet their needs. Face-to-face communication of results was valued by parents of SC carriers and appeared particularly necessary for those without prior knowledge of SC carrier status, or where English was not their first language. Indirect communication of results by letter appeared effective and feasible for parents more aware of SC carrier status from antenatal or earlier experience, and where this communication contained an unambiguous opening statement emphasizing, "your child is not ill".

Recommendations

See Executive Summary link www.hta.ac.uk/project/1510.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1510.asp.

Further research/reviews required

Further research is needed to: (a) design and evaluate information for parents approached for a repeat blood spot in CF screening; (b) explore the value of refining prescreening information to better prepare parents for the possibility of carrier identification; (c) develop and evaluate the accessibility and acceptability of translated forms of standardized SC carrier result information; (d) prospectively study or audit practice with the further establishment of screening programs; (e) investigate how health professionals use and present information across the screening pathway; (f) develop and evaluate support and training for health professionals involved in screening to be able to communicate relevant information; (g) examine the use of differing mixed service models according to local contexts; (h) investigate parents' attitudes towards, access to, and experience of further carrier testing for themselves or their other children, and its impact on later reproductive decisions. (For further details see Executive Summary link www.hta.ac.uk/project/1510.asp.)

Written by Professor Joe Kai, University of Nottingham, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/169

Title **Development of a Toolkit and Glossary to Aid in the Adaptation of Health Technology Assessment (HTA) Reports for Use in Different Contexts**

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Reference Volume 13.59. ISBN 1366-5278. www.hta.ac.uk/project/1511.asp

Aim

To develop a health technology assessment (HTA) adaptation toolkit and glossary of adaptation terms for use by HTA agencies in EU member states.

Conclusions and results

These resources have been developed to help HTA agencies make better use of HTA reports produced elsewhere. Policy makers and clinicians could use these resources to aid in understanding HTA reports written for other contexts. The main implication of this work concerns the potential to adapt HTA reports. If utilized, this should release resources to enable development of further HTA reports. Recommendations for development of the toolkit include the potential to develop an interactive Web-based version and to extend the toolkit to facilitate the adaptation of HTA reports on diagnostic testing and screening. The resulting toolkit is a collection of resources, eg, checklists of questions on relevance, reliability, and transferability of data and information, and links to useful websites, that help the user assess whether data and information in HTA reports can be adapted for different settings. The toolkit is designed for the adaptation of evidence synthesis rather than primary research. The accompanying glossary provides descriptions of meanings for HTA adaptation terms from HTA agencies across Europe. It seeks to highlight differences in the use and understanding of each word by HTA agencies. The toolkit and glossary are available for use by all HTA agencies and can be accessed via www.eunethta.net.

Recommendations

The toolkit has implications for practice: 1) Preparation of HTA reports requires both time and financial resources. Adapting an existing HTA report may reduce the cost and time incurred in producing new reports. 2) This may to lead to an increased potential for HTA organizations to have the resources available to report on a greater breadth of new health technologies.

Methods

The toolkit and glossary were developed by a partnership of 28 HTA agencies and networks across Europe (EUnetHTA work package 5), led by the UK's National Coordinating Centre for Health Technology Assessment (NCCHTA). Methods employed for the two resources were literature searching, a survey of adaptation experience, two rounds of a Delphi survey, meetings of the partnership and drawing on the expertise and experience of the partnership, two rounds of review, and two rounds of quality assurance testing. All partners were requested to provide input into each stage of development.

Further research/reviews required

Recommendations for further development of the toolkit are: 1) The toolkit is currently in a PDF version and there is the potential to develop an interactive Web-based version. 2) The toolkit could be extended to facilitate adaptation of HTA reports on diagnostic testing and screening. 3) There is scope for further testing, review, and improvement both within the EUnetHTA partnership and beyond to external organizations. 4) A wiki-version of the glossary could be developed. 5) More work could be undertaken to incorporate closer integration with other EUnetHTA outputs.

Written by Dr Ruairidh Milne, University of Southampton, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/170

Title **The Clinical and Cost Effectiveness of Testing For Cytochrome P450 Polymorphisms in Patients Treated with Antipsychotics: A Systematic Review and Economic Evaluation**

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Reference Volume 14.03. ISBN 1366-5278. www.hta.ac.uk/project/1714.asp

Aim

To determine whether testing for cytochrome P450 (CYP) polymorphisms in adults entering antipsychotic treatment for schizophrenia leads to improved outcomes, is useful in medical, personal or public health decision making, and is a cost effective use of healthcare resources.

Conclusions and results

Tests to determine genotypes appear to be accurate, but not all aspects of analytical validity were reported. Given the absence of convincing evidence from clinical validity studies, the lack of clinical utility and economic studies, and the unsuitability of published schizophrenia models, no model was developed. Instead, key features and data requirements for economic modeling are presented. For analytical validity, 46 studies of different genotyping tests for 11 different CYP polymorphisms (most commonly CYP2D6) were included. Sensitivity and specificity were high (99%-100%). For clinical validity, 51 studies were found. In patients tested for CYP2D6, an association between genotype and tardive dyskinesia (including Abnormal Involuntary Movement Scale scores) was found. The only other significant finding linked the CYP2D6 genotype to Parkinsonism. One small unpublished study met the inclusion criteria for clinical utility.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1714.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1714.asp.

Further research/reviews required

Although the evidence base does not support the use of pharmacogenetic testing in this area, it does indicate that further study in each of the key areas is needed to either demonstrate or refute the ability of pharmacogenetic testing to assist in developing individualized patient care in schizophrenia. Recommendations for future research cover both aspects of research quality and data that will be required to inform the development of future economic models. Analytical validity 1) Studies of analytical validity need to be explicit about patient selection, quality control, assay robustness, and the sensitivity and specificity of tests. Study findings should not only report on allele frequencies, but also report appropriate genotype data. Clinical validity 1) Further evidence must link phenotype to genotype. Prospective studies need to include larger numbers of patients with the UM (multiple copies of the wt allele) and poor metaboliser (mut/mut) phenotypes. 2) Studies need to consider the impact of environmental factors, eg, smoking, concomitant medicines, medication adherence, and ethnicity. In relation to medication adherence, genotypes need to be related not only to clinical parameters, but also to pharmacokinetic parameters. 3) Studies need to ensure that all currently used antipsychotics are investigated. However, given the uncertainty about the full extent of the role played by CYP2D6, further studies focusing on patients taking risperidone and olanzapine would also be useful. 4) Future research must consider a comprehensive approach that considers not only CYP isoforms involved in the metabolism of antipsychotics, but also other targets, eg, dopamine and 5-hydroxytryptamine receptors. Clinical utility 1) Prospective clinical utility studies are needed. As with clinical validity they should ensure that all currently used antipsychotics are investigated although, given their importance to the NHS (and the uncertainty about the full extent of the role played by CYP2D6), further studies focusing on patients taking risperidone and olanzapine would be particularly useful.

Written by Mr Nigel Fleeman, University of Liverpool, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/171

Title **A Systematic Review of Outcome Measures Used in Forensic Mental Health Research with Consensus Panel Opinion**

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Reference Volume 14.18. ISSN 1366-5278. www.hta.ac.uk/project/1583.asp

Aim

To use a structured review and a consensus panel to describe and assess outcome measures in forensic mental health research.

Conclusions and results

A wide range of domains are relevant in assessing outcomes of interventions in forensic mental health services. Evaluations need to consider public safety, but also clinical, rehabilitation, and humanitarian outcomes. Recidivism is a high priority; the public expects interventions that will reduce future criminal behavior. Greater attention must be given to validity of measurement, given the variety of approaches to measurement. More research is needed on methods to take account of the heterogeneity of seriousness of forms of recidivism in outcome measurement. Validity of self-report instruments regarding recidivism also needs further study. Mental health is an important dimension of outcome. The review provides support for the view that domains such as quality of life, social function, and psychosocial adjustment have not been extensively employed in forensic mental health research, but are relevant and important. The role of such instruments needs greater consideration. The final sample of eligible studies for inclusion in the review consisted of 308 separate studies obtained from 302 references. The consensus group agreed on 11 domains of forensic mental health outcome measurement, all of which were considered important. Nine different outcome measure instruments were used in more than 4 different studies. The most frequently used outcome measure was used in 15 studies. The consensus group found that many domains beyond recidivism and mental health were important, but under-represented in the review of outcomes. Current instruments that may show future promise in outcome measurement included risk assessment tools. The outcome measure of repeat offending behavior was the most frequently used, occurring in 72% of the studies included in the review. Its measurement varied with position in the criminal justice system, offence specification, and measurement method. The consensus group believed that recidivism is only an indication of the amount of antisocial acts that are committed.

Recommendations

Evaluations need to take account of public safety, but also clinical, rehabilitation, and humanitarian outcomes. Recidivism is a high priority; the public expects interventions that will reduce future criminal behavior. Greater attention needs to be given to validity of measurement, given the variety of approaches to measurement. More research is needed on methods to take account of the heterogeneity of seriousness of forms of recidivism in outcome measurement. Further research is needed on validity of self-report instruments regarding recidivism.

Methods

See Executive Summary link www.hta.ac.uk/project/1583.asp.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1583.asp.

Written by Professor Ray Fitzpatrick, University of Oxford, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/172

Title **Antenatal Screening for Hemoglobinopathies in Primary Care: A Cohort Study and Cluster Randomized Trial to Inform a Simulation Model. The Screening for Hemoglobinopathies in First Trimester (SHIFT) Trial**

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Reference Volume 14.20. ISSN 1366-5278. www.hta.ac.uk/project/1401.asp

Aim

To assess the effectiveness, acceptability, and feasibility of offering universal antenatal sickle cell and thalassaemia (SCT) screening in primary care when pregnancy is first confirmed; and to model the cost effectiveness of early screening in primary care versus standard care.

Conclusions and results

Offering antenatal SCT screening as part of pregnancy-confirmation consultations significantly increased the proportion of women screened before 10 weeks (70 days), from 2% in standard care (SC) to between 16% and 27% in primary care (PC), but additional resources may be required to implement this. No evidence supported offering fathers screening at the same time as women. For 1441 eligible women in the cohort phase, the median (interquartile range [IQR]) gestational age at pregnancy confirmation was 7.6 weeks (6.0-10.7 weeks) and 74% presented in primary care before 10 weeks. The median gestational age at screening was 15.3 weeks (IQR 12.6-18.0 weeks). Only 4.4% were screened before 10 weeks. The median delay between pregnancy confirmation and screening was 6.9 weeks (4.7-9.3 weeks). In the intervention phase, 1708 pregnancies from 25 practices were assessed for the primary outcome measure. The proportion of women screened by 10 weeks (70 days) was 9/441 (2%) in SC, compared with 161/677 (24%) in PC with parallel testing, and 167/590 (28%) in PC with sequential testing. The proportion of women offered screening by 10 weeks (70 days) was 3/90 (3%) in SC, compared with 321/677 (47%) in PC with parallel testing, and 281/590 (48%) in PC with sequential testing. The proportion of women screened by 26 weeks (182 days) was similar across the three groups: 324/441 (73%) in SC, 571/677 (84%, 0.09) in PC with parallel testing, and 481/590 (82%, 0.148) in PC with sequential testing. The screening uptake of fathers was 51/677 (8%) in PC with parallel testing, and 16/590 (3%) in PC with sequential testing, and 13/441 (3%) in SC. The predicted average total cost per pregnancy of offering antenatal SCT screening was estimated to be 13 pounds sterling (GBP) in standard care, GBP 18.50 in primary care with parallel testing, and GBP 16.40 in primary care with sequential testing. The incremental cost-effectiveness ratio (ICER) was GBP 23 in PC with parallel testing and GBP 12 in PC with sequential testing when compared with SC. Women offered testing in PC were as likely to make an informed choice as those offered screening by midwives later in pregnancy, but less than one-third of women overall made an informed choice about screening.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1401.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1401.asp.

Further research/reviews required

The following recommendations are equally weighted: 1) The principal value of early testing is that it provides carrier couples with the option of prenatal diagnostic testing in the early stages of pregnancy and, for those found to have an affected pregnancy, the option of a termination at an early stage. Evidence regarding the strength of value attached to earlier terminations is weak. It would be useful to determine the impact of gestational age at screening on uptake of prenatal diagnostic testing and reproductive decisions following the detection of affected pregnancies.

Written by Professor Theresa Marteau, Kings College London, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/173

Title **Early Referral Strategies for Management of People with Markers of Renal Disease: A Systematic Review of the Evidence of Clinical Effectiveness, Cost-Effectiveness and Economic Analysis**

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Reference Volume 14.21. ISSN 1366-5278. www.hta.ac.uk/project/1688.asp

Aim

To systematically review the evidence of the clinical and cost effectiveness of early referral strategies in managing people with markers of renal disease.

Conclusions and results

Despite the focus on the early identification and proactive management of chronic kidney disease (CKD) in the past few years, we have identified significant evidence gaps about how best to manage people with CKD. Some evidence suggests that care of people with CKD could improve, and because these people are at risk for both renal and cardiovascular outcomes, strategies to improve the management of people with CKD could potentially offer efficient use of care resources. Given the number of people having markers of kidney impairment, the need for further research to support change is urgent. In 36 relevant natural history studies, CKD was found to be a marker of increased risk of mortality, renal progression, and end-stage renal disease. Mortality was generally high and increased with stage of CKD. After adjustment for comorbidities, the relative risk of mortality among those with CKD identified in the general population increased with stage. Relative risk was higher in clinical populations. All 3 outcomes increased as the estimated glomerular filtration rate (eGFR) fell. Only 7 studies (no randomized controlled trials) were identified as relevant to assessing the clinical effectiveness of early referral strategies for CKD. In the 5 retrospective studies constructed from cohorts starting on renal replacement therapy (RRT), mortality was reduced in the early referral group (more than 12 months prior to RRT) even as late as 5 years after initiation of RRT. Only 2 studies included predialysis participants. One study, in people screened for diabetic nephropathy, reported a reduction in the decline of renal function associated with early referral to nephrology specialists (eGFR decline 3.4 ml/min/1.73 m2) when compared with a similar group that had no access to nephrology services until dialysis was required (eGFR decline 12.0 ml/min/1.73 m2). The second study, in a group of veterans with 2 creatinine levels of at least 140 mg/dl, reported that a composite endpoint of death or progression was lower in the group receiving nephrology follow-up than in those receiving primary care follow-up alone. The greatest effect was observed in those with stage 3 disease, or worse, after adjusting for comorbidities, age, race, smoking, and proteinuria – stage 3: hazard ratio (HR) 0.8 (95% confidence interval [CI] 0.61 to 0.9) or stage 4: HR 0.75 (95% CI 0.45 to 0.89). In the base-case analysis, all early referral strategies produced more quality-adjusted life-years (QALYs) than referral upon transit to stage 5 CKD (eGFR 15 ml/min/1.73 m2). Referral for everyone with an eGFR below 60 ml/min/1.73 m2 (stage 3a CKD) generated the most QALYs, and compared with referral for stage 4 CKD (eGFR < 30 ml/min/1.73 m2) had an incremental cost-effectiveness ratio of approximately 3806 pounds sterling (GBP) per QALY. Limitations: The Markov model relied on many assumptions due to a lack of data on the natural history of CKD in individuals without diabetes and a lack of evidence on the costs and effects of early referral. The findings were particularly sensitive to changes in eGFR decline rates and the relative effect of early referral on CKD progression and cardiovascular events; the latter parameter being derived from a single nonrandomized study.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1688.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1688.asp.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1688.asp.

Written by Dr Corri Black, Section of Population Health, University of Aberdeen, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/174

Title **A Randomized Controlled Equivalence Trial to Determine the Effectiveness and Cost-Utility of Manual Chest Physiotherapy Techniques in the Management of Exacerbations of Chronic Obstructive Pulmonary Disease (MATREX)**

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Reference Volume 14.23. ISSN 1366-5278. www.hta.ac.uk/project/1416.asp

Aim

To estimate the effect, if any, of manual chest physiotherapy (MCP) administered to patients hospitalized with chronic obstructive pulmonary disease (COPD) exacerbation on both disease-specific and generic health-related quality of life; and to compare the health service costs for those receiving and not receiving MCP.

Conclusions and results

Although MCP did not appear to affect longer-term quality of life, this does not mean that it has no therapeutic value to patients with COPD. Cost-effectiveness analysis suggested that its use was cost-effective, but this finding was uncertain. Hence, it would be difficult to justify providing MCP therapy on the basis of cost effectiveness alone. Of the 526 participants, 261 were allocated to MCP and 264 to control, with 186 participants evaluable in each arm. Intention to treat (ITT) analyses indicated no significant difference at 6 months postrandomization in total SGRQ score, SGRQ symptom score, SGRQ activity score, or SGRQ impact score. The imputed ITT and per-protocol results were similar. No significant differences were observed in any of the outcome measures or subgroup analyses. Compared with no MCP, employing MCP was associated with a slight loss in quality of life and lower health service costs, ie, cost saving of 410.79 pounds sterling (GBP). Based on these estimates, at a cost-effectiveness threshold of L = GBP 20 000 per QALY, MCP would constitute a cost-effective use of resources (net benefit = GBP 376.14). However, a high level of uncertainty was associated with these results, and it is possible that the lower health service costs could have been due to other factors.

Recommendations

In terms of longer-term quality of life, the use of MCP does not appear to affect outcome in patients hospitalized for COPD exacerbation. Although the cost-effectiveness analysis suggested that MCP was cost-effective, this finding is uncertain. Implications for health care: This study addressed the limitations of previous research by standardizing the delivery of MCP and obtaining a sample of sufficient size to derive statistically robust results for a patient-orientated, clinically meaningful outcome.

Methods

See Executive Summary link www.hta.ac.uk/project/1416.asp.

Further research/reviews required

With respect to the primary aim of the MATREX trial, further research is not required to demonstrate equivalence between receiving and not receiving MCP. Further research on cost-effectiveness is unlikely to yield gains, as the benefits of both MCP and no MCP were similar. Hence, the consequences of making the wrong decision are small. As such, the cost of further research is likely to outweigh the value of information that would be gained. However, the findings of this study do not mean that MCP has no therapeutic value for patients with COPD in specific circumstances. The research questions arising from this study, in order of priority, are: 1) Is MCP effective for patients with COPD producing high volumes of sputum? 2) Can the risk of oxygen desaturation during MCP be predicted? 3) Is the active cycle of breathing technique (ACBT) effective in treating COPD exacerbation? 3) What are the trends over time in admission and survival rates for COPD? 4) How can health-related resource use be more accurately identified?

Written by Dr Jane Cross, School of Allied Health Professions, University of East Anglia, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/175

Title **A Systematic Review and Economic Evaluation of the Clinical Effectiveness and Cost Effectiveness of Aldosterone Antagonists for Postmyocardial Infarction Heart Failure**

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Reference Volume 14.24. ISSN 1366-5278. www.hta.ac.uk/project/1817.asp

Aim

Two aldosterone inhibitors (spironolactone and eplerenone) are licensed for heart failure (HF) in the UK. Recent clinical guidelines recommend eplerenone after acute myocardial infarction (MI) for patients with symptoms and/or signs of HF and left ventricular dysfunction (LVSD).

Conclusions and results

Only two large randomized control trials (RCTs) of aldosterone inhibitors in patients with HF and LVSD were found: EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study), which examined the effectiveness of eplerenone in patients with HF within 3 to 14 days of an acute MI, and RALES (Randomized Aldactone Evaluation Study), which examined the effectiveness of spironolactone in the HF population. Structural similarity of spironolactone and eplerenone suggests that they may be interchangeable, but trial differences limited formal indirect comparison between the trials. A network of evidence from smaller trials was used to facilitate indirect comparison of eplerenone and spironolactone.

Relative safety data were limited from RCTs and observational sources. Hyperkalemia rates varied, but were generally higher than for placebo; data were insufficient to assess discontinuation because of hyperkalemia. Gynecomastia rates were higher with spironolactone. The decision analytic model indicated that, compared with usual care, use of an aldosterone antagonist appears to be a highly cost-effective strategy in managing postMI HF in the NHS. Eplerenone was the most cost-effective strategy for postMI HF; ICER of eplerenone compared with standard care was 4457 pounds sterling (GBP) per QALY, increasing to GBP 7893 per QALY if treatment continued over the patient's lifetime. In neither scenario did spironolactone appear cost effective. The ICER of eplerenone was consistently under the GBP 20 000 to GBP 30 000 per QALY threshold used to establish value for money in the NHS.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1817.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1817.asp.

Further research/reviews required

An adequately powered, well-conducted RCT that directly compares spironolactone and eplerenone is required to provide more robust evidence on the optimal management of postMI HF patients. Differences in mortality appear to be the major source of current uncertainty. Hence, design and follow-up should reflect this. Given the lack of evidence for either drug in terms of hospitalizations, additional data on nonfatal events requiring hospitalization and side effects would be important outcomes. Estimates of the expected value of perfect information appear sufficiently high to conclude that a head-to-head RCT is likely to provide value for money. Should a future RCT be considered, then a more formal assessment of the costs and benefits should be conducted using the cost-effectiveness model presented here to ensure that this is done efficiently and to assess the feasibility of conducting such a trial.

Written by Dr Claire McKenna, University of York, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/176

Title **Avoiding and Identifying Errors in Health Technology Assessment Models**

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Reference Volume 14.25. ISSN 1366-5278. www.hta.ac.uk/project/1672.asp

Aim

To provide a basis for further research on improving modeling for HTA decision support; and to describe the model development process as perceived by practitioners in the HTA community.

Conclusions and results

Four primary objectives are to: (1) describe the current understanding of errors in HTA models; (2) understand current processes for avoiding errors in developing, debugging, and critically appraising models for errors; (3) develop taxonomy of model errors; and (4) explore methods and procedures to reduce the occurrence of errors in models.

There was no common language in the discussion of modeling errors, with inconsistency in the perceived boundaries of what constitutes an error. Asked about the definition of model error, interviewees tended to exclude matters of judgment from being errors and focus on "slips" and "lapses", but this comprised less than 20% of the discussion on errors. Interviewees focused primarily on the softer elements of the modeling process, eg, defining the decision question and conceptual modeling, mostly the realms of judgment, skills, experience, and training. The original focus concerned model errors, but it may be more useful to refer to modeling risks. Several interviewees discussed concepts of validation and verification, with notable consistency in interpretation. The HTA error classifications were compared against existing classifications of model errors in the broader literature. Interviewees discussed examples of all major error types. Clarity and mutual understanding were identified as key issues for avoiding errors in HTA models. However, the implementation of techniques and processes for ensuring clarity is not framed within any overall strategy for structuring complex problems.

Recommendations

Published definitions of model validation and verification are consistent with the views expressed by the HTA community and are recommended as the basis for further discussions of model credibility. Such discussions should focus on risks, including errors of implementation, errors in matters of judgment, and violations. Research on modeling risks should recognize the complex network of cognitive breakdowns that lead to errors in models; existing research on the cognitive basis of human error should be included in an examination of modeling errors. There is a need to improve understanding of the skills needed to develop, operate, and use HTA models. Model credibility is the central concern of decision-makers using models. Interaction between modeler and decision maker in developing a mutual understanding of a model establishes that model's significance and its warranty. Hence, it is crucial not to externalize the concept of model validation from decision-makers and the decision-making process.

Methods

Qualitative study including in-depth interviews and methodological review.

Further research/reviews required

Further research on the theory of model verification and validation is required to provide a solid base for model development and processes for producing evidence-based policy and guidance. Research is required in the model development process, specifically (1) techniques and processes for structuring complex HTA models and (2) the model design and specification process and techniques reporting. Research is required to define, implement, and evaluate modifications to the modeling process with the aim to prevent errors and improve identification of errors in models.

Written by Mr James Chilcott, ScHARR, University of Sheffield, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/177

Title **Botuls: A Multicentre Randomized Controlled Trial to Evaluate the Clinical Effectiveness and Cost Effectiveness of Treating Upper Limb Spasticity due to Stroke with Botulinum Toxin Type A**

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Reference Volume 14.26. ISSN 1366-5278. www.hta.ac.uk/project/1408.asp

Aim

To compare the clinical and cost effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A plus an upper limb therapy program versus the upper limb therapy program alone.

Conclusions and results

There was no significant difference between the study groups (intervention: botulinum toxin type A plus upper limb therapy; control: upper limb therapy alone) for the primary outcome of improved arm function at 1 month. This was achieved by 30/154 (19.5%) in the control group and 42/167 (25.1%) in the intervention group ($p = 0.232$). No significant differences in improved arm function were seen at 3 or 12 months. In terms of secondary outcomes, muscle tone/spasticity at the elbow was decreased in the intervention group compared with the control group at 1 month. The median change in the Modified Ashworth Scale was – 1 in the intervention group compared to zero in the control group ($p < 0.001$). No difference in spasticity was seen at 3 or 12 months. Participants treated with botulinum toxin type A showed improvement in upper limb muscle strength at 3 months. The mean change in strength from baseline (upper limb component of the Motricity Index) was 3.5 (95% CI 0.1 to 6.8) points greater in the intervention group compared to the control group. No differences were seen at 1 or 12 months. Participants in the intervention group were more likely to undertake specific basic functional activities, eg, dress a sleeve, clean the palm, and open the hand for cutting fingernails. At 1 month, 109/144 (75.7%) of the intervention group and 79/125 (63.2%) of the control group had improved by at least 1 point on a 5-point Likert scale for at least one of these tasks ($p = 0.033$). At 3 months the corresponding proportions were 102/142 (71.8%) of the intervention group and 71/122 (58.2%) of the control group ($p = 0.027$). Improvement was sustained at 12 months for opening the hand to clean the palm and opening the hand to cut the nails, but not for other activities. Pain rating improved by 2 points on a 10-point severity rating scale in the intervention group versus zero points in the control group ($p=0.004$) at 12 months, but no significant differences were seen at 1 or 3 months. The base case incremental cost effectiveness ratio was 93 500 pounds sterling (GBP) per quality adjusted life year (QALY) gained. Estimation of the cost effectiveness acceptability curve for botulinum toxin type A plus the upper limb therapy program indicated that there was only a 0.36 probability of its being cost effective at a threshold ceiling ratio of GBP 20 000 per QALY (willingness to pay for a QALY by NHS decision makers).

Recommendations

This randomized controlled trial suggests that most stroke patients with upper limb spasticity will not achieve enhanced improvement in active upper limb function by the addition of botulinum toxin to an upper limb therapy program. However, botulinum toxin type A may improve the ability of some patients to undertake basic upper limb functional tasks and may reduce pain at 12 months. Despite some clinical benefits, the addition of botulinum toxin type A to an upper limb therapy program does not appear to be a cost-effective treatment for the patients included in this study.

Methods

See Executive Summary link www.hta.ac.uk/project/1408.asp.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1408.asp.

Written by Professor Helen Rodgers, Newcastle University, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/178

Title **Systematic Review of the Clinical Effectiveness and Cost Effectiveness of Rapid Point-Of-Care Tests for the Detection of Genital Chlamydia Infection in Women and Men**

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Reference Volume 14.29. ISSN 1366-5278. www.hta.ac.uk/project/1795.asp

Aim

To assess whether or not the point-of-care Chlamydia Rapid Test (CRT) could improve detection of genital chlamydia, and whether it, or any other point-of-care test, is more effective than current practice using nucleic acid amplification tests (NAATs) in terms of the number of cases of chlamydia detected and treated and the proportion of partners identified and treated.

Conclusions and results

Limited evidence suggests that NAATs remain the most accurate and cost-effective way to diagnose chlamydia infection. In some circumstances point-of-care tests could be provided in addition to existing NAAT services, but there is little evidence on point-of-care methods in such settings. Robust evidence of the diagnostic accuracy of point-of-care tests for different types of samples is required, as are studies evaluating clinical effectiveness outcomes for these tests in comparison with NAATs. The analysis included 13 studies enrolling 8817 participants. In the pooled estimates for CRT, sensitivity (95% CI) was 80% (73%-85%) for vaginal swab specimens and 77% (59%-89%) for first void urine (FVU) specimens. Specificity was 99% (99%-100%) for vaginal swab specimens and 99% (98%-99%) for FVU specimens. In the pooled estimates for a comparator point-of-care test (Clearview Chlamydia), sensitivity (95% CI) was 52% (39%-65%) for vaginal, cervical, and urethral swab specimens combined, and 64% (47%-77%) for cervical specimens alone. Specificity was 97% (94%-100%) for vaginal, cervical, and urethral swab specimens combined, and 97% (88%-99%) for cervical specimens alone. Results of the economic evaluation showed that for a hypothetical cohort of 1000 people, the current practice of NAAT testing (using polymerase chain reaction) would result in 12.63 people who were offered testing being correctly treated and having their sexual partners contacted, at a cost of 7070 pounds sterling (GBP) (for the whole cohort). For the CRT, the number being correctly treated would be 10.98, at a cost of GBP 7180. For the Clearview Chlamydia test, the number correctly treated would be 7.14, at a cost of GBP 7170. Hence, both point-of-care tests were more costly and less effective than current practice.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1795.asp.

Methods

Electronic searches, eg, in MEDLINE, EMBASE, BIOSIS, and CENTRAL, identified published and unpublished reports. The most recent search was conducted in November 2008. The types of studies considered were randomized controlled trials (RCTs) for the reviews of diagnostic accuracy and effectiveness, direct head-to-head studies for the review of diagnostic accuracy, and nonrandomized comparative studies if an insufficient number of RCTs were identified to review effectiveness. Participants were sexually active adolescents and adults being tested for or suspected of having genital chlamydia infection. The tests considered were the CRT and other comparator point-of-care tests using a NAAT as a reference standard. One reviewer screened the titles and abstracts of reports identified by the search strategy. Two reviewers independently assessed full-text reports of potentially relevant studies. One reviewer extracted data from the included full-text studies, which were checked by the second reviewer. For the diagnostic accuracy review, two reviewers independently assessed the quality of all included studies using a modified version of the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) instrument.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1795.asp.

Written by Ms Jenni Hislop, University of Aberdeen, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/179

Title **Systematic Review and Cost-Effectiveness Evaluation of 'Pill-In-The-Pocket' Strategy for Paroxysmal Atrial Fibrillation Compared to Episodic In-Hospital Treatment or Continuous Antiarrhythmic Drug Therapy**

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Reference Volume 14.31. ISSN 1366-5278. www.hta.ac.uk/project/1944.asp

Aim

To summarize the results of the rapid reviews of clinical and cost effectiveness of the pill-in-the-pocket (PiP) approach to treat patients with paroxysmal atrial fibrillation (PAF); and to develop an economic model to assess the cost effectiveness of PiP compared with in-hospital treatment (IHT) or continuous antiarrhythmic drugs (AADs) in treating patients with PAF.

Conclusions and results

Overall, a PiP strategy seems to be slightly less effective (ie, fewer QALYs gained) than AAD and IHT, but is associated with cost savings. A PiP strategy seems to be more efficacious and cost effective than an AAD strategy in men aged over 65 years and women aged over 70 years, but this is principally due to a slight difference in QALY gained by the PiP strategy. A change in clinical practice that includes the introduction of PiP may save costs, but also involves a reduction in clinical effectiveness compared to existing approaches used to treat patients with PAF. Uncertainty in the available clinical data means there was insufficient evidence to support a recommendation for using a PiP strategy in patients with PAF. Further research should identify outcomes of interest, eg, adverse events and recurrent AF episodes in a randomized controlled trial (RCT) setting because the only clinical study addressing these issues is a descriptive analysis. Patient preferences also need to be considered in future research designs. The search strategies for clinical studies identified 201 RCTs, of which 12 were deemed relevant to the decision problem as they included drugs used to treat PAF. Summary data were abstracted from these studies to inform the development of the economic model only. The model results indicate that the PiP strategy is slightly less effective than the other two strategies, but also less costly ¬– an incremental cost-effectiveness ratio of 45 916 pounds sterling (GBP) per QALY when compared to AAD, and GBP 12 424 per QALY when compared to IHT. One-way sensitivity analyses do not show substantial changes in relative cost effectiveness except in relation to the age of patients, where PiP dominates AAD in men aged over 65 years and in women aged over 70 years. At a threshold of GBP 25 000 per QALY, IHT has the maximum probability of being cost effective at this threshold. For threshold values between GBP 0 and GBP 9266 per QALY, PiP is the option exhibiting the maximum probability of being cost effective. The AAD strategy has a poor probability of being cost effective under any threshold. However, none of the strategies considered has more than a 40% probability of being cost effective at a threshold of GBP 25 000 per QALY at any threshold level. This demonstrates the uncertainty around the parameters and its effect on the decision to choose any one strategy over the others.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1944.asp.

Methods

Electronic searches identified clinical- and cost-effectiveness evidence describing the use of a PiP strategy to treat PAF; evidence published since the release of the Royal College of Physicians' national guidelines on AF in June 2006. An additional search was undertaken, excluding the term 'pill-in-the-pocket' to identify economic evaluations and costing studies describing the comparator treatments to support the development of the economic model.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1944.asp.

Written by Dr Carlos Martin Saborido, University of Liverpool, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/180

Chemoprevention of Colorectal Cancer: Systematic Review and Economic Evaluation

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Reference Volume 14.32. ISSN 1366-5278. www.hta.ac.uk/project/1696.asp

Aim

To evaluate the clinical and cost effectiveness of drug and micronutrient interventions in preventing colorectal cancer (CRC) and/or adenomatous polyps.

Conclusions and results

Interventions considered include: nonsteroidal antiinflammatory drugs (NSAIDs), including aspirin and cyclo-oxygenase-2 (COX-2) inhibitors; folic acid; calcium; vitamin D; and antioxidants, eg, vitamin A, vitamin C, vitamin E, selenium, and beta-carotene. Chemoprevention was assessed in the general population, in individuals at increased risk of CRC, and in individuals with familial adenomatous polyposis (FAP) or hereditary nonpolyposis colorectal cancer (HNPCC). A search identified 44 relevant RCTs and 6 ongoing studies. Studies of aspirin versus no aspirin in individuals with a history of adenomas or CRC demonstrated reductions in risk of adenoma recurrence and advanced adenoma incidence. In the general population, studies of aspirin with a 23-year follow-up demonstrated a reduction in CRC incidence. A small study of aspirin in FAP patients demonstrated a possible reduction in polyp size. Use of celecoxib in individuals with a history of adenomas gave reductions in risk of adenoma recurrence and advanced adenoma incidence. Studies of non-aspirin NSAIDs in individuals with FAP demonstrated reductions in polyp number and size. No studies assessed non-aspirin NSAIDs in the general population. Studies of calcium in individuals with a history of adenomas demonstrated a reduced risk of adenoma recurrence, but no significant reduction in risk of advanced adenomas. In the general population, there was no significant effect of calcium on risk of CRC, although studies were of relatively short duration. Calcium use by FAP patients produced no significant reduction in polyp number. Folic acid showed no significant effect on adenoma recurrence or advanced adenoma incidence in individuals with a history of adenomas, or on incidence of CRC in the general population, although population studies were of relatively short duration. Studies of antioxidants demonstrated no significant effect on adenoma recurrence in individuals with a history of adenomas, or on incidence of CRC in the general population. There were no studies of folic acid or antioxidants in individuals with FAP or HNPCC. Economic analysis suggests that chemoprevention has the potential to represent a cost-effective intervention, particularly when targeted at intermediate-risk populations following polypectomy. Both aspirin and NSAIDs are associated with adverse effects so it would be important to consider the risk-benefit ratio before recommending these agents for chemoprevention.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1696.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1696.asp.

Further research/reviews required

Some interventions (aspirin, NSAIDs, and calcium) significantly reduced adenoma recurrence in individuals with a history of adenoma. Further research is needed to investigate the longer-term risk-benefit of potentially effective chemopreventive agents (eg, whether there is a dose level with significant benefit without unacceptable toxicity), necessary treatment durations, whether an effect on colorectal cancer can be demonstrated, and for how long the benefits are maintained after the intervention is stopped. Larger studies with longer treatment (eg, 10 years or more) and follow-up (eg, 20 years) and studies assessing colorectal cancer incidence as an outcome would be valuable.

Written by Dr Katy Cooper, University of Sheffield, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/181

Title **Cross-Trimester Repeated Measures Testing for Down's Syndrome Screening: An Assessment**

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Reference Volume 14.33. ISSN 1366-5278. www.hta.ac.uk/project/1620.asp

Aim

To provide estimates and confidence intervals for the performance (detection and false-positive rates) of screening for Down syndrome using repeated measures of biochemical markers from first and second trimester maternal serum samples taken from the same woman.

