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Introduction

The International Network of Agencies for Health Technology Assessment (INAHTA) is a global network linking 41 non-profit, governmental institutions from 21 countries (2005).

INAHTA was established in 1993 with the aim

- To accelerate exchange and collaboration among HTA agencies
- To promote information sharing and comparison
- To prevent unnecessary duplication of activities.

The mission of INAHTA is

"To provide a forum for the identification and pursuit of interests common to health technology assessment agencies."

The INAHTA membership is open to any organization which

- Assesses technology in health care
- Is a non-profit organization
- Relates to a regional or national government
- Receives at least 50% of its funding from public sources.

The Network stretches from the USA, Canada, and Latin America to Europe, Australia, and New Zealand. The Secretariat is located at SBU in Sweden.

Further information on INAHTA is available at www.inahta.org

Title **Clinical and Cost Effectiveness of Capecitabine and Tegafur With Uracil for the Treatment of Metastatic Colorectal Cancer: Systematic Review and Economic Evaluation**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
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Reference Health Technol Assess 2003;7(32). Nov 2003. www.ncchta.org/execsumm/summ732.htm

Aim

To evaluate the clinical and cost effectiveness of capecitabine and tegafur with uracil (UFT/LV) as first-line treatments for patients with metastatic colorectal cancer, as compared with 5-fluorouracil/folinic acid (5-FU/FA) regimens.

Conclusions and results

Capecitabine treatment appeared to improve overall response rates and the adverse effect profile compared to 5-FU/LV treatment with the Mayo regimen, except in hand–foot syndrome. Time to disease progression or death after UFT/LV treatment was shorter (1 study) than after 5-FU/LV treatment with the Mayo regimen. Neither capecitabine nor UFT/LV improved health-related quality of life. The estimated total cost of capecitabine and UFT/LV treatments were compared with the cost of the Mayo regimen. Cost estimates were also presented for the modified and inpatient de Gramont regimens. RCTs showed no survival advantage from the oral drugs against the Mayo regimen. Cost savings of capecitabine and UFT/LV over the Mayo regimen were estimated. Drug acquisition costs were higher for the oral therapies than for the Mayo regimen, but were offset by lower administrative costs. Costs to treat adverse events were similar across the three regimens. Indirect comparison inferred no survival difference between oral drugs and the de Gramont regimens. Cost savings were estimated for capecitabine and UFT/LV over the modified and inpatient de Gramont regimens.

Recommendations

The results show a potential cost savings associated with oral therapies. No survival difference has been proven between oral drugs and the Mayo regimen. Evidence of a survival difference between the Mayo regimen and the de Gramont regimens was not identified. Improved progression-free survival and an improved adverse event profile have been shown for the de Gramont regimen over the Mayo regimen.

Methods

Systematic searches, selection against criteria, and quality assessment were used to obtain data from relevant studies. Costs were estimated through resource-use data from published trials and unpublished sponsor submissions. Unit costs were taken from published sources. The cost-effectiveness of capecitabine and UFT/LV was compared with three intravenous 5-FU/LV regimens widely used in the UK: the Mayo, the modified de Gramont (outpatient) regimen, and the inpatient de Gramont regimens.

Further research/reviews required

Inclusion of quality of life data in trials of colorectal cancer treatments The place of effective oral treatments in treating colorectal cancer. The safety mechanisms needed to ensure compliance and the monitoring of adverse effects. The optimum duration of treatment. The measurement of patient preferences. A phase III comparative trial of capecitabine and UFT/LV versus modified de Gramont treatment to determine survival advantage and to collate necessary economic data.

Written by Ms Sue Ward, School of Health and Related Research, University of Sheffield, UK

Title **Literature Searching for Clinical and Cost-effectiveness Studies used in Health Technology Assessment Reports Carried out for the National Institute for Clinical Excellence Appraisal System**

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Reference Health Technol Assess 2003;7(34). Nov 2003. www.ncchta.org/execsumm/summ734.htm

Aim

To contribute toward making searching for Technology Assessment Reports (TARs) more cost effective by suggesting an optimum literature retrieval strategy.

Conclusions and results

The median number of sources searched per TAR was 20. Six sources (CCTR, DARE, EMBASE, MEDLINE, NHS EED, and sponsor/industry submissions to National Institute for Clinical Excellence) were used in all reviews. Searching the MEDLINE, EMBASE, and NHS EED databases yielded 87.3% of the clinical effectiveness studies and 94.8% of the cost-effectiveness studies, rising to 98.2% when SCI, BIOSIS, and ASCO Online and 97.9% when SCI and ASCO Online, respectively, were added. The median number of sources searched for the 14 TARs that included an economic model was 9.0 per TAR. A sensitive search filter for identifying non-randomized controlled trials (RCT) retrieved only 85% of the known sample. In searching for non-RCT studies we recommend searching for the intervention alone and then scan records manually for those that look relevant.

Recommendations

Searching databases beyond the Cochrane Library, MEDLINE, EMBASE, and SCI (plus BIOSIS meeting abstracts) was seldom effective in retrieving additional studies for the clinical and cost-effectiveness sections of TARs (apart from reviews of cancer therapies, where searching the ASCO database is recommended). A more selective approach to database searching would make the TAR process more efficient. Searching non-database sources appears to be a productive way to identify further studies.

Methods

All sources used to search for clinical and cost-effectiveness studies were recorded. All studies in the clinical and cost-effectiveness sections of the TARs were identified, and their characteristics recorded. Each was also classified by publication type, and checked to see whether it was indexed in the following databases: MEDLINE, EMBASE, and then either the Cochrane Controlled Trials Register (clinical effectiveness studies) or the NHS Economic Evaluation Database (cost-effectiveness studies). Any study not found in at least one of these databases was checked to see whether it was indexed in the Science Citation Index (SCI) and BIOSIS, and the American Society of Clinical Oncology (ASCO) Online if a cancer review. Any studies still not found were checked to see whether they were in other databases.

Further research/reviews required

Prospective studies of many topics to investigate the effectiveness of extended searches in identifying extra studies. Testing the generalizability of findings from this study in an international context by comparative analysis on TARs from other INAHTA agencies. Assessing the quality of search strategies used in systematic reviews. Developing and testing search filters to retrieve different types of non-RCT studies. A followup study to find the proportion of unpublished drug company studies that are eventually published, and whether the conclusions of the published versions differ from the commercial in confidence versions.

Written by Dr Pam Royle, Dept of Public Health, University of Aberdeen, UK

Title **Redesigning Postnatal Care: A Randomized Controlled Trial of Protocol-based, Midwifery-led Care Focused on Individual Women's Physical and Psychological Health Needs**

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Reference Health Technol Assess 2003;7(37). Nov 2003. www.ncchta.org/execsumm/summ737.htm

Aim

To develop, implement, and test the cost effectiveness of redesigned postnatal care compared with current care on women's physical and psychological health.

Conclusions and results

At 4 and 12 months postpartum, the mean SF36 Mental Component Score (MCS) and Edinburgh Postnatal Depression Scale (EPDS) scores were significantly better in the intervention group, and the proportion of women with an EPDS score of 13+ (indicative of probable depression) was significantly lower relative to controls. The physical health score (SF36 -PCS) did not differ. Use of health services was significantly lower in the intervention group as was psychological morbidity reported at 12 months. Women's views about care were either more positive or did not differ. Intervention midwives were more satisfied with redesigned care than control midwives were with standard care. Intervention care was cost effective since outcomes were better and costs did not differ substantially.

Recommendations

The redesigned community postnatal care led by midwives, and delivered over a longer period, resulted in an improvement in women's mental health at 4 months postpartum, which persisted at 12 months and at an equivalent overall cost. There were fewer GP consultations during the first year in the intervention group, but no difference was detected in the physical health score used.

Methods

A cluster randomized controlled trial used general practice as the unit of randomization. Recruited women were followed up by postal questionnaire at 4 and 12 months postpartum, and further data were collected from midwife and general practice sources. Women's health problems were systematically identified and managed, led by midwives with general practitioner contact only when required. Symptom checklists and the EPDS were used at times to maximize the identification of problems and individual care and visit plans based on needs. Evidence based guidelines were used to manage needs. Care was delivered over a longer period.

Further research/reviews required

A summary is presented in the report.

Written by Prof Christine MacArthur, Department of Public Health & Epidemiology, University of Birmingham, UK

Title **Estimating Implied Rates of Discount in Healthcare Decision Making**

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Reference Health Technol Assess 2003;7(38). Nov 2003. www.ncchta.org/execsumm/summ738.htm

Aim

To consider whether implied rates of discounting from the perspectives of individual and society differ, and whether implied rates of discounting in health differ from those implied in choices involving finance or 'goods'.

Conclusions and results

The literature review revealed few empirical studies in representative samples of the population, few direct comparisons of public with private decision making, and few direct comparisons of health with financial discounting. Implied rates of discounting varied widely, and studies suggested that discount rates are higher the smaller the value of the outcome and the shorter the period considered. The relationship between implied discount rates and personal attributes was mixed, possibly reflecting the limited nature of the samples. Although direct comparisons were few, some studies found that individuals apply different rates of discount to social versus private, and health versus financial comparisons. The present study also found a wide range of implied discount rates, with little systematic effect of age, gender, educational level, or long-term illness. Both samples presented evidence that people chose a lower discount rate in comparisons made on behalf of society than in comparisons made for themselves. Both public and health professional samples tended to choose lower discount rates in health-related comparisons than in finance-related comparisons. Responses derived from hypothetical questions suggested that the detail of question framing could influence the implied rates of discount.

Recommendations

The study suggested that both the lay public and healthcare professionals consider that the discount rate appropriate for public decisions is lower than that for private decisions. This finding suggests that both lay people and healthcare professionals (who are used to making decisions on behalf of others) recognize that society is not simply an aggregate of individuals. It also implies a general appreciation that society is more stable and has a more predictable future than does the individual. There is fairly general support for this view in the theoretical literature and limited support in the few previous direct comparisons.

Methods

The study comprised a review of economics, health economics, and social science literature and also an empirical estimate of implied rates of discounting in four fields: personal financial, personal health, public financial, and public health, in samples representative of the public and of healthcare professionals.

Further research/reviews required

Further research is indicated, possibly involving more in-depth interviewing and drawing inference on real, rather than hypothetical, choices.

Written by Dr Robert West, Wales Heart Research Institute, University of Wales College of Medicine, UK

Title	**S.R.I.S. – Systematic Review of Isolation Policies and Screening Practices in Methicillin-Resistant S. Aureus Management**
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Reference	Health Technol Assess 2003;7(39). Nov 2003. www.ncchta.org/execsumm/summ739.htm

Aim

To review the evidence for the effectiveness of different isolation policies and screening practices in reducing the incidence of MRSA colonization and infection in hospital inpatients, and to develop transmission models to study the effectiveness and cost effectiveness of isolation policies in controlling MRSA.

Conclusions and results

Few pre-planned prospective intervention studies were found, and most failed to assess and adjust for confounding factors and intrinsic biases. Meta-analysis was not appropriate due to heterogeneity between studies. We identified over 4,000 studies, of which 46 met the criteria for data extraction. The studies were rated as presenting "weak evidence", "evidence", or "stronger evidence" that their interventions affected MRSA levels. The effect of isolation could not be assessed in 1/3 of the studies. Evidence in most of the remaining studies was consistent with isolation reducing MRSA, but was weak in over half. Six studies presented relatively strong evidence. Stochastic and fixed transmission dynamic models showed that the level of endemic MRSA in a hospital depended on the detection rate (screening) and the isolation capacity, provided neither was the limiting factor. The greater the capacity of an isolation facility, the greater and quicker the reduction of endemic MRSA. The earlier an isolation unit was opened, the sooner control was achieved, but endemic levels could still be reduced years later. Although large numbers of patients might overwhelm institutions with successful isolation units, this could be postponed for years, and the final endemic level would be lower than without the isolation ward. Economic models are hampered by a lack of reliable information on key parameters. However, under a range of plausible parameters, substantial savings could be achieved over 10 years compared with a policy of no isolation, provided the burden of unused isolation ward capacity and staff time was not too great.

Recommendations

Both the systematic review and modeling studies generated hypotheses suitable for testing in future prospective studies. There is no evidence that current guidelines to control MRSA are ineffective, and these should be maintained until further evidence to the contrary is available.

Methods

Systematic review of the literature with epidemiological and economic modeling.

Further research/reviews required

Planned prospective studies that assess and adjust for confounders are required. A variety of designs were suggested, eg, cluster randomized trials and pre-planned interrupted times series. Appropriate interventions to assess include isolation wards, single room isolation with audit and feedback of hand-hygiene, and nurse cohorting of patients isolated in single rooms. Economic studies of the consequences of MRSA colonization and infection are required, as are studies to develop appropriate statistical methods of evaluating outcomes of intervention studies.

Written by Dr Sheldon Stone, Dept of Geriatrics, Royal Free & University College School of Medicine, London, UK

Title **Multidisciplinary Pain Programs for Chronic Pain: Evidence From Systematic Reviews**

Agency **AHFMR, Alberta Heritage Foundation for Medical Research**
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Reference HTA 30, Jan 2003 (English). ISBN 1-896956-72-6 (print); ISBN 1-896956-74-2 (online): www.ahfmr.ab.ca/programs.html

Aim

To assess the efficacy/effectiveness and efficiency of multidisciplinary pain programs (MPPs) for treating patients with non-malignant chronic pain.

Conclusions and results

All of the reviewed clinical practice guidelines (CPGs) recommended a team approach for chronic pain patients, but the evidence for this was weak. Five systematic reviews met the inclusion criteria. Four were Cochrane reviews, and provided the best available evidence (Table 1).

Table 1: Summary of best available evidence for MPPs

Condition	Level of Evidence	Conclusion
Chronic low back pain	Strong	Effective
Chronic pelvic pain	Moderate	Likely to be effective
Fibromyalgia & widespread pain	Limited	Inconclusive
Neck and shoulder pain	Limited	Inconclusive

Caution should be used in generalizing these results. The MPPs were not standardized, and it is unknown whether the outcomes were due to a particular treatment or to interactions of multiple treatments. Also, patients in MPPs often do not represent all with chronic pain, and not all chronic pain patients should attend MPPs. The effects of other factors on outcomes are uncertain. One systematic review on economic effectiveness found the primary research to be flawed.

Recommendations

It is unclear which treatments are responsible for improvements in chronic pain patients in MPPs, or which patients do best under a particular individualized treatment plan. No conclusions can be drawn on the economic impact of MPPs.

Methods

This report is a tertiary, qualitative, systematic review. Published systematic reviews were analyzed for evidence on the efficacy, effectiveness, and economic aspects of MPPs for patients with non-malignant chronic pain. Information from Canadian CPGs was also included.

Further research/reviews required

A standardized operational definition of MPP is essential for future comparisons or evaluations. Research is needed on the various aspects of the multidisciplinary approach. Regional Health Authorities providing MPPs to manage chronic pain must establish appropriate data collection systems and conduct extensive evaluations to assess the efficiency and clinical effectiveness of intervention strategies. Hence, maintaining and monitoring outcome data should be a top priority of MPPs in Alberta.

Written by Maria Ospina and Christa Harstall, AHFMR, Canada

Title	**Nanotechnology in Medicine**
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Reference	TA 47/2003: Nanotechnology in medicine, 124 pages, (German); TA 47A/2003: Cutting nature's building blocks down to size, 10 pages (English)

Aim

This study aims to investigate the potential, risks, future applications, and effects of nanotechnology.

Conclusions and results

Nanotechnology is regarded as the key technology of the 21st century. Switzerland is currently providing substantial funding to support this branch of research. In terms of potential applications, nanotechnology is in its infancy. However, the experts consulted expect major advances by the year 2010, especially in the field of disease diagnosis. Diagnosis will be quicker, will be possible at the very early stages of a disease, and will provide more specific and more precise results than current methods. The results of nanoscientific research should bring about a marked improvement in therapies for some diseases by 2020. Experts are hoping to see advances in the early identification and treatment of cancer, cardiovascular diseases, and viral infections. Although the possibilities tend to be overestimated and the difficulties underestimated, opinion among experts is unanimous: nanoscience will mean drastic changes for traditional medicine. Nanorobots, however, are likely to remain in the realms of science fiction for some years to come.

Considerable uncertainty surrounds any evaluation of the opportunities and potential risks of nanotechnology. For example, how much pressure will society put on the individual if nanotechnologically improved genetic diagnosis makes comprehensive, forward-looking health care a possibility. People will possibly be more in tune with their bodies than they are today, and will have to make decisions about what they actually wish to know about themselves. Data protection and the private sphere will become a key issue. It is also possible that the boundary between sickness and health could become less clear. Half of the experts consulted regard the likelihood of toxicity from directly applied nanoparticles in medicine as something that cannot be ignored.

Recommendations

The authors of the TA-SWISS Study recommend establishing an interdisciplinary, independent committee of experts to assess the possible consequences of nanotechnology on an ongoing basis, and to provide early evaluation of those consequences. An appropriate committee of experts should agree to support risk research and permanent concomitant research into acceptance, the potential for misuse, and ethical and moral questions. In addition, there would have to be an appropriate committee to institute a permanent process of communication between researchers, companies, political groups, and the public.

Methods

TA-SWISS has initiated a study to clarify the medium- and long-term applications of nanotechnology and their effects in medicine. The time horizon for the investigation extends to 2020. The findings are based on an international, written survey of experts and involve more than 70 people from a variety of disciplines.

Written by Walter Grossenbacher-Mansuy, TA-SWISS, Switzerland

Title **Clinical Effectiveness and Cost Utility of Photodynamic Therapy for Wet Age-Related Macular Degeneration: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2003;7(09). Oct 2003. www.ncchta.org/execsumm/summ709.htm

Aim

To establish the clinical and cost effectiveness of photodynamic therapy (PDT) for the neovascular form of wet age-related macular degeneration (AMD) relative to current practice and in relation to current licensed indications.

Conclusions and results

The Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP), trial found consistent evidence at 1 and 2 years that verteporfin PDT resulted in less deterioration in visual acuity in the eye randomized than in the placebo-treated eye. This effect was statistically significant and clinically important. The Verteporfin in Photodynamic Therapy (VIP) trial showed a similar result. An increase in adverse events was associated with verteporfin PDT. Lack of heterogeneity between the results of TAP and VIP invited re-examination of the assumption that the nature of the wet AMD neovascular lesions has as much influence on the relative effect of verteporfin PDT as was predicted on the basis of an assessment of clinical heterogeneity. The results of subgroup analyses should be treated with caution. The impact of reduced deterioration in visual acuity should be based on whole trial estimates of effect. The report presents estimates of quality-adjusted life-years from cost-effectiveness studies, an economic model of base-case estimates, and sensitivity analyses. None of the estimates concerned wet AMD in the worse seeing eye. More favorable estimates of cost utility were only found in models extrapolating beyond 2 years, the limit of RCT data.

Recommendations

The balance of beneficial and disbeneficial clinical effects measured in the RCTs appears to favor verteporfin PDT. However, avoiding deterioration in visual acuity does not equate directly with improving patient function and quality of life. Also, function depends on vision in both eyes, not just the impact of wet AMD on one eye, and this needs be addressed. We believe that verteporfin PDT is an inefficient use of healthcare resources.

Methods

Randomized controlled trials (RCTs) and economic evaluations on clinical effectiveness and cost utility of PDT in AMD were systematically reviewed. Electronic databases, HTA and Internet sites, reference lists, conference abstracts, and the Novartis Industry submission on RCTs and economic evaluations were searched up to Aug/Sept 2001. Synthesis was mainly qualitative for clinical effectiveness and cost utility. Cost utility was analyzed. PDT with best supportive care was compared with best supportive care only, using clinical effectiveness data from one RCT, published utility and treatment cost studies, and blindness cost estimates.

Further research/reviews required

A large, multicenter, publicly funded, pragmatic, double-blind RCT is needed with parallel health economic evaluation to assess the impact of PDT on visual acuity, adverse events, and quality of life. There is no indication of the relationship between benefits and costs where wet AMD affects the worse seeing eye first. Treatment of wet AMD, with verteporfin, other types of PDT, and other new technologies are under investigation and should be kept under close review.

Written by Dr Catherine Meads, Department of Public Health & Epidemiology, University of Birmingham, UK

Title **The Inclusion of Reports of Randomized Trials Published in Languages Other than English in Systematic Reviews**

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Reference Health Technol Assess 2003;7(41). Dec 2003. www.ncchta.org/execsumm/summ741.htm

Aim

To assemble a large dataset of language restricted (English language RCTs only – EL) and language inclusive (including languages other than English – LOE) systematic reviews of conventional medicine (CM) and complementary and alternative medicine (CAM). To assess the quality of these reports by comparing different types of systematic reviews and associated RCTs; CM and CAM interventions; effects of language restrictions versus language inclusions, and whether other methodological factors, eg, statistical heterogeneity and publication bias, influence the results of systematic reviews.

Conclusions and results

The LOE RCTs were predominantly in French and German. Language inclusive/LOE systematic reviews had the highest quality compared to other types of reviews. CAM reviews were of higher quality than the CM reviews. The quality of EL RCT reports differed little compared with eight other languages. Differences in the quality of LOE reports vary depending on intervention type. The results suggest that it may be reasonable to exclude reports of RCTs in LOE from the analytical part of a systematic review. Since every type of CM RCT has not been included in the research, and it is uncertain as to when bias will be present by excluding LOE, it is prudent to search for all evidence. This result only applies to reviews of CM benefits. Systematic reviewers should not, however, neglect reports in LOE. Language restrictions on CAM significantly shift the estimates of effectiveness. Here, excluding trials reported in LOE reduced the intervention effect. The results do not appear to be influenced by statistical heterogeneity and publication bias.

Recommendations

Except for CAM systematic reviews, the quality of recently published systematic reviews is less than optimal. Language inclusive/LOE systematic reviews appear to be a marker for a better quality systematic review. Language restrictions do not appear to bias the estimates of a conventional intervention's effectiveness. The results of a CAM systematic review are subject to substantial bias if LOE reports are excluded.

Methods

The monograph included three types of systematic reviews. Fisher's exact test was applied to compare these with respect to their reporting characteristics and a systematic review quality assessment tool. The odds ratio of LOE trials versus EL trials was computed for each review. Several sensitivity analyses were performed.

Further research/reviews required

Developing a national database of systematic reviews is likely to facilitate meta-epidemiology research. To improve the quality of reporting on systematic reviews of RCTs, authors and medical journal editors need to agree to a standardized, evidence-based way of reporting. The QUOROM statement is one option for systematic reviews. The CONSORT statement is likely to improve the quality of reporting of randomized trials. In-depth examination of CAM trials and their influence on the conduct of systematic reviews is required. Aspects of CAM methodology and content need to be incorporated in critical appraisal skills training programs.

Written by Dr David Moher, Chalmers Research Group, Children's Hospital of Eastern Ontario Research Inst, Canada

Title **What Is the Best Imaging Strategy for Acute Stroke?**

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Reference Health Technol Assess 2004;8(01). Jan 2004. www.ncchta.org/execsumm/summ801.htm

Aim

To determine the best imaging strategy for stroke.

Conclusions and results

It is impossible to differentiate infarct from hemorrhage by clinical examination. CT is sensitive and specific for hemorrhage within the first *8 days of stroke only*. Suboptimal scanning used in epidemiology studies suggests that the frequency of PICH, as a cause of mild stroke, has been underestimated. Patients taking aspirin at the time of stroke are more likely to have a PICH as the cause of stroke than patients not on aspirin. There was no evidence that a few doses of aspirin given inadvertently to patients with acute PICH significantly increased the odds of death. There were no reliable data on the effect of antithrombotic treatment on functional outcome or given long term after PICH. Of 232 patients with mild stroke, 3% had a PICH and 15% had hemorrhagic transformation of an infarct. A specific MR sequence is required to identify prior PICH reliably. CT scanners were distributed unevenly in Scotland. 65% provide CT within 48 hours of stroke and 100% within 7 days for hospital-admitted patients. Access out of hours was variable and poor for outpatients. The average cost of a CT brain scan for stroke in the NHS in Scotland was £30.23 to £89.56 during working hours and £55.05 to £173.46 out of hours. Average length of stay was greatest for severe strokes and those who survived in a dependent state. For a cohort of 1,000 patients aged 70 to 74 years, the policy "scan all strokes within 48 hours", cost £10,279,728 and achieved 1,982.3 QALYs. The most cost effective strategy was "scan all immediately" (£9,993,676 and 1,982.4 QALYs). The least cost effective was "scan patients on anticoagulants, in a life threatening condition immediately and the rest within 14 days" (£12,592,666 and 1,931.8 QALYs). "Scan no patients" reduced QALYs (1,904.2) at increased cost (£10,544,000).

Recommendations

Strategies in which most stroke patients were scanned immediately cost least and achieved the most QALYs, as the cost of CT was swamped by the cost of inpatient care. Increasing independent survival by even a small proportion through early use of aspirin in most ischemic stroke cases (and avoiding inappropriate antithrombotic treatment in those with hemorrhagic stroke) reduced costs and increased QALYs.

Methods

We developed a decision analysis model to represent the pathway of care in acute stroke using "scan all patients within 48 hours" as the comparator against which to cost 12 alternative scan strategies. See monograph for sources of data.

Further research/reviews required

Future research should be directed at: the proportions of patients with stroke and recurrent stroke due to infarct or hemorrhage by age and severity of stroke; whether secondary prevention of ischemic events with antithrombotic treatment is safe and effective in patients with prior PICH, and if so what degree of ischemic vascular risk is required to outweigh any adverse effect of increased hemorrhagic events with aspirin; and the accuracy of imaging.

Written by Professor Joanna Wardlaw, Dept of Clinical Neurosciences, University of Edinburgh, UK

Title **A Systematic Review of the Role of Bisphosphonates in Metastatic Disease**

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Reference Health Technol Assess 2004;8(04). Feb 2004. www.ncchta.org/execsumm/summ804.htm

Aim

To identify evidence for the role of bisphosphonates in metastatic disease, in 3 areas: treating hypercalcemia, preventing skeletal morbidity, and adjuvant use. To perform an economic review of the literature and construct Markov models to evaluate the cost effectiveness of bisphosphonates in treating hypercalcemia and preventing skeletal morbidity.

Conclusions and results

Hypercalcemia: Due to the heterogeneity of studies, results could not be combined in a meta-analysis. Bisphosphonates are well tolerated with low incidence of side effects.

Skeletal morbidity – Primary analysis: On meta-analysis bisphosphonates, compared with placebo, significantly reduced the OR for V#, NV#, C#, RT and ↑Ca but not Ortho or SCC.

Adjuvant Use: Clodronate, given to patients with primary operable breast cancer with no metastatic disease significantly reduces the number of patients developing bone metastases. This benefit was not maintained once clodronate had been discontinued. Two trials reported significant survival advantages in treated groups but not in patients with advanced disease. Bisphosphonates reduce the number of bone metastases in early and advanced breast cancer.

Economic review (Hypercalcemia): Drugs with the longest cumulative duration of normocalcemia were most cost effective.

Economic review (Skeletal morbidity): The estimated cost to prevent SRE was £250 and £1,500 per event in patients with breast cancer and multiple myeloma respectively. The model suggested that bisphosphonate treatment is can save costs in breast cancer patients if fractures are prevented. The models were sensitive to the probability of averting SRE, the unit cost of SRE, and the price of bisphosphonate treatment.

Recommendations

Bisphosphonates normalize serum calcium in >70% of patients with hypercalcemia of malignancy within 2–6 days, they significantly reduce SREs and delay the time to first SRE in patients with bony metastatic breast cancer and multiple myeloma. Benefit appears at different times for different SREs. Bisphosphonates do not affect survival. The evidence is strongest for the efficacy of pamidronate and for intravenous over oral administration. In primary operable breast cancer, oral clodronate reduces the number of patients with bone metastases.

Methods

See monograph for description of methods.

Further research/reviews required

1) RCTs in other disease groups with a high incidence of skeletal metastases.
2) RCTs in the adjuvant setting over extended periods, with comparisons of newer more potent bisphosphonates, and oral vs IV routes of administration.
3) Further cost and quality of life data to identify cost effectiveness of reductions in SREs and delayed time to first SRE.
4) RCT to confirm optimum time to commence bisphosphonate therapy.
5) Studies to identify reasons for resistance to bisphosphonates, and develop drugs to block renal action of PTHrP.
6) RCT of maintenance therapy with bisphosphonates to delay time to relapse in hypercalcemic patients.

Written by Dr Polly Edmonds, Dept of Palliative Care & Policy, Kings College and St Thomas's School of Medicine, UK

Title **Systematic Review of the Clinical Effectiveness and Cost Effectiveness of Capecitabine (Xeloda®) for Locally Advanced and/or Metastatic Breast Cancer**

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Reference Health Technol Assess 2004;8(05). Feb 2004. www.ncchta.org/execsumm/summ805.htm

Aim

To examine the clinical effectiveness and cost effectiveness of oral capecitabine for locally advanced and metastatic breast cancer in relation to its licensed indications.

Conclusions and results

For capecitabine monotherapy, 12 uncontrolled observational studies were identified. The methodological quality of the studies was low. Capecitabine demonstrated antitumor activity, but was associated with a risk of hand–foot syndrome and diarrhea. Economic evaluation was hampered by the poor quality of published studies. Compared indirectly with vinorelbine, capecitabine showed lower costs and improved patient outcomes. For capecitabine combined with docetaxel, one randomized controlled trial (RCT) was identified. Combination therapy was superior to single-agent docetaxel in terms of survival, time to disease progression, and overall response. Adverse events were more frequent with combination therapy. Economic evaluation showed an improved QALY score for combination therapy with slightly reduced costs.

Recommendations

No conclusions could be drawn on the therapeutic benefit of capecitabine monotherapy; RCTs are required. Capecitabine was cost effective compared with vinorelbine, but the poor quality of the trials may invalidate this conclusion. Based on limited evidence, combined therapy was more effective than single-agent docetaxel and likely to be cost effective, but was associated with higher incidences of hand–foot syndrome, nausea, diarrhea, and stomatitis.

Methods

Two reviewers independently screened and assessed all titles and/or abstracts including economic evaluations. RCTs and observational studies that investigated capecitabine monotherapy, in patients pretreated with an anthracycline-containing regimen or a taxane, or capecitabine in combined with docetaxel, in patients pretreated with an anthracycline-containing regimen, were included. Economic evaluation was based on data reported by the manufacturer.

Further research/reviews required

There is an urgent need for basic research into the effectiveness of new second-, third-, and subsequent-line chemotherapy agents for treating advanced breast cancer. Good quality RCTs are needed to compare the effectiveness of capecitabine monotherapy with the alternative third- and subsequent-line therapies now available, and with best supportive care. Future trials should collect data on a range of outcomes, with particular emphasis on QoL and patient preferences. These data should facilitate cost-effectiveness analysis. Further RCTs investigating capecitabine in combination with docetaxel and alternative second-line therapies are required. Future trials should avoid selection bias. It is particularly important to analyze the data on an intention-to-treat basis, and that those assessing the outcome measure are blinded. With respect to time to event data, it is important to present the data in Kaplan–Meier survival curves and compare data using an HR with 95% CI. The presentation of dichotomous data in terms of RR with 95% CI, and absolute event rates, is also preferable.

Written by Ms Lisa Jones, CRD, UK

Title **Clinical Effectiveness and Costs of the Sugarbaker Procedure for the Treatment of Pseudomyxoma Peritonei**

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Reference Health Technol Assess 2004;8(07). Feb 2004. www.ncchta.org/execsumm/summ807.htm

Aim

This systematic review examines the clinical and cost effectiveness of the Sugarbaker procedure for treating pseudomyxoma peritonei (PMP) and the costs of the procedure in the UK.

