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Introduction

The International Network of Agencies for Health Technology Assessment (INAHTA) is a global network linking 45 non-profit, governmental institutions from 23 countries (2007).

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 includes members from North and Latin America, Europe, Australia, and New Zealand. The Secretariat is located at SBU in Sweden.

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

Title **Evaluation of Abnormal Uterine Bleeding: Comparison of Three Outpatient Procedures Within Cohorts Defined by Age, Menopausal Status, and Other Risk Factors**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
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Reference Health Technol Assess 2004;8(34). Sept 2004. www.hta.ac.uk/execsumm/summ834.htm

Aim

To compare 3 outpatient methods of endometrial evaluation (blind biopsy, ultrasound, hysteroscopy with biopsy) in terms of successful completion of investigation, clinician preferences, patient outcome, acceptability of method, satisfaction with clinical care, and cost effectiveness.

Conclusions and results

This study illustrates the complexity of investigations in women referred for abnormal bleeding. The methods were randomized separately in 3 risk groups: high (postmenopausal), moderate (over 40 years or with risk factors for endometrial cancer), and low (all other premenopausal women). Two biopsy devices (Pipelle sampler, Tao brush) were compared in the high- and moderate-risk groups.

Minor adverse events occurred in about 10% of patients having hysteroscopy (HS) and biopsy. More women reported these methods as *markedly unpleasant* compared to ultrasound, which had no adverse events. In moderate-risk women, Pipelle biopsy and Tao brush gave similar rates of acceptable samples, but in postmenopausal women the Tao brush was more successful. Women preferred Tao brush.

Visualizations were significantly better for ultrasound than for HS in the low- and moderate-risk groups, with a similar but nonsignificant trend in high-risk women. Ultrasound was significantly better than HS at detecting fibroids, but HS was significantly better at identifying polyps.

Ultrasound was more acceptable to women than HS and biopsy, but HS was not more unpleasant than biopsy. Hysteroscopy patients were least likely to want more investigation. Most women were reassured by their clinic visit, but those having biopsy alone were least reassured. At 10-months, high-risk women having HS (with biopsy) were the most positive about the clinic experience, and moderate-risk group were the most negative. At 10 months, hysteroscopy was viewed more favorably than ultrasound, but this effect disappeared by 24 months. Less than half of moderate-risk women (menstrual bleeding problems) rated their symptoms *much improved* at 10 months, and a quarter said their problem had not been cured. Resource use tended to be higher in moderate- and low-risk women. In the high-risk group, HS was marginally more cost effective than ultrasound. In the moderate-risk group the most cost-effective option was biopsy alone, and in the low-risk group it was ultrasound.

Recommendations

The relatively small differences in cost effectiveness suggest that other issues, eg, clinician preferences and patient perspectives, might influence the choice of investigative method. Tao brush is superior in obtaining adequate samples in postmenopausal women, and our clinicians expressed interest in it being made available. However, introducing the Tao brush for endometrial sampling has resource and training implications.

Methods

See Executive Summary link above.

Further research/reviews required

Postmenopausal women should be studied separately from premenopausal women. In premenopausal women with abnormal menstrual bleeding, about 60% reported their symptoms were *not much improved* at 10 months. Research is needed on the relatively poor outcome for these patients and to explore ways to integrate patient factors to optimize evaluation and treatment. The significance of benign pathologies in this group also needs clarification.

Data from this study can contribute toward further analyses of patient factors to inform decisions as to the most efficient and acceptable method of investigation for an individual patient.

Written by Professor Hilary Critchley and Dr Pamela Warner, University of Edinburgh Medical School, UK

Title **Supplementation of a Home-Based Exercise Program with a Class-Based Program for People with Osteoarthritis of the Knees: A Randomized Controlled Trial and Health Economic Analysis**

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Reference Health Technol Assess 2004;8(46). Nov 2004. www.hta.ac.uk/execsumm/summ846.htm

Aim

To determine if a home exercise program with a class-based program results in greater improvement in walking pain and locomotor function 6 and 12 months after terminating contact with the physiotherapist.

Conclusions and results

At all followups, patients from the supplemented group demonstrated greater improvement in locomotor function and decrease in pain while walking. Pooled estimates of effect were –2.89 seconds (95% CI –1.82 to –3.96) for locomotor function and 14.9 mm (95% CI –11.7 to –18.1) for walking pain, representing between-group differences of 12% and 27% respectively. The supplemented group also demonstrated small, but significant, improvements in balance, strength, WOMAC score, and the physical function and pain dimensions of the SF-36 ($p<0.05$). However, not all of these improvements were maintained over the 12-month followup period. There was no evidence that adherence to the home exercise program differed between the groups, although the supplemented group noted an increase in their physical activity. There was no evidence that mean QALY gains differed significantly between the groups. However, costs were slightly lower and QALY gains slightly higher in the group with the supplementary class-based program. Thus, for most reasonable values of a decision maker's willingness-to-pay for an additional QALY, adding a class-based program is likely to be cost effective. There was considerable uncertainty around this estimate, with a probability of 30% to 35% that the intervention was not cost effective.

Recommendations

Supplementing a home-based exercise program with a class-based exercise program led to superior improvement in the supplemented group. These clinically important improvements were still evident at review 12 months after treatment had ceased. The additional cost of the supplemented group was offset by reductions in resource use elsewhere in the system. Adherence to the home exercise program did not differ between the groups at the 6- and 12-month assessments, despite considerable difference in the intensity of the two treatments.

Methods

The trial was a pragmatic, single-blind, randomized clinical trial accompanied by a health economic assessment. Patients were randomly allocated to either home or home supplemented with class exercise programs. Both groups were given a home exercise program aimed at increasing lower limb strength, endurance, and improving balance. The supplemented group also attended knee classes by a physiotherapist, twice weekly for 8 weeks. Classes represented typical knee class provision in the UK. Assessments of impairment, disability, and handicap were made pretreatment, posttreatment, and at 6 and 12 months posttreatment. Analysis involved the use of a longitudinal linear model, ANCOVA. The economic evaluation looked at utilization of health service resources and assessed cost effectiveness by relating differential costs to differences in quality-adjusted life-years (QALYs) based on patients' responses to the EQ-5D.

Further research/reviews required

Future research should investigate methods of increasing adherence with home exercise and evaluate the interventions in the primary care setting.

Written by Dr Christopher J McCarthy, Central Manchester Healthcare Trust, United Kingdom

INAHTA Briefs

Issue 2006/53

Title **A Systematic Review to Examine the Impact of Psycho-Educational Interventions on Health Outcomes and Costs in Adults and Children with Difficult Asthma**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
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Reference Health Technol Assess 2005;9(23). June 2005. www.ncchta.org/execsumm/summ923.htm

Aim

To determine if psycho-educational interventions improve outcomes and constitute an efficient use of health resources for patients with difficult asthma.

Conclusions and results

In total, 278 citations associated with 188 different studies were initially identified for inclusion and classification. Of these, 57 studies with concurrent control groups that showed sufficient evidence of targeting difficult asthma were selected for in-depth review (35 in children, 21 in adults, and 1 with subgroups of both). In most cases, meta-analyses were not possible due to the variety of outcome measures used and inadequate reporting of data. Available data suggest psycho-educational interventions, as compared to routine care or minimal intervention, may reduce hospital admissions in adults and children and improve symptoms in children. However, effects on admissions may not extend to patients most at risk.

Recommendations

Valid conclusions could not be drawn on the relative effectiveness of the different interventions. Data on costs were limited in quantity and quality. However, the results suggest that psycho-educational interventions can reduce hospital admissions and asthma symptoms in children, and may reduce admissions in adults. Positive effects, particularly in adults, may not extend to patients most at risk. Studies in children also showed mainly positive effects on various measures of self-care behavior.

Methods

Systematic review.

Data sources: Electronic bibliographic databases, on-line research registers, conference abstracts, non-English language health research databases.

Study selection: Studies were reviewed in-depth if reviewers agreed that patients had at least one clear risk factor or indicator associated with difficult asthma and the study evaluated a personal educational or psychological intervention. Studies were classified into groups by the degree of reviewers' certainty that patients had difficult asthma and by the type of intervention.

Data extraction and validity: Studies including concurrent control groups were included for in-depth extraction of descriptive and outcome data. Quality of studies was assessed using published guidelines for quantitative effectiveness research designs and for economic studies.

Data synthesis: Results of controlled studies were described and summarized in tables and text format. Where studies of sufficiently similar interventions reported sufficient data about comparable outcomes, pooled relative risks or standardized mean differences and confidence intervals were estimated using meta-analysis.

Further research/reviews required

1. Incorporate results of studies still in progress into these results, and revision of conclusions
2. Further conceptualize interventions targeting different points, with a focus on developing more intensive, individualized, multidisciplinary approaches
3. Standardize reporting of complex interventions
4. Further standardize and validate outcomes for difficult and severe asthma
5. Develop tools to identify patients at risk from their asthma
6. Develop and evaluate costs and effects of clearly targeted, well-defined interventions in randomized trials with sufficient power to assess all important outcomes
7. Further methodological work to combine different effect size measures in systematic reviews.

Written by Ms Jane Smith, School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, UK

Title **Indirect Comparisons of Competing Interventions**

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Reference Health Technol Assess 2005;9(26). July 2005.
www.ncchta.org/execsumm/summ926.htm

Aim

- To survey the frequency of using indirect comparisons in systematic reviews and evaluate the methods used in analysis and interpretation.
- To identify alternative statistical approaches in analyzing indirect comparisons.
- To assess the properties of different statistical methods used to perform indirect comparisons.
- To compare direct and indirect estimates of the same effects in reviews.

Conclusions and results

Of the reviews found in DARE, 31/327 (9.5%) included indirect comparisons. Electronic searching yielded another 5 reviews including indirect comparisons. Few reviews carried out a formal analysis, and some based analysis on the naive addition of data from treatment arms. Few methodological papers were identified. Some valid approaches for aggregate data that involved standard software were found (adjusted indirect comparison, meta-regression, multiple logistic regression). Simulation studies showed that the naive method is liable to bias and also produces over-precise answers. Several methods yield correct answers if strong but unverifiable assumptions are met. Four times as many similarly sized trials are needed for the indirect approach to have the same power as directly randomized comparisons. Detailed case studies comparing direct and indirect comparisons of the same effect show considerable statistical discrepancies, the direction of which is unpredictable.

Recommendations

Systematic reviews to evaluate the effectiveness of interventions should use direct evidence from good-quality RCTs. If little or no such evidence exists, it may be necessary to look for indirect comparisons from RCTs. The reviewer should be aware that the results might be susceptible to bias. When making indirect comparisons in a systematic review, an adjusted indirect comparison method involving the random effects model should be used. If both direct and indirect comparisons are possible in a review, these should be done separately before considering whether to pool data.

Methods

The Database of Abstracts of Reviews of Effects (DARE) was searched for systematic reviews involving meta-analysis of randomized controlled trials (RCTs) that reported on direct and indirect comparisons, or indirect comparisons alone. A systematic review of MEDLINE and other databases was carried out to identify published methods for analyzing indirect comparisons. Study designs were created using data from the International Stroke Trial. Random samples of patients receiving aspirin, heparin, or placebo in 16 centers were used to create meta-analyses, with half of the trials comparing aspirin and placebo and half heparin and placebo. Methods for indirect comparisons were used to estimate the contrast between aspirin and heparin. The process was repeated 1000 times, and results were compared with direct comparisons and theoretical results. Detailed case studies were undertaken to compare the results of direct and indirect comparisons of the same effects.

Further research/reviews required

- Evaluate methods for analysis of indirect comparisons for continuous data
- Empirical research into how different methods of indirect comparison perform in cases where the treatment effect is large
- Determine when it is appropriate to look at indirect comparisons and how to judge when to combine both direct and indirect comparisons
- Compare evidence from indirect comparisons and nonrandomized studies
- Repeat the empirical investigations using individual patient data from a meta-analysis of several RCTs using different protocols
- Evaluate the impact of choosing different binary effect measures for the inverse variance method.

Written by Ms Alison Eastwood, CRD, University of York, United Kingdom

Title **Randomized Controlled Trial of the Cost Effectiveness of Water-Based Therapy for Lower Limb Osteoarthritis**

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Reference Health Technol Assess 2005;9(31). August 2005.
www.hta.ac.uk/execsumm/summ931.htm

Aim

1. To determine the efficacy of community water-based therapy in managing lower limb osteoarthritis in older patients (Does the treatment work if taken by the recipients?).
2. To assess the cost effectiveness of such an approach (Is the treatment effective, and is it cost-effective in practice?).
3. To establish the implications of delivering and sustaining a community-based water exercise program for older patients with lower limb osteoarthritis.

Conclusions and results

- Short-term efficacy of water exercise in managing lower limb osteoarthritis was confirmed, with effect sizes ranging from 0.44 on WOMAC pain to 0.76 on WOMAC physical function.
- Water exercise remained effective in the main study, but overall effect size was small, 0.25 on WOMAC pain at 1-year, a reduction ~10% in the group mean pain score. This had declined, and was nonsignificant, at 6 months postintervention.
- Mean cost difference estimates showed a saving in the water exercise group of £123 to £175/patient/annum and incremental cost effectiveness ratios ranged from £3838 to £5951, although it was not possible to determine a ceiling valuation (with 95% confidence) for comparison with competing approaches.
- Net reduction in pain (0.89 WOMAC units) was achieved at a net saving of £135 to £175/patient/annum, even after allowing for marginal costs of providing the exercise program, and favorably low ceiling valuation of £580 to £740 per WOMAC unit of pain reduction.

Recommendations

Group-based exercise in water for more than 1 year can significantly reduce pain and improve physical function in older adults with lower limb osteoarthritis and may be a useful adjunct in the managing osteoarthritis of the hip and/or knee. Wide variation in both the individual costs and the utility measures, combined with small effect sizes, limited the power of the project to detect a difference between the groups on the QALY-based analyses.

Methods

See Executive Summary link above.

Further research/reviews required

1. Mechanisms should be put in place to encourage greater and more effective collaboration between different centers to facilitate progress in lifestyle intervention studies.
2. Better and more cost-effective mechanisms need to be developed to obtain representative samples for public health interventions.
3. Infrastructure and workforce capacities for physical activity delivery and the potential extent to which health care may be supported in this way need to be determined.
4. More detailed research is required on the response of synovial joint tissues to dynamic mechanical load at various stages of the disease process.
5. More research is needed on access and environmental issues for physical activity programs for older people, both from a provider and a participant perspective.
6. Longitudinal data on the societal costs for managing osteoarthritis and trends in outcome measures are needed.

Written by Professor Tom Cochrane, University of Staffordshire, United Kingdom

Title **Cost Effectiveness and Safety of Epidural Steroids in the Management of Sciatica**

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Reference Health Technol Assess 2005;9(33). August 2005.
www.hta.ac.uk/execsumm/summ933.htm

Aim

- To verify, with an adequately powered study, the clinical effectiveness of epidural steroid injection (ESI) in treating sciatica
- To identify potential predictors of response to ESI
- To investigate the safety of lumbar ESI in patients with sciatica
- To evaluate the cost effectiveness of lumbar ESI.

Conclusions and results

Epidural steroid injection led to a transient benefit in ODQ and pain relief, compared to placebo at 3 weeks (p=0.017, NNT=11.4). There was no benefit over placebo between weeks 6 and 52. Using incremental QALYs, this equates to an additional 2.2 days of full health. Acute sciatica seemed to respond no differently from chronic sciatica. There were no significant differences in any other indices, eg, objective tests of function, return to work, or need for surgery at any point in time. There were no clinical predictors of response although the trial lacked sufficient power to be confident of this. Adverse events were uncommon, with no difference between groups. Costs per QALY to providers under the trial protocol were £44 701. Costs per QALY to purchasers were £354 171. If only one ESI was provided, then costs per QALY fell to £25 745 to the provider and £167 145 to the purchaser.

Recommendations

Cases of sciatica that present to secondary care produce major long-term morbidity. These patients have severe disability and distress, with a major impact on social functioning. The vast majority of these cases fail to respond to current conservative measures. ESI offers no sustained benefits to patients with sciatica in terms of pain, function, or need for surgery. We found no evidence for repeat injections in the short term, nor for their use early on in the care pathway. They do not prevent surgery. They appear relatively safe. ESI fails the QALY threshold recommended by NICE.

Methods

A pragmatic, prospective, multicenter, double-blind, randomized, placebo controlled trial with 12-month followup.

Further research/reviews required

Further work on the epidemiology of radicular pain is needed so that patients can be presented with better information on prognosis. ESI should be evaluated as part of a structured multidisciplinary approach. Better analgesic strategies are needed, combined with specialized rehabilitation. A register of all epidural steroid injections should be developed so that the true incidence of major complications can be accurately determined. Subgroups who may benefit from ESI should be identified. The use of radiological imaging and better assessment practices should be evaluated. Cost-utility data from other treatments should be compared.

Written by Dr Cathy Price, Southampton University Hospitals NHS Trust, United Kingdom

Title **A Trial of Problem-Solving by Community Mental Health Nurses for Anxiety, Depression, and Life Difficulties among General Practice Patients. The CPN-GP Study**

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Reference Health Technol Assess 2005;9(37). Sept 2005. www.hta.ac.uk/execsumm/summ937.htm

Aim

- To compare the effectiveness of problem solving by community mental health nurses (CMHN) and generic CMHN care against usual general practitioner (GP) care in reducing symptoms, alleviating problems, and improving social functioning and quality of life.
- To determine the cost utility, cost effectiveness, or cost minimization of each treatment compared to usual care, evaluating not only direct costs of treatment but also indirect costs, including time off work.

Conclusions and results

Twenty-four CMHNs were trained to provide problem-solving under supervision, and another 29 were referred patients for generic support. In total, 247 patients were randomized to the 3 arms of the study, referred by 98 GPs in 62 practices. All 3 groups of patients were greatly improved on average by the 8-week followup. No significant differences were found between the groups at 8 weeks or 26 weeks in symptoms, social functioning, or quality of life. Greater satisfaction with treatment was found in the CMHN groups. CMHN care represented a significant additional health service cost and there were no savings in sickness absence.

Recommendations

Specialist mental health nurse support is no better than support from GPs for patients with anxiety, depression, and reactions to life difficulties. Primary care trusts should restrict referrals of unselected patients with common mental disorders to specialist CMHNs. CMHNs could provide treatment for patients not responding to self-help or primary care team interventions in managed, stepped care systems.

Methods

A pragmatic randomized controlled trial with 3 arms: CMHN problem-solving, generic CMHN care, and usual GP care, with an economic evaluation.

Further research/reviews required

More research is needed in the following areas:

1. Research needs to address the predictors of chronicity in common mental disorders, to identify which patients are less likely to recover within a few months under usual GP care, and so target extra treatment to those who need it.
2. More research is needed into the effectiveness and cost effectiveness of PST for other disorders, eg, major depression, deliberate self-harm, and personality disorders, and for the prevention of mental disorders.
3. More research is needed into the effectiveness and cost effectiveness of facilitated self-help treatments for common mental disorders.
4. More research is needed into the effectiveness and cost-effectiveness of CMHN care for people with severe and enduring mental illness.