Conclusions and results

Using data on maternal serum samples taken between 11 and 13 weeks gestation and again in the second trimester, the study shows evidence of benefit from repeated measures of pregnancy-associated plasma protein-A (PAPP-A). If realized, the reduction of around 1% in false-positive rate with no loss in detection rate would give important benefits in terms of health service provision and the large number of invasive tests avoided. The benefit of using repeated measures decreased with increasing gestational age at the time of the first sample and was gone by 13 weeks gestation. More evidence is needed on earlier gestations (9 to 10 weeks) where repeated measures of PAPP-A may have very substantial benefits. The study showed little evidence of benefit from repeated measurements of unconjugated estriol (uE3) or human chorionic gonadotrophin (hCG).

Published distributional models for Down syndrome were inconsistent with the test data used for this study. Consequently, when these test data were classified using the published models, screening performance deteriorated substantially through the addition of repeated measures. This contradicts the optimistic results obtained from predictive modeling.

Recommendations

The evidence of potential benefit suggests the need for a prospective study of repeated measurements of PAPP-A with the first trimester serum sample taken between 9 and 11 weeks gestation. A formal clinical- and cost-effectiveness analysis should be undertaken.

Methods

Two independent test data sets including 121 pregnancies with Down syndrome and 605 controls were analyzed. These data had measurements of PAPP-A, uE3, and hCG taken in the first trimester and again in the second. Three prespecified analyses were undertaken: 1) independent tests of existing algorithms, 2) each of the two data sets was used to create a risk assessment algorithm that was tested on the other data set, and 3) an algorithm that used a pooled covariance matrix was fitted to the two data sets and assessed using a Bayesian approach, taking account of the uncertainty in parameter estimation.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1620.asp.

Written by Professor Dave Wright, University of Plymouth, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/182

Title **Exploring the Needs, Concerns and Behaviors of People With Existing Respiratory Conditions in Relation to the H1N1 Swine Influenza Pandemic: A Multicentre Survey and Qualitative Study**

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Reference Volume 14.34(1). ISSN 1366-5278. www.hta.ac.uk/project/2224.asp

Aim

To explore and compare information needs, worries, and concerns, and health-related behaviors regarding swine flu in people with respiratory conditions and their family members.

Conclusions and results

Participants were generally well-informed about swine flu, but more targeted information would have been welcomed. Participants were not highly anxious about swine flu, but did recognize risks for patients. Behavior change was modest, but in line with recommendations. Vaccination intent was high. Most patients (P) and family members (FM) wanted more information (n = 158, 62.5% P; n = 55, 54.4% FM), but few felt completely uninformed (n = 15, 5.9% P; n = 3, 3.0% FM). Most had already received information about swine flu (n = 187, 73.9% P; n = 78, 77.2% FM), mainly via a leaflet delivered to their home (n = 125, 49.4% P; n = 55, 54.5% FM). Information received was considered helpful (n = 154, 60.9% P; n = 77, 72.6% FM), but many wanted more condition-specific information (n = 141, 55.7% P; n = 60, 59.4% FM). More patients were worried than not worried about swine flu. Family members were less often concerned about personal risk than about risk to patients. Two-thirds incorrectly believed patients had increased risk of developing swine flu, but most correctly identified patients' greater risk of developing complications. Commonly adopted preventative measures were more frequent hand washing and greater use of sanitizing hand gel. In total, 212 patients (83.8%) and 69 family members (68.3%) were very/fairly likely to take up swine flu vaccination. Qualitative data mirrored survey findings.

Recommendations

See Executive Summary link www.hta.ac.uk/project/2224.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/2224.asp.

Further research/reviews required

1) Work to identify effective means of delivering targeted information to high-risk groups during a pandemic would be of particular value. 2) Follow-up to establish whether vaccination intentions were followed through (and, if not, why) would be of value. It would also be interesting to know why these patients and family members were so highly motivated and whether this could provide lessons for future vaccination programs. 3) Further research to improve understanding of risk perception (from the effects of swine flu and from vaccination) and its influence on decision-making in high-risk groups is needed. 4) Future work needs to establish whether issues identified by our participants regarding the role of the mass media would also be raised by people with respiratory conditions more widely, or by other high-risk groups. 5) Given the extensive reporting of the pandemic by the mass media, and health-related agencies' use of the mass media to communicate pandemic-related messages, work is urgently needed to explore the influence of mass media on pandemic-related knowledge and behavior in high-risk groups, and to better understand how mass media can most effectively be used to communicate risk data, especially to high-risk groups. 6) Issues of saliency suggest lessons for timing of future comparable research in a pandemic. 7) Our experiences highlight the need to recognize and develop strategies to overcome the challenges of including 'hard-to-reach' groups when undertaking short projects in the context of an ongoing pandemic.

Written by Prof Ann-Louise Caress, University of Manchester, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/183

Title **The Effectiveness of Nonpharmacological Interventions for Behavioural and Psychological Symptom Management for People With Dementia in Residential Care Settings**

Agency **HSAC, Health Services Assessment Collaboration**
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Reference Basu, A and Brinson, D. HSAC Report 2010; 3(19). ISBN 978-0-9864652-1-5 (online), ISBN 978-0-9864652-2-2 (print). ISSN 1178-5748 (online), ISSN 1178-573X (print)

Aim

To summarize the evidence on the relative effectiveness and safety of nonpharmacological interventions in managing behavioral and psychological symptoms of dementia (BPSD) in residential care settings, when compared to usual care.

Conclusions and results

While BPSD are often viewed as an entity, different component-outcomes have also been studied either singularly or in combination. The literature reports extensively on agitation, aggression, depression, and wandering. This review groups the studies for "best fit" based on the intervention and/or outcomes deemed to be the main focus of the research. Methods that have been trialed in residential care settings to reduce agitation and aggression and other BPSDs are diverse. The main findings from this review suggest that the training of staff members associated with care delivery in residential facilities, individually tailored behavioral modification programs, and incorporating physical activities, music therapy, and aromatherapy, might be beneficial in managing key elements of BPSD, most notably agitation, aggression, and/or several symptoms in combination. However, while bright light and Snoezelen therapy have been studied in various contexts, this review did not identify sufficient evidence to suggest that these were beneficial for people with dementia. One observation is the large number of studies reporting statistically significant benefits in both the intervention group and the control group. In the context of dementia care, this phenomenon demonstrates the potential positive effect of simple human attention and should not be overlooked. Another feature of dementia research is the propensity for individuals with dementia to respond to interventions in individualized ways. Simple case-by-case solutions may be as valid as more complex intervention programs.

Methods

The literature search included: MEDLINE, EMBASE, PsycINFO, CINAHL, the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), Database of Abstracts of Reviews of Effectiveness, Health Technology Assessment database, and the National Guideline Clearing House database. In addition, the bibliographies of included papers were examined for relevant studies. Searches were limited to English-language material published from 1999 through August 2009, and 4043 citations of different publication types were identified. The comprehensive search was followed by critical appraisal of the title and/or abstracts, and subsequently the full texts of the identified publications. The critical appraisal of literature followed the Australian National Health and Medical Research Council (NHMRC) guidelines, using the population-intervention-comparator-outcomes (PICO) framework. This iterative process resulted in 98 publications being included in the review.

Further research/reviews required

More studies specific to New Zealand are needed to assimilate and integrate relevant information on the use of nonpharmacological interventions in managing BPSD across the range of residential care settings in New Zealand; particularly studies focusing on the effects of training staff in delivering appropriate nonpharmacological interventions as first-line treatment and in effectively delivering individually tailored care.

Written by David Brinson, HSAC, New Zealand

INAHTA Briefs

Issue 2010/184

Title **Chronic Fatigue Syndrome: State of the Evidence and Assessment of Intervention Modalities in Québec**

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Reference ETMIS 2010 6 [2]. Printed French edition 978-2-550-59049-1, English summary (PDF) 978-2-550-59050-7. www.aetmis.gouv.qc.ca/site/en_publications2009.phtml

Aim

To review the evidence on chronic fatigue syndrome (CFS)/myalgic encephalomyelitis etiology and pathogenesis, best practices for clinical management, and organizational issues surrounding optimal management; and to inquire into Québec health professionals' need for education/training, patient care and service needs, and the cost of addressing them.

Results and conclusions

CFS is a complex, heterogeneous illness affecting an undetermined number of persons in Québec. Defined by diagnostic criteria for research purposes, this condition is officially recognized as a disease by the World Health Organization. Research to date has been unable to establish a single cause for this illness, although it has been linked to various infections, including Epstein-Barr virus and xenotropic murine leukemia virus-related virus. Numerous immunologic, endocrine, and psychoneurologic abnormalities have been described in sufferers. In the absence of a specific test, this condition can only be diagnosed by exclusion. Therapies such as cognitive behavioral therapy and graded exercise therapy seem to be effective and safe in the short term, while others, mostly pharmaceutical, have proven useful in treating comorbidities (mostly depression). Several health and social service professionals have admitted their lack of knowledge about the syndrome and voiced skepticism about its existence. Québec patients bemoaned the generalized lack of knowledge about CFS among professionals and the absence of care services and psychosocial support. In light of these findings, AETMIS recommends that organizers of continuing education in professional associations and corporations include CFS in their programs, and that the Ministère de la Santé et des Services sociaux and network administrators designate one or two centers of expertise dedicated to diagnostic and therapeutic/rehabilitation services, professional training, and research on epidemiology, etiology, pathophysiology, and care.

Methods

An evidence synthesis on CFS epidemiology, etiology, and pathogenesis; a systematic review of the efficacy and safety of CFS treatments; a review of clinical practice guidelines on the diagnosis and treatment or rehabilitation of patients with this illness; an economic analysis of treatment options; a literature search strategy including literature reviews and health technology assessment reports (Jan. 1994 to Feb. 2009); primary studies (Jan. 2005 to Feb. 2009) in English, French, Spanish, and Italian; an exhaustive grey literature search in May 2008 and a literature watch initiated in Feb. 2009; a contextual analysis performed by examining complementary documents for nonscientific literature and from Québec's medico-administrative databases and by consulting with care providers and key stakeholders; an online survey involving specialist physicians and GPs; and a primary study based on patient interviews to examine the needs of Québec patients.

Further research/reviews required

Observational studies are needed to determine the prevalence of CFS in Québec to analyze the impact of CFS on health and social service delivery and the disease's societal consequences.

Written by Guylaine Rouleau, Ugo Ceppi, Vibe Hjelholt Pederson, and Pierre Dagenais, AETMIS, Canada

INAHTA Briefs

Issue 2010/185

Title **Protein-sparing Modified Fast Diet: Efficacy, Safety and Clinical Use – Literature Review**

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Reference ETMIS 2010 6 [3]. Printed French edition 978-2-550-59207-5, English summary (PDF) 978-2-550-59208-2. www.aetmis.gouv.qc.ca/site/en_publications2009.phtml

Aim

To review the literature on protein-sparing modified fast (PSMF) diets and practices of physicians who recommend this type of diet to their patients.

Conclusions and results

The PSMF diet, which is generally defined as a very-low-calorie diet with an energy intake less or not greater than 3350 kJ (800 kcal) per day, is in no way indicated for people who are not overweight. In cases where people are required to lose weight, the leading recommendation by nutrition experts is to prescribe a personalized, balanced, moderately low-calorie diet. Experts are divided on the place of the PSMF diet as a therapeutic option for obesity. Some believe that the PSMF diet has no place in the current range of dietary interventions. Others, in official position statements, do not exclude its use and consider that it may be used for limited indications. Examination of the scientific evidence provided in studies on PSMF diets in clinical settings reveals the following: 1) Compliance with this diet is difficult, and attrition rates are high; 2) Short-term weight loss is rapid and significant and is accompanied by short-term changes in clinical and biological parameters suggesting improvements in some associated risks; 3) Its long-term efficacy for weight loss remains less certain, given the conflicting outcomes of the two meta-analyses evaluating this aspect; 4) No evidence was found to conclude on the benefit of repeated courses of PSMF; 5) Given the lack of evidence of long-term efficacy of this diet, and the need for medical monitoring, the principle of medical precaution is warranted; 6) When used, the PSMF diet should be an integral part of the patient's general support program conducted by a multidisciplinary team.

Methods

Identify systematic and narrative literature reviews, randomized controlled trials, and observational studies in MEDLINE, Cochrane Library, Dissertation & Theses, and Web of Science; Web search for expert recommendations and position statements on the PSMF diet and on the medical management of overweight; target the conduct and pathophysiology of the PSMF diet, its indications, safety, and efficacy in terms of weight loss and impact on overweight-related risk factors, psychological aspects, and the costs it incurs or saves, along with issues affecting care organization and involvement of professionals in such care.

Further research/reviews required

Need for: studies establishing the optimal amount of time that the protein-sparing stage should last; more studies on the safety of the PSMF diet in preoperative situations; studies on the effects of this diet on patient's mood and potential eating behavior problems; more studies on the cost of the PSMF diet or on the economic benefits that it could potentially generate; more studies on the extent and nature of health professional involvement in the process of a PSMF diet; in-depth studies on the potential costs and savings generated by PSMF diets; and studies drawing up a profile of the use of this type of diet in Québec and the outcomes achieved.

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INAHTA Briefs

Issue 2010/186

Title **Topical Negative Pressure Therapy for Wounds**

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Reference Ritchie K et al. 2010. HTA Report 12. Glasgow: NHS Quality Improvement Scotland 1-84404-912-4. www.nhshealthquality.org

Aim

To assess the clinical and cost effectiveness of treating wounds with topical negative pressure (TNP) therapy and to review other relevant aspects of using this technology.

Results and conclusions

Published evidence on the clinical and cost effectiveness of TNP therapy for wounds was generally of poor quality, and the evidence base was not considered robust. Different TNP devices are available, but the evidence identified was limited mainly to one manufacturer's device, and in many cases the manufacturer had sponsored the research.

Some evidence supports the use of TNP therapy, eg, in:

- grade III and IV pressure ulcers
- wounds caused by burns or trauma that require a skin graft
- wounds from surgical cuts for fractures deemed at high risk of healing problems
- open abdominal wounds with peritonitis
- open chest wounds.

While a lack of evidence does not prove that a therapy does not work, there is insufficient evidence to say whether TNP therapy is beneficial for: necrotizing faciitis, burns not being grafted, pilonidal sinus, and venous leg ulcers not being grafted. Patients with experience of TNP therapy believed that it expedited wound healing and a return to some level of normality, but were embarrassed by the odor and concerned that the device limited social activities. Varying levels of pain or discomfort were reported, and the need for consistent patient information was identified.

Recommendations

Several different wound types for which TNP therapy may be beneficial were identified, but clinicians were advised to continue to select treatment options based on individual needs and resources available. Health professionals delivering TNP therapy should participate in formal training, and the care team should consider changing dressings every 2 days to minimize odor. When discharged patients continue receiving TNP therapy at home, the hospital staff should work closely with the community care team in this transition.

Methods

Evidence identified by systematic literature searching and provided by experts was critically appraised and analyzed. A survey to determine current use and a qualitative study involved people experienced in TNP therapy to ascertain their views. The final report was peer reviewed.

Further research/reviews required

Well-designed studies, not funded by manufacturers of TNP devices, should aim to detect differences in time-to-healing for each of the common wound types targeted by TNP therapy, and should address the different devices, standard treatment, and costs.

Written by NHS QIS, Scotland

INAHTA Briefs

Issue 2010/187

Title **The Harmful Health Effects of Recreational Ecstasy: A Systematic Review of Observational Evidence**

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Reference Volume 13.06. ISBN 1366-5278. www.hta.ac.uk/project/1695.asp

Aim

To investigate the harmful health effects of taking ecstasy (3,4 methylenedioxymethamphetamine, MDMA) for recreational purposes.

Conclusions and results

A broad range of relatively low quality literature suggests that recreational use of ecstasy is associated with significant deficits in neurocognitive function (particularly immediate and delayed verbal memory) and increased psychopathological symptoms. The clinical significance of the exposure effect in individual cases will vary, but deficits are likely to be relatively small. Ecstasy is associated with acute harm, but appears to be a rare cause of death. Five Level I syntheses were identified. Small but significant deficits for ecstasy users compared to controls were reported, relating to attention, memory, psychomotor speed, executive systems functioning, and self-reported depressive symptoms. Data from Level II studies were directly pooled for 7 individual outcomes, suggesting that ecstasy users performed worse than controls on common measures of immediate and delayed verbal recall. No difference was seen in IQ. The 915 outcome measures identified in Level II studies were analyzed in broad domains. Ecstasy users performed significantly worse than polydrug controls in 13/16 domains and significantly worse than drug naïve controls in 7/12 domains for which sufficient data were available. The largest, most consistent exposure effects were seen in meta-analyses of memory (especially verbal and working memory. Former ecstasy users frequently showed deficits that matched or exceeded those seen among current users. At the aggregate level, the effects do not appear to be dose-related, but are variably confounded by other drug use, particularly alcohol. Of Level III evidence, in the 10 years to 2006, the np-SAD and the GMR recorded an average of around 50 drug-related deaths per year involving ecstasy; it was the sole drug implicated in around 10 cases per year. Retrospective case series, based on hospital emergency department records, reported a death rate up to 2% from emergency admissions related to ecstasy. Two major syndromes are most commonly reported as the immediate cause of death in fatal cases: hyperthermia and hyponatremia. For further details see Executive Summary link www.hta.ac.uk/project/1695.asp.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1695.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1695.asp.

Further research/reviews required

Large, population-based, prospective studies need to examine the time relationship between ecstasy exposure and neurocognitive deficits and psychopathological symptoms. Further research synthesis of the social and other indirect health harms of ecstasy would provide a more complete picture. Similar synthesis of the health harms of amphetamines would provide a useful comparison. Cross-sectional studies will add to the evidence base only if they are large, as representative as possible of the ecstasy-using population, use well-validated outcome measures, measure outcomes as objectively as possible with researchers blind to the ecstasy-using status of their subjects, report on all outcomes used, and provide complete documentation of possible effect modifiers. Cohorts should be matched for baseline factors, eg, IQ and exposure to alcohol. The heterogeneity of outcome measures used by different investigators is unhelpful: consensus on the most appropriate instruments to use should be sought.

Written by Mr Gabriel Rogers, PenTAG, University of Exeter, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/188

Title **Early High-Dose Lipid-Lowering Therapy to Avoid Cardiac Events: A Systematic Review and Economic Evaluation**

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Reference Volume 13.34. ISBN 1366-5278. www.hta.ac.uk/project/1700.asp

Aim

To evaluate the cost effectiveness of high-dose statins (atorvastatin 80 mg/day, rosuvastatin 40 mg/day and simvastatin 80 mg/day) versus simvastatin 40 mg/day in individuals with acute coronary syndrome (ACS).

Conclusions and results

We screened 3345 titles and abstracts for the review of clinical effectiveness, and retrieved and assessed 125 full papers. Of these, 30 papers describing 28 trials met the inclusion criteria. The Bayesian mixed treatment meta-analysis demonstrated a clear dose-response relationship in terms of reductions in low-density lipoprotein cholesterol (LDL-c), with rosuvastatin 40 mg/day achieving the greatest percentage reduction (56%) from baseline, followed by atorvastatin 80 mg/day (52%), simvastatin 80 mg/day (45%), and simvastatin 40 mg/day (37%). Although serious adverse events with statins are rare, their incidence is likely to be greater at higher doses. We used several clinical scenarios to explore the effect of adherence on the cost effectiveness of treatment regimens. Using a threshold of 20 000 pounds sterling (GBP) per quality-adjusted life-year (QALY) and assuming that the benefits and adherence rates observed in the clinical trials are generalizable to a clinical setting, and that individuals who do not tolerate the higher-dose statins are prescribed simvastatin 40 mg/day, then atorvastatin 80 mg/day and rosuvastatin 40 mg/day would be considered cost effective compared to simvastatin 40 mg/day in individuals with ACS. Simvastatin 80 mg/day is not well tolerated because of the high incidence of less severe adverse events, eg, myopathy, which are likely to affect adherence levels in clinical practice. Simvastatin 80 mg/day cannot be recommended due to the high incidence of adverse events. If the cost of atorvastatin decreases in line with that observed for simvastatin when the patent ends in 2011, atorvastatin 80 mg/day will be the most cost-effective treatment for all thresholds. If the cost reduces to 25% of the current value, atorvastatin 80 mg/day will be the most cost-effective treatment for thresholds between GBP 5000 and GBP 30 000 per QALY.

The reference case shows that at a threshold of GBP 20 000 per QALY, rosuvastatin is optimal treatment in patients with a recent history of ACS. This assumes that the additional incremental reductions in LDL-c observed in patients treated with rosuvastatin 40 mg/day compared with atorvastatin will transfer into corresponding changes in relative risks of cardiovascular events.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1700.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1700.asp.

Further research/reviews required

Large, long-term RCTs reporting effects in terms of clinical events are needed to determine optimum statin use in subgroups. These include head-to-head studies comparing higher-dose statins with lower-dose statins, studies of rosuvastatin, and studies comparing high-dose statin monotherapy with combination therapies. Studies recruiting high-risk groups should be considered. Long-term registry data are needed to determine adherence rates and adverse events for individual statins and doses when used in general practice. Studies exploring the effects of interventions designed to increase adherence to statin therapy in general clinical practice and in subgroups are also required.

Written by Ms Roberta Ara, SCHARR, University of Sheffield, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/189

Title **The Safety and Effectiveness of Different Methods of Ear Wax Removal: A Systematic Review and Economic Evaluation**

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Reference Volume 14.28. ISSN 1366-5278. www.hta.ac.uk/project/1698.asp

Aim

To synthesize evidence of the clinical and cost effectiveness of interventions available to soften and/or remove earwax and assessment of adverse events (AEs) associated with the interventions.

Conclusions and results

Twenty-six clinical trials in primary care (14 studies), secondary care (8 studies), or other care settings (4 studies) met the inclusion criteria for the review. Interventions included 16 different softeners, with or without irrigation, and in various comparisons. Participants, outcomes, timing of intervention, follow-up, and methodological quality varied among studies. On measures of wax clearance: Cerumol, sodium bicarbonate, olive oil, and water are all more effective than no treatment; triethanolamine polypeptide (TP) is better than olive oil; wet irrigation is better than dry irrigation; sodium bicarbonate drops followed by irrigation by nurse is more effective than sodium bicarbonate drops followed by self-irrigation; softening with TP and self-irrigation is more effective than self-irrigation only; and endoscopic de-waxing is better than microscopic de-waxing. AEs appeared to be minor and limited. Results of the exploratory economic model found that softeners followed by self-irrigation were more likely to be cost effective at 24 433 pounds sterling (GBP) per quality-adjusted life-year (QALY) than softeners followed by irrigation in primary care (GBP 32 130 per QALY) when compared to no treatment. Comparing the two active treatments showed that the additional gain (softeners followed by irrigation in primary care over softeners followed by self-irrigation) cost GBP 340 000 per QALY. Compared to no treatment over a lifetime, the incremental cost-effectiveness ratios for softeners followed by self-irrigation and of softeners followed by irrigation in primary care were GBP 24 450 per QALY and GBP 32 136 per QALY, respectively.

Recommendations

The systematic review of clinical and cost effectiveness found limited good-quality evidence, making it difficult to differentiate between the various methods for removing earwax in terms of clearing wax, improving quality of life, satisfaction, AEs, or cost effectiveness. Although it showed that softeners have an effect in clearing earwax and as precursors to irrigation, the specific softeners that have an effect remain uncertain. Evidence on the effectiveness of irrigation methods or mechanical removal was equivocal. The limited evidence on benefits and costs of methods of earwax removal meant that the economic evaluation was speculative and for illustration only. Its findings should not be used for policy decisions. Hence, further research is required to improve the evidence base. A well-conducted RCT incorporating economic evaluation would appear to be the most appropriate method to assess the different ways of providing the service (ie, practice nurse provision in primary care versus self-care) and the effectiveness of the different removal methods (i.e. softeners and mechanical removal). In such research it would be important to assess the acceptability of the different approaches to patients and practitioners to ensure the most appropriate research structure. Other studies could be considered to improve specific data (eg, a costing study of primary care costs); however, the poor quality of evidence suggests additional research would be required.

Methods

See Executive Summary link www.hta.ac.uk/project/1698.asp.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1698.asp.

Written by Professor Andrew Clegg, SHTAC, University of Southampton, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/190

Title **School-Linked Sexual Health Services for Young People (SSHYP): A Survey and Systematic Review Concerning Current Models, Effectiveness, Cost-Effectiveness and Research Opportunities**

Agency **NETSCC, HTA, NIHR Evaluation and Trials Coordinating Centre**

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Reference Volume 14.30. ISSN 1366-5278. www.hta.ac.uk/project/1662.asp

Aim

To identify forms of school-based sexual health services (SBSHS) and school-linked sexual health services (SLSHS) in the UK; to review and synthesize evidence from qualitative and quantitative studies on the effectiveness, acceptability, and cost effectiveness of these services.

Conclusions and results

The UK has no single, dominant service model. The systematic review demonstrated that the evidence base for these services remains limited and uneven, and draws largely on US studies. Qualitative research is needed to develop robust process and outcome indicators to evaluate SLSHS/SBSHS in the UK. These indicators could be used in local evaluations and in large, longitudinal studies of service and cost effectiveness. Future research should examine the impact of the differing services currently evolving in the UK, encompassing school-based and school-linked models, and models with and without medical practitioner involvement. Three broad types of UK sexual health service provision were identified: 1) SBSHS staffed by school nurses, offering minimal or basic levels of service; 2) SBSHS and SLSHS staffed by a multiprofessional team, but not medical practitioners, offering basic or intermediate levels of service; and 3) SBSHS and SLSHS staffed by a multiprofessional team, including medical practitioners offering intermediate or comprehensive service levels. The systematic review showed that SBSHS are not associated with higher rates of sexual activity among young people, or with an earlier age of first intercourse. There was evidence to show positive effects in terms of reductions in births to teenage mothers and in chlamydial infection rates in young men, but this evidence came primarily from the USA. Hence, the findings need to be tested in relation to UK-based services. Also, evidence suggests that broad-based, holistic service models, not restricted to sexual health, offer the strongest basis for protecting young people's privacy and confidentiality, countering perceived stigmatization, delivering the most comprehensive range of products and services, and maximizing service uptake. Findings from the service-mapping study indicate that broad-based services, eg, medical practitioner input in a multiprofessional team, meet the stated preferences of staff and young people most clearly. Partnership-based developments of this kind also conform to the broad policy principles embodied in the Every Child Matters framework in the UK and allied policy initiatives. However, neither these service models nor narrower ones have been rigorously evaluated as to their impact on the key outcomes of conception rates and sexually transmitted infection (STI) rates in the UK or other countries. Therefore, appropriate data were not found to support cost-effectiveness modeling.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1662.asp.

Methods

The study had two components: 1) the service mapping component was based on a postal questionnaire circulated to school nurses throughout the UK (14.6% response rate); and 2) semistructured telephone interviews with 51 service coordinators in NHS and local authority roles. Quantitative data from the questionnaire were analyzed using SPSS, primarily to produce descriptive statistics relating to staffing and facilities. Qualitative data from questionnaire free-text sections and from interviews were subject to thematic analyses.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1662.asp.

Written by Dr Jenny Owen, ScHARR, University of Sheffield, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/191

Title **Influenza A/H1N1v in Pregnancy: An Investigation of the Characteristics and Management of Affected Women and the Relationship to Pregnancy Outcomes for Mother and Infant**

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Reference Volume 14.34(2). ISSN 1366-5278. www.hta.ac.uk/project/2224.asp

Aim

To assess rates of and risk factors for adverse outcomes following AH1N1v infection in pregnancy; and to assess the adverse effects of the antiviral drugs and vaccines used in prevention and management.

Conclusions and results

Earlier treatment with antiviral agents is associated with improved outcomes for pregnant women. Further actions are needed in future pandemics to ensure that antiviral agents and vaccines are provided promptly to pregnant women, particularly via primary care. Research is needed on longer-term outcomes for infants exposed to AH1N1v influenza, antiviral drugs, or vaccines during pregnancy. The weekly incidence of ILI among pregnant women averaged 51/100 000 over the study period. Antiviral drugs were offered to 4.8% and vaccination to 64.8% of registered pregnant women. Of the 90 pregnant women with ILI presenting in primary care who were reported to the research team, 55 were prescribed antiviral drugs, and in 42 (76%) cases this was within 2 days of symptom onset. After comparison with 1329 uninfected pregnant women offered vaccination, pre-existing asthma was the only maternal factor identified as increasing risk of ILI presentation. Maternal obesity and smoking during pregnancy were associated with hospital admission with AH1N1v infection. Overall, 241 pregnant women were admitted to hospital with laboratory-confirmed AH1N1v infection. Of these women, 83% were treated with antiviral agents, but only 6% received antiviral treatment before hospital admission. Treatment within 2 days of symptom onset was associated with an 84% reduction in the odds of admission to an intensive therapy unit. Women admitted to hospital with AH1N1v infection were more likely to deliver preterm; a 3 times increased risk was suggested compared with an uninfected population cohort.

Recommendations

See Executive Summary link www.hta.ac.uk/project/2224.asp.

Methods

Prospective national cohort studies were conducted using different sources to identify women in three specific groups: 1) pregnant women suspected of being infected with AH1N1v or treated with antiviral medication and managed in the community; 2) pregnant women vaccinated against AH1N1v; and 3) pregnant women admitted to hospital with confirmed AH1N1v. Information about pregnancy management and outcomes was collected directly from health professionals caring for infected women in secondary care settings, and from health professionals and women themselves, with consent, where infection was managed in primary care. Women were identified through the following sources: 1) the UK Teratology Information Service collected data from general practices within and outside the Primary Care Research Networks and from self-notifications from affected women (some practices acted as sentinel sites, providing data on all presentations, antiviral prescriptions, and vaccinations); and 2) the UK Obstetric Surveillance System collected data through its network of collaborating clinicians in all consultant-led maternity units in the UK.

Further research/reviews required

Further research is needed on longer-term outcomes for infants exposed to AH1N1v influenza, antiviral drugs, or vaccines during pregnancy. This includes studies on how these factors affect: fetal development and congenital malformations, postnatal development, and potentially associated conditions, eg, childhood leukemia.

Written by Professor Simon Thomas, Newcastle University, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/192

Title **Randomized Controlled Trial and Parallel Economic Evaluation of Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR)**

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Reference Volume 14.35. ISSN 1366-5278. www.hta.ac.uk/project/1150.asp

Aim

To determine the comparative effectiveness and cost effectiveness of conventional ventilatory support versus extracorporeal membrane oxygenation (ECMO) for severe adult respiratory failure.

Conclusions and results

Compared with conventional management (CM), transferring adult patients with severe but potentially reversible respiratory failure to a single center specializing in treating severe respiratory failure, for consideration of ECMO, significantly increased survival without severe disability. This use of ECMO is likely to be cost effective compared to other technologies. In total, 180 patients (90 in each arm) were randomized from 68 centers. Of the 90 patients randomized to the ECMO arm, 68 received that treatment. ECMO was not given to: 3 patients who died prior to transfer, 2 who died in transit, 16 who improved with conventional treatment given by the ECMO team, and 1 who required amputation and could not be heparinized. Of the 90 patients who entered the CM (control) arm, 3 patients later withdrew and refused follow-up, leaving 87 patients for whom primary outcome measures were available. CM consisted of any treatment deemed appropriate by the patient's intensivist, with the exception of extracorporeal gas exchange. No CM patients received ECMO, although 1 received a form of experimental extracorporeal arteriovenous carbon dioxide removal support (a protocol violation). Fewer patients in the ECMO arm than in the CM arm had died or were severely disabled 6 months after randomization (33/90 [36.7%] versus 46/87 [52.9%] respectively). This equated to 1 extra survivor for every 6 patients treated. Only 1 patient (in the CM arm) was known to be severely disabled at 6 months. Patients allocated to ECMO incurred average total costs of 73 979 pounds sterling (GBP) compared to GBP 33 435 for those undergoing CM (UK prices, 2005). A lifetime model predicted the cost per quality-adjusted life-year (QALY) of ECMO to be GBP 19 252 (95% confidence interval GBP 7622 to GBP 59 200) at a discount rate of 3.5%. Lifetime QALYs gained were 10.75 for the ECMO group compared to 7.31 for the conventional group. Costs to patients and their relatives, including out-of-pocket and time costs, were higher for patients allocated to ECMO.

Recommendations

A limitation of this study is the lack of standardized care in the conventional arm (the conventional intensive care providers could not reach a consensus as to what constituted optimal care). An alternative strategy of transferring all patients to Glenfield to be cared for by the ECMO team was dismissed by collaborators as they did not consider the ECMO team to be sufficiently expert in providing conventional intensive care. The other option considered was to use a single center to provide all of the conventional care, but this was impossible as the UK has no such center. Hence, the trial team took the pragmatic decision to recommend what was proven to be the best ventilation strategy (the low volume ARDSNet protocol), but allow individual intensivists to determine what they thought was the best treatment for their patients. Had this decision not been taken, it would have been impossible to conduct the study. The pragmatic design meant that CESAR was comparing treatment in an expert center (where ECMO was part of the treatment algorithm) to treatment available to the general public in the UK as a whole.

Methods

See Executive Summary link www.hta.ac.uk/project/1150.asp.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1150.asp.

Written by Mr Giles Peek, University Hospitals of Leicester NHS Trust, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/193

Title **Newer Agents for Blood Glucose Control in Type 2 Diabetes: Systematic Review and Economic Evaluation**

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Reference Volume 14.36. ISSN 1366-5278. www.hta.ac.uk/project/1743.asp

Aim

To review the newer agents available for blood glucose control in type 2 diabetes: the glucagon-like peptide-1 (GLP-1) analogue, exenatide; dipeptidyl peptidase-4 (DPP-4) inhibitors, sitagliptin and vildagliptin; the long-acting insulin analogues, glargine and detemir; and to review concerns about the safety of the thiazolidinediones.

Conclusions and results

Clinical effectiveness. Exenatide and the gliptins are clinically effective in improving glycemic control. Exenatide improved glycemic control by around 1%, with the added benefit of weight loss. The gliptins were effective in improving glycemic control, reducing HbA1c level by about 0.8%, and were weight neutral. Glargine and detemir were equivalent to Neutral Protamine Hagedorn (NPH) insulin (and to each other) in terms of glycemic control, but had modest advantages in terms of hypoglycemia (especially nocturnal). Detemir, used once daily, appeared to cause slightly less weight gain than glargine, but the clinical significance was doubtful, and a slightly higher dosage was required. The glitazones can cause heart failure and fractures, but rosiglitazone appears to slightly increase the risk of cardiovascular events whereas pioglitazone reduces it. Eight trials examined the benefits of adding pioglitazone to an insulin regimen; in our meta-analysis, the mean reduction in HbA1c level was 0.54% (95% confidence interval [CI] −0.70 to −0.38). Hypoglycemia was marginally more frequent in the pioglitazone arms (relative risk [RR] 1.27, 95% CI 0.99 to 1.63). In most studies, those on pioglitazone gained more weight than those who were not.

Costs and cost effectiveness. Since glargine and detemir appeared to have only slight clinical advantages over NPH, but have much higher costs, they did not appear to be cost effective as first-line insulins for type 2 diabetes. Hence, the recent NICE guidelines recommended that NPH should be the preferred first-line insulin in treating type 2 diabetes. Neither did exenatide appear to be cost effective compared to NPH, but when used as third drug after failure of dual oral combination therapy, exenatide appeared cost effective compared to immediate glargine. The gliptins are similar to the glitazones in glycemic control and costs, and appeared to have fewer long-term side effects. Comparisons of sitagliptin and rosiglitazone, and of vidagliptin and pioglitazone, slowed clinical equivalence in terms of quality-adjusted life-years (QALYs), but the gliptins were marginally less costly. In terms of annual drug acquisition costs (in 2008), the gliptins were the cheaper of the new drugs, with annual costs of between 386 and 460 pounds sterling (GBP). Exenatide was more expensive, with an annual cost of around GBP 830. The cost of NPH insulin was much lower than the cost of glargine and detemir. Exenatide and the gliptins are useful additions to diabetes treatments.