Conclusions and results

Five retrospective case-series reports assessing the Sugarbaker procedure met the inclusion criteria for review. No studies comparing the Sugarbaker procedure with standard treatment or observational studies of standard treatment were included. All case-series were found to be of poor quality when judged against standard criteria for assessing methodological quality. Details of cytoreductive surgery and chemotherapy differed between studies, and not all patients in a series received the same treatment. There appears to be some benefit for people with PMP who undergo treatment with the Sugarbaker procedure. People with PMP have a 5-year and 10-year survival of approximately 50% and 18% respectively. Survival of patients undergoing the Sugarbaker procedure is about 90% at 2 years, between 60% and 90% at 3 years (depending on IPEC) and between 60% and 68% at 10 years. Complications of the Sugarbaker procedure were anastomotic leaks, fistula formation, wound infection, small bowel perforations/obstructions, and pancreatitis. One costing study (poor methodological quality, set in USA) was found. This study, along with UK unit price data and expert advice, was used to populate a Monte-Carlo simulation model to estimate the marginal cost of operating a service to provide treatment for PMP using the Sugarbaker technique rather than standard treatment. The Monte-Carlo simulation model showed that the cost for one patient over 5 years (max.) would be about £9,700 (SD about £1,300). The US study showed a ten-fold higher cost. The Monte-Carlo analysis showed modest variation around the mean. Length of procedure was most likely to influence cost variation. Sensitivity analysis could not be done for the alternative treatment.

Recommendations

The economic results are an example of the likely marginal costs of the Sugarbaker procedure, but more information about the current alternative is required. Trained, experienced staff is required, and inevitably time and cost will be involved in developing appropriate teams. Although the procedure requires some specialist equipment and maintenance these should have limited effect on setting up the service. PMP is a relatively rare condition (approx. 50 new cases per year in the UK) and the impact of increased demand for services should be limited. Evidence is needed on the effectiveness of maximal cytoreductive surgery compared with surgical debulking, using different intraoperative intraperitoneal chemotherapy strategies and for the effectiveness of treatments in patients with residual disease after maximal efforts at cytoreduction.

Methods

Evidence of the clinical effectiveness of the Sugarbaker procedure for PMP was synthesized through a narrative review with full tabulation of results of all included studies. The economic modeling used a Monte-Carlo simulation model populated with UK price data to estimate likely UK costs.

Further research/reviews required

Further research involving high-quality prospective cohort studies with economic evaluations would be valuable.

Written by Dr Andrew Clegg, Wessex Institute for Health Research and Development, University of Southampton, UK

Title **Psychological Treatment for Insomnia in the Regulation of Long-term Hypnotic Drug Use**

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Reference Health Technol Assess 2004;8(08). Feb 2004. www.ncchta.org/execsumm/summ808.htm

Aim

To evaluate the clinical and cost impact of providing, in routine general practice settings, a cognitive-behavior therapy (CBT) package for insomnia to long-term hypnotic drug users with chronic sleep difficulties; and to identify factors associated with variations in clinical outcomes.

Conclusions and results

At 3- and 6-month followups, patients treated with CBT showed improved global PSQI scores and improvements in the SF-36 dimensions of vitality at 3 months and physical functioning and mental health at 6 months. CBT-treated patients also reported reductions in the frequency of hypnotic drug use compared with the control group, with many CBT-treated patients reporting zero drug use at followup. Clinical improvements were maintained in the CBT group at the 12-month followup, with PSQI scores and the frequency of hypnotic drug use continuing to show significant reductions relative to the control group. Multiple regression analyses of PSQI scores in the sleep clinic group alone indicated that the magnitude of pre- to post-treatment change in overall sleep quality was closely related to Hospital Anxiety and Depression Scale depression scores at 3-, 6-, and 12-month followups. In each model, higher depression scores at baseline were associated with poorer treatment outcomes. No significant relationship was found between the patient's age and PSQI outcomes in any of the analyses. In the sleep clinic group, reduced drug use showed no significant association with the hypnotic product consumed. At the 3-month followup low-frequency drug use was reported by 22.9% (8/35) of temazepam users, 33.3% (5/15) of nitrazepam users, and 38.9% (7/18) of zopiclone users. The total cost of service provision was £154.40 per patient (1999/2000 prices). The mean incremental cost per quality-adjusted life-year (QALY) at 6 months was £3,418; this figure was insensitive to changes in costs. A simple model also showed that extending the evaluation period beyond 6 months might improve the cost effectiveness of CBT. Including hidden costs associated with hypnotic drug treatment (eg, accidents) also reduces the cost per QALY ratio, but to a much lesser degree.

Recommendations

In routine general practice, psychological treatment for insomnia can improve sleep quality, reduce hypnotic drug use, and improve health-related quality of life at a favorable cost in long-term hypnotic users with chronic sleep difficulties. These positive outcomes appear robust over time, persisting for at least 1 year among the more treatment-adherent patients. While the benefits may be reduced in patients with higher levels of psychological distress, the study indicates that older age presents no barrier to successful treatment outcomes.

Methods

A pragmatic cluster randomized controlled trial with two treatment arms (a CBT-treated 'sleep clinic' group, and a 'no additional treatment' control group), with post-treatment assessments starting at 3, 6, and 12 months.

Further research/reviews required

Further research should assess the long-term clinical and cost effectiveness of psychological treatments for insomnia among nonhypnotic-using patients and establish the minimum psychological treatment input required.

Written by Professor Kevin Morgan, Loughborough University, UK

Title **Evaluating Nonrandomized Intervention Studies**

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Reference Health Technol Assess 2003;7(27). Sept 2003. www.ncchta.org/execsumm/summ727.htm

Aim

To consider methods and related evidence for evaluating bias in nonrandomized intervention studies.

Conclusions and results

In the systematic reviews, 8 studies compared results of randomized and nonrandomized studies across multiple interventions using meta-epidemiological techniques. We identified 194 tools for assessing nonrandomized studies: 60 tools covered at least 5 of 6 prespecified internal validity domains; 14 tools covered 3 of 4 core items of particular importance for nonrandomized studies; 6 tools were thought suitable for systematic reviews. Of 511 systematic reviews that included nonrandomized studies, only 169 (33%) assessed study quality, and 69 reviews investigated the impact of quality on study results in a quantitative manner. The new empirical studies estimated the bias associated with nonrandom allocation, and found that the bias could lead to consistently over- or underestimating treatment effects. Also, bias increased variation in results for both historical and concurrent controls. The biases were large enough to lead studies falsely to conclude significant findings of benefit or harm. Four strategies for case-mix adjustment were evaluated: none adequately adjusted for bias in historically and concurrently controlled studies. Logistic regression on average increased bias. Propensity score methods performed better, but were not satisfactory in most situations. Investigation revealed that adjustment can only be adequate in the unrealistic situation when selection depends on a single factor.

Recommendations

Results of nonrandomized studies may differ from results of randomised studies of the same intervention and may be misleading when the treated and control groups are similar in key prognostic factors. Standard methods of case-mix adjustment do not guarantee removal of bias. Residual confounding may be high even with prognostic data, and adjusted results might appear more biased than unadjusted results. Most quality assessment tools omit key quality domains. Healthcare policies based on nonrandomized studies or systematic reviews of nonrandomized studies may need re-evaluation if the uncertainty in the true evidence base was not fully appreciated when policies were made. Nonrandomized studies should only be undertaken when RCTs are infeasible or unethical.

Methods

Three systematic reviews and new empirical investigations were conducted. The reviews considered, regarding nonrandomized studies:

1. Existing evidence of bias
2. Content of quality assessment tools, and
3. Ways that study quality has been assessed and addressed.

The empirical investigations were conducted, generating nonrandomized studies from two large, multicenter randomized controlled trials (RCTs) and selectively resampling trial participants according to allocated treatment, centre, and period.

Further research/reviews required

Apply resampling methodology in other clinical areas to ascertain whether the biases described are typical. Develop or refine existing quality assessment tools for nonrandomized studies. Investigate how quality assessments of nonrandomized studies can be incorporated into reviews and the implications of individual quality features for interpretation of a review's results. Examine reasons for the apparent failure of case-mix adjustment methods. Further evaluate the role of the propensity score.

Written by Mr Jonathan Deeks, Centre for Statistics in Medicine, University of Oxford, UK

Title **A Systematic Review and Economic Decision Modeling for the Prevention and Treatment of Influenza A and B**

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Reference Health Technol Assess 2003;7(35). Nov 2003. www.ncchta.org/execsumm/summ735.htm

Aim

To establish the clinical and cost effectiveness of amantadine, oseltamivir, and zanamivir compared to standard care for treating and preventing influenza.

Conclusions and results

The systematic review of treating influenza found that oseltamivir reduced the median duration of symptoms in the influenza-positive group by 1.38 days for the otherwise healthy adult population, 0.5 day for the high-risk population, and 1.5 days for the child population. This compared to 1.26 days, 1.99 days, and 1.3 for the similar groups for inhaled zanamivir. The systematic review on preventing influenza found the relative risk reduction to be approximately between 75% and 90% for oseltamivir and 70% and 90% for inhaled zanamivir, depending on the strategy and population. For the economic model, a base case was constructed that focused on the benefits of shortening the influenza illness. This base case found that, compared to standard care, the estimated range in cost per quality-adjusted life year (QALY) was £6,190 to £31,529 for healthy adults, £4,535 to £22,502 for the 'high-risk' group, £6,117 to £30,825 for children, and £5,057 to £21,781 for elderly in residential care. We also conducted a sensitivity analysis that involved extrapolating the observed reductions in pneumonia in the NI trials to hospitalizations and deaths. In all four models the cost effectiveness of NIs is substantially improved by this extrapolation.

Recommendations

Cost effectiveness varies markedly between the intervention strategies and target populations. The estimate of cost effectiveness is sensitive to variations in key parameters of the model, eg, the proportion of all influenza-like illnesses that are influenza. The effectiveness literature used in the economic decision model spans many decades, and caution should be exercised when interpreting the results of indirect intervention comparisons from the model.

Methods

A systematic review and meta-analysis of evidence from randomized trials investigated the effectiveness of oseltamivir and zanamivir compared to standard care in treating and preventing influenza A and B. An additional systematic review investigated the effectiveness of amantadine in treating and preventing influenza A in children and the elderly. Economic decision models were constructed to examine the cost effectiveness and cost utility of the alternative strategies for treating and preventing influenza A and/or B.

Further research/reviews required

Randomized trials that directly compare the two NI drugs and with amantadine would help identify the most appropriate drug treatment. Evidence is needed on the effectiveness of NIs in treating 'high-risk' individuals and on the effectiveness of NIs in preventing influenza in elderly residential care settings. There is insufficient evidence on the effectiveness of antiviral drugs in decreasing hospitalizations and deaths. These events are rare and this information is most likely to be obtained from observational studies. There is a need for high quality-of-life data for estimating utilities in cost per QALY studies. Appraisal and development of rapid diagnostic testing is needed to evaluate this technique alongside antiviral drugs.

Written by Professor Karl Graham Nicholson, Infectious Diseases Unit, Leicester Royal Infirmary, UK

Title **The Effectiveness and Cost Effectiveness of Microwave and Thermal Balloon Endometrial Ablation for Heavy Menstrual Bleeding: Systematic Review and Economic Modeling**

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Reference Health Technol Assess 2004;8(03). Feb 2004. www.ncchta.org/execsumm/summ803.htm

Aim

To estimate the clinical and cost effectiveness of microwave endometrial ablation (MEA) and thermal balloon endometrial ablation (TBEA) for heavy menstrual bleeding (HMB), compared with the existing (first-generation) endometrial ablation (EA) techniques of transcervical resection (TCRE) and rollerball (RB) ablation, and hysterectomy.

Conclusions and results

A systematic review of first-generation EA methods versus hysterectomy shows that EA had fewer complications and a shorter recovery period than hysterectomy for HMB. Satisfaction and effectiveness were high for both EA and hysterectomy. Costs were lower with EA, but the difference narrows over time. Our systematic review found that second-generation EA techniques are an alternative to first-generation techniques for HMB. Second-generation techniques may also offer an alternative surgical treatment to hysterectomy. Using the economic model to assess cost effectiveness, costs were slightly higher for MEA compared to TBEA, and differences in quality-adjusted life-years (QALYs) were negligible. Costs were slightly lower for MEA compared to TCRE and RB ablation, and MEA accrued slightly more QALYs. Compared to hysterectomy, MEA costs less and accrues slightly fewer QALYs. Costs were lower for TBEA compared to TCRE and RB ablation, and TBEA accrued slightly more QALYs. Compared to hysterectomy, TBEA costs moderately less and accrues moderately fewer QALYs. However, the data are too uncertain to draw firm conclusions.

Recommendations

Few significant differences distinguish the outcomes of first- and second-generation EA methods. Second generation methods have significantly lower operating and theatre times and avoid the risk of some adverse effects. Compared to hysterectomy, TCRE and RB are performed quicker, hospitalization is shorter, and return-to-work is faster. Hysterectomy has more adverse effects and is more expensive, but retreatment leads this difference to decrease over time. Satisfaction with hysterectomy is initially higher, but the difference with EA is not significant after 2 years. The economic model suggests that second-generation techniques are more cost effective than first-generation techniques of EA for HMB. Both TBEA and MEA appear to be less costly than hysterectomy, although the latter results in more QALYs.

Methods

A detailed search strategy identified systematic reviews and controlled trials of MEA and TBEA versus first-generation techniques for EA. In addition to electronic database searching, reference lists were hand-searched and information sought from manufacturers of EA devices and from experts in the field. A deterministic Markov model was developed to assess cost effectiveness. Data for the model were taken from the best available source.

Further research/reviews required

Further research is suggested to directly compare the cost effectiveness of second-generation EA techniques, to carry out longer term followup for all methods of EA in RCTs, and to develop more sophisticated modeling studies.

Written by Ruth Garside, Peninsula Technology Assessment Group, University of Exeter, UK

INAHTA Briefs

Issue 2004/43

Title **A Systematic Review and Economic Evaluation of Magnetic Resonance Cholangiopancreatography Compared with Diagnostic Endoscopic Retrograde Cholangiopancreatography**

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Reference Health Technol Assess 2004;8(10). Mar 2004. www.ncchta.org/execsumm/summ810.htm

Aim

To compare the clinical and cost effectiveness of magnetic resonance cholangiopancreatography (MRCP) with diagnostic endoscopic retrograde cholangiopancreatography (ERCP) for the investigation of biliary obstruction.

Conclusions and results

The median sensitivity for choledocholithiasis (13 studies) was 93% and the median specificity was 94%. The median likelihood ratio for a positive value was 15.75 and for a negative value 0.08. Reported sensitivities for malignancy were somewhat lower, ranging from 81% to 86%, and specificities ranged from 92% to 100%. There was some evidence that MRCP is an accurate diagnostic test in comparison to ERCP, although the quality of studies was moderate. Claustrophobia prevented at least some patients from having MRCP in 10 of the 28 studies. The other 18 studies did not mention claustrophobia. The probability of avoiding unnecessary diagnostic ERCP is estimated at 30%. These patients could avoid the unnecessary risk of complications and death associated with diagnostic ERCP, and substantial cost saving would be gained. The overall expected cost saving associated with MRCP is £149, and the overall expected gain in quality-adjusted life-year is estimated at 0.011.

Recommendations

Some evidence shows that MRCP is an accurate investigation compared with diagnostic ERCP, although the values for malignancy compared with choledocholithiasis were somewhat lower. The quality of studies was moderate. Limited evidence on patient satisfaction showed that patients preferred MRCP to diagnostic ERCP. The estimated clinical and economic impacts of diagnostic MRCP versus diagnostic ERCP are favorable. The baseline estimate is that MRCP may reduce cost and improve quality of life outcomes compared with diagnostic ERCP.

Methods

The data sources were searched, and selected studies were assessed using quality criteria. We identified 28 prospective diagnostic studies reporting several suspected conditions, plus one of patient satisfaction. Analyses were performed to establish sensitivities, specificities, likelihood ratios, and confidence intervals. The relative cost effectiveness of adopting MRCP scanning in investigating the biliary tree was undertaken using a probabilistic economic model.

Further research/reviews required

Further research is suggested to compare MRCP and diagnostic ERCP with final diagnosis and also with the full range of target conditions; to examine patient satisfaction and ways of reducing problems with claustrophobia; to look at protocols to help identify who could benefit most from MRCP or ERCP; to assess the relative need and urgency of patient access to magnetic resonance imaging services, and to determine how demand would affect availability and potential cost savings.

Written by Dr Eva Kaltenthaler, ScHARR-TAG, University of Sheffield, UK

Title **Breech Birth at Term. Vaginal Delivery or Cesarean Section?**

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Reference SMM Report No. 3/2003. ISBN 82-14-02956-2; Systematic review

Aim

To review current knowledge on the method of delivery for breech birth at term. The review group also assesses external cephalic version. Norwegian practice with breech birth is presented. Information on long-term effects on morbidity and mortality for both child and mother are of relevance.

Conclusions and results

Vaginal delivery for term breech birth is advisable in suitable cases after a careful selection process, given the facilities for fetal electronic monitoring, experienced obstetric staff, facilities for emergency cesarean section, and a good neonatal service. The external validity of the results of the Term Breech Trial (TBT) to Norwegian practice is questionable. Many of the centers and countries participating in the study differ from Norway as regards antenatal care, birth surveillance, delivery experience, and pediatric service. Perinatal and neonatal mortality are considerably lower in Norway than in the TBT. The data presented from four Norwegian hospitals (two published reports and two unpublished) confirm a low risk of complications by vaginal delivery in these hospitals.

It was not feasible to conduct a study similar to the TBT in Norway or the Nordic countries. As perinatal mortality and morbidity are low in these countries such a study would require a very large study population.

External cephalic version may reduce the frequency of breech births, but is not shown to affect perinatal mortality. The Norwegian practice of external cephalic version is poorly documented.

Recommendations

The expert group recommends establishing a national breech birth registry for continuous surveillance of delivery practice and results. This is a prerequisite in a field where practical obstetric skill is mandatory for good results.

Methods

Relevant databases were searched, including MEDLINE, EMBASE, CINAHL, MiDirs, Cochrane Controlled Clinical Database, Cochrane Database of Systematic Reviews, Database of Abstracts and Reviews of Effectiveness, and NHS Centre for Reviews and Dissemination.

Written by Lise Lund Håheim, SMM, Norway

INAHTA Briefs

Issue 2004/45

Title **Assessment of Photodynamic Therapy Using Porfimer Sodium for Esophageal, Bladder, and Lung Cancers**

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Reference Technology brief prepared for AÉTMIS, 2004 (AÉTMIS 04-01). Internet access to full text. ISBN 2-550-42651-7 (original French version ISBN 2-550-42481-6)

Aim

To evaluate the efficacy of photodynamic therapy using porfimer sodium (PDT-PF) for its approved oncological indications.

Conclusions and results

In treating lung, bladder, and superficial esophageal cancers: Findings seem to indicate that PDT-PF has a therapeutic effect, but the evidence is insufficient to indicate any advantage over available treatments.

In palliative treatment of advanced esophageal cancer: Studies suggest, with a limited level of evidence, that the efficacy of PDT-PF is similar to other palliative treatments (Nd: Yag laser ablation; metal stents). The cost of PDT-PF is apparently much higher than stents, which are easy to use and already in widespread use.

In treating Barrett's esophagus: In-depth examination is needed of the long-term efficacy of PDT.

Recommendations

In treating lung, bladder, and superficial esophageal cancers: PDT-PF should be used only in clinical research, and public coverage should not be authorized.

In palliative treatment of advanced esophageal cancer: PDT-PF should be considered an option when recognized treatments are contraindicated.

In treating Barrett's esophagus: PDT-PF should be fully assessed before it is introduced in current practice.

Methods

A literature search strategy located two HTA agency reports, one French (1999) and one American (1997 and 2002). MEDLINE was searched for articles published between 01/97 and 12/03. Studies retrieved were assessed according to the scheme outlined in the Canadian Guide to Clinical Preventative Health Care.

Further research/reviews required

In palliative treatment of advanced esophageal cancer: The efficacy of PDT-PF should undergo further clinical research.

In general: A technology watch should be implemented to track technological advances in PDT and, in particular, its new applications.

Written by Lonny Erickson, Van Hung Nguyen, and Séraphin Niamba, AÉTMIS, Canada

Title **Hormone Replacement Therapy After Breast Cancer**

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Reference SMM Report No. 2/2003. ISBN 82-14-02957-0; Systematic review

Aim

To perform a systematic review of the literature and assess the scientific evidence on the following issue: Does HRT increase or decrease the risk of breast cancer recurrence or breast cancer death in patients with previous breast cancer?

Conclusions and results

Of the 2,659 articles found, only 8 were considered relevant to the question. Of these, 2 were of moderate quality, and were included as evidence. The remaining 6 were given a lower quality score by the expert group and were excluded. All studies were observational, and no randomized controlled trials (RCTs) articles could be found.

Although neither of the studies indicated an increased risk of breast cancer recurrence, the documentation currently available is too weak to allow firm conclusions to be drawn in either direction.

Ongoing randomized controlled trials (RCTs) may provide the answers in a few years.

In the meantime, it would be beneficial to the patients if clinicians could agree on a common information strategy.

The need for more research in this area was clearly revealed, and should be given substantial attention and support. Women who seek HRT should be encouraged to participate in the ongoing trials.

Methods

Clinical trials relevant to the above objective were identified by searches in EMBASE, MEDLINE, PubMed, Cochrane Database of Systematic Reviews and Protocols, and Cochrane Controlled Trials Register. In addition, a hand search was conducted of reference lists in the reviewed papers.

Written by Berit S Mørland, SMM, Norway

Title **PCI in Acute Myocardial Infarction**

Agency **SMM, The Norwegian Centre for Health Technology Assessment**
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Tel: +47 22 06 79 61, Fax: +47 22 06 79 79; www.sintef.no/smm

Reference SMM Report No. 5/2002. ISBN 82-14-02951-1

Aim

To assess the scientific evidence comparing percutaneous coronary intervention (PCI) and thrombolysis in acute myocardial infarction.

Conclusions and results

Twenty randomized clinical trials were identified and assessed. However, three older trials were known only from conference abstracts and were excluded. A meta-analysis of the remaining 17 studies yielded the following main conclusions:

- Primary PCI is a better treatment than thrombolysis for patients with acute myocardial infarction admitted to an invasive center. The combined outcome of death, reinfarction, or stroke in the acute phase is nearly halved, one such outcome is avoided for every 16 patients treated with PCI. Results more than one year after the infarction still significantly favor PCI.
- Patients with acute infarction can be safely transported to an invasive center if the transport time is less than 3 hours.
- As both time to treatment and hospital- and operator volume are important for the outcome, the optimal treatment for acute myocardial infarction will differ in different places.

Recommendations

Because of the importance of reducing time to treatment, good routines are needed to minimize all delays. Clear treatment algorithms should be established for each geographical area.

Methods

Randomized clinical trials comparing PCI and thrombolysis as acute treatment of myocardial infarction were identified from references in the Cochrane review "Primary angioplasty versus intravenous thrombolysis for acute myocardial infarction" (43), MEDLINE, EMBASE and the abstract collections from recent cardiology conferences. The assessment was performed by an expert group of Norwegian cardiologists coordinated by an HTA expert from the Norwegian Centre for Health Technology Assessment (SMM).

Written by Kurt I Myhre, SMM, Norway

Title **Primary Treatment of Ovarian Cancer**

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Reference SMM Report No. 5/2003. ISBN 82-14-029530-3; Systematic review

Aim

To assess the scientific evidence on the clinical effect of four main treatment options in the primary treatment of epithelial ovarian cancer:

i) Adjuvant chemotherapy and/or adjuvant radiotherapy

ii) Cytoreductive surgery

iii) Neoadjuvant chemotherapy in advanced disease

iv) Postoperative chemotherapy in advanced disease.

Conclusions and results

- Current data are inconclusive regarding the effect of adjuvant therapy.
- Several large retrospective studies consistently identify the size of the largest residual disease after primary cytoreductive surgery as an independent determinant of prognosis. Hence, the effect of cytoreductive surgery is only indirectly documented.
- The effect of neoadjuvant chemotherapy in advanced ovarian cancer is uncertain.
- The effect of nonplatinum chemotherapy regimens after primary surgery in advanced ovarian cancer is not documented. Available documentation shows significant difference in survival favoring the use of platinum agents in combination chemotherapy. Addition of paclitaxel to platinum further improves survival. Carboplatin plus paclitaxel is currently the standard first-line therapy.

Methods

A systematic review focused on clinical evidence from studies of best available quality reporting the clinical effect of the above mentioned treatment methods in primary ovarian cancer. Clinical effect includes effect on overall survival, disease-free survival, and progression-free survival, adverse effects/complications, and quality of life.

Studies published from 1970–2001 were identified by searches in MEDLINE, EMBASE, and the Cochrane Controlled Clinical Database Register, and by manual searches in relevant journal indexes and reference lists of articles. An updated search was performed in October 2002. Studies were systematized according to treatment method and study design (methods i and iv: meta-analyses and/or randomized controlled trials, method ii and iii: case series only), and critically assessed for relevance, quality, and validity. Of 2,227 publications identified, only 45 studies rated as having high or moderate quality, according to the study design in question, were accepted as the basis of the systematic review.

The included studies were distributed as follows:

method i) 4 randomized trials

method ii) 12 case series

method iii) one case, and

method iv) 3 meta-analyses and 25 randomized trials.

Further research/reviews required

This systematic review demonstrates the need for more clinical studies on survival outcomes for all treatment methods of primary epithelial ovarian cancer.

Written by Anita Lyngstadaas, SMM, Norway

Title **Surgery for Morbid Obesity**

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Reference SMM Report No. 1/2003. ISBN 82-14-02948-1; Systematic review

Aim

To assess the effects of different surgical techniques for people suffering from morbid obesity. The clinical endpoints were weight loss, impact on comorbidity factors, quality of life, mortality, and complications of surgery.

Conclusions and results

Gastric bypass, biliopancreatic diversion, and duodenal switch yield the greatest weight loss. However, these methods are comprehensive, and biliopancreatic diversion is associated with serious malabsorptive disorders. In comparison, gastric banding yields lower weight loss, but fewer short-term complications and reoperations.

Surgery should be undertaken only after comprehensive, multidisciplinary assessment. A center of expertise in the surgical management of obesity should be established, and include healthcare professionals such as psychologists, physicians, a specialist surgeon, a specialist anesthetist, physiotherapist, endocrinologist, and dieticians.

People considering surgery to achieve weight loss should discuss, in detail and with appropriate healthcare professionals, the potential benefits and long-term implications of surgery. This includes associated risks, complications, and postoperative mortality.

Methods

The report is based on systematic reviews and guidelines. An additional search for literature (randomized controlled trials, controlled trials and meta-analyses) was performed for 2001–2002 to identify more recent studies on topics about which the systematic reviews yielded little information.

The following databases were searched: the Cochrane Controlled Trial Register, Database of Abstracts of Reviews of Effectiveness (DARE), International Network of Agencies for Health Technology Assessment (INAHTA) database, MEDLINE, EMBASE, National Guideline Clearinghouse, PRODIGY Guidance, NICE (National Institute for Clinical Excellence), and SIGN (Scottish Intercollegiate Guidelines Network). The literature search identified seven systematic reviews and three guidelines. The search for primary literature yielded 175 hits (MEDLINE) and 129 hits (EMBASE), 13 possibly relevant studies were assessed, and 6 of these studies were included.

Written by Ellen M Nilsen, SMM, Norway

Title **Use of Palliative Surgery in the Treatment of Cancer Patients**

Agency **SMM, The Norwegian Centre for Health Technology Assessment**
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Reference SMM Report No. 8/2003. ISBN 82-14-03237-7; Systematic review

Aim

To assess the literature on elective palliative procedures in the surgical specialties of gastroenterologic surgery, neurosurgery, thoracic surgery, urology, and orthopedic surgery.

Conclusions and results

Gastroenterological surgery (partial list):

- Stent and laser treatment give quick, palliative relief of symptoms from dysphagia in cancer of the esophagus. Laser treatment often requires repeated sessions. Self-expanding metal stents yield fewer complications and have replaced plastic tubes.
- Stents and bypass surgery of obstructed bile ducts due to malignancy give equal palliation of icterus and pruritus. Stent insertion may use less resources than surgery. The complication rates of the two methods do not differ in randomized trials.

Neurological surgery:

- Cytoreductive surgery is superior to biopsy in improving quality of life and survival in intracranial cancer.
- Surgery of metastases to the brain is useful in single metastasis and stable cancer.

Orthopedic surgery (partial list):

- Metastases to the long bones and hip may require surgery to relieve pain and maintain function. This demands surgical stabilization and immediate functionality.
- Surgery of metastases to the back is required to support a fracture site and when radiation therapy fails to relieve pain.

Thoracic surgery (partial list):

- Survival can increase by surgical removal of metastases from primary cancers of other organs. Best results: metastases from cancer of the testis and soft tissue carcinomas.
- Treating obstructions from cancer of the central airways can prevent pain, obstructed breathing, and infection. Treatment mode: laser or stenting.

Urological surgery (partial list):

- Transurethral resection (TUR) is the most common treatment for local symptoms, eg, hemorrhage and obstruction due to cancer of the prostate and bladder. Stent is a good alternative to TUR or catheter in waiting for the effect of hormonal treatment.
- Local symptoms of bladder hemorrhage are commonly treated by TURB. Rinsing the bladder with a solution of aluminum is an alternative if hemorrhaging does not stop.

Methods

A systematic literature search included MEDLINE, HTA database, Cochrane Controlled Clinical Trials, Cochrane Database of Systematic Review, Database of Abstracts of Reviews of Effectiveness (DARE), NHS Economic Evaluation Database, CancerLit, and EMBASE for 1966–2003. Controlled clinical trials were preferred, but when not available studies of a lower evidence level that presented the best available evidence on the subject were accepted.

Written by Lise Lund Håheim, SMM, Norway

INAHTA Briefs

Issue 2004/51

Title **Cleaning Routines in Operating Theaters**

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Reference SMM Report No. 9/2003. ISBN 82-14-03240-7; Systematic review

Aim

To systematically evaluate the scientific documentation on cleaning of operating theatres, ie, washing/disinfecting surfaces and equipment, and how these routines influence rates of postoperative wound infection. The effect of compressed air/gas-driven surgical power tools on postoperative wound infection is also addressed.

Conclusions and results

No solid documentation was found regarding an association of cleaning and postoperative wound infections. The effect of disinfecting the floor has not been demonstrated. Thorough cleaning after the last operation appears to be reasonable. The same applies after septic operations. Using ultraviolet light during the surgery is proven to reduce postoperative wound infections in a subgroup of clean wounds only.

Relevant literature was not found on the risk of postoperative wound infections from using power tools during surgery, or the customary use of rest time between operations.

There are no Norwegian regulations on specific cleaning routines of operating theatres. Our survey assessing routines of daily cleaning of operating theatres in Norwegian hospitals revealed that the units had specific routines and that routines varied between hospitals and, in some instances, within a hospital.

Given no increase in the incidence of postoperative infections, the option of reducing cleaning time between clean operations will depend on the balance between additional costs and cost benefit.

Methods

A literature search included the following databases: MEDLINE, EMBASE, CINAHL, MiDirs, Cochrane Controlled Clinical Database, Cochrane Database of Systematic Reviews, Database of Abstracts and Reviews of Effectiveness, NHS Centre for Reviews and Dissemination.

The literature search included publications from 1966 and onward and written in English, German, French, or a Scandinavian language.