Written by Professor Anthony Kendrick, University of Southampton, United Kingdom

Title **The Causes and Effects of Socio-Demographic Exclusions from Clinical Trials**

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Reference Health Technol Assess 2005;9(38). October 2005.
www.hta.ac.uk/execsumm/summ938.htm

Aim

To investigate the causes and effects of excluding women, older people, and ethnic groups from clinical trials, focusing on two drugs, statins and NSAIDs (non steroidal anti-inflammatory drugs).

Conclusions and results

Excluding people from clinical trials who are likely to need, or benefit from, the intervention could compromise the external validity (generalizability) of clinical trials.

1. In the USA the discourse includes equitable access of different groups. The UK debate is limited.
2. Trial populations: *Statins:* Average age of trial participants was 58.5 years, only 16.3% were women. Statins reduced CVD incidence by about 25% in men and women. Older people up to 75 years also benefited. *NSAIDs:* Average age was 61.9 years, and women were well represented (68.5%). Ethnicity was not well reported for either drug.
3. Drug utilization. *Statins:* Used to treat 23% of the cohort. Statin users were younger than non-statin users and had superior outcomes. *NSAIDs:* High current exposure to NSAIDs increased the risk for GI side effects and renal impairment. Side-effect risk increased with age, being female diminished risk.
4. Population in need. *Statins:* An estimated 537 000 CVD cases would qualify for statins in England per year. Women constitute 45% of this population, two thirds being 65+. Need varies by ethnic group. No sex bias in prescribing was found, but use was more common in younger people. *NSAIDs:* 6.3% of adults aged 35+ reported hip and/or knee pain associated with OA. 3.9% of adults used prescribed analgesics; they were more likely to be women and older (65+).
5. The mismatch: *Statins:* Women formed half the "with need" and "on treatment" populations, but were markedly under-represented in trials. Those aged 65+ formed nearly two thirds of the "with need" population, but only one fifth of trial samples, and were less likely to be treated than younger subjects. *NSAIDs:* Women formed two thirds of trial samples, the "with need", and "on treatment" populations. People aged 65+ formed three fifths of the "on treatment" population, but were under-represented in trials.
6. Meta-analysis might overcome problems of low inclusion in assessing relative effectiveness, but assessing side effects in different groups would require massive trials. Measures of absolute effectiveness are vital to analyze benefit, harm, and cost effectiveness. Measurements involving underlying risk levels will be severely biased if population groups are not adequately represented.

Recommendations

Exclusion from trials of women, older people, and ethnic minorities has been a relatively neglected issue in the UK, and there is confusion about diversity issues. Under-representation occurs, but in drug trials it may not always affect the external validity of relative effect estimates. Measures of absolute effectiveness, absolute harm, and cost effectiveness are associated with different underlying risk levels in different sociodemographic groups, and under-representation will bias absolute effect estimates. The complexity of the issues made development of a single, comprehensive theoretical model impossible.

Methods

See Executive Summary link above.

Further research/reviews required

- Multidisciplinary assessment of realistic options for trialists to address the issue of exclusion
- Clarify the use of ethnic categories in health research, and the implications of different dimensions of aging and sex/gender
- Identify barriers and facilitators to the involvement of different population groups in research
- Further investigate the susceptibility of men to NSAID adverse events
- Develop a "register of registries and databases" and explore how to improve linked health information systems in the UK.

Written by Professor Paul Dieppe, University of Bristol, United Kingdom

Title **Displaced Intracapsular Hip Fractures in Fit, Older People: A Randomized Comparison of Reduction and Fixation, Bipolar Hemiarthroplasty and Total Hip Arthroplasty**

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Reference Health Technol Assess 2005;9(41). Oct 2005. www.hta.ac.uk/execsumm/summ941.htm

Aim

To determine the clinical effects and resource consequences of 3 contrasting surgical treatments in fit older patients with displaced intracapsular hip fractures.

Conclusions and results

Most displaced intracapsular hip fractures occur in older unfit patients and are generally treated by uncemented hemiarthroplasty. Orthopedic management remains controversial for patients aged 60 years and older who are otherwise fit.

Reduction and fixation, cemented bipolar hemiarthroplasty, and total hip replacement (THR) are the 3 options usually considered. Mortality rates were similar. Further surgery rates were highest in the fixation groups (39% vs 5% bipolar hemiarthroplasty vs 6% THR). Forty-four (37%) of those allocated fixation suffered fixation failure within 2 years of the index operation. Eleven participants had a hip dislocation, but only 6 of these were allocated arthroplasty. Of the 5 dislocations in the fixation groups, 4 followed revision surgery after fixation failure. Rates of other serious morbidity did not differ significantly between the groups. The fixation group had statistically significantly worse Hip Rating Questionnaire scores than both arthroplasty groups at 4 and 12 months, reflecting poorer scores in all subscales. Those allocated THR had, on average, better overall scores than those allocated hemiarthroplasty, and this was significant at 24 months. Results of the prespecified subgroup analyses suggested that the differences between the groups were more pronounced in those aged 60 to 74 years than in those aged 75 and over. The results for the EQ-5D measure followed a broadly similar pattern. At 4 and 12 months, the THR group had the best scores and the fixation group the worst scores. At 24 months, however, the bipolar hemiarthroplasty groups had the lowest scores, and these were now significantly worse than scores in the THR group. Although fixation was initially less costly when compared to bipolar hemiarthroplasty, this short-term cost advantage was eroded by the significantly increased costs of subsequent hip-related admissions. Compared to bipolar hemiarthroplasty, the cumulative additional costs over 2 years for all hip-related episodes following fixation was £3346 higher (95% CI £1075 to £5618). No significant differences emerge in either the costs of the initial inpatient episode or non-hip-related admissions following the initial episode. A similar pattern of cost differences emerged in comparing fixation with THR, although only the difference in hip-related admission costs was statistically significant. In comparing bipolar hemiarthroplasty and THR, the CIs around the hip-related admission costs were wide, reflecting the small numbers readmitted (4 vs 5), and there were no significant differences between these two groups. Adjustments for age, sex, randomizing to 2 or 3 options, and varying the cost of hip-related admissions and prostheses had little impact on these findings.

Recommendations

Based on our findings, we no longer recommend treating displaced intracapsular hip fractures with reduction and fixation in previously fit older patients. Some form of cemented arthroplasty is our treatment of choice. In this study, THR appeared to perform better than bipolar hemiarthroplasty at 2 years, but ideally this finding needs replication in other trials.

Methods

See Executive Summary link above.

Further research/reviews required

Long-term followup of the arthroplasty patients in this study might help identify the reasons for the deterioration in function in bipolar hemiarthroplasty patients observed at 2-year followup. It would also determine if the satisfactory outcome of THR is maintained.

Written by Mr John Keating, University of Edinburgh, United Kingdom

Title **Systematic Review and Evaluation of Methods of Assessing Urinary Incontinence**

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Reference Health Technol Assess 2006;10(6). February 2006.
www.hta.ac.uk/execsumm/summ1006.htm

Aim

- To identify, appraise, and summarize evidence on methods of diagnostic assessment of male and female urinary incontinence: specifically urodynamic stress incontinence (USI) and detrusor overactivity (DO).
- To synthesize the evidence using meta-analysis or pooling individual sensitivity and specificity data.
- To construct an economic model to examine the cost effectiveness of common primary care tests.
- To identify gaps in the literature and to prioritize future clinical and research questions.

Conclusions and results

Generally, reporting in the primary studies was poor. There was a lack of literature in the key clinical areas and minimal literature on diagnosis in men. Only a few studies could be combined or synthesized, providing the following results.

A clinical history for diagnosing USI in women was found to have a sensitivity of 0.92 and a specificity of 0.56, and for DO a sensitivity of 0.56 and specificity of 0.88. Seven studies compared a pad test with multichannel urodynamics, but it was difficult to draw conclusions about diagnostic accuracy. Of the 4 studies comparing urinary diary with multichannel urodynamics, only 1 presented data in a way that allowed sensitivity and specificity to be calculated. Reported values of 0.88 and 0.83 suggest that a urinary diary may be effective in diagnosing DO in women. We examined the incremental cost effectiveness of 3 primary care tests (diary, pad test, and validated scales) used in addition to history and found the diary had the lowest cost effectiveness ratio. Using ultrasound to determine leakage was effective in diagnosing USI in women (sensitivity 0.94, specificity 0.83).

Recommendations

The search identified 6009 papers, whereof 129 were included in the review. Clinical interpretation was difficult because few studies could actually be synthesized and conclusions drawn. However, the following information could be deduced from the data:

- In primary care, a large share of women with USI can be correctly diagnosed from clinical history alone.
- In diagnosis, the diary appears to be the most cost effective of the 3 primary care tests used.
- Ultrasound imaging may offer a valuable alternative to urodynamic investigation.
- The clinical stress test is effective in diagnosing USI.
- If a patient is to undergo an invasive urodynamic procedure, multichannel urodynamics is likely to yield the most accurate result.
- There is minimal literature on the diagnosis of UI in men.

Methods

See Executive Summary link above.

Further research/reviews required

Large, high-quality primary studies evaluating the use of several diagnostic methods in a primary care setting are needed to verify the results of this systematic review. To inform future health policy decisions, such studies should assess clinical effectiveness (ie, diagnostic accuracy) and the costs and quality of life. Given the demographics of the UK population, and the reported high prevalence of urinary incontinence, an increasing burden will be placed on health services in terms of diagnostic assessment and appropriate treatment. Hence, it is crucial to identify the most clinically and cost-effective diagnostic methods. Recommendations of the STARD (standards for reporting diagnostic accuracy) initiative should be followed to ensure the accuracy and completeness of reporting.

Written by Dr Jennifer Martin, University of Leicester, United Kingdom

Title **Gastric Electrical Stimulation (Enterra™ Therapy System) for the Treatment of Gastroparesis**

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; www.ahfmr.ab.ca

Reference HTA Report #37, January 2006 (English). ISBN 1-894927-32-X (print), 1-894827-33-8 (online): www.ahfmr.ab.ca/hta/

Aim

To present evidence on the efficacy/effectiveness, safety, and efficiency of gastric electrical stimulation (GES) (Enterra™ Therapy system) in treating patients with severe gastroparesis.

Conclusions and results

Ten studies met the inclusion criteria: 1 multicenter, randomized, placebo-controlled, double-blind crossover study; 1 prospective nonrandomized comparative study that compared GES therapy with medication; and 8 case series studies. Four of the 10 studies reported results from patients who were included in previous studies. The studies were generally weak in methodological design (case series) and quality of execution. A randomized crossover study compared stimulation ON and OFF with the GES device. At 1-month followup, both diabetic and idiopathic patients showed improvements in symptoms and vomiting frequency. Differences between the stimulation ON and OFF periods were statistically significant, or not, depending on how the results were analyzed. Results from the 5 case series studies that reported on patients who were not part of another published study indicated:

- Significant symptomatic improvement at 6 to 12 months after GES implantation (4 studies).
- Significant improvement in nutritional status (3 studies) at 6 to 20 months after implantation.
- Significant improvement in quality of life (2 studies) at 6- and 12-month followup.
- Reduction in supplementary enteral and parenteral feeding (4 studies) at 12-month followup, although these results were not confirmed statistically.

GES does not cause the muscle of the stomach to contract and has only a modest effect on gastric emptying. Since the mechanism of action of GES remains unclear, some authors have suggested that the symptomatic improvements may be due to a placebo effect. The most common adverse events were infection or erosion at the implant site (required removal of the system) and electrode dislodgement. Health Canada has approved the Enterra™ Therapy system as a Class 3 device to treat chronic, intractable nausea and vomiting.

Recommendations

The evidence is insufficient to support routine use of this procedure. GES should be considered as a last resort for adults with severe gastroparesis when all conventional treatment regimes have failed. GES implantation should be performed by trained professionals only.

Methods

Original studies published in English were identified by systematically searching PubMed, EMBASE, HealthSTAR, the Cochrane Library, Web of Science, library collections, and the websites of regulatory agencies, evidence based resources, health technology assessment agencies, research registers, and guidelines sites from January 2000 to November 2005. Position papers, guidance reports, and regulatory status information were included. Internet search engines were used to locate grey literature.

Further research/reviews required

Clear patient selection criteria and a system for collecting followup safety data need to be developed. Controlled studies are planned or ongoing. Once this research is published, GES should be reviewed again to determine if its safety and efficacy status has changed.

Written by Carmen Moga and Christa Harstall, AHFMR, Canada

Title **Strategies to Reduce Emergency Department Overcrowding**

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Reference HTA Report #38, February 2006 (English). ISBN 1-894927-34-6 (print), 1-894827-35-4 (online): www.ahfmr.ab.ca/hta/

Aim

To identify strategies for reducing emergency department (ED) overcrowding and to assess their efficacy/effectiveness based on published and unpublished evidence.

Conclusions and results

Two systematic reviews and 23 primary studies met the inclusion criteria. The 2 systematic reviews suggested that interventions such as the presence of a social worker in the ED, cost sharing/co-payment, or primary gatekeeping might be effective in reducing unnecessary ED attendance. Both reviews found that patient education was not effective in reducing ED attendance. In the 23 primary studies, most strategies addressed contributory factors in the ED rather than external factors. The better quality studies found that effective strategies for reducing ED overcrowding included:

Decrease ED demand by:

- Pre-emptive ambulance distribution based on real-time information on ED occupancy.

Increase throughput by, eg:

- Reorganizing the staff and structure of the ED
- Changing provider staffing based on a queuing analysis
- Establishing a multidisciplinary care coordination team
- Including faculty members in ED triage.

Promote timely access to inpatient beds (alleviate access block) by:

- Increasing the number of intensive care unit beds
- Improving bed management.

Increase system-wide efficiency by:

- Increasing emergency physician coverage
- Designating physician coordinators
- Introducing new hospital policies on ED procedures
- Sharing process differences among hospitals in a large multihospital system.

Recommendations

This report serves as a benchmark for published research and identifies areas for improvement. The lack of standard definitions for outcome measures made it difficult to compare results across studies. The generally poor methodological quality of the studies precluded formulating any definitive conclusions on the effectiveness of the strategies examined. Each ED has its own primary problem associated with overcrowding and needs to prioritize the issues faced.

Methods

Original studies published in English and German were identified by systematically searching PubMed, EMBASE, HealthSTAR, the Cochrane Library, CINAHL, Dissertation Abstracts, Web of Science, library collections, and the websites of evidence based resources, health technology assessment agencies, research registers, and guidelines sites from January 1993 to December 2005. Internet search engines were used to locate grey literature.

Further research/reviews required

Research is needed on input and output components and on throughput. Standardized definitions of ED overcrowding are essential for meaningful research, as is development of valid, reliable, and sensitive outcome measures. Adoption of standardized measures by all provincial regional health authorities would enable comparison of strategies and adoption of the most effective and efficient.

Written by Bing Guo and Christa Harstall, AHFMR, Canada

Title **Impact of Radiation Wait Times on Risk of Local Recurrence of Breast Cancer: Early Stage Cancer with No Chemotherapy**

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Reference CADTH Technology Report, Issue 46, May 2004. ISBN 1-894978-33-1 (print).
Full text available at www.cadth.ca/media/pdf/155_breastcancerwl_tr_e.pdf

Aim

To assess the relationship between the risk of local recurrence of breast cancer and waiting times for radiation therapy after breast conservation surgery among women with early stage breast cancer who are not receiving chemotherapy.

Conclusions and results

Six relevant, retrospective, observational studies were selected from the 194 potentially relevant studies identified. Waiting times varied from 7 weeks to 20 weeks. Followup time varied from a mean of 5.0 years to a median of 8.4 years. The results were consistent between studies, revealing no differences in the rate of local recurrence of breast cancer among women who had to wait longer for radiation therapy after surgery (up to 12 weeks) compared to those who received earlier therapy (less than 8 weeks). From these studies, 12 weeks can therefore be considered an "acceptable" waiting time. As there were too few women waiting longer than 12 weeks, risk for this group was not evaluated. The impact of radiation therapy wait times on survival was not evaluated.

Recommendations

Not applicable.

Methods

For this systematic review, 11 electronic databases were searched for literature published between January 1997 and June 2003. Hand searching and back referencing were done to locate grey literature and to identify additional studies cited by other authors. For relevant information on guidelines and waiting times, 150 websites were examined. Heads of radiation departments across Canada were asked to identify relevant unpublished manuscripts of abstracts. Two reviewers independently selected articles based on defined criteria. Study quality was assessed using a "strength of evidence" scale from the Canadian Task Force on Preventive Health Care.

Further research/reviews required

More research is needed to address the psychological impact of waiting for radiation therapy.

Written by Benk V, Fisher A, Glazer D, and Paszat L, CADTH, Canada

Title **Interferon-Based Therapies for Chronic Hepatitis C Virus Infection: An Assessment of Clinical Outcomes**

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Reference CADTH Technology Report, Issue 47, May 2004. ISBN 1-894978-28-5 (print).
Full text available at www.cadth.ca/media/pdf/171_hepc_tr_e.pdf

Aim

- To explore the effectiveness of interferon-based combination drugs by examining mortality and serious morbidity during treatment of chronic hepatitis C virus (HCV) infection.
- To consider the withdrawals due to adverse events, the quality of life, and the virologic markers related to use of the following recommended treatments:
  - Standard interferon (IFN) plus ribavirin versus standard IFN therapy alone
  - Standard IFN plus ribavirin versus pegylated IFN plus ribavirin.

Conclusions and results

Fifty-three unique randomized controlled trials describing treatment of adults with persistent, detectable viremia from HCV infection were identified. Fifty-one of these trials randomized at least one treatment arm to receive standard IFN plus ribavirin and another to receive standard IFN alone. The remaining two trials provided evidence of the effect of using pegylated IFN combined with ribavirin versus standard IFN and ribavirin. Results of the meta-analysis indicated that information is lacking on quantity or quality of life related to IFN-based treatment. Also, morbidity and mortality after therapy with ribavirin added to standard IFN could not be estimated from the randomized trial evidence. Pegylated IFN combined with ribavirin can increase the need for urgent medical attention when compared with standard IFN plus ribavirin. Pegylated IFN plus ribavirin therapy can reduce the risk of persistent viremia and liver enzyme elevation to the greatest degree, when it is compared with standard IFN plus ribavirin therapy, or with standard IFN therapy alone.

Recommendations

Not applicable.

Methods

Reports of randomized controlled trials were identified from a comprehensive systematic review conducted by the Agency for Health Research and Quality (AHRQ) in 2002. Supplemental trial reports were identified from bibliographic databases, manufacturer's information, and from the United States Food and Drug Administration's website. A meta-analysis was conducted on these studies to determine the incidence of death and serious morbidity by analyzing the serious adverse events occurring during the clinical trails and the withdrawals due to adverse events. Data were abstracted by two independent reviewers.

Further research/reviews required

Information on quantity or quality of life related to IFN-based treatment is lacking.

Written by Husereau D, Bassett K, and Koretz R, CADTH, Canada

Title **Comparison of Lung Volume Reduction Surgery with Medical Management for Emphysema**

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Reference CADTH Technology Report, Issue 48, December 2004. ISBN 1-894978-45-5 (print).
Full text available at www.cadth.ca/media/pdf/176_lvrs_tr_e.pdf

Aim

- To assess the evidence on whether lung volume reduction surgery (LVRS) improves quality of life, defers death, or affects lung function in patients with emphysema, compared to medical management (ie, drugs, oxygen, and lung rehabilitation).
- To identify the risks associated with LVRS, and to evaluate what level of risk is appropriate in patients with compromised quality of life.