Methods

See Executive Summary link www.hta.ac.uk/project/1743.asp.

Further research/reviews required

More economic analysis is required to establish when it becomes cost effective to switch from NPH to a long-acting analogue. Long-term follow-up studies of exenatide and the gliptins are needed to confirm safety and to provide data on how long they are efficacious in a progressive disease. The combination of insulin and GLP-1 analogue therapy appears logical, and trials are required. More research is needed on how to motivate people with type 2 diabetes to lose weight.

Written by Professor Norman Waugh, University of Aberdeen, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/194

Title **A Systematic Review of Photodynamic Therapy in the Treatment of Pre-Cancerous Skin Conditions, Barrett's Oesophagus and Cancers of the Biliary Tract, Brain, Head and Neck, Lung, Oesophagus and Skin**

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Reference Volume 14.37. ISSN 1366-5278. www.hta.ac.uk/project/1854.asp

Aim

To systematically review the clinical effectiveness and safety of photodynamic therapy (PDT) in treating Barrett's esophagus, precancerous skin conditions, and the following cancers: biliary tract, brain, head and neck, lung, esophageal, and skin.

Conclusions and results

Evidence of effectiveness was found for PDT in treating actinic keratosis (AK) and nodular basal cell carcinoma (BCC) in relation to placebo, and possibly for treating Barrett's esophagus. However, the effectiveness of PDT in relation to other treatments is not apparent. High-quality trials need to compare PDT with relevant comparators for all meaningful outcomes, eg, quality of life and adverse effects. Research is also needed on patient experience of PDT and on its cost effectiveness. We included 88 trials reported in 141 publications. For AK, the only evidence of effectiveness was that PDT appeared to be superior to placebo. For Bowen's disease, better outcomes with PDT were suggested when compared to cryotherapy or fluorouracil. For BCC, PDT may result in similar lesion response rates to surgery or cryotherapy, but with better cosmetic outcomes. For nodular lesions, PDT appeared to be superior to placebo and less effective than surgery, but suggestive of better cosmetic outcome. For Barrett's esophagus, PDT in addition to omeprazole appeared to be more effective than omeprazole alone in long-term ablation of high-grade dysplasia and slowing or preventing progression to cancer. Firm conclusions could not be drawn for PDT in esophageal cancer. Research is needed on the role of PDT in lung cancer. For cholangiocarcinoma, PDT may improve survival when compared to stenting alone. Evidence on PDT for brain cancer and cancers of the head and neck was limited. Across the conditions and sites investigated, a wide variety of photosensitizes were used, and no serious adverse effects were linked to PDT.

Recommendations

1) Photodynamic therapy is most accepted in treating malignant and premalignant, nonmelanoma skin lesions. We found evidence of effectiveness for treating AK and nodular BCC in relation to placebo. However, we do not fully know the effectiveness of PDT in relation to other treatments. 2) The evidence suggests that PDT might be useful in treating Barrett's esophagus, but its effectiveness in relation to other treatments is not apparent. 3) The evidence for the other sites and conditions examined in this review is insufficient to draw firm conclusions. 4) We found no evidence implying that PDT should definitely not be used for certain clinical conditions.

Methods

See Executive Summary link www.hta.ac.uk/project/1854.asp.

Further research/reviews required

1) The optimal parameters of PDT need to be identified across the conditions studied. 2) High-quality trials need to compare PDT with relevant comparators for all meaningful outcomes, eg, quality of life and adverse events. Such trials should aim to establish the place of PDT in treating a given condition and should identify if subgroups of patients might respond differently to PDT. 3) Good-quality research is needed on patient experiences of PDT across the conditions investigated. 4) High-quality trials on rarer cancers, eg, brain and head and neck, are difficult to conduct. If RCTs cannot be conducted, other types of evidence may be considered. 5) This review will need to be updated as the results of ongoing trials become available.

Written by Mrs Debra Fayter, University of York, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/195

Title **Towards Single Embryo Transfer? Modeling Clinical Outcomes of Potential Treatment Choices Using Multiple Data Sources: Predictive Models and Patient Perspectives**

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Reference Volume 14.38. ISSN 1366-5278. www.hta.ac.uk/project/1535.asp

Aim

To collate cohort data from 5 treatment centers and the Human Fertilization and Embryology Authority (HFEA); to develop predictive models for live birth and twinning probabilities from fresh and frozen embryo transfers and predict outcomes from treatment scenarios; and to understand patients' perspectives and use the modeling results to investigate the acceptability of twin reduction policies.

Conclusions and results

For any one transfer, single embryo transfer (SET) has about a one-third loss of success rate relative to double embryo transfer (DET). This can be only partially mitigated by patient and treatment cycle selection, which may be criticized as unfair as all patients receiving SET will have a lower chance of success than they would with DET. However, considering complete cycles (fresh plus frozen transfers), it is possible for repeat SET to produce more live births than repeat DET. Such a strategy would require support from funders, acceptance by patients of cryopreservation, and the burden of additional transfer cycles. Future work should include development of improved clinical and regulatory database systems, surveys to quantify patients' beliefs and experiences and develop approaches to meet their information needs, and randomized controlled trials comparing policies of repeated SET with repeated DET. Statistical analysis revealed no characteristics that specifically predicted multiple birth outcomes beyond those that predicted treatment success. In fresh transfer following egg retrieval, SET would lead to about a one-third reduction in live birth probability compared to DET, a result consistent with the limited data from clinical trials. Selecting patients based on prognostic indicators might mitigate about half of the loss in live births associated with SET in the initial fresh transfer while achieving a twin rate of 10% or less.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1535.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1535.asp.

Further research/reviews required

There is an urgent need for better-quality data that permit evaluation of complete cycles (fresh plus frozen) and link multiple treatments of the same women. Existing clinical and regulatory database systems do not provide data that can answer key questions. With such data our conclusions could be confirmed and analyses extended to consider interclinic differences and additional covariates. 1) Research is needed to adapt data monitoring tools for use in monitoring twin rate targets, and provide evaluation tools to clinics and regulators. 2) Some patient antipathy to SET may be amenable to carefully tailored and accurate information that considers patients' beliefs and experiences. Surveys need to quantify the extent of these beliefs and develop approaches to meet patients' information needs. 3) Our methods could be extended to consider various embryo selection policies, based on biomarkers or extended culture. As data become available, further simulation studies would be informative in determining their optimal use. 4) Methods for optimizing success rates, while reducing twin rates, need to be tested in randomized trials with full treatment endpoints.

Written by Dr Steve Roberts, Biostatistics Group, University of Manchester, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/196

Title **Sugammadex for the Reversal of Muscle Relaxation in General Anesthesia: A Systematic Review and Economic Assessment**

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Reference Volume 14.39. ISSN 1366-5278. www.hta.ac.uk/project/1780.asp

Aim

To determine the clinical and cost effectiveness of sugammadex for the reversal of neuromuscular blockade (NMB).

Conclusions and results

Sugammadex may be a cost-effective option compared with neostigmine + glycopyrrolate for reversal of moderate NMB and also provides the facility to recover patients from profound blockade. Rocuronium + sugammadex could be considered as a replacement for succinylcholine for rapid sequence induction (and reversal) of NMB, but this might not be a cost-effective option in some types of patients at current list prices for sugammadex. Uncertainties remain about whether the full benefits of sugammadex can be realized in clinical practice. The review of clinical effectiveness included 4 randomized active-control trials of sugammadex, 9 randomized placebo-controlled trials, and 5 studies in special populations. The included trials indicated that sugammadex produces more rapid recovery from moderate or profound NMB than do placebo or neostigmine. Median time to recovery from moderate blockade was 1.3 to 1.7 minutes for rocuronium + sugammadex, 21 to 86 minutes for rocuronium + placebo, and 17.6 minutes for rocuronium + neostigmine. In profound blockade, median time to recovery was 2.7 minutes for rocuronium + sugammadex, 30 to >90 minutes for rocuronium + placebo, and 49 minutes for rocuronium + neostigmine. Results for vecuronium were similar. Recovery from NMB was faster with rocuronium reversed by sugammadex 16 mg/kg after 3 minutes (immediate reversal) than with succinylcholine followed by spontaneous recovery (median time to primary outcome 4.2 versus 7.1 minutes). The evidence base for modeling cost effectiveness is limited. However, assuming that the reductions in recovery times observed in the trials can be achieved in routine practice, and can be used productively, sugammadex (2 mg/kg [4 mg/kg]) is potentially cost effective at its current list price for routine reversal of rocuronium-induced moderate (profound) blockade, if each minute of recovery time saved can be valued at approximately 2.40 pounds sterling (GBP) (GBP 1.75) or more.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1780.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1780.asp.

Further research/reviews required

1) Evaluate the effects of replacing succinylcholine with rocuronium + sugammadex for rapid induction and reversal of NMB on morbidity, mortality, patient-reported outcomes, and resource use. 2) Collect data on the use of sugammadex in clinical practice to obtain better estimates of the incidence and implications of rare major adverse events, eg, allergic/anaphylactic reactions. 3) Evaluate outcomes of sugammadex use in routine surgery for which there is little information, eg, patient-reported outcomes, clinical signs of recovery, resource use, and costs. 4) Evaluate the use of sugammadex in pediatric and obstetric practice. 5) Evaluate the need for further randomized trials of sugammadex. 6) Evaluate the use of a 4-mg/kg dose of sugammadex for immediate reversal of blockade induced by low-dose (0.6-mg/kg) rocuronium in routine settings. 6) Evaluate new theatre practices that could potentially make optimum use of the time saved by using sugammadex, eg, a nationwide prospective study. 7) Evaluate the effects of using different combinations of anesthesia and analgesia with sugammadex, specifically in situations where potent inhalational agents have been used but discontinued. 8) Quantify the mortality risk of patients with different clinical characteristics in the setting of rapid induction of NMB.

Written by Mr Duncan Chambers, CRD, University of York, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/197

Title **Treatment of Multiple Missing Teeth in Adults with Rare Diseases by Using Implant-Supported Denture**

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Aim

To assess the clinical value of procedures for treating adults with dental agenesis due to rare genetic diseases.

Conclusions and results

This assessment was carried out within the framework of the Rare Diseases Program set up by the French Ministry of Health and Solidarity and is intended to advise the French National Health Insurance (NHI) on the reimbursement of procedures.

Rehabilitation with removable implant-supported dentures is a good alternative to conventional dentures in treating multiple dental agenesis. Implant-supported dentures have considerable functional, esthetic, and psychological advantages over conventional dentures. In these specific genetic syndromes the safety and efficacy of surgical and prosthetic procedures depend on interdisciplinary management, which is decisive for successful treatment outcomes.

Recommendations

HAS' opinion is that these procedures should be reimbursed. For preimplant surgery of atrophic jaws, HAS recommends critical assessment of the need and the appropriate type of bone or soft tissue augmentation procedure involving less risk of complications.

Methods

Clinical data published from January 2000 to October 2010 – obtained from a document search of MEDLINE and the Cochrane Library – were critically analyzed. The analysis included 21 case series (syndromal agenesis), 19 systematic reviews, 3 guidelines, and 5 technology reports (implant rehabilitation of edentulous patients). A multidisciplinary working group consisting of 8 odontologists and 3 maxillary surgeons discussed the results of this analysis. Conclusions have been reviewed by the Commission d'Evaluation des Actes Professionnels (CEAP), the HAS specialized appraisal committee.

Written by Françoise SAINT-PIERRE, HAS, France

INAHTA Briefs

Issue 2010/198

Title **Measuring the Length of the Cervical Canal of the Neck of the Uterus Using Transvaginal Ultrasound, Usefulness for Prediction of Spontaneous Premature Delivery**

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Aim

To assess the diagnostic power of uterine neck length measurement by transvaginal ultrasound in predicting spontaneous preterm delivery.

Conclusions and results

Measuring uterine neck length by transvaginal ultrasound is predictive of spontaneous preterm delivery regardless of the population investigated. Although the sensitivity and positive predictive value of this investigation alone do not enable reliable prediction of spontaneous preterm delivery, the measurement does make it possible to estimate a level of risk for it. Hence, the utility of the measurement will depend on the risk/benefit ratio of the treatments aimed at preventing spontaneous preterm delivery.

Recommendations

HAS holds the view that measuring uterine neck length by transvaginal ultrasound can help select patients who might benefit from specific therapy, particularly in the case of:

- Symptomatic patients with signs of threatened preterm delivery
- Asymptomatic patients with an identified risk factor (uterine malformation, history of spontaneous preterm delivery, of late miscarriages, or of uterine neck surgery).

In asymptomatic patients without an identified risk factor, and in the case of dichorionic twin pregnancies, measurement of uterine neck length by transvaginal ultrasound offers no benefit.

Methods

Clinical data published between January 1999 and May 2010 were critically analyzed. The analysis included 33 studies obtained from a literature search of the Cochrane Library and MEDLINE databases. A multidisciplinary working group consisting of 4 midwives, 2 radiologists, 6 gynecologists-obstetricians, and 1 neonatologist-pediatrician discussed the results of this analysis.

Further research/reviews required

Defining a threshold below which a decision to treat is taken is of key importance. To improve accuracy in predicting spontaneous preterm delivery, studies need to better define a specific threshold as a function of term. The utility of the measurement depends on the risk/benefit ratio of the treatments envisaged. An assessment of the risks and benefits of these treatments is needed.

Written by Olivier Allaire, HAS, France

Title **The Scientific Knowledge Base for Treatment of Patients with Cleft Lip, Alveolus and/or Palate**

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Aim

To present the evidence base for the effectiveness of interventions in treatment and follow-up of patients with cleft lip, alveolus, and/or palate.

Conclusions and results

The evidence base for current practice in treatment and follow-up of children and adults with cleft lip, alveolus, and/or palate is low or very low. This does not mean that current practice is poor. It means that existing research is too uncertain to provide good evidence for conclusions about the relative effectiveness of different interventions, sequencing, and optimal times for cleft lip and palate surgery, of the effectiveness of interventions for maxillary protraction, and of the different follow-up and habilitation interventions.

Recommendations

- Intercenter cooperation to recruit patients to large, multicenter, randomized controlled trials.
- Continuing systematic evaluation of each center's treatment results and comparison with other centers, eg, as done in the Eurocleft project.

Methods

The systematic review was performed in accordance with the handbook of the Norwegian Knowledge Centre for the Health Services. We conducted a thematically broad search for references about cleft lip, alveolus, or palate or velocardiofacial syndrome. The search was then limited to systematic reviews and primary studies with a prospective, controlled design. We imposed no language restrictions. The Cochrane Library, MEDLINE, EMBASE, CINAHL, ERIC, and Norart (a Norwegian database of Nordic journal articles) were searched. Two persons independently assessed the methodological quality of the included articles. Likewise, two persons decided which data to extract and present in result tables. In instances where data were presented for different follow-up periods, we emphasized the last reported data.

Except for a meta-analysis of results from one comparison, we prepared a descriptive summary of the data.

Written by Louise Forsetlund, NOKC, Norway

INAHTA Briefs

Issue 2010/200

Title **Prosthetic Rehabilitation of Partially Dentate or Edentulous Patients**

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Reference Rapport nr: 204. ISBN 978-91-85413-40-9, ISSN 1400-1403.
www.sbu.se/sv/Publicerat/Gul/Tandforluster/

Aim

To evaluate scientific support for the following questions:

- How do people perceive losing their teeth and living with varying degrees of tooth loss, and how do people respond to rehabilitation of this condition?
- How do people perceive oral quality of life influenced by rehabilitation of tooth loss of varying severity?
- What effects do the current methods of rehabilitation have after 5, 10, and 15 years?
- How effective is immediate loading of dental implants compared with conventional treatment?
- What complications, risks, and side effects are associated with the methods investigated?
- How cost effective are the different methods, and what is the present distribution of the different treatment methods in the population?

Conclusions and results

- Tooth loss is associated with deterioration in quality of life. Many people with tooth loss experience loss of self-esteem, lower social status, and functional deterioration.
- Treating tooth loss signifies a return to normal lifestyle and improved quality of life.
- Patients with single tooth loss can be rehabilitated by tooth-supported bridges, resin-bonded bridges, or implant-supported crowns (5-year survival for crowns and implants is >90%).
- Rehabilitation of extensive tooth loss can be achieved by bridgework supported by the natural teeth or implants, or with a removable partial denture (95% of implant bridges can be expected to survive 5-10 years). Rehabilitation of patients who have lost teeth is mainly in the form of fixed-tooth or implant-retained prostheses,
- Patients with edentulism, or maxillary or mandibular edentulism, can be rehabilitated with complete dentures supported by the oral mucosa, or implant-supported constructions (5-year survival is >90% for implant-retained bridges and mandibular overdentures).
- The evidence is insufficient to determine which treatment method yields the best results in terms of esthetics and function, or is the most cost-effective.

Methods

The conclusions of the report are based solely on human studies. Studies were restricted to randomized controlled trials, controlled clinical trials, and cohort studies. A special protocol was used to scrutinize study quality. The initial analysis sorted study data by themes. Results of the selected studies were merged in a secondary qualitative analysis.

Further research/reviews required

- Studies of different patient groups need to compare different methods of treating varying severity of tooth loss. Observation periods of 5 years or longer are needed.
- Studies need to analyze treatment outcomes in different patient groups and methods, particularly treatment outcome from the patient's perspective.
- Little is known about the cost-effectiveness of methods used to treat tooth loss. Studies need to disclose the benefits and costs of treatment methods from an economic perspective. Epidemiological studies on oral health should estimate the need for treatment resources and analyze the effects of allocated resources.
- There is insufficient analysis of financial aspects of rehabilitation in patients with tooth loss. Patients' willingness to pay for such treatment also needs to be addressed.

Written by Sofia Tranæus, SBU, Sweden

INAHTA Briefs

Issue 2010/201

Title **Methods of Diagnosis and Treatment in Endodontics - A Systematic Review of the Literature**

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Reference Report no: 203. ISBN 978-91-85413-39-3, ISSN 1400-1403.
www.sbu.se/sv/Publicerat/Gul/Rotfyllning/

Aim

To address several specific questions, including:

- How well can different diagnostic methods determine the condition of pulp in teeth with different types of injury (eg, caries, trauma)?
- How well can different radiographic methods demonstrate bone loss at the root apex?
- Are there effective methods to treat pulpal inflammation to preserve pulp?
- How effective are different treatments when the pulp is necrotic?
- How effective are orthograde and retrograde treatments of root filled teeth showing signs of periapical inflammation?
- What serious side effects are associated with root canal therapy?
- Which methods are most cost effective in diagnosing and treating diseases in dental pulp?

Conclusions and results

- It is not possible to determine which diagnostic methods disclose whether vital but injured pulp can be maintained without root filling.
- The effects of different methods of instrumentation, disinfection, and root filling in root canal therapy are insufficiently studied.
- An investigation of practice by Swedish dentists shows wide variation in treatments and materials (except in the use of engine-driven instrumentation).
- Prospective studies on root canal therapy need to show how teeth can be preserved without risk of recurrence of symptoms, periradicular inflammation, or tooth fracture.
- A national registry with quality indicators is needed for follow-up evaluation of pulpal and root canal treatments.

Methods

The conclusions are based solely on human studies restricted to randomized controlled trials, controlled clinical trials, and prospective cohort studies. Post-mortem studies were accepted to assess reliability of different radiographic methods to diagnose periapical bone lesions. Case reports were included on serious side effects and complications of root canal.

Further research/reviews required

Randomized studies and prospective observational studies with follow-up are needed to:

- evaluate diagnostic methods that can determine the condition of the pulp in teeth afflicted by deep caries, trauma, or other forms of injury
- determine the reliability of digital volume tomography (CBCT) in diagnosing changes in the periapical bone
- show whether pulp exposed by caries or other causes is best treated by measures to preserve the pulp, eg, pulp capping/partial pulpotomy
- improve knowledge of specific treatment factors that explain why many endodontic treatments do not achieve an optimal outcome
- investigate if modern techniques/instrumentation improve root canal outcomes
- study survival of root filled teeth and factors that influence loss of endodontically treated teeth
- investigate the risk of pain/swelling in teeth with persistent but asymptomatic periapical inflammation or risk that the area of periapical bone destruction will increase
- study the risk to general health from untreated periapical inflammatory processes.

Written by Sofia Tranæus, SBU, Sweden

INAHTA Briefs

Issue 2010/202

Title **Multicentre Randomized Controlled Trial of the Clinical And Cost Effectiveness of a Bypass-Surgery-First Versus a Balloon-Angioplasty-First Revascularization Strategy for Severe Limb Ischemia Due to Infra-Inguinal Disease. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial**

Agency NETSCC, HTA, NIHR Evaluation and Trials Coordinating Centre

Reference Volume 14.14. ISBN 1366-5278. www.hta.ac.uk/project/1070.asp

Aim

To compare a bypass-surgery-first with a balloon-angioplasty-first revascularization strategy in patients with severe limb ischaemia (SLI) due to infrainguinal disease requiring immediate/early revascularization.

Conclusions and results

Our findings suggest that in patients with SLI due to infrainguinal disease the decision whether to perform bypass surgery or balloon angioplasty first appears to depend upon anticipated life expectancy. Patients expected to live <2 years should usually be offered balloon angioplasty first as it is associated with less morbidity and cost in the short term (12 months). Patients expected to live beyond 2 years should usually be offered bypass surgery first, especially where a vein is available as a conduit. Many patients who could not undergo a vein bypass would probably have been better served by a first attempt at balloon angioplasty rather than prosthetic bypass. The failure rate of angioplasty in SLI is high (about 25%), and patients who underwent bypass after failed angioplasty fared significantly worse than those who underwent surgery as their first procedure. The interests of a significant share of BASIL patients may have been best served by primary amputation followed by high-quality rehabilitation. Further research needs to confirm or refute the BASIL findings and recommendations; validate the BASIL survival prediction model in a separate cohort of patients with SLI; examine the clinical and cost effectiveness of new endovascular techniques and devices; and compare revascularization with primary amputation and with best medical and nursing care in SLI patients with the poorest survival prospects. Amputation-free survival (AFS) at 1 and 3 years was not significantly different for surgery and angioplasty. Interim analysis showed that surgery was associated with significantly lower immediate failure, higher 30-day morbidity, and lower 12-month reintervention rates than angioplasty; 30-day mortality was similar. Beyond 2 years from randomization, hazard ratios (HRs) were significantly reduced for both AFS (adjusted HR 0.37; 95% CI 0.17 to 0.77; p = 0.008) and overall survival (OS) (HR 0.34; 95% CI 0.17 to 0.71; p = 0.004) for surgery relative to angioplasty. By 2008 all but four patients had been followed for 3 years, some for over 7 years: 250 (56%) were dead, 168 (38%) were alive without amputation, and 30 (7%) were alive with amputation. Considering follow-up as a whole, AFS and OS did not differ between treatments but for patients surviving beyond 2 years from randomization, bypass was associated with reduced HRs for AFS (HR 0.85; 95% CI 0.50 to 1.07; p = 0.108) and OS (HR 0.61; 95% CI 0.50 to 0.75; p = 0.009), equating to an increase in restricted mean OS of 7.3 months (p = 0.02) and AFS of 5.9 months (p = 0.06) during the subsequent follow-up period. Vein bypasses and angioplasties performed better than prosthetic bypasses.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1070.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1070.asp.

Further research/reviews required

The Delphi studies should be repeated to determine whether there has been any convergence of views as to the relative merits of bypass surgery and balloon angioplasty in SLI.

Written by Professor Andrew Bradbury, and Professor Sampson Gamgee, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/203

Title **A Randomized Controlled Trial of Cognitive Behavior Therapy and Motivational Interviewing for People with Type 1 Diabetes Mellitus With Persistent Sub-Optimal Glycaemic Control: A Diabetes and Psychological Therapies (Adapt) Study**

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Reference Volume 14.22. ISSN 1366-5278. www.hta.ac.uk/project/1312.asp

Aim

To determine whether 1) motivational enhancement therapy (MET)+cognitive behavior therapy (CBT) compared with usual care, 2) MET compared with usual care, 3) or MET+CBT compared with MET was more effective in improving glycemic control when delivered by general nurses with additional training in these techniques.

Conclusions and results

A combination of MET and CBT may be useful for patients with persistent suboptimal diabetic control. MET alone appears less effective than usual care. Economic evaluation was inconclusive. In people with type 1 diabetes, 1659 were screened and 344 were randomized to MET+CBT (n=106), MET (n=117) and to usual care (n=121). The 12-month follow-up rate for HbA1c was 88% (n=305). The adjusted mean 12-month HbA1c was 0.45% lower in those treated with MET+CBT (95% confidence interval [CI] 0.16% to 0.79%, p=0.008) than for usual care; 0.16% lower in those treated with MET (95% CI 0.20% to 0.51%, p=0.38) than for usual care; and 0.30% lower with MET+CBT than with MET (95% CI −0.07% to 0.66%, p=0.11). The higher the HbA1c, and the younger the participant at baseline, the greater the reduction in HbA1c. The interventions had no effect on secondary outcomes. The economic evaluation was inconclusive. Both interventions were associated with increased healthcare costs than for usual care alone. Social costs showed no significant difference. Cost effectiveness ratios, up to 1 year, varied widely according to whether QALY estimates were based on EQ-5D or SF-36 and whether imputed or complete data were used.

Recommendations

1) Diabetes professionals can be trained to deliver diabetes-specific MET and CBT competently in the context of concurrent supervision. 2) A combined MET and CBT approach may be useful in individuals with persistent suboptimally controlled diabetes, but MET appeared less effective than usual diabetes practices and MET+CBT. 3) Compared to usual care, at a minimum of 48 636 pounds sterling (GBP) per QALY gain, neither intervention fell within a notional policy-making threshold of cost effectiveness. MET+CBT achieved additional HbA1c improvements at a lower cost (GBP 1756 per additional point improvement) than MET. MET+CBT had a higher probability of cost effectiveness than MET based on HbA1c outcomes, but MET dominated on the basis of QALYs estimated from both EQ-5D and SF-36. Probabilities of cost effectiveness are higher based on HbA1c outcomes than on QALY outcomes. Hence, decisions to provide such interventions depend on the relative importance of these two outcomes.

Methods

See Executive Summary link www.hta.ac.uk/project/1312.asp.

Further research/reviews required

1) To identify quantitatively and qualitatively the components of the complex intervention that was associated with improvement in glycemic control to inform future generations of RCTs. 2) To examine whether the effects are sustained >12 months. 3) To compare variations of therapy, eg, whether additional sessions, electronic formats, or treating depression are associated with additional effectiveness or cost effectiveness. 4) To conduct a discrete choice experiment to understand how people with diabetes appraise the value of psychological treatments to help improve diabetes control, taking account personal costs.

Written by Dr Khalida Ismail, Institute of Psychiatry, Kings College London, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/204

Title **Systematic Review and Economic Modeling of the Effectiveness and Cost Effectiveness of Non-Surgical Treatments for Women with Stress Urinary Incontinence**

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Reference Volume 14.40. ISSN 1366-5278. www.hta.ac.uk/project/1612.asp

Aim

To assess the clinical and cost effectiveness of nonsurgical treatments for women with stress urinary incontinence (SUI) through systematic review and economic modeling.

Conclusions and results

Direct pairwise comparison and mixed treatment comparison (MTC) analysis showed that the treatments were more effective than no treatment. Delivering PFMT in a more intense fashion, either through extra sessions or with biofeedback, appeared to be the most effective treatment (PFMT extra sessions vs NT odds ratio [OR] 10.7, 95% CrI 5.03 to 26.2; PFMT + BF vs NT OR 12.3, 95% credible interval 5.35 to 32.7). Only when success was measured by improvement was there evidence that basic PFMT was better than no treatment (PFMT basic vs NT OR 4.47, 95% CrI 2.03 to 11.9). Cost-effectiveness analysis showed that for cure rates, the strategy using lifestyle changes and PFMT with extra sessions followed by tension-free vaginal tape (TVT) (lifestyle advice–PFMT extra sessions–TVT) had a probability >70% of being considered cost effective for all threshold values for willingness to pay (WTP) for a QALY up to 50 000 pounds sterling (GBP). For improvement rates, lifestyle advice–PFMT extra sessions–TVT had a probability >50% of being considered cost effective when society's WTP for an additional QALY exceeded GBP 10 000. The results were most sensitive to changes in the long-term performance of PFMT and also in the relative effectiveness of basic PFMT and PFMT with extra sessions. More intensive forms of PFMT appear worthwhile, but further research must define an optimal form of more intensive therapy that is feasible and efficient for the NHS, and provide more evidence from large, well-designed studies.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1612.asp.

Methods

1) A survey of women with SUI to identify outcomes important to them (using a Patient Generated Index [PGI]); 2) A systematic review and meta-analysis of nonsurgical treatments for SUI to identify the most effective; 3) Economic modeling of nonsurgical and surgical treatments for SUI to find out which combinations are most cost effective. The survey identified areas of importance to women suffering from SUI, using a PGI. In total, 188 women were invited to take part. Literature searching included the Cochrane Incontinence Group Specialized Register (March 2008), electronic databases (1980 to March 2008), and websites of relevant professional organizations and manufacturers. Randomized controlled trials (RCTs) and quasi-RCTs (alternate allocation) were eligible.

Further research/reviews required

Conclusions are based on data from a limited number of small trials. More intensive forms of PFMT appear worthwhile, but research is required to define an optimal form of more intensive therapy that is feasible and efficient for the NHS to provide. Further evidence from large, well-designed studies is required to provide a definitive answer. Any further research on long-term outcomes, benefit assessment, or costs should be incorporated into an updated economic evaluation.

Written by Professor Luke Vale, University of Aberdeen, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/205

Title **A Multicentred Randomized Controlled Trial of a Primary-Care Based Cognitive Behavioral Program for Low Back Pain. The Back Skills Training (Best) Trial**

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Reference Volume 14.41. ISSN 1366-5278. www.hta.ac.uk/project/1358.asp

Aim

To estimate the clinical effectiveness of active management (AM) in general practice vs AM plus a group-based, professionally led, cognitive behavioral approach (CBA) for subacute and chronic low back pain (LBP); to measure the cost of each strategy for 12 months and estimate cost effectiveness.

Conclusions and results

Between April 2005 and April 2007, 701 participants (420 female) were randomized: 233 to AM and 468 to AM+CBA. The mean age was 54 years and mean baseline Roland Morris Disability Questionnaire (RMQ) was 8.7. Outcome data were obtained for 85% of participants at 12 months. Benefits in a range of outcome measures favored CBA with no evidence of group or therapist effects. CBA resulted in at least twice as much improvement as AM. Mean additional improvement in the CBA arm was 1.1 (95% confidence interval [CI] 0.4 to 1.7), 1.4 (95% CI 0.7 to 2.1), and 1.3 (95% CI 0.6 to 2.1) change points in the RMQ at 3, 6, and 12 months respectively. Additional improvement in Modified Von Korff Scale (MVK) pain was 6.8 (95% CI 3.5 to 10.2), 8.0 (95% CI 4.3 to 11.7), and 7.0 (95% CI 3.2 to 10.7) points, and in MVK disability was 4.3 (95% CI 0.4 to 8.2), 8.1 (95% CI 4.1 to 12.0), and 8.4 (95% CI 4.4 to 12.4) points at 3, 6, and 12 months respectively. At 12 months, 60% of the AM+CBA arm and 31% of the AM arm reported some or complete recovery. Mean cost of attending a CBA course was 187 pounds sterling (GBP) per participant with an additional benefit in QALYs of 0.099 and an additional cost of GBP 178.06. Incremental cost-effectiveness ratio was GBP 1786. Probability of CBA being cost effective reached 90% at about GBP 3000 and remained at that level or above. At a cost-effectiveness threshold of GBP 20 000, the CBA group had nearly 100% probability of being cost effective. User perspectives on acceptability of group treatments were sought via semistructured interviews. Most were familiar with key messages of AM; most who had attended group sessions had retained key messages and two-thirds talked about reduced fear avoidance and changes in behavior. Group sessions appeared to provide reassurance, lessen isolation, and enable participants to learn strategies from each other. Long-term effectiveness and cost effectiveness of CBA in treating subacute and chronic LBP made this intervention attractive to patients, clinicians, and purchasers. Short-term (3-month) clinical effects were similar to those found in high-quality studies of other therapies, and benefits were maintained and increased over the long term (12 months). Cost per QALY was about half that of competing interventions for LBP. Since the intervention can be delivered by existing NHS staff following brief training, the back skills training program could be implemented in the NHS with relative ease.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1358.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1358.asp.

Further research/reviews required

Future research on implementation of the CBA program will help ensure that the benefits we found can be translated into a reduction in LBP and associated disability. Further work is needed to examine alternative strategies to delivery, particularly where these improve patient choice and ability to attend sessions or gain the cognitive skills and behavioral stimulus. The effects of package on generalized physical health-related quality of life give some evidence that CBA may be of help for other musculoskeletal disorders.

Written by Professor Sarah Lamb, University of Warwick, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/206

Title **Recombinant Human Growth Hormone for the Treatment of Growth Disorders in Children: A Systematic Review and Economic Evaluation**

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Reference Volume 14.42. ISSN 1366-5278. www.hta.ac.uk/project/1755.asp

Aim

To assess the clinical and cost effectiveness of recombinant human growth hormone (rhGH) compared with treatment strategies without rhGH for children with growth hormone deficiency (GHD), Turner syndrome (TS), Prader-Willi syndrome (PWS), chronic renal insufficiency (CRI), short stature homeobox-containing gene deficiency (SHOX-D), and being born small for gestational age (SGA).

Conclusions and results

Recombinant human growth hormone is licensed for short stature associated with GHD, TS, PWS, CRI, SHOX-D, and being born SGA. The systematic review included 28 randomized controlled trials (RCTs) in 34 publications. GHD: Children in the rhGH group grew 2.7 cm/year faster than untreated children and had a statistically significantly higher height standard deviation score (HtSDS) after 1 year: −2.3 ± 0.45 versus −2.8 ± 0.45. TS: In one study, treated girls grew 9.3 cm more than untreated girls. In a study of younger children, the difference was 7.6 cm after 2 years. HtSDS values were statistically significantly higher in treated girls. PWS: Infants receiving rhGH for 1 year grew significantly taller (6.2 cm more) than those untreated. Two studies reported a statistically significant difference in HtSDS in favor of rhGH. CRI: rhGH-treated children in a 1-year study grew an average of 3.6 cm more than untreated children. HtSDS was statistically significantly higher in treated children in two studies. SGA: Criteria were amended to include children of 3+ years with no catch-up growth, with no reference to mid-parental height. Only one of the RCTs used the licensed dose; the others used higher doses. Adult height (AH) was approximately 4 cm higher in rhGH-treated patients in the one study to report this outcome, and AH-gain SDS was also statistically significantly higher in this group. Mean HtSDS was higher in treated than untreated patients in four other studies (significant in two). SHOX-D: After 2 years' treatment, children were approximately 6 cm taller than the control group and HtSDS was statistically significantly higher in treated children. The incremental cost per quality adjusted life-year (QALY) estimates of rhGH compared with no treatment were: 23 196 pounds sterling (GBP) for GHD, GBP 39 460 for TS, GBP 135 311 for PWS, GBP 39 273 for CRI, GBP 33 079 for SGA, and GBP 40 531 for SHOX-D. The probability of treatment of each of the conditions being cost effective at GBP 30 000 was: 95% for GHD, 19% for TS, 1% for PWS, 16% for CRI, 38% for SGA, and 15% for SHOX-D. Statistically significantly larger HtSDS values were reported for rhGH-treated children with GHD, TS, PWS, CRI, SGA, and SHOX-D. rhGH-treated children with PWS also showed statistically significant improvements in body composition. Only treatment of GHD would be considered cost effective at a willingness-to-pay threshold of GBP 20 000 to 30 000 per QALY gained. Future research should include studies exceeding 2 years that report near-final height or final adult height.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1755.asp.

Methods

The systematic review of clinical effectiveness used a priori methods as described in the research protocol. We searched key databases (e.g. MEDLINE, EMBASE, NHS Economic Evaluation Database) for relevant studies (in English) from their inception to June 2009. Relevant conferences, bibliographies of included papers, our expert advisory group, and manufacturers' submissions to NICE were also consulted to identify additional published or unpublished references. We developed an economic model using the best available evidence to determine cost effectiveness in the UK.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1755.asp.