Written by Lise Lund Håheim, SMM, Norway

Title	**Spinal Manipulation for Infantile Colic**
Agency	**CCOHTA, Canadian Coordinating Office for Health Technology Assessment** 865 Carling Avenue, Suite 600, Ottawa, Ontario K1S 5S8 Canada; Tel: +1 613 226 2553, Fax: +1 613 226 5392
Reference	CCOHTA Technology Report, Issue 42, Nov 2003. ISBN 1-894978-11-0 (print); ISBN 1-894978-12-9 (electronic): www.ccohta.ca

Aim

- To determine whether manipulating the spine, by itself, can reduce the signs and symptoms of infantile colic.
- To assess the safety of spinal manipulation for this indication.

Conclusions and results

Four randomized controlled trials involving spinal manipulation performed by chiropractors met the inclusion criteria: two trials published in peer-reviewed journals, one conference abstract, and one unpublished manuscript. Quality scores for all four reports as measured by the Jadad scale were low. None of the trials provided information about adverse events. This systematic review found no convincing evidence that spinal manipulation alone can affect the duration of infantile colic symptoms. The effect of spinal manipulation on sleep time, parental anxiety, quality of life, and number of colic diagnoses could not be determined using available evidence. As the presence or absence of adverse events was not described in any of the trial reports reviewed, potential harm from the spinal manipulation of infants with colic could not be determined.

Recommendations

Not applicable.

Methods

The research literature was systematically reviewed to identify clinical trials of infants with colic. Relevant trials were identified after searching electronic databases, contacting experts, manually searching conference abstracts and reference lists of retrieved reports, and visiting the websites of pediatric and chiropractic associations. Two reviewers independently assessed the quality of each trial report. Inclusion criteria focused on study design, participants, interventions, safety, and measured outcomes.

Further research/reviews required

More rigorous research is needed to adequately measure the safety and efficacy of spinal manipulation in treating infantile colic. Greater efforts must be made to compare infants of similar age. Issues to consider include placebo response rates as high as 83%, the self-limiting quality of colic symptoms, and the fact that colic plays itself out over several months.

Written by Husereau D, Clifford T, Aker P, Leduc D, and Mensinkai S, CCOHTA, Canada

Title **Telephone Triage Services: Systematic Review and a Survey of Canadian Call Center Programs**

Agency **CCOHTA, Canadian Coordinating Office for Health Technology Assessment**
865 Carling Avenue, Suite 600, Ottawa, Ontario K1S 5S8 Canada;
Tel: +1 613 226 2553, Fax: +1 613 226 5392

Reference CCOHTA Technology Report, Issue 43, Nov 2003. ISBN 1-894978-13-7 (print); ISBN 1-894978-14-5 (electronic): www.ccohta.ca

Aim

- To evaluate the clinical impact of teletriage services through their effects on health service use, safety, self-care and informal care, satisfaction, health-related quality of life, and access to other resources.
- To examine the economic impact (costs, cost effectiveness) of teletriage services.
- To summarize the characteristics and evaluation of Canadian teletriage programs.

Conclusions and results

Clinical Review: Ten studies met the inclusion criteria; six were randomized controlled trials, and all were from the US or UK. Various delivery models were compared. Despite differences in interventions, the studies indicated that teletriage decreased immediate practitioner visits without increasing adverse outcomes, eg, subsequent hospitalizations, emergency department visits, or deaths. About half of the calls were managed by telephone alone. Caller satisfaction ranged from 55% to 90% for registered nurse (RN) triage, and about 70% for medical doctor triage.

Economic Review: No published Canadian economic studies were found. Three Canadian jurisdictions that have undertaken economic analysis for their call center programs estimate that the cost per triage call ranges from C $10 to C $27, based on the number of staff employed and the population served. Three cost studies for RN teletriage – one UK study and one US study – were examined. Two of the studies demonstrated statistically significant cost savings for after-hours teletriage, mainly due to reductions in emergency department and physician visits.

Program Survey: Response rate was 100%. Seven Canadian jurisdictions have province-wide teletriage programs (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, and New Brunswick) and the other six have identified a need.

Recommendations

Not applicable.

Methods

To address the first two objectives, the research literature was systematically reviewed. Using a standard tool, two reviewers screened all citations to identify teletriage services evaluated using comparative study designs. Two independent reviewers extracted data, evaluated methodological quality, and analyzed the data. To gather data on teletriage in Canada, all provincially and territorially funded programs and key contacts were identified, and jurisdictional representatives were surveyed by written questionnaire.

Further research/reviews required

Comparative research – both international and in Canada – is needed to determine the "best" model for teletriage services.

Written by Stacey D, Noorani HZ, Fisher A, Robinson D, Joyce J, and Pong RW, CCOHTA, Canada

Title	**Bisphosphonate Agents for the Management of Pain Secondary to Bone Metastases: A Systematic Review of Effectiveness and Safety**
Agency	**CCOHTA, Canadian Coordinating Office for Health Technology Assessment** 865 Carling Avenue, Suite 600, Ottawa, Ontario K1S 5S8 Canada; Tel: +1 613 226 2553, Fax: +1 613 226 5392
Reference	CCOHTA Technology Report, Issue 45, Jan 2004. ISBN 1-894978-19-6 (print); ISBN 1-894978-20-x (electronic): www.ccohta.ca

Aim

To examine the effectiveness and safety of specific bisphosphonate agents, compared with placebo and other analgesics, in managing the pain of bone metastases.

Conclusions and results

Fifty articles were found, including studies of mixed quality. The complexity of measuring pain limited interpretation of the results. Bisphosphonates were found to be moderately effective in relieving painful bone metastases compared with placebo when patients were assessed at 12 weeks. No one drug regimen (lower or higher doses of pamidronate, clodronate, or zoledronate) was found to be superior to another, and the effect was not limited to any specific cancer. No studies were found with adequate outcomes to allow comparisons of bisphosphonates with therapies such as other analgesic regimens, palliative radiotherapy, and palliative chemotherapy.

Recommendations

When making treatment choices, the delayed effect (benefit at 12 weeks) and adverse effects of bisphosphonates should be considered.

Methods

This study focused on five bisphosphonates: etidronate, clodronate, pamidronate, zoledronate, and ibandronate. Updating a 2001 Cochrane review, the research literature was searched extensively to identify randomized controlled trials that compared pain outcome with bisphosphonate treatment to 1) placebo, 2) no treatment, 3) other bisphosphonates, or 4) other treatments. Two reviewers independently discarded studies that did not fulfil the inclusion criteria, and then assessed the quality of the randomized controlled trials that were included. The primary outcome of interest was short-term pain relief (within 12 weeks). Secondary outcomes included reductions in analgesic use, mean pain scores, mean analgesic scores, and adverse effects.

Further research/reviews required

Future research should incorporate standard methods of reporting pain outcomes, including measurement of the proportion of patients achieving pain relief. Also, standard deviations should be used when reporting continuous variables, eg, pain score and morphine equivalent.

Written by Wong R, Shukla VK, Mensinkai S, and Wiffen P, CCOHTA, Canada

Title **Principles of Screening for Type 2 Diabetes**

Agency **ANAES, French National Agency for Accreditation and Evaluation in Healthcare**
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Reference ANAES Report. French, English summary. Feb 2003. www.anaes.fr/anaes/Publications.nsf/nZIPFile/RA_LILF-5MGKN5/$File/diabete_rap_2003.zip

Aim

- To assess the benefit of screening for type 2 diabetes in metropolitan France.
- To draw up proposals for implementing a screening program.

Conclusions and results

Appropriateness of a screening program (critical literature analysis):

Clinical benefit: WHO criteria suggest that targeted screening for type 2 diabetes in metropolitan France would have clinical benefits. Most published guidelines conclude that targeted opportunist screening is useful.

Economic benefit: Cost-benefit modeling results for screening are at the threshold of positive and were sensitive to the hypotheses studied. No solid economic reasons support or reject screening.

Practical aspects of a screening program:

- *Targeted opportunist screening* of subjects aged over 45 with at least one risk indicator for type 2 diabetes, in addition to age; metabolic syndrome marker according to ANAES definitions; family history of diabetes, in women, history of gestational diabetes and/or birth of a child weighing more than 4 kg, history of temporary induced diabetes. Screening should involve fasting venous blood glucose testing at a laboratory. Studies show that followup and management of positive blood glucose tests needs to improve. Tests should be repeated every 3 years in subjects with negative results, every year in subjects with fasting hyperglycemia, and between 1 and 3 years in subjects with one or more risk indicator
- *Targeted screening in the community* in subjects aged over 45 who belong to a risk group. The test could be a fasting venous blood glucose test in a lab or blood glucose measurement from a capillary sample. Followup procedures will be the same as for opportunist screening.

Simultaneous screening for diabetes and cardiovascular risk factors should be recommended.

Recommendations

These guidelines should be implemented while studies are being carried out to verify the prevalence of undiagnosed diabetes, to assess the feasibility of the recommended programs, and to provide short-term assessment of these programs.

Methods

Literature review and analysis. ANAES searched the MEDLINE, EMBASE, Pascal, and Cochrane databases (1996–2003) for relevant consensus conferences, guidelines, systematic reviews, and clinical trials (in English or French). Content pages of journals published in the past 6 months, references cited in the articles selected, the grey literature, and relevant websites were searched. Studies were selected based on level of evidence and quality of design (using checklists). The report was submitted to a working group of 12 experts and to a multidisciplinary peer review group of 16 experts recruited from relevant societies.

Prepared by ANAES, France

INAHTA Briefs

Issue 2004/56

Title **Sentinel Node Biopsy (SNB) in Breast Cancer – Progress Report**

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Reference ANAES Report, Oct 2002

Aim

To update the assessments of sentinel node biopsy (SNB), focusing on feasibility and reliability, technical steps in the procedure, impact on surgery, and economic analysis.

Conclusions and results

- *Feasibility and reliability:* SNB was feasible and able to diagnose lymph node involvement under certain conditions. The examination has been incorporated into TNM staging since 2003. A meta-analysis and 5 systematic reviews have reported 66% to 100% identification of the SN, with 0% to 17% false negatives depending on the study (10 preliminary studies of 100+ patients, with SNB followed by axillary clearance (AC)).
- *Technical steps of the procedure:* One of the 12 studies on tracer choice was randomized, but case series of isotope methods, injection site, and learning curve had design deficiencies. Histopathology methods varied and were not standardized.
- *Impact on surgery:* One of the 2 prospective unrandomized studies and 2 case series did not show recurrence in patients without SN involvement who had not undergone AC. No comparative trials (with AC) have assessed short- and medium-term local and regional complications, nor long-term followup (disease control and survival). These trials, and a trial of the impact of SNB on management strategies for breast cancer and quality of life, are in progress.
- *Economic assessment:* No studies compared SNB and AC.

Methods

ANAES systematically searched MEDLINE, EMBASE, Pascal, CancerLit and Cochrane Library databases, relevant websites, and grey literature between 1996 and June 2002 for consensus conferences, guidelines, systematic reviews, and economic studies, and between 2000 and June 2002 for clinical trials. Contents pages of specialist journals and references from articles were also searched. References were selected on level of evidence and design quality (review checklist) for studies, eliminating redundant studies (comparative trials and series of more than 100 cases for feasibility, 50 cases for technical steps, accuracy of data sources and analyses). The report was submitted to a working group of 13 experts and a multidisciplinary peer review group of 21 experts (surgeons, histopathologists, nuclear medicine specialists, oncologists), recruited from the relevant professional societies.

Further research/reviews required

While awaiting the results of multicenter trials in progress that compare SNB and AC in relation to lymph node involvement:

- Professional societies should draw up protocols to define the conditions under which SNB should be performed (standardization of the various steps, training stage for multidisciplinary teams, indications for lymph node sampling, and decision trees)
- Clinical researchers should study unresolved technical aspects and new indications (in relation to previous treatment, tumor characteristics, non-axillary lymph nodes)
- Patients undergoing SNB without AC should take part in a followup protocol
- Economic studies should analyze direct and indirect costs within the framework of clinical protocols.

Written by Caroline Latapy and Anne Isabelle Poullié, ANAES, France

INAHTA Briefs

Issue 2004/57

Title **Assessment of Intensity-Modulated Radiotherapy**

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Reference ANAES Report, May 2003

Aim

To assess the efficacy, safety, availability, and economic aspects of intensity-modulated radiotherapy (IMRT).

Conclusions and results

- The term "intensity-modulated radiotherapy" covers different technologies. There is no consensus definition of IMRT. IMRT is significantly more complex than any other radiotherapy technique, and requires rigorous and specific quality assurance.
- The 8 clinical trials selected presented a low level of evidence: a dose-escalation study and 7 case series, only one of which was a prospective study.
- The literature review provided insufficient information to determine a clinical risk/benefit ratio for this emerging technique. Limited clinical data show that IMRT is feasible for treating prostate, head /neck, central nervous system, breast, and gynecological cancers.
- Investment in IMRT depends much on the equipment and staff already available within the healthcare organization. A cost/efficacy ratio for IMRT could not be determined as no studies of adequate design quality were found.
- The practice survey reflects the current availability of IMRT in France: 87.7% of centers that responded did not use the technique, but 46.5% planned to introduce it within the next 3 years. Twelve centers had treated 159 patients between June 2000 and December 2002, mainly for prostate cancer (79.9%) and head and neck cancer (17%).

Methods

ANAES searched the MEDLINE, EMBASE and Pascal databases, useful websites, and the grey literature (between 1995 and 2002). Studies were selected according to their level of evidence and design quality (using review checklists). As there was little information in the literature, ANAES carried out a quantitative (postal questionnaire) and qualitative (onsite visits) practice survey. A working group (10 experts) and a multidisciplinary peer review group (13 experts), recruited from the relevant professional societies, validated the report.

Further research/reviews required

- IMRT is an emerging external radiotherapy technique. Its clinical applications have yet to be studied.
- Specific guidelines for this technique need to be drawn up to define the optimum human and equipment resources, quality assurance, and training for care staff.

Written by Dr Marie-Claude Hittinger and Nathalie Preaubert, ANAES, France

INAHTA Briefs

Issue 2004/58

Title **Low Intensity Ultrasound (Exogen™) for the Treatment of Fractures**

Agency **AÉTMIS, Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé**
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Reference Technology brief prepared for AÉTMIS (AÉTMIS 03–05).
Internet access to full text. ISBN 2-550-41956-1 (original addition ISBN 2-550-41721-6)

Aim

To assess the safety and efficacy of low intensity ultrasound (LIUS) (Exogen™) to accelerate bone fracture healing and reduce bone fracture complications.

Conclusions and results

Safety: Available studies do not report any adverse effects.

Efficacy: The efficacy evidence is weak for the following three indications:

1. Acceleration of fracture healing: LIUS may be effective in healing of fractures treated without surgery, but the evidence is weak. Research design weaknesses were found in the primary studies reviewed and in the one meta-analysis available
2. Prevention of fracture non-union: No evidence shows that LIUS can prevent non-union in higher-risk patient populations. No studies examine the efficacy of Exogen for this purpose
3. Treatment of non-union: The strength of the efficacy evidence for Exogen in treating non-union is weakened by the absence of randomized studies and by indications that the method of analysis (self-pairing used in case series) did not control for long-term natural healing.

Recommendations

The level of evidence is insufficient to recommend the use of Exogen, except as an exceptional treatment option in a limited number of patients. Specifically, in the case of non-union of tibial fractures, which have a grim prognosis, LIUS is a reasonable consideration after failed surgical intervention, and after the consolidation process, as measured by multiple-view serial radiographs, has ceased for several months. For other non-union fracture sites, the use of Exogen should be evaluated on the basis of a specific prognosis and clinical context.

Methods

AÉTMIS conducted a systematic review of the scientific literature up to September 2003.

The safety and efficacy evidence gathered had to be interpreted in the absence of a strong tradition of evidence-based medicine in orthopedics. The recommendations of the report tried to strike a balance between the clinical need for treatment and this lack of evidence.

Further research/reviews required

Assessment of the efficacy of Exogen was complicated by the lack of practice standards for treating specific fracture conditions and the lack of standards for measuring treatment outcomes. A culture of evidence-based medicine should be fostered within orthopedics. Before this treatment is made available to a large number of patients, or for a broader range of indications, strong evidence from high quality, randomized, controlled trials should required.

Written by Dr Reiner Banken, consulting researcher, AÉTMIS, Canada

Title	**Effectiveness of Physical Therapy**
Agency	**GR, Health Council of the Netherlands** Gezondheidsraad, Postbus 16052, NL-2500 BB Den Haag, The Netherlands; Tel: +31 70 3407520, Fax: +31 70 3407523
Reference	Health Council of the Netherlands. Publication No. 1999/20. Full text available at www.healthcouncil.nl (in Dutch, Executive Summary in English). Appendixes (systematic reviews) in English.

Aim

To review the current state of knowledge as regards the effectiveness of physical therapy in musculoskeletal disorders: electrotherapy, laser therapy, ultrasound therapy. Physiotherapists often use physical therapy in the restricted sense – ie, forms of treatment in which various types of apparatus are used to provide physical stimuli – particularly in treating musculoskeletal disorders. Although physical therapies are in widespread use, in recent years increasingly more experts have questioned the effectiveness of these therapies.

Conclusions and results

The Health Council has reviewed three systematic reviews (two of them were commissioned and supported by the Council) to establish what conclusions could be drawn regarding the effectiveness of electrotherapy, laser therapy, and ultrasound therapy. The review covered 169 RCTs. With few exceptions, the reviews present little or no evidence that the therapies concerned are effective in treating a wide range of conditions. The lack of convincing evidence contrasts sharply with the relatively large-scale and frequent use of these therapies in the Netherlands. Hence, widespread use in mainstream care is not justified.

Recommendations

The professional bodies for physiotherapy should initiate a policy to encourage members to change their procedures. These efforts should tie in with the quality improvement initiatives (eg, the formulation and revision of guidelines) that the professional bodies have been developing in recent years.

Methods

Review of systematic reviews of RCTs. Expert committee. Peer review of draft report.

Further research/reviews required

Further research is recommended for applications where slight evidence of effectiveness was found. These applications are:

1. Electrotherapy for arthrosis
2. Laser therapy for pain relief and the treatment of rheumatoid arthritis, and
3. Ultrasound therapy for 'tennis elbow'.

Written by Gabriël HM ten Velden, GR, The Netherlands

Title	**Therapeutic Exercise**
Agency	**GR, Health Council of the Netherlands** Gezondheidsraad, Postbus 16052, NL-2500 BB Den Haag, The Netherlands; Tel: +31 70 3407520, Fax: +31 70 3407523
Reference	Health Council of the Netherlands. Publication No. 2003/22. Full text available at www.healthcouncil.nl (in Dutch, with Executive Summary in English)

Aim

To review the current state of knowledge with regard to the effectiveness of therapeutic exercise.

Conclusions and results

Exercise therapy has been shown to be effective for patients with cystic fibrosis, COPD, claudicatio intermittens, osteoarthritis of the knee, and subacute and chronic low back pain. There are also indications that exercise therapy is effective in patients with Parkinson's disease, ankylosing spondylitis, osteoarthritis of the hip, and in those who have suffered stroke. Exercise therapy is not effective in patients with acute low back pain. There is insufficient evidence to support or refute the effectiveness of exercise therapy for patients with rheumatoid arthritis, shoulder complaints, neck complaints, RSI, asthma, and brochiectasis.

Recommendations

The local (national) trend in physiotherapy to emphasize exercise therapy should be strongly supported.

Methods

Review of systematic reviews of RCTs. Expert committee. Peer review of draft report.

Further research/reviews required

The Council advises that:

1. For disorders where evidence is lacking or insufficient, the effectiveness of exercise therapy should be further investigated according to current guidelines for the methodological quality and reporting of RCTs and systematic reviews
2. The effectiveness of the various types of exercise therapy should be compared, and
3. Methods to maintain, in the long term, the short-term effects of exercise therapy should be developed and evaluated.

Written by Gabriël HM ten Velden, GR, The Netherlands

Title **Contours of the Basic Health Care Benefit Package**

Agency **GR, Health Council of the Netherlands**
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Reference Publication No. 2003/02E. Full text available at www.healthcouncil.nl

Aim

As part of the planned reform of the health insurance system (a new system is expected to be introduced in the Netherlands in 2006), the Minister of Health, Welfare, and Sport has requested the Health Council of the Netherlands to 'formulate an opinion with regard to the workable, scientifically based criteria for identifying which services should be included in a basic package'. The Health Council gives an account of its findings in this advisory report.

Conclusions and results

Two sets of criteria have been designated, distinguishing a 'solidarity package' from compulsory insurance. The individual 'disease burden' combined with 'cost-effectiveness' forms a good basis upon which to define a basic package that, in accordance with the principle of solidarity (rich with poor, young with old, and healthy with sick) will be accessible to all. These criteria have been applied in several situations. For a compulsory package, additional criteria are required (eg, to protect individuals from their own decisions that may prove to have adverse consequences in the longer term, or to protect individuals against unfavorable decisions made by others): the costs of treatment, nursing care (possibly in relation to the insured's income level); the extent to which the disorder to be prevented or treated may afflict other people; the preventive nature of services; and the impact that service utilization has on the efficiency of health care as a whole. The two sets of criteria may result in a single basic package, but a 'solidarity' and a 'compulsory' basic package need not necessarily coincide. Based on the analytical distinction drawn by the Council, it is, in principle, feasible to identify a smaller 'compulsory' package within the 'solidarity' package. Considerations such as actuarial feasibility may have a bearing on the governmental decisions in the matter.

Recommendations

Before a new health insurance system is introduced, government should establish a national framework that supports rational decision making. This framework will need to accommodate transparent procedures for defining the package since applying the criteria will require a qualified approach.

Methods

A comprehensive review of the literature on priority setting in health care and the legal/social/ethical aspects. Expert committee. Peer review of draft report.

Further research/reviews required

Research is needed in cases where data on individual disease burden or cost effectiveness are missing or incomplete. Furthermore, there is a need for research that contributes to effective decision making on rationing issues.

Written by Gabriël HM ten Velden, GR, The Netherlands

Title	**Efficacy, Safety, and Effectiveness of Drug Eluting Stents**
Agency	**UETS, Unidad de Evaluación Tecnologías Sanitarias, Agencia Laín Entralgo** (Lain Entralgo Agency), C/ Gran Vía 27, 8ª, ES-28013 Madrid, Spain; Tel: +34 91 3089418, Fax: +34 91 3089458; www.madrid.org/lainentralgo/estudios/marcevalua/ffevalua.htm
Reference	Eficacia, seguridad y efectividad de los stents recubiertos de farmacos, June 2003

Aim

To review the scientific evidence related to efficacy, effectiveness, and safety of drug eluting stents used to revascularize primary lesion in the native coronary artery and to treat in-stent restenosis. A secondary objective is to review costs and economic analysis reports published on drug eluting stents.

Conclusions and results

In the past few years, studies have been developed to assess the effectiveness of drug eluting stents. The initial studies, FIM, RAVEL, and SIRIUS, present sufficient evidence on safety and efficacy in small groups of patients for the revascularization of coronary artery primary lesions with sirolimus coated stents. The evidence from these controlled and randomized trials suggests that stents with sirolimus are efficacious and safe in preventing angiographic restenosis and major cardiac adverse events in de novo lesions with specific, non-complex characteristics (only 12 months of followup). The TAXUS, ELUTES, and ASPECT trials also suggest that stents coated with paclitaxel are efficacious and safe in revascularizing primary lesions in coronary arteries. However, followup data from long-term clinical trials are lacking. Low-quality scientific evidence suggests that drug eluting stents for treatment of in-stent restenosis lesions are effective in preventing restenosis. Nevertheless, the results of international in-stent restenosis registry studies are optimistic in this high-risk group.

Recommendations

Although enough evidence suggests the effectiveness of the technology in specific primary lesions in native coronary arteries, further long-term studies are required to confirm the optimistic results. The technology must be used under study conditions in subgroups of patients different from those presented by the published scientific evidence. The use of drug eluting stents in these patients is essentially experimental and, as such, should be subject to ethics committee approval and informed consent by patients. A system for ongoing monitoring and evaluation should be established to assess long-term efficacy and safety.

Methods

The following electronic databases were searched: MEDLINE, INAHTA, and NHS CRD databases (DARE, HTA Database, NHS-EED Database Economic Evaluations of Health Care Interventions), Cochrane Database of Systematic Reviews, and the Controlled Clinical Trials Database.

Further research/reviews required

To clarify benefits of the technology in particular patients with complex lesions and higher risk of restenosis it is necessary to develop new studies that overcome the limitations of the existing studies.

Written by Andradas E and Blasco JA, UETS, Spain

Title **Systematic Review and Modeling of the Investigation of Acute and Chronic Chest Pain Presenting in Primary Care**

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Reference Health Technol Assess 2004;8(02). Feb 2004. www.ncchta.org/execsumm/summ802.htm

Aim

To ascertain the value of methods – including clinical features, resting and exercise electrocardiography, and rapid access chest pain clinics (RACPCs) – used in the diagnosis and early management of acute coronary syndrome (ACS), suspected acute myocardial infarction (MI), and exertional angina.

Conclusions and results

For acute chest pain, no clinical features in isolation were useful in ruling in or excluding an ACS, although the most helpful clinical features were pleuritic pain and pain on palpation. ST elevation was the most effective ECG feature for determining MI, and a completely normal ECG was reasonably useful at ruling this out. Results from 'black box' studies of clinical interpretation of ECGs found very high specificity, but low sensitivity. Point-of-care testing with troponins was cost effective in a simulation of management strategies for suspected ACS. Prehospital thrombolysis based on ambulance telemetry was more effective, but more costly than if performed in hospital. In chronic chest pain, resting ECG features were not found to be useful. In exercise ECG, ST depression performed only moderately well, although this did improve for a 2 mm cutoff. Other methods of interpreting the exercise ECG did not dramatically improve the results. Weak evidence suggested that RACPCs may be associated with reduced hospital admission of patients with noncardiac pain, better recognition of ACS, earlier specialist assessment of exertional angina, and earlier diagnosis of noncardiac chest pain. A simulation exercise of models for investigating suspected exertional angina predicted RACPCs to result in earlier diagnosis of confirmed coronary heart disease (CHD) and noncardiac chest pain than models of care based on open access exercise tests or routine cardiology outpatients, but they were more expensive. The benefits of RACPCs disappeared if waiting times for further investigation (eg, angiography) were long (6 months).

Recommendations

Emergency referral is justified for suspected ACS. ECG interpretation in acute chest pain can be highly specific for diagnosing MI. Point-of-care testing with troponins is cost effective in triaging patients with suspected ACS. Resting ECG and exercise ECG have limited value in diagnosing CHD.

Methods

Searches identified studies on patients with acute chest pain (data on the diagnostic value of clinical features or ECG), patients with chronic chest pain (data on the diagnostic value of resting or exercise ECG), or the effect of RACPC. Likelihood ratios (LRs) were calculated for each study, and pooled LRs were generated with 95% confidence intervals. A Monte Carlo simulation evaluated different assessment strategies for suspected ACS, and a discrete event simulation evaluated models for assessing suspected exertional angina.

Further research/reviews required

Determine the most appropriate model of care to ensure accurate triaging of patients with suspected ACS. Establish the cost effectiveness of prehospital thrombolysis in rural areas. Determine the relative cost effectiveness of rapid access chest pain clinics compared with other innovative models of care. Investigate how rapid access chest pain clinics should be managed. Establish the long-term outcome of patients discharged from RACPCs.

Written by Dr Jonathan Mant, Department of Primary Care and General Practice, University of Birmingham, UK

Title **Improving the Evaluation of Therapeutic Interventions in Multiple Sclerosis: Development of a Patient-Based Measure of Outcome**

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Reference Health Technol Assess 2004;8(09). Feb 2004. www.ncchta.org/execsumm/summ809.htm

Aim

To develop a patient-based, disease-specific measure of the health impact of MS that is clinically useful, scientifically sound, and suitable as an outcome measure in clinical trials and routine clinical practice to monitor the progress of MS patients.

Conclusions and results

Stage 1: A pool of 129 items was generated.

Stage 2: From this item pool we developed a 29-item measure of the physical (20 items) and psychological (9 items) impact of MS – the Multiple Sclerosis Impact Scale (MSIS-29).

Stage 3: The MSIS-29 satisfied recommended psychometric criteria for rigorous measurement. Data quality was excellent: missing data were low, item level test-retest reliability was high, and scale scores could be generated for >98% of respondents. Item descriptive statistics, item convergent and discriminant validity, and factor analysis supported summing items to produce two summary scores. MSIS-29 physical and psychological scale scores showed good variability, low floor and ceiling effects, good internal consistency, and test-retest reliability. Correlations with other measures and confirmation of hypotheses about group differences provided evidence for the validity of the MSIS-29 as a measure of the physical and psychological impact of multiple sclerosis. Effect sizes (physical scale = 0.82, psychological scale = 0.66) provided preliminary evidence for responsiveness.

Recommendations

The 29-item MSIS-29 is a new measure of the physical and psychological impact of MS that satisfied traditional psychometric criteria for reliable and valid measurement. There is preliminary evidence of responsiveness. The MSIS-29 is particularly appropriate in clinical trials to evaluate therapeutic effectiveness from the patient's perspective.

Methods

Standard traditional psychometric methods were used to develop the MSIS-29 in three stages. See monograph for details.

Further research/reviews required

1. Further evaluations of the MSIS-29 in different samples and settings will help clarify its strengths and weaknesses and further define its role in clinical practice and research.
2. Head-to-head comparisons of the full spectrum of psychometric properties of the MSIS-29 and existing MS outcome measures should be undertaken to determine the advantages and disadvantages of different instruments and how they complement each other.
3. Further evaluations of the MSIS-29 using newer psychometric methods, eg, Rasch item analyses and Item Response Theory.
4. The specificity of the MSIS-29 to MS and applicability to other neurological conditions should be tested.
5. A larger followup interview survey would be useful for feedback, especially in questions deemed irrelevant by subgroups (ie, ethnic minority groups, older people).
6. Validation of the MSIS-29 in other languages.

Written by Dr Jeremy Hobart, Department of Neurology, Peninsula Medical School, Derriford Hospital, UK

Title **Use of Modeling to Evaluate new Drugs for Patients With a Chronic Condition: The Case of Antibodies Against Tumor Necrosis Factor in Rheumatoid Arthritis**

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Reference Health Technol Assess 2004;8(11). Mar 2004. www.ncchta.org/execsumm/summ811.htm

Aim

To address the structural issues relating to effects on mortality and quality of life (QoL) and to identify data on the general QoL pattern in rheumatoid arthritis (RA) patients through a restructured, enhanced version of the Birmingham Preliminary Model (BPM).

Conclusions and results

A survey of rheumatologists shows that RA has different manifestations and responds to different agents in different patients. Hence, summarization of practice is difficult and open to criticism for oversimplification. However, the findings generally agree with other surveys and trends, eg, increasing acceptance of methotrexate as the first line drug of choice in RA patients, especially in aggressive disease. The newer agents, antibodies against tumor necrosis factor (anti-TNF) are starting to be used. The focus of the Birmingham Rheumatoid Arthritis Model (BRAM) on a drug sequence helped to avoid the incremental cost effectiveness of new treatments appearing lower than they really are when inappropriate comparators are used. BRAM was run for the strategies representing current UK practice to test the effect on the results of using the disease-modifying antirheumatic sequence. The results differed little from the base-case results.

Recommendations

This work achieved more realistic modeling of real-life clinical pathways and events, as it has developed from the BPM to the BRAM. The approach reflected in the BRAM is applicable to other chronic conditions, especially those involving a sequential approach to therapeutic options. The model was successfully restructured to consider different treatment sequence, including the sequence that best represents current practice in the UK.