Conclusions and results

Seven randomized controlled trials involving 1412 patients met the inclusion criteria and were considered reasonably well designed to provide an acceptable level of evidence.

Compared to medical management, LVRS does improve quality of life. Meta-analysis showed that LVRS offers a survival advantage compared with medical management for patients whose emphysema mainly affects the upper lobes of the lung and whose baseline exercise capacity is low. For patients with severe emphysema, however, LVRS is a palliative treatment. Although it improves quality of life, lung function, and exercise tolerance compared with medical management alone, it increases the short-term risk of death. There is no reduction in overall death rate at 2-year followup. Based on the compromised quality of life experienced by patients with severe emphysema, an acceptable level of surgical risk is difficult to define. Data on the associated risks are poorly documented.

Recommendations

Not applicable.

Methods

A systematic literature review identified randomized controlled trials that compared LVRS to medical management. Outcomes analyzed included quality of life, complications arising from treatment, mortality, shortness of breath, level of blood gases, exercise function, and pulmonary function. Where possible, meta-analyses were done to derive a statistical summary. Case-series studies were included to further elucidate the complications and mortality associated with LVRS. Trials and studies were independently selected by two reviewers. Methodological quality was assessed using the Jadad scale.

Further research/reviews required

More trials are needed to confirm which subgroup of patients is likely to benefit from LVRS. Randomized controlled trials are needed to compare LVRS and medical management in regard to safety issues and the occurrence and extent of adverse events.

Written by Banerjee S, Babidge W, Miller J, Smith J, Noorani HZ, Cuncins-Hearn A, and Mensinkai S, CADTH, Canada

Title	**Guidelines for the Economic Evaluation of Health Technologies: Canada [3rd edition]**
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Reference	CADTH Technology Report, March 2006. ISBN 1-897257-08-2 (print). Full text available at www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf

Aim

To assist the "doers" of economic evaluations (ie, analysts) to produce credible and standardized economic information that is relevant and useful to decision makers in Canada's publicly funded healthcare system.

Conclusions and results

The guidelines give standards for the conduct and reporting of high-quality economic evaluations that can be reviewed and compared by decision makers. Each section of the economic guidelines addresses a specific topic on the conduct or reporting of economic evaluations. A high-quality economic evaluation should provide decision makers with information that is useful, relevant, and timely. In addition, evaluations should be based on rigorous analytical methods, be balanced and impartial (credible), and be transparent and accessible to the reader.

Recommendations

These guidelines provide recommendations for preparing credible and standardized economic information that is relevant and useful to decision makers in Canada's publicly funded healthcare system.

Methods

Not applicable.

Further research/reviews required

Not applicable.

Written by Canadian Agency for Drugs and Technologies in Health, CADTH, Canada

Title **Non-physicians Performing Screening Flexible Sigmoidoscopy: Clinical Efficacy and Cost Effectiveness**

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Reference CADTH Technology Report, Issue 60, January 2006. ISBN 1-897257-00-7 (print).
Full text available at www.cadth.ca/media/pdf/277_endoscopist_model_tr_e.pdf

Aim

To review evidence relating to the clinical evidence, safety, and cost effectiveness of the non-physician endoscopists (NPE) model compared with the physician endoscopist model for screening sigmoidoscopy.

Conclusions and results

Seventeen studies, including one survey, were selected for the clinical review.

Given the information available, it would appear that non-physician endoscopy is a viable model for Canada, because it might lead to increased screening availability and reduced waiting times. The NPE model would help meet the challenge of screening people at an average risk of colorectal cancer (CRC) – a large and growing segment of the population. This alternative to endoscopy, done solely by physicians, can provide economical CRC screening if proficiency is established and patient satisfaction is assured.

Recommendations

Not applicable.

Methods

Published and unpublished literature was systematically searched for studies reporting clinical outcomes of endoscopies performed by non-physicians (NPE), and from those performed by physicians. The outcomes investigated were the rate of polyp detection, rate of cancer detection, mean depth of endoscope insertion, and mean procedural time. Safety endpoints included the incidence of perforation, bleeding, infection, death, and the number of patients withdrawn because of adverse events. Patient satisfaction was also examined. Comparisons were made whenever possible between non-physician and physician endoscopy. The cost effectiveness of the two approaches was also examined using a cost minimization analysis.

Further research/reviews required

There is a need to standardize the training protocol for NPE.

Written by Ho C, Jacobs P, Sandha G, Noorani HZ, and Skidmore B, CADTH, Canada

Title **Transdermal Hormone Replacement Therapy Patches for Women with Postmenopausal Symptoms: Economic Analysis of Short-term Use**

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Reference CADTH Technology Report, Issue 61, January 2006. ISBN 1-894978-84-6 (print).
Full text available at www.cadth.ca/media/pdf/250_costbenefit_HRT_tr_e_.pdf

Aim

To present an economic analysis of transdermal patches for the short-term treatment of postmenopausal symptoms in women.

Conclusions and results

Eight studies reporting on 9 unique RCTs met the inclusion criteria of the clinical search, and the data were used as inputs to the economic model. The economic analysis found that transdermal hormone replacement therapy (HRT) patches are not cost effective relative to oral HRT for either the moderate or severe postmenopausal symptom groups. Relative to no treatment, transdermal HRT patches may be cost effective for women with moderate or severe symptoms. This suggests that transdermal patches may be an appropriate treatment option for patients who do not tolerate oral HRT, especially if they are experiencing severe postmenopausal symptoms.

Recommendations

Not applicable.

Methods

A literature search was performed to select relevant clinical studies as inputs for the economic model. The search covered the years 1990 through to May 2004. The studies considered were randomized controlled trials (RCTs) that compared the efficacy of transdermal HRT patches with oral HRT, or the efficacy of transdermal HRT patches with placebo patches. A decision analytic Markov model was developed to assess the costs and quality-adjusted life-years (QALYs) of women who were using HRT for postmenopausal symptoms in the short term (2 to 3 years). Separate analyses were performed for women with severe symptoms and women with moderate symptoms. Cost effectiveness was assessed in terms of transdermal HRT patches relative to oral HRT, and transdermal HRT patches relative to no treatment. The perspective taken was that of a third-party payer.

Written by Brown A, Coyle D, Chen S, Cumming D, and Mensinkai S, CADTH, Canada

Title **Newborn Screening for Medium Chain Acyl-CoA Dehydrogenase Deficiency Using Tandem Mass Spectrometry: Clinical and Cost Effectiveness**

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Reference CADTH Technology Report, Issue 62, March 2006. ISBN 1-897257-02-3 (print).
Full text available at www.cadth.ca/media/pdf/297_tandemmass_tr_e_no-appendices.pdf

Aim

To conduct a systematic review of the clinical and economic literature on the use of tandem mass spectrometry (MS/MS) in newborn screening for medium chain acyl-CoA dehydrogenase deficiency (MCADD) as opposed to clinical diagnosis.

Conclusions and results

Twenty-one studies (15 full-length reports, 6 abstracts) of limited quality met the selection criteria for clinical evaluation. The clinical sensitivity and specificity of MS/MS-based screening for MCADD were very high. Most patients detected by newborn screening were asymptomatic, while most who presented clinically had potentially irreversible damage. The percentage of fatal cases among those diagnosed clinically was significantly higher than that among those diagnosed by screening. The economic review and analysis showed that screening results in more quality-adjusted life-years (QALY) and lower morbidity and mortality compared with no screening. Also, screening is cost effective compared to no screening, if willingness to pay is $50 000 per QALY. The primary economic analysis using Canadian data showed that screening is cost effective if willingness to pay is $20 000 per QALY. Not all parents may want their newborns screened for MCADD, but they should be informed about the risks and given the option to refuse.

Recommendations

Not applicable.

Methods

A systematic review of the clinical and economic literature was performed. For the clinical review, published and unpublished sources were searched for studies reported between 1995 and 2005. Two independent reviews selected cohort studies related to newborn screening for MCADD using MS/MS and studies comparing outcomes of MS/MS-based screening and clinical diagnosis. Information on incidence, clinical validity, and genetics of MCADD detected by MS/MS and clinical diagnosis and the outcomes of disability and mortality were recorded. Study quality was assessed using QUADAS. The economic search was conducted from 1995 onwards. Two independent researchers selected studies and used the British Medical Journal (BMJ) 35-item checklist to assess quality. Data were extracted using a structured form.

Further research/reviews required

Further studies are needed on the long-term health consequences of MCADD, health improvements due to early detection, and health-related quality of life among MCADD patients.

Written by Tran K, Banerjee S, Li H, Noorani HZ, Mensinkai S, and Dooley K, CADTH, Canada

Title	**Portable Ultrasound Devices in Emergency Departments**
Agency	**CADTH, Canadian Agency for Drugs and Technologies in Health** Suite 600, 865 Carling Ave, Ottawa, ON K1S 5S8, Canada; Tel: +1 613 226 2553, Fax: +1 613 226 5392; publications@cadth.ca, www.cadth.ca
Reference	CADTH Technology Report, Issue 63, March 2006. ISBN 1-897257-10-4 (print), 1-897257-11-2 (electronic). Full text available at www.cadth.ca/media/pdf/384_Portable_Ultrasound_tr_e_no-appendices.pdf

Aim

To review and analyze evidence relating to the effective use of portable ultrasound (pU/S) by professionals who are not trained radiologists; to review and evaluate existing guidelines regarding the use of pU/S devices; and to examine the ethical and legal implications of their use.

Conclusions and results

Emergency department (ED) use of pU/S by non-radiologists for assessment of abdominal trauma, abdominal aortic aneurysm (AAA), and ectopic pregnancy improves diagnostic certainty. There is no convincing evidence that ED pU/S administered by a non-radiologist has an impact on health outcomes, or improved time to diagnosis, or operative treatment. The non-therapeutic advantages of using this technique are that it is easier to use and repeat, inexpensive to perform with available technology, and is non-invasive. There is evidence of misdiagnosis from using pU/Sin EDs, which is associated with inexperience. There is additional evidence of improved performance from training non-radiologist physicians. Training programs that use didactic and practical sessions (a minimum of 50 scans for each medical use) improve effectiveness. Misdiagnoses with pU/S scans performed by trained non-radiologist physicians can still occur, but at rates similar to those observed in similar studies of radiologist performed U/S scans.

Recommendations

Not applicable.

Methods

The literature was searched using a defined search strategy that included biomedical databases and websites of regulatory, HTA, and other relevant agencies. The bibliographies of selected papers were searched for further references. Case series and comparative studies that focused on pU/S use by non-radiologists in EDs in patients with suspected abdominal trauma, AAA, or ectopic pregnancy were included. A quantitative review of the clinical effectiveness of pU/S use in EDs was conducted. Summary likelihood ratios (LRs) and post-test probabilities in clinical scenarios were calculated, based on the data from individual studies, to evaluate the clinical effectiveness of ED pU/S. A qualitative-review approach was adopted to answer questions related to legal and ethical implications.

Further research/reviews required

Additional prospective, comparative, high-quality studies, designed to measure the impact of ED pU/S on efficiency, while monitoring clinical efficacy, would be helpful for making evidence-based decisions. The body of evidence describing diagnostic performance needs to be supplemented with results that demonstrate the effect of this intervention on diagnostic reasoning and time to definitive care.

Written by Chen S, Husereau D, Noorani H, Tran K, Boudreau R, Lentle B, Rowe B, and Keating T, CADTH, Canada

Title **Infliximab and Etanercept in Patients with Rheumatoid Arthritis: A Systematic Review and Economic Evaluation**

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Reference CADTH Technology Report, Issue 64, March 2006. ISBN 1-897257-04-X (print).
Full text available at www.cadth.ca/media/pdf/123_infliximab_tr_e_no-appendices.pdf

Aim

To provide a clinical review and economic evaluation relating to the introduction of infliximab and etanercept to the sequence of disease-modifying anti-rheumatic drugs (DMARDs) used in treating rheumatoid arthritis (RA).

Conclusions and results

Two randomized trials reported data based on recommended Canadian doses and the recommended patient population. Compared to placebo, infliximab and etanercept are effective treatments for RA in terms of improving symptoms and in preventing radiological damage. The analysis failed to find convincing evidence that either treatment is a cost-effective alternative.

Recommendations

Not applicable.

Methods

Published trials of infliximab and etanercept were identified through a comprehensive literature search and included for further analysis if the studies lasted a minimum of 6 months and reported on patients who were at least 16 years of age and met the American College of Rheumatology (ACR) criteria for RA. Two researchers abstracted data on study characteristics and assessed study quality using the Jadad scale. Studies were pooled, where appropriate, and analyzed using intention-to-treat data. Primary outcomes were the ACR criteria for 20%, 50%, and 70% improvement. Functional, radiological, and clinical outcomes were also assessed. Cost-effectiveness and cost-utility analyses were used to evaluate the economic data. Analysis was restricted to the approved dose for use in Canada.

Further research/reviews required

More long-term randomized trials are needed to corroborate these findings and to determine the benefit-to-harm ratio, including an evaluation of potentially rare or delayed adverse events, and the sustainability of treatment response to infliximab and etanercept in patients with longstanding RA. Ongoing postmarketing surveillance is required to establish effectiveness and to determine the incidence of adverse events and the sustainability of treatment response.

Written by Coyle D, Judd M, Blumenauer B, Cranney A, Maetzel A, Tugwell P, and Wells GA, CADTH, Canada

Title	**Long-acting ß 2-agonists for the Maintenance Treatment of Chronic Obstructive Pulmonary Disease in Patients with Reversible and Non-Reversible Airflow Obstruction: A Systematic Review of Clinical Effectiveness**
Agency	**CADTH, Canadian Agency for Drugs and Technologies in Health** Suite 600, 865 Carling Ave, Ottawa, ON K1S 5S8, Canada; publications@cadth.ca, www.cadth.ca
Reference	CADTH Technology Report, Issue 65, March 2006. ISBN 1-897257-12-0 (print). Full text available at www.cadth.ca/media/pdf/219_LABA_tr_e_no-appendices.pdf

Aim

To critically examine the clinical effectiveness of inhaled long-acting ß 2-agonists in patients with stable chronic obstructive pulmonary disease (COPD) and reversible or non-reversible airway obstruction.

Conclusions and results

Thirty-three unique trials were identified, 64% were of higher quality (Jadad ≥3).

Long-acting ß 2-agonists did not have any significant advantages over placebo in reducing mortality and upper respiratory tract infections, or in improving exercise capacity and tolerability. Compared with placebo, long-acting ß 2-agonists have a demonstrated effect in reducing COPD exacerbations and hospitalizations in patients with mild to severe COPD. Long-acting ß 2-agonists did not demonstrate a significant advantage compared with either anticholinergic agent in most functional outcome measures. Salmeterol is not as well tolerated as tiotropium. No data were available to compare the tolerability of formoterol with tiotropium.

Recommendations

Not applicable.

Methods

Published literature was identified by searching electronic databases from 1992 onward. Grey literature was obtained by searching the websites of health technology assessment and related agencies, clinical trial registries, and the websites of relevant associations. Relevant literature, published and unpublished, was selected by two reviewers working independently. Randomized controlled trials (RCTs) were selected and assessed for study design quality (Jadad scale) and information on the following were abstracted: deaths, serious or life threatening adverse events, COPD exacerbations, upper respiratory tract infections (URTIs) during treatment, hospitalizations during treatment, rescue short-acting ß 2-agonist use for acute symptomatic relief, symptom-free days, dyspnea, lung function tests, walk tests, and quality of life measures. Trials were included if they compared long-acting ß 2-agonists (salmeterol or formoterol) with placebo or with an anticholinergic agent (ipratropium or tiotropium), with or without short-acting inhaled ß 2-agonists on an as-needed basis. Meta-analyses of long-acting ß 2-agonists versus placebo, and long-acting ß 2-agonists versus anticholinergics were performed.

Further research/reviews required

There is an urgent need for experts to set internationally accepted standards for outcome measures in COPD drug trials and establish a minimum number of objective outcome measures to prove the efficacy and effectiveness of these drugs.

Written by Shukla VK, Chen S, Boucher M, Mensinkai S, and Dales R, CADTH, Canada

Title **BRCA1 and BRCA2 Predictive Genetic Testing for Breast and Ovarian Cancers: A Systematic Review of Clinical Evidence**

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Reference CADTH Technology Report, Issue 66, March 2006. ISBN 1-894978-98-6 (print).
Full text available at www.cadth.ca/media/pdf/175_brca_tr_e.pdf

Aim

To evaluate the analytical and clinical validity of BRCA1/2 genetic testing; to assess the contribution of molecular testing to genetic counseling and clinical management; and to discuss the ethical and psychosocial issues inherent in BRCA1/2 testing.

Conclusions and results

There is no compelling evidence that one test performs better than another, and there is no clear evidence to suggest testing will lead to decisions that result in long-term health benefits. Knowledge about the association of cancer and genetics is limited in the general population. Test results influence individual risk perception, emotional states, and social issues. Counseling reduces the perceived risk and the associated anxiety, and increases the uptake of testing. Until better information becomes available, other factors such as test availability ease of implementation, regulatory considerations, and price should be considered in deciding the method used for testing.

Recommendations

Not applicable.

Methods

A defined search strategy and selection criteria were used to identify published and grey literature. A study was included for review if it met the eligibility criteria established a priori by two independent reviewers. Study quality was assessed and data were extracted regarding molecular methods, analytical validity, psychosocial impact, ethical issues, and clinical management.

Further research/reviews required

Decisions regarding BRCA1/2 testing need to be revisited. Scientific data are accumulating rapidly. If the expansion of testing and the creation of best practices are pursued, an update of this report should be considered.

Written by McGahan L, Kakuma R, Ho C, Bassett K, Noorani HZ, Joyce J, Allanson J, and Taylor S, CADTH, Canada

Title **Emergency Department Overcrowding in Canada: What are the Issues and What can be Done?**

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Reference CADTH Technology Report, Issues 67.1–67.4, May 2006. ISSN 1203-9012 (print).
Full text available at www.cadth.ca/index.php/en/hta/reports-publications/search/publication/621

Aim

To summarize the results of 5 studies covering different aspects of overcrowding in Canadian emergency departments (EDs).

Conclusions and results

Emergency department overcrowding is a frequent and significant occurrence across Canada. Among respondents to an ED director survey, 62% reported overcrowding as a major or severe problem in 2004 and 2005, and was more likely to occur in EDs with 50 000 or more visits annually, communities with a population of at least 150 000, university affiliated hospitals, trauma centers, and EDs with 30 or more treatment spaces.

A lack of beds may lead to overcrowding. Most respondents (85%) perceived a lack of admitting beds to be a major or serious cause of overcrowding.

Measures of ED overcrowding and their collection require consistency. Inconsistent methods of collecting, defining, and measuring information related to overcrowding, create a confusing picture of the issues facing EDs.

Electronic collection of data and contributions to a national data system should be considered. Electronic ED information systems are available in Canada, but only 39% of ED directors surveyed reported using them.

Fast track systems can reduce overcrowding. Evidence suggests that fast tracking patients with minor injuries or illnesses can reduce ED length of stay, waiting time, and the number of patients who leave without being seen.

Ambulance diversion strategies, short stay units, staffing changes, and system-wide complex interventions should also be further explored. Limited evidence suggests that these interventions to address overcrowding should be encouraged and monitored.