Written by Ms Jackie Bryant, SHTAC, University of Southmapton, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/207

Title **Group Cognitive Behavioral Therapy for Postnatal Depression: A Systematic Review of Clinical Effectiveness, Cost Effectiveness and Value of Information Analyses**

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Reference Volume 14.44. ISSN 1366-5278. www.hta.ac.uk/project/1663.asp

Aim

To evaluate the clinical and cost effectiveness of group cognitive behavioral therapy (CBT) compared to current packages of care for women with postnatal depression (PND).

Conclusions and results

Six studies (3 randomized controlled trials [RCTs] and 3 nonrandomized trials) met the inclusion criteria for the quantitative review. Two studies met the inclusion criteria for the qualitative review. Both were treatment evaluations incorporating qualitative methods. Since only one study was deemed appropriate for the decision problem, a meta-analysis was not performed. This study indicated that the reduction in the Edinburgh Postnatal Depression Scale (EPDS) score through group CBT compared with routine primary care (RPC) was 3.48 (95% confidence interval [CI] 0.23 to 6.73) at the end of the treatment period. At 6-month follow-up the relative reduction in EPDS score was 4.48 (95% CI 1.01 to 7.95). There was no adequate evidence on which to assess group CBT compared with treatments for PND other than RPC, usual care, or waiting list groups. Two studies of group CBT for PND were included in the qualitative review. Both studies demonstrated patient acceptability of group CBT for PND, although negative feelings toward group CBT were also identified. A de novo economic model was constructed to assess the cost effectiveness of group CBT. The base-case results indicated a cost per quality-adjusted life-year (QALY) of 46 462 pounds sterling (GBP) for group CBT compared with RPC. The 95% CI for this ratio ranged from GBP 37 008 to GBP 60 728. There was considerable uncertainty in the cost per woman of running a CBT course, of the appropriateness of efficacy data to the decision problem, and the residual length of benefit associated with group CBT. Analyses that fitted distributions to the cost of treatment and the duration of comparative advantage reported a cost per QALY of GBP 36 062 (95% CI GBP 20 464 to GBP 59 262).

Analyses of the expected value of information showed a considerable expected benefit in conducting further research.

Recommendations

Evidence from the clinical effectiveness review provides inconsistent and low-quality information on which to base interpretations for service provision. Three of the included studies provide some indication that group psychoeducation incorporating CBT is effective compared with RPC. Enough doubt exists in the quality of the study, the level of CBT implemented in the group programs, and the applicability to a PND population to significantly limit any interpretation. The place of group CBT in a stepped care program needs to be identified, and a clearer referral process for group CBT is needed. There is also a requirement to make clearer assessments of the facilitators and resources required for group CBT (including training needs) and to provide a clear method of assessing suitable participants for the treatment. Further research to obtain better data on the costs of running group CBT for PND sessions and on the expected quality-of-life gains associated with treatment appears to be a cost effective use of resources.

Methods

See Executive Summary link www.hta.ac.uk/project/1663.asp.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1663.asp.

Written by Dr Matt Stevenson, ScHARR, University of Sheffield, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/208

Title **Evaluation of Triage Methods Used to Select Patients with Suspected Pandemic Influenza for Hospital Admission: Cohort Study**

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Reference Volume 14.46(3). ISSN 1366-5278. www.hta.ac.uk/2225

Aim

To use the initial waves of the 2009 H1N1 pandemic to evaluate existing triage methods in patients presenting with suspected pandemic influenza (PI), and to determine whether an improved triage method could be developed.

Conclusions and results

Data were collected and analyzed from 481 cases across 3 hospitals. Most of the cases were children, with 347 of 481 (72%) aged 16 years or less. There were 5 poor outcomes: 2 deaths and 3 survivors who required respiratory support. The 5 patients with poor outcomes had CURB-65 scores of 0, 1 (3 cases), and 2, and PMEWS scores of 1, 5, 6, 7, and 8. The swine flu hospital pathway was positive in 3 of 5 cases. The C-statistic for each method was CURB-65 0.78 (95% confidence interval [CI] 0.58 to 0.99), PMEWS 0.77 (95% CI 0.55 to 0.99), and the swine flu hospital pathway 0.70 (95% CI 0.45 to 0.96). Patients with a higher CURB-65 score were more likely to be admitted (p <0.001): 25 out of 101 (25%) with a score of 0; 11 of 24 (46%) with a score of 1; 7 of 8 (88%) with a score of 2; and the patient with a score of 3 were admitted. Admitted patients had a higher mean PMEWS score (4.6 vs 2.0, p <0.001). The C-statistics for CURB-65, PMEWS and the swine flu hospital pathway in adults in terms of discriminating between those admitted and discharged were 0.65 (95% CI 0.54 to 0.76), 0.76 (95% CI 0.66 to 0.86), and 0.62 (95% CI 0.51 to 0.72) respectively. Concerns were raised about the use of existing triage methods for patients with suspected PI, as these methods may fail to discriminate between patients who will have an adverse outcome and those with a benign course. Clinicians in the study did not generally appear to admit or discharge on the basis of these methods, despite their recommended use. Further research is required to evaluate existing triage methods and develop new triage tools for suspected PI.

Recommendations

See Executive Summary link www.hta.ac.uk/2225.

Methods

We undertook a prospective cohort study of patients with suspected PI presenting to the emergency department (ED) of 4 hospitals during the second wave of the 2009 H1N1 pandemic. ED staff identified patients with suspected PI and completed a standardized assessment form that included the elements of the CURB-65 score, PMEWS, the swine flu hospital pathway, and other measures. Outcome assessment was based on researcher review of hospital computer records and case notes. Patients who died or required respiratory, cardiovascular, or renal support during the 30-day follow-up were defined as having a poor outcome. Patients who survived to 30 days without requiring respiratory, cardiovascular, or renal support were defined as having a good outcome. We recorded whether they were treated with antiviral agents or antibiotics, and the length and location of any hospital stay. We planned to assess CURB-65, PMEWS and the swine flu clinical pathway by calculating the area under the receiver-operator characteristic curve (C-statistic) for discriminating between cases with and without a poor outcome. We also planned to use multivariable logistic regression to determine the independent predictive value of presenting clinical characteristics and routine tests and to develop two new triage scores: one based on initial assessment only and the other based on all ED data.

Further research/reviews required

Further research is required to: evaluate existing triage tools and develop new triage methods for suspected PI; and to determine the feasibility and acceptability to patients of undertaking research during a pandemic using confidential patient information without consent.

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INAHTA Briefs

Issue 2010/209

Virus Shedding and Environmental Deposition of Novel A (H1N1) Pandemic Influenza Virus

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Reference Volume 14.46(4). ISSN 1366-5278. www.hta.ac.uk/2225

Aim

To collect data on patients infected with pandemic H1N1 2009 (swine flu).

Conclusions and results

Primary objective: to correlate the amount of virus detected in a patient's nose with that recovered from his/her immediate environment (surface swabs and air samples) and with symptom duration and severity. Secondary objectives: to describe virus shedding and duration according to major patient characteristics: adults versus children, and those with mild illness (community patients) versus those with more severe disease (hospitalized patients).

Of the 43 subjects followed up, 19 were proven to be infected with pandemic H1N1 virus. The median duration of virus shedding from the 19 infected cases was 6 days when detection was performed by polymerase chain reaction (PCR), and 3 days when detection was performed by a culture technique. Over 30% of cases remained potentially infectious for at least 5 days. Only 2/397 (0.5%) community and none of the hospital swabs taken revealed virus on surfaces. Five subjects had samples of the air around them collected, and virus was detected by PCR from 4; some of the air particles in which virus was detected were small enough to be inhaled and deposited deep in the lungs. Despite some limitations caused by the small number of subjects recruited, important observations have been made. The finding that over 30% of infected individuals have infectious virus in their noses for 5 days or more has infection control implications. The evidence for the significance of both contact and bioaerosol routes of transmission, depends upon demonstrating that viable virus is deposited from an infected patient. This has been shown for touched fomites. Virus has been demonstrated by PCR in air samples, but the results of live virus testing are inconclusive.

Recommendations

The data generated suggest that contact transmission of pandemic influenza via fomites may be less important than hitherto emphasized, whereas transmission via bioaerosols at short range may be possible, ie, high-level personal protective equipment (PPE) might be needed by healthcare workers when attending patients with pandemic influenza. Further work is being undertaken to consolidate these findings as they have important potential implications for the protection of healthcare workers and the formulation of advice to households, nationally and internationally.

Methods

Adults and children, both in hospital and from the community, who had symptoms of pandemic H1N1 infection, were enrolled and visited every day during follow-up for a maximum of 12 days. Information about symptoms was collected and samples were taken, including nose swabs and swabs from surfaces and objects (fomites) around patients (eg, door handles, remote controls). Samples of air were obtained using validated sampling equipment. These samples were tested for the presence of pandemic H1N1 virus, using PCR to detect virus genome and an immunofluorescence technique to detect viable (live) virus.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/2225.

Written by Dr Ben Killingley, University of Nottingham, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/210

Title **Relapse Prevention in UK Stop Smoking Services: Current Practice, Systematic Reviews of Effectiveness and Cost-Effectiveness Analysis**

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Reference Volume 14.49. ISSN 1366-5278. www.hta.ac.uk/project/1617.asp

Aim

To assess the effectiveness and cost effectiveness of relapse prevention in NHS Stop Smoking Services (SSS).

Conclusions and results

Qualitative research with 16 NHS SSS managers indicated that there was no shared understanding of what relapse prevention meant, or of the kinds of interventions that should be used. The systematic review included 36 studies that randomized and delivered interventions to abstainers. Self-help behavioral interventions delivered to abstainers who had achieved abstinence unaided were effective in preventing relapse to smoking at long-term follow-up (odds ratio [OR] 1.52, 95% confidence interval [CI] 1.15 to 2.01). The following pharmacotherapies were effective as relapse prevention interventions (RPIs) after their successful use as cessation treatments: bupropion at long-term follow-up (pooled OR 1.49, 95% CI 1.10 to 2.01); nicotine replacement therapy (NRT) at medium- (pooled OR 1.56, 95% CI 1.16 to 2.11) and long-term follow-ups (pooled OR 1.33, 95% CI 1.08 to 1.63), and one trial of varenicline also indicated effectiveness. The health economic analysis found that RPIs are highly cost effective. Compared to no intervention; bupropion resulted in an incremental quality-adjusted life-year (QALY) increase of 0.07, with a concurrent NHS cost saving of 68 pounds sterling (GBP); for NRT, spending GBP 12 resulted in a 0.04 incremental QALY increase; varenicline resulted in a similar QALY increase as NRT, but at almost 7 times the cost. Extensive sensitivity analyses demonstrated that cost-effectiveness ratios were more sensitive to variations in effectiveness than cost and that cost effectiveness generally remained for bupropion and NRT. Varenicline also demonstrated cost effectiveness at a willingness-to-pay threshold of GBP 20 000 per QALY, but exceeded this when inputted values for potential effectiveness were at the lower end of the range explored. For all drugs, there was substantial relapse to smoking after treatment courses had finished. Quit attempts involving NRT appeared to have the highest early relapse rates, when trial participants would be expected to still be on treatment, but for those involving bupropion and varenicline little relapse was apparent during this time. Based on the evidence, RPIs are expected to be effective and cost effective if incorporated into routine treatment in the NHS SSS. While staff in the NHS SSS largely favored providing RPIs, guidance would be needed to encourage the adoption of the most effective RPIs, as would incentives that focused on the importance of sustaining quit attempts beyond the currently monitored 4-week targets.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1617.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1617.asp.

Further research/reviews required

Some NHS SSS are providing RPIs, but where this occurs, those with the weakest evidence base are generally used, illustrating a requirement for the emerging evidence base and guidance to be made available as soon as possible.

Written by Dr Tim Coleman, University of Nottingham, NETSCC, United Kingdom

INAHTA Briefs

Issue 2010/211

Title **LIFELAX - Diet and LIFEstyle versus LAXatives in the Management of Chronic Constipation in Older People: Randomized Controlled Trial**

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Reference Volume 14.52. ISSN 1366-5278. www.hta.ac.uk/project/1310.asp

Aim

To investigate the clinical and cost effectiveness of laxatives versus dietary and lifestyle advice, and standardized versus personalized dietary and lifestyle advice.

Conclusions and results

The trial planned to recruit and retain 1425 patients from 57 practices, but only 154 patients were recruited from 19 practices. Baseline patient characteristics suggest that they experienced few symptoms of constipation, and constipation had no major impact on their quality of life. Most patients were satisfied with their laxatives, and levels of anxiety and depression were low. Daily diaries (maintained for 6 months) were an acceptable method of outcome data collection. Due to low recruitment rates, firm conclusions could not be drawn about the effectiveness of the interventions. For the economic evaluation, all of the trial arms experienced a reduction in utility. Data on related healthcare costs show a cost saving of 13.34 pounds sterling for those in the personalized arm, compared to the control arm, and a smaller cost saving for the standardized arm. No statistical evidence suggested that either the personalized intervention arm or the standardized intervention arm was associated with significant changes in utility at 3 months compared to the control arm. Cost minimization indicated that the personalized arm appeared to be the preferred course, producing the greatest cost savings. The qualitative process evaluation highlighted several factors that contributed to the conduct and progress of the trial, which may be relevant to others conducting research on a similar topic or population.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1310.asp.

Methods

We used a prospective, pragmatic, 3-armed cluster (at the GP level) randomized trial with an economic evaluation and integrated process evaluation. Fifty-seven general practices were allocated to 1 of 3 arms: prescription of laxatives; standardized, nonpersonalized dietary and lifestyle advice; personalized dietary and lifestyle advice, with reinforcement. Patients were aged 55 years or over with chronic constipation, living in private households. The primary outcome was the constipation-specific PAC-SYM/PAC-QOL. Secondary outcomes comprised: EQ-5D, reported number of bowel movements per week; the presence/absence of other Rome II criteria for constipation; adverse effects of treatment; and relapse rates. These data were collected through diaries, postal questionnaires, and telephone interviews. The qualitative process evaluation comprised semistructured interviews with purposive samples of: members of the project management and steering group; general practitioners, practice managers and nurses working to recruit and deliver patients to the trial and conduct the interventions; and (3) patients participating in the trial. We used a combination of qualitative research techniques, following Glaser and Strauss' model of constant.

Further research/reviews required

The process evaluation identified several issues regarding the development and implementation of RCTs. The problem of the trial's topic, setting, and training packages might have been identified had a prior feasibility study been conducted. However, numerous system-wide problems, eg, the changing RM&G guidelines and research briefs that did not match General Medical Service's contracts, also taxed the capacity of the trial to be successful.

Written by Professor Elaine McColl, Newcastle University, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/001

Title **Use of Point-Of Care Devices in Patients With Oral Anticoagulation: A Health Technology Assessment**

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Reference Report no. 117(C). Year 2009

Aim

To examine the clinical and cost effectiveness of using point-of-care (POC) devices by general practitioners (GPs), in anticoagulation clinics, or by patient self-testing (PST) and self-management (PSM), compared to standard laboratory testing for international normalized ratio (INR) monitoring.

Conclusions and results

Twenty randomized controlled trials (RCTs) were selected for a meta-analysis. The quality of the underlying evidence was moderate. Compared to laboratory testing in usual care, only PST (OR: 0.54-95% CI: 0.30-0.97) and PSM (OR: 0.39-95% CI: 0.27-0.56) had a significant impact on thromboembolic events. Only PSM had a significant impact on mortality (OR: 0.55-95% CI: 0.42-0.72). We found no impact of POC on major bleeding. With an equal number of tests as in the studied sample (15 tests), the use of POC was a cost-saving strategy compared to laboratory testing for all POC strategies (probability >70%). In every scenario investigated, PSM resulted in significantly more "life years gained" (LYG) than usual care and was on average cost-saving, except if 100% of GP consultations were maintained and 52 tests per year were performed (1757 euros (EUR) /LYG; 95%CI: Dominant to EUR 6521/LYG).

Recommendations

Organization of long-term oral anticoagulation monitoring should be directed toward PSM and, to a lesser extent, PST for selected and well-trained patients.

Methods

Major electronic databases were systematically searched. Results on major bleeding, thromboembolic events, and deaths were pooled in meta-analyses. The economic evaluation used the perspective of the Belgian healthcare payer. Cost data were obtained from Belgian charges databases. Uncertainty was handled by a probabilistic sensitivity analysis, and several scenarios were analyzed.

Further research/reviews required

We found only one RCT that addressed GP use of POC devices and another one that addressed the use of POC devices in anticoagulation clinics.

Written by Jeanine Gailly, KCE, Belgium

INAHTA Briefs

Issue 2011/002

Title **High-Intensity Focused Ultrasound (HIFU) for the Treatment of Localized Prostate Cancer**

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Aim

To evaluate the clinical effectiveness of high-intensity focused ultrasound (HIFU) therapy for early localized prostate cancer.

Conclusions and results

HIFU therapy is used as primary treatment for low- and intermediate-risk, localized, prostate cancer (T1-2 NxM0) in patients over 70 years of age and for local recurrence of prostate cancer after failure of radiotherapy.

Owing to the poor quality of evidence identified (case series only, and in most cases a short follow-up), it is not possible to give a firm answer to the question: Are the advantages of HIFU sufficient to counterbalance the complications and uncertainty of the long-term results, compared to standard treatment options including either deferred (watchful waiting) or immediate (in the event of recurrence) hormonal treatment? The main areas affected by adverse events of HIFU therapy were mainly the urinary tract (postoperative obstruction and infection; long-term incontinence), the rectum (rectal fistulae), and potency (impotence).

Recommendations

Recommended update in 5 years, at the earliest.

Methods

The assessment strategy consisted of an in-depth literature search and analysis of scientific data (published and unpublished studies), followed by consultation of a multidisciplinary working group comprised of French urologists, radiotherapists, a medical oncologist, a primary care physician, and a patient. Twenty-one case series were identified, these relating to approximately 2500 selected patients treated with different Ablatherm® (n=13) or Sonablate® (n=8) devices from the same manufacturer over time. The literature data and analysis were discussed with the working group. The Committee for Assessment of Medical and Surgical Procedures reviewed the conclusions. The HAS Board approved the final report before publication.

Further research/reviews required

Areas recommended for further research are: Controlled clinical trials and/or observational studies with sufficient follow-up to measure benefits in terms of survival, long-term adverse effects, and quality of life.

Written by Paul Merckx, HAS, France

INAHTA Briefs

Issue 2011/003

Title **A Pragmatic Randomized Controlled Trial to Compare Antidepressants With a Community-Based Psychosocial Intervention for the Treatment of Women With Postnatal Depression: The RESPOND Trial**

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Reference Volume 14.43, ISSN 1366-5278. www.hta.ac.uk/project/1373.asp

Aim

To: 1) evaluate clinical effectiveness at 4 weeks of antidepressant therapy compared to general supportive care for mothers with postnatal depression (PND); 2) compare outcomes at 18 weeks of those randomized to antidepressant therapy with those randomized to listening visits as the first intervention (both groups were to be allowed to receive the alternative intervention after 4 weeks if the woman or her doctor so decided); and 3) assess acceptability of antidepressants and listening visits to users and health professionals.

Results and conclusions

At 4 weeks, women were more than twice as likely to have improved if they had been randomized to antidepressants compared to listening visits, which started after the 4-week follow-up, ie, after 4 weeks of general supportive care (primary intention-to-treat [ITT], 45% versus 20%; odds ratio [OR] 3.4, 95% confidence interval [CI] 1.8 to 6.5, $p < 0.001$). Explanatory analyses emphasized these findings. At 18 weeks, ITT analysis revealed that the proportion of women improving was 11% greater in the antidepressant group, but logistic regression analysis showed no benefit for one group over the other (62% versus 51%, OR 1.5 [95% CI 0.8 to 2.6], $p = 0.19$). Overall, there was a difference between the groups in favor of the antidepressant group of about 25 percentage points at 4 weeks, which reduced at 18 weeks. No statistical support existed for a benefit of antidepressants at 18 weeks, but 95% CIs could not rule out a clinically important benefit. Trial design meant that by 18 weeks many of the women initially randomized to listening visits were also receiving antidepressants, and more vice versa. The lack of evidence for differences at 18 weeks is likely to reflect a combination of reduced power and the considerable degree of switching across the two interventions. Qualitative interviews with women revealed a preference for listening visits, but an acceptance that antidepressants might be necessary. Women found both antidepressants and listening visits effective depending on their circumstances and preferences. They wished to be reassured that their GP and health visitor (HV) were offering continuity of care focusing on their particular set of circumstances. Interviews with GPs and HVs revealed a lack of collaboration in managing care for women with PND; neither professional group was willing to assume responsibility. The trial indicates that early treatment with antidepressants leads to clinical benefit for women with PND.

Recommendations

This study has shown that at 4 weeks, antidepressants were significantly superior to general supportive care. The data also confirm that a substantial number of women suffer from depression in the 6-month postnatal period. There is an urgent need for GPs and HVs to agree on care pathways for these women. Starting women on antidepressants early in the illness is likely to result in the fastest resolution of symptoms, which will require GPs and HVs to accept responsibility for making the diagnosis and agreeing on management for individual women. The need to ensure adequate services for PND is heightened by the potential for long-term adverse consequences for the women and their children.

Methods

See Executive Summary link www.hta.ac.uk/project/1373.asp.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1373.asp.

Written by Professor Deborah J Sharp, University of Bristol, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/004

Title **Open-Label, Randomized, Parallel-Group, Multicentre Study to Evaluate the Safety, Tolerability and Immunogenicity of an AS03B/Oil-In-Water Emulsion- Adjuvanted (AS03B) Split-Virion Versus Non-Adjuvanted Whole-Virion H1N1 Influenza Vaccine in UK Children 6 Months to 12 Years of Age**

Agency NETSCC, HTA, NIHR Evaluation and Trials Coordinating Centre

Reference Volume 14.46(1). ISSN 1366-5278. www.hta.ac.uk/2225

Aim

To evaluate the safety, tolerability, and immunogenicity of an AS03B/oil-in-water emulsion-adjuvanted (AS03B) split-virion versus nonadjuvanted whole-virion H1N1 influenza vaccine in UK children aged 6 months to 12 years.

Conclusions and results

Among 937 children receiving vaccine, per-protocol seroconversion rates were higher after the AS03B-adjuvanted vaccine than after the whole-virion vaccine (98.2% vs 80.1% in children <3 years, 99.1% vs 95.9% among those aged 3-12 years), as were severe local reactions (3.6% vs 0.0% in those <5 years, 7.8% vs 1.1% in those aged 5-12 years), irritability in children <5 years (46.7% vs 32.0%), and muscle pain in older children (28.9% vs 13.2%). The second dose of the adjuvanted vaccine was more reactogenic than the first, especially for fever >38.0°C in those <5 years of age (22.4%vs 8.9%). The adjuvanted vaccine, although reactogenic, was more immunogenic, especially in younger children, indicating the potential for improved immunogenicity of influenza vaccines in this age group.

Recommendations

In this first direct comparison of an AS03B-adjuvanted split-virion vaccine versus whole-virion nonadjuvanted H1N1 vaccine, the adjuvanted vaccine – while reactogenic – was more immunogenic, especially in younger children, indicating the potential for improved immunogenicity of influenza vaccines in this age group.

Methods

The safety, reactogenicity, and immunogenicity of a tocopherol/oil-in-water emulsion-adjuvanted (AS03B) egg culture-derived split-virion H1N1 vaccine and a nonadjuvanted cell culture-derived whole-virion vaccine, given as a two-dose schedule, 21 days apart, were compared in a randomized, open-label trial of children aged 6 months to 12 years. Local reactions and systemic symptoms were collected for 1 week postimmunization, and serum was collected at baseline and after the second dose.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/2225.

Written by Dr Claire Waddington, University of Oxford, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/005

Title **Evaluation of Droplet Dispersion During Non-Invasive Ventilation, Oxygen Therapy, Nebulizer Treatment and Chest Physiotherapy in Clinical Practice: Implications for Management of Pandemic Influenza and Other Airborne Infections**

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Reference Volume 14.46(2). ISSN 1366-5278. www.hta.ac.uk/2225

Aim

To evaluate the characteristics of droplet/aerosol dispersion around delivery systems during noninvasive ventilation (NIV), oxygen therapy, nebulizer treatment, and chest physiotherapy by measuring droplet size, geographical distribution of droplets, and decay in droplets over time after the interventions were discontinued.

Conclusions and results

NIV using a vented mask produced droplets in the large size range (>10 µm) in patients (p=0.042) and coryzal subjects (p=0.044) compared with baseline values, but not in normal controls (p=0.379), However, this increase in large droplets was not seen using the NIV circuit modification. Chest physiotherapy produced droplets predominantly of >10 µm (p=0.003), which, as with NIV droplet count in the patients, had fallen significantly by 1 m. Oxygen therapy did not increase droplet count in any size range. Nebulized saline delivered droplets in the small- and medium-size aerosol/droplet range, but did not increase large-size droplet count. NIV and chest physiotherapy are droplet- (not aerosol-) generating procedures, producing droplets of >10 µm. Due to their large mass, most fall out onto local surfaces within 1 m. The only device producing an aerosol was the nebulizer, and the output profile is consistent with nebulizer characteristics rather than dissemination of large droplets from patients.

Recommendations

The findings suggest that healthcare workers providing NIV and chest physiotherapy, working within 1 m of an infected patient, should have a higher level of respiratory protection, but that infection control measures designed to limit aerosol spread, eg, negative-pressure rooms, may have less relevance. The results may have infection control implications for other airborne infections (eg, severe acute respiratory syndrome and tuberculosis) and for pandemic influenza infection.

Methods

Three groups were studied: 1) normal control subjects, 2) subjects with coryzal symptoms, and 3) adult patients with chronic lung disease who were admitted to hospital with an infective exacerbation. Each group received O2, NIV using a vented mask system and a modified circuit with nonvented mask and exhalation filter, and nebulized saline. The patient group had a period of standardized chest physiotherapy treatment. Droplet counts in mean diameter size ranging from 0.3 to >10 µm were measured with a counter placed adjacent to the face (D1) and at 1 m (D2) from subject/patient at the height of the nose/mouth of an average healthcare worker.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/2225.

Written by Dr Anita Simonds, Royal Brompton Hospital, London, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/006

Title **A Systematic Review of Positron Emission Tomography (PET) and Positron Emission Tomography/Computed Tomography (PET/CT) for the Diagnosis of Breast Cancer Recurrence**

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Reference Volume 14.50. ISSN 1366-5278. www.hta.ac.uk/project/2051.asp

Aim

To review the accuracy of PET and PET/CT in diagnosing breast cancer (BC) recurrence by assessing their value compared to current practice and compared with each other.

Conclusions and results

Of the 28 studies included in the review, 25 presented patient-based data and 7 presented lesion-based data for PET, and 5 presented patient-based data and 1 presented patient- and lesion-based data for PET/CT; 16 studies conducted direct comparisons with 12 comparing the accuracy of PET or PET/CT with conventional diagnostic tests and 4 with MRI. For patient-based data (direct comparison) PET had significantly higher sensitivity (89%, 95% confidence interval [CI] 83% to 93% vs 79%, 95% CI 72% to 85%, relative sensitivity 1.12, 95% CI 1.04 to 1.21, p=0.005) and significantly higher specificity (93%, 95% CI 83% to 97% vs 83%, 95% CI 67% to 92%, relative specificity 1.12, 95% CI 1.01 to 1.24, p=0.036) compared with conventional imaging tests (CITs) – test performance did not appear to vary according to the type of CIT tested. For patient-based data (direct comparison) PET/CT had significantly higher sensitivity compared with CT (95%, 95% CI 88% to 98% vs 80%, 95% CI 65% to 90%, relative sensitivity 1.19, 95% CI 1.03 to 1.37, p=0.015), but the increase in specificity was not significant (89%, 95% CI 69% to 97% vs 77%, 95% CI 50% to 92%, relative specificity 1.15, 95% CI 0.95 to 1.41, p=0.157). For patient-based data (direct comparison) PET/CT had significantly higher sensitivity compared with PET (96%, 95% CI 90% to 98% vs 85%, 95% CI 77% to 91%, relative sensitivity 1.11, 95% CI 1.03 to 1.18, p=0.006), but the increase in specificity was not significant (89%, 95% CI 74% to 96% vs 82%, 95% CI 64% to 92%, relative specificity 1.08, 95% CI 0.94 to 1.20, p=0.267). For patient-based data, we found no significant differences in the sensitivity or specificity of PET when compared with MRI. In the one lesion-based study, there was no significant difference in the sensitivity or specificity of PET/CT when compared with MRI. Available evidence suggests that for the detection of BC recurrence PET, in addition to conventional imaging techniques, may generally offer improved diagnostic accuracy compared with current standard practice. However, uncertainty remains around its use as a replacement for, rather than an add-on to, existing imaging technologies. In addition, PET/CT appeared to show clear advantage over CT and PET alone in diagnosing BC recurrence.

Recommendations

See Executive Summary link www.hta.ac.uk/project/2051.asp.

Methods

The systematic review included a search for primary studies (no language restrictions) in MEDLINE (Ovid) and EMBASE (Ovid) from database inception to May 2009. Studies of PET or PET/CT in patients with history of BC and suspected recurrence were selected for inclusion. Studies were excluded if: 1) investigations were conducted for screening or staging of primary BC; 2) nonstandard PET or PET/CT technology was used; 3) the reference standard was inadequate or undefined; 4) or raw data were unavailable to calculate diagnostic accuracy. Both comparative and noncomparative studies were included. Two reviewers independently extracted data and assessed quality. Any disagreements were resolved by consensus. Direct and indirect comparisons were made between PET and PET/CT and between these technologies and methods of conventional imaging. A meta-analysis was performed using a bivariate random effects model. Patient- and lesion-based data were analyzed separately. Subgroup analysis was conducted to investigate variation in the accuracy of PET in certain populations or contexts. Sensitivity analysis was used to examine the reliability of primary outcome measures.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/2051.asp.

Written by Dr Mary Pennant, The University of Birmingham, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/007

Title **Bariatric Surgery in Diabetic Type 2 Patients With CMI 30 kg/m2**

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Reference Núm.2009/01-2.
www.sergas.es/Docs/Avalia-t/avalia-t200901-2-cirugiadiabetes.pdf

Aim

To evaluate the usefulness of bariatric surgery in treating type 2 diabetes mellitus.

Conclusions and results

A significant reduction in glycosylated hemoglobin (HbA1c) concentration (%) was observed in nonobese diabetic patients versus controls when biliopancreatic diversion or gastric bypass (GB) procedures were used. Control (reduction in HbA1c %) was successfully achieved in most patients using type I or II laparoscopic sleeve gastrectomy. In one study, laparoscopic GB reduced the HbA1c% from 9.4% to 8.5%, although there was marked variability among patients. In another study, however, the mean HbA1c value (%) was significantly reduced ($p<0.001$). The LAP-BAND® procedure resulted in resolution in 50% of patients and improvement in the remaining 50%.

Recommendations

An intense debate surrounds the inclusion criteria for this surgery (with assessments of low methodological quality for diabetic patients with BMI ≤30 kg/m2), as opposed to the abundant literature addressing and assessing the safety, effectiveness, and cost effectiveness of other types of preventive and therapeutic interventions. Hence, it is essential to identify the inclusion criteria to be applied when using these techniques on nonobese diabetic subjects.

Methods

In February 2010, we conducted a systematic review of the literature using the following databases: Cochrane Library Plus; NHS Centre for Reviews and Disseminations; Health Technology Assessment (HTA); Database of Abstracts of Reviews of Effectiveness (DARE); NHS Economic Evaluation Database (NHSEED); Clinical Trials; MEDLINE; and EMBASE. Papers were selected on the basis of pre-established inclusion and exclusion criteria.

The information was summarized in evidence tables, and study quality was assessed using a specific scale.

Further research/reviews required

Further research on bariatric surgery is needed to establish the clinical usefulness of this technique.

Written by eannette Puñal Riobóo, Galician Department of Health, AVALIA-T, Spain

INAHTA Briefs

Issue 2011/008

Title **Interferon Release Assays (Igras) for Diagnosis of Latent Tuberculosis Infection and Active Tuberculosis**

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Reference Núm.2009/01-1.
www.sergas.es/Docs/Avalia-t/avalia-t-200901-1-interferongamma.pdf

Aim

To assess the efficacy/effectiveness of interferon-γ release assays (IGRAs) versus the tuberculin skin test (TST) in diagnosing latent tuberculosis infection (LTI) and tuberculosis (TB).

Conclusions and results

For diagnosis of LTI, contact studies have reported a sensitivity (S) of around 50% for the T-SPOT test and a lower S for the QuantiFERON-TB Gold In-Tube (QFT-GIT) test (11%-42%). Among HIV-positive and drug-dependent subjects, the QFT-GIT (60%-90%) appears to be more sensitive than the T-SPOT (33%-50%). The T-SPOT was observed to have higher S among military and immunocompromised (rheumatoid arthritis) subjects (100%). IGRAs registered a specificity (SP) >70% in diagnosis of LTI, except in the case of drug-dependent subjects among whom the QFT-GIT achieved an SP of 67%. As regards diagnosis of TB, both the T-SPOT and QFT-GIT displayed sensitivities comparable to that of TST, while IGRAs seemed to be more specific than the TST.

Recommendations

IGRAs are useful tests for ruling out LTI, since they display a higher SP than does the TST. Nevertheless, a positive result in such tests, ie, suspicion of LTI, should be confirmed with imaging and/or microbiological tests. The Spanish Society of Pneumology and Thoracic Surgery (Sociedad Española de Neumología y Cirugía Torácica - SEPAR) has proposed that in vitro interferon-γ techniques could be used to confirm a negative result for TST in immunodepressed subjects, and a positive result in vaccinated subjects. Hence, if the test were negative, LTI would be ruled out, and if it were positive, infection would be confirmed.

Methods

In February 2010, we systematically reviewed the literature using the following databases: Cochrane Library Plus, NHS Centre for Reviews and Disseminations, Clinical Trials, MEDLINE, and EMBASE. Papers were selected on the basis of pre-established inclusion and exclusion criteria. The information was summarized in evidence tables, and study quality was assessed using a specific scale.

Further research/reviews required

Studies targeting larger samples in different population groups are needed to identify subjects in whom these tests would be more cost effective.

Written by Jeannette Puñal Riobóo, Galician Department of Health, AVALIA-T, Spain

INAHTA Briefs

Issue 2011/009

Title **Serum Procalcitonin Levels as a Diagnosis Tool in Bacterial Respiratory Tract Infections**

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Reference Núm.2009/01-3.
www.sergas.es/Docs/Avalia-t/avalia-t-200901-3-procalcitonina.pdf

Aim

To ascertain the clinical usefulness of procalcitonin (PCT) as a marker of respiratory tract infection of bacterial etiology.

Conclusions and results

According to the bibliography reviewed, PCT appears to be a useful marker for diagnosing bacterial respiratory infections, and can be useful in reaching a differential diagnosis of respiratory infection caused by pneumococcus versus other bacteria. However, it does not appear to help diagnose respiratory infection due to atypical bacteria or viruses. Compared to clinical practice guidelines or empirical treatment, PCT-guided management of antibiotic treatment in patients with respiratory tract infections appears to reduce both the antibiotic prescription rate and the duration of drug treatment, but not the length of hospital stay.

Recommendations

The high specificity of PCT means that it can effectively rule out the presence of bacterial infection, which in turn implies a reduction in the administration of inappropriate antibiotic treatment in nonbacterial infections. On the other hand, its low sensitivity would make it necessary to reassess the bacterial infection.

Methods

A specific search strategy was designed for each of the following databases: Cochrane Library Plus; NHS Centre for Reviews and Disseminations; Clinical Trials.gov; Current Control Trials; Web of Science (WOK); MEDLINE; and EMBASE. This strategy was implemented in September 2010. Papers were selected on the basis of pre-established inclusion and exclusion criteria. Relevant data were systematically extracted from the studies selected and then summarized in evidence tables.

Further research/reviews required

Since the studies were conducted in a hospital setting, some authors indicate that cost-effectiveness studies in different health settings (primary care, hospital emergencies, etc.) are necessary to ascertain the contexts in which PCT tests are more cost effective and to draw up the necessary protocols for using these tests in lower respiratory tract infections.