Methods

This report uses the BRAM to evaluate two new anti-TFN drugs, etanercept and infliximab, used in treating RA. A rapid systematic review was conducted of physician surveys on the use of DMARDs (disease-modifying antirheumatic drugs) in adult RA patients. A postal survey of consultant rheumatologists in the UK then identified the drug sequences for the model. Using the model, a series of analyses were run. The issue of specifying the correct comparison was investigated using two separate analyses: comparing anti-TNFs with placebo, and comparing a sequence using anti-TNFs with a sequence representing current practice in the UK.

Further research/reviews required

The impact of DMARDs on QoL. The impact of DMARDs on patient life expectancy. Variation in compliance rates across DMARDs. Costs associated with RA incurred by patients and their families, including fuller coverage of adverse events of DMARDs. The costs and benefits of other DMARD sequences (which could be explored using the BRAM).

Written by Dr Pelham Mervyn Barton, Health Services Management Centre, University of Birmingham, UK

Title **Routine Examination of the Newborn: The EMREN Study. Evaluation of an Extension of the Midwife Role Including a Randomized Controlled Trial of Appropriately Trained Midwives and Pediatric Senior House Officers**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
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Reference Health Technol Assess 2004;8(14). Mar 2004. www.ncchta.org/execsumm/summ814.htm

Aim

To assess the implications and cost effectiveness of extending the role of midwives to include the routine (24-hour) examination of the healthy newborn usually carried out by junior doctors.

Conclusions and results

No statistical difference was found between senior house officer (SHO) and midwife examinations in appropriate referral rates to hospital or community, or in inappropriate referral rates to hospital. Video taped assessments were rated as carried out more appropriately by the midwives than by the SHOs. Overall maternal satisfaction was high, and higher when a midwife rather than an SHO examined. Few new health problems were identified at the 10-day examination. From the National Survey, it was estimated that midwives examine about 2% of babies in England. If midwives were to examine all babies where there were no complications of birth or antenatal history, the savings would be about £2 per baby born, equivalent to savings of £1.2 million nationally. Were midwives to examine all babies on normal wards, savings would increase to about £4.30 per baby born or £2.5 million nationally. Representatives of the professional bodies were of the opinion that having trained midwives carrying out the examination would be valuable.

Recommendations

All components of the study were consistent in showing benefits, or at least no significant barriers, in having suitably qualified, trained midwives carry out the examinations. Developing the role of the midwife to include examination of the newborn is likely to result in improved quality of examinations and higher satisfaction from mothers. It would slightly reduce overall health service costs, with some increased resources needed by midwifery departments, and some decrease in the resource needs of pediatric departments.

Methods

The study included a prospective randomized controlled trial (RCT) with mother and baby dyads randomized to either SHO or midwife for the routine examination of the newborn. Midwives and SHOs were videoed while performing the examinations. An independent consultant and a senior midwife rated the videos. Extensive interviews, surveys, consultations, and assessments were also carried out. Routine examinations of the newborn babies were carried out about 24 hours following birth, and further examinations were performed at home by the community midwife for half the babies in each group at 10 days.

Further research/reviews required

Further research is needed on: the value of conducting the examination at home rather than in hospital; the overall unsatisfactory quality of the examination of the hips; and appropriate inclusion criteria on which babies midwives should examine.

Written by Professor Joy Townsend, PEHRU, London School of Hygiene and Tropical Medicine, UK

Title **Involving Consumers in Research and Development Agenda Setting for the NHS: Developing an Evidence Based Approach**

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Reference Health Technol Assess 2004;8(15). Apr 2004. www.ncchta.org/execsumm/summ815.htm

Aim

To look at the processes and outcomes of identification and prioritization in both national and regional R&D programs in health and elsewhere, drawing on experiences of success and failure. To identify the barriers to, and facilitators of, meaningful participation by consumers in research identification and prioritization.

Conclusions and results

Of 286 documents that explicitly mentioned consumer involvement in identifying or prioritizing research topics, 91 were general discussions, 160 reported specific efforts to include consumers in identifying or prioritizing research topics, and 51 reported consumers identifying or prioritizing research topics in the course of other work. Detailed reports of 87 specific examples were identified. Most reports were descriptive, written by researchers who were key actors in involving consumers. A few reports were written by consumer participants. Fewer still were by independent researchers. Hence, our conclusions are not based on rigorous research, but implications for policy are drawn from reports and comparative analyses.

Recommendations

Productive methods for involving consumers require appropriate skills, resources, and time to develop and follow working practices. The more that consumers are involved, the more that research programs will learn from and about consumers. Research programs embarking on collaborations should approach well-networked consumers and provide them with information, resources, and support to empower them in key roles for consulting their peers and prioritizing topics. Consultations should engage consumer groups directly and repeatedly in facilitated debate. In discussing health services research, more resources and time are required if consumers are drawn from groups whose main interest is not health.

Methods

A framework was devised to examine ways of involving consumers in research. It identified key features, eg, types of consumers involved, whether consumers or researchers initiated the involvement, the degree of consumer involvement (consultation, collaboration or consumer control), forums for communication (eg, committees, surveys, focus groups), methods for decision-making, and practicalities of implementation. Context (institutional, geographical, and historical setting) and underpinning theories were viewed as important variables for analyzing examples of consumer involvement. This innovative framework was then applied to the review data from reports selected for inclusion and interviews.

Further research/reviews required

To develop and evaluate different training methods, information, education and other support for consumers and those wishing to involve them. To address the barriers to consumers' ideas influencing research agendas. To carry out prospective comparative studies of different methods for involving consumers. Addressing the processes and outcomes of consensus development that involves consumers would further advance research on collective decision-making.

Written by Dr Sandy Oliver, Social Science Research Unit, University of London, UK

Title **A Multicentre Randomized Controlled Trial of Minimally Invasive Direct Coronary Bypass Grafting Versus Percutaneous Transluminal Coronary Angioplasty With Stenting for Proximal Stenosis of the Left Anterior Descending Coronary Artery**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
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Reference Health Technol Assess 2004;8(16). Apr 2004. www.ncchta.org/execsumm/summ816.htm

Aim

To compare the clinical and cost effectiveness of minimally invasive direct coronary artery bypass grafting (MIDCAB) versus percutaneous transluminal coronary angioplasty (PTCA) with stenting in patients with proximal stenosis of the left anterior descending coronary artery. The trial was called AMIST, ie, Angioplasty versus Minimally Invasive Surgery Trial.

Conclusions and results

One hundred participants were randomized, 50 to PTCA and 50 to MIDCAB. This was 28% of the planned sample size. There were no serious imbalances in characteristics between groups. Six randomized participants did not receive the assigned interventions. Median times to intervention were 35 days and 44 days for PTCA and MIDCAB (p=0.18). There were no conversions to surgery in the PTCA group, but three conversions to median sternotomy in the MIDCAB group. Two deaths occurred in the MIDCAB group, but no other major adverse events. Statistically significant differences existed between the medians for the two groups for total, post-procedure, and intensive care length of stay (all p<0.0001). Eighty-four randomized patients completed 12 months followup, and median followup was 20.5 months. The duration of followup did not differ between groups for randomized patients (p=0.84). All randomized participants were included in the primary analysis of survival free from cardiac-related events. Estimated cumulative percentages experiencing events at 1 year for MIDCAB and PTCA groups were 7.1% and 9.2% respectively (hazard ratio 0.77, 95% CI 0.38 to 1.57, p=0.47).

Differences between groups in mean Seattle Angina and Coronary Revascularization Outcome Questionnaire scores at 3, 6, and 12 months after the index procedure favored MIDCAB, but were small and most failed to reach statistical significance. Differences in SF36 and EuroQol favored MIDCAB, but were again small and usually not statistically significant.

Total NHS procedure costs were £1,648 and £946, and the costs of resources used during one year of followup were £1,033 and £843, respectively for MIDCAB and PTCA. The difference in utility between the groups after 12 months followup was not statistically significant. Based on NHS costs, the incremental cost-utility ratio for MIDCAB was £44,600 per (EuroQol) QALY, and rose to £58,724 if patient costs were included. We found no evidence from AMIST that MIDCAB is more effective than PTCA. MIDCAB was clearly a more expensive procedure. Given the small and nonsignificant differences in effectiveness between MIDCAB and PTCA, and the higher costs of MIDCAB, it is unlikely that MIDCAB represents a cost effective use of resources in the reference population. Our main caution in interpreting these findings arises from the small sample size; a real difference in effectiveness of the size hypothesized may exist, but the trial had insufficient power to detect it. There were few complications with either intervention.

Methods

RCT; further details of the research methods can be found in the monograph.

Further research/reviews required

Details of the recommendations of the research can be found in the monograph.

Written by Professor Gianni Angelini, Bristol Heart Institute, University of Bristol, UK

Title **Does Early Magnetic Resonance Imaging Influence Management or Improve Outcome in Patients Referred to Secondary Care with Low Back Pain? A Pragmatic Randomised Controlled Trial**

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Reference Health Technol Assess 2004;8(17). May 2004. www.ncchta.org/execsumm/summ817.htm

Aim

To establish whether the early use of sophisticated imaging techniques, eg, magnetic resonance imaging (MRI) or computed tomography (CT) influences the clinical management and outcome of patients with low back pain (LBP) and whether it is cost effective.

Conclusions and results

Participants in both groups reported improvements in health status at 8 and 24 months, with slightly better scores in the 'early imaging' group. The mean difference for the ALBP score was 3.05 points at 8 months (p=0.005) and 3.62 points at 24 months (p=0.002). The 'early imaging' group also had significantly greater improvement in many subscales of the SF-36 at 8 months, but only for the Bodily Pain subscale at 24 months. For the EQ-5D, the difference was only significant at 24 months. Other than the share of participants receiving imaging (90% versus 30%) there were few differences in management throughout the 24-month followup. Total outpatient consultations in the two groups were similar, but more people in the 'early imaging' group had return outpatient appointments during the 8-month followup (p<0.001). At 24 months the number of outpatient appointments did not differ. Clinicians' diagnostic confidence, between trial entry and followup, increased for both groups with a significantly greater increase in the 'early imaging' group (p=0.01). Therapeutic confidence did not differ, and increased in both groups with time. The cost of imaging was the main determinant of the difference in total costs between groups, and it was estimated that 'early imaging' could provide an additional 0.07 QALYs, on average, over the 24-month followup. The mean incremental cost per QALY of 'early imaging' was £800. The results were sensitive to the imaging costs and confidence intervals surrounding estimates of average costs and QALYs.

Recommendations

The early use of sophisticated imaging does not appear to affect management overall. Although outcome scores improved slightly, this is of questionable clinical significance. However, imaging was associated with an increase in clinician's diagnostic confidence, particularly for nonspecialists. Decisions on the use of sophisticated imaging in this context will depend on judgments about the value of the observed differences in outcome and whether these justify the extra costs.

Methods

The study design was a pragmatic multicenter randomized controlled trial using a standard two-parallel group approach incorporating economic evaluation. A controlled 'before and after' approach was used in a subgroup to assess the impact of 'early imaging' on clinicians' diagnostic and therapeutic confidence. Patients who consented to participate were randomly allocated to 'early imaging' or 'delayed, selective imaging'. The referring clinician chose the imaging modality and patient management plan.

Further research/reviews required

Determine if more rapid referral to sophisticated imaging and secondary care for certain categories of LBP is important. Investigate the effect of MRI on patient expectation and reassurance.

Written by Professor Fiona J Gilbert, Department of Radiology, University of Aberdeen, UK

Title **The Clinical and Cost Effectiveness of Anakinra for the Treatment of Rheumatoid Arthritis in Adults: A Systematic Review and Economic Analysis**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
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Reference Health Technol Assess 2004;8(18). May 2004. www.ncchta.org/execsumm/summ818.htm

Aim

To review the evidence of the clinical and cost effectiveness of anakinra, an interleukin-1 receptor antagonist (IL-1Ra), in treating rheumatoid arthritis (RA) in adults.

Conclusions and results

Five high-quality randomized controlled trials (RCTs) of anakinra in adult RA patients were identified. Results of the clinical trials were consistent with clinical benefit as measured by the American College of Rheumatology (ACR) composite response rate at 6 months. Response rates varied across the trials, which may reflect the size of the trials and the range of doses evaluated. Consistent benefit was seen at the higher dose. Benefit was evident with monotherapy and in combination with methotrexate. Data on the efficacy endpoints in a large pragmatic safety study have not been made available, which is of concern. Anakinra was associated with a high incidence of injection-site reactions. Serious adverse events were infrequent, but longer term followup is required. No published economic evaluations of anakinra in RA patients were identified. The Birmingham Rheumatoid Arthritis Model (BRAM) gives a base-case estimate of the incremental cost-effectiveness ratio (ICER) of anakinra of £106,000 to £604,000/quality-adjusted life-year (QALY). Substantial variations were made in key parameters in sensitivity analyses. ICERs were responsive, but did not drop below £50,000/QALY in any univariate sensitivity analysis.

Recommendations

Based on ACR response, anakinra is modestly effective in treating RA, but no conclusions can be drawn on the effect of treatment on disease progression. Adjusted indirect comparison suggests that anakinra may be significantly less effective at relieving the clinical signs and symptoms of RA than tumor necrosis factor (TNF) inhibitors used in combination with methotrexate, but these results should be interpreted with caution. BRAM produces an ICER for anakinra substantially higher than those for infliximab and etanercept. However, patients may respond to anakinra when they have not responded to other TNF inhibitors. Anakinra may yield a clinically significant improvement in some patients that could not otherwise be achieved.

Methods

Studies were identified that included RCTs or economic evaluations of anakinra in adult patients with RA. Health economic reviews were assessed. Data were extracted and quality assessed using a structured approach. BRAM was used to compare disease-modifying antirheumatic drug (DMARD) sequences chosen to reflect current clinical practice, with and without anakinra, at different points in the DMARD sequence.

Further research/reviews required

RCTs to evaluate the efficacy, safety, and cost of anakinra over the longer term. Comparative trials of anakinra with other DMARDs and biological modifiers. Assessment of anakinra in treating patients who failed to achieve benefit while taking infliximab or etanercept. Assessment of the impact of DMARDs and anakinra on joint replacement, mortality, and quality of life. Controlled clinical trials of combination therapy with two anticytokines. Investigation of newer biological therapies. Utility of radiographic outcomes in clinical trials of RA.

Written by Dr Amanda Burls, Department of Public Health & Epidemiology, University of Birmingham, UK

Title **Islet Cell Transplantation for the Treatment of Non-uremic Type 1 Diabetic Patients with Severe Hypoglycemia**

Agency **AHFMR, Alberta Heritage Foundation for Medical Research**
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Reference HTA 31, April 2003 (English). ISBN 1-896956-47-5 (print); ISBN 1-896956-51-3 (online): www.ahfmr.ab.ca/programs.html

Aim

To assess the efficacy/effectiveness, safety and status of islet cell transplantation alone (ITA) in treating patients with brittle type 1 diabetes who do not have kidney disease and have not received a previous organ transplant.

Conclusions and results

Studies have reported on combined islet cell and kidney transplantation in type 1 diabetic patients with end-stage renal failure. No controlled trials have compared ITA with other treatments. A new ITA method, the Edmonton protocol, uses a novel steroid-free immunosuppressive regimen that is less toxic to the pancreatic beta cells and kidneys, an islet cell preparation media that is devoid of xenoprotein contamination, a much shorter cell preparation time, and islet cells derived from multiple cadaveric donors rather than a single donor. Short-term results from the Edmonton series are promising. By January 2002, 17 patients had received the Edmonton protocol. Of the 15 consecutive patients with at least 1 year followup, 12 patients were insulin independent after ITA. After 2 years, four out of six patients were still off insulin. No patient experienced hypoglycemia following ITA, although followup was short. ITA is a minimally invasive procedure that appears to be safe. The risks are primarily related to the procedure itself and the immunosuppressive regimen. The Immune Tolerance Network has launched an international trial to confirm and extend the results of the Edmonton series.

Recommendations

Limited evidence suggested that ITA is effective in controlling labile diabetes and restoring the ability to recognize hypoglycemia in a select group of patients in the short term. The long-term hormonal effects of ITA are unknown. ITA is a promising procedure that may become an alternative therapy for the small subgroup of patients with type 1 diabetes who have hypoglycemia in the absence of kidney disease. The Edmonton protocol is still under development, and ITA should not be considered 'standard care' for non-uremic patients with type 1 diabetes and severe hypoglycemia.

Methods

This report is a qualitative systematic review of primary clinical research. Two researchers reviewed the abstracts, selected the studies, and extracted the data. The methodological quality of the included studies was not formally assessed.

Further research/reviews required

Determine if ITA prevents or arrests complications associated with chronic diabetes, and whether its hormonal effect is durable. Refine techniques to measure islet cell function and viable cell mass so that the metabolic effects of ITA can be evaluated with more certainty. ITA uses multiple cadaveric organs to treat one patient. Whether this potentially induces an antibody response that will preclude the patient from receiving further organ transplants is unknown. The ethical issue of using multiple scarce organs to treat one patient has yet to be addressed.

Written by Bing Guo, Christa Harstall, and Paula Corabian, AHFMR, Canada

Title	**Surgical Treatments for Deep Venous Incompetence**
Agency	**AHFMR, Alberta Heritage Foundation for Medical Research** Health Technology Assessment Unit, Suite 1500, 10104-103 Avenue NW, Edmonton, Alberta T5J 4A7, Canada; Tel: +1 780 423 5727, Fax: +1 780 429 3509
Reference	HTA 32, July 2003 (English). ISBN 1-896956-61-0 (print); ISBN 1-896956-63-7 (online): www.ahfmr.ab.ca/programs.html

Aim

To critically appraise and synthesize the published evidence on the short- and long-term efficacy/effectiveness of surgical techniques for patients with deep venous insufficiency (DVI), and attendant skin changes/ulceration, that is refractory to standard care.

Conclusions and results

Two randomized controlled trials and 12 nonrandomized comparative studies reported on a variety of procedures ranging from superficial venous surgery (SVS) and subfascial endoscopic perforator surgery (SEPS) through to deep venous reconstruction (including valvuloplasty, transplantation, and transposition) to treat DVI. Deficiencies in reporting, methodological weakness, and marked interstudy heterogeneity regarding patient selection, postoperative management, surgical method, definition of abnormal venous hemodynamics, symptom grading, and diagnostic and venous function testing precluded definitive synthesis of the data.

Recommendations

Limited evidence suggested that combined SVS/valvuloplasty is relatively safe and potentially more effective than SVS alone in preventing ulcer recurrence in patients with primary DVI in both the short- and midterm. Evidence for the efficacy of valvuloplasty, bypass, transplantation, SEPS, and iliac stenting in treating DVI was inconclusive. Optimum surgery for patients with deep venous obstruction or secondary valvular incompetence remains unclear.

Methods

Studies on nonpregnant patients being treated for deep or mixed deep/ superficial/ perforator chronic venous insufficiency were identified by searching PubMed, EMBASE, CINAHL, Cochrane Library, Science Citation Index, and websites of various health technology assessment agencies, research registers, and guideline sites from January 1990 to July 2003. Randomized controlled trials and nonrandomized comparative studies were included (no language restrictions).

Further research/reviews required

Due to the complex, long-term nature of chronic venous insufficiency and problems with patient selection and ethics, it is unlikely that a large controlled trial will be conducted to ascertain the safety and efficacy of surgery for DVI. However, standardized reporting and collection of data in a registry would be a move forward. Also, professional bodies should consider providing guidance, eg, an evidence based treatment algorithm, that would define when to perform SVS in patients with mixed or deep venous insufficiency and what type of surgery is appropriate for different indications. Patients requiring surgery for DVI have usually failed all other therapies. While it is important to know whether surgery for deep venous incompetence works, it may be equally important to quantify why less invasive treatments have failed.

Written by Ann Scott and Paula Corabian, AHFMR, Canada

Title **Ovulation Induction Drug Therapy for Anovulatory Infertility Associated With Polycystic Ovary Syndrome**

Agency **AHFMR, Alberta Heritage Foundation for Medical Research**
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Reference HTA 33, March 2004 (English). ISBN 1-896956-85-8 (print); ISBN 1-896956-87-4 (online): www.ahfmr.ab.ca/programs.html

Aim

To critically appraise and synthesize the published evidence regarding the safety and efficacy/effectiveness of ovulation induction (OI) drug therapy to manage anovulatory infertility associated with polycystic ovary syndrome (PCOS) in women of reproductive age.

Conclusions and results

The question of which is the safest and most effective OI drug therapy for women with PCOS could not be definitively answered. Twelve randomized controlled trials (RCTs) and 6 systematic reviews showed:

- Clomiphene citrate (CC) remains the pre-eminent treatment because of its relative safety, effectiveness in achieving ovulation, simple mode of administration, and comparatively low cost
- Gonadotrophin therapy is the next treatment choice for women who do not ovulate or conceive in response to CC therapy
- Metformin as a pretreatment and co-treatment with CC was successful in increasing the chances of achieving pregnancy in selected cases
- The clinical utility of using pulsatile gonadotrophin releasing hormone (GnRH) for this indication remains to be established
- There is no clinical advantage in the routine use of GnRH analogue in addition to gonadotrophin therapy.

Recommendations

Reliable data were limited. OI drug therapy appears to be effective, but the evidence is insufficient to identify the safest and most effective agent. Candidates for OI drug therapy should be informed in advance about their chances of achieving pregnancy and the potential risks. Appropriate OI therapy should encompass careful use of the drug, close monitoring for adverse events, and long-term followup. Gonadotrophin therapy should be restricted to centers with appropriate expertise.

Methods

Literature databases and websites of health technology assessment agencies, research registers, and guidelines were systematically searched (Jan. 1993 to Oct 2003). RCTs comparing OI drug therapy with other OI treatments, placebo, or no treatment in women of reproductive age with anovulatory infertility associated with PCOS were included. The selected RCTs were screened and analyzed by two reviewers using predetermined quality criteria. Systematic reviews reporting on the safety and efficacy/effectiveness of OI drug therapy alone for this indication were also included.

Further research/reviews required

Large scale, well-designed, well-executed RCTs with longer followup are needed. Accurate and detailed subclassification of women with PCOS would also be helpful. Data on the overall cost of the various OI drug therapies are needed to help patients make decisions and to augment the formulation of policy for using this therapy.

Written by Paula Corabian and Ann Scott, AHFMR, Canada

Title **Diagnosis and Screening of Colorectal Cancer**

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Reference Kræft i tyktarm og endetarm. Diagnostik og screening. Medicinsk Teknologivurdering 2001;3(1) ISBN 87-90951-56-3 (print); ISBN 87-90951-57-3 (online): www.cemtv.dk/publikationer/docs/Kolorektal/marts2001/index.html

Aim

Colorectal cancer mortality is higher in Denmark than in comparable countries except Great Britain. Against this background an assessment was initiated. The diagnostic strategy employed until now has been rectoscopy combined with x-ray. This strategy should be assessed in relation to:

1. Sigmoidoscopy combined with x-ray examination of the colon
2. Colonoscopy compared with sigmoidoscopy and x-ray examination
3. Sigmoidoscopy combined with fecal blood testing, and
4. Description of a model for screening.

Conclusions and results

Rectoscopy was found to be obsolete and should not be used to diagnose patients with colorectal symptoms. Sigmoidoscopy should be used as the primary endoscopic method combined with fecal occult blood testing. If the blood test is positive, colonoscopy is recommended. Colonoscopy is the method of examination that has the highest sensitivity to colorectal cancer and adenomas, but is expensive and is performed by specialists.

Periodic fecal blood screening every second year or every year was found to be effective in detecting age-related cases of intestinal cancer at early stages. Danish population (5.2 million) screening was estimated to reduce mortality from colorectal cancer by 360 to 500 cases per year.

Recommendations

Changing the diagnostic strategy over the next 5 years is recommended. The possible presence of colorectal cancer should be considered in patients over 40 years of age who experience bleeding, changes in bowel habits, or other intestinal symptoms. Initial examinations should be performed by a general practitioner. Specific diagnostic examinations (sigmoidoscopy and colonoscopy) should be handled centrally by endoscopic entities to secure a high-quality standard.

Methods

The study, carried out by DACEHTA and an interdisciplinary expert group, included systematic literature reviews on clinical evidence and evaluations of patient-related aspects, organizational aspects, and economic consequences.

Further research/reviews required

Feasibility studies are needed before a final national screening program can be recommended.

Written by Pia Bruun Madsen and Peter Matzen, DACEHTA, Denmark

Title **Accelerated Systematic Review of Implantable Spinal Infusion Devices for Chronic Pain and Spasticity**

Agency **ASERNIP-S, Australian Safety and Efficacy Register of New Interventional Procedures – Surgical**

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Reference ASERNIP-S Report Number 42, May 2003, ISBN (0-909844-63-1)

Full text available: www.surgeons.org/asernip-s/publications.htm

Aim

To assess the safety and efficacy of implantable spinal infusion devices for treating chronic pain and spasticity.

Conclusions and results

The use of implantable spinal infusion devices appears to be safe. Drug-related adverse events occur, as they do when chronically administered via the systemic route, although perhaps less than for systemic administration. Device-related adverse events occur with replacement or revision rates ranging from 3% to 17% and the explantation rate varying from 0% to 21% in the reviewed literature. Infusion of drugs via implantable spinal infusion devices appears efficacious, with significant reductions in pain measured via visual analogue scales for pain. Improvements in care and activities of daily living were reported for patients with spasticity. The included randomized controlled trial also showed a reduction in toxicity, when compared to medical management, and this reduction impacted on the cumulative survival of the group implanted with the spinal infusion device. Cost studies showed that implantable spinal infusion devices are less costly in the long term than medical management. Short-term costs of implantable infusion devices are high, due to the cost of screening, the device itself, and implantation of the device. Implantable infusion devices were not cost effective when circumstances of high adverse events and high cost of care were simulated. Hence, it is important to carefully select a patient group that is suitable for implantation and likely to retain the implant. Infusion of opioid agents for treating chronic pain or baclofen for treating spasticity, intrathecally via implantable infusion devices appears to be safe and effective, although this conclusion is based on limited evidence.

Methods

MEDLINE, PREMEDLINE, EMBASE, Current Contents and PubMed were searched, using Boolean search terms, from inception to April 2003. The Internet was also searched in February 2003. Searches were conducted without language restrictions.

Written by Simpson BJ et al, ASERNIP-S, Australia

Title	**Accelerated Systematic Review of Spinal Cord Stimulation (Neurostimulation)**
Agency	**ASERNIP-S, Australian Safety and Efficacy Register of New Interventional Procedures – Surgical** PO Box 553 Stepney, Australia; Tel +61 8 83637513, Fax +61 8 83622077; college.asernip@surgeons.org
Reference	ASERNIP-S Report Number 43, ISBN (0-909844-62-3) Full text available: www.surgeons.org/asernip-s/publications.htm

Aim

To assess the effectiveness and safety of spinal cord stimulation (neurostimulation).

Conclusions and results

Spinal cord stimulation (SCS) was shown to be effective in relieving pain in only some of the included studies, but the small patient numbers may have limited the ability of studies to detect clinically important differences. SCS appears to be relatively safe, although the long-term safety and effectiveness of SCS have not yet been evaluated.

Nine RCTs of spinal cord stimulation covering five indications were included – four angina trials, one failed back surgery syndrome, two critical limb ischemia, one complex regional pain syndrome, and one painful diabetic neuropathy. SCS was more effective in terms of pain relief or reducing anginal attacks when compared with placebo or delayed implantation, but no difference was found in the comparisons with CABG or switching SCS on and off in the same patient. For critical limb ischemia, SCS was more effective in relieving pain than analgesia alone, but no difference was found when SCS plus best medical treatment was compared with best medical treatment alone. For complex regional pain syndrome, SCS was more effective in relieving pain than physiotherapy, but no difference was found between SCS and placebo for painful diabetic neuropathy. The most frequently reported complications were electrode or lead displacements, which required reintervention and repositioning, although these complications are decreasing as the technology improves. A small number of implant and battery failures have been noted, as has one duodenal perforation and two dural punctures. Infection at the implant site appears to be relatively common.

Methods

MEDLINE and PreMEDLINE were searched up to April 2003, and the Cochrane Library Issue 2, 2003 was searched for reports of randomized controlled trials (RCTs) comparing SCS with an alternative treatment, placebo, or no treatment. RCTs were included if they reported pain or pain relief as an outcome.

Written by Middleton PM et al, ASERNIP-S, Australia

Title **A Randomized Controlled Trial to Evaluate the Clinical and Cost Effectiveness of Hickman Line Insertions in Adult Cancer Patients by Nurses**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
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Reference Health Technol Assess 2003;7(36). Nov 2003. www.ncchta.org/execsumm/summ736.htm

Aim

To examine the clinical and cost effectiveness of image-guided Hickman line insertions versus blind Hickman line insertions undertaken by nurses in adult cancer patients.

Conclusions and results

No statistically significant difference was found between the mean cost per patient in the two arms of the trial. The only statistically significant difference in clinical outcomes was the frequency of catheter-tip misplacement, which was higher in the blind arm of the trial. At very low costs, the image-guided approach dominates the blind approach as fewer costs and greater benefits are incurred. It is evident that nurses previously inexperienced in the procedure can be trained to insert Hickman lines successfully both at the bedside and under image guidance within a 3-month period.

Recommendations

This report indicates that nurse insertion of Hickman lines in most adult cancer patients is both safe and effective. However, image-guided insertion may be preferred in a select group of patients. The results reveal that skills and expertise can be transferred from trainer to trainee through a relatively short, but intensive, training course. It is also evident that patients support nurse insertion. Further research is suggested.

Methods

A cost-effectiveness analysis alongside a randomized controlled trial of two interventions:

1. Blind insertion of a Hickman line, and
2. Image-guided insertion of a Hickman line.

Further research/reviews required

Further research is suggested to compare the safety and efficacy of nurse versus doctor insertions in particular subgroups of patients and also to assess the quantity and quality of current service provision to inform NHS decision making in this area.

Written by Ms Angela Boland, Liverpool Reviews & Implementation Group, University of Liverpool, UK

Title **Effectiveness and Efficiency of Guideline Dissemination and Implementation Strategies**

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Reference Health Technol Assess 2004;8(06). Feb 2004. www.ncchta.org/execsumm/summ806.htm

Aim

To systematically review the effectiveness and costs of guideline development, dissemination, and implementation strategies. To estimate the resource implications of these strategies. To develop a framework for deciding when it is efficient to develop and introduce clinical guidelines.

Conclusions and results

The inclusion criteria were met by 235 studies reporting 309 comparisons, whereof 73% of comparisons evaluated multifaceted interventions (MFI). The maximum number of replications of a specific MFI was 11 comparisons. Most comparisons reporting dichotomous process data reported improvements in care, but the effects within and across interventions varied considerably. Commonly evaluated single interventions were reminders, dissemination of educational materials, and audit and feedback. Twenty-three comparisons of MFIs involved educational outreach. Most interventions observed modest to moderate improvements in care. No relationship was found between the number of component interventions and the effects of MFIs. Only 29.4% of comparisons reported economic data. Most studies used process measures as the primary endpoint, but only three guidelines were evidence based. Survey respondents rarely identified existing budgets to support guideline dissemination and implementation. Generally, respondents thought that only dissemination of educational materials and short educational meetings were feasible within current resources.

Recommendations

Given imperfect evidence on the efficiency of guideline dissemination and implementation strategies, decision makers must use considerable judgment about how best to use limited resources. They need to consider the potential clinical areas for clinical effectiveness activities, the likely benefits and costs required to introduce guidelines, and the likely benefits and costs resulting from changes in provider behavior.

Methods

Single estimates of dichotomous process variables were derived for each study comparison based upon the primary endpoint or the median measure across several reported endpoints. Separate analyses were used to compare different types of intervention. The study also explored whether the effects of MFIs increased with the number of intervention components. Studies reporting economic data were critically appraised. A survey to estimate the feasibility and likely resource requirements of guideline dissemination and implementation strategies in UK settings was carried out with key informants from primary and secondary care.