No evidence of effectiveness could be identified for many broadly adopted interventions in Canada. These include float nurse pools, senior ED physician flow shifts, home or community care workers assigned on site to the ED, overcensus on wards, orphan clinics, "colored" codes to decongest ED, and "overload" units for in-patients.

Recommendations

Not applicable.

Methods

Five studies (surveys, systematic reviews, Delphi study), detailed in four reports, were conducted to examine the issues and explore solutions to the overcrowding in Canadian emergency departments. (See full report for details.)

Further research/reviews required

There is a need for more investigations of high methodological quality on the specific effects of these interventions and how they might affect quality of care and patient outcomes.

Written by Rowe BH, Bond K, Ospina MB, Blitz S, Friesen C, Schull M, Innes G, Afilalo M, Bullard M, Campbell SG, Curry G, Holroyd B, Yoon P, and Sinclair D, CADTH, Canada

Title **Artificial Skin Grafts in Chronic Wound Care: A Meta-analysis of Clinical Efficacy and a Review of Cost Effectiveness**

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Reference Technology Report, Issue 52, February 2005. ISBN 1-894978-50-1 (print), 1-894978-51-X (electronic). Full text: www.cadth.ca/media/pdf/252_artificial_skin_grafts_tr_e.pdf

Aim

To examine the clinical safety, efficacy, and cost effectiveness of artificial skin grafts for patients with chronic skin wounds such as diabetic foot ulcers and venous leg ulcers.

Conclusions and results

Twenty-three reports describing 17 RCTs and 6 economic studies were reviewed.

The results of clinical trials show that artificial skin grafts promote wound closure, resulting in more frequent and more rapid healing of chronic diabetic foot ulcers, when compared with standard therapy. Evidence is limited concerning clinical efficacy of artificial skin grafts used for venous leg ulcers. In the short term, the use of artificial skin leads to increased costs. After one year, however, its clinical effects may result in net savings.

Recommendations

Not applicable.

Methods

Published literature was obtained by using a defined strategy to search multiple databases and by hand searching the bibliographies of selected papers. A meta-analysis of RCTs was performed to compare standard care alone versus the clinical outcomes for artificial skin use plus standard care.

The proportion of patients who had complete wound healing (CWH) with or without an artificial skin graft was summarized over different time frames (for all types of ulcers), for venous leg ulcers and diabetic foot ulcers separately, and for Dermagraft and Apligraf separately. The time to healing and the incidence of adverse events were summarized from clinical trials. The economic consequences of using artificial skin products in venous leg ulcers and diabetic foot ulcers were examined.

Further research/reviews required

More trials are needed to provide enough data to confidently evaluate other skin graft products.

Written by Ho C, Tran K, Hux M, Sibbald G, and Campbell K, CADTH, Canada

Title **Economic Evaluation of Drug Eluting Stents**

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Reference CADTH Technology Report, Issue 53, February 2005.
ISBN 1-894978-56-0 (print), 1-894978-57-9 (electronic).
Full text available at www.cadth.ca/media/pdf/272_drug_eluting_stents_tr_e.pdf

Aim

To examine the cost effectiveness of drug eluting stents (DES) relative to bare metal stents (BMS) from the perspectives of both a tertiary care hospital and a provincial ministry of health. The impact on expenditures if DES were to become widely adopted in treating patients with coronary heart disease was also examined. These questions were addressed through an economic evaluation and a budget impact analysis.

Conclusions and results

Mortality and myocardial infarction (MI) rates did not differ with DES compared to BMS. Drug eluting stents are associated with higher costs and lower target lesion revascularization (TLR) when compared with BMS. From a hospital perspective, the paclitaxel eluting stent involved an additional cost relative to BMS of between $26 562 and $29 048 per TLR avoided. From a provincial health ministry perspective, the ICER for the paclitaxel stent was estimated at $25 202 to $27 687 per TLR avoided. For the sirolimus eluting stent, from a hospital perspective, the ICER was $12 527 to $16 600 per TLR avoided. From a provincial health ministry perspective, it was $11 133 to $15 192 per TLR avoided. The impact on the 2003 Ontario budget of converting 40% of patients considered to be at high risk of restenosis from BMS to DES was estimated to be an additional $4.8 to $14.6 million per year depending on the stent cost ($1200 and $2400 respectively). If all BMS patients were converted to DES in Ontario, then $12.1 to $48.9 million could be added to the provincial budget. While DES are more costly than BMS, their use is associated with a significantly lower 1-year rate of restenosis, which avoids associated treatment costs. Long-term survival data are unavailable.

Recommendations

Not applicable.

Methods

A decision analytic model was developed to compare the cost effectiveness of sirolimus and paclitaxel DES relative to BMS, using a cost per TLR avoided. The model simulated the 1-year resource consumption and clinical outcomes for patients undergoing percutaneous coronary interventions (PCI) and receiving either a DES or BMS in two pivotal studies (SIRIUS and TAXUS IV) and a meta-analysis of sirolimus and paclitaxel DES studies. The model was based on clinical trial data and treatment algorithms for acute coronary syndrome. Perspectives were those of a tertiary care teaching hospital, and the total expected costs and outcomes for DES versus BMS were compared in an incremental cost-effectiveness analysis. A budget impact analysis and several sub-analyses were performed.

Further research/reviews required

Given that costs were the key source of uncertainty in the analysis, there is a need for better data collection at the provincial and national levels. A national cardiovascular database to record procedural data and costs would meet that need.

Written by Mittmann N, Brown A, Seung SJ, Coyle D, Cohen E, Brophy J, Title L, and Oh P, CADTH, Canada

Title **Economic Evaluation of Glycoprotein IIb/IIIa Inhibitors in Patients Undergoing Percutaneous Coronary Intervention with Stenting**

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Reference CADTH Technology Report, Issue 54, March 2005. ISBN 1-894978-63-3 (print), 1-894978-62-5 (electronic). Full text: www.cadth.ca/media/pdf/203_glycoproteins_tr_e.pdf

Aim

To review the economic evidence on the use of GP IIb/IIIa inhibitors as adjunct therapy in percutaneous coronary interventions (PCI) with stenting, and to perform economic evaluations (from the perspective of a Canadian provincial health insurance payer) on the cost effectiveness of abciximab and eptifibatide.

Conclusions and results

The economic evaluation in this study suggests that eptifibatide and abciximab can be considered to be cost effective adjuncts for controlling complications in patients undergoing elective and urgent PCI. The incremental cost-effectiveness analysis for abciximab in the general study population showed a higher overall cost and better outcomes, with a result that is consistent with what is generally considered to be cost effective. For eptifibatide in the general study population, and for both drugs in those with diabetes, the analysis showed lower costs and better outcomes when compared with usual care. We caution against a direct comparison of eptifibatide and abciximab based on the available data.

Recommendations

Not applicable.

Methods

A literature search identified full economic evaluations that compared percutaneous coronary interventions (PCI) alone to PCI with abciximab or eptifibatide. Five studies met the inclusion criteria for the review. Decision analytic modeling was done to estimate the short-term and long-term cost effectiveness of the two drugs.

Further research/reviews required

The review of economic evidence supported the need for an up-to-date economic evaluation of GP IIb/IIIa inhibitors in a Canadian context.

Written by Brown A, Mittmann N, Seung SJ, Cohen E, Oh P, Tang Z, Noorani HZ, and Mensinkai S, CADTH, Canada

Title **A Review of Guidelines for Referral of Patients to Sleep Laboratories**

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Reference CADTH Technology Report, Issue 55, May 2005.
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Full text available at www.cadth.ca/media/pdf/183_sleeplabs_tr_e.pdf

Aim

To identify recommendations presented in guidelines by professional bodies that address the investigation of individuals in sleep laboratories; and to review the nature, quality, and relevance of the evidence cited in support of these recommendations.

Conclusions and results

Thirty-seven guidelines and associated reviews covering the following applications of sleep laboratory investigation were identified: obstructive sleep apnea (diagnosis, titration, and followup); other respiratory disorders; chronic lung disease; obstructive sleep apnea, repeat PSG, and other conditions in children; sudden infant death syndrome; treatment for snoring; insomnia; depression with insomnia; narcolepsy; restless legs syndrome; and parasomnias. Of the 81 recommendations identified, 46 are supported by evidence from primary studies, 4 are supported by an absence of available evidence, and 31 have no evidence or are supported by consensus. The cited evidence from the primary studies was judged to be highly relevant to the recommendation in 18 cases, of some relevance in 22 cases, and of little or no relevance in 6 cases. The level of evidence for many applications is of limited quality and some cited studies are not relevant to the recommendations made. Many recommendations reflect consensus positions, and no evidence is cited in support. Further good quality studies are needed concerning many sleep laboratory applications.

Recommendations

Not applicable.

Methods

Electronic databases were searched for guidelines and associated reviews, which appeared from 1992 onwards, on the use of sleep laboratory investigations for sleep disorders. The searches were not limited to the English language and were updated periodically. Guidelines and associated reviews were selected, and recommendations related to the selection of patients for examination in sleep laboratories were identified. Publications cited in support of the recommendations were reviewed considering the type and design of the study, population, and quality and relevance of the evidence. For each sleep laboratory application, pertinent guideline recommendations were listed and the studies cited in support were reviewed. The quality and relevance of evidence in support of recommendations were rated on 3-point scales.

Further research/reviews required

Further good quality studies of many sleep laboratory applications are needed.

Written by Hailey D, Tran K, Dales R, Mensinkai S, and McGahan L, CADTH, Canada

Title **Costs and Outcomes of Chiropractic Treatment for Low Back Pain**

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Reference CADTH Technology Report, Issue 56, July 2005.
ISBN 1-894978-83-8 (print), 1-894978-82-X (electronic).
Full text available at www.cadth.ca/media/pdf/225_chiro_tr_e.pdf

Aim

To review the clinical and economic implications of chiropractic care in treating lower back pain (LBP).

Conclusions and results

Eighteen review articles and 4 trials published later were identified. Relative costs were examined from 10 economic studies.

Chiropractic care for LBP is similar in effectiveness to standard medical care and physical therapy. Studies showed that the 3 treatment methods had similar effects on pain relief and functional improvement. No clear cost advantage was found for any of the 3 methods studied. One of the economic studies compared chiropractic care with physical therapy and found costs to be similar. Cost results varied among the studies comparing chiropractic care with standard medical care. Chiropractic care was similar to physical therapy and as effective as, or better than, standard medical care for improving time lost from work.

Recommendations

Not applicable.

Methods

Review articles were searched using a predefined strategy. An economic filter was applied for the search of economic studies. Two reviewers independently selected clinical studies for inclusion if they reported on adult populations with chronic or acute LBP who were receiving chiropractic intervention and were compared to adults receiving standard nonsurgical care. Data were abstracted and study quality was evaluated using the Oxman and Guyatt Scale for quality assessment of the systematic reviews, the Jadad scale for RCTs, and the Newcastle-Ottawa Quality Assessment Scale for non-RCTs. Clinical outcomes included pain level or functional status. The primary outcome for economic studies was an incremental measure of the implication of moving from the comparator to the intervention. Results from the studies were summarized, and a qualitative comparison was undertaken.

Further research/reviews required

A well-designed Canadian study that compares the cost effectiveness of LBP care provided by chiropractors, physical therapists, and primary care physicians would be of benefit.

Written by Brown A, Angus D, Chen S, Tang Z, Milne S, Pfaff J, Li H, and Mensinkai S, CADTH, Canada

Title **Lung Volume Reduction Surgery for Emphysema: Systematic Review of Studies Comparing Different Procedures**

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Reference CADTH Technology Report, Issue 57, August 2005. ISBN 1-894978-86-2 (print), 1-894978-85-4 (electronic). Full text: www.cadth.ca/media/pdf/176a_lvrs_tr_e.pdf

Aim

To evaluate the clinical benefit and harm of different lung volume reduction (LVRS) procedures.

Conclusions and results

Four RCTs and 10 cohort studies met the inclusion criteria. Of the 4 RCTs, 3 compared LVRS procedures with or without buttressing, and 1 compared laser versus staple procedures. Of the 10 cohort studies, 2 compared unilateral with bilateral procedures, 5 compared median sternotomy (MS) with video-assisted thoracoscopic surgery (VATS), 1 compared unilateral with bilateral procedures and MS with VATS, and 2 compared staged and simultaneous procedures.

Limited evidence from RCTs of low quality suggest that buttressing the staple lines may provide better results than no buttressing, and that LVRS using the stapling procedure may be better than the laser resection method. The studies comparing unilateral versus bilateral procedures, staged versus simultaneous procedures, or MS versus VATS were nonrandomized. The evidence from these studies is weak and inconsistent, and it is impossible to conclude definitively if one procedure offers an advantage compared with the other procedure.

Recommendations

Not applicable.

Methods

Relevant studies were identified by searching electronic databases and websites. Randomized controlled trials (RCTs) and cohort studies were selected for inclusion if they compared different LVRS procedures for treating emphysema and reported at least one of several outcomes.

The relative benefit and harm of different LVRS procedures were determined by examining their impact on quality of life (QoL), complications associated with treatment, mortality, shortness of breath (dyspnea), and pulmonary function.

Further research/reviews required

Unless appropriate RCTs are undertaken, uncertainty will continue as to which LVRS procedures are the most beneficial.

Written by Banerjee S, Babidge W, Noorani HZ, Cuncins-Hearn A, Miller J, Smith J, and Mensinkai S, CADTH, Canada

Title **Cholinesterase Inhibitors for Alzheimer's Disease: A Systematic Review of Randomized Controlled Trials**

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Reference CADTH Technology Report, Issue 58, September 2005. ISBN 1-894978-68-4 (print), 1-894978-69-2 (electronic). Full text: www.cadth.ca/media/pdf/217_cholinesterase_tr_e.pdf

Aim

To critically examine evidence related to the efficacy, safety, and acceptability of using cholinesterase inhibitors (ChEIs) in individuals with mild to moderate Alzheimer disease (AD).

Conclusions and results

Twenty-five clinical trials that collectively measured 29 outcomes were used in this review. Cholinesterase inhibitors had a modest impact on functional performance and global outcomes. The clinical significance of this improvement is difficult to predict. Patients on galantamine and rivastigmine experienced adverse events (AE) that led to a greater likelihood of discontinuing the treatment, although ChEIs did not cause an increase in the number of patients experiencing serious AE or death. Donepezil did not improve quality of life (QoL) or prevent institutionalization, but whether or not this is a class effect remains to be determined. Comparisons suggest that ChEIs have comparable efficacy, but methodological limitations prevent definitive conclusions.

Recommendations

Not applicable.

Methods

A comprehensive search strategy was developed to identify published and unpublished literature. Studies were selected if they reported on randomized, parallel group design trials of at least 12 weeks and if trial participants had evidence of mild to moderate, possible or probable AD, based on established diagnostic criteria. Trials comparing a ChEI with placebo or with another treatment were included, and there were no language restrictions. Meta-analysis was performed when sufficient quantitative data were provided. Where applicable, sensitivity analyses were performed for quality of trials and language of publications. The benefit and harm of using ChEIs to manage mild to moderate AD was determined by examining changes in functional performance, global improvement, quality of life (QoL), adverse events, and serious adverse events. The effects that using ChEIs had on rates of institutionalization and persistence with therapy were also examined.

Further research/reviews required

The knowledge gaps that continue with ChEIs include the impact of these drugs on outcomes, eg, rate and timing of institutionalization, beneficial effects on QoL, functional performance, and long-term effectiveness.

Written by Perras C, Shukla VK, Lessard C, Skidmore B, Bergman H, and Gauthier S, CADTH, Canada

Title **CT and MRI for Selected Clinical Disorders: A Systematic Review of Clinical Systematic Reviews**

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Reference CADTH Technology Report, Issue 59, October 2005. ISBN 1-894978-88-9 (print), 1-894978-88-7 (electronic). Full text: www.cadth.ca/media/pdf/322_ctmri_tr_e.pdf

Aim

To summarize the evidence from systematic reviews (SRs) reporting on the clinical effectiveness of computed tomography (CT) and magnetic resonance imaging (MRI) in investigating specific clinical conditions of the chest, cardiovascular, neurological, and urological systems.

Conclusions and results

Forty-eight articles were included, reporting on 49 SRs that examined CT and MRI for 11 clinical conditions.

Based on studies of the diagnostic accuracy of CT and MRI as compared with traditional gold standard investigations, promising evidence was found for applications in carotid artery disease, peripheral vascular disease, pulmonary embolism, renal artery stenosis, and stroke. Findings were more cautious for cerebral aneurysms, coronary artery disease, and lung cancer screening, while SR evidence was sparse regarding the use of these technologies for investigating headaches, head injuries, and seizures. No SR evidence was found for cerebral arteriovenous malformations or urolithiasis. Evidence of effectiveness from recent systematic reviews indicates that CT and MRI technologies can improve diagnostic certainty in some medical conditions. In other conditions, the evidence was less than compelling, or not available. There was no evidence that CT and MRI technology has an effect on patients' health or management.

Recommendations

Not applicable.

Methods

Published literature from 2000 to November 2004 was identified and retrieved using a well-defined search strategy. References were included if they were SRs, covered the 13 conditions of interest, and examined CT and MRI technologies for investigating these conditions. Two authors independently applied selection criteria in screening. From the included references, information was extracted into evidence tables and analyzed. In addition, all included references were assessed for quality using two separate tools, one developed by Oxman and Guyatt and the other, examining diagnostic imaging efficacy, by Fryback and Thornbury.

Further research/reviews required

Further research could examine the evidence for using CT and MRI to investigate other clinical conditions and focus on various specialized investigative uses of these technologies, eg, CT angiography (CTA), MR angiography (MRA), and therapeutic uses. CT and MRI technology has advanced rapidly, and findings from the systematic reviews identified may not be sufficiently contemporary to be useful for clinicians and decision makers.

Written by Foerster V, Murtagh J, Lentle BC, Wood RJ, Reed MH, Husereau D, and Mensinkai S, CADTH, Canada

Title **Management of Chronic (Non-Cancer) Pain: Organization of Health Services**

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Reference Technology brief prepared for AETMIS (AETMIS 06-04). Internet access to full text.
ISBN 2-550-46601-2 (print), 2-550-46602-0 (PDF)

Aim

To review chronic pain (CP) management systems in other jurisdictions and analyze the implications of this evidence for improving chronic pain management services in Québec.

Conclusions and results

In 1996, the reported prevalence of CP in the adult Quebec population was 24% for women and 20% for men. Coherent and consistent CP services would benefit the economy, the healthcare system, families, communities, and the individuals who suffer "pain that has persisted beyond the normal tissue healing time, usually taken to be 3 months". In a health technology assessment (HTA) framework, this report describes the organizational components and modes of intervention used by 3 healthcare systems (Australia, France, and the US Veterans Health Administration – VHA) for people with non-cancer-related CP.

Quebec services are fragmented and inequitable, and waiting times are long. The few multidisciplinary pain clinics are not sufficiently funded to provide the most effective treatments, and third-party payers sometimes determine treatment options. Professional education in CP management is often inadequate. While a myriad of clinical practice guidelines for CP treatment exist, their impact on patient outcomes has been rarely studied systematically. In general, research shows that better outcomes are achieved when care is integrated between general practitioners and physiotherapists, psychologists, and other allied professionals. The 3 systems in this study organized pain services hierarchically, with specialization, complexity, and multidisciplinarity increasing as the patient moves up the hierarchy. The VHA system has incorporated quality control measures for all of its pain management services, while France appears to have documented the implementation of its system rather than patient outcomes.