Written by Jeannette Puñal Riobóo, Galician Department of Health, AVALIA-T, Spain

Title **Ultrafiltration for Decompensated Heart Failure**

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Reference VA Technology Assessment Program Brief Overview, January, 2010.
www.va.gov/vatap

Aim

To determine if ultrafiltration should be used for Veterans Affairs (VA) patients with decompensated heart failure.

Conclusions and results

Twenty-three journal articles met the inclusion criteria. Three systematic reviews and 1 reference study pertained to ultrafiltration. These articles found that ultrafiltration was safe and effective at removing excess fluid from patients with decompensated heart failure, but more research is needed to determine optimal rates of fluid removal, termination timeline, and cost effectiveness.

The remaining 19 articles explored related topics to treat or avoid decompensated heart failure. Positive outcomes have been found with techniques such as patient education for self-monitoring, telemonitoring, and discharge planning with postdischarge support.

Recommendations

Based on the available literature, it is safe to assume that the positive results of ultrafiltration observed in the United Kingdom can be transferred to the United States, but further research is recommended.

Methods

We conducted a literature search in the following databases for articles in English published between 2000 and 2010: PubMed, MEDLINE, EMBASE, INAHTA, and the Cochrane Library, using the search terms "ultrafiltration", "decompensated heart failure", "volume overload", and "cardiorenal syndrome".

Further research/reviews required

More research is needed with greater patient populations; blinded studies, if possible; follow-up beyond 2 to 3 months; outcome measurements based on quality of life and mortality; and additional independent studies. Five clinical trials are in progress comparing ultrafiltration to other treatments. One of these trials explores if kidney dysfunction can result from overzealous ultrafiltration.

Written by Karen Flynn, DDS, MS, VATAP, USA

Title **Screening for Oral Cancer**

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Reference VA Technology Assessment Program Brief Overview, September, 2009.
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Aim

To determine the best evidence for the use of toluidine blue (TB) in Veterans Health Administration (VHA) dental clinic screening programs for oral squamous cell carcinoma (OSCC).

Conclusions and results

We found 7 systematic reviews of oral cancer screening, including 1 duplicate publication. Only 2 reviews mentioned TB as a diagnostic tool, and neither review included evidence that met the United States Preventive Services Task Force's (USPSTF) standards for screening programs. Generally, research on diagnostic aids used in oral cancer management is restricted to lower level technical efficacy and diagnostic accuracy studies. Hence, their impact on management decisions and/or patient outcomes remains to be defined.

Recommendations

At this time, TB should be considered an aid to oral cancer diagnosis and not an appropriate tool for use in population screening programs for oral cancer.

Methods

A literature search was conducted for systematic reviews, evidence based guidelines, and economic analyses published in English between 1990 and 2009 in the following databases: Cochrane Library, MEDLINE, and INAHTA. Articles with adult human subjects were included, as were subsequently published, review-eligible, clinical trials.

Further research/reviews required

More stringent research is needed to determine the advantages and drawbacks of oral cancer screening, as is further research regarding effective treatments for oral cancer.

Written by Karen Flynn, DDS, MS, VATAP, USA

Title **Transcranial Magnetic Stimulation for Depression**

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Reference VA Technology Assessment Program Brief Overview. January, 2010.
www.va.gov/vatap

Aim

To determine the effectiveness of transcranial magnetic stimulation (TMS) to inform its appropriate use in the Veteran population.

Conclusions and results

Four independent reviews pertaining to depression and 6 related reviews (eg, TMS for schizophrenia, its safety and cost) met the inclusion criteria. While on the surface, TMS may appear to be an attractive alternative to electroconvulsive therapy, the inconsistent effectiveness information and uncertainty regarding optimal technical parameters prevent making firm conclusions about its effectiveness.

Recommendations

Better treatments for depression are needed, as is research on patient preferences and acceptability of TMS versus alternatives.

Methods

The Technology Assessment Program (TAP) first catalogued available reviews, and then updated them with eligible studies that would change review conclusions. Searches of MEDLINE and the Cochrane Library using the terms "magnetic stimulation" and "depression", along with publication types (systematic review, meta-analysis) were performed to identify reviews published in English from 2000 to 2009 that synthesized research in adult human patients. Searches for subsequently published review-eligible studies were conducted in November 2009, and all searches were updated in January 2010.

Further research/reviews required

Thirty-eight clinical trials are in progress regarding the use of TMS to treat depression and nondepression conditions, which will hopefully address unanswered questions surrounding its clinical use.

Written by Karen Flynn, DDS, MS, VATAP, USA

Title **Systematic Reviews of Strategies for Changing Clinician Behavior to Improve Patient Outcomes**

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Reference VA Technology Assessment Program Brief Overview. November, 2007.
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Aim

To identify effective interventions for changing clinician practice and improving patient outcomes, focusing on continuing education, guideline implementation, and computerized clinical decision support systems.

Conclusions and results

Seven overviews and 18 additional systematic reviews met the inclusion criteria. For continuing medical education, these articles concluded that active participation and multifaceted interventions are superior to passive or single interventions. Other useful means to change clinicians' behavior were: active approaches, audits, feedback, local opinion leaders, educational outreach, and reminders. However, the effects on patient outcomes have not been adequately studied. Passive dissemination, eg, mailing educational material, was not useful.

Recommendations

No specific recommendations were made in this report.

Methods

A literature search for articles published in English between 1990 and 2007 was conducted in the Cochrane Library and Effective Practice and Organization of Care databases. The search terms were "continuing education", "behavior change", "guideline", and "decision support system".

Further research/reviews required

Further research is needed to understand the complex challenges of changing clinician behavior and improving patient outcomes. Future systematic reviews need improved methodological quality.

Written by Karen Flynn, DDS, MS, VATAP, USA

Title **Quality and Safety of Surgery: Three Queries for VHA Surgical Service**

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Reference VA Technology Assessment Program Brief Overview. March, 2008.
www.va.gov/vatap

Aim

To search the literature to answer 3 questions: 1) Has a threshold rate of unplanned or emergency surgical procedures been documented? 2) What model programs for surgical quality improvement are found in the literature? 3) Which interventions are effective for preventing surgical errors, eg, retained foreign bodies or wrong-site surgery?

Conclusions and results

Question 1: 6 primary studies and no systematic reviews were found in the literature. None of these studies define a rate of emergency surgical procedures that can be used as a quality indicator. Question 2: 13 articles were found. Two programs emerged as praiseworthy: the Veterans Health Administration's National Surgical Quality Improvement Program and the United Kingdom's National Confidential Enquiry Into Perioperative Deaths. Question 3: 5 systematic reviews were found. To prevent errors, preventative counts and protocols are widely used in operating rooms.

Recommendations

No recommendations can be made for Questions 1 and 3. For Question 2: Berwick's "New Way" approach to quality improvement (JAMA 2006;295(3):324-327) may provide insight on issues such as resources and staffing.

Methods

Literature searches were conducted using specific search terms for each question. The following databases were searched: INAHTA, PubMed, MEDLINE, EMBASE, Dialog Information Services, and the Cochrane Library. Search terms included: surgical quality indicators, quality assurance, trends, quality improvement, National Surgical Quality Improvement Program, Continuous Improvement in Cardiac Surgery Program, Neurosurgery Consultants Board, emergency surgery, surgical errors, sentinel events, error prevention, wrong site, retained foreign bodies, and surgical safety.

Further research/reviews required

For Question 1: unplanned returns to the operating room may be used as a quality indicator. For Question 3: effectiveness testing is needed for the protocols, especially during emergency situations.

Written by Karen Flynn, DDS, MS, VATAP, USA

Title **Systematic Reviews for Patient-Centered Care**

Agency **VATAP, VA Technology Assessment Program**
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Reference VA Technology Assessment Program Brief Overview. August, 2010.
www.va.gov/vatap

Aim

To conduct a literature review about patient-centered care, focusing on articles regarding ethnic-specific programs, patient education, and clinician-patient communication.

Conclusions and results

Twenty-two Cochrane Reviews and 11 print journal systematic reviews were found. Twelve pertained to patient education or self management, and 4 pertained to ethnic-specific patient-centered care programs. Most reviews found the quality or quantity of research insufficient to conclude if patient-centered care improved patients' health. However, there was some consensus that it enhanced patients' knowledge and adherence to treatment.

Recommendations

No recommendations were made.

Methods

A literature search for articles published in English between 2000 and 2010 was conducted in the following databases: PubMed, Cochrane Library, EMBASE, and INAHTA.

Further research/reviews required

Additional quality research on patient-centered care is needed.

Written by Karen Flynn, DDS, MS, VATAP, USA

INAHTA Briefs

Issue 2011/016

Title **Circulator Boot™ for Lower Limb Vascular Insufficiency**

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Reference VA Technology Assessment Program Bibliography, October, 2009.
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Aim

To identify evidence on the effectiveness of end-diastolic pneumatic compression devices, eg, the Circulator Boot™, in preventing amputation caused by lower limb vascular insufficiency.

Conclusions and results

One overview and 9 systematic reviews/meta-analyses addressed the use of various intermittent pneumatic compression devices in preventing or treating chronic venous or arterial insufficiency. Evidence for the Circulator Boot™ is limited to a handful of observational studies, primarily from a single investigator group led by the physician who invented the technology. For treating venous leg ulcers, the evidence suggests that using some form of external mechanical compression therapy is better than nothing, but the relative benefit of intermittent pneumatic compression (IPC) versus other alternatives, particularly compression bandages, is unclear. Evidence for the effectiveness of IPC alone, or in combination with anticoagulants, in reducing the risk of venous thromboembolism (VTE) is conflicting. Evidence for the use of IPC in peripheral arterial disease is emerging, but inconclusive.

Recommendations

The evidence currently available is insufficient to permit conclusions regarding the relative effectiveness of the Circulator Boot™ as a treatment option for chronic venous insufficiency (CVI).

Methods

The INAHTA database and MEDLINE, EMBASE, and the Cochrane Library, were searched for articles published in English from 2000 to 2009. Searches included terms describing Circulator Boot concepts, CVI, vein or venous leg ulcers, pneumatic compression devices, and IPC devices. End references of retrieved articles were reviewed, as were the data cited on the Circulator Boot™ Corporation's website.

Further research/reviews required

Randomized clinical trials are needed to properly assess the effectiveness of end-diastolic pneumatic compression devices such as the Circulator BootTM. Trials should address optimal administration, risks, and benefits derived from different types of mechanical compression, patient compliance, quality of life, organizational aspects of care, and economic evaluation.

Written by Elizabeth Adams, MPH, VATAP, USA

INAHTA Briefs

Issue 2011/017

Is Neonatal Screening for Cystic Fibrosis Recommended in Belgium?

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Reference Report no. 132, 2010. www.kce.fgov.be/index_en.aspx?SGREF=9470&CREF=16709

Aim

To answer the following questions: What is the evidence supporting neonatal cystic fibrosis (CF) screening in terms of benefits and harms? Is CF newborn screening (NBS) cost effective? What organizational, ethical, legal, and budgetary aspects are to be considered when introducing CF NBS in Belgium?

Conclusions and results

Implementation of a CF neonatal screening program in Belgium could help avoid a potentially long, painful, and costly diagnostic odyssey and will improve height and weight gain in children diagnosed early. CF NBS could also benefit pulmonary status and reduce the therapy burden, but this is not based on RCT data. The beneficial effects on survival may have become undetectable given the improvement in care. The benefits of CF NBS override potential harms only if several quality criteria for screening are strictly followed. The budget impact of implementing CF NBS is small compared to the annual budget expenditures to reimburse CF DNA tests.

Recommendations

- Immediately after diagnosis, children with CF should have the highest level of affordable care, as improvements in the quality have dramatically impacted on survival.
- Quality of care in CF centers should be audited regularly and should be brought to a uniformly high level. This should be a requirement for CF centers to keep their funding.
- Implementing local CF NBS programs without evaluation of patient outcome should be avoided.
- Public funding of two largely overlapping screening programs should be questioned (CF NBS program and large-scale opportunistic CF carrier screening of future parents).

The decision to implement CF NBS depends on the balance of benefits and harms. To limit potential harms, CF NBS should be implemented only if certain conditions are met (see full report).

Methods

A multidisciplinary team including pediatricians in charge of CF care, scientists, and experts in neonatal screening, ethics, and legal issues carried out the project. Additional external experts in CF NBS and preventive care representatives from two communities in Belgium regularly reviewed the progress of the project. Systematic literature reviews focused on the effectiveness and cost effectiveness of CF NBS. Organizational, ethical, legal, and budgetary aspects were covered based on additional data collection, published data, and analyses of the Belgian CF registry at the Institute of Public Health.

Further research/reviews required

- Evaluate the integration of the PAP test into the screening algorithm.
- Study the best practice for CF patient follow-up, including the respective roles of CF specialist centers, pediatricians, and GPs.

Written by Frank Hulstaert, KCE, Belgium

INAHTA Briefs

Issue 2011/018

Title **Remote Monitoring for Patients With Implanted Defibrillator. Technology Evaluation and Broader Regulatory Framework**

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Reference Report nr 136C, 2010.
www.kce.fgov.be/index_en.aspx?SGREF=9470&CREF=17656

Aim

To describe the technology of remote monitoring systems specifically for implantable cardioverter defibrillators (ICDs); to systematically review the evidence on clinical and cost effectiveness; and to study broader organizational, reimbursement, and legal aspects of emerging technologies in remote monitoring.

Conclusions and results

Scant evidence is available on direct patient benefits, although the partial replacement of in-clinic follow-up by remote monitoring seems reasonably safe in ICD patients with no, or mild, symptoms. Legal and organizational hurdles hamper the integration of remote cardiac monitoring.

Recommendations

- Specific legal guidance for interpreting and applying relevant legislation should be developed. To prevent defensive practices, detailed clinical guidelines should address how to deal with this emerging technology. - In the absence of proven safety, effectiveness, and cost effectiveness, conditional reimbursement of remote monitoring could be considered once there are sufficient indications of efficacy and safety.

Methods

Technology: Conversations with physicians and staff of implanting centers; the involved ICD manufacturers; peer-reviewed overview literature and a recent NHS report.

Clinical effectiveness and safety: Systematic reviews and horizon scanning reports for 2006 to 2010 through the CRD databases and the Cochrane Library; websites of INAHTA member organizations; incremental search to identify additional clinical trials and studies; EUnetHTA Joint Action database; INAHTA 'List Serv' network; and US registration site of clinical trials.

Economic literature review: MEDLINE, Econlit, Psychinfo, EMBASE, the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment (HTA) database, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials and the Database of Abstracts of Reviews of Effects (DARE) performed in July 2009 and updated in June 2010. Legal aspects: Standard European legal databases; records of the European Court of Justice; Juridat and Jura databases and the national websites of the courts.

Organizational aspects: Scientific and grey literature and contacts with ICD manufacturers.

Further research/reviews required

If the large ongoing trials would offer indications of relevant patient benefits or efficiency gains, a conditional reimbursement scheme might be considered with limited access and evidence collection on safety, quality of life, and health outcomes. This should allow for further exploration to what extent follow-up visits can be effectively and safely reduced for those patients.

Written by Imgard Vinck, KCE, Belgium

INAHTA Briefs

Issue 2011/019

Title **Cardiac Resynchronisation Therapy. A Health Technology Assessment**

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Reference Report no. 145C, 2010.
www.kce.fgov.be/index_en.aspx?SGREF=5211&CREF=18664

Aim

To answer the following questions: 1) Is cardiac resynchronization therapy (CRT) safe and clinically effective? What is the comparative effectiveness of CRT-P versus CRT-D?; 2) Is CRT cost effective and consequently, should this mode of therapy be reimbursed in eligible patients?; and 3) Should the implantation of CRT devices be restricted to specialized centers?

Conclusions and results

1) In patients with NYHA class III (and IV): Randomized trials have shown that CRT-P and CRT-D prolong life when added to optimal medical therapy in subsets of patients with NYHA class III/IV heart failure (HF). This has been best documented in drug-refractory patients with symptomatic chronic HF who were in sinus rhythm, who had a severely depressed systolic heart function and severe intraventricular conduction delays. Our modeling with the data from the largest of these trials in combination with Belgian demographic data revealed that in NYHA class III/IV patients, CRT-P increases longevity on average 1.31 years compared to optimal treatment. Likewise, addition of a defibrillator function to CRT-P (i.e. CRT-D) in those patients would prolong life on average 0.80 years. In this study, the survival benefit for CRT-P was not significant, but in meta-analyses the gain became a significant 1.83 years. (See full report for further details.)

2) In patients with NYHA class II (and I): No trials have been performed to compare CRT-P and/or CRT-D with optimal medical therapy in patients with only mild symptoms of HF. Three large trials comparing CRT-D with ICD have been published, mostly including NYHA class II patients. In two of them, no mortality benefit could be documented. (See full report for further details.)

Recommendations

1) Reimbursement for CRT-P appears to be justified. Scientific studies reveal a nonsignificant trend suggesting that CRT-D could prolong survival in these patients compared with CRT-P, but the additional cost is excessive.

2) Based on the specific technical requirements and skills required for CRT implant surgery, we recommend a minimum threshold of 20 CRT implants a year per center.

3) Implant doctors should be encouraged to discuss the advantages and drawbacks of CRT with their patients. CRT can only partially remedy the problems of HF and often has complications.

Methods

1) Clinical effectiveness. The review of the clinical effectiveness is based mainly on the evidence identified in the guideline from the European Society of Cardiology, since the updated (August 2010) guideline was considered sufficiently comprehensive and up-to-date.

2) Economic evaluation. This economic review is a rapid health technology assessment (HTA). Due to time constraints, a limited search was performed. The initial search of the HTA database of the Centre for Reviews and Dissemination (CRD) of the UK's National Health Service (NHS) yielded the 2007 HTA by Fox et al. as the most recent health-economic evaluation. This report featured a well-documented, systematic search performed in January 2006.

Written by Van Brabandt H, KCE, Belgium

INAHTA Briefs

Issue 2011/020

Title **Cost-utility of Vaccination Against Chickenpox in Children and Against Herpes Zoster in Elderly in Belgium**

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Reference Report nr 151, 2010

Aim

Vaccination against chickenpox (Varicella): To assess the effectiveness and cost effectiveness of different childhood vaccination strategies against chickenpox versus no vaccination. The strategies include vaccination against chickenpox with and without herpes zoster booster vaccination.

Vaccination against herpes zoster (shingles): To assess the cost effectiveness of universal vaccination against herpes zoster versus no vaccination in different age cohorts (60 to 85 years of age).

Conclusions and results

Vaccination against chickenpox: If the exogenous boosting hypothesis is confirmed, vaccinating children in Belgium against chickenpox would not be cost effective for many decades after vaccination, due to the expected increase in the annual cases of herpes zoster (HZ) following the introduction of such a vaccination program. If the exogenous boosting hypothesis is proven wrong, large-scale 2-dose vaccination in Belgium against chickenpox is probably cost effective at current vaccine price levels.

Vaccination against herpes zoster: Substantial uncertainty exists about which data source and/or model to use to estimate several key variables. This uncertainty increases with increasing age of the cohort considered for vaccination, and has a major impact on whether HZ vaccination can be considered cost effective in Belgium, and at which ages.

Recommendations

Vaccination against chickenpox: A universal chickenpox vaccination program cannot be recommended due to a reasonable risk that such an intervention may cause more harm than benefit.

Vaccination against herpes zoster: Vaccination of adults and elderly against shingles cannot be recommended based on the cost-effectiveness analyses at current vaccine prices.

Methods

Vaccination against chickenpox: An extensively studied and improved dynamic model was used, allowing detailed exploration of age-specific VZV disease transmission dynamics. Most of the input parameters are based on Belgian data. We used age-specific social contact data to derive transmission patterns that provided the best fit to Belgian seroprevalence data.

Vaccination against herpes zoster: A deterministic compartmental static model was developed, which tracks individuals to develop HZ according to their age. Most of the input parameters are based on Belgian data. This is the first study that estimated HZ-related costs and QALY loss as a function of a severity of illness score (SOIS). To obtain age- and SOIS-specific estimates, flexible statistical models are fitted to the data. (See full report for further details.)

Further research/reviews required

Industry and medical agencies should be made aware of the importance of making public all study results that are crucial for improving the accuracy of cost-effectiveness analyses. Research agenda: a large prospective study measuring age-specific herpes zoster-related severity of illness and QALY loss in the general community is urgently needed.

Written by Frank Hulstaert, KCE, Belgium

INAHTA Briefs

Issue 2011/021

Title **Cardiac Markers in Coronary Disease and Heart Failure in Outpatient Medicine**

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Aim

To clarify the indications and nonindications of cardiac markers in managing coronary disease and heart failure in outpatient medicine.

Conclusions and results

Based on critical analysis of the literature and the reasoned position of the working group, the indications and nonindications of cardiac-marker determination are as follows:

- Determination of myocardial necrosis markers is not indicated in the management of suspected acute coronary syndrome (ACS) in outpatient medicine, such management being based principally on a call to SAMU (French emergency medical service) center 15. The only exception is cases where an asymptomatic patient seeks medical advice for chest pain that occurred >72 h previously, which is suspected of having been an uncomplicated ACS, and where the ECG results are not helpful. In this case, the assessment undertaken can include determination of the blood levels of a troponin. Determination of the other markers of myocardial necrosis (ASAT, LDH, total CPK, myoglobin, and CK-MB) is not indicated.
- Determination of troponin is not indicated in managing chronic heart failure (CHF).
- Determination of natriuretic peptides is indicated in the initial diagnosis of CHF when the symptoms are atypical. Concentrations below 100 ng/l for BNP and below 300 ng/l for NT-proBNP make this diagnosis unlikely.
- Determination of natriuretic peptides for the sole purpose of establishing a prognosis is not indicated in CHF.
- Routine detection of left-ventricular dysfunction through determination of natriuretic peptides in asymptomatic populations with or without a risk factor for HF is not indicated.
- In patients with stable CHF on optimal treatment, repeated determination of natriuretic peptides in the context of therapeutic monitoring is not indicated. In cases of a clinical suspicion of decompensation of CHF, determination of natriuretic peptides can help guide the diagnostic and therapeutic approach. In the presence of a typical clinical picture of decompensation, determination of natriuretic peptides is not indicated.
- It is necessary to properly distinguish BNP from NT-proBNP and, in the case of the monitoring of a given patient, to always order measurement of the same natriuretic peptide, determined in the same laboratory.
- Determination of natriuretic peptides is not indicated in prognosis of stable chronic coronary disease.
- Determination of HS CRP is not indicated in primary prevention of coronary disease.

Methods

The assessment of using cardiac-marker determinations was based on critical analysis of the literature; literature selection was limited to summary documents (recommendations, HTAs, systematic reviews, and meta analyses) published between January 2005 and May 2010 (EMBASE, MEDLINE, Pascal, and search of specialist websites). Fifty-three articles were analyzed. A multidisciplinary working group consisting of 13 experts discussed this analysis. The report was examined by the Commission d'évaluation des actes professionnels (Committee for the Assessment of Professional Procedures) and then validated by the HAS Board.

Written by Candice Legris, HAS, France

INAHTA Briefs

Issue 2011/022

Title **Place of Breast MRI in the Pre-Treatment Locoregional Spread Assessment of Breast Cancer**

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Aim

To evaluate the diagnostic accuracy of breast MRI and the various factors influencing it; and to estimate the usefulness of breast MRI in the pretreatment locoregional spread assessment of breast cancer.

Conclusions and results

The sensitivity of breast MRI in detecting additional lesions, which is greater than that of mammography, comes with false positives in proportions that vary according to the populations studied. These false positives mean that caution is needed when considering any change in therapeutic management on the basis of breast MRI results. Hence, breast MRI in the pretreatment locoregional spread assessment of breast cancer should be reserved for clearly defined situations.

Recommendations

HAS recommends breast MRI in pretreatment locoregional assessment in the following situations:

- When a lack of agreement between clinical features, mammography, and ultrasonography could lead to a change in therapeutic management
- When difficult treatment choices have to be made (oncoplastic surgery, conservative treatment or mastectomy, neoadjuvant treatment)
- In women under 40 years of age
- In women with a high familial risk of breast cancer.

There are no data about the contralateral breast to confirm or deny the usefulness of breast MRI in examining the contralateral breast.

Methods

We critically analyzed clinical data published from 01/1999 to 09/2009 from a document search of the MEDLINE and Cochrane Library databases (103 studies were analyzed). A multidisciplinary working group consisting of 6 radiologists, 1 radiotherapist, 1 anatomopathologist, 4 gynecologists, 2 oncologists, and 1 plastic surgeon discussed the results of this analysis. The *Commission d'Evaluation des Actes Professionnels* (CEAP), the HAS specialized appraisal committee, reviewed the conclusions.

Further research/reviews required

The data currently available are insufficient to rule on the impact of breast MRI pretreatment assessment on recurrence and patient survival. Long-term studies are needed before this question can be answered.

Written by Olivier Allaire, HAS, France

INAHTA Briefs

Issue 2011/023

Title **Intensity-Modulated Radiotherapy for the Treatment of Prostate Cancer: A Systematic Review and Economic Evaluation**

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Reference Volume 14.47. ISSN 1366-5278. www.hta.ac.uk/project/1788.asp

Aim

To evaluate the clinical and cost effectiveness of intensity-modulated radiotherapy (IMRT) for radical treatment of prostate cancer (PC).

Conclusions and results

No randomized controlled trials (RCTs) of IMRT versus 3-dimensional conformal radiotherapy (3DCRT) in PC were available, but 13 nonrandomized studies comparing IMRT with 3DCRT were found (5 were abstracts). One abstract reported overall survival. Biochemical relapse-free survival was not affected by treatment group, except where the dose differed between groups, in which case higher dose IMRT was favored over lower dose 3DCRT. Most studies reported an advantage for IMRT in GI toxicity, attributed to increased conformality of treatment compared with 3DCRT, particularly with regard to volume of rectum treated. Genitourinary toxicity was indicated to be worse for patients treated with dose escalated IMRT, but most studies did not find a significant treatment effect. Health-related quality of life (HRQoL) improved for both treatment groups following radiotherapy, with any group difference resolved by 6 months after treatment. No comparative studies of IMRT versus prostatectomy were identified. No comparative studies of IMRT in PC patients with bone metastasis were identified. The comparative data of IMRT versus 3DCRT seem to suggest that higher doses (up to 81 Gy) can improve biochemical survival in patients with localized PC, concurring with data on CRT. The data also suggest that toxicity can be reduced by increasing conformality of treatment, particularly as regards GI toxicity, which can be more easily achieved with IMRT than 3DCRT. Whether differences in GI toxicity between IMRT and 3DCRT are sufficient for IMRT to be cost-effective is uncertain, depending on the difference in incidence of GI toxicity, its duration, and the cost difference between IMRT and 3DCRT.

Recommendations

Clinical advice suggests that most radiotherapy (RT) centers already possess the equipment required to deliver IMRT, but that lack of available staff hinders implementation. 3DCRT may be safely delivered at the currently recommended total dose of 74 Gy, and there is no evidence that PSA survival is improved by giving IMRT at the same dose as 3DCRT. There is evidence that IMRT reduces toxicity, in particular late GI toxicity. The magnitude of the difference is uncertain, which, together with uncertainties in other variables makes the cost effectiveness of IMRT in comparison to 3DCRT uncertain. Assuming a difference in late GI toxicity of 15%, the probability of IMRT being more cost effective than 3DCRT is only true for a MAICER of ≥30 000 pounds sterling (GBP).

Methods

A systematic literature review of the clinical and cost effectiveness of IMRT in PC was conducted. Comparators were 3DCRT or radical prostatectomy. Outcomes sought were overall survival, biochemical relapse-free survival, toxicity, and HRQoL. We searched 15 electronic bibliographic databases (eg, MEDLINE, EMBASE, CINAHL, MEDLINE In-Process & Other Non-Indexed Citations) in January 2009 and updated in May 2009. Reference lists of relevant articles were checked. Only studies in English were included. An economic model was developed to examine the cost effectiveness of IMRT in comparison to 3DCRT. Four scenarios were modeled based on the studies, which reported both prostate-specific antigen (PSA)survival and late gastrointestinal (GI) toxicity. In two scenarios equal PSA survival was assumed for IMRT and 3DCRT, the other two having greater PSA survival for the IMRT cohort. As data on clinical outcomes were limited, the model estimates progression to clinical failure and PC death from the surrogate outcome of PSA failure.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1788.asp.

Written by Ms Silvia Hummel, ScHARR, University of Sheffield, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/024

Systematic Review of the Links Between Human Resource Management Practices

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Reference Volume 14.51. ISSN 1366-5278. www.hta.ac.uk/project/1590.asp

Aim

To assess the results from systematic reviews of the evidence on human resource management (HRM) and performance.

Conclusions and results

Work design practices that enhance employee autonomy and control influenced outcomes. Consistent evidence indicated a positive impact of increased job control on employee outcomes, eg, job satisfaction, absence, and health. The small number of studies reviewed supported the involvement of employees in design/implementation of changes that affect their work. In health literature, employee involvement through quality improvement teams resulted in improved patient outcomes. Findings were positive for the impact of training on the intended outcomes of the initiatives. Support for the impact of performance management practices was apparent, in particular the effects of feedback on performance outcomes and the use of participative goal setting. The relationship between intermediate outcomes and productivity-enhancing behaviors were generally significant. Although longitudinal studies of intermediate outcomes and final outcomes were sparse, associations were found for job satisfaction and organizational climate with organizational performance. Some potentially effective practices for both health and nonhealth areas were identified, and HRM methods could be used to support change processes in the NHS; the findings relating to work organization are promising as regards changes in methods of service delivery. Using training to help implement change is highlighted, but multilevel studies embracing the individual, team, and organizational level are needed. Studies should look into interventions to improve HR outcomes and performance, and allow for pre- and postintervention measurement of practices and outcomes.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1590.asp.

Methods

Broad categories of HRM interventions and intermediate outcomes were generated: 10 HRM categories and 12 intermediate outcome categories. Seven patient final outcomes were derived from the NHS Performance Indicators and the NHS Improvement Plan. We included only longitudinal studies, providing some evidence of the causal direction of relationships between HRM and relevant outcomes. The health-specific literature focused on the impact of HRM on patient outcomes. Information is presented on the reliability of measures in each of the intermediate outcome areas.

Further research/reviews required

Developing a 'big science' project that permits repeat surveys, a broad coverage of practices, independent audits of practices, and reliable and valid performance measures would be desirable. Smaller-scale projects would be useful, but would have more value if set in the context of bigger studies. Existing data sets, eg, the WERS and Healthcare Commission (HCC) staff survey, could be revised to take account of some of the learning from this and other overviews. The intermediate variables between HR practices and organizational performance need more attention, and multilevel studies embracing the individual, team, and organizational level (and, in the case of the NHS, Trust level) are needed. Studies of interventions aimed at improving HR outcomes and performance should be encouraged, along with a mechanism to bring together researchers and organizations before interventions take place. This would allow pre- and postintervention measurement of relevant HRM practices and outcomes.

Written by Dr Malcolm Patterson, University of Sheffield, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/025

Title **Clinical Effectiveness and Cost Effectiveness of Stem Cell Transplantation in the Management of Acute Leukemia: A Systematic Review**

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Reference Report no 14.54. ISSN 1366-5278. www.hta.ac.uk/project/1789.asp

Aim

To provide a systematic overview of the best available evidence on the clinical and cost effectiveness of stem cell transplantation (SCT) in treating acute leukemia.

Conclusions and results

Specific objectives: 1) systematically identify and review published systematic reviews, meta-analyses, and economic literature; 2) systematically identify new evidence from randomized controlled trials (RCTs) and donor versus no donor (DvND) studies not included in previous reviews and meta-analyses; and 3) map information from the above sources and inventory the best available evidence to help inform future research.

Fifteen systematic reviews/meta-analyses met the inclusion criteria for the review of clinical effectiveness, 13 of which were published from 2004 onward. Most reviews appeared to have omitted an appreciable proportion of potentially available evidence. The best available evidence for effectiveness of allogeneic SCT using stem cells from matched sibling donors came from DvND studies: sufficient evidence supported the use of allogeneic SCT in adult acute myeloid leukemia (AML) in first complete remission (CR1) except in good-risk patients, in childhood AML in CR1 (role of risk stratification unclear), and in adult acute lymphoblastic leukemia (ALL) in CR1 (role of risk stratification unclear). There was conflicting evidence in childhood ALL in CR1 and a paucity of evidence from DvND studies for all decision problems concerning patient groups in second or subsequent remission or with refractory disease (CR2+). The best available evidence for effectiveness of autologous SCT came from RCTs: evidence suggested that autologous SCT was similar to or less effective than chemotherapy. There was a paucity of evidence from published reviews of RCTs for comparisons between different sources of stem cells and between different SCT techniques. Nineteen studies met the inclusion criteria in the cost-effectiveness review, most reporting only cost information, and only one incorporating an economic model. Despite a wealth of information on costs, and some on cost-effectiveness of allogeneic SCT in adults with AML, very limited evidence concerned relative costs and cost effectiveness for other decision problems covered in this report. Firm conclusions could not be drawn on the cost effectiveness of SCT in the UK NHS.

Recommendations

This report summarizes best available evidence and discusses its implications, but does not make recommendations about policy or about clinical care.

Methods

For clinical effectiveness, a systematic review of published systematic reviews and meta-analyses was carried out, supplemented with searches and mapping of recent RCTs and DvND studies not covered in existing reviews. A systematic review of cost and cost-effective studies was also conducted.

Further research/reviews required

Priorities for further research were offered according to the gaps in the evidence identified in the report.

Written by Dr Yen-Fu Chen, University of Birmingham, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/026

Title **Predictive Clinico-Pathological Features Derived From Systematic Autopsy Examination of Patients Who Die With A/H1N1 Influenza Infection in the UK 2009-2010 Pandemic**

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Reference Volume 14.55(2). ISSN 1366-5278.
www.netscc.ac.uk/supporting_research/flu_project_portfolio/098418.asp

Aim

To gather all available clinical pathology information from autopsies on UK patients dying with known or suspected influenza A/H1N1 infection; and to evaluate comorbidities present in these deceased patients, correlating them with H1N1-related and treatment-associated pathology, determining their relative contributions, and estimating significant features associated with death.

Conclusions and results

Sixty-eight autopsy reports were received: 19 children (0-15 years) and 49 adults (16+ years). All but 2 autopsies were medicolegal, and only 2 (3% of total) were consented. This sample represents 15% of the known 457 deaths from H1N1. Median age at death was 6 years in children and 41 years in adults. Deaths in children were associated with congenital diseases (47%, 9/19), particularly of the heart and central nervous system. The autopsied children were not obese. Deaths in adults were associated with pregnancy (3 cases in the study, but nationally 12/457 H1N1-associated deaths were noted), obesity (50% of adults had a body mass index ≥30 kg/m2) and chronic respiratory disease (12%, 6/49 adults). Diabetes did not emerge as a risk factor for death, but learning difficulties did. Nearly all deaths (94%, 64/68) were a consequence of H1N1 infection in the respiratory tract. In more than one-third (41%, 28/68) of the deaths, bacterial secondary infection was the significant complication; the pneumococcus was the most common agent identified (25%, 7/28). The major comorbidities associated with death from H1N1 infection were obesity, chronic respiratory disease, and pregnancy. Young age at death was confirmed. Congenital disease in children and learning difficulties in adults were also important, but diabetes was not. This methodology of gathering data for research has potential for use in other public health questions, but is dependent on the cooperation of the medicolegal services.

These results reinforce the need to enquire further into the pathogenesis of severe and fatal H1N1 disease, and the circumstances of clinical presentation and rapid evaluation in a time of epidemic influenza.

Recommendations

See Executive Summary link www.netscc.ac.uk/supporting_research/flu_project_portfolio/098418.asp.

Methods

To obtain autopsy reports, standard request letters were sent by e-mail to all histopathologists in the UK on the Royal College of Pathologists list, all the coroners' jurisdictions in England, Wales, and Northern Ireland, and to procurators fiscal in Scotland. The letters asked for autopsy reports of the autopsied deceased who included: those with H1N1 infection, proven before or after death, and those in whom swine flu was unproven but most likely to have been present; those in whom H1N1 was a minor pathology and those in whom it was the immediate cause of death; those whose cause of death mentioned 'swine flu', 'swine influenza' or 'H1N1 infection'; and those of any age from infancy to old age.

Further research/reviews required

See Executive Summary link www.netscc.ac.uk/supporting_research/flu_project_portfolio/098418.asp.