Further research/reviews required

Develop and validate a coherent theoretical framework of health professional and organizational behavior and behavior change to better inform the choice of interventions in research and service settings. Estimate the efficiency of dissemination and implementation strategies in the presence of different barriers and effect modifiers.

Written by Professor Jeremy Grimshaw, Institute of Population Health, University of Ottawa, Canada

Title **Clinical Effectiveness and Cost Effectiveness of Neonatal Screening for Inborn Errors of Metabolism Using Tandem Mass Spectrometry: A Systematic Review**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
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Reference Health Technol Assess 2004;8(12). Mar 2004. www.ncchta.org/execsumm/summ812.htm

Aim

To evaluate the clinical and cost effectiveness of tandem mass spectrometry (MS) based neonatal screening for inborn errors of metabolism (IEM).

Conclusions and results

Evidence from the reviews of IEM found that the UK screening program for phenylketonuria (PKU) was well established, and there was universal agreement that neonatal screening for PKU was justified. Of the many other disorders that can be detected by tandem MS, the best candidate condition for a new screening program, was medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency. For many other IEM that can be detected by tandem MS, robust clinical evidence was limited. Cost-effectiveness analysis using economic modeling indicated that substituting the use of tandem MS for existing technologies for screening of PKU alone could not be justified. However, results from the economic modeling indicate that the addition of screening for MCAD deficiency as part of a neonatal screening program for PKU using tandem MS would be economically attractive. Using an operational range of 50,000 to 60,000 specimens per system per year, the mean incremental cost for PKU and MCAD deficiency screening combined using tandem MS from the model was – £23,312 for each cohort of 100,000 neonates screened. This cost saving is associated with a mean incremental gain of 59 life-years. Additional economic modeling using the available evidence does not support including other inherited metabolic diseases in a neonatal screening program.

Recommendations

The evidence appears to support the introduction of tandem MS into a UK neonatal screening program for PKU and MCAD deficiency combined. Tandem MS has the potential for simultaneous multidisease screening using a single analytical technique. Although the marginal cost of extending the program to include other conditions may be relatively small, the application of this new technology to PKU and MCAD deficiency screening does not imply the wholesale inclusion of all disorders detectable by tandem MS.

Methods

This review updates of two previous health technology assessment reports of neonatal screening for IEM. These reports have been updated by a systematic review of published research (between 1995 and January 2002) on neonatal screening of inherited metabolic disorders using tandem MS. This was supplemented by a search for economic literature and the application of a modeling exercise to investigate the economics of using tandem MS in a neonatal screening program in the UK.

Further research/reviews required

Further research should focus primarily on the long-term effectiveness of treatment strategies on adverse outcomes (disabilities and impairments) under conventional management and the potential impact of early diagnosis using tandem MS.

Written by Abdullah Pandor, ScHARR Technology Assessment Group, Sheffield, UK

Title **Positron Emission Tomography (PET) – Diagnostic and Clinical Use**

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Reference SMM Report No. 6/2003. ISBN 82-14-02971-6

Aim

To update the knowledge on diagnostic and clinical use of PET by summarizing the findings of recent health technology assessment (HTA) reports and systematic reviews of relevance.

Conclusions and results

The report is based on 14 HTA reports and 3 systematic reviews.

- Many references in the reports overlap, and they generally conclude in agreement. The clinical use of PET as diagnostic tool has increased during the period, despite the lack of good documentation on clinical effectiveness. The main areas of use are still within oncology, neurology, and cardiology.
- HTA reports published after the INAHTA report of 1999 and the SMM report in 2000 conclude that PET is more accurate than other diagnostic procedures for several indications in oncology and should therefore be used.
- This applies mainly in diagnosing non-small cell lung cancer (NSCLC) and solitary pulmonary nodules, staging of Hodgkin's disease, identifying metastasis from malignant melanoma and colorectal cancer, and in finding tumors in the head/neck.
- It is important to note that PET is still in the development phase. Hence, examinations should be performed within the framework of clinical trials since there is a need for knowledge collected systematically.

It is also important to note that "PET scanning should be used only if the results of the test will affect patient management".

Methods

A literature search for 2001–2003 was performed in the following databases: Health Technology Assessment (HTA) database, Database of Abstracts of Reviews of Effectiveness (DARE), NHS Economic Evaluation Database (NHSEED), TRIP database.

Written by Berit Mørland, SMM, Norway

INAHTA Briefs

Issue 2004/81

Title **Therapeutic Use of Hematopoietic Stem Cells From Cord Blood**

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Reference SMM Report No. 4/2003. ISBN 82-14-02970-8

Aim

To evaluate the scientific basis for the therapeutic use of cord blood stem cells.

Conclusions and results

- Autologous transplants of stem cells have yet to be reported or documented. Published results on the therapeutic use of stem cells from cord blood regard allogeneic use.
- More than 2,000 patients (about 1,600 children and 400 adults) have been transplanted with allogeneic stem cells from cord blood. While results from both related and unrelated donors are reported for children, cord blood transplantations in adults have been almost exclusively from unrelated donors.
- The clinical results of allogeneic transplants of cord blood stem cells have been compared only to results of allogeneic stem cells from bone marrow or peripheral blood in retrospective studies. These results suggest that the clinical effect of cord blood transplant, at least in children, may be comparable to transplants with stem cells from bone marrow or peripheral blood.
- The number of stem cells in the cord blood graft is often insufficient to obtain adequate engraftment.
- The risk of graft-versus-host disease is probably less in transplants with cord blood than transplants using allogeneic stem cells from bone marrow or peripheral blood with comparable HLA matching.

Methods

We systematically reviewed all available literature reporting on the clinical outcome of transplantation with the use hematopoietic stem cells from cord blood. Controlled and uncontrolled studies were included for further assessment. Clinical outcomes assessed were overall survival, disease-free/progression-free/event-free survival, engraftment, and complications/adverse effects. Studies were identified by computer-based searches in MEDLINE. Additional studies were identified by hand searching reference lists of relevant primary and secondary publications, and by manual searches using author names and text words. Studies were systematized according to study design and critically assessed for relevance, quality, and validity. Among 435 publications identified, 67 reported results of transplantation of cord blood stem cells. Of these, only 17 studies were found to meet the inclusion and quality criteria, thus, constituting the basis of the systematic review. Fifty publications were not accepted due to overlapping data, double publications, and/or low quality/validity defined as less than 20 patients or less than 10 patients per disease indication. Three cohort studies and 14 case series were included. The cohort studies have a retrospective design with historical controls. Two patient series are registry studies that report results from a large number of patients. None of the studies are population based.

Written by Anita Lyngstadaas, SMM, Norway

Title **Prophylactic Removal of Wisdom Teeth**

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Reference SMM Report No. 10/2003. ISBN 82-14-03241-5

Aim

To assess the scientific evidence on prophylactic removal of impacted wisdom teeth as regards the incidence of surgical complications associated with prophylactic removal, the morbidity associated with retention, quality of life, and economic aspects.

Conclusions and results

No randomized controlled trials were identified that compared outcomes of early removal versus deliberate retention of asymptomatic third molars. The report includes 11 patient series, 5 cohort studies, 2 case-controlled studies, 6 cross-sectional studies and 1 decision analysis. Studies on complications related to prophylactic removal report a relatively high prevalence of deep residual periodontal defects at the distal surface of the mandibular second molar after surgical extraction of the adjacent impacted third molar. However, there was a low incidence of pain, permanent nerve damage (more than 6 months) on inferior alveolar and lingual nerve, fractures, or serious infection. Studies on complications related to retention report a relatively high incidence of pericoronitis and caries, with higher incidence of periocoronitis related to partially erupted third molars compared to fully retained. Only low incidence of root resorption of second molar teeth, cysts, and tumors was found. This report is based on evidence from studies that use small selected patient groups. Hence, it is difficult to make conclusions and recommendations. Dentists in Norway recommend prophylactic removal of third molars when the future likelihood of third molars causing problems is high, and the incidence of postoperative complications is low. This includes partially erupted wisdom teeth. Removal of asymptomatic, fully retained wisdom teeth is not recommended. Since the report is based on less-than-optimal studies, the patient's preference needs to be decisive.

Methods

The report is based on a systematic review from UK (NCCHTA, 2000) and guidelines from NICE and SIGN in addition to an updated systematic review on studies published from 1999 to May 2003. Norwegian /Scandinavian practice was also included in a search of studies from 1980 to May 2003. The following databases were searched: the Cochrane Controlled Trial Register, Database of Abstracts of reviews of Effectiveness (DARE), International Network of Agencies for Health Technology Assessment (INAHTA) database, MEDLINE, EMBASE, National Guideline Clearinghouse, PRODIGY Guidance, NICE (National Institute for Clinical Excellence), SIGN (Scottish Intercollegiate Guidelines Network), OHE Economic Evaluations Database, and NHS Economic Evaluation Database. The literature search for primary literature identified 1109 abstracts that were reviewed, 145 possibly relevant studies were assessed, and 25 studies were included in the report. Ten studies were included on Norwegian/Scandinavian practice.

Written by Ellen M Nilsen, SMM, Norway

Title The Cost Effectiveness of Lifestyle Advice

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Reference SMM Report No. 7/2003. ISBN 82-14-02970-8

Aim

To review national and international research that might elucidate a new scheme with a physician's fee for lifestyle counseling, referred to in Norway as "green prescription".

Conclusions and results

The report is based on a short literature summary, mostly of reviews.

- It is possible to influence physician behavior through economic incentives (eg, "green prescription"), educational visits to doctors' offices, audit and feedback, and other initiatives. The effects are usually moderate or even absent, but seem to be stronger when several strategies are combined.
- It is possible to change patients' lifestyle (diet, physical activity, smoking habits, drinking habits, etc) with general practitioner counseling to patients who visit for reasons other than those associated with lifestyle. The effects seem to be better when combining oral information with other initiatives, eg, written material and patient followup. The effects are often weak and decrease over time.
- Lifestyle changes through a change in diet and physical activity can be cost effective in the sense that quality and length of life are improved at an acceptable cost to society. The studies are based partly on optimistic projections about behavior change, and it is doubtful whether the initiatives will be cost effective.
- It is possible to reduce the use of medications with lifestyle interventions, but carrying out the interventions might cost more than the savings gained from a lower use of medications.
- Only a few studies explored the effects on life expectancy. There is little evidence that a change in physical activity and diet would yield more than a few additional months of life, on average.
- Patient co-payments tend to reduce the use of preventive services. This effect seems to be strongest in low socioeconomic groups.

Methods

Three literature searches were conducted; one concerning the effect of different strategies for changing physician behavior, one concerning the effect of strategies for changing patients' food/diet and physical activity, and one concerning cost effectiveness and medication savings. The searches were conducted in DARE, HTA and Cochrane, except the search regarding cost effectiveness, where only the OHE-HEED database was used.

Written by Ivar Sønbø Kristiansen and Torbjørn Wisløff, SMM, Norway

Title	**A Systematic Review of Intraoperative Ablation for the Treatment of Atrial Fibrillation**
Agency	**ASERNIP-S, Australian Safety and Efficacy Register of New Interventional Procedures – Surgical**
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Reference	ASERNIP-S Report Number 38, July 2004, ISBN 0-909844-64-x.
	Full text available: www.surgeons.org/asernip-s/publications.htm

Aim

To assess the safety and efficacy of intraoperative surgical ablation techniques in treating atrial fibrillation (AF) compared to other surgical procedures, including cardiac surgery (CS) alone, or the Maze-III procedure, the current 'gold standard' surgical treatment for AF.

Conclusions and results

Sixty-nine studies using intraoperative ablation were identified, plus 15 studies with Maze-III surgery as a benchmark. Evidence was mostly limited by the many variations of energy sources and ablation patterns used in the studies. The primary efficacy outcome was conversion to normal sinus rhythm (SR), which was greater with cryotherapy ablation (CA), radiofrequency ablation (RFA), and microwave ablation (MWA) versus CS alone. Conversion to SR was at least 68% for all the different energy sources and lesion sets. There were no consistent differences in efficacy between CA versus Maze-III, and insufficient evidence for this comparison using other energy sources. There were no consistent differences in mortality when ablation was compared to CS or Maze-III surgery, and there did not appear to be any greater risk of bleeding with CA or RFA versus CS. Evidence was insufficient to draw conclusions about stroke incidence. Small numbers of esophageal perforation and circumflex artery stenosis were reported, mostly in case reports. All esophageal perforations were associated with unipolar nonirrigated RFA.

Recommendations

The ASERNIP-S Review Group agreed on the following classifications and recommendations:

Evidence rating – The available evidence was assessed as being poor.

Safety – There was insufficient evidence to determine if intraoperative ablation was more or less safe than cardiac surgery alone, or the Maze-III procedure. Associated risks relating to longer bypass times, plus the possibility of esophageal perforation and circumflex artery injuries, are potential concerns. No studies compared intraoperative ablation with medical management of AF, hence, safety could not be evaluated.

Efficacy – Intraoperative ablation is at least as efficacious as cardiac surgery alone, or the Maze-III procedure. No studies compared intraoperative ablation with medical management of AF, hence, efficacy could not be evaluated.

Methods

Medical literature databases from inception to January 13, 2004 were searched as were conference abstracts, references in retrieved studies, and studies using the Maze-III procedure for benchmark data. Studies selected were randomized controlled trials (RCT), non-randomized comparative studies, and case series that included intraoperative ablation using any of the available energy sources and any standardized lesion pattern. Data from studies were extracted by a researcher using standardized data extraction tables developed a priori and checked by a second researcher. See monograph for details.

Further research/reviews required

RCT of intraoperative ablation, designed and powered sufficiently to measure long-term survival and stroke rate. The comparator would be cardiac surgery alone. Surgeons performing intraoperative ablation in treating AF should participate in a national audit.

Written by Hazel S et al, ASERNIP-S, Australia

INAHTA Briefs

Issue 2004/85

Title **Mid-wheel Drive Powered Wheelchairs**

Agency **AÉTMIS, Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé**
2021, avenue Union, bureau 1040, Montréal, Québec, Canada H3A 2S9;
Tel: +1 (514) 873-2563, Fax: +1 (514) 873-1369; aetmis@aetmis.gouv.qc.ca, www.aetmis.gouv.qc.ca

Reference Report prepared for AÉTMIS (AÉTMIS 03-05).
Internet access to full text. ISBN 2-550-41834-4 (original addition ISBN 2-550-41732-1)

Aim

To advise the Régie de l'assurance maladie du Québec (RAMQ) on whether to add mid-wheel drive powered wheelchairs (MWDs) to its list of insured devices, and if so, to recommend eligibility requirements for potential users.

Conclusions and results

Limited evidence shows that MWDs perform as well as conventionally-powered wheelchairs. In general, MWDs have characteristics as good as, or superior to, those of rear-wheel drives (RWDs) and front-wheel drives (FWDs), especially their better maneuverability in tight spaces. However, questions can be raised about the quality of mobility products in general. In one U.S. study, 9 out of 15 wheel chairs (including MWDs) failed at least 1 of 11 standards tests. MWDs appear reasonably priced. No studies detailed specific eligibility requirements for MWD users.

Recommendations

AÉTMIS recommends that RAMQ add MWDs to the list of insured mobility products, provided they comply with the standards set for powered wheelchairs. Given the poor performance of more than half the wheelchairs tested (on at least one criteria), RAMQ should perform compliance tests on more than one of the same brand of chair that it considers purchasing.

Based on the lack of information regarding eligibility requirements, the current practice of relying on the judgement healthcare practitioners within the multidisciplinary team should remain the method for determining eligibility.

Methods

AÉTMIS reviewed the laws, regulations, and standards governing the manufacturing, distribution, and sale of powered wheelchairs. AÉTMIS looked for comparative controlled studies on the effectiveness, safety, and cost of different models of powered wheelchairs. Conventional databases (eg, MEDLINE) yielded sparse results, while a web search found 2 well-designed studies. These studies led to the recommendations above.

Written by François Pierre Dussault, AÉTMIS, Canada

Title **Technology Overview: da Vinci Surgical Robotic System**

Agency **ASERNIP-S, Australian Safety and Efficacy Register of New Interventional Procedures – Surgical**
PO Box 553 Stepney, Australia; Tel +61 8 83637513, Fax +61 8 83622077; college.asernip@surgeons.org

Reference ASERNIP-S Report Number 45, ISBN 0-909844-65-8;
Full text available: www.surgeons.org/asernip-s/publications.htm

Aim

To provide information on the use of the da Vinci surgical robotic system for all types of surgery, and to addresses cost and resource use, legal, regulatory, and company issues, surgical training, and other policy issues. The information is intended to help decision makers formulate evidence-based recommendations on the use and uptake of the da Vinci system.

Conclusions and results

Robotic surgery offers benefits over conventional laparoscopic or open surgery. However, a significant learning curve and substantial costs are involved in its purchase, service, and maintenance. Frequent hardware and software updates can be expected. Sixty-seven studies (8 comparative, 59 case series/reports) were included from the following surgical specialties: urology (18), cardiovascular (19), general (19), thoracic (7), gynecology (2), and pediatric (2). The evidence is insufficient to determine the safety or efficacy of robotic surgery compared with conventional open or laparoscopic surgery for any surgical application. Most studies have small samples and short followup. Operative times with the robotic system were generally longer. The length of hospital stay may be shorter, but is influenced by hospital protocols. Complication rates appear to be similar. Case series/reports established the feasibility of robotic surgery in a wide range of procedures and described complications. Most authors were positive, but also reported problems, eg, adjusting to the robotic system, set-up, and technical difficulties. A learning curve (or a volume effect) was evident in many studies. As experience with the robotic system increased, operative times, complications, and conversions tended to decrease.

Recommendations

Potential purchasers of a da Vinci surgical robotic system should consider whether the volume of procedures is sufficient to overcome the learning/volume effect and offset the start-up and fixed costs of the system.

Methods

A systematic search of electronic databases (MEDLINE, EMBASE, PubMed, and Cochrane Library) using Boolean search terms was conducted (1996 to April 2004). Other Internet databases were also searched. We checked reference lists of other health technology assessments of robotic surgery. The searches had no language restrictions. The Intuitive Surgical website was searched for product information and relevant trials. English language studies of any type that reported on the use of the da Vinci system for any surgical application were included.

Further research/reviews required

Given the paucity of studies comparing robotic surgery with conventional surgery, high-quality randomized trials and thorough economic evaluations are required.

Written by Tooher R, Pham C, et al, ASERNIP-S, Australia

Title **Laparoscopic Ventral Hernia Repair: An Accelerated Systematic Review**

Agency **ASERNIP-S, Australian Safety and Efficacy Register of New Interventional Procedures – Surgical**
PO Box 553 Stepney, Australia; Tel +61 8 83637513, Fax +61 8 83622077; college.asernip@surgeons.org

Reference ASERNIP-S Report Number 41, ISBN 0-909844-66-6;
Full text available: www.surgeons.org/asernip-s/publications.htm

Aim

To assess the safety and efficacy of laparoscopic ventral hernia repair in comparison with open ventral hernia repair.

Conclusion and results

Based on the current level of evidence, the relative safety and efficacy of the laparoscopic approach in comparison with the open approach remains uncertain. However, results from the included studies suggest some advantages for laparoscopic repair over open repair. The laparoscopic approach may be more suitable for straightforward hernias and open repair reserved for the more complex hernias. Laparoscopic ventral hernia repair appears to be an acceptable surgical operation that can be offered by surgeons proficient in advanced laparoscopic techniques.

Data from the included studies – 2 randomized controlled trials (RCTs) and 8 non-randomized comparative studies – suggest that the laparoscopic approach may have some advantages over open repair. The laparoscopic approach appears to have a lower recurrence rate and require a shorter hospital stay, with a rate of conversion to open surgery of 0% to 14%. Complications from the open approach tend to be wound-related, whereas the laparoscopic approach reported wound-related and procedure-related complications. Complications appear to be less frequent in laparoscopic repair.

Methods

Search strategy – MEDLINE, EMBASE, Current Contents, and PubMed were searched from inception to January 2004 and the Cochrane Library Issue 1, 2004 was searched for randomized controlled trials (RCTs) comparing laparoscopic ventral hernia repair with open ventral hernia repair. The York (UK) Centre for Reviews and Dissemination databases, Clinicaltrials.gov, National Research Register, relevant online journals, and the Internet were searched in January 2004.

Study selection – Studies containing safety and efficacy data on the laparoscopic approach of ventral hernia repair in the form of RCTs and other controlled or comparative studies were included.

Data collection and analysis – Data from the included studies were extracted by the ASERNIP-S researcher using standardized data extraction tables developed a priori. A second researcher checked the data.

Written by Pham C et al, ASERNIP-S, Australia

Title **Chronic Periodontitis – Prevention, Diagnosis, and Treatment**

Agency **SBU, The Swedish Council on Technology Assessment in Health Care**
PO Box 5650, SE-114 86 Stockholm, Sweden;
Tel: +46 8 412 32 00, Fax: +46 8 411 32 60; info@sbu.se, www.sbu.se

Reference SBU Report 169, 2004, ISBN 91-87890-96-8

Aim

To investigate the evidence for different methods to prevent gingivitis and to diagnose and treat chronic periodontitis. Economic aspects were considered. The question of chronic periodontitis as a risk factor for other diseases whose etiology may be linked to non-specific infection was also addressed.

Conclusions and results

Partial list (for all conclusions, see www.sbu.se):

- An electric toothbrush is more effective than a manual toothbrush for reducing gingivitis.
- The number of periapical radiographs can be considerably reduced when a clinical examination, along with bitewing radiographs of the molars or a panoramic radiograph, precedes a radiographic examination.
- Bitewing and periapical radiographs have low reliability for identifying small marginal bone changes (less than 1 mm) over time. Thus, routine radiographic examinations at regular intervals are not indicated.
- The absence of bleeding on probing is a good predictor of periodontal stability.
- Regardless of whether flap surgery is performed, mechanical debridement reduces probing pocket depth and improves probing attachment level.
- Local or systemic adjunctive antibiotic therapy does not produce better clinical outcomes in terms of reducing probing pocket depth or improving probing attachment level than mechanical debridement alone.
- Scientific evidence is lacking for determining cost effectiveness and patient-perceived quality in the various types of prevention, diagnosis, and treatment of chronic periodontitis.
- Scientific evidence is contradictory or lacking as to whether chronic periodontitis is a risk factor for coronary heart disease, stroke, diabetes mellitus, chronic obstructive pulmonary disease, rheumatoid arthritis, preterm birth, and low birth weight.

Methods

Electronic databases were used in the primary search for literature dating back to 1966. The findings of a study had to be applicable to the questions posed by the report, ie, appropriate outcome measures, followup period, and study design. The reviewers rated the quality and internal validity of each study. The scientific evidence for each conclusion was rated based on the quality and internal validity of the studies.

Further research/reviews required

Needed are studies on cost effectiveness, patient-perceived diagnosis and treatment quality, studies using various combinations of diagnosis and outcomes, and studies that reflect tooth survival.

Written by Susanna Axelsson, SBU, Sweden

Title **Home-Based Chemotherapy for Cancer: Issues for Patients, Caregivers, and the Healthcare System**

Agency **AÉTMIS, Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé**
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Reference Technology brief prepared for AETMIS, 2004 (AÉTMIS 04-02).
Internet access to full text. ISBN 2-550-42584-7 (French edition ISBN 2-550-42578-2)

Aim

To assess the effectiveness, safety, and costs of home-based chemotherapy for cancer control and cure in adults and children. To examine the issues of service delivery, access, patient preference, satisfaction, and quality of life.

Conclusions and results

The evidence is insufficient to support the superior clinical effectiveness (based on survival, remission, or tumor control) of home chemotherapy. Evidence is also insufficient regarding cost savings or improvements to the patient's quality of life (although such improvements are consistently noted anecdotally by caregivers). Home delivery can be a safe and acceptable option for some cancer patients who choose it, but the approach is resource intensive and requires a well-integrated, collaborative team of specially trained healthcare professionals. The priority in rural areas should be 'closer- to-home' chemotherapy.

Recommendations

- Evaluate existing home-based programs (criteria identified in report) to provide data on effectiveness, costs, and patient acceptability.
- Standardize policies and service components (organizational structure, staffing, training, communications, emergency support, patient followup, etc.) and deliver services through regional mechanisms.
- Build and maintain communication links among members of a multidisciplinary care delivery team.
- Anticipate the costs of transferring skills from oncology to community nursing.
- Develop a comprehensive model (a part of which is home delivery) for cancer care in Quebec.

Method

Literature review: Semi-structured interviews with service providers in selected institutions in Quebec (n=10) and Ontario (n=6) on the benefits, barriers, facilitating factors, and challenges in providing home chemotherapy. The Ontario interviews were for comparison as this province has similar demographics but a markedly different organizational structure for cancer care.

Further research/reviews required

Comprehensive evaluations of current programs in Quebec. Research into necessary cost shifting among Quebec hospitals, home care services, patients, and caregivers that would accompany the expansion of home-based care. Documentation of patient quality-of-life and satisfaction factors.

Written by Lucy Boothroyd and Pascale Lehoux, AÉTMIS, Canada

Title **Hospital Technology at Home: Portable Oxygen Therapy in COPD**

Agency **AÉTMIS, Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé**
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Reference Technology brief prepared for AÉTMIS (AÉTMIS 04-03).
Internet access to full text. ISBN 2-550-42737-8 (French addition ISBN 2-550-42806-4)

Aim

To summarize evidence on the efficacy, safety, and cost effectiveness of portable oxygen equipment in treating chronic obstructive pulmonary disease (COPD), to evaluate Canadian service delivery models, to review the psychosocial, legal, and ethical implications of home oxygen programs, and to provide guidance for Quebec policy.

Conclusions and results

Long-term oxygen therapy (LTOT) is shown to prolong the lives of patients with COPD, but evidence on the costs and benefits of portable oxygen therapy is limited. The first controlled trial on costs and benefits showed no benefits in quality of life, compliance with treatment, or exercise tolerance, but the sample was small (n=22). Criteria for prescribing portable oxygen therapy do not exist, although the US and UK have adopted some guidelines. Organization and delivery of home oxygen in Québec is decentralized and highly variable. No data have been gathered on the use, cost, or health outcomes of this service.

Recommendations

MSSS should: Define the indications for need regarding all types of portable oxygen equipment; develop a standardized instrument for assessing and monitoring eligible patients; develop standard procedures for prescribing, covering, and monitoring portable oxygen use; set up the infrastructure for a coherent home oxygen therapy program that includes portable oxygen equipment; and consider establishing a central patient registry that could be used to assess delivery, access, and health outcomes. MSSS is encouraged to work in partnership with health professionals, research groups, and patient representatives to implement a care program that is effective, efficient, and fair for all patients.

Methods

Review of the published literature, analysis of data on services provided to Québec COPD patients, interviews with clinical and administrative leaders of home oxygen therapy programs and home delivery services in Québec, and a key informant survey with home oxygen program leaders in Ontario and Alberta.

Further research/reviews required

Further research is needed on: the link between smoking and COPD, the costs and benefits of different portable systems, complementary or alternative therapies for COPD, current Québec practices for LTOT delivery, the effect of patient education and support on health outcomes, and instruments that assist the routine collection of quality-of-life data for COPD patients on LTOT in clinical practice.

Written by Susan Law and Pascale Lehoux, AÉTMIS, Canada

INAHTA Briefs

Issue 2004/91

Title **An Economic Analysis of Drug-Eluting Coronary Stents: A Québec Perspective**

Agency **AÉTMIS, Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé**
2021, avenue Union, bureau 1040, Montréal, Québec, Canada H3A 2S9;
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Reference Technology brief prepared for AÉTMIS (AÉTMIS 04-04).
Internet access to full text. ISBN 2-550-42953-2 (French edition ISBN 2-550-42933-8)

Aim

To quantify the benefits and costs associated with using drug eluting stents (DES), rather than bare metal stents (BMS), in treating stenosis of the coronary arteries.

Conclusions and results

The analysis indicates that universal adoption of DES would significantly reduce the rate of repeat revascularization interventions in Québec. However, the analysis also reveals that universal use of DES would require significant additional healthcare funding, even after considering the savings from a lower restenosis rate. Based on current intervention rates, and the estimated reduction in re-intervention rates, the universal application of DES technology would cost an additional $35.2 million, with no lives saved or myocardial infarctions avoided. If only 20% of patients (high risk) were given DES, the cost increase would be $4.7 million.

Recommendations

Because of the relatively low rates of restenosis currently observed in Québec (a baseline 9-month rate with BMS of 12.8%), the most cost-effective strategy at this time would involve limited use of DES for carefully selected, high-risk patients. If DES is adopted for some percentage of the population, access to this technology must be equal for equally deserving patients (similar selection criteria) at all centers performing PCI. The details and evaluation of all DES interventions should be recorded in a provincial registry (with AÉTMIS or the Réseau québécois de cardiologie tertiaire as guarantors of the registry).

Method

The study reviewed all randomized clinical trials comparing DES to BMS, and all Québec medico-administrative databases describing local current practice patterns. The economic analysis was conducted from the perspective of the Québec Ministry of Health and Social Services. A major strength of this report is that it used objective data to construct a realistic, transparent, economic model to provide cost estimates.

Further research/reviews required

To collect data systematically on health outcomes of patients treated with DES and BMS and to reassess (6 to 12-month intervals) the recommendations in this report in view of the new data.

Written by James Brophy and Lonny Erickson, AÉTMIS, Canada

Title	**Leukoreduction. Considerations for a National Blood Transfusion Safety Policy**
Agency	**KCE, Belgian Health Care Knowledge Centre** Residence Palace (10th floor), Wetstraat 155, 1040 Brussels, Belgium; Tel: +32 2 287 33 88, Fax: +32 2 287 33 85
Reference	Sept 2004. KCE Reports vol. B. www.kenniscentrum.fgov.be/nl/publicaties.html (in Dutch), www.kenniscentrum.fgov.be/fr/Publications.html (in French)

Aim

To evaluate the scientific rationale of universal leukoreduction in Belgium and to assess the clinical, economic, social, and legal consequences.

Conclusions and results

The safety and quality of transfusion blood is high in Belgium, as it relies on unpaid voluntary donors and strict quality control. The incremental cost to the healthcare payer is € 25 per unit for filtering white blood cells from red blood cell concentrates for transfusion. The consensus is that selective leukoreduction is highly effective and cost effective relative to no leukoreduction. Selected patients groups include immunocompromised patients, pregnant women, transplant patients, polytransfusion patients, and patients with HLA alloimmunization. It is unclear whether universal leukoreduction, ie, leukoreduction for all units of blood, is cost effective. The decision to implement universal leukoreduction in most European countries was aimed at preventing the transmission of variant Creutzfeldt-Jakob disease (vCJD) by blood transfusion. Outside the UK, this risk is low, and universal leukoreduction is probably of limited clinical benefit. The incremental cost to the healthcare payer for universal leukoreduction is estimated to be € 7.71 million per year in Belgium (2003 prices). A basic problem is legal accountability. The law is vague on this issue, and blood banks are increasingly faced with legal uncertainty. They pay huge insurance premiums that are disproportional to the quality and safety measures they take. The (European) law suggests that maximum blood safety should be pursued, which inevitably leads to investments defined by technological possibilities rather than by objective need and efficiency.

Recommendations

The major issues concern financial and legal accountability for hazards related to blood transfusion. If policy makers decide not to implement universal leukoreduction in Belgium, they need to take over this financial and legal accountability from the blood banks. If it is decided to implement universal leukoreduction, the public should be appropriately informed about the consequences, ie, the loss of efficiency in allocating scarce healthcare resources.