In a multidisciplinary pain clinic (MPC), treatment extends to improving the patient's physical, psychological, social, and occupational functioning. A recent HTA report found strong evidence for the effectiveness of MPCs for low back pain, moderate evidence for pelvic CP, and limited evidence for widespread body, neck, and shoulder CP. MPCs offer integrated professional care, a one-record system, uniform patient management processes, and rehabilitative care if pain continues after intensive treatment.

Recommendations

- CP should be considered a priority in Quebec's healthcare system.
- A service hierarchy is required, with a focus on efficient and effective patient referral.
- An interdisciplinary approach at all levels of care is essential.
- CP services and patient outcomes should be monitored and assessed systematically.
- CP patients must be viewed as part of the solution, and educated accordingly.
- The "patient navigator" model in Quebec cancer care could be a useful coordination model.
- Professional education should focus on risk factors for CP, and timely diagnosis and treatment to prevent chronicity.

Methods

Published and 'grey' literature search. A conceptual framework was used to present material and to attempt to link organizational innovations (in structure and process) with outcomes in CP.

Further research/reviews required

There is a role for evaluative research in examining the effectiveness and financial implications of different modes of intervention and treatments in CP.

Written by Patricia L Dobkin and Lucy J Boothroyd, AETMIS, Canada

Title **Pharmacological and Surgical Treatment of Obesity. Residential Treatment of Severely Obese Children in Belgium**

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Reference KCE reports vol 36, 2006.
http://kce.fgov.be/index_en.aspx?SGREF=5211&CREF=7296

Aim

To assess pharmacological (orlistat, sibutramine, rimonabant) and surgical treatment of obesity, and to analyze long-term residential care for severely obese children in Belgium.

Conclusions and results

There is no evidence on the effectiveness of orlistat, sibutramine, and rimonabant in treating obesity. Bariatric surgery is more effective than nonsurgical treatment for long-term weight loss and control of some comorbid conditions, particularly diabetes, in severely obese patients. However bariatric procedures differ widely in terms of long-term effectiveness and safety, and important gaps in scientific knowledge exist in this field. Risks can be high. There is no evidence that gastric banding has a better risk/benefit ratio than the current standard Roux-en-Y. Only severe obesity can justify the risks and uncertainties associated with bariatric surgery. A volume-outcome relationship has been described for most bariatric procedures including gastric banding. Long-term residential care of severely obese children (on average, 1 school-year) is effective in the short-term, but is very expensive, might have some disadvantages (less family involvement), and no data exist to assess its long-term effectiveness.

Recommendations

Orlistat, sibutramine, and rimonabant are weight-loss drugs, but should not be promoted as a chronic treatment for obesity. In Belgium, bariatric surgery should be reimbursed only for patients with a BMI ≥40, or BMI ≥35 with documented diabetes, and practice of bariatric surgery needs to be strictly limited to 'centers of excellence'. Long-term effectiveness of residential care for severely obese children should be documented and funding reassessed in 5 years pending the results of this study.

Methods

Systematic review of the literature.

Written by Lambert M-L, Kohn L, Vinck I, Cleemput I, Vlayen J, Van De Sande S, Ramaekers D, Beguin C, Gerkens S, Thissen J-P, and Thimus D, KCE, Belgium

Title **Telehealth: Clinical Guidelines and Technological Standards for Telerehabilitation**

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Reference Technology brief prepared for AETMIS (AETMIS 06-03). Internet access to full text.
ISBN 2-550-46942-9 (print), 2-550-46943-7 (PDF)

Aim

To propose clinical guidelines and technical standards that would foster the optimal telerehabilitation use, and to examine certain economic, legal, ethical, human, and organizational factors to highlight their importance in implementing programs successfully.

Conclusions and results

This is the second of 3 reports on different applications of telehealth (telepsychiatry, telerehabilitation, telepathology). In telerehabilitation, patients and health professionals communicate in real time via videoconferencing. Studies indicate that telerehabilitation can improve the continuity of care. Clinical activities suitable for telerehabilitation are: assessing clinical status, making a diagnosis, providing rehabilitation services, and dispensing technical aids from a distance. Because of their multidisciplinary nature, rehabilitation activities are well suited to telerehabilitation, tele-expertise, and teletraining. However, telerehabilitation is contraindicated in patients who refuse it, or have physical impairments preventing coherent communication, or have a health problem that cannot be evaluated via this technology or supervised from a distance.

Little has been done to assess the economic aspects of telerehabilitation, and methodological problems in analyzing the evidence often make it difficult to compare face-to-face consultations with telerehabilitation. From a societal perspective, the incremental cost estimate assumes that telerehabilitation activities take up the equivalent of 1.5 days per week. According to the experts consulted, this assumption is a realistic estimate of actual needs and considers the resources currently available. The room, equipment, and transmission lines could also be used for tele-education and tele-expertise in other fields, which would help offset the initial investment. Given the insufficiency of information and the approximateness of economic outcomes, the implementation of telerehabilitation should be followed by rigorous field assessments.

Because of patient/therapist discomfort with the distance and the equipment, care providers need training to help smooth the transition for their patients. Legislation and guidelines are needed to ensure that consent is obtained and that confidentiality is maintained.

Two aspects are discussed from an ethical standpoint: 1) the future prospect of increased access to specialized services in remote areas; and 2) the transformation of the traditional therapeutic relationship (face-to-face consultation). Telerehabilitation alone cannot be viewed as the solution to the problem of providing good coverage throughout the province.

Recommendations

Clinical guidelines: To provide service that is "relatively equivalent" to conventional therapy, telerehabilitation must be supported by a central reservation system, a generic consultation tool, thorough record keeping, standard agreements between the service governing and delivery bodies, remuneration mechanisms, training for providers, dispute resolution procedures, and staff coordination.

Technological standards: Effective services require consulting room standards (size, color, lighting, noise) and equipment standards (remote control cameras, telephone and fax, the H.264 compression standard, and a 384-Kbps reserved-bandwidth connection).

Methods

Literature search, expert interviews, equipment testing.

Further research/reviews required

The expanded implementation of telerehabilitation should be accompanied by a rigorous ongoing assessment of cost, satisfaction, quality, and accessibility.

Written by Pineau G, Moqadem K, St-Hilaire C, Perreault R, Levac É, and Hamel B, with the collaboration of Bergeron H, Obadia A, and Caron L, AETMIS, Canada

Title **Bone-Anchored Hearing Aids**

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Reference Report prepared for AETMIS (AETMIS 06-05). Internet access to full text.
ISBN 2-550-46520-2 (print, French edition), 2-550-47186-5 (PDF)

Aim

To update the list of hearing aids insured under the Health Insurance Act by assessing bone-anchored hearing aids, as part of amending the regulation on hearing devices.

Conclusions and results

According to the AETMIS assessment, which is based on limited evidence, bone-anchored hearing aids yield audiometric benefits and a subjective improvement in post-implantation quality-of-life. These benefits emerge especially for users of bone-conduction hearing aids, but also for those who wear conventional hearing aids and suffer from chronic middle-ear infections. Eligible patients include children aged 5 years and older, although attention must be paid to the greater risk for complications, eg, skin infections. Other applications for the bone-anchored hearing aid, such as bilateral implantation, unilateral sensorineural hearing loss, or tinnitus, are not yet based on evidence of clinical utility and must be considered experimental.

Methods

Literature search: MEDLINE and the Cochrane Library, and manufacturers' product documentation.

Written by François Bergeron, AETMIS, Canada

Title **Vacuum-Assisted Breast Biopsy**

Agency **AETMIS, Agence d'évaluation des technologies et des modes d'intervention en santé**
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Reference Report prepared for AETMIS (AETMIS 06-06). Internet access to full text.
ISBN 2-550-47119-9 (print, French edition), 2-550-47427-9 (PDF)

Aim

To examine the quality of scientific evidence supporting the use of vacuum-assisted breast biopsy and the advisability of offering this procedure to patients requiring a breast biopsy after detection of a nonpalpable mammographic abnormality.

Conclusions and results

Vacuum-assisted breast biopsy (VAB) is a technique designed to take a breast-tissue sample at the site of a nonpalpable mammographic abnormality to verify whether or not it is cancerous, and if so, to guide further clinical therapy.

There is a clinical consensus that percutaneous biopsy (core-needle biopsy) under ultrasound or stereotactic guidance is a less invasive and less costly procedure than open surgical biopsy, and that it accurately diagnoses most breast abnormalities. A variant of this technique, vacuum-assisted breast biopsy, is being used in at least 14 centers in Québec and accounted for roughly 3000 of the 13 000 percutaneous biopsies performed in 2004. Hence, it is important to know if the clinical benefits of this technique warrant expanding its use and covering its high costs.

This technical note assesses the scientific evidence on the diagnostic performance of VAB in relation to that of conventional core-needle biopsy. It also examines the economic aspects and the quality-assurance measures required to guarantee that percutaneous biopsies yield maximum benefits while avoiding errors and complications.

The analysis was limited by the lack of comparative studies, given that all the studies report on the experience of healthcare teams using either one or the other technique. Nevertheless, the available data suggest that vacuum-assisted biopsy offers a slight diagnostic advantage, with a 3.1% rate of undetected cancers for conventional (non-vacuum-assisted) biopsies compared with 1.6% for VAB. The vigilance of a multidisciplinary team of experts who can detect any discordance between mammographic and biopsy findings should identify most of these missed cases. The limited clinical gains attributed to VAB do not justify the appreciable cost increases associated with this procedure.

In conclusion, vacuum-assisted breast biopsy should not replace conventional percutaneous biopsy for all biopsies of nonpalpable breast abnormalities. However, some clinical indications may justify the use of VAB, and it would be important for an expert committee to identify these indications. All percutaneous biopsies of nonpalpable breast abnormalities should be performed only in centers that have achieved a high level of expertise in diagnosing breast abnormalities, and that have multidisciplinary teams collaborating closely to assess the cases and review diagnostic performance in the use of these percutaneous techniques.

Methods

Literature search: MEDLINE and INAHTA databases.

Written by Wilber Deck, AETMIS, Canada

Title **A Review of the Scientific Literature for Diagnosis and Treatment of Chronic Fatigue Syndrome/Myalgic Encephalopathy (CFS/ME)**

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Reference Report no 9-2006. ISBN 82-8121-097-4. 2006. In Norwegian, English summary.
www.kunnskapssenteret.no/filer/CSF_ME_nettversjon090606.pdf

Aim

To assess and synthesize the evidence base for diagnosing and treating chronic fatigue syndrome/myalgic encephalopathy (CFS/ME).

Conclusions and results

Diagnosis: The recommendations for diagnosis are based on guidelines for clinical diagnosis of CFS/ME published by British, Australian, Canadian, and other groups.

- Patient history includes extreme fatigue lasting at least 6 months triggered by disproportional demands, and is unpredictable, does not improve by rest, or is worsened by physical or mental effort. Other symptoms are, eg, sore throat, swollen lymph nodes, painful joints and muscles, headache, and sleeping problems. Comorbidities may include fibromyalgia or irritable bowel syndrome. The course varies.
- Differential diagnoses, eg, metabolic diseases, diabetes, coeliac disease, cancer, bipolar or depressive conditions, neurological disease, and Addison's disease must be ruled out. No diagnostic test can verify the diagnosis, nor point to the best treatment.

Treatment: Cognitive behavioral therapy, graded exercise therapy, pharmacological treatment, immunological treatment, supplements and alternative/complementary treatment. Documentation is low or very low for most outcomes:

- Cognitive behavioral therapy suggests improved physical function and quality of life, but it is uncertain if the treatment influences mental health.
- Graded exercise therapy suggests reduced fatigue, but effects on depression or quality of life are not documented. Dropout was high, especially with high-intensity exercise.
- No evidence recommends pharmacological treatment unless there is relevant comorbidity.
- Immune modulating treatment has uncertain effects, but could have serious adverse effects.
- Effects of supplements and alternative/complementary medicine are uncertain.
- Few studies investigated the effects of treatment in children and adolescents.
- No studies investigated the effects of treatment in the severely ill or disabled.

Methods

The overview of the scientific knowledge is based on systematic reviews and a search of recent primary and qualitative studies. The assessment was done stepwise, starting with 1168 abstracts and ending with 6 systematic reviews, 5569 abstracts of RCTs/CCTs and ending with 4 RCTs on adults and 3 RCTs on children/adolescents. We identified 807 qualitative studies and included 18. Level of documentation was based on GRADE.

A review team performed the assessment, with input from 2 patient organizations. The literature was searched via the Cochrane Database of Systematic Reviews, DARE, MEDLINE, EMBASE, PsycINFO, and AMED. Patients with CFS, ME, postviral fatigue syndrome, and chronic fatigue and immunodysfunctional syndrome were included. Interventions included any kind of treatment for CFS/ME. All outcomes were considered, and fatigue, physical and mental health, and quality of life are reported.

Further research/reviews required

Studies on better treatment for severely ill or disabled sufferers are insufficient. Evidence on children and adolescents is scarce, and for adults the level of documentation is low or very low. Diagnostic criteria vary by study, making comparisons difficult. Empirical studies on treatment experiences are missing. CFS/ME symptoms are subjective. Qualitative studies show that patients feel stigmatized and mistrusted, and doctors find it challenging to diagnose and treat CFS/ME. The prevalence, prognosis, and cause of CFS/ME remain unclear. More research is needed.

Written by Lillebeth Larun et al, NOKC, Norway

Title **Contribution of BRCA1/2 Mutation Testing to Risk Assessment for Susceptibility to Breast and Ovarian Cancer**

Agency **AETMIS, Agence d'évaluation des technologies et des modes d'intervention en santé**
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Reference Report prepared for AETMIS (AETMIS 06-02). Internet access to full text.
ISBN 2-5550-46358-7 (print), 2-550-46359-5 (PDF)

Aim

To clarify the contribution of BRCA1/2 molecular tests in risk assessment and genetic counseling of individuals and families with hereditary breast and ovarian cancer (HBOC).

Conclusion and results

This systematic literature review addresses: 1) prevalence and penetrance of BRCA1/2 mutations; 2) risk assessment models and testing indications; 3) clinical validity of molecular tests; and 4) the impact of molecular testing on risk assessment and genetic counseling. The Canadian Agency for Drugs and Technologies in Health (CADTH, formerly known as CCOHTA) also reviewed BRCA1/2 molecular testing. Its report addressed the analytical validity of molecular tests, the impact of molecular testing for clinical management, and psychosocial and ethical issues. The complementary nature of the work by AETMIS and CADTH researchers is clearly an asset, and conclusions must take both reports into account.

This report clarifies the nature of scientific evidence needed to underpin policy questions raised by the use of genetic testing technology and address unresolved questions and uncertainties. Important limitations in the evidence on prevalence, penetrance, and clinical validity include: the lack of a consensual definition of HBOC; the quality of study designs and reporting of data that are not up to epidemiological standards for molecular test evaluation studies; and variability in the study population selection criteria and molecular testing protocols.

The conceptual and empirical limitations in assessing clinical validity led to adopting an alternate definition and computational approach for clinical sensitivity of BRCA1/2 testing. This approach takes into account uncertainty regarding the true mutation status of test-negative families. Future research should rely on sound methodology (eg, avoiding selection biases) and concerted efforts across defined geographical areas, with agreed-upon selection criteria and testing indications, standardized techniques, monitoring of practices, and regular revision of strategies in the light of new data.

Genetic testing is recommended for high-risk families only, and there is general concordance for broadly defined risk factors (eg, early onset of breast cancer, male breast cancer). However, there is little consensus on the criteria to guide testing within these broad risk factors.

To support clinical decision making, different statistical models have been developed to estimate the probability of a BRCA1/2 mutation, or the risk of developing cancer. None of these models has been unanimously adopted in clinical practice.

Regarding its contribution to risk assessment, testing primarily benefits families in which a BRCA1/2 mutation has been discovered. In unaffected relatives who undergo testing and are found not to carry the mutation, breast cancer risk reduces from a high prior probability to a post-test risk comparable to that in the general population. Unaffected relatives who are found to carry the mutation are at substantially higher cancer risk than the general population.

Recommendations

None.

Methods

Systematic literature review.

Further research/reviews required

A followup AETMIS report is in preparation. It builds on the present work, the recent CADTH report, other systematic reviews, and AETMIS research on organizational and economic issues related to cancer genetics services.

Written by Julie Tranchemontagne, Lucy Boothroyd and Ingeborg Blancquaert, AETMIS, Canada

Title **Methods for Expected Value of Information Analysis in Complex Health Economic Models: Developments on the Health Economics of Beta Interferon and Glatiramer Acetate for Multiple Sclerosis**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
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Reference Health Technol Assess 2004;8(27). June 2004. www.ncchta.org/execsumm/summ827.htm

Aim

To develop methods to perform expected value of perfect information (EVPI) analysis in computationally expensive models and to report on the health economics of interferon-β and glatiramer acetate in managing multiple sclerosis (MS) using this methodological framework.

Conclusions and results

A review of metamodeling approaches suggested that the simpler techniques, eg, linear regression, may be easier to implement, but their predictive accuracy may be limited. More complex methods, eg, Gaussian process (GP) metamodeling and neural networks, tend to use less-restrictive assumptions about the relationship between model inputs and net benefits, and may be more accurate in estimating EVPIs. Assuming independent treatment efficacy, the *per patient* EVPI for all uncertainty parameters in the ScHARR MS model is GBP 8855. This leads to a population EVPI of GBP 86 208 936 (the upper estimate for the overall EVPI over 10 years). Assuming all treatment efficacies are perfectly correlated, the overall per patient EVPI is GBP 4271. This leads to a population EVPI of GBP 41 581 273 (the lower estimate for the overall EVPI over 10 years). The partial EVPI analysis, using both the linear regression metamodel and GP metamodel, suggests the need for further research on the long-term impact of these therapies on disease progression, the proportion of patients dropping off therapy, and the relationship between the expanded disability status scale (EDSS), quality of life, and cost of care.

Recommendations

The applied methodology points toward using more sophisticated metamodeling approaches to obtain greater accuracy in estimating EVPI. Programming requirements, software availability, and statistical accuracy should be considered when choosing metamodeling techniques. Simpler, more accessible techniques are open to greater predictive error. Sophisticated methodologies may enhance accuracy within non-linear models, but are more difficult to implement and may require specialist expertise. Only a few metamodeling techniques, including GP modeling, have been applied, their suitability for use in EVPI analysis is yet to be demonstrated.

Methods

A methodological framework was developed for undertaking EVPI analysis for complex models. The framework identifies conditions for calculating EVPI numerically, where the one-level algorithm sufficiently approximates the two-level algorithm, and whereby metamodeling techniques may accurately approximate the original simulation model. Metamodeling techniques, eg, linear regression, neural networks, and GP, were systematically reviewed and critically appraised. Linear regression metamodeling, GP metamodeling, and the one-level EVPI approximation were used to estimate partial EVPIs using the ScHARR MS cost-effectiveness model.