Written by Professor Sebastian Lucas, Guy's and St Thomas' Hospital Trust, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/027

Title **Assessment of Baseline Age-Specific Antibody Prevalence and Incidence of Infection to Novel Influenza A H1N1 2009**

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Reference Volume 14.55(3). ISSN 1366-5278.
www.netscc.ac.uk/supporting_research/flu_project_portfolio/099501.asp

Aim

To document: 1) prevalence of cross-reactive antibodies to H1N1 2009 by age group in the population of England prior to arrival of the pandemic strain virus; and 2) age-specific incidence of infection by month by measuring increases in the proportion of individuals with antibodies to H1N1 2009 by age.

Conclusions and results

Preexisting, cross-reactive antibodies to H1N1 2009 were detected in the baseline sera and increased with age, particularly in those born before 1950. Prediction of immunological protection derived from the baseline serological analysis was consistent with lower clinical attack rates in older age groups. The high levels of susceptibility in children <15 years, along with their mixing in school, resulted in the highest attack rates in this age group. Serological analysis by region confirms geographical differences in timing of major pandemic waves. London had a big first wave among the 5- to 14-year age group, with the rest of the country reducing the gap after the second wave. Cumulative incidence in London remained higher throughout the pandemic in each age group. By the end of the second wave it is estimated that as many as 70% of school-aged children in London had been infected. Taken together, these observations are consistent with observations from previous pandemics in 1918, 1957, and 1968 – that the major impact of influenza pandemics is on younger age groups, with a pattern of morbidity and mortality distinct from seasonal influenza epidemics. Serological analysis of appropriately structured, age-stratified and geographically representative samples can provide an immense amount of information to set in context other measures of pandemic impact in a population, and provide the most accurate measures of population exposure. National scale seroepidemiology studies require cross-agency coordination, multidisciplinary working, and considerable scientific resource.

Recommendations

See Executive Summary link www.netscc.ac.uk/supporting_research/flu_project_portfolio/099501.asp.

Methods

Serum panels collected from various sources in the English health system before, during, and after the pandemic waves in the UK, were assembled and tested with serological assays to assess influenza H1N1 2009-specific protective antibody. Residual aliquots of samples submitted to 16 microbiology laboratories in 8 regions in England in defined age groups in 2008 and stored by the Health Protection Agency (HPA) serological surveillance program were used to document age-stratified prevalence of antibodies to H1N1 2009 prior to the arrival of the pandemic in the UK. For timely measurement of the monthly incidence of infection with H1N1 2009 between August 2009 and April 2010, the microbiology serum collections were supplemented by collection of residual sera from chemical pathology laboratories in England. Incidence in sequential months during the pandemic was estimated from changes in prevalence between time points and also by a likelihood-based method. Development of sensitive and specific assays for measuring antibodies to H1N1 2009 in humans poses technical challenges of virus selection and characterization, development of reagents, and assay validation. Hemagglutination inhibition and microneutralization assays were developed and used by the HPA to document the prevalence of baseline cross-reactive antibodies in the population prior to arrival of the pandemic strain in the UK, and to investigate the penetration of H1N1 2009 in the population after the first and second waves.

Further research/reviews required

See Executive Summary link www.netscc.ac.uk/supporting_research/flu_project_portfolio/099501.asp.

Written by Professor Elizabeth Miller, Health Protection Agency, London, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/028

Title **Assessing the Surgical Skills of Trainees in the Operating Theatre: A Prospective Observational Study of the Methodology**

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Reference Volume 15.01. ISSN 1366-5278. www.hta.ac.uk/project/1626.asp

Aim

To compare user satisfaction and acceptability, reliability, and validity of 3 different methods of assessing the surgical skills of trainees by direct observation in the operating theatre across a range of surgical specialties and index procedures.

Conclusions and results

Of 558 patients, 437 (78%) cases were included in the study, and 51 consultant clinical supervisors, 56 anesthetists, 39 nurses, 2 surgical care practitioners, and 4 independent assessors provided 1635 assessments on 85 trainees undertaking the 437 cases. In total, 749 Procedure Based Assessments (PBAs), 695 Non Technical Skills for Surgeons (NOTSS), and 191 Objective Structured Assessment of Technical Skills (OSATS) were performed. Non obstetrics and gynecology (O&G) clinical supervisors and trainees provided mixed, but predominantly positive, responses on a range of applications of PBA. Most felt that PBA was important in surgical education, would use it again, and did not feel that it added time to the operating list. Overall satisfaction of O&G clinical supervisors and trainees with OSATS was not as high, and most those who used both preferred PBA. Most anesthetists and nurses felt that NOTSS allowed them to rate interpersonal skills more easily than cognitive skills, that it had formative value, and that it was a valuable adjunct in assessing technical skills. PBA demonstrated high reliability (G >0.8 for only 3 assessor judgments on the same index procedure). OSATS had lower reliability (G >0.8 for 5 assessor judgments on the same index procedure). Both were less reliable on a mix of procedures because of strong procedure-specific factors. A direct comparison of PBA between O&G and non O&G cases showed a striking difference in reliability. Within O&G, a good level of reliability (G >0.8) could not be obtained using a feasible number of assessments. Conversely, the reliability within non O&G cases was exceptionally high, with only 2 assessor judgments being required. The reasons for this difference probably include the more summative purpose of assessment in O&G and the much higher proportion of O&G trainees in this study with training concerns. The reliability of NOTSS was lower than that for PBA. Reliability for the same procedure (G >0.8) required 6 assessor judgments. However, as procedure-specific factors exerted a lesser influence on NOTSS, reliability on a mix of procedures could be achieved using only 8 assessor judgments. PBA and NOTSS showed better construct validity than OSATS, the year of training and the number of recent index procedures performed being significant independent predictors of performance. We found little variation in scoring between different procedures or different designations of assessor. The results suggest that PBA reliable, valid, and acceptable in assessing technical skills of surgical trainees.

Recommendations

Specialties that use OSATS may wish to consider changing the design or switching to PBA. NOTSS should be considered for the assessment of nontechnical skills.

Methods

The 3 methods selected were PBA, OSATS, and NOTSS. PBA is used routinely to assess the technical skills of surgical trainees, OSATS is used in the same way for obstetric and gynecology (O&G) trainees, and NOTSS is a newly developed tool for assessing nontechnical skills.

Further research/reviews required

Whatever workplace-based assessment method is used, the purpose, timing, and frequency of assessment require detailed guidance.

Written by Professor Jonathan Beard, Sheffield Teaching Hospitals NHS Trust, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/029

Title **Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) for the Assessment of Axillary Lymph Node Metastases in Early Breast Cancer: Systematic Review and Economic Evaluation**

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Reference Volume 15.04. ISSN 1366-5278. www.hta.ac.uk/project/1848.asp

Aim

To evaluate the diagnostic accuracy, cost effectiveness, and effect on patient outcomes of positron emission tomography (PET), with or without computed tomography (CT), and magnetic resonance imaging (MRI) in evaluating axillary lymph node metastases in patients with newly diagnosed early-stage breast cancer.

Conclusions and results

The clinical effectiveness review included 45 citations relating to 35 studies: 26 studies of PET and 9 studies of MRI. Of the 7 studies evaluating PET/CT (n=862), mean sensitivity was 56% (95% confidence interval [CI] 44%-67%) and mean specificity 96% (95% CI 90%-99%). Of the 19 studies evaluating PET only (n=1729), mean sensitivity was 66% (95% CI 50%-79%) and mean specificity 93% (95% CI 89%-96%). PET performed less well for small metastases; mean sensitivity was 11% (95% CI 5%-22%) for micrometastases (≤2 mm; 5 studies; n=63), and 57% (95% CI 47%-66%) for macrometastases (>2 mm; 4 studies; n=111). The smallest metastatic nodes detected by PET measured 3 mm, while PET failed to detect some nodes >15 mm. Studies in which all patients were clinically node negative showed a trend toward lower sensitivity of PET compared to studies with a mixed population. Across 5 studies evaluating ultrasmall super-paramagnetic iron oxide (USPIO)-enhanced MRI (n=93), mean sensitivity was 98% (95% CI 61%-100%) and mean specificity 96% (95% CI 72%-100%). Across 3 studies of gadolinium-enhanced MRI (n=187), mean sensitivity was 88% (95% CI 78%-94%) and mean specificity 73% (95% CI 63%-81%). In the single study of in vivo proton magnetic resonance spectroscopy (n=27), sensitivity was 65% (95% CI 38%-86%) and specificity 100% (95% CI 69%-100%). USPIO-enhanced MRI showed a trend toward higher sensitivity and specificity than gadolinium-enhanced MRI. Studies demonstrated that PET and MRI have lower sensitivity and specificity than SLNB and 4-NS, but are associated with fewer adverse events. Included studies indicated a significantly higher mean sensitivity for MRI than for PET, with USPIO-enhanced MRI providing the highest sensitivity. However, sensitivity and specificity of PET and MRI varied widely between studies, and MRI studies were relatively small. Hence, results should be interpreted with caution. Decision modeling based on these results suggests that the most cost-effective strategy is to replace SLNB or 4-NS with MRI. This strategy reduces costs and increases quality-adjusted life-years (QALYs) because adverse events are fewer for the majority of patients. However, this strategy leads to more false-negative cases at higher risk of cancer recurrence and more false-positive cases that would undergo unnecessary axillary lymph node dissection.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1848.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1848.asp.

Further research/reviews required

If MRI is deemed clinically acceptable (either to replace SLNB or 4-NS or as an additional test), then further large, well-conducted studies of MRI, particularly using USPIO, would be useful to obtain more robust data on sensitivity and specificity, adverse effects, and the optimum criteria for defining a node as metastatic. Further data on the long-term impact of lymphoedema on cost and patient utility would be valuable, as would studies that compare effectiveness and cost-effectiveness of SLNB and 4-NS. More robust UK cost data is needed for 4-NS, SLNB, MRI, and PET.

Written by Dr Katy Cooper, ScHARR, University of Sheffield, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/030

Title **A Systematic Review and Economic Evaluation of the Use of Tumor Necrosis Factor-Alpha (TNF-A) Inhibitors, Adalimumab And Infliximab, for Crohn's Disease**

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Reference Volume 15.06. ISSN 1366-5278. www.hta.ac.uk/project/1652.asp

Aim

To review the evidence on the clinical and cost effectiveness of infliximab and adalimumab.

Conclusions and results

Based on 11 trials, evidence from both induction and maintenance trials indicated that both adalimumab and infliximab therapy were beneficial compared with placebo (standard care) in adults with moderate-to-severe CD and, for infliximab, in adults with fistulizing CD; results were statistically significant for some time points. Between 6% and 24% (adalimumab), and 21% and 44% (infliximab) more patients achieved remission with anti-TNF-A antibodies than with placebo in the induction trials. Between 24% and 29% (adalimumab), and 14% and 24% (infliximab) more patients achieved remission with anti-TNF-A antibodies in the 2 large maintenance trials at reported follow-up. In fistulizing CD, between 29% and 42% (induction trial) and 23% (maintenance trial) more patients achieved a >50% reduction in fistulas with infliximab than with placebo at reported follow-up. Results from maintenance trials were almost exclusively based on subgroups of responders. No direct evidence showed that responders were more likely to benefit from treatment than nonresponders in the longer term. Few differences were found between treatment and standard care arms for selected adverse events, though high proportions of scheduled crossovers resulted in a lack of a true placebo group in most of the maintenance trials. No published studies on the cost-effectiveness of adalimumab were identified. The 4 independently funded studies identified for infliximab suggested high cost-effectiveness ratios (all >50 000 pounds sterling [GBP]/quality-adjusted life-year [QALY] for nonfistulizing disease and all above GBP 100 000/QALY for fistulizing disease). A budget impact assessment suggested that total cost to the NHS in England and Wales for induction in severe disease only could range between GBP 17M and GBP 92M and for maintenance for 1 year between GBP 140M and GBP 200M. Findings from a de novo economic model were that for induction, both adalimumab and infliximab are cost effective (dominant relative to standard care) in managing severe CD, and adalimumab (but not infliximab) is cost effective for moderate CD, according to limits generally accepted by NICE. Based on the analysis presented here, neither drug is likely to be cost effective as maintenance therapy for moderate or severe disease. Most importantly, the analysis indicated that many patients would achieve remission under standard care and that the incidence of relapse among those in remission was such that maintenance therapy would have to show greater effectiveness than at present and/or be much less costly than it currently is to reach the levels of generally accepted cost effectiveness. Any future trials need to be designed to meet the particular challenges of measuring and quantifying benefit in this patient group.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1652.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1652.asp.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1652.asp.

Written by Dr Catherine Meads, Barts and the London School of Medicine and Dentistry, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/031

Title **Accuracy of Bacterial DNA Testing for Central Venous Catheter-Associated Bloodstream Infection in Children With Cancer**

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Reference Volume 15.07. ISSN 1366-5278. www.hta.ac.uk/project/1449.asp

Aim

To improve detection and treatment of central venous catheter (CVC)-associated bloodstream infection in children (aged 0-18 years) with cancer admitted with fever.

Conclusions and results

1) The bacterial DNA test detected two-thirds (95% confidence interval [CI] 44% to 83%) of children classified with probable CVC-associated infection – specificity was 88% (95% CI 84%-92%). Although high bacterial DNA concentrations were associated with subsequent CVC removal and long duration of intravenous (IV) antibiotic treatment, the test did not improve the prediction of these outcomes over and above clinical signs of CVC-associated infection combined with blood culture results. 2) High DNA load was predictive of CVC removal and IV treatment duration, before blood culture results became available at 48 hours after sampling. 3) Limited evidence shows that antibiotic lock treatment reduces the risk of recurrent CVC-associated infection or CVC removal (pooled relative risk 0.7, 95% CI 0.47-1.05), but prophylactic use of antimicrobial locks halved the risk of bloodstream infection (pooled incidence rate ratio 0.43, 95% CI 0.36-0.51). Contrary to this, the national survey of pediatric oncology centers found that locks are being used for treatment rather than prevention, and that problems related to the formulation of lock solutions currently impede a shift to their prophylactic use in children. 4) Most IV treatment days would be saved by early stopping of treatment in children at low risk of infection. Strong evidence supports the use of antimicrobial locks in preventing CVC-associated infection; few of these studies involved children with cancer. The analysis does not support routine bacterial DNA testing on admission to detect CVC-associated infection, but repeated testing (as a marker of microbial load) should be evaluated in high-risk groups. Further research should determine the effectiveness of antibiotic locks in treating CVC-associated infection.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1449.asp.

Methods

The diagnostic accuracy study involved 8 pediatric oncology centers in the UK and was coordinated through the Children's Cancer and Leukemia Group (CCLG). Children aged 0 to 18 years with a CVC or implanted CVC port considered to be required for a minimum of 3 months were invited to participate in the study. Eligible patients were enrolled when they presented with a febrile episode if they had not received IV antibiotic therapy during the preceding 2 weeks. Samples were collected at the time of presentation to hospital with fever for routine blood cultures and for bacterial DNA testing. Clinical data were collected via standard questionnaires at the time of admission and at 4 weeks after presentation. Definitions of CVC-associated infection were agreed before the start of the study, and these allowed classification of fever episodes into probable, possible, unlikely, and unclassifiable groups. The results of the accuracy study have been published [Millar et al. Molecular diagnosis of vascular access device-associated infection in children being treated for cancer or leukemia. Clin Microbiol Infect 2008;14(3):213-220].

Further research/reviews required

For further details see Executive Summary link www.hta.ac.uk/project/1449.asp.

Written by Dr Michael Millar, Department of Infection, NHS Trust, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/032

Title **A Multicentre Randomized Controlled Trial and Economic Evaluation of Ion-Exchange Water Softeners for the Treatment of Eczema in Children: The Softened Water Eczema Trial (SWET)**

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Reference Volume 15.08. ISSN 1366-5278. www.hta.ac.uk/project/1520.asp

Aim

To determine whether installing an ion-exchange water softener in the home could improve atopic eczema in children and, if so, to establish its likely cost and cost effectiveness.

Conclusions and results

Target recruitment was achieved (n=336). The analyzed population included 323 children who had complete data. The mean change in primary outcome (Six Area, Six Sign Atopic Dermatitis [SASSAD]) at 12 weeks was –5.0 (standard deviation [SD] 8.8) for the water softener group (group A) and –5.7 (SD 9.8) for the usual care group (group B) (mean difference 0.66, 95% confidence interval [CI] –1.37 to 2.69, p=0.53). Per-protocol analysis supported the main analysis. No evidence showed that the treatment effect varied between children with and without mutations in the filaggrin gene. No between-group differences were found in the 3 secondary outcomes that were assessed blindly (use of topical medications; night-time movement; proportion showing reasonable, good, or excellent improvement). Small, but statistically significant, differences favoring the water softener were found in 3 of the secondary outcomes assessed by participants (Patient-Oriented Eczema Measure; well-controlled weeks; Dermatitis Family Index). Results of the economic evaluation suggest that from an NHS perspective ion-exchange water softeners are unlikely to be a cost-effective intervention for children with atopic eczema. Water softeners provided no additional benefit to usual care in this study population. Small, but statistically significant, differences were found in some secondary outcomes reported by parents, but such improvements were likely the result of response bias. Whether or not the wider benefits of installing a water softener in the home are sufficient to justify purchasing a softener is something for individual householders to consider on a case-by-case basis. This trial demonstrated overwhelming demand for nonpharmacological interventions in treating eczema, which should be considered when prioritizing future research.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1520.asp.

Methods

The Softened Water Eczema Trial (SWET) was a pragmatic, randomized controlled trial (RCT) of children aged 6 months to 16 years with moderate or severe atopic eczema. All lived in hard water areas (≥200 mg/l calcium carbonate) in England. Participants were randomized to receive either immediate installation of an ion-exchange water softener plus their normal eczema care for 12 weeks (group A), or normal eczema care alone for 12 weeks (group B). At 12 weeks the primary outcome was assessed, after which water softeners were removed for participants in group A, or installed for a period of 4 weeks for those in group B. Additional data were collected between weeks 12 and 16 to conduct within-group comparisons to determine the possible duration of benefit effects in group A and speed of onset of possible benefit in group B. The primary outcome of change in eczema severity at 12 weeks was measured using the SASSAD score, which records 6 signs of eczema in 6 areas of the body. Research nurses who were unaware of treatment allocation measured the SASSAD score. Pilot work had demonstrated that blinding participants with a sham unit was only partially successful. Hence, participants and their families were not blinded to allocation group in the main SWET study.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1520.asp.

Written by Dr Kim Thomas, University of Nottingham, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/033

Title **Cost Effectiveness of Screening High-Risk HIV-Positive Men Who Have Sex With Men (MSM) and HIV-Positive Women for Anal Cancer**

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Reference Volume 14.53. ISSN 1366-5278. www.hta.ac.uk/project/1489.asp

Aim

To estimate the cost effectiveness of screening for anal cancer in the high-risk, HIV-positive population – in particular, men who have sex with men (MSM) – by developing a model that incorporates the national screening guidelines criteria.

Conclusions and results

The reference case cost-effectiveness model for MSM found that screening for anal cancer is unlikely to be cost effective. The negative aspects of screening include utility decrements associated with false-positive results and treatment for high-grade anal intraepithelial neoplasia (HG-AIN). Sensitivity analyses showed that removing these utility decrements improved the cost effectiveness of screening. Combined with higher regression rates from low-grade anal intraepithelial neoplasia (LG-AIN), the lowest expected incremental cost-effectiveness ratio was >44 000 pounds sterling (GBP) per quality-adjusted life-year (QALY) gained. Probabilistic sensitivity analysis showed that no screening retained over 50% probability of cost effectiveness at a QALY value of GBP 50 000. The screening model for HIV-positive women showed an even lower likelihood of cost effectiveness (the most favorable sensitivity analyses reported an incremental cost per QALY of GBP 88 000).

Recommendations

This report clearly shows that many of the criteria for assessing the need for a population screening program have not been met for anal cancer. Knowledge is limited regarding the epidemiology and natural history of the disease, and good-quality evidence on the effectiveness of anal cancer screening is lacking. The absence of such data, combined with the possible reluctance of high-risk groups to attend an anal cancer screening program, makes introduction of population-based screening for anal cancer difficult. Cost-effectiveness analyses of screening for anal cancer emphasize this conclusion. The results show little likelihood that screening any of the identified high-risk groups would improve health at a reasonable cost. These results could be confirmed by updating key parameters. The most efficient way to proceed would be to audit the accuracy of the cancer registries' identification of cases of anal cancer and audit the proportion of cancer cases that occur in HIV-positive men and HIV-positive women, and/or MSM. If the data show that the screening model has underestimated the impact of anal cancer in any of the populations evaluated then an evaluative study of the effects of treatment for HG-AIN may be justified.

Methods

Systematic literature reviews addressed the epidemiology and natural history of anal cancer, screening technologies and screening policies, and cost effectiveness of candidate technologies/programs/policies. Two decision-analytical models were developed and populated to analyze the cost effectiveness of screening in HIV-positive and HIV-negative MSM, and in HIV-positive women.

Further research/reviews required

Many of the criteria for assessing the need for a screening program were not met. Further studies could assess whether the screening model has underestimated the impact of anal cancer, the results of which might justify an evaluative study of the effects of treatment for HG-AIN.

Written by Ms Carolyn Czoski-Murray, University of Leeds, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/034

Title **The Swine Flu Triage (SWIFT) Study: Development and Ongoing Refinement of a Triage Tool to Provide Regular Information to Guide Immediate Policy and Practice for the Use of Critical Care Services During the H1N1 Swine Influenza Pandemic**

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Reference Volume 14.55(5). ISSN 1366-5278.
www.netscc.ac.uk/supporting_research/flu_project_portfolio/098601.asp

Aim

To use existing critical care and early pandemic data to inform care during the influenza A 2009 (H1N1) pandemic (with a possible use for triage if demand for critical care seriously exceeded supply); and to monitor the impact of the H1N1 pandemic on critical care services, in real time, with regular feedback to critical care clinicians and other relevant jurisdictions to inform ongoing policy and practice.

Conclusions and results

Modeling: Cancelled or postponed, elective or scheduled surgery saved calendar days of critical, Level 3, and advanced respiratory care of 17%, 11%, and 10%, respectively. Savings varied across units. Using routine, physiological variables, the best triage models, for all and for acute respiratory admissions, achieved only satisfactory concordance of 0.79 and 0.75, respectively. Applying the best model on all admissions indicated that approximately 12.5% of calendar days of critical care could be saved. Cohort study: Research governance approvals were achieved for 192 acute hospitals, for 91 within 1 day of central research and development approval across the 5 countries. In total, 1725 cases (562 confirmed) were reported. Confirmed cases were young (mean 40 years), had low severity of acute illness on presentation (61% CURB-65 [confusion, urea, respiratory rate, blood pressure, age over 65 years] 0–1), but had long stays in critical care (median 8.5 days) and were likely to be ventilated (77% for median 9 days). Risk factors for acute hospital death were similar to those for general critical care admissions. SWIFT was rapidly established. Models based on routine physiology suggested limited value for triage. More data and further modeling are warranted. The pandemic did not approach the worst-case scenario modeling, and UK-confirmed H1N1 cases appeared similar to those reported internationally.

Recommendations

See Abstract link www.netscc.ac.uk/supporting_research/flu_project_portfolio/098601.asp.

Methods

See Abstract link www.netscc.ac.uk/supporting_research/flu_project_portfolio/098601.asp.

Further research/reviews required

Further research on triage modeling, at each step in the care pathway, is a high priority and important for critical care decision-making. Such research should have two main themes: 1) development and validation of triage models; and 2) potential use of such models in critical care decision-making. With respect to the first theme, given that triage decisions in a pandemic should be made for all patients considered for critical care (not just those afflicted by the pandemic), data for, and research on, developing and testing the utility of triage models for critical care does not require a pandemic situation. However, developing such triage models requires collecting accurate data on all acute hospital admissions potentially requiring critical care. This would enable fuller exploration of decision-making around critical care admission and data on the duration and trajectory of critical illness; enabling exploration of triage models to consider earlier discontinuation of critical care for patients initially admitted to critical care. In addition to conventional validation of such triage models, validation could also encompass a comparison with subjective clinical decision-making and assessment of the potential impact of any triage model on future pandemics.

Written by Professor Kathryn Rowan, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/035

Title **An Evidence Synthesis of Qualitative and Quantitative Research on Component Intervention Techniques, Effectiveness, Cost-Effectiveness, Equity and Acceptability of Different Versions of Health-Related Lifestyle Advisor Role in Improving Health**

Agency NETSCC, HTA, NIHR Evaluation and Trials Coordinating Centre
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Reference Volume 15.09. ISSN 1366-5278. www.hta.ac.uk/project/1661.asp

Aim

To identify the component intervention techniques of health-related lifestyle advisors (HRLAs) in the UK and similar contexts, and the outcomes of HRLA interventions.

Conclusions and results

Although 269 studies were identified, 243 were excluded. The 26 included studies addressed chronic care, mental health, breastfeeding, smoking, diet and physical activity, screening, and human immunodeficiency virus (HIV) infection prevention. Overall, the evidence was insufficient to either support or refute the use of HRLAs to promote health and improve quality of life (QoL). Cost effectiveness of the interventions is uncertain. Economic analysis showed that HRLA interventions were cost effective in chronic care and smoking cessation, inconclusive for breastfeeding and mental health, and not cost effective for screening uptake and diet/physical activity. HRLA interventions for HIV prevention were cost effective, but not in a UK context. Evidence was variable, giving only limited support to HRLAs having a positive impact on health knowledge, behaviors, and outcomes. Levels of acceptability appeared to be high. HRLAs acted as translational agents, at times removing barriers to prescribed behavior or helping to create facilitative social environments. Reporting of processes to access or capitalize on indigenous knowledge was limited. Ambiguity was apparent with respect to the role and impact of lay and peer characteristics of the interventions. A future program of research on HRLA could benefit from further emphasis on identifying needs, broadening population focus and intervention aims, measuring outcomes, and reviewing evidence.

Recommendations

1) Interventions that are low cost and have some effect are recommended. 2) Further recognition of the Indigenous Knowledge (IK) base of the HRLA may be required. 3) Training of HRLAs may be worthy of particular attention, as provider and LA-identified learning needs must be balanced. 4) The process of message tailoring and the effectiveness of including different aspects of community allegiance and IK require further exploration. 5) Target groups, their characteristics, and particular needs must be more clearly defined. 6) Intervention approaches need to be more explicit. 7) Peership and layness need to be considered and defined for particular settings. 8) Short-, medium-, and long-term intervention outcomes need to be clearly identified and measured.

Methods

In preparing to synthesize the evidence, a process of problem definition and intervention modeling to facilitate classification of the various intervention dimensions was undertaken: eliciting stakeholder views, secondary analysis of the National Survey of Health Trainer Activity, and telephone survey of health trainer leads/coordinators. The electronic database search included the Applied Social Sciences Index and Abstracts (ASSIA), EMBASE, NHS Economic Evaluation Database (NHS EED), MEDLINE, and PsycINFO, relevant journals, and reference lists. Searches were conducted from inception to September 2008. (For details see Executive Summary link above in the project hyperlink.) Based on agreed criteria and procedures, studies were selected and data abstracted. Narrative, realist, and economic approaches were required to synthesis the data.

Further research/reviews required

To form a research program on HRLA around identifying needs, broadening the population focus and aims of intervention, measuring outcomes, and reviewing evidence.

Written by Dr Susan M. Carr, Northumbria University, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/036

Title **Computerized Decision Support Systems in Order Communication for Diagnostic, Screening or Monitoring Test Ordering: Systematic Reviews of the Effects and Cost Effectiveness of Systems**

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Reference Volume 14.48. ISSN 1366-5278. www.hta.ac.uk/project/1786.asp

Aim

1) To investigate which computerized decision support systems (CDSS) are used in order communication systems (OCS) in the UK and the impact of CDSS in OCS for diagnostic, screening or monitoring test ordering compared to OCS without CDSS.

2) To determine what features of CDSS are associated with clinician or patient acceptance of CDSS in OCS and what is known about the cost effectiveness of CDSS in diagnostic, screening or monitoring test OCS compared to OCS without CDSS.

Conclusions and results

Results of included studies were mixed and equivocal, but showed benefits from using CDSS in conjunction with OCS over and above OCS alone. Considering the findings of primary and secondary outcomes, CDSS significantly improved practitioner performance in 15 of 24 studies. Only 2 studies covered the cost effectiveness of CDSS: a Dutch study reported a mean cost decrease of 3% for blood tests orders (639 euros [EUR]) in each of the intervention clinics compared with a 2% (EUR 208) increase in control clinics in test costs. A Spanish study reported a significant increase in the cost of laboratory tests from EUR 41.8 per patient per annum to EUR 47.2 after implementation of the system. Considering the findings of primary and secondary outcomes, CDSS showed a statistically significant benefit on either process or practitioner performance outcomes in nearly two-thirds of the studies. Four studies that assessed adverse effects of test cancellation or delay found no significant detrimental effects of additional utilization of healthcare resources or adverse events. We believe that a well-designed, comprehensive survey is needed and possibly evaluation studies, eg, cluster randomized controlled trials, and full economic evaluations alongside trials to assess the impact of CDSS in conjunction with OCS versus OCS alone for diagnostic, screening or monitoring test ordering in the NHS. Economic evaluation should incorporate the full costs of potentially developing, testing, and installing the system, including staff training costs.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1786.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1786.asp.

Further research/reviews required

We need to establish which CDSS in OCS are being piloted, implemented, or deployed in the NHS and the type of systems (eg, hospital or laboratory information systems) with which they interface. A comprehensive survey, eg, of individual Strategic Health Authorities, user sites, primary care trusts, and pathology services, is warranted to establish which systems are in place or likely to be implemented in the context of the National Project for Information Technology (NpfIT). The results of such a survey would hopefully inform system commissioners of the best way to rigorously evaluate the CDSS in OCS that are being implemented. Scant evidence from the UK addresses the impact of CDSS in OCS versus OCS alone. We found no evidence on the impact of 'off the shelf' CDSS of relevance to the NpfIT and the NHS. Hence, we need to establish whether any 'grey' literature is available from NHS Trusts that have implemented OCS. Such information could be useful in designing and implementing evaluation studies of CDSS within OCS in the NHS.

Written by Ms Caroline Main, PenTAG, University of Exeter, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/037

Title **The Clinical Effectiveness and Cost Effectiveness of Long-Term Weight Management Schemes for Adults: A Systematic Review**

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Reference Volume 15.02. ISSN 1366-5278. www.hta.ac.uk/project/2036.asp

Aim

To assess the long-term clinical and cost effectiveness of multicomponent weight management schemes for adults in terms of weight loss and maintenance of weight loss.

Conclusions and results

We identified 3358 references, of which 12 were included in the clinical effectiveness review. Five randomized controlled trials (RCTs) compared multicomponent interventions with nonactive comparator groups. Generally, weight loss appeared to be greater in the intervention groups than in the comparator groups. Two RCTs compared multicomponent interventions that focused on diet. These studies presented no statistically significant differences in weight loss between interventions. Four RCTs compared multicomponent interventions that focused on physical activity. We found little consistency in the pattern of results, in part owing to the differences in the interventions. The intervention in one RCT focused on the goal-setting interval, and weight loss appeared to be greatest in those given daily goals versus weekly goals. Overall, where measured, it appeared that most groups began to regain weight at further follow-up. Of the 419 studies identified in the cost-effectiveness searches, none met the full inclusion criteria. Our review describes 2 economic evaluations, but caution is required in their interpretation since they did not meet all inclusion criteria. These studies used lifetime chronic disease models, and the models included the costs and benefits of avoiding chronic illness. Both studies found the interventions to be cost effective, with estimates varying between –473 pounds sterling (GBP) and GBP 7200 per quality-adjusted life-year gained. Since methodological omissions from these studies were apparent, caution is required in interpreting the results. Long-term multicomponent weight management interventions were generally shown to promote weight loss in overweight or obese adults. Weight changes were small, however, and weight regain was common. There were few similarities between the included studies; consequently an overall interpretation of the results was difficult. Some evidence suggests that weight management interventions are likely to be cost effective, but caution is necessary due to limitations in both of the cost-evaluation studies described.

Recommendations

See Executive Summary link www.hta.ac.uk/project/2036.asp.

Methods

Data sources: A sensitive search strategy was designed and applied to 10 electronic bibliographic databases (eg, MEDLINE, EMBASE, Cochrane Library) from inception to December 2009. Bibliographies of related papers were screened, key conferences and symposia were searched, and experts were contacted to identify additional published and unpublished references. Study selection: Independently, 2 reviewers screened titles and abstracts for eligibility. Inclusion criteria were defined a priori and applied to the full text of retrieved papers by 2 reviewers using a standard form. Clinical effectiveness studies were included if participants were adults with a body mass index >25 kg/m2; if the interventions were well-described multicomponent (diet, exercise, behavior therapy) weight management approaches with a weight loss outcome; and if the studies were RCTs with at least 18 months' follow-up. Studies in the systematic review of cost effectiveness were required to be cost-effectiveness analyses. Data extraction and quality assessment: Data extraction and assessment of methodological quality was undertaken by one reviewer and checked by a second. Differences in opinion were resolved through discussion or recourse to a third reviewer at each stage.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/2036.asp.

Written by Dr Emma Loveman, Southampton Health Technology Assessment Centre, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/038

Title **A Randomized Controlled Trial of Post-Operative Radiotherapy Following Breast-Conserving Surgery in a Minimum-Risk Population. Quality Of Life at 5 Years in the PRIME Trial**

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Reference Volume 15.12. ISSN 1366-5278. www.hta.ac.uk/project/1697.asp

Aim

To assess whether omission of postoperative radiotherapy (RT) in women with low-risk axillary node-negative breast cancer (tumor size <5 cm [T0–2] although the eligibility criteria further reduce the eligible size to a maximum of 3 cm) treated by breast-conserving surgery and endocrine therapy improves quality of life and is more cost effective.

Conclusions and results

The hypothesized improvement in overall quality of life with the omission of RT was not seen in the summary domains of the European Organization for Research in the Treatment of Cancer (EORTC) scales. Some differences were apparent in subscales of the EORTC questionnaires, and insights into the impact of treatment were also provided by the qualitative data obtained by open-ended questions added by the trial team. Differences were most apparent shortly after the time of completion of RT. RT was then associated with increased breast symptoms and with greater (self-reported) fatigue, but with lower levels of insomnia and endocrine side effects. These statistically significant differences in breast symptoms persisted for up to 5 years after RT (mean difference, RT was 5.27 units greater than no RT, 95% confidence interval [CI] of 1.46 to 9.07) with similar, though nonsignificant, trends in insomnia. No significant difference was found in the overall quality-of-life measure, with the no RT group having 0.36 units greater quality of life than the RT group (95% CI –5.09 to 5.81). Breast RT is tolerated well by most older breast cancer patients without impairing their overall health-related quality of life (HRQoL). Although HRQoL should always be taken into account when determining treatment, our results show that adding RT does not impair overall quality of life. Further economic modeling on the longer-term costs and consequences of omitting RT is required.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1697.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1697.asp.

Further research/reviews required

Primary recommendation for further research: Further economic modeling of longer-term costs and consequences of omitting RT. Secondary recommendations: 1) Omission of RT in this group of patients has a short-term economic benefit. However, evidence of the longer-term benefit requires longer follow-up to determine local recurrence rates with and without postoperative whole breast RT. 2) Investigate the application of novel methodologies (eg, touch-screen technology) to capture and grade comorbidities and quality of life at baseline and in clinical follow-up. 3) Investigate the influence of specific types and degrees of comorbid disease on quality of life. 4) Refine methodologies and develop software to integrate the prediction of recurrence rates from breast cancer with the competing effects of mortality from other diseases. 5) Develop a validated questionnaire/scale to assess the impact of access to healthcare services for older patients.

Written by Dr Linda Williams, University of Edinburgh, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/039

Title **Venus III: A Randomized Controlled Trial of Therapeutic Ultrasound in the Management of Venous Leg Ulcers**

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Reference Volume 15.13. ISSN 1366-5278. www.hta.ac.uk/project/1451.asp

Aim

To compare the clinical and cost effectiveness of low-dose ultrasound delivered in conjunction with standard care against standard care alone in treating hard-to-heal venous ulcers.