Methods

The literature on the clinical benefits and economic consequences of leukoreduction was reviewed. Experts in the field were actively involved in the research. The incremental cost of universal leukoreduction for healthcare payers was based on the number of blood donations in 2003, the percentage blood units currently leukoreduced (25%), and the reimbursement of leukoreduced versus nonleukoreduced blood. The perspective of the healthcare payer was taken.

Further research/reviews required

More research is needed on the legal issues of accountability for hazards related to blood transfusion. A precautionary blood safety policy should be based on the participation in decision making of all relevant actors: blood donors, patients, and healthcare providers. More research is needed on how these actors can be involved in decision making.

Written by Dr Cleemput I, Dr Ramaekers D, Dr Leys M, and Dr Bonneux L, KCE, Belgium

Title **Evaluation of Photodynamic Therapy for the Treatment of Exudative Age-related Macular Degeneration (ARMD) with Subfoveal Neovascularization: A Technology Assessment**

Agency **AÉTMIS, Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé**
2021, avenue Union, bureau 1040, Montréal, Québec, Canada H3A 2S9

Reference Technology brief (AÉTMIS 04-05). Internet access to full text: www.aetmis.gouv.qc.ca. (French edition ISBN 2-550-43007-7)

Aim

To assess the efficacy of photodynamic therapy (PDT) in treating ARMD, and to examine the costs, care organization, and services involved in applying PDT in Québec.

Conclusions and results

Neovascular ARMD, which currently affects 16,000 Québecers, is the only treatable form of this degenerative condition of the retina. The efficacy of PDT (using verteporfin as a photosensitizer) is well established for ARMD with: a) predominately classic neovascularization (more than 50%) and b) pure occult neovascularization. PDT reduces moderate to severe loss of visual acuity for people with these conditions and reduces the number of people who become legally blind after 2 years. Economic analysis favors PDT in patients with either of these conditions if improvement in quality of life is taken into account (the report provides data on the cost utility ratio and net annual budget impact). Budgetary restraints, the nature of the condition, and the unavailability of specialists have led to inconsistent access to PDT in Québec.

Recommendations

AÉTMIS recommends that:

- PDT be considered a technology that effectively slows the progression of certain forms of ARMD
- ARMD be recognized as an important public health problem
- Québec initiatives to manage ARMD population-wide be made part of a broader effort to manage preventable blindness
- A task force be established to create a concrete care and service plan in light of this research.

Method

AÉTMIS conducted:

- A systematic review of the scientific literature (1975 to June 2004)
- Interviews with experts in ophthalmology and visual rehabilitation
- Semi-structured interviews with specialists, receptionists, and nurses at all Québec hospitals and selected private clinics concerning the organization of care and services provided to ARMD patients.

Tests of a Markov-type decision tree to predict the costs and effects of: a) the PDT treatment option for all Québecers diagnosed with ARMD and b) a non-treatment option.

Further research/reviews required

The Vision Network/FRSQ should prioritize the evaluation of ARMD detection tools and undertake further research on care and services related to preventable blindness in Québec.

Written by Kathy Larouche and Sophie Rochon, AÉTMIS, Canada

Title **Interventional and Intraoperative Magnetic Resonance Imaging**

Agency **AHFMR, Alberta Heritage Foundation for Medical Research**
Health Technology Assessment Unit, Suite 1500, 10104–103 Avenue NW, Edmonton, Alberta T5J 4A7 Canada; Tel: +1 780 423 5727, Fax: +1 780 429 3509

Reference IP 17, March 2004 (English). ISBN 1-896956-92-0 (print); ISBN 1-896956-94-7 (online): www.ahfmr.ab.ca/programs.html

Aim

To overview the safety, efficacy/effectiveness, cost, and utilization of real-time magnetic resonance imaging (MRI) during interventional and surgical procedures in Canada.

Conclusions and results

Only 4 nonrandomized, comparative studies met the inclusion criteria (1 on interventional MRI, 3 on intraoperative MRI). Postoperative morbidity rates were similar for interventional MRI-guided brain biopsy and conventional stereotactic methods. One death followed stereotactic biopsy, but no deaths occurred in the interventional MRI group. Intraoperative MRI in monitoring brain tumor resection substantially increased operative time compared to conventional surgery, with no discernible effect on perioperative anesthetic outcome. Conversely, the hospital stay was generally shorter after intraoperative MRI. Intraoperative MRI in resection control of supratentorial cavernous hemangiomas did not affect the amount of pathology resected, compared to standard neuronavigation methods. Significantly more tumor volume was resected in patients with high-grade gliomas. No studies reported adverse events directly related to intraoperative MRI, or to the conventional procedures that intraoperative MRI was compared to. Due to confounding from the learning curve effect, the results may underestimate the capabilities of interventional/intraoperative (I/I) MRI, but methodological flaws in the studies obscured the overall magnitude or direction of this bias. It is unclear whether the equivocal results are a consequence of limitations in study design, the I/I MRI procedure itself, or both. Canada has 4 I/I MRI facilities, and 2 additional centers may soon acquire I/I units.

Recommendations

Interventional and intraoperative MRI is a high-cost, developmental technology. No major safety concerns have been identified. Due to its recent genesis, the scope, applicability, efficacy, and cost effectiveness of this technology have not been established.

Methods

All original, published, randomized controlled trials and nonrandomized comparative studies, with at least 10 patients in each study arm, were identified by systematically searching (Jan 1990 to Jan 2004) PubMed, EMBASE, HealthStar, the Cochrane Library, Science Citation Index, and the websites of various health technology assessment agencies, research registers, and guideline sites. No language restriction was applied. Only studies of interventional or surgical procedures that utilized near real-time MRI to guide or monitor aspects of the procedure at the time it was being performed were included.

Further research/reviews required

The included studies used MRI only as a tool to guide or monitor interventional and operative neurosurgical procedures. Hence, the clinical utility of MRI to guide or monitor other interventions, eg, percutaneous biopsy or endoscopic abdominal surgery, is unknown. Concurrently controlled studies assessing the effect of I/I MRI on patient management and outcomes will provide the information on whether I/I MRI has broader clinical applications.

Written by Ann Scott, AHFMR, Canada

INAHTA Briefs

Issue 2004/95

Title **Low Density Lipoprotein Apheresis for the Treatment of Familial Hypercholesterolemia**

Agency **AHFMR, Alberta Heritage Foundation for Medical Research**
Health Technology Assessment Unit, Suite 1500, 10104–103 Avenue NW, Edmonton, Alberta T5J 4A7 Canada; Tel: +1 780 423 5727, Fax: +1 780 429 3509

Reference IP 18, April 2004 (English). ISBN 1-896956-92-0 (print); ISBN 1-896956-94-7 (online): www.ahfmr.ab.ca/programs.html

Aim

To present evidence on the safety and efficacy/effectiveness of using apheresis to lower the concentration of low density lipoprotein (LDL) cholesterol in patients with familial hypercholesterolemia.

Conclusions and results

The report focused on two selective LDL apheresis systems: dextran sulfate cellulose (DSC) Liposorber and heparin induced LDL precipitation (HELP). Six controlled studies compared a combined LDL apheresis (DSC system) and drug therapy with drug therapy alone. Two further studies compared the DSC or HELP system with other apheresis systems. Weak evidence suggested that the DSC Liposorber system, combined with lipid lowering drug therapy, lowered LDL cholesterol in patients >50 years of age with severe familial hypercholesterolemia when treated at least once every 2 weeks for at least 1 year. The mean decrease in LDL cholesterol ranged from 34% to 81%. In combined therapy, the contribution of LDL apheresis to the treatment effect was unclear. Two studies concluded that all of the systems (Immunoadsorption, Liposorber, HELP, Lipidifiltration) decreased the levels of LDL cholesterol (mean decrease ranged from 54% to 65%). Adverse effects associated with DSC and HELP were hypotension, nausea, and vomiting. These effects were transient.

Recommendations

Information from the reviewed studies must be considered cautiously. Generalization of the results to a local context is challenging since none of the studies were conducted in Canada, and most used only the DSC system. For economic and ethical reasons, the decision to include LDL apheresis in the service package for patients with familial hypercholesterolemia is difficult. Planning processes must weigh costs and access against the gravity of the disease, the poor quality of life, and the life expectancy of patients with homozygous familial hypercholesterolemia. A national registry for patients with familial hypercholesterolemia and severe hyperlipidemia would be useful.

Methods

All original comparative studies published in English were identified by systematically searching (Jan 1998 to Mar 2004) PubMed, EMBASE, HealthStar, the Cochrane Library, Science Citation Index, and the websites of health technology assessment agencies, research registers, and guideline sites.

Further research/reviews required

Multicenter, concurrently controlled studies with long-term followup should assess whether LDL apheresis is more effective than drug therapy or plasmapheresis (alone or in combination with standard care) in treating patients with familial hypercholesterolemia. The effectiveness and safety of LDL apheresis in certain groups, eg, children or pregnant/lactating women, should also be evaluated. Randomized controlled crossover studies would be appropriate since they avoid the ethical problem of withholding LDL apheresis from patients who may need it. Cost-benefit and cost-effectiveness analyses are needed to assess the economic consequences of LDL apheresis versus alternative treatments, eg, drug therapy or plasmapheresis. The use of valid quality-of-life measures in these analyses is essential.

Written by Carmen Moga and Christa Harstall, AHFMR, Canada

Sclerotherapy for Leg Varicose Veins

Agency **AHFMR, Alberta Heritage Foundation for Medical Research**
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Reference IP 19, May 2004 (English). ISBN 1-896956-96-3 (print); ISBN 1-896956-98-x (online): www.ahfmr.ab.ca/programs.html

Aim

To conduct a systematic review of the published research on the use of sclerotherapy to manage varicose veins of the legs.

Conclusions and results

The role of sclerotherapy and its association with surgery in managing varicose veins is unclear. The reviewed evidence suggests that:

- Standard sclerotherapy is the treatment of choice for reticular varicosities, telangiectasia, and other small, unsightly blood vessels
- Sclerotherapy as first-line treatment for larger varicose veins (saphenous or nonsaphenous) is controversial
- Following surgery, sclerotherapy may achieve good results for varicose veins that have not fully disappeared, or recur.

The appropriate technique and sclerosant for various types of varicose veins is still under debate. Polidocanol, sodium tetradecyl sulfate, and hypertonic saline are potentially safe and effective sclerosants in the short-term, but there is no standard protocol for their use. Endosclerotherapy and foam sclerotherapy (with ultrasound guidance) appear to be efficacious for uncomplicated varicose veins. However, these techniques are evolving and need further evaluation.

Recommendations

The role of sclerotherapy in managing symptomatic varicose leg veins, particularly in relation to other treatment options, has yet to be clearly defined. Which sclerotherapy approach is the most efficacious and for what group of patients remains unknown. Patients should be educated about sclerotherapy for leg varicose veins since potential serious complications and cosmetic deterioration must be weighed against the benefits.

Methods

The literature (Jan 1998 to Feb 2004) was systematically searched. Sources included the Cochrane Library, CRD Databases, EBM Reviews – ACP, CINAHL, ECRI, MEDLINE, PreMEDLINE, EMBASE, and HealthSTAR. Websites of practice guidelines, regulatory agencies, evidence-based resources, and other HTA agencies were also searched. Randomized controlled trials comparing sclerotherapy with another, or no, treatment in patients with leg varicose veins were included. One reviewer assessed the quality of the selected trails. Systematic reviews, guidelines, and consensus documents on the use of sclerotherapy for this indication were also included. A Canadian specialist with expertise in sclerotherapy for leg varicose veins provided clinical input.

Further research/reviews required

Priority areas for future research are to establish uniform and objective criteria to diagnose and select patients, to define treatment failure and recurrence, and to measure outcomes. Objective evaluation of the efficacy and appropriate use of the numerous sclerotherapy techniques is also essential.

Written by Paula Corabian and Christa Harstall, AHFMR, Canada

Title **Refractive Surgery – A Health Technology Assessment**

Agency **DACEHTA, Danish Centre for Evaluation and Health Technology Assessment**
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Reference DACEHTA Report 2004;4(2). Danish, English summary.
ISBN 87-91437-19-9 (online): www.sst.dk/publ/Publ2004/refraktionskirurgi.pdf

Aim

To describe the technological, patient-related, organizational, and economic aspects of refractive surgery in Denmark and to establish alternative models for its future organization. Refractive surgery, broadly defined, encompasses all forms of surgical intervention aimed at eliminating or attenuating optical refractive errors.

Conclusions and results

Technology: Based on systematic literature review up to 2002 it is concluded that excimer laser based corneal refractive surgery can eliminate or greatly reduce myopia up to 10 dioptres, hyperopia up to 4 dioptres, and astigmatism up to 4 dioptres. LASIK surgery is possibly preferable for high corrections, while PRK may be safer for lower corrections.

Patients: Based on questionnaire responses from over 250 previously operated patients it can be concluded that the vast majority are satisfied with the result of a corneal refractive procedure. Many patients feel that their night vision is compromised after surgery. Two percent of all patients report much worse vision after surgery.

Organization: Based on questionnaires to all Danish ophthalmologists, an estimated 2,500 excimer laser based procedures were performed in 2000, most in private practice. Indications for free treatment are medical (including high myopia and/or astigmatism, anisometropia) and sociomedical (job, education requirements).

Economy: Socioeconomic calculations revealed that corneal refractive surgery is cost effective. Young patients with mild or moderate myopia benefit most, as expenses for glasses and/or contact lenses often can be eliminated for many years.

Recommendations

- Treatment centers should improve communication with referring ophthalmologists, and unified Danish guidelines for ophthalmologists should be drawn up on referral, prognosis, side effects, and risks of refractive surgery.
- One or more of the Danish university departments should continue to provide excimer laser-based refractive surgery treatments for medical and sociomedical indications, and steps should be taken to ensure more intensive average utilization of apparatus capacity.
- The number of patients referred to the public health service for treatment of nearsightedness should be closely monitored, and the degree of nearsightedness should be used as a supplementary instrument for regulating the number of patients offered treatment.

Methods

A systematic literature review was used to assess the technologies. Questionnaires to operated patients, non-operated myopic subjects, and Danish ophthalmologists were used to assess patient satisfaction after surgery, attitudes on refractive surgery, and selection of patients for free treatment in university hospitals. Cost-effectiveness analysis was used to calculate the possible socioeconomic benefit of refractive surgical procedures.

Further research/reviews required

Refractive surgery is a rapidly developing field. As the number of intraocular lens implantation in phakic eyes is increasing, an HTA of this rather invasive treatment technique for refractive errors is required.

Written by Hjortdal JØ et al, DACEHTA, Denmark

Title **Rapid Assessment of EPO to Treat Anaemia in Cancer Patients**

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Reference DACEHTA Report 2004;6(1). Danish, English summary. ISBN 87-91437-18-0 (online): www.sst.dk/publ/Publ2004/epo/epo_rapport_270204_final.pdf

Aim

Several countries in Europe have begun to use erythropoietin (EPO) systematically in treating anemic cancer patients with malignant tumors receiving chemotherapy. EPO appeared to be on its way into Danish health services and needed assessment. In 2003, the Danish Society of Oncology developed a set of guidelines, and DACEHTA was asked by the National Cancer Steering Group to carry out a rapid assessment of the consequences of implementing these guidelines.

Conclusions and results

A meta-analysis demonstrated that treatment with EPO resulted in an increased hemoglobin level in the blood and a moderate reduction (less than 1 unit) in the need for blood transfusion. Due to different methodologies, the Cochrane review was inconclusive concerning quality-of-life. It was estimated that 3,335 patients (39% of the patients receiving chemotherapy) annually would need to be offered EPO treatment – at an average cost per patient of 6,175 to 8,590 euros.

Recommendations

DACEHTA recommended that further clinical studies should be performed, especially concerning quality-of-life and side effects, before EPO treatment could be recommended on a routine basis to the estimated patient group. If, at a later stage, more convincing evidence becomes available concerning the effect of EPO treatment and/or showing that the cost of treatment is decreasing, it will be relevant to conduct a new assessment, eg, a health technology assessment.

Methods

The analysis of clinical effectiveness and patient aspects was based on a recent Cochrane review in combination with economic evaluations and analysis, based on literature studies, extracts from registers, and local data collection.

Further research/reviews required

Further research is needed regarding the effects on quality of life, on the size of the cancer tumor, on survival, and on the side effects of the treatment. It may be relevant to conduct more diagnosis-related clinical studies, as some patient groups will perhaps benefit more than others will from EPO treatment.

Written by Vestergaard M et al, DACEHTA, Denmark

Title **Economic Evaluations in International Health Technology Assessments – A Study of Methodologies**

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Reference Danish Health Technology Assessment 2003;5(1). ISBN 87-91361-74-5 (online).
www.sst.dk/publ/Publ2004/Sundhedsoekonomiske_evalueringer_MTV.pdf

Aim

To investigate the economic content of international health technology assessments (HTAs) and to assess international practices in this field. The project focuses on the methods used in international HTA reports rather than on the actual results. Both the doers involved in conducting HTAs and the users of the results may benefit from this report. The presumed target group has a basic knowledge of economic terms in general and economic evaluation in particular.

Conclusions and results

Most of the economic evaluations in HTAs were conducted after collecting clinical data, using secondary data from literature reviews or meta-analyses. The data were often combined in decision analytical modeling. This approach is not observed to the same extent in economic evaluation in general, probably due to the nature of health technology assessment as a synthesis of clinical and other evidence gathered from a systematic literature review.

The use of cost-utility analysis was more widespread in HTA studies than in the general evaluations, and cost-benefit analysis was used in two cases. This indicates the application of advanced methods of economic evaluation in these health technology assessments. With respect to the identification of resource use, patient costs and time costs were more frequently identified in the HTA economic evaluations than in the general economic evaluations. Unfortunately, the perspective of the economic evaluation was not clearly stated in half of the health technology assessments.

Despite the existence of several formal guidelines for economic evaluation, the methodology used in evaluation, and its quality, appear to vary. Conducting an economic evaluation can be difficult, as suggested by the number of HTA economic evaluations that did not state the study perspective, did not perform discounting when relevant, did not perform sensitivity analysis, and used average costing/charges rather than marginal costing – issues important in economic evaluations.

Methods

A Systematic review. *Data sources:* HTA reports published by INAHTA members. *Types of studies assessed:* economic evaluations. Sixty-seven international HTA reports were systematically selected and examined based on a checklist composed specifically for this project. The checklist focuses on the design chosen for economic evaluation, the included costs and health gains, measurement and valuation of costs and health outcomes, discounting of future costs and health gains, incremental analysis, and sensitivity analysis. The results were then compared to the methodology used in a sample of economic evaluations undertaken in the health area in general.

Written by Larsen RJ et al, DACEHTA, Denmark

Title	**Treatments for Spasticity and Pain in Multiple Sclerosis: A Systematic Review**
Agency	**NCCHTA, National Coordinating Centre for Health Technology Assessment** Mailpoint 728, Boldrewood, University of Southampton, Southampton SO16 7PX, United Kingdom; Tel: +44 2380 595586, Fax: +44 2380 595639
Reference	Health Technol Assess 2003;7(40). Nov 2003. www.ncchta.org/execsumm/summ740.htm

Aim

To identify the drug treatments currently available to manage spasticity and pain in multiple sclerosis (MS), and to evaluate their clinical and cost effectiveness.

Conclusions and results

There is limited evidence of the effectiveness of 4 oral drugs for spasticity: baclofen, dantrolene, diazepam, and tizanidine. Tizanidine appears to be no more effective than comparator drugs such as baclofen and has slightly different side-effects. Despite claims that it causes less muscle weakness, there was very little evidence that tizanidine performed any better in this respect than other drugs, although it is more expensive. The findings of this review are consistent with reviews of the same treatments for spasticity derived from other etiologies. There is good evidence that both botulinum toxin (BT) and intrathecal baclofen are effective in reducing spasticity, and both are associated with functional benefit. However, they are invasive, and substantially more expensive. None of the studies included in the review of pain were designed specifically to evaluate the alleviation of pain in MS patients, and there was no consistency regarding the use of validated outcome measures. It was suggested that, although expensive, the use of intrathecal baclofen may be associated with significant savings in hospitalization costs related to bed-bound patients at risk of developing pressure sores, thus enhancing its cost effectiveness. No studies of cost effectiveness were identified in the review of pain. There is evidence, albeit limited, of the clinical effectiveness of baclofen, dantrolene, diazepam, tizanidine, intrathecal baclofen, and BT and of the potential cost effectiveness of intrathecal baclofen in treating spasticity in MS.

Recommendations

Many of the interventions are not licensed for alleviation of pain or spasticity in MS, and the lack of evidence on their effectiveness may limit widespread use. Forthcoming information relating to the use of cannabinoids in MS may result in there being better evidence of the effectiveness of new treatments than of any of the currently used drugs. It may therefore be of value to carry out double-blind, randomized controlled trials of interventions used in current practice, where outcomes could include functional benefit and impact on quality of life.

Methods

Systematic searches identified 15 interventions for treating spasticity and 15 interventions for treating pain. The quality and outcomes of the studies were evaluated. Reviews of treatment of spasticity and pain when due to other etiologies were also sought.

Further research/reviews required

Further research into the development and validation of outcomes measures for pain and spasticity may also be useful, as perhaps would cost-utility studies.

Written by Ms Suzy Paisley, ScHARR Rapid Reviews Group, University of Sheffield, UK

Title **The Impact of Screening on Future Health-promoting Behaviours and Health Beliefs: A Systematic Review**

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Reference Health Technol Assess 2003;7(42). Dec 2003.
www.ncchta.org/execsumm/summ742.htm

Aim

To carry out a systematic review to examine the effects of cholesterol, breast, and cervical screening on actual or intended health promoting behaviors and health beliefs.

Conclusions and results

Cholesterol Screening: The studies reviewed suggest that cholesterol screening had a positive effect on health behaviors. These positive findings need to be interpreted in the light of methodological issues, eg, participation was voluntary and those screened were possibly more motivated to change. Hence, the results cannot be generalized to the entire population. Other factors include the lack of reliability and validity of tools to measure changes in health behaviors, study attrition, and uncertainty of self-reports. Also, uncertainty of long-term changes, inaccurate risk assessment, perception of seriousness of risk status due to lack of symptoms, readiness to accept advice, convenience, and cost of followup should be considered. All but 2 studies reported reduced blood cholesterol levels, suggesting that successful lifestyle changes were made.

Breast and Cervical Screening: Many studies have not directly measured whether breast and cervical screening affect future health behaviors and beliefs. Few studies have collected baseline measures. Hence, it is difficult to address the effects of these screening programs on future health beliefs and behaviors. Evidence suggests that women who attend breast and cervical screening once are likely to reattend, and attendance is associated with several positive health behaviors. Many of the studies were cross-sectional, or relied on retrospective data where the temporal relationship between screening and these behaviors cannot be assessed. It cannot be confirmed whether the associations observed were a result of screening or because these women have a certain set of health behaviors and beliefs irrespective of their experience of screening. No literature was found on cost effectiveness regarding the wider implications of screening (only on reduction of disease-specific mortality/morbidity).

Recommendations

All 3 screening programs are associated with high levels of favorable health behaviors and beliefs, but recommended followup after screening is often not adhered to. Most research has been restricted to outcomes related to the condition being screened for. To fully explore the effects of screening on future health behaviors and beliefs, a wider range of outcomes should be studied. There were few qualitative studies that could have provided a better understanding of how and why participants are affected by the processes they have undergone.

Methods

Data Sources: Systematic searches of 11 electronic databases (1980 to 2000) were conducted.

Study Selection: Studies that investigated the impact of cholesterol, breast, and cervical screening programs on health promoting behaviors and beliefs were assessed for inclusion.

Data Extraction: The data extraction form and quality assessment criteria were developed using the guidelines produced by the NHS Centre for Reviews and Dissemination.

Data Synthesis: Data were extracted and a qualitative synthesis was conducted. Reviewers categorized the outcomes as beneficial or detrimental to health. This categorization was based on a value judgment that considered statistical and clinical significance.

Further research/reviews required

These are discussed in the monograph.

Written by Dr Premila Webster, Department of Public Health, University of Oxford, UK

INAHTA Briefs

Issue 2005/03

Title **Clinical Effectiveness and Cost-effectiveness of Pioglitazone and Rosiglitazone in the Treatment of Type 2 Diabetes: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2004;8(13). Mar 2004. www.ncchta.org/execsumm/summ813.htm

Aim

To evaluate the clinical and cost effectiveness of pioglitazone and rosiglitazone in treating type 2 diabetes.

Conclusions and results

Of the 1,272 studies identified, 9 met the inclusion criteria. Clinical evidence showed that glitazones reduce glycosylated hemoglobin by approximately 1% and are more effective at higher than at lower doses. Glitazone treatment is associated with weight gain, but data on long-term effects were not available. No prospective RCTs compared pioglitazone to rosiglitazone, but both treatments indicated similar effects. There are no published economic studies on pioglitazone or rosiglitazone. Manufacturers provided economic evaluations for both glitazones. Sensitivity analyses suggest that the cost per quality-adjusted life-year (QALY) of rosiglitazone is most sensitive to dose and treatment effect. In two scenarios comparing rosiglitazone to metformin and sulfonylurea combination therapy, the cost effectiveness of rosiglitazone switches from around £10,000 per QALY to being dominated by the comparator strategy. However, the baseline result should be interpreted with caution.

Recommendations

Clinical evidence showed that glitazones can reduce glycosylated hemoglobin; however, no peer-reviewed data were available on their long-term effects, nor did any prospective RCTs compare pioglitazone with rosiglitazone.

Methods

Electronic databases, reference lists of relevant articles, and 14 research-related resources were consulted via the Internet. A systematic review of the literature aimed at identifying all papers relating to the glitazones. The Jadad method was used to assess the methodological quality of randomized controlled trials (RCTs). A generic proforma for critical appraisal of modeling studies in health economics was used to systematically review the economic assessment studies. This was supplemented by a detailed review of the disease-specific factors within the studies. Where possible, key outcomes were compared. Readers should note that information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence (NICE). Such information was made available to the NICE Appraisals Committee, but has been removed from this version of the report.

Further research/reviews required

Research already undertaken in this area should be published, preferably in peer-reviewed journals. Direct head-to-head comparisons of the glitazones in combination with metformin or sulfonylurea would be helpful. The current license arrangements do not allow for routine use of the glitazones in triple oral combination therapy, or in combination with insulin. Evidence is emerging on use of the glitazones in such combinations; hence, prospective RCTs would be useful. These studies could examine short-term transition strategies and longer term management. The impact of the glitazones in delaying transfer to insulin and the impact on long-term outcomes should also be considered for investigation.

Written by Mr James Chilcott, ScHARR-TAG, University of Sheffield, UK

Title **Assessment of Cardiac Rehabilitation Service for Patients with Heart Diseases**

Agency **ICTAHC, Israeli Center for Technology Assessment in Health Care**
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Reference I-MOH-MT-OT-11369 SAL 2005

Aim

Public funding covers cardiac rehabilitation for patients in Israel after myocardial infarction and coronary artery bypass surgery. This assessment aims to review the evidence on the efficacy, effectiveness, and cost of cardiac rehabilitation programs for patients with other heart diseases, to broaden the indications currently approved in Israel.

Conclusions and results

Cardiac rehabilitation is a comprehensive service consisting of nutritional counseling, risk factor management, psychosocial management, physical activity counseling, and exercise training. A wealth of clinical evidence supports widespread application of cardiac rehabilitation. A Cochrane systematic review demonstrates that exercise-based cardiac rehabilitation is effective in reducing cardiac death in patients with coronary heart disease. Moreover, the results show a significant net reduction in risk factors. A meta-analysis of trials in patients with chronic heart failure showed clear evidence of an overall reduction in mortality after participation in a cardiac rehabilitation program. Other evidence supports the efficacy of cardiac rehabilitation in patients with chronic heart failure and in patients who have undergone percutaneous revascularization, heart valve surgery, or heart transplantation. Cardiac rehabilitation in general, and supervised exercise training in particular, were both found to be effective ways to increase functional capacity, favorably modify disease-related risk factors, reduce symptoms, detect signs and symptoms of disease before they become serious complications, and improve quality of life. Research reviewing several economic evaluations of different cardiac rehabilitation alternatives found comprehensive cardiac rehabilitation to be a cost-effective intervention following an acute coronary event. A separate review of the evidence on the cost effectiveness of cardiac rehabilitation concluded that the costs are justified in terms of mortality and quality of life, and that there is a substantial cost saving to the healthcare provider over a 3-year span, or longer. The Israeli Cardiovascular Union supports inclusion of cardiac rehabilitation services on the National List of Healthcare Services that are nationally funded.

Recommendations

Public funding should be provided for a rehabilitation program for cardiac patients: after insertion of an ICD defibrillator, with cardiac output less than 35%, and functional NYHA classes 2,3, and posttherapeutic catheterization.

Methods

A literature search was conducted using MEDLINE and the Cochrane Library.

Scientific statements and clinical guidelines of medical associations in Israel, the USA, and Europe were reviewed.

Written by Orna Tal, Orly Tamir, and Nina Hakak, ICTAHC, Israel

INAHTA Briefs

Issue 2005/05

Title **Efficacy and Effectiveness of Neocate Infant Formula**

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Reference I-MOH-MT-LM SAL 2003

Aim

Neocate infant formula is provided in Israel through public funding as an elemental diet for infants (especially for those under 12 months of age) suffering from two rare genetic disorders (cystic fibrosis and familial dysautonomia) with proven whole protein intolerance and other gastrointestinal disorders. This assessment aims to review evidence for the efficacy and effectiveness of supporting Neocate infant formula for all patients with an indicated elemental diet due to proven whole protein intolerance and other gastrointestinal disorders.

Conclusions and results

Neocate is a hypoallergenic elemental amino acid-based infant formula designed to provide complete nutritional support for infants with cow milk allergy and multiple food protein intolerance. These infants are often exposed to severe infections and even death, in addition to being mostly dependent on parenteral nutrition. Very few clinical studies have addressed this issue. Nevertheless, based on the literature available, there is strong evidence that Neocate is an effective and essential alternative diet for these infants.

A study involving children with severe short bowel syndrome was designed to assess the impact of an amino acid-based, complete infant formula on enteral feeding tolerance and parenteral nutrition requirement. The results demonstrate a significant increase in intestinal function, a decrease in hospitalization, and a decrease in bacterial sepsis episodes and central line insertions.

An evaluation study was performed in infants with multiple food protein intolerance. After treatment with Neocate, the patients were challenged with the formula previously best tolerated. Onset of adverse reactions occurred during the formula challenge, thus suggesting Neocate to be an effective substitute formula for these patients.

Recommendations

Neocate is highly recommended as an alternative diet for infants with multiple food protein intolerance. All HMOs in Israel recommend this substitute for patients allergic to milk protein and their usual substitutes. Neocate will be discussed for inclusion in the National List of Healthcare Services for 2005.

Methods

MEDLINE was used to search the literature. Specialists in the field were consulted, and recommendations from a consensus conference on "nutritional medicine" were reviewed.

Written by Limor Menahem, Orna Tal, Orly Tamir, and Nina Hakak, ICTAHC, Israel

Title **Clinical Effectiveness and Cost-effectiveness of Prehospital Intravenous Fluids in Trauma Patients**

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Reference Health Technol Assess 2004;8(23). Jun 2004. www.ncchta.org/execsumm/summ823.htm

Aim

To systematically review the evidence on the effectiveness (in terms of mortality and morbidity) of prehospital intravenous (IV) fluid replacement, compared with no IV fluid replacement or delayed fluid replacement, in trauma patients with no head injury who have hemorrhage-induced hypotension due to trauma.