Further research/reviews required

Further clinical research is required on the relationship between the EDSS, costs of care and health outcomes, the rates at which patients drop off therapy, and the impact of disease-modifying therapies on MS progression. Further methodological research is indicated concerning inclusion of epidemiological population parameters in EVPI analyses, development of criteria for selecting a metamodeling approach, application of metamodeling techniques in EVSI information, and expected net benefit of sampling (ENBS) analyses.

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

Title **Coronary Artery Stents: A Rapid Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2004;8(35). September 2004.
www.hta.ac.uk/execsumm/summ835.htm

Aim

To assess the effectiveness and cost effectiveness of using coronary artery stents in patients with coronary artery disease (CAD).

Conclusions and results

The inclusion criteria were met by 50 randomized controlled trials comparing the use of stents with percutaneous transluminal coronary angioplasty (PTCA), 6 comparing stents with coronary artery bypass grafting (CABG), and 12 comparing drug eluting stents (DES) with non-DES. No studies were included that compared DES with PTCA or DES with CABG. Stents were found to be more effective than PTCA in preventing major adverse cardiac events and revascularizations. In multiple-vessel disease there was no evidence of a difference in mortality (at 1 year) between patients treated surgically and those receiving a stent. Patients treated surgically required fewer revascularizations. There is no evidence of a difference in mortality between patients receiving DES and those treated with bare metal stents (BMS) at 1 year. A reduction in event rate at 9 and 12 months was found in patients treated with DES. This event rate is primarily made up of increased revascularization rates in patients treated with BMS. Two-year outcome data from one study indicated that this benefit of DES continues over the longer term. Quality of life data suggest that revascularization procedures reduce the patient's quality of life for a short period only. The economic model indicated long-term trends in cost effectiveness. CABG was found initially to be more expensive than BMS in multivessel disease and may have higher immediate risks, but over time the cost differential is reduced and long-term outcomes favor CABG over stenting. A similar situation was found for DES versus CABG in multiple-vessel disease. DES might not be considered a cost-effective alternative to BMS in single-vessel disease by policy makers due to substantially higher costs and a small outcome benefit.

Recommendations

DES might be considered cost effective if the additional costs (compared with BMS) were substantially reduced, the outcome benefits with DES were much improved, and/or its use targeted subgroups of patients at greatest risk for reintervention. Long-term clinical studies are needed that focus on outcomes, eg, mortality.

Methods

The review followed accepted guidelines for systematic reviews. Randomized controlled trials were included that compared PTCA versus PTCA with stent, stent versus CABG, and DES versus non-DES in patients with CAD in native or graft vessels and those with stable angina or acute coronary syndrome and unstable angina. The review included data on the following outcome measures: combined event rate or event-free survival, death, acute myocardial infarction, target vessel revascularization, repeat treatment (by PTCA alone; PTCA and stenting or CABG), and binary restenosis. An economic model was based on extrapolation of trends in mortality and revascularization from clinical trials data to a 5-year time horizon.

Further research/reviews required

Further research should consider: differences among stents; head-to-head comparisons within DES, CABG compared with DES; and evaluation of newer non-DES against DES. Evaluation of the effects of revascularization procedures, especially repeat revascularization procedures, on quality of life would be useful, as would development and testing of risk assessment tools to identify patients likely to need further revascularizations.

Written by Dr Ruaraidh Hill, Liverpool Reviews and Implementation Group, University of Liverpool, UK

Title **Review of Guidelines for Good Practice in Decision-analytic Modeling in Health Technology Assessment**

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Reference Health Technol Assess 2004;8(36). September 2004.
www.ncchta.org/execsumm/summ836.htm

Aim

To identify existing guidelines and develop a synthesized guideline plus accompanying checklist, and to provide guidance on key theoretical, methodological, and practical issues and consider the implications of this research for what might be expected of future decision-analytic models.

Conclusions and results

Fifteen studies met the inclusion criteria and were reviewed and consolidated into a single set of brief statements of good practice. From this, a checklist was developed and applied to 3 independent decision-analytic models. The checklist provided guidance on key issues for model evaluation, but was too general to show the specific nuances of each model. Searches helped identify important data for inclusion in the model, but the quality of life searches were problematic, eg, the published search filters did not focus on those measures specific to cost-effectiveness analysis. Of the 11 studies meeting the criteria on the effect of selection bias, 5 concluded that a nonrandomized trial design is associated with bias and 6 studies found similar estimates of treatment effects from observational studies or nonrandomized clinical trials and randomized controlled trials (RCTs). One purpose of developing the synthesized guideline and checklist was to provide a framework for critical appraisal by the various parties assessing health technology (eg, the guideline and checklist can be used by groups that review other analysts' models, and by analysts to develop their models). The Expert Advisory Group (EAG) felt that the guidance and checklist would be useful, although the checklist should not be used as a substitute for critical appraisal in determining the quality of a model.

Recommendations

The review of current guidelines showed that although authors may provide a consistent message on some aspects of modeling, in other areas conflicting attributes are presented in different guidelines. Generally, the checklist appears to identify aspects of the model that should be of particular concern to the reader, but cannot identify the appropriateness of the model structure and structural assumptions. This is a general problem with generic checklists and does not reflect any shortcoming with the synthesized guidance and checklist developed here. The assessment of the checklist, and feedback from the EAG, indicated the importance of its use in conjunction with a more general checklist or guidelines on economic evaluation.

Methods

A systematic review of good practice guidelines aimed to identify and summarize the guidelines available to assess the quality of decision-analytic models used in health technology assessment. A synthesized good practice guidance and checklist were developed. Two topics in decision-modeling were considered, ie, identification of parameter estimates from published literature, and bias in parameter estimates. A systematic literature review identified studies concerning quantification of bias in parameter estimates and the implication of this bias.

Further research/reviews required

Research in the following areas would be valuable: the quantification of selection bias in noncontrolled studies and in controlled observational studies; the level of bias in the different non-RCT study designs; a comparison of results from RCTs with those from other nonrandomized studies; assessment of the strengths and weaknesses of alternative ways to adjust for bias in a decision model; and how to prioritize searching for parameter estimates.

Written by Laura Ginnelly, Centre for Health Economics, University of York, United Kingdom

Title **Clinical and Cost Effectiveness of Continuous Subcutaneous Insulin Infusion for Diabetes**

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Reference Health Technol Assess 2004;8(43). October 2004.
www.ncchta.org/execsumm/summ843.htm

Aim

To assess the clinical and cost effectiveness of continuous subcutaneous insulin infusion (CSII) compared with multiple daily injections (MDI) in the delivery of intensive insulin therapy for treatment of diabetes mellitus.

Conclusions and results

Twenty studies comparing CSII with MDI were identified. Quality was generally poor. In adults with Type 1 diabetes, glycated hemoglobin was lowered by 0.61% (95% CI –1.29 to 0.07) in longer term studies, but improvement was less when excluding a study using bovine ultralente. A reduction in insulin dose with CSII of about 12 units per day (–11.90, 95% CI –18.16 to 5.63) was found in short-term studies, with smaller differences in longer term studies. Body weight and cholesterol levels were similar between treatments. Hypoglycemic events did not differ significantly between CSII and MDI in most trials, but some found fewer events with CSII, and 1 found more hypoglycemia and hypoglycemic coma with CSII. The studies were inconsistent regarding patient preference, but progress has been made with insulin pumps and injector pens since publication of many of the older studies. No difference in glycated hemoglobin between CSII and MDI was found in pregnancy; 1 study found patients with CSII required less insulin, but 2 other studies found no significant difference. One study of adolescents found lower glycated hemoglobin and insulin dose with CSII, whereas a second study found no significant difference. In CSII, analogue insulin was associated with lower glycated hemoglobin levels than soluble insulin. No economic evaluations comparing CSII with MDI were identified. The estimated additional cost of CSII compared to MDI varies from GBP 1091 per year to GBP 1680 per year, according to the make of the insulin pump and its estimated life. These estimates include the costs for the insulin pump, CSII consumables, and the initial education for patients in switching from MDI to CSII. Consumables (eg, infusion sets) are the largest annual cost category for CSII.

Recommendations

Compared to optimized MDI, CSII shows a modest but worthwhile improvement in glycated hemoglobin in adults with Type 1 diabetes. Longer term benefits of such a difference in glycated hemoglobin have not been established, but it is expected to reduce long-term complications. More immediate primary benefits from CSII may relate to its impact on the incidence of hypoglycemic events and the dawn phenomenon, and greater flexibility of lifestyle. However, evidence is limited, and the quality-of-life information is based on testimonies from patients having a positive experience of CSII. The estimated cost to the NHS per year for CSII would be around GBP 3.5 million in England and Wales if 1% of people with Type 1 diabetes used CSII, GBP 10.5 million for 3%, and GBP 17.5 million for 5%.

Methods

Data sources included electronic databases, references of relevant articles, and contact with experts. Two reviewers used predefined criteria to assess the studies for inclusion in the systematic review. Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer. Data on clinical effectiveness were synthesized through a narrative review with full tabulation of all eligible studies, using meta-analysis where appropriate.

Further research/reviews required

Research should focus on wider benefits of CSII, eg, flexibility of lifestyle and quality of life, and on the psychological impact of wearing a device 24 hours every day. Research into the use of CSII in children of different ages is also needed.

Written by Dr Jill Colquitt, SHTAC, Wessex Institute for Health R&D, United Kingdom

Title **Clinical Effectiveness and Cost-Effectiveness of Drotrecogin Alfa (activated) (Xigris) for the Treatment of Severe Sepsis in Adults: A Systematic Review and Economic Evaluation**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
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Reference Health Technol Assess 2005;9(11). March 2005. www.hta.ac.uk/execsumm/summ911.htm

Aim

To assess the clinical and cost-effectiveness of drotrecogin alfa (activated) in treating adults with severe sepsis in a UK context.

Conclusions and results

The evidence came primarily from the PROWESS randomized controlled trial, which showed a statistically significant absolute reduction in 28-day mortality of 6.5%. Longer term survival benefit was maintained to 90 days. By 9 months, the trend toward increased median survival was nonsignificant, although the survival curves did not cross. Results presented by the number of organ dysfunctions were not statistically significant, but when mortality rates for those with two or more organ failures were combined, the relative risk of death was significantly lower in those treated with drotrecogin alfa (activated) compared with placebo. Cost-effectiveness studies of drotrecogin alfa (activated) treatment have used various methods to estimate benefits, estimating an incremental gain per treated patient (with severe sepsis) of 0.38 to 0.68 life-years. For patients with severe sepsis and multiple organ dysfunction, the manufacturer estimated an incremental gain of 1.115 life-years per treated patient, compared to 1.351 life-years estimated by the Southampton Health Technology Assessments Centre (SHTAC). Three cost-effectiveness studies in US and Canadian patient groups report that additional costs per patient treated range from USD 10 000 to 16 000 for patients with severe sepsis. Using 28-day survival data in patients with severe sepsis and multiple organ dysfunction, the manufacturer estimates an additional mean cost of GBP 5106 per treated patient. An analysis of UK patients with severe sepsis and multiple organ dysfunction estimates an additional mean cost of GBP 6661 per patient treated. The manufacturer's cost-effectiveness estimate for drotrecogin alfa (activated) in UK patients with severe sepsis and multiple organ dysfunction showed GBP 6637 per quality-adjusted life-year (QALY) based on 28-day effectiveness data, and GBP 10 937 per QALY based on longer term followup data. SHTAC developed an independent cost-effectiveness model and estimated a base-case cost per QALY of GBP 8228 in patients with severe sepsis and multiple organ failure (28-day survival data). Simulation results indicate that where the NHS is willing to pay GBP 20 000 per QALY, drotrecogin alfa (activated) is cost effective in 98.7% of cases.

Recommendations

For severe sepsis and severe sepsis with multiple organ failure in a UK context, drotrecogin alfa (activated) plus best supportive care is likely to be considered clinically and cost effective compared to best supportive care alone. Introducing drotrecogin alfa (activated) will add substantial costs to the NHS. Up to 16 570 patients could be eligible for treatment in England and Wales, with an estimated annual drug acquisition cost of over GBP 80 million, excluding VAT.

Methods

A systematic review of the literature and an economic evaluation were undertaken. Data were synthesized through a narrative review with full tabulation of results from included studies.

Further research/reviews required

Further research is required on the longer term impact of drotrecogin alfa (activated) on mortality and morbidity in UK patients with severe sepsis, on the clinical and cost effectiveness of drotrecogin alfa (activated) in children (under 18 years) with severe sepsis, and on the effect of the timing of dosage and duration of treatment on outcomes in severe sepsis.

Written by Mr Colin Green, SHTAC, Wessex Institute for Health R&D, United Kingdom

Title **A Methodological Review of How Heterogeneity Has Been Examined in Systematic Reviews of Diagnostic Test Accuracy**

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Reference Health Technol Assess 2005;9(12). March 2005.
www.hta.ac.uk/execsumm/summ912.htm

Aim

To review how heterogeneity has been examined in systematic reviews of diagnostic test accuracy studies.

Conclusions and results

The 189 systematic reviews that met the inclusion criteria included a median of 18 studies. Meta-analyses had a higher median number (22 studies) compared to narrative reviews (11 studies). Graphic plots showing the spread of study results were provided in 56% of meta-analyses; in 79% these were plots of sensitivity and specificity in the receiver operating characteristic (ROC) space. Statistical tests to identify heterogeneity were used in 32% of reviews: 41% of meta-analyses and 9% of reviews using narrative syntheses. The x2 test and Fisher's exact test to assess heterogeneity in individual aspects of test performance were most common. In contrast, only 16% of meta-analyses used correlation coefficients to test for a threshold effect. A narrative synthesis was used in 30% of reviews. Of the meta-analyses, 52% carried out statistical pooling alone, 18% conducted only summary ROC (SROC) analyses, and 30% used both methods. In SROC analyses, the main differences between the models used were the weights chosen for the regression models, although in 42% of cases the use, or choice, of weight was not provided. The proportion of reviews using statistical pooling alone declined from 67% in 1995 to 42% in 2001, with a corresponding increase in the use of SROC methods, from 33% to 58%. Two-thirds of those using SROC methods carried out statistical pooling rather than presenting only SROC models. Reviews using SROC analyses often presented results as a combination of sensitivity and specificity. Three-quarters of meta-analyses attempted to investigate statistically possible sources of variation, using subgroup or regression analysis. The impact of clinical or sociodemographic variables was investigated in 74% of these reviews and test- or threshold-related variables in 79%. At least one quality-related variable was investigated in 63% of reviews. Within this subset, the most common variables were the use of blinding, sample size, the reference test used, and the avoidance of verification bias.

Recommendations

The emphasis on pooling individual aspects of diagnostic test performance and the under-use of statistical tests and graphic approaches to identify heterogeneity might reflect uncertainty about the most appropriate methods to use and greater familiarity with more traditional indices of test accuracy. This indicates the complexity of performing such reviews. In these cases it is strongly suggested that a statistician familiar with the field should be involved in the meta-analyses.

Methods

Systematic reviews that evaluated a diagnostic or screening test by including studies that compared a test with a reference test were identified from DARE. Reviews with structured abstracts (up to December 2001) were screened for inclusion. Data extraction was undertaken using standardized data extraction forms.

Further research/reviews required

Further methodological work on the statistical methods for combining diagnostic test accuracy studies is needed, as are sufficiently large, prospectively designed, primary studies of diagnostic test accuracy comparing two or more tests for the same target disorder. Use of individual patient data meta-analysis in diagnostic test accuracy reviews should be explored to consider heterogeneity in more detail.

Written by Ms Jacqueline Dinnes, Wessex Institute for Health R&D, University of Southampton, United Kingdom

Title **Laparoscopic Surgery for Inguinal Hernia Repair: Systematic Review of Effectiveness and Economic Evaluation**

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Reference Health Technol Assess 2005;9(14). May 2005.
www.hta.ac.uk/execsumm/summ914.htm

Aim

To determine whether laparoscopic methods are more effective and cost effective than open mesh methods of inguinal hernia repair, and whether laparoscopic transabdominal preperitoneal (TAPP) repair is more effective and cost effective than laparoscopic totally extraperitoneal (TEP) repair.

Conclusions and results

Thirty-seven randomized controlled trials (RCTs) and quasi-RCTs met the inclusion criteria on effectiveness. The systematic review of economic evaluations included 14 studies. Laparoscopic repair (LR) was associated with an earlier return to usual activities, less persisting pain and numbness, and fewer cases of wound/superficial infection and hematoma. However, it was also associated with longer operation times and a higher rate of serious complications in respect of visceral (especially bladder) injuries. Initially, no difference was found in the hernia recurrence rate, but later inclusion of data from a large trial suggested that recurrences might be slightly more common after laparoscopic surgery. The review found LR to be about GBP 300 to 350 per patient more costly to the health service than open repair. The economic model also suggested that the LR techniques are more costly. Estimates of incremental cost per additional day at usual activities were between GBP 86 and GBP 130. Where productivity costs were included, they eliminated the cost differential between LR and open repair. The economic model showed that the incremental cost per QALY of LR compared with open mesh repair was likely to be less than GBP 20 000.

Recommendations

Open flat mesh appears to be the least costly option for managing unilateral hernias, but provides fewer quality adjusted life years (QALYs) than TEP or TAPP. (On average, TEP appears to be less costly and more effective than TAPP.) In managing symptomatic bilateral hernias, LR appears to be more cost effective. Taking into account possible repair of contralateral occult hernias, TEP repair is the most likely to be considered cost effective at threshold values for the cost per additional QALY of GBP 20 000, but conclusions are tentative. Laparoscopic techniques may allow patients to return to usual activities faster, and reduce loss of income. For the NHS, greater use of LR would increase the need for training, but perhaps also the risk of serious complications. Assessing chronic pain should be addressed prospectively, using standard definitions to measure the degree of pain. More evidence is needed on the utility loss caused by persisting pain and numbness, and on the risk of surgical complications. This might be best addressed by prospective population-based registries of new surgical procedures to complement randomized trials assessing relative effectiveness.

Methods

Dichotomous outcome data were combined using the relative risk method, and continuous outcomes were combined using the Mantel–Haenszel weighted mean difference method. Time to return to usual activities was described using hazard ratios derived from individual patient data meta-analysis. We updated a review of economic evaluations from 2001 and performed an economic evaluation. This involved estimating cost effectiveness, to compare LR with open flat mesh, using a Markov model with data from the systematic review (time horizon up to 25 years).

Further research/reviews required

- Changes in the balance of advantages and disadvantages when hernias are recurrent or bilateral.
- Methodologically sound RCTs to assess the relative merits and risks of TAPP and TEP.
- Methodological research on the complexity of laparoscopic groin hernia repair and the improvement of performance that accompanies experience.

Written by Professor Adrian Grant, Health Services Research Unit, University of Aberdeen, United Kingdom

Title **Clinical Effectiveness, Tolerability, and Cost Effectiveness of Newer Drugs for Epilepsy in Adults: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2005;9(15). May 2005.
www.hta.ac.uk/execsumm/summ915.htm

Aim

To examine the clinical effectiveness, tolerability, and cost effectiveness of gabapentin (GBP), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), tiagabine (TGB), topiramate (TPM), and vigabatrin (VGB) for epilepsy in adults.