Conclusions and results

Regarding the median time to complete ulcer healing of all ulcers, we found a small, and statistically not significant, difference in favor of standard care (median 328 days, 95% confidence interval [CI] 235 days, inestimable) compared to ultrasound (median 365 days, 95% CI 224 days, inestimable). The groups did not differ in the proportion of patients with ulcers healed at 12 months (72/168 in ultrasound vs 78/169 standard care), nor in the change of ulcer size at 4 weeks. No evidence indicated a difference in recurrence of healed ulcers. The two groups did not differ in HRQoL (measured using the Short Form questionnaire-12 items). More adverse events were associated with ultrasound than with standard care. Ultrasound therapy as an adjuvant to standard care was found not to be cost effective when compared to standard care. The mean cost of ultrasound was 197.88 pounds sterling (GBP) (bias-corrected 95% CI – GBP 35.19 to GBP 420.32) higher than standard care per participant per year. We found a significant relationship between ulcer healing and area and duration at baseline. In addition, centers with high recruitment rates had the highest healing rates. Low-dose ultrasound, delivered weekly during dressing changes, added to the package of current best practice (dressings, compression therapy) did not increase ulcer healing rates, affect quality of life (QoL), or reduce recurrence. It was associated with higher costs and more adverse events. We found no evidence that adding low-dose ultrasound to standard care for hard-to-heal ulcers aids healing, improves QoL, or reduces recurrence. It increases costs and adverse events. The relationship between ulcer healing rates and patient recruitment is worthy of further study.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1451.asp.

Methods

Design: A multicenter, pragmatic, parallel, two-armed randomized controlled trial with an economic evaluation. Allocation was concealed, treating nurses and patients were aware of allocation, and outcome assessment was by treating-nurse report confirmed by blinded review of photographs at healing and 7 days later. Setting: Community nurse services; community leg ulcer clinics; hospital outpatient leg ulcer clinics, among both urban and rural settings in England, Scotland, Northern Ireland, and Ireland. Participants: Patients were eligible to participate in the trial if they presented with a venous leg ulcer of >6 months' duration or >5 cm^2 and an ankle-brachial pressure index of ≥0.8. Interventions: Participants in the intervention group received low-dose ultrasound (0.5 W/ cm^2) delivered at 1 MHz, pulsed pattern of 1:4, applied to periulcer skin weekly for up to 12 weeks alongside standard care. Standard care consisted of low-adherent dressings and compression therapy, renewed as recommended by the patient's nurse and modified if required to reflect changes in ulcer and skin condition.

Further research/reviews required

We identified large variation in healing rates by trial centers, with centers recruiting more patients to the trial having higher healing rates. We controlled for ulcer area and duration; hence, it is unlikely that the difference in healing rates could be attributed to these prognostic factors being distributed differently across sites (ie, larger/old ulcers in one site). The relationship between ulcer healing rates and patient recruitment is worthy of further study.

Written by rofessor Andrea Nelson, School of Healthcare, University of Leeds, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/040

Title **The Clinical Effectiveness and Safety of Prophylactic Retinal Interventions to Reduce the Risk of Retinal Detachment and Subsequent Vision Loss in Adults and Children With Stickler Syndrome: A Systematic Review**

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Reference Volume 15.16. ISSN 1366-5278. www.hta.ac.uk/project/2156.asp

Aim

To assess the evidence for the clinical effectiveness and safety of primary prophylactic interventions for preventing retinal detachment (RD) in previously untreated eyes without RD in patients with Stickler syndrome.

Conclusions and results

The literature search identified 1444 unique citations, of which 4 studies satisfied the inclusion criteria. The 2 principal studies were retrospective cohort studies with control groups in populations with type 1 Stickler syndrome. One study evaluated 360° cryotherapy (n=204) and the other focal or circumferential laser treatment (n=22). Both studies reported a statistically significant difference in the rate of RD per eye between the groups receiving prophylaxis and the controls. However, both studies were subject to a high risk of bias. The results of the two supporting studies of Wagner-Stickler patients were either relatively inconsistent or unreliable. No study reported any major or long-term complications associated with the interventions. Despite the weaknesses of the evidence, the rate of RD in the intervention groups, especially the cryotherapy group, was lower than the rate either experienced in the study control groups or reported in other studies of untreated Stickler syndrome populations not exposed to prophylaxis. Only 360° cryotherapy and focal and circumferential laser treatment have been evaluated for the type 1 Stickler syndrome population, and then only by a single retrospective, controlled, cohort study in each case. Both of these studies report a significant difference between intervention and control groups (principally no treatment) and no major or long-term side effects or complications. Since both studies have a high risk of bias, the relative effectiveness of either intervention is uncertain.

Recommendations

See Executive Summary link www.hta.ac.uk/project/2156.asp.

Methods

We systematically reviewed the evidence for the clinical effectiveness and safety of primary prophylactic interventions in preventing RD in previously untreated eyes without RD in patients with Stickler syndrome. The primary outcome of interest was RD postprophylaxis. An information specialist searched 11 databases for published and unpublished literature. No restrictions were placed on language, date, or study design (other than requiring that studies have a comparator group). Two reviewers double-screened all titles and abstracts of the citations retrieved by the search to identify studies that satisfied the inclusion criteria. Any disagreements were resolved by discussion or reference to the full paper. Both reviewers independently extracted and quality assessed all included studies. The references of these studies were checked for further relevant citations. The authors of any studies with potential but unspecified Stickler syndrome patients in their study sample were contacted to retrieve any further data on the efficacy of interventions in this population.

Further research/reviews required

A service priority is to determine reliably the prevalence of Stickler syndrome, ie, how many individuals have type 1 or type 2 Stickler syndrome, and their risk of retinal detachment and subsequent blindness. A nonrandomized, prospective, cohort comparison study, in which eligible participants are treated, followed-up, and analyzed in one of three study arms (no treatment, laser therapy, or cryotherapy) would potentially enhance certainty about the relative efficacy of prophylaxis versus no prophylaxis and cryotherapy versus laser therapy. Alternatively, continued follow-up and analysis of existing study data, and data collection from relevant sample populations, are required to assess the long-term risks of blindness, retinal detachment, and prophylaxis.

Written by Dr Christopher Carroll, ScHARR, University of Sheffield, NETSCC, United Kingdom

Title **Recombinant Activated Factor VII for Prevention of Bleeding Unrelated to Hemophilia: Clinical and Economic Systematic Review**

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Reference CADTH Technology Report, Issue 124, February 2010. ISBN: 978-1-926680-36-1 (print); ISBN: 978-1-926680-37-8 (online)

Aim

To assess the clinical and cost effectiveness of using recombinant activated factor VII (rFVIIa) to prevent bleeding in individuals without hemophilia, inherited platelet disorders, or other coagulopathies during liver transplantation, prostatectomy, cardiac surgery, or when needing supratherapeutic anticoagulation.

Conclusions and results

No consistent benefit of rFVIIa therapy was detected among studies evaluating the prevention of bleeding in patients undergoing prostatectomy, liver transplantation, or cardiac surgery. The risk of adverse events after the prophylactic use of rFVIIa in surgical patients is unknown. No conclusions can be drawn about the effectiveness or safety of using rFVIIa to prevent bleeding in patients who have received supratherapeutic doses of anticoagulant agents. Conclusions regarding cost effectiveness of rFVIIa cannot be made based on the available data.

Recommendations

Not applicable.

Methods

We conducted a systematic review of the clinical and economic literature that compared rFVIIa to a different dose, to a placebo, to no treatment, or to other relevant indication-specific standard therapies. Clinical outcome measures included the following: all-cause mortality; health-related quality of life; serious adverse events; thromboembolic adverse events; need for blood transfusion; volume of red blood cells (RBCs), fresh frozen plasma, cryoprecipitate, platelets, or plasma volume expander solutions transfused; operation times; and length of hospital stay. In the supratherapeutic anticoagulated patient population, the number of patients with bleeding was also included.

Further research/reviews required

More research is needed to provide more and better quality data.

Written by Murphy G, Tsakonas E, Ndegwa S, Anderson D, Barkun J, and Mierzwinski-Urban M., CADTH, Canada

INAHTA Briefs

Issue 2011/042

Title **Clopidogrel versus Other Antiplatelet Agents in the Secondary Prevention of Vascular Events in Adults with Cerebrovascular Disease: Clinical and Cost- Effectiveness Analyses**

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Reference CADTH Technology Report, Issue 123, December 2009. ISBN: 978-1-926680-34-7 (print) ISBN: 978-1-926680-35-4 (online)

Aim

To compare the clinical and cost effectiveness of clopidogrel, alone or in combination with acetylsalicylic acid (ASA) versus other antiplatelet regimens including ASA, ticlopidine, dipyridamole, and combination fixed-dose ASA and extended-release dipyridamole (ERDP) in secondary prevention of myocardial infarction (MI), stroke, or vascular death in adult patients with cerebrovascular events (stroke, transient ischemic attack); to determine the optimal duration of treatment with clopidogrel in secondary prevention of vascular events in adult patients with cerebrovascular events; and, to review North American clinical practice guideline recommendations for the use of clopidogrel.

Conclusions and results

The estimates of effects with clopidogrel, ticlopidine, and dipyridamole relative to ASA were inconclusive. Economic analysis found ASA to be the most cost-effective option in secondary prevention of recurrent stroke in patients with a mean age of 60 years at the time of their initial stroke. For patients in this age group who do not tolerate ASA, ASA-ERDP may be a cost-effective alternative. ASA-ERDP was the most cost-effective option in patients aged 70 years or older at the time of their initial stroke. These conclusions assume a willingness-to-pay threshold of $50 000 per QALY, and are subject to the limitations of the analysis.

Recommendations

Not applicable.

Methods

Two systematic reviews (1 clinical, 1 economic) of studies comparing clopidogrel with other antiplatelet therapies in managing stroke patients were conducted according to a prior protocol. Economic evaluation was performed to determine the cost effectiveness of clopidogrel, ASA, ASA plus clopidogrel, dipyridamole, ASA-ERDP, or ticlopidine in managing stroke patients. Clinical practice guidelines were reviewed and assessed.

Further research/reviews required

Further research is needed to answer many of the questions posed in this report due to unavailability of studies using direct comparisons or studies evaluating duration of treatment.

Written by Banerjee S, Brown A, Hutton B, McGahan L, Asakawa K, Clark M, Severn M, Cox JL, and Sharma M., CADTH, Canada

Title **Pulmonary Rehabilitation for Chronic Obstructive Pulmonary Disease: Clinical, Economic and Budget Impact Analysis**

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Reference CADTH Technology Report, Issue 126, March 2010. ISBN: 978-1-926680-38-5 (print); ISBN: 978-1-926680-39-2 (online)

Aim

To evaluate the effect of pulmonary rehabilitation (PR) programs for chronic obstructive pulmonary disease (COPD) on clinical and economic outcomes, and to assess the health services impact.

Conclusions and results

Specifically, our objectives are: to compare the clinical effectiveness of PR and pharmacotherapy (together) with pharmacotherapy alone; to determine the effectiveness of elements of PR programs, eg, aerobic exercise, education, strength training, nutritional and psychosocial interventions; to determine the cost effectiveness of PR and pharmacotherapy compared to pharmacological therapy alone; and, to assess the health services impact of implementing PR for adults with COPD in Canada.

Pulmonary rehabilitation (PR) was associated with improvements in short-term health-related quality of life, mental health measures, and activity levels in patients with stable COPD, at an additional cost. PR was also associated with a reduced number of hospitalizations. Findings suggested that patients with COPD could benefit from the use of PR regardless of age, sex, or disease severity. Home-based PR programs provided similar benefits to hospital-based outpatient PR programs. The appropriate duration and content of PR programs is unclear.

Recommendations

Not applicable.

Methods

We conducted a systematic review of the clinical and economic literature to assess the effectiveness of pharmacotherapy (usual care) and pharmacotherapy plus PR. We also performed a cost-effectiveness analysis using a health system perspective and estimated the budget impact of additional services. PR consisted of 3 sessions per week at 2.5 hours per session over 6 weeks. COPD prevalence data were used to estimate the number of patients to receive PR, and the budget impact of additional services was estimated by multiplying the unit cost of PR by the number of additional persons served per year.

Further research/reviews required

Factors that contribute to successful long-term management of COPD with PR (maintenance, program structure, content, and location) require further investigation.

Written by Hailey D, Jacobs P, Stickland M, Chuck A, Marciniuk DD, Mayers I, and Mierzwinsky-Urban M, CADTH, Canada

INAHTA Briefs

Issue 2011/044

Title **Polymerase Chain Reaction Tests for Methicillin-Resistant Staphylococcus aureus in Hospitalized Patients: Clinical and Cost-Effectiveness Analyses**

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Reference CADTH Technology Report, Issue 125, March 2010. ISBN: 978-1-926680-40-8 (print); ISBN: 978-1-926680-41-5 (online)

Aim

To evaluate the screening accuracy and clinical and cost effectiveness of polymerase chain reaction testing (PCR) compared to conventional screening tests (chromogenic agar) or no screening for methicillin-resistant *Staphylococcus aureus* (MRSA) in a hospital setting.

Conclusions and results

In the clinical review, PCR demonstrated a high degree of accuracy, lower turnaround times for obtaining test results, and a reduction in isolation days for patients. Lower MRSA colonization, infection, and transmission rates were also observed with PCR, but definitive conclusions were limited in some studies. Cost effectiveness varied with the pre-emptive isolation scenario used and was responsive to the number and proportion of high-risk contacts per visit between a healthcare worker and patient, and to the costs of patient isolation. Under conditions of pre-emptive isolation, BD GeneOhm MRSA (multi-site specimen) was less costly and more effective than other screening methods. Compared to no screening, BD GeneOhm MRSA (multi-site specimen) screening cost 20 430 Canadian dollars (CAD) to prevent 1 case of MRSA. Without pre-emptive isolation, it cost CAD 17 500 to prevent 1 MRSA case with BD GeneOhm MRSA (multi-site specimen) versus no screening, and CAD 49 505 versus chromogenic agar. To avoid 1 MRSA case with chromogenic agar versus no screening, it cost CAD 4078.

Recommendations

Not applicable.

Methods

We systematically reviewed the literature to determine the screening test accuracy and clinical benefits of PCR versus chromogenic agar and conducted a cost-effectiveness analysis to compare PCR, chromogenic agar, and no screening for MRSA in a hospital setting.

Further research/reviews required

Future research is needed to examine how the use of PCR for MRSA screening affects quality of care and treatment outcomes in adult and pediatric populations. Also, more studies on community-acquired MRSA are needed.

Written by Polisena J, Membe SK, Chen S, Leroux T, Cimon K, McGill S, Forward K, and Gardam M, CADTH, Canada

INAHTA Briefs

Issue 2011/045

Title **Triple Therapy for Moderate-to-Severe Chronic Obstructive Pulmonary Disease**

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Reference CADTH Technology Report, Issue 127, May 2010. ISBN: 978-1-926680-46-0 (print); ISBN: 978-1-926680-47-7 (online)

Aim

To evaluate the comparative clinical effectiveness, cost effectiveness, and health service impact of triple therapy in treating moderate-to-severe chronic obstructive pulmonary disease (COPD).

Conclusions and results

The evidence was insufficient to determine whether triple therapy was clinically superior to dual bronchodilator therapy or combination (LABA+ICS) therapy in treating moderate-to-severe COPD. Compared to the use of tiotropium alone, triple therapy was associated with a decrease in the number of COPD hospitalizations, improved lung function, and better quality-of-life measures in patients with moderate-to-severe COPD. The incremental cost-utility ratio of triple therapy (tiotropium+LABA+ICS) compared with monotherapy (tiotropium) was estimated to be $111 458 per quality-adjusted life-year (QALY). The cost per QALY of triple therapy varied depending on the source of efficacy data and the assumed cost of the LABA plus ICS. Using the base-case analysis, triple therapy would be cost effective if willingness to pay exceeded $111 458 per QALY. Otherwise monotherapy would be the cost-effective treatment.

Recommendations

Not applicable.

Methods

We conducted systematic reviews of clinical and economic literature to compare triple therapy (LAAC+LABA+ICS) with dual bronchodilator therapy (LAAC+LABA, regular use SAAC+LABA), combination therapy (LABA+ICS), or monotherapy (LAAC). Due to heterogeneity in the selected studies, we did not perform a meta-analysis. For the economic assessment, we performed a cost-utility analysis using a Markov model and taking a publicly funded healthcare perspective. In the base-case analysis, 65-year-old patients with severe-to-moderate COPD comprised the starting cohort. Comparators were monotherapy (tiotropium), dual bronchodilator therapy (tiotropium+LABA), and triple therapy (tiotropium+LABA+ICS). The time horizon was 5 years.

Further research/reviews required

More studies comparing therapies for COPD are needed.

Written by Gaebel K, Blackhouse G, Robertson D, Xie F, Assasi N, McIvor A, Hernandez P, and Goeree R, CADTH, Canada

INAHTA Briefs

Issue 2011/046

Title **Vancomycin or Metronidazole for Treatment of Clostridium difficile Infection: Clinical and Economic Analyses**

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Reference CADTH Technology Report, Issue 136, January 2011. ISSN: 1922-6101 (print); ISSN: 1922-611X (online)

Aim

To evaluate the relative clinical effectiveness, cost effectiveness, and budget impact of using vancomycin or metronidazole in managing initial episodes of moderate to severe *Clostridium difficile* infection (CDI) in children or in adults, and to review clinical practice guideline recommendations.

Conclusions and results

The use of metronidazole or vancomycin produces a similar clinical cure rate in patients with initial or recurrent moderate CDI. A higher clinical cure rate is reported with vancomycin in patients with initial or recurrent severe CDI. The use of oral vancomycin by patients with severe disease will incur an incremental cost of $1161 per clinical cure. However, this cost-effectiveness ratio may be lower if generic IV vancomycin is used in hospitals ($346 per clinical cure), and the use of vancomycin may result in net health expenditure reductions if it has an impact on complication rates and reduces hospitalization costs. Practice guidelines recommend the use of oral vancomycin for severe initial episodes of CDI and oral metronidazole for nonsevere episodes.

Recommendations

Not applicable.

Methods

In a systematic review of the relative effectiveness of vancomycin and metronidazole in adults or children with moderate or severe CDI, we used the following outcome measures: cure, recurrences, complications, and, serious adverse events. A primary economic analysis compared the cost effectiveness of first-line therapy with vancomycin versus metronidazole in patients with severe CDI. We used budget impact analysis to compare the incremental costs of first-line treatment using vancomycin versus metronidazole in hospitalized patients with severe CDI. In addition, we reviewed and assessed clinical practice guidelines.

Further research/reviews required

Larger studies are needed to compare the relative efficacy of vancomycin and metronidazole for key clinical outcomes in different patient populations.

Written by Perras C, Tsakonas E, Ndegwa S, Conly J, Valiquette L, and Farrah K, CADTH, Canada

INAHTA Briefs

Issue 2011/047

Title	**Clopidogrel versus Other Antiplatelet Agents for Secondary Prevention of Vascular Events in Adults with Acute Coronary Syndrome or Peripheral Vascular Disease: Clinical and Cost-Effectiveness Analyses**
Agency	**CADTH, Canadian Agency for Drugs and Technologies in Health** Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada;
Reference	CADTH Technology Report, Issue 133, November 2010. ISSN: 1922-6101 (print); ISSN: 1922-611X (online)

Aim

To compare the clinical and cost effectiveness of clopidogrel, alone or in combination with acetylsalicylic acid (ASA), versus other antiplatelet regimens for secondary prevention of vascular events in adult patients with acute coronary syndrome (ACS) or peripheral vascular disease (PVD); to determine the optimal duration of treatment with clopidogrel in secondary prevention of vascular events in the same population; and to review North American clinical practice guideline recommendations for the use of clopidogrel.

Conclusions and results

Dual therapy with clopidogrel and ASA was more efficacious than ASA alone in patients with ACS and no ST-segment elevation, but with increased risk of major bleeding. No studies were available by which to determine the optimal duration of treatment using clopidogrel in secondary prevention of vascular events. For patients with a mean age 60 at initial event or PVD diagnosis, treatment options including clopidogrel were the most cost effective compared to ASA alone in secondary prevention of vascular events. In patients with ACS, clopidogrel plus ASA was found to be the most cost effective of ASA, clopidogrel plus ASA, or clopidogrel alone. In patients with PVD, clopidogrel alone was the most cost effective, but clopidogrel plus ASA becomes most cost effective as the mean age increases. Practice guidelines recommend a combination of clopidogrel and ASA for patients with ACS. However, clopidogrel alone is recommended for patients with ACS or PVD and an intolerance or allergy to ASA.

Recommendations

Not applicable.

Methods

Two systematic reviews, 1 clinical and 1 economic, of studies comparing clopidogrel with other antiplatelet agents in patients with ACS or PVD were conducted, according to a priori protocols. A search for clinical guidelines was conducted, and an economic evaluation was performed to determine the cost effectiveness of clopidogrel, ASA, or ASA plus clopidogrel in managing patients with ACS and patients with PVD.

Further research/reviews required

More research on patients with ACS or PVD is needed to answer many of the research questions posed.

Written by Banerjee S, Brown A, McGahan L, Asakawa K, Hutton B, Clark M, Severn M, Sharma M, and Cox JL, CADTH, Canada

INAHTA Briefs

Issue 2011/048

Title **Second-Line Therapy for Patients With Diabetes Inadequately Controlled on Metformin: A Systematic Review and Cost-Effectiveness Analysis**

Agency **CADTH, Canadian Agency for Drugs and Technologies in Health**
Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada;
Tel: +1 613 226 2553, Fax: +1 613 226 5392; publications@cadth.ca, www.cadth.ca

Reference Optimal therapy report vol. 4 no. 2. 2010 January

Aim

To systematically review the clinical evidence pertaining to second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy; and based on the results of the systematic review, conduct a cost-effectiveness analysis.

Conclusions and results

We identified evidence for 8 classes of second-line antidiabetes therapies in adults with type 2 diabetes inadequately controlled with metformin monotherapy. The methodological quality of the evidence was generally low. All agents achieved statistically significant reductions in A1C, and there were no statistically significant differences between drug classes. A modest increase in body weight was observed with most second-line therapies. We found little evidence regarding the effect of second-line antidiabetes drugs on the long-term complications of diabetes or mortality. Sulfonylureas were the most cost-effective second-line therapy in patients inadequately controlled on metformin, due primarily to their lower cost compared to insulin and newer agents. Cost-effectiveness results were robust to variations in model inputs and assumptions. Sulfonylureas are equally efficacious as other agents when used as second-line treatment after inadequate control with metformin monotherapy, and represent the most cost-effective treatment option.

Methods

The literature search included electronic databases, grey literature, reference lists, conference abstracts, and stakeholder consultation. Mixed treatment comparison and pairwise meta-analyses were conducted to pool trial results, when appropriate. Numerous sensitivity analyses were performed to examine robustness of meta-analytic results. We used the United Kingdom Prospective Diabetes Study Outcomes Model to forecast diabetes-related complications and cost consequences. Treatment effect estimates were obtained from the systematic review of clinical evidence. Other inputs for the model were derived from published and unpublished sources. We performed numerous sensitivity analyses to examine the robustness of results to variation in model inputs and assumptions.

Written by CADTH, Canada

INAHTA Briefs

Issue 2011/049

Title	**Clopidogrel Compared With Other Antiplatelet Agents for Secondary Prevention of Vascular Events in Adults Undergoing Percutaneous Coronary Intervention: Clinical and Cost-Effectiveness Analyses**
Agency	**CADTH, Canadian Agency for Drugs and Technologies in Health** Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada;
Reference	CADTH Technology Report, Issue 131, November 2010. ISSN: 1922-6101 (print); ISSN: 1922-611X (online)

Aim

To compare the clinical and cost effectiveness of clopidogrel, alone or in combination, with acetylsalicylic acid (ASA) versus other antiplatelet regimens for secondary prevention of vascular events in adult patients undergoing percutaneous coronary intervention (PCI); to determine the optimal duration of treatment with clopidogrel in the same population; and, to review related North American clinical practice guideline recommendations for the use of clopidogrel.

Conclusions and results

Clopidogrel and ticlopidine are at least as effective as ASA in secondary prevention of vascular events. Compared to ASA, clopidogrel, and especially ticlopidine, are associated with a higher risk of major bleeds. A review of composite endpoint data (eg, death, MI, stroke, revascularization, and major bleeds) suggests that the use of ASA plus clopidogrel reduces the rate of cardiovascular events compared to ASA alone. A review of the composite endpoints data indicated that clopidogrel (compared to ticlopidine) was associated with fewer blood disorders. Economic evaluation showed that for patients undergoing PCI at age 60, one year of dual antiplatelet therapy with ticlopidine and ASA, followed by lifetime ASA, may be a more cost-effective treatment (compared to clopidogrel plus ASA, and ASA monotherapy) in secondary prevention of vascular events.

Recommendations

Not applicable.

Methods

We conducted systematic reviews of clinical and economic studies that compared clopidogrel to other antiplatelet agents in patients undergoing PCI. A primary economic analysis aimed to determine the cost effectiveness of clopidogrel plus ASA, ticlopidine plus ASA, or ASA in managing patients. Clinical practice guideline recommendations were reviewed and assessed.

Further research/reviews required

More research should directly compare several clinical outcomes and different dosages and should investigate quality of life. In addition, more information on the clinical effectiveness of ticlopidine would be of value to decision makers.

Written by Chen SY, Russell E, Banerjee S, Hutton B, Brown A, Asakawa K, McGahan L, Clark M, Severn M, Cox J, and Sharma M., CADTH, Canada

Title **Palivizumab Prophylaxis Against Respiratory Syncytial Virus**

Agency **CADTH, Canadian Agency for Drugs and Technologies in Health**
Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada;
Tel: +1 613 226 2553, Fax: +1 613 226 5392; publications@cadth.ca, www.cadth.ca

Reference Technology Report number 80, 2007

Aim

To examine the evidence for the cost and clinical effectiveness of palivizumab prophylaxis versus no prophylaxis against lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk for RSV.

Conclusions and results

Palivizumab was shown to reduce RSV-associated hospitalization compared to placebo in premature children, some of whom had bronchopulmonary dysplasia, and reduce RSV-associated hospitalization in children with hemodynamically significant congenital heart disease. A recent review states that the cost effectiveness of palivizumab is difficult to assess because of the lack of high-quality cost-benefit analyses. The CPS recommends that palivizumab be considered for children at highest risk, eg, those with bronchopulmonary dysplasia, and children born at ≤32 weeks gestation. Palivizumab is an expensive option, but it is shown to be effective in certain groups of infants and children.

Methods

A literature search encompassed key health technology assessment sources, including bibliographic databases and grey literature. Retrieval was limited to works in English or French on human population, and no date restrictions were applied. Studies investigating the clinical effectiveness of palivizumab were limited to systematic reviews, health technology assessments, and randomized controlled trials. Any type of cost analysis or economic evaluation was considered.

Written by Dunfield L and Mierzwinski-Urban M, CADTH, Canada

Title **Pulsed Dye Laser Therapy for Port Wine Stains**

Agency **CADTH, Canadian Agency for Drugs and Technologies in Health**
Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada;
Tel: +1 613 226 2553, Fax: +1 613 226 5392; publications@cadth.ca, www.cadth.ca

Reference Technology Report number 78, 2007

Aim

To examine the evidence regarding the clinical and cost effectiveness of pulse dye laser (PDL) therapy for port wine stains (PWS), and determine if the effectiveness of PDL therapy varies according to clinical situations or patient groups.

Conclusions and results

The literature suggests that PDL therapy is beneficial, particularly when compared with the alternatives. Success is greater when patients are treated during childhood or adolescence, and when visible PWS are targeted to limit stigmatization. Patients vary in their response to PDL depending on factors such as skin and lesion types. The focus of therapy is to lighten the color of a lesion, but its texture, height, and area may be unaffected. All patients require multiple PDL sessions, although studies vary in terms of optimal numbers of sessions and length of treatment, and determination of the point at which to cease therapy. Although most evidence supports PDL for initial therapy, other devices may be required in addition to PDL to treat residual or resistant PWS. It may be difficult to define treatment parameters given the variable characteristics of lesions and potential for recurrence. Cost effectiveness is unknown.

Methods

A literature search encompassed key health technology assessment resources, international health technology agencies, and a focused Internet search. Due to the large volume of literature, the search was limited to articles published in English between 2000 and November 2006. The draft report was internally reviewed and then externally reviewed by peer reviewers.

Further research/reviews required

Long-term studies of PDL for PWS are needed.

Written by Foerster V, Murtagh J, and Fiander M, CADTH, Canada

INAHTA Briefs

Issue 2011/052

Title **Positron Emission Tomography (PET) in Oncology: A Systematic Review of Clinical Effectiveness and Indications for Use**

Agency **CADTH, Canadian Agency for Drugs and Technologies in Health**
Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada;
Tel: +1 613 226 2553, Fax: +1 613 226 5392; publications@cadth.ca, www.cadth.ca

Reference 2010

Aim

To determine the clinical effectiveness of positron emission tomography (PET) in oncology compared to computed tomography (CT) and magnetic resonance imaging (MRI) when used as an adjunct to CT or MRI; and to determine the indications for PET use in oncology.

Conclusions and results

The included studies suggest that PET may be similarly, or more, effective than other imaging modalities (CT or MRI) for some oncologic indications. Moderate-quality evidence indicates that PET is effective in diagnosing or detecting cancer of the breast, pancreas, head and neck, and lung. Low-quality, consistent, evidence suggests that PET may be useful in diagnosing cancer of unknown primary origin when conventional workup has failed. Evidence is available for the use of PET in staging non-small-cell lung carcinoma. Moderate-quality evidence supports staging or restaging in colorectal, esophageal, head and neck, and breast cancer. Using PET to monitor treatment response in lymphoma and metastatic breast cancer is supported. PET that is used to restage or detect residual disease or recurrence is supported by evidence reported to be of moderate quality. This information and an evaluation of the impact of PET on patient management and assessments of cost-effectiveness would contribute to informed decision-making.

Methods

A literature search encompassed key health technology assessment resources, international health technology agencies, and a focused Internet search. The search was limited to articles written in English. Results were limited to English language publications only. Filters were applied to limit retrieval to systematic reviews, health technology assessments, meta-analyses, and guidelines. A grey literature search was undertaken. Two independent reviewers screened articles for selection. Any disagreements were resolved through discussion until consensus was achieved.

Written by Mujoomdar M, Moulton K, and Nkansah E, CADTH, Canada

INAHTA Briefs

Issue 2011/053

Title **Follow-up to the Role of Pharmacologic Management in Neovascular Age-Related Macular Degeneration: Clinical and Cost-Effectiveness**

Agency **CADTH, Canadian Agency for Drugs and Technologies in Health**
Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada;
Tel: +1 613 226 2553, Fax: +1 613 226 5392; publications@cadth.ca, www.cadth.ca

Reference 2009

Aim

To provide an economic update to the assessment of the clinical and cost effectiveness of pharmacologic management in neovascular age-related macular degeneration (AMD).

Conclusions and results

Recent work by CADTH has shown that treatment with ranibizumab may not be perceived as cost effective by Canadian health authorities, but only at the margin. Using a less frequent dosing schedule than those used in clinical studies, treatment with ranibizumab would dominate both photodynamic therapy and pegaptanib strategies. However, policy makers are cautioned that the evidence to support the effectiveness of this strategy is weak. Treatment of patients with AMD using bevacizumab dominates treatment with ranibizumab, assuming that bevacizumab has a similar effect on visual deterioration to that found with ranibizumab, and that the side-effect profile is similar. This is a strong assumption upon which to base the modeling strategy, where little more than anecdotal evidence is available to support it.

Methods

This report provides a further analysis of existing information. A new literature search was not required. Readers are asked to refer to the original report for a complete description of the analytical methods. Several databases were searched, and no limits were placed on language and publication date. Filters were applied to limit retrieval to systematic reviews, meta-analyses, health technology assessments, randomized controlled trials, controlled clinical trials, and economic studies. Internet sources were also searched.

Written by Kymes S, Vollman D, and Spry C, CADTH, Canada

INAHTA Briefs

Issue 2011/054

Title **Computed Tomography for Pediatric Patients: Review of Clinical Effectiveness and Indications for Use**

Agency **CADTH, Canadian Agency for Drugs and Technologies in Health**
Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada;
Tel: +1 613 226 2553, Fax: +1 613 226 5392; publications@cadth.ca, www.cadth.ca

Reference 2009

Aim

To determine the clinical effectiveness of computed tomography (CT) scanners with various numbers of slices for pediatric patients in obtaining acceptable images for diagnosis and minimizing radiation dose for common indications, eg, head CT for trauma, chest CT, cardiac CT, and abdominal CT.

Conclusions and results

We found little published evidence. Although studies on adult populations have been performed, only two multislice computed tomography (MSCT) studies involved pediatric patients and mentioned the number of slices. Based on data from the included studies, the image quality of 64-MSCT and 16-MSCT was comparable, and the 64-slice scanner resulted in reduced radiation exposure. A comparison between a 16-slice MSCT scanner and magnetic resonance imaging (MRI) showed that CT was not as sensitive as diffusion-weighted MRI in detecting brain injuries in children.

Methods

A literature search encompassed key health technology assessment resources, international health technology agencies, and a focused Internet search. The search was limited to articles published in English. The initial search filters were expanded to include observational studies when no relevant articles were identified during the first search. We used the Google search engine to search for information on the Internet. Two independent reviewers screened articles for selection. Any disagreements were resolved through discussion until consensus was achieved.

Further research/reviews required

Well-designed clinical studies are needed to inform evidence-based decisions about using MSCT in a pediatric population. No recent, relevant, clinical practice guidelines were identified. Hence, there is a need to develop guidance for clinicians on the use of MSCT in children.

Written by Chen S, Moulton K, and Spry C, CADTH, Canada

INAHTA Briefs

Issue 2011/055

Title **Fecal Immunochemical Testing in Colorectal Cancer Screening of Average Risk Individuals: Economic Evaluation**

Agency **CADTH, Canadian Agency for Drugs and Technologies in Health**
Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada;
Tel: +1 613 226 2553, Fax: +1 613 226 5392; publications@cadth.ca, www.cadth.ca

Reference 2009

Aim

To determine the cost effectiveness of fecal immunochemical testing (FIT) in colorectal cancer screening of average-risk individuals as compared to fecal occult blood test (FOBT) and colonoscopy and a strategy of no screening.

Conclusions and results

Based on available evidence, FIT appears to be superior to FOBT screening, particularly in detecting polyps. Further study is warranted. Compared to no screening, FIT-mid was associated with a cost per quality-adjusted life year of $4350, which was robust to sensitivity analysis. If jurisdictions implement screening programs using FIT, volume-based contracts could be used to achieve lower prices for the FIT assays. To optimize FIT test performance, programs could include the testing of 2 to 3 stool samples

Methods

This report is a further analysis of existing information that was gathered using the methods that were described in two CADTH reports. Hence, a literature search was not required. The original report includes a complete description of methods and analysis. Base-case, sensitivity, and probabilistic sensitivity analyses were undertaken.

Written by Heitman S, Au F, Hilsden R, and Manns B, CADTH, Canada

INAHTA Briefs

Issue 2011/056

Title **Radioimmunotherapies for Non-Hodgkin Lymphoma: Systematic Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines**

Agency **CADTH, Canadian Agency for Drugs and Technologies in Health**
Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada;
Tel: +1 613 226 2553, Fax: +1 613 226 5392; publications@cadth.ca, www.cadth.ca

Reference 2009

Aim

To determine the clinical and cost effectiveness of using radioimmunotherapies in treating non-Hodgkin lymphoma (NHL) and guidelines for using radioimmunotherapies in the treatment of NHL.

Conclusions and results

Based on the evidence, the use of 131I-tositumomab and 90Y-ibritumomab may be treatment options for patients with refractory or relapsed NHL. The guidelines recommended the use of these drugs in patients with NHL that is refractory to chemotherapy. The cost-effectiveness information, which was not presented from a Canadian perspective, suggests that the use of 131I-tositumomab may be a cost-effective option during third- or fourth-line NHL treatment, depending on a third-party payer's willingness to pay for a quality-adjusted life year. The evidence suggests that the use of 131I-tositumomab and 90Y-ibritumomab be reserved for individuals with follicular NHL whose initial treatment fails to produce a response.