Conclusions and results

Although 4 relevant randomized controlled trials (RCTs) were identified, 3 were poorly designed and/or conducted. One good-quality RCT suggested that IV fluids might be harmful in patients with penetrating injuries. No evidence was found on the relative effectiveness of IV fluids in patients with blunt versus penetrating trauma. No reliable evidence was found from systematic reviews to suggest that a particular type of fluid is more beneficial compared to another type, although there was a trend favoring crystalloids over colloids. The relative costs of using IV fluids versus not using them were found to be similar, and changes in the use of fluids would therefore have no cost consequences for the ambulance service. A more detailed cost-effectiveness analysis would require further information on the relative consequences (mortality, morbidity) of different resuscitation strategies.

Recommendations

The review found no evidence to suggest that prehospital IV fluid resuscitation is beneficial, and some evidence that it may be harmful. This evidence is not conclusive, particularly for blunt trauma. A UK Consensus Statement and, to a lesser extent, the UK Joint Royal Colleges Ambulance Liaison Committee guidelines represent a more cautious approach to fluid management than previously advocated and are therefore consistent with the limited evidence base.

Methods

Search strategies were defined to identify RCTs and previous systematic reviews relating to the use of IV fluids in a prehospital (or other) setting compared to no fluids or delayed fluids. Inclusion and exclusion criteria were applied to identified studies, and key quality criteria of included studies were checked. Data were extracted independently by two reviewers. Economic evaluations were systematically sought and appraised.

Further research/reviews required

Further research is required on hypotensive (cautious) resuscitation versus delayed or no fluid replacement, particularly in blunt trauma. There is also a need to improve the quality of data collection and analysis of routinely collected ambulance call-out data.

Written by Ms Janine Dretzke, Dept of Public Health and Epidemiology, University of Birmingham, UK

Title **Newer Hypnotic Drugs for the Short-term Management of Insomnia: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2004;8(24). Jun 2004. www.ncchta.org/execsumm/summ824.htm

Aim

To assess the clinical and cost effectiveness of zaleplon, zolpidem, and zopiclone (Z-drugs) compared with benzodiazepines.

Conclusions and results

Twenty-four studies involving 3,909 patients met the inclusion criteria (17 studies comparing a Z-drug with a benzodiazepine and 7 comparing a Z-drug with another Z-drug). Outcomes were rarely standardized and differed in interpretation. Variations in assessment and the level of information make comparisons difficult. Hence, meta-analysis included only a small number of outcomes. Some evidence suggests that zaleplon gives shorter sleep latency, but shorter sleep duration, than zolpidem. No economic model describes the costs and benefits of the newer hypnotic drugs for insomnia. In the short-term, no systematic evidence is available on significant outcome variations between the different classes of drugs or between individual drugs within each class. The acquisition cost of the individual drugs varies significantly.

Recommendations

The short-acting drugs seem equally effective and safe, but there is no evidence that one is more cost-effective than any other. Analysis of the additional costs to the NHS, depending on the rate of change from benzodiazepine to Z-drug prescriptions, at current levels of hypnotic prescribing, range from £2 million to £17 million per year. Research is needed in this area since none of the existing trials adequately compare these medications. Further consideration should be given to a formal trial to allow head-to-head comparison of key drugs in a double-blind randomized controlled trial (RCT) lasting at least 2 weeks and sufficient in size to draw reasonable conclusions. Such trial should include a placebo arm. It should also collect good-quality data on sleep outcomes, particularly quality of life and daytime drowsiness. We do not believe that a formal study of the risk of dependency is feasible at present.

Methods

The review included RCTs that compared benzodiazepines to the Z-drugs, or any two of the nonbenzodiazepine drugs, in insomnia patients. Data on the following outcome measures were considered: sleep onset latency, total sleep duration, number of awakenings, quality of sleep, adverse effects, and rebound insomnia. A search was also undertaken for study designs that evaluated issues related to adverse events (eg, dependency and withdrawal symptoms). Full economic evaluations that compared two or more options and considered both costs and consequences (eg, cost effectiveness, cost-utility analysis, or cost-benefit analysis undertaken in the context of high-quality RCTs) were considered for inclusion in the review.

Further research/reviews required

The management of long-term insomnia is suggested for further investigation. Considering the frequency of this symptom and its recurring course, the short-term trial of medication and lack of long-term followup undermine attempts to develop evidence based guidelines for the use of hypnotics in this condition, or indeed for its whole management.

Written by Dr Yenal Dundar, Liverpool Reviews & Implementation Group (LRiG), University of Liverpool, UK

INAHTA Briefs

Issue 2005/08

Title	**EVALUATE Hysterectomy Trial: A Multicentre Randomised Trial Comparing Abdominal, Vaginal and Laparoscopic Methods of Hysterectomy**
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Reference	Health Technol Assess 2004;8(26). Jun 2004. www.ncchta.org/execsumm/summ826.htm

Aim

The EVALUATE study was 2 parallel randomized trials, one comparing laparoscopic hysterectomy (LH) with abdominal hysterectomy (AH) and the other comparing LH with vaginal hysterectomy (VH). The trials were designed to: (1) test the null hypothesis of no significant difference between LH and AH; and LH and VH; and (2) appraise the cost and cost effectiveness to health service and patients of AH, VH, and LH.

Conclusions and results

Clinical: Compared with AH, LH showed a higher rate of major complications (11.1% vs 6.2% p=0.02), less postoperative pain (visual analogue scale score of 3.51 vs 3.88 p=0.01) and shorter hospital stay (3 vs 4 days), but took longer to perform (84 vs 50 minutes). At 6 weeks postoperative, ALH showed a significantly better scores than AH in the physical component of short form 12, Body Image Scale , and frequency of sexual intercourse. These differences were not observed at 4 or 12 months after surgery. No significant differences in outcome were found between LH and VH except that VLH took longer to perform and had a higher rate of detecting unexpected pathology.

Economic: Compared to vaginal hysterectomy, VLH had a higher mean cost per patient of £401 and higher mean QALYs of 0.0015 resulting in an incremental cost per QALY gained of £267,333. The probability that VLH is cost effective was below 50% for a large range of willingness-to-pay values for an additional QALY. Compared to abdominal hysterectomy, ALH had a higher mean cost per patient of £186 and higher mean QALYs of 0.007, resulting in an incremental cost per QALY gained of £26,571. If the NHS is willing to pay £30,000 for additional QALYs, the probability that ALH is cost effective is 56%.

Recommendations

Abdominal trial – LH shows a significantly higher risk of major complications and takes longer to perform than AH. LH shows less pain, quicker recovery, and better short-term quality of life (QoL) after surgery than AH. The cost effectiveness of LH is finely balanced, depending on the threshold value the NHS attaches to an additional QALY and the balance of reusable equipment versus disposable consumables. The surgeon must determine the optimum balance between patient benefits and the risk of severe complications.

Vaginal trial – Clinical results were not conclusive, as the study was not designed to have sufficient power to detect a statistically significant result. LH was not cost effective relative to VH.

Methods

Please see the full monograph for details of the methods.

Further research/reviews required

Application and relevance of QoL measures following hysterectomy, and long-term followup. Patient preferences – balance between risks and benefits of the various forms of hysterectomy. Reducing complication rates. Improving gynecological surgical training. Surgeon effect in surgery trials. Care pathways for hysterectomy. Additional pathology identification in LH. Meta-analysis / further trial of VH versus LH.

Written by Ms Vicky Napp, CTRU, Leeds, UK

INAHTA Briefs

Issue 2005/09

Title **Effectiveness and Cost-effectiveness of Imatinib for First-line Treatment of Chronic Myeloid Leukaemia in Chronic Phase: A Systematic Review and Economic Analysis**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
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Reference Health Technol Assess 2004;8(28). Jul 2004. www.ncchta.org/execsumm/summ828.htm

Aim

To evaluate the effectiveness of imatinib as first-line treatment for chronic myeloid leukemia (CML) compared with interferon-alpha (IFN-alpha), hydroxyurea, and bone marrow transplantation (BMT), and the cost effectiveness of imatinib compared with IFN-alpha and hydroxyurea.

Conclusions and results

Intention-to-treat analysis showed that imatinib was associated with complete cytogenetic response (CR) at 12 months followup of 68%, compared with 20% for the IFN-alpha plus Ara-C group. An estimated 98.5% of people taking imatinib, and 93.1% taking IFN-alpha plus Ara-C had not progressed to accelerated or blast phases at 12 months. Overall survival was not statistically significantly different. Withdrawal due to side effects was 2% for imatinib and 5.6% for IFN-alpha plus Ara-C. The study presents data on cross-over due to intolerance, quality of life (QoL), median complete CR, median withdrawal due to side effects, and median and long-term survival. Direct comparison between imatinib and hydroxyurea or BMT was not possible. Simple indirect comparison with hydroxyurea suggests that imatinib is more effective. Comparison of imatinib and BMT is not currently possible. The incremental cost-effectiveness ratio (ICER) of imatinib compared with IFN-alpha was estimated as £26,180 per quality-adjusted-life-year (QALY) gained. Imatinib appears less cost effective when compared to hydroxyurea with an estimated ICER of £86,934 per QALY.

Recommendations

Imatinib appears to be more effective than current standard drug treatments in terms of CR and progression-free survival, with fewer side effects. There is uncertainty about longer term outcomes, the development of resistance to imatinib, the duration of response, and the place of imatinib relative to BMT. New issues arise continually, eg, optimal management pathways and combination therapies.

Methods

Selected studies and full-text articles were screened and selected. Survival was the key outcome measure. Surrogate outcome measures included HR (hematological response) and CR. As no published cost-effectiveness studies compared imatinib and IFN-alpha, a Markov model was constructed to assess cost effectiveness. This was compared with models submitted to the National Institute for Clinical Excellence by the manufacturer of imatinib.

Further research/reviews required

Long-term followup data from the first- and second-line imatinib trials. Investigation of specific subgroups, eg, high-risk patients, the elderly, children, or those eligible for BMT. Long-term comparisons of imatinib and BMT in early stages of CML. Use of imatinib combined with other therapies, and further detailed economic studies. Impact of CML and imatinib on QoL.

Written by Dr Ken Stein, Director, Peninsula Technology Assessment Group, University of Exeter, UK

Title **VenUS1: A Randomised Controlled Trial of Two Types of Bandage for Treating Venous Leg Ulcers**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
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Reference Health Technol Assess 2004;8(29). Jul 2004. www.ncchta.org/execsumm/summ829.htm

Aim

To compare the clinical and cost effectiveness of the multilayer, elastic 4-layer bandage (4LB) and multilayer, inelastic short stretch bandage (SSB) in healing venous leg ulcers.

Conclusions and results

Between Apr 1999 and Dec 2000, 387 people were recruited to the trial (39% of those approached). Main reasons for exclusion were: patients unsuitable for compression, ankle/brachial pressure index (ABPI) lower than 0.8, diabetes mellitus, and maximum ulcer length less than 1 cm. Patients were aged 23 to 97 years at trial entry (mean age 71 years). Most patients in the trial (82%; 316/387) had a reference ulcer area ≤10 cm^2. To test the difference over time of Kaplan Meier curves for the 2 bandage groups, the log-rank test was used to compare the distribution of the cumulative times-to-healing of individuals in the 2 trial groups. The difference in distribution was not statistically significant at the 5% level. To explore the effect of several prognostic factors on the distribution of times-to-healing in the 2 bandage groups, a Cox proportional hazards model was fitted to the data. After adjusting healing times for the effects of other variables (center, baseline ulcer area, duration, episodes, ankle mobility, weight) a statistically significant treatment effect favoring the 4LB was identified. The probability of healing for individuals in the SSB treatment arm is significantly lower than that for people treated with the 4LB, indicating that individuals on the SSB are less likely to heal than those on the 4LB. Our base case economic analysis showed that, in comparison to the SSB, the 4LB is a dominant strategy, ie, associated with greater health benefits and lower costs than the SSB. This result is explained by the greater number of community nurse visits required by participants in the SSB arm.

Recommendations

The 4LB, currently the UK standard compression bandage for venous leg ulcers, was more clinically and cost effective than the SSB. The SSB would be a reasonable alternative for patients who like it and will not tolerate the 4LB.

Methods

A pragmatic, multicenter, open, randomized controlled trial, incorporating economic evaluation was conducted. Patients with venous leg ulcers were randomized to either 4LB or SSB delivered within their usual care arrangements (community based, District Nurse led services; community leg ulcer clinics; hospital leg ulcer clinics with community outreach). Followup continued for 12 months, or until healing, whichever occurred first.

Further research/reviews required

Relationship between bandager skill, application technique, and ulcer healing (including the potential for patients and/or their carers to apply bandages effectively). Relative cost effectiveness of community leg ulcer clinics. Nurse decision making in venous ulcer management (to better understand the influences on treatment choice and the frequency of treatment visits).

Written by Professor Nicky Cullum, Department of Health Sciences, University of York, UK

Title **Systematic Review of the Effectiveness and Cost Effectiveness, and Economic Evaluation, of Myocardial Perfusion Scintigraphy for the Diagnosis and Management of Angina and Myocardial Infarction**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
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Reference Health Technol Assess 2004;8(30). Jul 2004. www.ncchta.org/execsumm/summ830.htm

Aim

To assess the effectiveness and cost effectiveness of single photon emission computed tomography (SPECT) myocardial perfusion scintigraphy in diagnosing and managing angina and myocardial infarction (MI).

Conclusions and results

Included were 21 diagnostic and 46 prognostic studies, 2 studies comparing SPECT with electrocardiography (ECG)-gated SPECT, and 1 study comparing SPECT with attenuation-corrected SPECT. The diagnostic values of SPECT were generally higher than those of stress ECG. SPECT may be able to identify lower risk patients for whom coronary angiography (CA) might be avoided. Normal SPECT scans were associated with a benign prognosis and medical rather than invasive management. Four studies of post-MI patients reported SPECT to be valuable in stratifying patients into at-risk groups for further cardiac events. The 2 studies comparing SPECT with ECG-gated SPECT found in favor of gated SPECT. The study comparing SPECT with attenuation-corrected SPECT reported the latter to be more accurate. Systematic review of economic evaluations indicated that strategies involving SPECT were likely either to be dominant or to produce more QALYs at an acceptable cost. There was less agreement about which of the strategies was optimal. An economic model suggested that, for low prevalence, the incremental cost per unit of output (true positives diagnosed, accurate diagnosis, QALY) for the move from stress ECG–SPECT–CA and from stress ECG–CA to SPECT–CA might be considered worthwhile. The least costly and least effective strategy was stress ECG–SPECT–CA. Sensitivity analysis suggested that the cost effectiveness of SPECT–CA improved if SPECT results allowed for adopting a management strategy without recourse to CA. As time decreased, the incremental cost per QALY increased.

Recommendations

Measurement of outcomes, management, setting, and patient characteristics varied considerably. The evidence tended to favor SPECT in terms of test sensitivity (based on a relatively small number of diagnostic studies). SPECT added valuable independent, incremental prognostic information to that from stress ECG and/or CA, which helped to risk-stratify patients and influence how their condition was managed. All of the prognostic studies were observational and may be biased by unknown confounding factors. Although the ECG-gated and attenuation-corrected SPECT findings seem promising, it is difficult to draw conclusions from so few studies.

Methods

Please refer to the full monograph for details of the methods.

Further research/reviews required

Further research is needed on the effectiveness and cost effectiveness, diagnostically and prognostically, of (a) gated and attenuation-corrected SPECT compared with standard SPECT, (b) standard SPECT compared with stress echocardiography, and (c) the uncertainty surrounding the results presented in the cost-effectiveness analysis.

Written by Mr Graham Mowatt, Health Services Research Unit, University of Aberdeen, UK

Title **A Pilot Study on the Use of Decision Theory and Value of Information Analysis as Part of the NHS Health Technology Assessment Programme**

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Reference Health Technol Assess 2004;8(31). Jul 2004. www.ncchta.org/execsumm/summ831.htm

Aim

To assess the potential for decision analysis and value of information analysis (DA-VOI) to contribute to the process of achieving the greatest return, in terms of outcomes, eg, health gain, from the resources available to the NHS Health Technology Assessment (HTA) Program.

Conclusions and results

Although none of the research topics identified by NCCHTA met all the criteria for inclusion as case studies in the pilot, it was possible to construct appropriate decision analytic models and conduct probabilistic sensitivity analysis for each topic. In each case, the 3 core tasks were completed within the time required by the NCCHTA research prioritization process. The brief case study reports described the decision problem, summarized the evidence base, and characterized decision uncertainty via cost-effectiveness acceptability curves. Implications for research in each area were presented at a general level, and for the design of future research, eg, in terms relevant patient groups and comparators, and whether experimental design was likely to be required. Feedback on the DA-VOI analysis and its presentation suggested that the explicit consideration of available evidence was useful in making priority decisions. Several issues must be considered when using DA-VOI analysis, particularly the quality of evidence used in the model and the feasibility of undertaking such analysis in the existing timelines. Feedback indicated that the background document should be adapted for a non-technical audience.

Recommendations

1. DA-VOI requires stakeholders to be clear about the nature of the decision problem
2. DA-VOI needs explicitness about which existing data should be used in the first part of the analysis and how data that exhibit particular weaknesses should be 'down-weighted'
3. There would be advantages to making the development of the vignette and the use of DA-VOI an integrated process
4. There is a need to identify, and secure access to, relevant clinical experts early in the analysis
5. If some degree of implementation of DA-VOI takes place within the Program, careful evaluation and ongoing development is essential.

Methods

Please refer to the full monograph for details of the methods.

Further research/reviews required

1. Methods for efficient literature searching. This would focus most searching and review attention on those variables to which the model's results are most sensitive and with the highest EVPI
2. Methods of evidence synthesis (multiple parameter synthesis) to consider the evidence surrounding multiple comparators and networks of evidence
3. Ways in which the value of sample information can be used by the NHS HTA Program and other research funders to decide on the most efficient design of new evaluative research.

Written by Professor Mark Sculpher, Centre for Health Economics, University of York, UK

Title **Clinical Effectiveness and Cost-effectiveness of Clopidogrel and Modified-release Dipyridamole in the Secondary Prevention of Occlusive Vascular Events: A Systematic Review and Economic Evaluation**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
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Reference Health Technol Assess 2004;8(38). Oct 2004. www.ncchta.org/execsumm/summ838.htm

Aim

To examine the clinical and cost effectiveness of 2 alternative antiplatelet agents, clopidogrel and modified-release (MR)-dipyridamole, relative to prophylactic doses of aspirin for the secondary prevention of occlusive vascular events.

Conclusions and results

In the CAPRIE trial, the point estimate for the primary outcome, ie, ischemic stroke, myocardial infarction (MI), or vascular death, favored clopidogrel over aspirin, but the boundaries of the confidence intervals raise the possibility that clopidogrel is not more beneficial than aspirin. Regarding secondary outcomes, a non-significant trend favored clopidogrel over aspirin. The number of patients reporting bleeding disorders in the clopidogrel group did not differ from the aspirin group. The incidences of rash and diarrhea were statistically significantly higher in the clopidogrel group than the aspirin group. The aspirin group had a higher incidence of indigestion/nausea/vomiting than the clopidogrel group. Hematological adverse events were rare in both groups. No cases of thrombotic thrombocytopenic purpura were reported in either group. Treatment with MR-dipyridamole alone did not significantly reduce the risk of any of the primary outcomes reported in ESPS-2 compared with treatment with aspirin. Acetylsalicylic acid (ASA)–MR-dipyridamole was significantly more effective than aspirin alone in patients with stroke or transient ischemic attacks (TIAs) at reducing the outcome of stroke and marginally more effective at reducing stroke and/or death. ASA–MR-dipyridamole did not statistically significantly reduce the risk of death compared to aspirin. The number of strokes was statistically significantly reduced in the ASA–MR-dipyridamole group versus the MR-dipyridamole group. Results in the other primary outcomes, stroke and/or death, and death, favored ASA–MR-dipyridamole, but the findings were not statistically significant. The number of bleeding complications did not differ between the groups, but the incidence was significantly lower in the MR-dipyridamole group. More patients in the MR-dipyridamole treatment groups experienced headaches compared to patients receiving aspirin alone. The York model assessed, under several different scenarios, the cost effectiveness of differing combinations of treatment strategies in 4 patient subgroups. The results of the model were sensitive to the assumptions made in the alternative scenarios, in particular the impact of therapy on non-vascular deaths.

Recommendations

Please see the full monograph for recommendations.

Methods

Please see the full monograph for methods.

Further research/reviews required

Evaluation of the combination of clopidogrel and aspirin (for secondary prevention of occlusive vascular events). Randomized, direct comparisons of clopidogrel and MR-dipyridamole in combination with aspirin (to inform treatment of patients with a history of stroke and TIA). Trials to compare treatment with clopidogrel and MR-dipyridamole (for secondary prevention of vascular events in patients demonstrating genuine intolerance to aspirin).

Written by Ms Lisa Jones and Dr Rob Riemsma, CRD, UK

Title **Clopidogrel Used in Combination with Aspirin Compared with Aspirin Alone in the Treatment of Non-ST-segment-elevation Acute Coronary Syndromes: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2004;8(40). Oct 2004. www.ncchta.org/execsumm/summ840.htm

Aim

To systematically review the clinical and cost effectiveness of clopidogrel in combination with standard aspirin therapy, compared with standard therapy alone for treating non-ST-segment elevation acute coronary syndromes (ACS).

Conclusions and results

One randomized controlled trial (RCT), the CURE trial, was double-blinded, placebo- controlled, and of high quality. It showed that clopidogrel plus aspirin was significantly more effective than placebo plus aspirin in patients with non-ST-segment elevation ACS for the composite outcome of death from cardiovascular causes, non-fatal myocardial infarction, or stroke over the 9-month treatment period. However, clopidogrel was associated with significantly more episodes of bleeding. Five systematic reviews showed aspirin to be associated with a significantly higher incidence of hemorrhagic stroke, extracranial hemorrhage, and gastrointestinal hemorrhage compared to placebo. A model found clopidogrel to be cost effective compared with standard care alone in patients with non-ST-elevation ACS, as long as the NHS is willing to pay £6,078 per quality of life year (QALY). Although 12 months of clopidogrel treatment was cost effective for the overall cohort, provisional findings indicate that shorter treatment may be more cost effective in patients at low risk.

Recommendations

The CURE trial indicates that the benefit of clopidogrel plus aspirin is largely related to a reduction in Q-wave myocardial infarction. There was no statistically significant benefit in relation to mortality. Much of the benefit derived from clopidogrel is achieved by 3 months, with further small benefit over the remaining 9 months of chronic treatment.

Methods

Rigorous criteria were used to select studies. The quality of RCTs was assessed according to criteria based on CRD Report No. 4. The quality of systematic reviews was assessed according to the guidelines for the Database of Reviews of Effects (DARE) criteria. The quality of economic evaluations was assessed according to a specifically tailored checklist. The clinical effectiveness and cost effectiveness of clopidogrel in combination with standard therapy compared with standard therapy alone were synthesized through a narrative review with full tabulation of the results of the included studies. A cost-effectiveness model was constructed for the economic evaluations, using the best available evidence to determine cost effectiveness in a UK setting.

Further research/reviews required

A prospective trial that randomized patients to various durations of therapy would be required to estimate the exact length of time that clopidogrel plus standard therapy should be prescribed for patients with non-ST-segment ACS. This would accurately assess whether a 'rebound' phenomenon occurs in patients if clopidogrel were stopped after 3 months of treatment.

Written by Ms Caroline Main, Centre for Reviews and Dissemination, University of York, UK

INAHTA Briefs

Issue 2005/15

Title **Provision, Uptake, and Cost of Cardiac Rehabilitation Programmes: Improving Services to Under-represented Groups**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
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Reference Health Technol Assess 2004;8(41). Oct 2004. www.ncchta.org/execsumm/summ841.htm

Aim

To estimate the need for and to update estimates of outpatient cardiac rehabilitation (CR) in the UK; identify patient groups not receiving CR; review effectiveness of methods to improve uptake and adherence to CR; and estimate cost implications of increasing uptake of CR.

Conclusions and results

In England, Wales, and Northern Ireland 146,000 patients with acute myocardial infarction, unstable angina, or following revascularization were potentially eligible for CR. In England in 2000, 45% to 67% were referred with 27% to 41% attending. For ischemic heart disease, including angina pectoris and heart failure, annual eligibility would be 299,000, with referral and attendance (R&A) of 22% to 33% and 13% to 20% respectively. R&A were similar in Wales, but lower in Northern Ireland. Most studies were small, of short duration, and low quality. Hence, none of the findings can be considered definitive. Few studies reported costs.

Uptake: Eight studies (3 randomized) evaluated methods to improve uptake. These supported motivational use of letters, pamphlets, home visits, and, to some extent, trained lay visitors.

Adherence: Fourteen studies (7 randomized) evaluated methods to improve attendance or maintenance of lifestyle associated with CR. Self-management techniques showed value in promoting adherence to lifestyle changes.

Professional compliance: Six studies (2 randomized) evaluated methods to improve uptake and adherence by improving professional compliance with guidelines and good practice. No effective interventions were identified. In 2001, CR cost about £350 (staff only) and £490 (total) per patient. Costs of outpatient CR by UK NHS were about £15–24 million. Staff-to-patient ratio and duration of treatment partly explained the variation in cost per patient. In modeling services on an intermediate staff configuration, about 13% more patients could be treated with the same budget. If the most modest services were provided, 40% more patients could be treated. An approximate 200%–790% budget increase would be required to provide CR to all potentially eligible patients.

Recommendations

Please see the full monograph for recommendations.

Methods

Please see the full monograph for methods.

Further research/reviews required

Compare cost effectiveness of comprehensive multidisciplinary rehabilitation with simpler outpatient regimens. Economic and patient preference studies of effects of different methods to use increased funds for CR and evaluate the impact of increased funding. Evaluate interventions to promote attendance in all patients and underrepresented groups. Standardized audit methods involving modern records systems, staff training, and dialogue between service contributors. Standardized criteria for patient eligibility and data collection to estimate need and provision of CR. Extension of low-cost interventions and good practice in rehabilitation centers. Qualitative studies to identify further areas for intervention. Systematic review to include grey literature and non-UK studies.

Written by Professor Shah Ebrahim, Professor in Epidemiology of Ageing, University of Bristol, UK

INAHTA Briefs

Issue 2005/16

Title **Involving South Asian Patients in Clinical Trials**

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Reference Health Technol Assess 2004;8(42). Sept 2004.
www.ncchta.org/execsumm/summ842.htm

Aim

To extend knowledge of South Asian patients' understanding of trials, and of the processes which facilitate or inhibit their involvement in them.

Conclusions and results

Motivations for trial participation were identified as: to help society, to improve own health or that of family and friends, obligation to the doctor, and to increase scientific knowledge. Deterrents were identified as: concerns about drug side effects, busy lifestyles, language, previous bad experiences, mistrust, and feelings of not belonging to British society. There was no evidence of antipathy among South Asians to the concept of clinical trials, and younger respondents were more knowledgeable than older ones. Problems were more likely to be associated with service delivery. Lack of being approached was a common response. Lay-reported factors that might affect South Asian participation in clinical trials include: age, language, social class, sense of not belonging/mistrust, culture, and religion. Awareness of clinical trials varied among groups. Indian respondents were most likely to be aware, while less than half of the Pakistani and Bangladeshi respondents were aware of clinical trials. Attitudes toward clinical trial participation were more similar than different between South Asian and the general population. Important decisions, eg, clinical trial participation, were likely to be made by family members who were younger and fluent in English. Social class appeared to be more important than ethnicity. Older South Asians and those from working class backgrounds appeared to be more mistrustful. Approachable patients (same gender, social class, fluent in English) tended to be 'cherry picked' for clinical trials. This was justified because of inadequate time, resources, and support. South Asian patients might be systematically excluded from trials due to the extra cost and time associated with their inclusion, particularly in relation to the language barrier. Under-representation might also be due to passive exclusion associated with cultural stereotypes. Other characteristics such as gender, age, educational level, and social class can also affect trial inclusion.

Recommendations

Exclusion from trials is inequitable since evidence suggests that people who take part have better clinical outcomes. Unless South Asian people are routinely included in trials, the diseases they are disproportionately disposed to will remain poorly understood and treated. Excluding minority ethnic groups undermines the government's NHS plan to tackle inequalities. It is also important to sustain the widespread applicability of trial findings to the whole population. Excluding a sub-set of the population could have implications for the safety and efficacy of new drugs. Participation of minority ethnic groups in trials would help to reduce alienation and mistrust.

Methods

A review of the literature on minority ethnic participation in clinical trials was followed by 3 qualitative, semi-structured interview studies. Interviews were taped, transcribed (translated) and analyzed by framework analysis.

Further research/reviews required

Responses when invited to participate. Role of methodological and organizational barriers to recruitment. Complexities of recruitment from a health professional perspective. Developing culturally sensitive research methods. Magnitude of under-recruitment. Strategies to encourage inner city, single-handed GP participation. Other factors affecting trial inclusion eg age, gender, educational level, and sociocultural background.

Written by Dr Brenda Leese, Centre for Research in Primary Care, University of Leeds, UK

INAHTA Briefs

Issue 2005/17

Title **Identification and Assessment of Ongoing Trials in Health Technology Assessment Review**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
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Reference Health Technol Assess 2004;8(44). Nov 2004.
www.ncchta.org/execsumm/summ844.htm

Aim

To assess the importance of ongoing trials in health technology assessment reviews (HTARs) for the National Institute for Clinical Excellence and to provide practical recommendations for identifying ongoing trials and assessing their possible impact.

Conclusions and results

Identification of ongoing trials is common in HTARs. Of 32 HTARs, 23 identified one or more ongoing trials. In 8 of the 23, information on ongoing trials was not considered in the evidence synthesis and research recommendations. All 32 HTARs searched for unpublished studies, and/or ongoing trials and/or grey literature and trial registers. The assessment of 6 commonly used trial registers suggested that most registers provided sufficient information for reviewers to decide the relevance of ongoing trials. At times it is difficult to know whether ongoing trials identified from different sources (registers) are the same trials or belong to the same multicenter trials. The ISRCTN (the International Standard Randomized Controlled Trial Number) is the most reliable system, but has not been widely adopted. Qualitative assessment compared major features of completed and ongoing trials. Quantitative methods to assess the impact of ongoing trials include cumulative meta-analysis related methods, fail-safe N, Bayesian data monitoring, and Bayesian interim predictions. The most useful quantitative method may be the Bayesian predictive probability. A case study indicated that the appropriate use of quantitative methods would strengthen findings from narrative assessment of possible impact of ongoing trials.

Recommendations

Searching for ongoing trials in effectiveness reviews should be more thorough and explicit. Conversely, primary researchers, in particular those working with multicenter trials, should label ongoing trials more clearly, preferably by ISRCTN. Qualitative assessment of identified ongoing trials is crucial and informative. Available quantitative methods could be used to strengthen findings from narrative assessment, although further research and more empirical examples are required. Information from ongoing trials may contribute to syntheses of results, conclusions and recommendations for future research.

Methods

Ongoing trials (or trials in progress) were defined as any trials that have started but where the results are not yet available, or only interim results are available for HTARs. This methodological review included:

1. Assessment of ongoing trials in HTARs completed by the end of August 2002
2. Survey and assessment of trial registers and other sources of ongoing trials
3. Summary and assessment of methods to assess the possible impact of ongoing trials.

Further research/reviews required

Future research is suggested to identify and assess ongoing trials in other systematic reviews of effectiveness of healthcare interventions; existing and new methods for incorporating information on ongoing trials; comparing estimated impacts with the actual results of ongoing trials; and to incorporate findings from the assessment of ongoing trials into decision models.