Conclusions and results

The included systematic review reported that newer antiepileptic drugs (AEDs) were effective as adjunctive therapy compared to placebo. For newer versus older drugs, data were available for all 3 monotherapy AEDs, although data for OXC and TPM were limited. Sixty-seven RCTs compared adjunctive therapy with placebo, older AEDs, or other newer AEDs. For newer AEDs versus placebo, a trend was observed in favor of newer drugs, and there was evidence of statistically significant differences in proportion of responders favoring newer drugs. However, there was little good-quality evidence from clinical trials to support the use of newer monotherapy or adjunctive therapy AEDs over older drugs, or to support the use of one newer AED in preference to another. In general, data relating to clinical effectiveness, safety, and tolerability failed to demonstrate consistent and statistically significant differences between the drugs. The exception was comparisons between newer adjunctive AEDs and placebo, where significant differences favored newer AEDs. However, trials often had relatively short-term treatment durations and often failed to limit recruitment to either partial or generalized onset seizures, thus limiting the applicability of the data. Newer AEDs, used as monotherapy, may be cost effective in treating patients who have experienced adverse events with older AEDs, who have failed to respond to the older drugs, or where such drugs are contraindicated. The integrated economic analysis also suggested that newer AEDs used as adjunctive therapy may be cost effective compared to the current treatment alone given a QALY of about GBP 20 000.

Methods

Over 36 electronic databases and Internet resources were searched from inception to May/September 2002. Bibliographies of retrieved articles were searched and pharmaceutical company submissions examined for further studies. Two reviewers independently screened all titles and abstracts and decided on the inclusion/exclusion of studies based on fulltext articles. Data were extracted by one reviewer and checked by another. Two reviewers, using specified criteria, independently assessed the quality of included studies. Disagreements were resolved by discussion. Clinical effectiveness, adverse events, and cost effectiveness were assessed in separate analyses. An integrated economic analysis on the costs and effects of newer and older AEDs allowed direct comparisons of long-term costs and benefits.

Further research/reviews required

There is a need for more direct comparisons of AEDs in clinical trials, considering different treatment sequences in monotherapy and adjunctive therapy. Length of followup needs to be considered. Trials are needed that recruit patients with either partial or generalized seizures; that investigate effectiveness and cost effectiveness in patients with generalized onset seizures; and that investigate effectiveness in specific populations of epilepsy patients, and studies evaluating cognitive outcomes to use more stringent testing protocols and a more consistent approach in assessing outcomes. Further research is required to assess the quality of life in trials of epilepsy therapy using preference-based measures of outcomes that generate cost-effectiveness data. Future RCTs should use CONSORT guidelines and observational data to provide information on AEDs in actual practice, including details of treatment sequences and doses.

Written by Dr Carol Forbes, CRD, United Kingdom

Title **Clinical Effectiveness and Cost Effectiveness of Immediate Angioplasty for Acute Myocardial Infarction: Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2005;9(17). May 2005.
www.hta.ac.uk/execsumm/summ917.htm

Aim

To review the evidence on clinical and cost effectiveness of immediate angioplasty after myocardial infarction.

Conclusions and results

The results consistently showed an advantage of immediate angioplasty (percutaneous coronary intervention; PCI) over hospital thrombolysis. The updated meta-analysis showed that mortality is reduced by about one-third, from 7.6% to 4.9% in the first 6 months, and by about the same in studies of up to 24 months. Reinfarction is reduced by over half, from 7.6% to 3.1%. Stroke is reduced by about two-thirds, from 2.3% with thrombolysis to 0.7% with PCI, with the difference attributed to hemorrhagic stroke. Caution is needed in interpreting some of the older trials since changes (eg, increase in stenting and the use of the glycoprotein IIb/IIa inhibitors) may improve the results of PCI. Little evidence compares prehospital thrombolysis with immediate PCI. Research on thrombolysis followed by PCI, known as 'facilitated PCI', is under way, but results were unavailable. Much of the marginal mortality benefit of PCI over hospital thrombolysis may be lost if door-to-balloon time were more than an hour longer than door-to-needle time. Conversely, within the initial 6 hours, the later patients present, the greater the relative advantage of PCI. Results suggest that PCI is more cost effective than thrombolysis, providing additional benefits in health status at some extra cost. In the longer term, higher recurrence and reintervention rates in thrombolysis patients are expected to reduce the cost difference.

Recommendations

If both interventions were routinely available, the economic analysis favors PCI. However, few units in England could offer routine, immediate PCI services at present. The resource implications of starting such services would be considerable, but cannot be quantified without a detailed survey. However, they include both capital and revenue: an increase in catheter laboratory costs. The greatest problem concerns staffing, which would take years to resolve. A gradual incrementalist approach based on clinical networks, with transfer to centers that offer PCI, could be considered. An option in rural areas might be to promote an increase in prehospital thrombolysis, with PCI for thrombolysis failures.

Methods

For clinical effectiveness, a comprehensive review of randomized control trials (RCTs) was used for efficacy. A selection of observational studies, eg, case series or audit data, was used for effectiveness in routine practice. RCTs of thrombolysis were used to assess the relative value of prehospital and hospital thrombolysis. Observational studies were used to assess the representativeness of patients in the RCTs and to determine whether different groups have different capacity to benefit. Clinical effectiveness was synthesized through a narrative review with full tabulation of results of all included studies and a meta-analysis to provide a precise estimate of absolute clinical benefit. Effects of the growing use of stents were considered. Economic modeling used an NHS perspective to develop a decision-analytical model of cost effectiveness, focusing on short-term (6 months) opportunity costs.

Further research/reviews required

There is a need for data on the long-term consequences of treatment, the quality of life of patients after treatment, and the effects of PCI following thrombolysis failure.

Written by Norman Waugh for Aberdeen HTA Group, University of Aberdeen, United Kingdom

Title **Clinical and Cost Effectiveness of Newer Immunosuppressive Regimens in Renal Transplantation: A Systematic Review and Modeling Study**

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Reference Health Technol Assess 2005;9(21). May 2005.
www.hta.ac.uk/execsumm/summ921.htm

Aim

To examine the clinical and cost effectiveness of the newer immunosuppressive drugs for renal transplantation: basiliximab, daclizumab, tacrolimus, mycophenolate (mofetil and sodium), and sirolimus.

Conclusions and results

The newer immunosuppressant drugs (basiliximab, daclizumab, tacrolimus and MMF) consistently reduced the incidence of short-term (1-year) acute rejection compared with conventional immunosuppressive therapy. The independent use of basiliximab, daclizumab, tacrolimus and MMF was associated with a similar absolute reduction in 1-year acute rejection rate (approximately 15%). However, the effects of these drugs did not appear to be additive. Thus, the addition of one of these drugs to a baseline immunosuppressant regimen was likely to affect adversely the incremental cost effectiveness of the addition of another. The trials did not assess how the improvement in short-term outcomes, together with the side-effect profile associated with each drug, translated into changes in patient-related quality of life. The impact of the newer immunosuppressants on long-term graft loss and patient survival remains uncertain.

The absence of both long-term outcome and quality of life from trial data makes assessment of the clinical and cost effectiveness on the newer immunosuppressants contingent on modeling based on extrapolations from short-term trial outcomes. The choice of the most appropriate short-term outcome (eg, acute rejection rate or measures of graft function) for such modeling remains a matter of clinical and scientific debate. The decision to use acute rejection in the meta-model in this report was based on the findings of a systematic review of the literature of predictors of long-term graft outcome.

See the full report for a detailed description of the results from randomized controlled trials (RCTs) included in this systematic review and modeling study.

Recommendations

Only a small proportion of the RCTs identified in this review assessed patient-focused outcomes, eg, quality of life. Since immunosuppressive drugs have both clinical benefits and specific side effects, the balance of these harms and benefits could best be quantified through future trials using quality of life measures.

Methods

The review of clinical effectiveness followed explicit quality standards. Several sources were used to search for reviews and primary studies. Inclusion was based on predefined criteria. Data were extracted and quality-assessed. Each of the 5 company submissions to NICE contained cost-effectiveness models. A 3-stage critique of the company models was undertaken and included model checking, model description, and model rerunning.

Further research/reviews required

Most trials have been designed solely with drug licensing in mind, and are powered to examine short-term changes in clinical outcome (eg, acute rejection rate). Future trials need to include quality-of-life measures, examine effects in high-risk patients and children, and improve their reporting. Several issues in this area make RCTs potentially difficult to design and undertake (eg, comparing multiple therapies). Consideration should be given to collecting prospective observational outcome data on immunosuppressant regimens, possibly via a national registry.

Written by Dr Rod S Taylor, Dept of Public Health & Epidemiology, University of Birmingham, United Kingdom

INAHTA Briefs

Issue 2006/100

Title **A Systematic Review and Economic Evaluation of Alendronate, Etidronate, Risedronate, Raloxifene, and Teriparatide for the Prevention and Treatment of Postmenopausal Osteoporosis**

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Reference Health Technol Assess 2005;9(22). June 2005. www.hta.ac.uk/execsumm/summ922.htm

Aim

To evaluate the use of alendronate, etidronate, risedronate, raloxifene, or teriparatide to reduce the risk of osteoporotic fracture in postmenopausal women.

Conclusions and results

Ninety randomized controlled trials (RCTs) met the inclusion criteria. They related to 5 interventions (alendronate, etidronate, risedronate, raloxifene, and teriparatide) and 5 comparators (calcium, calcium plus vitamin D, calcitriol, hormone replacement therapy, and exercise), and placebo or no treatment. All 5 interventions reduce the risk of vertebral fracture in women with severe osteoporosis with adequate calcium intakes. However, none of these drugs has been demonstrated, by direct comparison, to be significantly more effective than either each other or the other active interventions reviewed in this report. The intervention costs of treating all osteoporotic women for 5 years were 900 to 1500 million British pounds (GBP) for alendronate, etidronate, risedronate, and raloxifene. The cost per QALY ratios fell dramatically with age. (See the full report for a detailed description of the cost per QALY of the interventions.)

Recommendations

Of the 5 interventions, only alendronate and risedronate show significant reductions in hip fracture using RCT data from postmenopausal women with low bone mineral density (BMD). In postmenopausal women unselected for low BMD, only raloxifene appeared to reduce the risk of vertebral fracture. None of the 5 interventions reduced the risk of nonvertebral fracture. All of the proposed interventions provided gains in QALYs compared to no treatment in women with sufficient calcium and vitamin D intakes. Estimated costs varied widely by intervention and differed markedly by age, with some interventions saving costs at higher age ranges in patients with a prior fracture.

Methods

Studies that met the review's entry criteria were eligible for inclusion in the meta-analyses, provided they reported fracture incidence. Meta-analysis used the random effects model. A model was constructed to estimate the cost effectiveness of osteoporosis interventions. The model calculated the number of fractures that occurred and provided the costs associated with osteoporotic fractures and QALY. Breast cancer was also modeled, as some interventions have been shown to affect the risk of this condition.

Further research/reviews required

A stronger evidence base is needed on the efficacy of fracture prevention in the very elderly. The results calculated for women aged 80 years assumed the applicability of results from RCTs (where a minority of patients were of this age). If this were not true, then the results would be markedly different. To assess accurately the true potential of raloxifene, reanalysis should be conducted using a dedicated breast cancer model. Results for women at the threshold of osteoporosis, and with a prior fracture that ignore these benefits, produced a high cost per QALY ratio (>GBP 70 000), which fell significantly (<GBP 40 000) when including the effect on breast cancer. The latter results cannot be guaranteed, owing to simplifying assumptions on the etiology, costs, and QALYs of breast cancer. The cost effectiveness of teriparatide depends on the assumed efficacy on hip fracture. Since the decrease is nonsignificant, a further trial is recommended to reduce the uncertainty in this parameter.

Written by Dr Matt Stevenson, ScHARR, University of Sheffield, United Kingdom

Title **Imatinib for the Treatment of Patients with Unresectable and/or Metastatic Gastrointestinal Stromal Tumors: Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2005;9(25). July 2005. www.hta.ac.uk/execsumm/summ925.htm

Aim

To assess the clinical and cost effectiveness of imatinib in treating unresectable and/or metastatic, KIT-positive, gastrointestinal stromal tumors (GISTs), relative to current standard treatments.

Conclusions and results

Evidence from published uncontrolled trials involving 187 patients, and from abstracts reporting similar uncontrolled trials involving 1700 patients, indicates that approximately 50% of imatinib-treated individuals with advanced GIST experience at least a 50% reduction in tumor mass. Although useful data are accumulating, it is not possible to predict which patients may respond in this way. Also identified were 15 studies where possible GIST patients had been treated with therapies other than imatinib or best supportive care. Imatinib-treated patients experienced relatively mild adverse effects. Overall, imatinib was well tolerated. Patients on the highest dose regimen may experience dose-limiting drug toxicity. The Novartis economic evaluation of imatinib for unresectable and/or metastatic GIST was assessed. A modified Novartis model estimated the cost per quality-adjusted life-year (QALY) in British pounds (GBP) at GBP 85 224 after 2 years, GBP 41 219 after 5 years, and GBP 29 789 after 10 years. The results from a new Birmingham model were also within the range of estimates from the modified Novartis model.

Methods

As there were no randomized trials that directly compared imatinib with the current standard treatment in patients with advanced GIST, this review included nonrandomized controlled studies, cohort studies, and case series that reported effectiveness results of treatment with imatinib and/or other interventions in patients with advanced GIST. The effectiveness assessment was based on a comparison of results from imatinib trials and results from studies of historical control patients. Economic evaluation was based mainly on an assessment and modification (when judged necessary) of a model submitted by Novartis.

Further research/reviews required

More emphasis should be placed on quality of life in trials involving patients with advanced malignancy. Adverse events should be reported to facilitate intertrial comparisons, and long-term followup of adverse events is needed. Patients diagnosed with GIST are a heterogeneous group. Subgroup analysis concerning which, if any, patient types respond better or worse to imatinib is needed. Many uncertainties surround imatinib prescription, eg, duration of treatment, dose, drug resistance, and the optimum time to give the drug. Ongoing trials may resolve some of these uncertainties, and ongoing trials on adjuvant therapy in patients with primary disease may answer the question of timing. Secondary research, eg, an update of this systematic review, is recommended when ongoing trials reach completion.

Written by Ms Jayne Wilson, Dept of Public Health and Epidemiology, University of Birmingham, United Kingdom

Title **The Effectiveness and Cost Effectiveness of Pimecrolimus and Tacrolimus for Atopic Eczema: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2005;9(29). July 2005.
www.hta.ac.uk/execsumm/summ929.htm

Aim

To consider the effectiveness and cost effectiveness of pimecrolimus for mild to moderate atopic eczema and tacrolimus for moderate to severe atopic eczema compared with current standard treatment in adults and children.

Conclusions and results

The pimecrolimus trial reports were of varying quality. However, when compared with a placebo (emollient), pimecrolimus was found to be more effective and to improve quality of life. Little evidence is available about pimecrolimus compared with topical corticosteroids. Compared with a placebo (emollient), both 0.03% and 0.1% tacrolimus were found to be more effective. Compared with a mild corticosteroid, 0.03% tacrolimus is more effective in children as measured by a 90% or better improvement in the Physician's Global Evaluation (PGE). Compared with potent topical corticosteroids, no significant difference in effectiveness is seen with 0.1% tacrolimus as measured by a 75% or greater improvement in the PGE. Minor adverse effects at the application site are common with tacrolimus. However, this did not lead to increased rates of withdrawal from treatment in trial populations. The PenTag economic model demonstrates a large degree of uncertainty, which was explored in both deterministic and stochastic analyses. This is the case for the cost effectiveness of pimecrolimus and tacrolimus in first- or second-line use compared with topical steroids. In all cases immunosuppressant regimes were estimated to be more costly than alternatives, and differences in benefits were small and uncertain.

Recommendations

Limited evidence from a small number of randomized controlled trials (RCTs) would suggest that pimecrolimus is more effective than placebo treatment in controlling mild to moderate atopic eczema. Although greater than for pimecrolimus, the evidence base for tacrolimus in moderate to severe atopic eczema is also limited. At both 0.1% and 0.03% potencies, tacrolimus appears to be more effective than the placebo treatment and mild topical corticosteroids. However, these are not the most clinically relevant comparators. Compared with potent topical corticosteroids, no significant difference was shown. Short-term adverse effects with both immunosuppressants are relatively common, but appear to be mild. Experience of long-term use of the agents is lacking, so the risk of rare but serious adverse effects remains unknown. No conclusions can be confidently drawn about the cost effectiveness of pimecrolimus or tacrolimus compared with active topical corticosteroid comparators.

Methods

The systematic review was carried out using standard methodological guidelines and a stringent quality assessment strategy. A state transition (Markov) model was developed to estimate the cost utility of tacrolimus and pimecrolimus separately, compared with current standard practice with topical corticosteroids, a) as first-line treatment and b) as second-line treatment. Pimecrolimus was also compared to emollients only.

Written by Dr Ken Stein, Peninsula TA Group, University of Exeter, United Kingdom

Title **The Clinical Effectiveness and Cost Effectiveness of Implantable Cardioverter Defibrillators: A Systematic Review**

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Reference Health Technol Assess 2005;9(36). September 2005.
www.hta.ac.uk/execsumm/summ936.htm

Aim

To review the clinical effectiveness and cost effectiveness of implantable cardioverter defibrillators (ICDs) for arrhythmias.

Conclusions and results

The review included 8 randomized controlled trials (RCTs), 2 systematic reviews, and 1 meta-analysis, all of which met the inclusion criteria. The RCTs varied in quality, with most trials having a Jadad quality score of 1/5 or 2/5, owing to the nature of comparing a device with drug therapy and the impossibility of double-blinding. Mortality was the outcome measure of interest, and was reported as all-cause mortality in most trials and sudden cardiac death in some trials. Eleven economic evaluations of ICDs for arrhythmias were identified. None were shown to have high internal and external validity. One unpublished study relevant to the UK was identified. The evidence suggests that ICDs reduce mortality in patients with: a) previous ventricular arrest or symptomatic sustained ventricular arrhythmias; b) no previous sudden cardiac episode or previous ventricular arrhythmia, but reduced left ventricular function due to coronary artery disease with asymptomatic nonsustained ventricular arrhythmia and sustained tachycardia that could be induced electrophysiologically; and c) severe left ventricular dysfunction (ejection fraction ≤30%) after myocardial infarction. Quality of life (QoL) data are inconsistent, but suggest that QoL is impaired in patients who received numerous shocks from implanted devices. Studies show that ICDs improve survival compared to drug treatment, but at considerably higher cost. In the published literature, incremental costs per life-year gained ranged from 27 000 US dollars (USD) to 213 543 Canadian dollars (CAD), and incremental cost per quality-adjusted life-year from USD 71 700 to USD 558 000.

Recommendations

The use of ICDs in the UK is increasing, but the technology remains underutilized compared with other developed countries. Extending the current indications to patients with prior myocardial infarction and depressed heart function would impact on costs and service provision.

Methods

A systematic review of the literature on clinical and cost effectiveness was undertaken. The Jadad criteria were used to assess the quality of selected RCTs, and criteria developed by the NHS Centre for Reviews and Dissemination were used to assess selected systematic reviews. Economic evaluations were quality assessed by their internal validity (ie, the methods used) using a series of relevant questions, and external validity (ie, generalizability of the economic study to the population of interest) by modified standard criteria. The clinical effectiveness and cost effectiveness of ICDs for arrhythmias were synthesized through a narrative review with full tabulation of results of all included studies.