Methods

A literature search encompassed key health technology assessment resources, international health technology agencies, and a focused Internet search. The search was limited to articles published in English. Grey literature was identified by searching the websites of health technology assessment agencies, professional associations, and other specialized databases. These searches were supplemented by hand-searching the bibliographies and abstracts of key papers, and through contacts with appropriate experts and agencies. Two individuals screened and selected articles for inclusion in the report. Any disagreements were resolved through discussion until consensus was achieved.

Written by Pohar R, Clark M, and Nkansah E, CADTH, Canada

INAHTA Briefs

Issue 2011/057

Title **Self-Directed Cognitive Behavioral Therapy for Adults with Diagnosis of Depression: Systematic Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines**

Agency **CADTH, Canadian Agency for Drugs and Technologies in Health**
Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada;
Tel: +1 613 226 2553, Fax: +1 613 226 5392; publications@cadth.ca, www.cadth.ca

Reference 2010

Aim

To determine clinical and cost effectiveness and identify the evidence-based guidelines for using self-directed cognitive behavioral (CBT) therapy in treating adults diagnosed with depression.

Conclusions and results

Overall, the reviewed evidence indicated that self-directed CBT improved the clinical ratings of depressive symptoms, and that it could be a cost-effective therapy option for individuals with mild to moderate depression. Given the limited evidence, it was uncertain whether self-directed CBT was effective in everyone with depression, eg, those with more severe depressive symptoms. Also, it was uncertain whether one form of self-directed CBT was superior to another form of self-directed CBT. This report does not explore factors that optimize the outcomes of self-directed CBT (eg, degree of assistance).

Methods

A literature search encompassed key health technology assessment resources, international health technology agencies, and a focused Internet search. The search was limited to clinical articles published in English. No filters were used to limit retrieval by study type. Grey literature was also searched. Two authors selected articles for inclusion. Any disagreements were resolved through discussion until consensus was achieved.

Written by Boudreau R, Moulton K, and Cunningham J, CADTH, Canada

INAHTA Briefs

Issue 2011/058

Title **Positron Emission Tomography for Cardiovascular Disease: A Review of the Clinical Effectiveness**

Agency **CADTH, Canadian Agency for Drugs and Technologies in Health**
Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada;
Tel: +1 613 226 2553, Fax: +1 613 226 5392; publications@cadth.ca, www.cadth.ca

Reference 2010

Aim

To assess the clinical effectiveness of positron emission tomography (PET) in diagnosing and managing coronary artery disease (CAD); and to identify and assess the quality of the guidelines for using PET to diagnose and manage CAD.

Conclusions and results

PET was found to be a useful tool in diagnosing CAD, particularly in patients with an intermediate likelihood of CAD, those who are obese, or those unable to exercise. The role of PET in identifying patients with CAD who might benefit from revascularization is unclear. A lack of evidence from studies with high internal validity and the quality of the evidence used by guideline development groups may be a consideration when deciding to use PET to diagnose or manage patients with CAD.

Methods

A literature search encompassed key health technology assessment resources, international health technology agencies, and a focused Internet search. The search was limited to articles published in English. Filters were applied to limit the retrieval to systematic reviews, health technology assessments, meta-analyses, randomized controlled trials, controlled clinical trials, observational studies, and guidelines. Two independent reviewers screened articles using predefined criteria. Any disagreements were resolved through discussion until consensus was achieved.

Written by Mujoomdar M, Clark M, and Nkansah E, CADTH, Canada

INAHTA Briefs

Issue 2011/059

Title **Hyperbaric Oxygen Therapy for Difficult Wound Healing: Systematic Review of Clinical Effectiveness and Cost-Effectiveness**

Agency **CADTH, Canadian Agency for Drugs and Technologies in Health**
Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada;
Tel: +1 613 226 2553, Fax: +1 613 226 5392; publications@cadth.ca, www.cadth.ca

Reference 2010

Aim

To examine the clinical and cost effectiveness of hyperbaric oxygen therapy (HBOT) for diabetic pressure ulcers, nondiabetic pressure ulcers, delayed radiation-induced injury, thermal burns, skin grafts and flaps, and post organ transplantation revascularization.

Conclusions and results

Overall, the authors of the identified studies found that HBOT was clinically and cost effective when used to treat patients with diabetes who have chronic ulcers in lower extremities. Overall, the best evidence on the use of adjunctive HBOT was associated with treatment of chronic diabetic wounds. The evidence that supported its use, however, was unreliable. No evidence was identified on the use of HBOT in post organ transplantation revascularization. Despite many recommendations on the use of HBOT as adjunctive treatment for specific indications, there is little evidence on its clinical and economic benefits.

Methods

Multiple databases were searched for information on HBOT. Methodological filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and economic studies. Grey literature sources were also searched. Two authors selected articles for inclusion. Any disagreements were resolved through discussion until consensus was achieved.

Written by Boudreau R, Moulton K, and McGill S, CADTH, Canada

INAHTA Briefs

Issue 2011/060

Title **Epidermal Growth Factor Receptor Mutation Analysis in Advanced Non-Small Cell Lung Cancer: A Review of the Clinical Effectiveness and Guidelines**

Agency **CADTH, Canadian Agency for Drugs and Technologies in Health**
Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada;
Tel: +1 613 226 2553, Fax: +1 613 226 5392; publications@cadth.ca, www.cadth.ca

Reference 2010

Aim

To assess the clinical effectiveness of epidermal growth factor receptor (EGFR) mutation analysis using polymerase chain reaction (PCR) to identify patients with advanced non-small-cell lung cancer (NSCLC) who are likely to respond to treatment with tyrosine kinase inhibitors (TKI); to assess the diagnostic performance of polymerase chain reaction-based methods that are used to evaluate EGFR mutations in patients with advanced NSCLC ; and to assess the quality of guidelines on testing for EGFR mutations in patients with NSCLC.

Conclusions and results

Evidence from observational studies suggests that PCR-based approaches can be used to identify mutations in the EGFR gene with a similar sensitivity to that of direct sequencing. PCR-based tests are likely useful for identifying patients with NSCLC who are likely to respond to treatment with a TKI. In several studies, genetic material was microdissected from tumor-rich areas. This may require additional expertise and incur cost. Most of the studies did not use a commercially available reagent kit. Commercially available kits may have quality-control advantages over assays developed "in-house" as regards quality control in a clinical laboratory setting.

Methods

A literature search encompassed key health technology assessment resources, international health technology agencies, and a focused Internet search. The search was limited to articles published in English. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, observational studies, and guidelines. Two independent reviewers screened articles using predefined criteria. Any disagreements were resolved through discussion until consensus was achieved.

Written by Mujoomdar M, Moulton K, and Spry C, CADTH, Canada

INAHTA Briefs

Issue 2011/061

Title **Epidermal Growth Factor Receptor Mutation Analysis in Advanced Non-Small Cell Lung Cancer: Review of Economic Evaluations and Framework for Economic Analyses**

Agency **CADTH, Canadian Agency for Drugs and Technologies in Health**
Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada;
Tel: +1 613 226 2553, Fax: +1 613 226 5392; publications@cadth.ca, www.cadth.ca

Reference 2010

Aim

To determine how to assess the cost effectiveness of epidermal growth factor receptor (EGFR) mutation analysis in identifying patients with advanced non-small-cell lung cancer who are likely to respond to treatment with tyrosine kinase inhibitors.

Conclusions and results

A framework for a decision analytic cost-utility analysis was developed to assess the cost effectiveness of EGFR mutation analysis compared versus the option of no EGFR mutation analysis. A systematic review of economic studies found limited evidence on the cost effectiveness of the EGFR mutation analysis, and one study (a conference presentation) was reviewed. The proposed modeling framework presented in this report was flexible, allowing analysts to adjust the model for jurisdictional needs in EGFR mutation tests and subsequent therapeutic regimens. With the accumulation of clinical evidence on the test validity and clinical utility of EGFR mutation analysis, analysts will be able to conduct formal cost-effectiveness analyses, which help guide future reimbursement decisions on EGFR mutation analysis.

Methods

A literature search encompassed key health technology assessment resources, international health technology agencies, and a focused Internet search. The search was limited to articles published in English. Filters were applied to limit retrieval to economic studies. Two independent reviewers screened articles using predefined criteria. A framework for a decision analytic cost-utility analysis was developed to assess the cost effectiveness of EGFR mutation analysis versus the option of no EGFR mutation analysis.

Written by Asakawa K, Coyle D, Chen S, Mujoomdar M, and Spry C, CADTH, Canada

INAHTA Briefs

Issue 2011/062

Title **Cost Effectiveness of Blood Glucose Test Strips in the Management of Adult Patients with Diabetes Mellitus**

Agency **CADTH, Canadian Agency for Drugs and Technologies in Health**
Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada;
Tel: +1 613 226 2553, Fax: +1 613 226 5392; publications@cadth.ca, www.cadth.ca

Reference Optimal therapy report; vol. 3 no.3. 2009 May

Aim

To determine the cost effectiveness of blood glucose test strips in managing adult patients with diabetes mellitus.

Conclusions and results

The strength of the economic conclusions is limited by available clinical evidence. Within the limitations of modeling and available data, the report concludes that routine use of self-monitoring of blood glucose (SMBG) in all patients with noninsulin-treated type 2 diabetes mellitus is associated with an incremental cost of $113,643 per quality-adjusted life-year (QALY) gained, relative to no SMBG; and a reduction in the price of blood glucose test strips would improve the cost effectiveness of SMBG. For patients with insulin-treated type 2 diabetes mellitus, results suggest that SMBG testing frequencies beyond 21 test strips per week require large A1C estimates of effect to achieve favorable incremental cost per QALY estimates.

Methods

Prior to conducting this economic analysis, a systematic review was conducted to identify primary studies that compared SMBG with no SMBG, or different frequencies of SMBG, in patients with diabetes. In general, this systematic review elicited few studies that explored the effect of SMBG in patients with insulin-treated diabetes. However, the evidence was more robust for patients with noninsulin-treated type 2 diabetes mellitus. An incremental cost-utility analysis of SMBG using blood glucose test strips, compared with not performing SMBG, was conducted using the UKPDS Outcomes Model.

Further research/reviews required

Further well-designed RCTs are needed to explore the impact of SMBG on health-related quality of life and the incidence of hypoglycemia in patients with either insulin- or noninsulin-treated type 2 diabetes mellitus.

Written by CADTH, Canada

INAHTA Briefs

Issue 2011/063

Title **Systematic Review of Use of Blood Glucose Test Strips for the Management of Diabetes Mellitus**

Agency **CADTH, Canadian Agency for Drugs and Technologies in Health**
Suite 600, 865 Carling Ave, Ottawa, Ontario K1S 5S8 Canada;
Tel: +1 613 226 2553, Fax: +1 613 226 5392; publications@cadth.ca, www.cadth.ca

Reference Optimal therapy report; vol. 3 no.2. 2009 May

Aim

To identify and synthesize the available clinical evidence on the efficacy, safety, and optimal frequency of self-monitoring of blood glucose (SMBG) in patients with type 1, type 2, and gestational diabetes.

Conclusions and results

Within the limitations of available evidence, this report concludes the use of SMBG appears to be associated with improvements in glycemic control among patients with insulin-treated type 2 diabetes. Use of SMBG in patients with type 2 diabetes who are not using insulin is associated with a statistically significant, albeit clinically modest, improvement in glycemic control. Performing SMBG may reduce the number of symptomatic hypoglycemic events in patients using sulfonylureas. There was little or no evidence that SMBG provides other benefits, eg, improved quality of life, or greater patient satisfaction. Longer-term studies are needed to determine whether or not SMBG reduces diabetes-related clinical endpoints or mortality. Studies of specific subgroups within this population who may be more likely to benefit from SMBG are also warranted. The effect of using SMBG in women with gestational diabetes requires further investigation.

Methods

A systematic review encompassed randomized controlled trials and observational studies comparing SMBG with no SMBG, or comparing different SMBG frequencies. Studies were identified through electronic databases, grey literature, reference lists, and stakeholder consultation. Meta-analyses were conducted to pool trial results, when appropriate.

Further research/reviews required

No studies attempted to measure the degree to which subjects actually implemented the advice given on appropriate implementation of SMBG results. Future studies should explore this area. Also, future trials reporting patient compliance with self-interpretation and application of SMBG results could provide valuable information to optimize the use of blood glucose test strips.

Written by CADTH, Canada

INAHTA Briefs

Issue 2011/064

Title **MAVARIC - A Comparison of Automation-Assisted and Manual Cervical Screening: A Randomized Controlled Trial**

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Reference Volume 15.03. ISSN 1366-5278. www.hta.ac.uk/project/1462.asp

Aim

To compare automation-assisted reading of cervical cytology with manual reading using the histological endpoint of cervical intraepithelial neoplasia grade II (CIN2) or worse (CIN2+). Secondary objectives included assessing the slide ranking facility of the Becton Dickinson (BD) FocalPoint™ Slide Profiler, especially "No Further Review" (NFR), and automated versus manual in terms of productivity and cost effectiveness.

Conclusions and results

The proportion of abnormal cytology management results by grade were: borderline, 3.6%; mild dyskaryosis, 2.4%; and moderate and severe dyskaryosis combined, 1.22%. These were similar to England as a whole. Non-negative cytology amounted to 5.47% in the paired arm and 5.52% in the manual-only arm. In the paired arm, the proportion of discordant pairs on final result was 3.8% (1850/48 271); for 1.3% (625/48 271); the discordance was between inadequate and negative. Discordant pairs occurred in both directions with respect to manual and automated reading. There were 192 additional low-grade/HPV-positive abnormalities detected by manual reading only (manual positive/auto negative) and 47 additional high-grade abnormalities detected by manual reading only in the paired arm. The overall referral rate to colposcopy was 4.7%. The proportion with CIN2+ was 1.6% (398/24 566) and 1.5% (707/48 271) for the manual and paired arms respectively (p=0.10). The primary outcome of the relative sensitivity for CIN2+ of automated reading compared with manual reading in the paired arm was 0.92 (95% confidence interval [CI] 0.85 to 0.95). Relative specificity was 1.006 (95% CI 1.005 to 1.007). Productivity in terms of the number of slides read per day by primary screeners was estimated to be 60% to 80% higher for automated reading than for manual reading. The overall costs per case of CIN2+ detected were almost identical between automated and manual reading (2892 pounds sterling [GBP], 95% CI GBP 2720 to GBP 3098; and GBP 2838, 95% CI GBP 2676 to GBP 3030 respectively). The overall costs per case of cervical intraepithelial neoplasia grade III (CIN3) or worse (CIN3+) detected are also similar between automated and manual reading (GBP 4762, 95% CI GBP 4378 to GBP 5245; and GBP 4775, 95% CI GBP 4400 to GBP 5244 respectively). Hence, manual screening is slightly more expensive and effective, and could be considered cost effective compared to automated reading if decision makers were willing to pay at least GBP 5000 for each additional case of CIN2+ detected. NFR in the BD FocalPoint GS Imaging System was reported in 22% of slides and was a reliable indicator of the absence of underlying disease, with only 3.1% of detected CIN2+ being missed by NFR, and even more so if NFR was restricted to routine screening slides. When both savings in staff time to read slides and the additional equipment costs were taken into account, utilizing the NFR option generated cost savings.

Recommendations

See Executive Summary link www.hta.ac.uk/project/1462.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/1462.asp.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1462.asp.

Written by Professor Henry Charles Kitchener, University of Manchester, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/065

Title **Palivizumab for Immunoprophylaxis of Respiratory Syncytial Virus (RSV) Bronchiolitis in High-Risk Infants and Young Children: Systematic Review and Additional Economic Modeling of Subgroup Analyses**

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Reference Volume 15.05. ISSN 1366-5278. www.hta.ac.uk/project/2056.asp

Aim

To estimate the cost effectiveness of immunoprophylaxis of respiratory syncytial virus (RSV) using palivizumab in different subgroups of children with or without chronic lung or heart disease (CLD or CHD) who are at high risk of serious morbidity from RSV infection.

Conclusions and results

Thirteen studies were included. Analysis of 16 128 subgroups showed that prophylaxis with palivizumab may be cost effective at a willingness-to-pay threshold of 30 000 pounds sterling (GBP)/quality-adjusted life-year (QALY) for some subgroups. For example, for children without CLD or CHD, the cost-effective subgroups included those <6 weeks old at the start of the RSV season who had at least 2 other risk factors that were considered in this report and were born at 24 weeks gestational age (GA) or less, but did not include children aged >9 months at the start of the RSV season or had a GA of >32 weeks. For children with CLD, the cost-effective subgroups included children aged <6 months at the start of the RSV season who were born at 28 weeks GA or less, but did not include children aged >21 months at the start of the RSV season. For children with acyanotic CHD, the cost-effective subgroups included children aged <6 months at the start of the RSV season who were born at 24 weeks GA or less, but did not include children aged >21 months at the start of the RSV season. For children with cyanotic CHD, the cost-effective subgroups included children aged <6 weeks at the start of the RSV season who were born at 24 weeks GA or less, but did not include children aged >12 months at the start of the RSV season. Prophylaxis with palivizumab does not represent good value for money based on the current UK incremental cost-effectiveness ratio threshold of GBP 30 000/QALY when used unselectively in children without CLD/CHD or children with CLD or CHD. In summary, the cost-effective subgroups for children who had no CLD or CHD must contain at least 2 other risk factors apart from GA and birth age. The cost-effective subgroups for children who had CLD or CHD do not necessarily need to have any other risk factors except GA and birth age.

Recommendations

See Executive Summary link www.hta.ac.uk/project/2056.asp.

Methods

Searches were conducted for prognostic and hospitalization studies from 1950 to 2009. The database of all references from the original report was sifted to find any relevant studies that might have been missed. Risk factors identified from the systematic review of included studies were analyzed and synthesized using STATA. The base-case decision-tree model developed in the original HTA journal publication was used to derive the cost effectiveness of immunoprophylaxis of RSV using palivizumab in different subgroups of preterm infants and young children at high risk of serious morbidity from RSV infection. Cost-effective spectra of prophylaxis with palivizumab compared to no prophylaxis were derived for children without CLD/CHD, children with CLD, children with acyanotic CHD, and children with cyanotic CHD.

Further research/reviews required

For further details see Executive Summary link www.hta.ac.uk/project/2056.asp.

Written by Dr Catherine Meads, University of London, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/066

Title **Etanercept, Infliximab and Adalimumab for the Treatment of Psoriatic Arthritis: A Systematic Review and Economic Evaluation**

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Reference Volume 15.10. ISSN 1366-5278. www.hta.ac.uk/project/2053.asp

Aim

To determine the clinical effectiveness, safety, and cost effectiveness of etanercept, infliximab, and adalimumab in treating active and progressive psoriatic arthritis (PsA) in patients who respond inadequately to standard treatment (including disease-modifying antirheumatic drugs).

Conclusions and results

Pooled estimates of effect demonstrated a significant improvement in patients with PsA for all joint disease and functional status outcomes at 12 to 14 weeks' follow-up. Biologic treatment significantly reduced joint symptoms for etanercept (relative risk [RR] 2.60, 95% confidence interval [CI] 1.96 to 3.45), infliximab (RR 3.44, 95% CI 2.53 to 4.69) and adalimumab (RR 2.24, 95% CI 1.74 to 2.88), with 24-week data demonstrating maintained treatment effects. Trial data demonstrated a significant effect of all 3 biologics on skin disease at 12 or 24 weeks. Evidence synthesis showed that infliximab appeared to be most effective across all outcomes of joint and skin disease. The response in joint disease was greater with etanercept than with adalimumab, whereas the response in skin disease was greater with adalimumab than with etanercept, but the differences are not statistically significant. Under base-case assumptions, etanercept was the most likely cost-effective strategy for patients with PsA and mild-to-moderate psoriasis if the threshold for cost effectiveness was 20 000 pounds sterling (GBP) or GBP 30 000 per QALY. All biologics had a similar probability of being cost effective for patients with PsA and moderate-to-severe psoriasis at a threshold of GBP 20 000 per QALY. The data indicated that etanercept, infliximab, and adalimumab were efficacious in treating PsA compared to placebo, with beneficial effects on joint symptoms, functional status, and skin. Short-term data suggested that these biologic agents can delay joint disease progression and evidence to support their use in treating PsA is convincing. Future research would benefit from long-term observational studies with large samples of patients with PsA to demonstrate that beneficial effects are maintained, along with further monitoring of the safety profiles of the biologic agents.

Recommendations

Long-term observational studies with large samples of PsA patients are required to demonstrate that beneficial effects for joint and skin disease and improvement of function are maintained. In particular, data on the effects of joint disease progression and long-term Health Assessment Questionnaire progression while responding to biologic agents and health-related quality of life are required. Withdrawal rates due to lack of efficacy and adverse events should also be reported.

Methods

The evidence on clinical efficacy, safety, and cost effectiveness of etanercept, infliximab, and adalimumab in treating PsA was systematically reviewed. Ten electronic databases (eg, MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials) were systematically searched for data up to June 2009. Industry submissions were searched for additional unpublished data. Randomized controlled trials (RCTs) (including open-label extensions) were included in the evaluation of efficacy. Safety data were sought from RCTs and observational studies reporting serious adverse events (eg, infections, malignancies, and tuberculosis activation) for a minimum of 500 patients in any indication receiving one or more of the biologic agents of interest.

Further research/reviews required

See Executive Summary www.hta.ac.uk/project/2053.asp.

Written by Mr Mark Rodgers, University of York, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/067

Title **Adalimumab, Etanercept, Infliximab, Rituximab and Abatacept for the Treatment of Rheumatoid Arthritis After The Failure of a Tumor Necrosis Factor Inhibitor: A Systematic Review and Economic Evaluation**

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Reference Volume 15.14. ISSN 1366-5278. www.hta.ac.uk/project/2055.asp

Aim

To assess the clinical and cost effectiveness of adalimumab (ADA), etanercept (ETN), infliximab (IFX), rituximab (RTX), and abatacept (ABT) in patients with RA who have tried conventional agents, but failed to improve after a first tumor necrosis factor (TNF) inhibitor.

Conclusions and results

The systematic review included 35 studies: 5 randomized controlled trials (RCTs), 1 comparative study, 1 controlled study, and 28 uncontrolled studies. One RCT (REFLEX) assessed the effectiveness of RTX. At 6 months significantly more patients treated with RTX achieved ACR 20 (relative risk [RR]=2.85, 95% confidence interval [CI] 2.08 to 3.91) and ACR70 (RR=12.14, 95% CI 2.96 to 49.86) response compared with placebo. Differences between groups in favor of RTX were observed at 6 months for mean change from baseline in Disease Activity Score 28 (DAS28) (mean difference –1.50, 95% CI –1.74 to –1.26) and in Health Assessment Questionnaire (HAQ) score (mean difference –0.30, 95% CI –0.40 to –0.20). One RCT (ATTAIN) assessed the effectiveness of ABT. At 6 months significantly more patients treated with ABT achieved ACR20 (RR=2.56, 95% CI 1.77 to 3.69) and ACR70 (RR=6.70, 95% CI 1.62 to 27.80) compared to those treated with placebo. Significant differences between groups in favor of ABT were observed at 6 months for mean change from baseline in DAS28 score (mean difference –1.27, 95% CI –1.62 to –0.93) and in HAQ score (mean difference –0.34, insufficient data to calculate 95%CI). Twenty-eight uncontrolled studies observed improvement in patients who switched to ADA, ETN, or IFX after discontinuing previous TNF inhibitor(s). The systematic review included 4 studies on cost-effectiveness. Independent economic evaluation undertaken by the assessment group showed that compared with disease-modifying antirheumatic drugs, the incremental cost-effectiveness ratios (ICERs) were 34 300 pounds sterling (GBP) per quality-adjusted life-year (QALY) for ADA, GBP 38 800 for ETN, GBP 36 200 for IFX, GBP 21 200 for RTX, and GBP 38 600 for ABT. RTX dominates the TNF inhibitors and the ICER for ABT compared with RTX is over GBP 100 000 per QALY. RCT evidence suggests that RTX and ABT are more effective than supportive care. Data from observational studies suggest that use of an alternative TNF inhibitor may offer some benefit, but uncertainties remain as to the magnitude of treatment effects and their cost effectiveness. Future research should include head-to-head trials comparing the clinical and cost effectiveness of the technologies against each other and emerging biologics.

Recommendations

See Executive Summary www.hta.ac.uk/project/2055.asp.

Methods

Clinical effectiveness: A systematic review of primary studies (excluding nonrandomized studies with <20 patients in a treatment arm) was undertaken. Databases searched included the Cochrane Library, MEDLINE, and EMBASE and other sources up to July 2009. Further data were obtained from dossiers submitted to NICE by manufacturers of the technologies. Inclusion decisions, quality assessment, and data extraction were undertaken according to predefined criteria. Owing to heterogeneity between studies and insufficient data, results were not pooled. Cost effectiveness: A systematic review of published studies on the costs and cost effectiveness of the technologies and a review of the dossiers submitted to NICE by the manufacturers were undertaken. Model-based economic evaluations of the cost effectiveness of the technologies from the perspective of the UK National Health Service (NHS) were carried out.

Further research/reviews required

See Executive Summary www.hta.ac.uk/project/2055.asp.

Written by Dr Yen-Fu Chen, Epidemiology & Biostatistics Unit, University of Birmingham, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/068

Processes in Recruitment to Randomized Controlled Trials of Medicines for Children (RECRUIT): A Qualitative Study

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Reference Volume 15.15. ISSN 1366-5278. www.hta.ac.uk/project/1530.asp

Aim

To investigate clinical trial recruitment processes from the perspective of parents, young people, and practitioners to identify strategies to improve recruitment and its conduct across the spectrum of trials of medicines for children.

Conclusions and results

Practitioners were concerned to avoid overburdening parents, and some indicated that they found approaching families about trials to be aversive. By contrast, parents did not mind being asked about trials and did not describe the approach as burdensome. Some parents viewed the trial approach as a positive opportunity. Parents and young people took little active part in the trial discussions and asked few questions. They were satisfied with how they had been approached, and spoke of how they had felt involved, valued, cared for, and comfortable to interject during the discussion. Yet, we identified several parents who had important misunderstandings about the trial. We found few differences between parents who consented and those who declined a trial. Parents' trial decisions were influenced by their perceptions of the trial in relation to their child's safety and well-being, potential benefits to the child and family, potential benefits to others, and the practicality of participation. Of these, parents' main consideration was safety. Parents', young people's and practitioners' views of what was important when considering a trial were broadly convergent, but families gave greater importance than practitioners to the trial's practical requirements. All parties highly valued the face-to-face trial discussion and wanted shorter, less complex, written information. Parents did not feel pressured by the trial team to participate, but some described how their personal values made them reluctant to decline. Several parents who declined described a passing sense of discomfort with the decision. Concerns of some practitioners that families would be overburdened were unfounded; parents did not object to being asked about research. Practitioners may benefit from support that helps them feel personally more at ease in approaching families about trials. Parents and young people often described the trial discussions in strongly positive terms and emphasized the importance of the social and emotional aspects of these encounters. Informed consent training could be enhanced if it similarly emphasized these aspects of recruitment; the misunderstandings we identified indicate how this training could help practitioners improve the clarity of their trial discussions with families. Guidelines on informed consent documents should note that all groups thought that these documents should be shorter and more straightforward.

Recommendations

See Executive Summary www.hta.ac.uk/project/1530.asp.

Methods

This qualitative interview and observational study (RECRUIT) ran alongside 4 diverse trials of medicines for children. Data were verbatim transcripts of (1) audio-recorded trial recruitment discussions between practitioners and families (n=41) and (2) semistructured interviews exploring the experience of trial recruitment from the perspective of parents (62 individuals from 60 families), young people (n=22), and recruiting practitioners (19 doctors and 12 research nurses). Of the 60 families, 39 were randomized and on trial, 10 declined, 3 were randomized but withdrew, and 8 were ineligible. Interpretive analyses using the general principles of the constant comparative method were combined with descriptive summaries of recorded trial discussions comprising some quantitative measures.

Further research/reviews required

See Executive Summary www.hta.ac.uk/project/1530.asp.

Written by Dr Valerie Shilling, University of Liverpool, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/069

Title **Peginterferon Alfa and Ribavirin for Chronic Hepatitis C in Patients Eligible for Shortened Treatment, Re-Treatment or in HCV/HIV Co-Infection: A Systematic Review and Economic Evaluation**

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Reference Volume 15.17. ISSN 1366-5278. www.hta.ac.uk/project/2043.asp

Aim

To assess the clinical and cost effectiveness of peginterferon alfa and ribavirin in treating chronic hepatitis C virus (HCV) in 3 specific patient subgroups affected by recent license changes: those eligible for shortened treatment courses, ie, those with low viral load (LVL) and who attained a rapid virological response (RVR) at 4 weeks of treatment; those eligible for re-treatment following previous nonresponse or relapse; and those co-infected with human immunodeficiency virus (HIV).

Conclusions and results

In total, 2400 references were identified. The review of clinical effectiveness included 6 good-quality RCTs that fulfilled the inclusion criteria, all reporting peginterferon alfa and ribavirin therapy in patients eligible for shortened treatment. No RCTs comparing peginterferon and ribavirin with BSC were identified for the re-treatment or co-infection populations. The results suggest that chronic HCV patients who have LVL at baseline and who achieve an RVR can be treated with shortened courses of therapy (24 weeks for genotype 1, 16 weeks for genotype 2/3) and achieve SVR rates that are comparable to those who receive the standard duration of treatment (ranges 84%–96% vs 83%–100%, respectively). Since patient numbers in the LVL/RVR subgroups were small, and none of the trials was powered for this subgroup analysis, the results should be interpreted with caution. In the one trial reporting virological relapse rates in the subgroup of patients with LVL/RVR, rates were low and not statistically significantly different between those treated for 24 versus 48 weeks (3.6% vs 0%, respectively, difference 3.6%, 95% confidence interval [CI] –7.2% to 6.6%, p = 1.000). A Markov state-transition model estimated the cost effectiveness of treatment strategies for each subgroup of patients with HCV. In the cost-effectiveness analysis of shortened treatment with peginterferon alfa-2a, incremental cost-effectiveness ratios (ICERs) ranged from 35 000 pounds sterling (GBP) to GBP 65 000 for patients with genotype 1, whereas in patients with genotypes 2 and 3 shortened treatment dominated standard treatment. For patients with genotype 1 with LVL/RVR, shortened treatment with peginterferon alfa-2b dominated standard treatment. In patients with genotype 1 and those with genotype non-1 who were re-treated with peginterferon alfa-2a, the ICERs were GBP 9169 and GBP 2294, respectively. In patients with genotypes 1 and 4, who were re-treated with peginterferon alfa-2b, the ICER was GBP 7681, whereas re-treatment dominated BSC for patients with genotypes 2 and 3. In patients co-infected with HCV/HIV, who were receiving peginterferon alfa-2a, the ICER was GBP 7941 per quality-adjusted life-year (QALY) gained in patients with genotypes 1 and 4; whereas in patients with genotypes 2 and 3, peginterferon alfa-2a dominated BSC. In co-infected patients receiving peginterferon alfa-2b the ICER was GBP 11 806 in genotypes 1 and 4, and GBP 2161 in genotypes 2 and 3.

Recommendations

See Executive Summary link www.hta.ac.uk/project/2043.asp.

Methods

See Executive Summary link www.hta.ac.uk/project/2043.asp.

Further research/reviews required:

Further RCT evidence is needed, particularly in people who have not responded to, or relapsed following, treatment.

Written by Dr Debbie Hartwell, SHTAC, University of Southampton, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/070

Title **Observational Study to Investigate Vertically Acquired Passive Immunity in Babies of Mothers Vaccinated Against H1N1v During Pregnancy**

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Reference Vol. 14.55(01). ISSN 1366-5278.
www.netscc.ac.uk/supporting_research/flu_project_portfolio/0984136.asp

Aim

To determine the proportion of babies who acquired passive immunity to A/H1N1v, born to mothers who accepted vaccination as part of the national vaccination program while pregnant (during the second and/or third trimesters) against the novel A/H1N1v influenza virus (exposed group) compared with unvaccinated (unexposed) mothers.

Conclusions and results

The primary endpoint in the study was the serological results of the cord blood samples for immunity to A/H1N1v. The results from this study demonstrate evidence of background humoral immunity in babies of unvaccinated mothers of 25% to 30%. Humoral immunity in babies of vaccinated mothers was present in 80% of the group. The difference in positive immunity between the babies of unvaccinated and vaccinated mothers was statistically significant (X2, p <0.001).

This study provides evidence that maternal vaccination against monovalent A/H1N1v can provide humoral immunity to the unborn child that may protect the baby against acquiring the infection early in infancy when treatment options for infection are limited (because antiviral medications and immunization are not licensed, have theoretical unwanted effects, or might not be effective in this age group). The study findings reveal a highly significant difference in HI titers between babies born to mothers vaccinated with pandemic-specific vaccine against A/H1N1v during the 2009 to 2010 pandemic period. The results will provide support to policy makers and clinicians in advocating immunization for pregnant women in future influenza epidemic and pandemic events and will help pregnant women make informed choices about vaccination under such circumstances.

Recommendations

Continued circulation of 2009 A/H1N1-like viruses is uncertain, but is possible as seasonal influenza in years to come. It is possible that future seasonal waves may display increased virulence. Given the adverse outcomes experienced for a small proportion of pregnant women during the influenza pandemic of 2009 to 2010, this study provides useful evidence to support vaccination in pregnancy to protect both the mother and baby.

Methods

See Executive Summary www.netscc.ac.uk/supporting_research/flu_project_portfolio/0984136.asp.

Further research/reviews required

See Executive Summary www.netscc.ac.uk/supporting_research/flu_project_portfolio/0984136.asp.

Written by Dr Richard Puleston, University of Nottingham, NETSCC, United Kingdom

INAHTA Briefs

Issue 2011/071

Title **Growth Monitoring for Short Stature: Update of a Systematic Review and Economic Model**

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Reference Volume 15.11. ISSN 1366-5278. www.hta.ac.uk/project/2230.asp

Aim

To compare different screening rules and/or referral cut-offs for identifying children with disorders of short stature. We updated a previous systematic review and economic model that addressed the same question.

Conclusions and results

The systematic review included 1 study. The study was not UK based, but had been identified in the brief as relevant to the UK setting. The study's authors examined the performance of several rules to determine sensitivity and specificity of referral for short stature in 4 patient groups and 3 reference groups in the Netherlands. They derived an algorithm for referral based on the optimal rules. No new studies were located that provided appropriate quality-of-life or utilities data for the economic model. The model was based on the previous assessment, which was updated to better reflect current clinical practice in the UK. We compared 2 alternative monitoring strategies – one based on the study identified in our systematic review (Grote strategy) and the other based on UK consensus (UK strategy). We identified that the UK strategy was the least effective and least costly, with a mean gain of 0.001 QALYs at a mean cost of 21 pounds sterling (GBP). The Grote strategy was both more expensive and more effective, with a mean cost of GBP 68 and a mean QALY gain of 0.042. The incremental cost-effectiveness ratio was GBP 1144 per QALY gained. This assessment contributes further knowledge, but does not provide definitive answers on how to monitor growth. Considerable variation and uncertainty remains around current growth screening practices in the UK. We were unable to evaluate (through the use of identified studies and modeling) an optimal referral cut-off and age at which to screen. We identified several research questions that would further inform referral strategies, which would involve further primary and secondary data collection.

Recommendations

See Executive Summary www.hta.ac.uk/project/2230.asp.

Methods

We undertook a systematic review to identify studies that compared growth monitoring/screening strategies. This review updates our previous assessment – Fayter D, et al. A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions. Health Technol Assess 2007;11(22). Our search covered a range of databases from January 2005 to November 2009 with no language or publication restrictions. As part of our search strategy, we aimed to identify new studies containing quality-of-life/utilities data to use in the economic model. Two reviewers examined full papers for relevance. One reviewer extracted data and one checked the data, and authors were contacted for supplementary information where required. We summarized the results narratively. We developed a probabilistic decision analytic model to estimate the costs and quality-adjusted life-year (QALY) gains. The model adopted the perspective of the UK NHS and personal social services. The price year was 2009, and we used an annual discount rate of 3.5%. The model was a cohort model, assuming a homogeneous population of 5-year-olds at baseline.

Further research/reviews required

See Executive Summary www.hta.ac.uk/project/2230.asp.

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