Written by Dr Fujian Song, Institute of Health, University of East Anglia, UK

INAHTA Briefs

Issue 2005/18

Title **Generalisability in Economic Evaluation Studies in Healthcare: A Review and Case Studies**

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Reference Health Technol Assess 2004;8(49). Dec 2004. www.ncchta.org/execsumm/summ849.htm

Aim

To focus on generalizability in *economic evaluation* as applied to health services. The *context* which is the primary focus of this report is the *location* in which the study was undertaken and/or the *decision maker* for whom the study was undertaken.

Conclusions and results

Unit costs associated with particular resources are most frequently cited as generating variability in economic results between locations. No studies were identified which explicitly considered factors causing variability in the results of economic studies over time. Regression analysis has been advocated as a means of looking at variability in economic results across locations. The decision analytic model has been the main means by which cost-effectiveness has been adapted from trial to non-trial locations. The review failed to identify major literature on variability in cost effectiveness over time, although emerging literature using Bayesian decision theory may be of value. There was little use of the statistical approaches identified in the methods review to assess variability by location. The case study demonstrated the value of multilevel modeling (MLM). Where clustering exists by location, MLM facilitates correct estimates of the uncertainty in cost-effectiveness results. MLM also provides a means of estimating location-specific cost-effectiveness. Few studies were explicit about their target decision maker(s)/jurisdictions. The studies in the review generally made more effort to ensure that their cost inputs were specific to their target jurisdiction than their effectiveness parameters. Standard sensitivity analysis was the main way of dealing with uncertainty in the models. The modeling case study illustrated how effectiveness and cost data can be made location-specific. In particular, on the effectiveness side, the example showed the separation of location-specific baseline events, and pooled estimates of relative treatment effect which are assumed exchangeable across locations.

Recommendations

At the design stage of a study, selection of study sites should focus on those representative of the jurisdiction(s) for which economic data are required. There is value in collecting data on the characteristics of trial centers which could be used as covariates in a regression model. Resource use data (eg hospital days) should be reported separately from the unit costs of those resources. MLM should be considered for assessing the degree of clustering in cost and effectiveness data in trial locations. Reporting more information on the centers/countries in a study can help decision-makers to interpret the relevance of results. Given the focus on a decision, any analysis should be clear about the specification of the decision problem and the relevant decision-maker(s) and jurisdiction(s). It is important to distinguish parameter uncertainty from variability or heterogeneity, where the latter is concerned with how parameter estimates vary across 'contexts'.

Methods

Please see the full monograph for methods.

Further research/reviews required

The most appropriate basis to select centers into multicenter trials, and contenders for location-level covariates in multilevel models.

Written by Professor Mark Sculpher, Centre for Health Economics, University of York, UK

INAHTA Briefs

Issue 2005/19

Title	**Health Care Technology at Home: Issues in Organization and Delivery in Québec**
Agency	**AÉTMIS, Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé** 2021, avenue Union, bureau 1040, Montréal, Québec, Canada H3A 2S9; Tel: +1 514 873 2563, Fax: +1 514 873 1369; aetmis@aetmis.gouv.qc.ca, www.aetmis.gouv.qc.ca
Reference	Technology brief AÉTMIS 04-06, 2004. Internet access to full text. ISBN 2-550-43249-5 (French edition ISBN 2-550-43248-7) 119 pages.

Aim

To identify the organizational issues associated with an increased use of health care technology at home, and provide recommendations regarding the development of such services in Québec.

Conclusions and results

Most industrialized countries aim to increase the scope of health services delivered at home. Globally, funding for home care has increased markedly over the past 10 years. In Canada, the home care budget represents a small part of the total health bill. Home care is not regulated by the Canada Health Act, or coordinated by a national policy, and eligibility, cost, quality, and access to these services vary across the country. This report details the prevalence and patterns of use of technology at home in Québec and presents four aspects that require immediate attention:

- *The interface between community-based and specialized, hospital-based home care.* As the range of home-delivered technologies expands, local service providers (CLSC's in Quebec) and hospitals must increasingly bring multidisciplinary teams and specialized equipment together to serve patients well. How are these organizations adapting to new staff roles and services?
- *Increased responsibility delegated to patients and caregivers.* Very few studies have investigated the knowledge and skills required to manipulate home care technologies appropriately. Who is ultimately accountable for the quality of care delivered at home?
- *Risks associated with home environments.* What is the impact on families of the risk-taking associated with home delivery of services?
- *Implementation of home care services despite the lack of evidence about cost effectiveness.* High-tech home care services are not always cost effective. Further research should be conducted and results discussed with clinicians and policymakers.

The report also summarizes the organizational, social, ethical, and legal dimensions of technology-enhanced home care, as described in the literature.

Recommendations

- Establish innovative organizational mechanisms that support the delivery of coordinated home care.
- Increase the level of support for patients and caregivers.
- Revisit the medicalization of the home. Reconsider the rationale for the rapid development of technology-enhanced home care.
- Support high quality research into the cost effectiveness of home care.

Method

The report is based on a broad review of the international literature and data from a mail-back survey sent to 140 Quebec CLSC's which aimed to document the organizational framework in which CLSC's integrate four home-based technologies.

Written by Pascale Lehoux and Susan Law with the collaboration of Lucy Boothroyd, AÉTMIS, Canada

INAHTA Briefs

Issue 2005/20

Title **Comparison of the Insulin Pump and Multiple Daily Insulin Injections in Intensive Therapy for Type 1 Diabetes**

Agency **AÉTMIS, Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé**
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Reference AÉTMIS 04–07. Internet access to full text. French edition ISBN 2-550-43606-7. English summary available on line.

Aim

- To assess the safety, efficacy, and cost effectiveness of insulin pump therapy compared to multiple daily insulin injections in treating type 1 diabetes.
- To incorporate patient and health professional perspectives on introducing the pump into Québec's healthcare system.

Conclusions and results

Insulin pump therapy administers fast-acting insulin subcutaneously via a portable, battery-operated, programmable pump.

Efficacy: In the general adult diabetic population, data show that the pump can lead to modest improvement in glycemic control compared to multiple injections with NPH, at no additional risk. The efficacy gain is greater for adults and children who meet specific clinical and psychosocial criteria. The pump is as effective as multiple injections with glargine in adults.

Quality of life: Studies do not show improvement in patients using the pump, but respondents considered the benefits of pump use important in several areas of daily life.

Cost effectiveness: Data for the pump are limited. The high cost of the pump, and the predicted availability of insulin glargine in Québec should reduce interest in pump therapy for adult diabetics. AÉTMIS concludes that this technology offers advantages for a limited and selected group of type 1 diabetics, with specific clinical characteristics. The pump is safe, and could offer significant improvement in glycemic control for this group, in motivated patients who are adequately trained and supported by a specialized team.

Recommendations

- Continue to base the preferred therapeutic approach to type 1 diabetes on intensive therapy with multiple daily insulin injections, for both adults and children.
- Consider creating a multidisciplinary task force to identify criteria for patient selection and pump prescription; designate participating clinics and professional support teams; develop selection, education, and followup tools; monitor implementation and reevaluate.
- Develop a consistent policy for insulin pump use as part of a broader initiative for managing diabetes in Québec.
- Examine insurance coverage for the pump as an exceptional treatment modality, and institute systematic auditing and monitoring procedures.

Method

Review of 2 HTA reports (2000, 2002) and examination of literature published from 2002 to 2004. Analysis of 34 self-administered patient questionnaires, and face-to-face interviews with health professionals from 7 adult and pediatric hospitals.

Written by Brigitte Coté (public health) and Carole St-Hilaire, AÉTMIS, Canada

INAHTA Briefs

Issue 2005/21

Title **Liquid Oxygen Therapy at Home**

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Reference AÉTMIS 04–08. Internet access to full text. ISBN 2-550-43750-0
(French edition ISBN 2-550-43751-9) vi-13 p.

Aim

The costs and benefits of portable oxygen systems for home use by patients with chronic obstructive pulmonary disease (COPD) were assessed in an AÉTMIS report published in 2004. The agency was subsequently asked, by the provincial ministry of health and social services, to assess the costs and benefits specific to portable liquid oxygen therapy, as compared to compressed gas or oxygen concentrator systems. AÉTMIS was also asked to assess implications for the use of portable liquid oxygen in Québec's home oxygen program.

Conclusions and results

Because liquid oxygen therapy is a lighter system than either the compressed gas or oxygen concentrator systems, it may be prescribed to patients who need to leave their homes on a regular basis. Access to this type of oxygen therapy varies within and across Canadian jurisdictions, largely depending on the patient's insurance coverage (eg use is higher in Ontario where it is covered by provincial health insurance).

In Québec this type of system is considered an exceptional treatment provided only to patients who spend lengthy periods outside their homes.

Compared to other home oxygen systems, there are no data to indicate that liquid systems allow for longer periods of therapy, improve life quality, increase patient adherence to a therapy regime, or increase mobility. On the other hand, one study (Sweden) reported that liquid oxygen is 4 times as expensive as standard therapy.

A small minority of patients with COPD (ie those with active lifestyles) would likely benefit from the enhanced portability of liquid oxygen therapy.

Recommendations

- Encourage a consensus approach for researchers, clinicians and decision-makers to identify the appropriate types of patients and conditions for prescribing liquid oxygen therapy, and how its use should be monitored.
- This process should be conducted within the more global process of developing guidelines for home oxygen services in general.
- There is some uncertainty among the providers about the priority of setting liquid oxygen therapy criteria, given competing needs.

Method

AÉTMIS reviewed the scientific literature available in a number of databases, as well as other documents and government reports.

Further research/reviews required

As indicated in the broader review of portable oxygen therapy (AÉTMIS, 2004), it is highly unlikely that there will be further trials to help resolve questions concerning the use of liquid oxygen therapy. New portable oxygen supply systems are being tested for clinical use and may provide alternatives to liquid oxygen therapy in the future.

Written by Susan Law, AÉTMIS, Canada

Title **Postural Support Devices**

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Reference AÉTMIS 03–07. Internet access to full text. ISBN 2-550-42137-X
(French edition ISBN 2-550-41953-7) x-47 p

Aim

To investigate available postural support devices (PSDs) – including their components and methods of construction – and to establish the efficacy, safety, and cost of each product.

Conclusions and results

Québec wheelchair users are prescribed a wide range of PSDs that are covered by Québec health insurance (Régie de l'assurance maladie du Québec, or RAMQ). In 2002, prescriptions for seat and back cushions, and leg, foot, arm, head, or neck rests cost RAMQ nearly $10 million, with the unit cost ranging from $80 to over $800. RAMQ asked AÉTMIS to investigate postural support devices.

RAMQ became aware that the price it paid for PSD products varied by as much as a factor of two, depending on the supplier. Some institutions consistently offered their patients the 'upmarket' product, even though evidence on the efficacy, safety, and comparative cost of PSDs is practically nonexistent.

Few studies have been conducted on PSDs, and no system exists to objectively compare wheelchair cushions across manufacturers. Much of the knowledge required for RAMQ decision-making is still being generated. The International Organization for Standardization (ISO) has recently mandated a working group to set standards.

This report includes an updateable selection grid that cross-references nearly 500 PSD products with major evaluation criteria. It also includes some preliminary selection criteria.

Recommendations

AÉTMIS recommends that RAMQ:

- Adopt the minimal selection grid created for this report
- Use this information immediately to implement billing procedures with institutions and suppliers
- Form a consensus group (including prescribers, users, suppliers, and experts) to design a more complete selection grid
- Consider implementing relational databases that cross-tabulate information relevant to administering the program and, in particular, to current and emerging equipment standards.

Methods

AÉTMIS identified all PSD comparative studies through a search of bibliographic databases. This led to the sponsorship of a report (by Rachid Aissaoui, the former principal investigator of the Natural Sciences and Engineering Research Council Industrial Research Chair on Wheelchair Seating Aids) to document all PSD products.

The information in the selection grid created by Rachid Aissaoui was drawn from manufacturers' websites. The report's authors did not have access to the products, nor did they perform standardized tests on them. Existing studies were used to identify the product evaluation criteria and some preliminary product selections.

Written by Francois Pierre Dussault, AÉTMIS, Canada

INAHTA Briefs

Issue 2005/23

Title **Moderately Elevated Blood Pressure**

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Reference SBU Report 170, 2004, ISBN volume 1 91-87890-97-6, volume 2 91-85413-00-3, Summary and Conclusions and Volume 2 are available in English on www.sbu.se

Aim

To update the SBU report on Moderately Elevated Blood Pressure from 1994 with information from blood pressure studies published from 1994 to 2004. The report evaluates different treatment options, including cost effectiveness.

Conclusions and results

Elevated blood pressure (BP) is a risk factor for coronary heart disease, stroke and other cardiovascular disease. In Sweden, about 27% of the adult population of both genders (20 years and older) have hypertension. Of these, 80% have a medium or high risk for disease. Only 20% to 30% of those treated reach a BP below 140/90 mm Hg. Women have a lower absolute risk of cardiovascular disease than men. However, antihypertensive treatment reduces the relative risk equally in women and men.

Lifestyle changes, eg, physical activity, weight loss, and smoking cessation can minimize the risk factors for cardiovascular disease. Treatment to lower blood pressure reduces the risk for stroke, myocardial infarction, and premature death in hypertensives of both sexes.

The antihypertensive drugs ordinarily used in Sweden – thiazide diuretics, ACE inhibitors, angiotensin receptor blockers and beta blockers – are equally effective (reduction of approximately 10/5 mm Hg) when administered separately. Since the efficacy of different drugs can vary by individual, one may need to change or add medications to reduce BP.

At least half of all patients with type 2 diabetes have hypertension. The effect of hypertension treatment on the absolute risk of cardiovascular disease morbidity and mortality is greater with concurrent diabetes. In people with type 2 diabetes, the impact on relative risk is also greater. Patients whose treatment is based on drugs that directly affect the renin–angiotensin–aldosterone system are less likely to develop type 2 diabetes than those whose treatment is based on a thiazide diuretic combined with a beta blocker or on a calcium channel blocker.

Choice of medication has a major impact on drug costs and cost effectiveness. Prescribing the least expensive equivalent medication when possible would reduce drug costs and improve cost effectiveness compared with current prescription patterns.

The ethical dilemma of treating an apparently healthy person with drugs for a long period should be weighed against the risks of withholding treatment that may prevent disease.

Methods

The report is based on a systematic review of CT studies of hypertension treatment. Meta-analysis was used in evaluating the literature on left ventricular hypertrophy. Model calculations for various treatment options were based on Swedish risk data.

Further research/reviews required

More knowledge is needed on: how to improve patient compliance with antihypertensive treatment and suitable ways for health professionals to adopt the desired changes; effects of non-pharmacological treatments; how to treat elderly people (>80 years of age) with hypertension; and the possibility to arrest dementia by lowering BP.

Certain antihypertensive drugs appear to be a risk factor for diabetes, but long-term studies are needed on the consequent effect on the risk for cardiovascular disease. The impact of moderate changes in glucose metabolism on the risk for diabetes mellitus and cardiovascular disease should also be studied.

Written by Helena Dahlgren, SBU, Sweden

INAHTA Briefs

Issue 2005/24

Title **Androgenic-Anabolic Steroids and Violence**

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Reference Report no 4-2004, www.kunnskapssenteret.no/filer/rapport4.04.pdf

Aim

To review the scientific literature on the use of androgenic-anabolic steroids (AAS) to elucidate whether there is a connection between such use and aggressive/violent behavior.

Conclusions and results

- There is good evidence that low doping doses influence the level of aggressiveness only slightly, or not at all.
- There is no evidence that moderate doping doses (75–200 mg AAS daily orally, or 50–100 mg daily as injection) increase aggressiveness.
- No studies have investigated different AAS concurrently or used repeatedly over long periods of time. Doses used in the experimental studies are far lower than doses used by many athletes. Accordingly, there is no evidence based on experiments of the effect of such regimens or doses.
- Experimental studies using the highest doses show some evidence that high doses of AAS in some individuals may trigger mania or hypomania, mental states that may include increased aggressiveness.
- Population studies show a clear association between the use of AAS, aggressiveness, and violence (both as perpetrator and as victim). It is unclear whether there is any causal connection. In subcultures with high use of AAS there is also more use of alcohol and illicit drugs, more high-risk behavior, and more acceptance of violent behavior.
- Some case series and several case reports describe persons who have used AAS and performed violent acts. However, these publications are purely descriptive and do not give good evidence on causality.

Methods

A literature search was performed in the following databases: MEDLINE, EMBASE, PsycLit, Toxline, INAHTA, and the Cochrane collaboration. The search identified 1,677 articles, whereof 146 were retrieved in full text. The HTA report is based on 25 of these studies. The studies finally included were read and discussed by all group members.

Written by Kurt I Myhre, NOKC, Norway

INAHTA Briefs

Issue 2005/25

Title **Effectiveness of Physical Therapy, Restricted to Electrotherapy and Exercise, for Osteoarthritis of the Knee**

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Reference Report no 7-2004, ISBN 82-8121-007-0

Aim

To evaluate the effectiveness of physical therapy, restricted to electrotherapy and exercise, for osteoarthritis of the knee. The clinical endpoints were pain, physical function, sickness days, and quality of life.

Conclusions and results

Both home-based exercise and exercise led by a physical therapist improved pain, function, and quality of life in patients with osteoarthritis of the knee. The exercise programs must last for at least 8 weeks to have significant effects.

Both laser and TENS had significant effects on pain relief by the end of treatment (2–4 weeks). However, evidence for the effects by laser is weaker than for TENS. There is a lack of evidence regarding effect on osteoarthritis of the knee after treatments including ultrasound and pulsed electromagnetic fields.

The effect of physiotherapy (exercise, laser, and TENS) persists for 1 to 3 months after the end of treatment.

Methods

The report is based on two existing systematic reviews (from the Netherlands and Canada), in addition to an updated systematic review on studies published from 1998 to January 2004. Relevant databases searched were the Cochrane Library, DARE, INAHTA database, PEDro, National Guidelines Clearinghouse, OHE Economic Evaluations Database, NHS Economic Evaluation Database, MEDLINE, and EMBASE. Systematic reviews and randomized controlled trials were included and meta-analysis was performed. The report includes 36 randomized controlled studies and 10 systematic reviews.

Written by Nilsen EM, Bjordal JM, Holm I, Johansen O, Zapffe K, NOKC, Norway

INAHTA Briefs

Issue 2005/26

Title	**Prevention of Restenosis: Intracoronary Brachytherapy**
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Reference	Report no 8-2004, ISBN 82-8121-008-7

Aim

Patients undergoing percutaneous coronary intervention (PCI) are at increased risk of restenosis at the site of the procedure. Approaches to prevent restenosis such as systemic or local drug administration do not efficiently prevent restenosis. Intracoronary brachytherapy interferes with the proliferative and inflammatory responses leading to development of in-stent restenosis. We aimed to undertake a systematic review and meta-analysis, and explore the cost and health consequences of intracoronary brachytherapy for patients with in-stent restenosis.

Conclusions and results

Nine RCTs were included that analyzed clinical effects of either gamma (5) or beta brachytherapy (4) in patients with in-stent restenosis. In total, 1,700 patients were included in these trials.

Mortality: None of the included studies or the meta-analysis of these studies had the statistical power to assess the effect on mortality. The relative risk of cardiac mortality after 8 to 12 months of followup was 1.33 (95% CI 0.61–2.92) for gamma brachytherapy and 1.78 (95% CI 0.58–5.45) for beta brachytherapy compared with placebo.

Myocardial infarction: No study, or the meta-analysis, had the statistical power to draw conclusions regarding risk of myocardial infarction following intracoronary brachytherapy.

Thrombosis: Patients treated with intracoronary brachytherapy were at increased risk for thrombosis compared with placebo: relative risk 2.18 (95% CI 01.00–4.76).

Reintervention (PCI or CABG): Intracoronary brachytherapy (beta or gamma irradiation) reduced the risk for revascularization compared with placebo RR 0.56 (95% CI 0.46–0.68) for gamma brachytherapy and RR 0.66 (95% CI 0.52–0.84) for beta brachytherapy.

Cost effectiveness: Intracoronary brachytherapy was not considered cost effective. The incurred costs for avoiding one revascularization procedure was 626,000 Norwegian kroner (NOK) or around 79,000 €.

Methods

Eligible studies were identified by searches in MEDLINE from 1966 until March 1, 2004. Nine RCTs comparing intracoronary brachytherapy with placebo were included.

Written by Kløw N-E, Rotevatn S, Steigen T, Vatne K, Wisløff T, Kristiansen I S, and Norderhaug I, NOKC, Norway

INAHTA Briefs

Issue 2005/27

Title **Prevention of Restenosis: Drug Eluting Stents**

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Reference Report no 8-2004, ISBN 82-8121-008-7

Aim

Drug eluting stents are rapidly disseminating following positive results from a few pioneer randomized controlled trials (RCTs). The effect of drug eluting stents on restenosis seems well established from a few individual trials. The effect on mortality, myocardial infarction, and thrombosis can only be addressed through a systematic review and meta-analysis of these trials. Thus, we aimed to undertake a systematic review and meta-analysis, and explored the cost and health consequences of replacing bare metal stents (BMS) with drug eluting stents (DES).

Conclusions and results

We included 13 RCTs that compared clinical effectiveness of DES with BMS. In total, 6,000 patients were included in these trials.

Mortality: None of the included studies, or the meta-analysis of these studies, had the statistical power to assess effect on mortality. The relative risk for all-cause mortality was 1.39 (95% CI 0.75–2.58), and the respective rates were 2.9% in the DES group and 2.1% in the BMS group. The incidence of cardiac mortality after 2 years was 1.4% in the DES group and 1.9% in the BMS group, relative risk 0.74 (95% confidence interval 0.37–1.48).

Myocardial infarction: After 2-year followup, the rate of MI was 4.3% in the DES group and 4.7% in the BMS group (RR 0.93, 95% CI 0.68–1.27).

Thrombosis: Late thrombosis was infrequent and similar between the two treatment groups: relative risk (0.98, 95% CI 0.46–2.06).

Reintervention (PCI or CABG): Drug eluting stents reduced the need for repeat interventions. The actual reintervention rates were 4.8% in the DES group and 16.9% in the BMS group (RR 0.34, 95% CI 0.23–0.50).

Cost effectiveness: Replacing BMS with DES implies health benefit to patients, but also additional costs to the healthcare system. The incurred costs for avoiding one revascularization procedure was 39,000 Norwegian kroner (NOK) or around 5,000 €. Sensitivity analyses revealed that the cost effectiveness of DES depends heavily on acquisition price of the device, risk of restenosis, and rate of reintervention in routine practice.

Methods

Eligible studies were identified by searches in MEDLINE from 1966 until March 1, 2004, ongoing and unpublished studies were identified from cardiology web sources and updates of included studies followed until November 2004.

Further research/reviews required

Results from ongoing trials will be important to evaluate the safety of drug eluting stents.

Written by Kløw N-E, Rotevatn S, Steigen T, Vatne K, Wisløff T, Kristiansen I S, and Norderhaug I, NOKC, Norway

INAHTA Briefs

Issue 2005/28

Title **Advance Directives for End-of-life Care in the Elderly – Effectiveness of Delivery Modes**

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Reference IP 20, August 2004 (English). ISBN 1-896956-93-9 (print); ISBN 1-896956-95-5 (online): www.ahfmr.ab.ca/programs.html

Aim

To examine the research evidence on the effectiveness of different methods for delivering advance directives to the elderly and to describe the utilization of advance directives in Alberta, Canada.

Conclusions and results

One systematic review and 10 randomized controlled trials (RCTs) met the inclusion criteria. The types of interventions used in the RCTs included: written educational materials alone (1 RCT); written material plus an educational videotape (3 RCTs); written materials plus an interactive seminar (1 RCT); an education session plus telephone reminder (1 RCT); physician-initiated discussion (3 RCTs); and a comprehensive nurse-initiated education program (1 RCT).

Limited evidence indicates that mailing written materials alone increased the advance directive (AD) completion rate by 18%. Compared to provision of written materials alone, the addition of educational videotapes did not increase the completion rate, whereas adding an interactive seminar significantly increased the AD completion rate by 38%. An education session plus a telephone reminder did not increase AD completion rates when compared to an education session alone. Physicians discussing ADs with outpatients increased completion rates by 15% to 16%. The most comprehensive and complex education program, Let Me Decide (LMD), increased completion rates by at least 45%. However, both competent nursing home residents and family members of incompetent residents completed the ADs in this study.

Many different formats of ADs are currently available in Canada. Alberta's Personal Directive Act does not require healthcare professionals to inquire about personal directives. Capital Health evaluated the LMD Personal Directive Program in 2002 and encountered some difficulties in implementing the program, which had originated in Ontario.

Recommendations

The optimal method to increase discussions with older patients about end-of-life healthcare and the completion of written directives remains unclear. Providing written materials plus an interactive seminar significantly increased AD completion rates, compared to written materials alone. A comprehensive and time-intensive educational program that included both competent elderly persons and family members of incompetent persons significantly increased completion rates, but the results could not be compared to other studies because of differences in study design and reporting. Since there is no provincial policy on advance healthcare planning in Alberta, regional health authorities may choose to implement customized programs. Applying a directive program modeled on a program from another province may be challenging due to differences in legislation between provinces.

Methods

Systematic reviews and RCTs were identified by systematically searching PubMed, EMBASE, HealthStar, the Cochrane Library, Science Citation Index, and the websites of health technology assessment agencies and guidelines sites from January 1993 to March 2004. The study population included seniors aged 55 years or older.

Further research/reviews required

Further research is required to find the best strategy for increasing the completion rate of written directives among seniors. It is also important to identify the type of professional that is best qualified to deliver advance directive programs, since this may be differ depending on the method of delivery and complexity of the advance directive, the setting, the availability of resources, and the target population.

Written by Bing Guo, Christa Harstall, AHFMR, Canada

INAHTA Briefs

Issue 2005/29

Title **Living Donor Liver Transplantation in Children**

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Reference IP 21, August 2004 (English). ISBN 1-896956-97-1 (print); ISBN 1-896956-99-8 (online): www.ahfmr.ab.ca/programs.html

Aim

To evaluate the published evidence on the safety, efficacy, and current status of living donor liver transplantation (LDLT) for treating end stage liver disease in children.

Conclusions and results

Donors: The LDLT donor operation is lengthy, but rarely results in the need for blood transfusion. On average, donors remain in hospital for at least 5 days. The mortality rate for live donors was 0.15%, and up to 1 in 10 donors experience adverse effects. As many as 4% of donors will undergo another operative procedure because of complications related to LDLT.

Recipients: The overall patient and graft survival rates were similar for cadaveric whole liver transplantation and LDLT. There was no clear benefit conferred by either graft type with respect to vascular complications, bile leak, reoperation, or graft dysfunction. However, subgroup analysis of registry data suggested that LDLT resulted in significantly lower mortality and graft failure rates, compared to cadaveric whole grafts, in children younger than 2 years. The opposite was the case for children aged between 2 and 16 years. Children undergoing reduced size liver transplantation (RSLT) generally fared worse than those who underwent LDLT. Graft and patient survival rates declined over time after RSLT and were much lower than those for LDLT at 5 years. RSLT recipients were also more likely to experience vascular complications.

LDLT produced better actuarial graft and patient survival rates at 1 year than split liver transplantation, but by 5 years there was no difference between the two graft types. The risk of graft dysfunction and bile leak or bleeding from the cut liver surface was similar for both procedures.

Recommendations

The evidence base for LDLT is incomplete. Limited evidence suggests that LDLT is superior to all forms of cadaveric liver transplantation in children younger than 2 years. However, the safety and efficacy of LDLT was equivalent to, and in some cases worse than, split liver transplantation and whole liver cadaveric donation in older children. Despite its limitations, LDLT is a life saving procedure for some individuals where alternative transplant options are not available, eg, very small children or elective patients whose condition is likely to deteriorate before a cadaveric graft becomes available.

It is unlikely that LDLT would be performed at centers with an abundant supply of cadaveric organs. Future initiatives in LDLT must aim to achieve minimal morbidity and zero mortality for donors. Centers performing LDLT must adhere to an extremely high standard of care that includes standard protocols for preoperative evaluation of potential donors, postoperative followup of donors and recipients, and strong psychosocial evaluation and support programs.

Methods

Data were collected on children (aged <18 years) undergoing liver transplantation for any indication. All original, published systematic reviews, comparative studies with at least 10 recipients in each study arm, or case series studies reporting outcomes for at least 10 donors were identified by searching electronic literature databases and websites of health technology assessment agencies, research registers, and guidelines sites from 1995 to June 2004. No language restriction was applied.

Further research/reviews required

Initiatives are under way in some countries to prospectively collect and analyze data on pediatric liver transplants to quantify recipient and graft survival rates, identify potential prognostic factors, and ascertain how liver transplantation and immunosuppression affect the growth of children. These initiatives, together with an ongoing audit of graft donor outcomes, form an essential part of the requisite evaluation of LDLT.

Written by Ann Scott, AHFMR, Canada

INAHTA Briefs

Issue 2005/30

Title **Low Level Laser Therapy for Wound Healing: An Update**

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Reference IP 22, October 2004 (English). ISBN 1-894927-02-8 (print); ISBN 1-894927-03-6 (online): www.ahfmr.ab.ca/programs.html

Aim

To update data presented in a previous health technology assessment (HTA) report completed in October 1999 on the efficacy/effectiveness and safety of low level laser therapy (LLLT) in treating chronic wounds, specifically leg ulcers and pressure sores.

Conclusions and results

The low energy lasers most commonly used for wound treatment are the gallium arsenide, gallium aluminum arsenide infrared semiconductor, and the helium neon devices. To date, neither Health Canada nor the US Food and Drug Administration have approved low energy lasers for use in wound healing.

Two systematic reviews were identified that met the inclusion criteria. Nine clinical trials published after the systematic reviews were also included. The systematic reviews concluded that no evidence supported the routine use of LLLT for wound healing in patients with venous leg ulcers, pressure sores, or chronic wounds, although LLLT poses little or no safety risk to patients. The 9 clinical trials supported these findings and suggested that other therapies, eg, ultrasound and electrical stimulation, may be more beneficial for promoting wound healing.

The most significant flaw in the LLLT literature was the absence of standardized protocols. Clinical studies were heterogeneous with respect to laser type, pulse frequency and duration, power, and wavelength; the amount of energy delivered to the tissues; applicator placement; and frequency and duration of treatment.

Recommendations

Although 5 years have passed since the last AHFMR review of LLLT, the findings remain unchanged. Recent published studies indicate that LLLT is not an effective adjunct treatment to conventional therapy for accelerating wound healing. Regional clinical practice should not be modified to incorporate LLLT in wound management at this time. In Alberta, LLLT should only be offered in a research setting to patients with chronic ulcers that are resistant to conventional therapy. Other alternative therapies, eg, electrical stimulation and ultrasound, should be considered as adjunct therapies to conventional wound healing practices before LLLT.

Methods

All original, clinical trials published in English were identified by systematically searching PubMed, EMBASE, the Cochrane Library, NHS Centre for Reviews and Dissemination, CINAHL, and the websites of various health technology assessment agencies, research registers, regulatory agencies, and guidelines sites from January 1999 to June 2004. Internet search engines were also used to locate grey literature.

Further research/reviews required

Well-designed randomized controlled trials are needed to determine whether changes in treatment schedules and laser parameters could improve wound healing outcomes. It is currently unclear what the optimal treatment schedule is and which patients would benefit most from LLLT. Future research should include detailed reporting of concomitant therapy and patient characteristics, eg, ulcer size, etiology, severity, and duration, which can affect wound healing. Similarly, more research is needed to evaluate the effectiveness of other technologies, eg, ultrasound, electrical stimulation, and electromagnetic therapy, in promoting wound healing.

Written by Anita Simon, AHFMR, Canada

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