Further research/reviews required

Further research is needed on the risk stratification of patients in whom ICDs are most likely to be clinically and cost effective. An evaluation of shock frequency on QoL is also required.

Written by Mrs Jackie Bryant, NCCHTA/Wessex Institute for Health R&D, Southampton, United Kingdom

Title **The Effectiveness and Cost Effectiveness of Dual-Chamber Pacemakers Compared with Single-Chamber Pacemakers for Bradycardia Due to Atrioventricular Block or Sick Sinus Syndrome: Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2005;9(43). Nov 2005. www.hta.ac.uk/execsumm/summ943.htm

Aim

To estimate the effectiveness and cost effectiveness of dual-chamber pacemakers versus single-chamber atrial or single-chamber ventricular pacemakers in treating bradycardia due to sick sinus syndrome (SSS) or atrioventricular block (AVB).

Conclusions and results

The searches retrieved 1 systematic review of effectiveness and cost effectiveness, 4 parallel-group, randomized controlled trials (RCTs), and 28 crossover trials. Dual-chamber pacing was associated with lower rates of atrial fibrillation, particularly in SSS, than ventricular pacing, and prevents pacemaker syndrome. Higher rates of atrial fibrillation were seen with dual-chamber pacing than with atrial pacing. Complications were more frequent in dual-chamber pacemaker insertion. The 5-year cost of a dual-chamber system, including cost of complications and clinical events, was estimated to be around 7400 British pounds (GBP). The overall cost difference between single and dual systems is not large over this period: about GBP 700 more for dual-chamber devices. The cost effectiveness of dual-chamber compared with ventricular pacing was estimated to be around GBP 8500 per quality-adjusted life-year (QALY) in AVB and GBP 9500 in SSS over 5 years, and around GBP 5500 per QALY in both populations over 10 years. Under more conservative assumptions, the cost effectiveness of dual-chamber pacing is around GBP 30 000 per QALY. Probabilistic sensitivity analysis showed that under the base-case assumptions, dual-chamber pacing is likely to be considered cost effective at willingness-to-pay levels that are generally considered acceptable by policy makers. In contrast, atrial pacing (applicable in SSS but not AVB) may be cost effective compared with dual-chamber pacing.

Recommendations

Dual-chamber pacing results in small, but potentially important, benefits in populations with SSS and/or AVB compared with ventricular pacemakers. Pacemaker syndrome is crucial in determining cost effectiveness, but difficult to quantify due to difficulties in standardizing diagnosis and measuring severity. Dual-chamber pacing is common in the UK, and recipients tend to be younger. Current evidence is insufficient to inform policy on specific groups that could benefit most from pacing with dual-chamber devices.

Methods

A systematic review was carried out of RCTs. Standard frameworks were used to appraise the quality of selected studies. Meta-analyses, using random effects models, were carried out where appropriate. Limited exploration of heterogeneity was possible. Two frameworks were used in critical appraisal of economic evaluations. A decision-analytic model was developed using a Markov approach to estimate the cost effectiveness of dual-chamber versus ventricular or atrial pacing over 5 and 10 years as cost per QALY. Uncertainty was explored using one-way and probabilistic sensitivity analyses.

Further research/reviews required

Further important research is under way. Outstanding research priorities include the economic evaluation of UKPACE studies on the classification, diagnosis, and utility associated with pacemaker syndrome and evidence on the effectiveness of pacemakers in children.

Written by Dr Ken Stein, Peninsula TA Group, University of Exeter, United Kingdom

Title **Clinical and Cost Effectiveness of Autologous Chondrocyte Implantation for Cartilage Defects in Knee Joints: Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2005;9(47). Dec 2005. www.hta.ac.uk/execsumm/summ947.htm

Aim

To support a review of the guidance issued by the National Institute for Health and Clinical Excellence (NICE) in December 2000 by examining clinical and cost effectiveness evidence on autologous cartilage transplantation.

Conclusions and results

Four randomized controlled trials (RCTs) and observational data from case series were included. The trials studied 266 patients and the observational studies up to 101 patients. Two studies compared autologous chondrocyte implantation (ACI) with mosaicplasty, the third compared ACI with microfracture, and the fourth compared matrix-guided ACI (MACI®) with microfracture. Followup was 1 year in one study, and up to 3 years in the remaining three studies. The first trial of ACI versus mosaicplasty found that ACI gave better results than mosaicplasty at 1 year. Overall, 88% had excellent or good results with ACI versus 69% with mosaicplasty. About half of the biopsies after ACI showed hyaline cartilage. The second trial of ACI versus mosaicplasty found little difference in clinical outcomes at 2 years. Disappointingly, biopsies from the ACI group showed fibrocartilage rather than hyaline cartilage. The trial of ACI versus microfracture also found only small differences in outcomes at 2 years. Finally, the trial of MACI versus microfracture contained insufficient long-term results, but the study does show the feasibility of doing ACI by the MACI technique. It also suggested that after ACI, it takes 2 years for full-thickness cartilage to be produced. Reliable costs per quality-adjusted life-year (QALY) could not be calculated owing to the absence of necessary data. Simple short-term modeling suggests that the quality of life gain from ACI versus microfracture would have to be between 70% and 100% greater over 2 years for it to be more cost effective within the GBP 20 000 to 30 000 per QALY cost-effectiveness thresholds. However, if the gains in quality of life could be maintained for a decade, increments relative to microfracture would only have to be 10%–20% greater to justify additional treatment costs within the cost-effectiveness band indicated above. Followup from the trials has been only up to 2 years, with longer term outcomes uncertain.

Recommendations

Evidence is insufficient to say that ACI is cost effective compared with microfracture or mosaicplasty. Longer term outcomes are required. Economic modeling suggests that ACI could be cost effective since it is more likely to produce hyaline cartilage, which is more likely to be durable and prevent osteoarthritis in the longer term (eg, 20 years).

Methods

Evidence on clinical effectiveness was obtained from randomized trials, supplemented by data from selected observational studies for longer term results and the natural history of chondral lesions. Because of a lack of long-term results on outcomes such as later osteoarthritis and knee replacement, only illustrative modeling was done.

Further research/reviews required

Further research is needed into earlier methods of predicting long-term results. Basic science research is also needed into factors that influence stem cells to become chondrocytes and to produce high-quality cartilage, as it may be possible to have more patients developing hyaline cartilage after microfracture. Study is also needed into cost-effective methods of rehabilitation and the effect of early mobilization on cartilage growth.

Written by Professor Norman Waugh, Dept of Public Health, University of Aberdeen, United Kingdom

Title **Systematic Review of Effectiveness of Different Treatments for Childhood Retinoblastoma**

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Reference Health Technol Assess 2005;9(48). December 2005.
www.hta.ac.uk/execsumm/summ948.htm

Aim

To provide the evidence base on clinical effectiveness of different treatments for childhood retinoblastoma, building on previous work completed in October 2003.

Conclusions and results

The review included 31 individual studies from 42 publications. Apart from 1 non-randomized controlled trial, only comparative studies of observational design were available for any of the treatments. Four of the included studies were prospective, and the remaining 27 were retrospective. Most of the studies were of radiotherapy or chemotherapy, with few studies available on enucleation or focal treatments such as brachytherapy, photocoagulation, cryotherapy, and thermotherapy. Methodological quality was generally poor, with a high risk of bias in all included studies. The main problems related to how treatment was allocated and lack of consideration of potentially confounding factors, eg, initial disease severity, in the study design and data analysis. The evidence base for effectiveness of treatments for childhood retinoblastoma is extremely limited. Owing to the limited evidence, it was not possible to make meaningful, robust conclusions about the relative effectiveness of different treatment approaches for childhood retinoblastoma.

Recommendations

In the authors' opinion, the evidence base for the effectiveness of treatments for childhood retinoblastoma is not sufficiently robust to provide clear guidance for clinical practice. While many of the studies reported high levels of treatment success, the relative effectiveness and adverse effects of treatment were unclear.

Methods

Seventeen databases were searched, up to April 2004. Two reviewers independently assessed studies for inclusion. Studies of participants diagnosed with childhood retinoblastoma, any interventions, and all clinical outcomes were eligible for inclusion. Randomized and non-randomized controlled trials and cohort studies with clear comparisons between treatment groups were included. Methodological quality was assessed, and a narrative synthesis was conducted. Where possible, studies assessing common interventions were grouped together, with prospective and retrospective studies grouped separately. Emphasis was placed on prospective studies.

Further research/reviews required

Ideally, good-quality, randomized controlled trials (RCTs) assessing the effectiveness of different treatment options for childhood retinoblastoma are required. Research is required on all the treatments currently used for this condition. Where RCTs are not feasible for ethical or practical reasons, only high-quality, prospective, non-randomized studies should be given consideration, owing to the generally higher risk of bias in retrospective studies. To reduce the risk of confounding due to allocation by clinical indication, studies should compare patients with similar disease severity rather than compare patients of mixed disease severities. Standardized outcomes should be agreed for use in studies assessing the effectiveness of treatment. These outcomes should encompass the potentially important beneficial effects and adverse effects of treatment, eg, loss of visual acuity and cosmetic outcome.

Written by Dr Catriona McDaid, CRD, University of York, United Kingdom

Title **The Effectiveness and Cost Effectiveness of Parent Training/ Education Programs for the Treatment of Conduct Disorder, Including Oppositional Defiant Disorder, in Children**

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Reference Health Technol Assess 2005;9(50). Dec 2005. www.hta.ac.uk/execsumm/summ950.htm

Aim

To assess the clinical and cost effectiveness of parent training programs in treating children with conduct disorder (CD) up to the age of 18 years.

Conclusions and results

Many of the 37 randomized controlled trials that met the inclusion and exclusion criteria lacked methodological detail. Studies were clinically heterogeneous as regards population, type of parent training/education program, and content, setting, delivery, length, and child behavior outcomes. Vote counting and meta-analysis revealed a consistent trend across all studies toward short-term effectiveness (up to 4 months) of parent training/education programs (compared with control) as measured by a change in child behavior. Pooled estimates showed a statistically significant improvement on the Eyberg Child Behavior Inventory frequency and intensity scales, the Dyadic Parent–Child Interaction Coding System and the Child Behavior Checklist. No studies reported a statistically significant result favoring control over parent training/education programs. There were few statistically significant differences between different parent training/education programs, although there was a trend toward more intensive interventions (eg, longer contact hours, additional child involvement) being more effective. The cost of treating CD is high, with costs incurred by many agencies. Criminality incurs the greatest cost, followed by education, foster and residential care, and state benefits. Only a small proportion of these costs fall on health services. Using a 'bottom-up' costing approach, the costs per family of providing parent training/education programs range from 629 to 3839 British pounds (GBP), depending on the type and style of delivery. Using the conservative assumption that there are no cost savings from treatment, a total lifetime gain of 0.1 in quality of life would give a cost per quality-adjusted life-year of between GBP 38 393 and GBP 6288 depending on program delivery and setting.

Recommendations

Parent training/education programs appear to be an effective and potentially cost-effective therapy for children with CD. However, the relative effectiveness and cost effectiveness of different models (such as therapy intensity and setting) require further investigation.

Methods

The effectiveness review identified and evaluated relevant studies. A quantitative synthesis of behavioral outcomes across trials was undertaken using 2 approaches: vote counting and meta-analysis. The economic analysis consisted of reviewing previous economic/cost evaluations of parent training/education programs and the economic information in sponsors' submissions; exploring in detail the costs of parent training/education programs; and a de novo modeling assessment of the cost effectiveness of parent training/education programs. The potential budget impact to the health service of implementing such programs was also considered.

Further research/reviews required

Further research is required on the impact of parent training/education programs on the quality of life for children with CD and their parents/carers, on longer term child outcomes, and on the effectiveness and cost effectiveness of different models of parent training/education programs.

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

Title **The Clinical and Cost Effectiveness of Donepezil, Rivastigmine, Galantamine, and Memantine for Alzheimer's Disease**

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Reference Health Technol Assess 2006;10(1). January 2006.
www.hta.ac.uk/execsumm/summ1001.htm

Aim

To review the best quality evidence on the clinical and cost effectiveness of donepezil, rivastigmine, and galantamine for mild to moderately severe Alzheimer's disease (AD) and of memantine for moderately severe to severe AD.

Conclusions and results

For mild to moderately severe AD, the study suggested that all 3 treatments were beneficial when assessed using cognitive outcome measures. Global outcome measures were positive for donepezil and rivastigmine, but mixed for galantamine. Results for measures of function were mixed for donepezil and rivastigmine, but positive for galantamine. Behavior and mood measures were mixed for donepezil and galantamine, but showed no benefit for rivastigmine. Two published RCTs of memantine were included, suggesting it is beneficial based on functional and global measurements. The effect of memantine on cognitive and behavior and mood outcomes is less clear. Literature on the cost effectiveness of donepezil, rivastigmine, and galantamine was dominated by industry-sponsored studies that varied in methods and results.

Of the 3 UK studies, 2 report donepezil as not cost effective. Cost-effectiveness analysis undertaken in this review suggests that the cost per quality-adjusted life-year (QALY) exceeds 80 000 British pounds (GBP) for donepezil. Treatment reduces the mean time spent in full-time care by 1.42 to 1.59 months (over a 5-year period). From 4 published cost-effectiveness studies, 2 UK studies report additional costs with rivastigmine treatment. Cost-effectiveness analysis undertaken in this review suggests that the cost per QALY exceeds GBP 57 000 for rivastigmine. Treatment reduces the mean time spent in full-time care by 1.43 to 1.63 months (over a 5-year period). From 5 published cost-effectiveness studies, 1 UK study reports a cost per QALY of GBP 8693 for 16 mg galantamine treatment and GBP 10 051 for 24 mg galantamine treatment. Cost-effectiveness analysis undertaken in this review suggests that the cost per QALY exceeds GBP 68 000 for galantamine. Treatment reduces the time spent in full-time care by 1.42 to 1.73 months (over a 5-year period). From 2 published cost-effectiveness studies, 1 reports on an analysis for the UK, finding that memantine treatment saves cost and delays disease progression. Our review did not model the cost effectiveness of memantine separately. However, where alternative parameter inputs on the cost structure and utility values were used in a reanalysis (industry model), the cost effectiveness ranged between GBP 37 000 and GBP 52 000 per QALY.

Recommendations

For donepezil, rivastigmine, and galantamine, the costs saved by reducing the mean time spent in full-time care do not adequately offset the costs of treatment to bring estimated cost effectiveness to levels generally accepted by NHS policy makers. It is difficult to draw conclusions on the cost effectiveness of memantine; it is suggested that further amendments to the potentially optimistic industry model (measure of effect) would offer higher cost per QALY estimates.

Methods

A systematic review of the literature and an economic evaluation were undertaken.

Further research/reviews required

Future research should address the quality of outcome measures, quality-of-life instruments for patients and carers, effects of interventions lasting beyond 12 months, comparisons of benefits between interventions, and predictions of disease progression.

Written by Dr Emma Loveman, SHTAC, Wessex Institute for Health R&D, United Kingdom

Title **The Clinical Effectiveness and Cost Effectiveness of Computed Tomography Screening for Lung Cancer: Systematic Reviews**

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Reference Health Technol Assess 2006;10(3). January 2006.
www.hta.ac.uk/execsumm/summ1003.htm

Aim

To examine the clinical and cost effectiveness of screening for lung cancer using computed tomography (CT) to assist policy making and to clarify research needs.

Conclusions and results

Twelve studies of CT screening for lung cancer were identified, including 2 randomized controlled trials (RCTs) and 10 studies of screening without comparator groups. The quality of reporting in these studies varied, but the overall quality was adequate. The 2 RCTs were short (1 year) and provided no evidence that screening improves survival or reduces mortality. The proportion of people with abnormal CT findings varied widely between studies (5–51%). False positives varied among countries, eg, in the USA there are more nodules due partly to prevalence of histoplasmosis. Hence, the generalizability of studies is an issue. The prevalence of lung cancer detected was between 0.4% and 3.2% (number needed to screen to detect one lung cancer = 31 to 249). Incidence rates of lung cancer were lower (0.1–1% per year). Detection of stage 1 and resectable tumors was high, 100% in some studies. Adverse events were poorly reported. Incidental findings of other abnormalities requiring medical followup were as high as 49%. The review included 6 full economic evaluations of population CT screening programs for lung cancer. The magnitude of cost-effectiveness ratios varied widely. None was set in the UK, and generalization was complicated by wide variation in the data used in different countries and a paucity of UK data for comparison. All 6 made the assumption that CT screening for lung cancer reduced mortality, but the evidence does not support that assumption. Absence of evidence of health gains from screening for lung cancer means that it is not feasible at this time to develop a reliable economic argument for CT screening for lung cancer in the UK. There is evidence of increased risk of lung cancer in some occupational groups, but the role of screening has not been demonstrated by the current studies.

Recommendations

The accepted National Screening Committee criteria are not currently met, with no RCTs, no evidence to support clinical effectiveness, and no evidence of cost effectiveness.

Methods

A systematic review was undertaken, and selected studies were assessed using the checklists and methods described in NHS Centre for Reviews and Dissemination (CRD) Report 4. Separate narrative summaries were done for clinical and cost effectiveness. Cost-effectiveness analysis resulting in a cost per quality-adjusted life-year was not feasible, but the main elements of such an appraisal were summarized and key issues relating to the evidence base were discussed.

Further research/reviews required

RCTs are needed to examine the effect of CT screening on mortality to determine the rate of positive screening and detected lung cancers. Research is needed on the natural history and epidemiology of screening-detected lung cancers, particularly small, well-differentiated adenocarcinomas, and the impact on quality of life. Increased collection is needed of UK health service data regarding resource use and safety data for lung cancer management and services. Research is needed into the feasibility and logistics of tracing people who have worked in industry where they were exposed to lung carcinogens.

Written by Dr Corri Black, Department of Public Health, University of Aberdeen, United Kingdom

INAHTA Briefs

Issue 2006/110

Title **Comparison of Conference Abstracts and Presentations with Full-Text Articles in the Health Technology Assessments of Rapidly Evolving Technologies**

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Reference Health Technol Assess 2006;10(5). Feb 2006. www.hta.ac.uk/execsumm/summ1005.htm

Aim

To assess the quality and use of data from conference abstracts and presentations in health technology assessments (HTAs), compared to the full-text articles, in relation to the development of technology assessment reviews (TARs).

Conclusions and results

Seven TAR groups completed and returned the survey. Five out of seven groups reported a general policy that included searching for and including studies available as conference abstracts/presentations. Policy and practice vary across TAR groups regarding searching for and inclusion of studies available as conference abstracts/presentations. There is also variation in the level of detail reported in TARs regarding the use of abstracts/presentations. Hence, TAR teams should be encouraged to state explicitly their search strategies for identifying conference abstracts and presentations, their methods for assessing these for inclusion, and how the data were used and their effect on the results. Comprehensive searching for trials available as conference abstracts/presentations is time consuming and may be of questionable value. However, there may be a case for searching for and including abstract/presentation data if, eg, other sources of data are limited. If conference abstracts/presentations are to be included, the TAR teams need to allocate additional time for searching and managing data from these sources. Incomplete reporting in conference abstracts and presentations limits the ability of reviewers to assess confidently the methodological quality of trials.

Recommendations

Where conference abstracts and presentations are considered for inclusion in the review, the TAR teams should increase their efforts to obtain further study details by contacting trialists. Where abstract/presentation data are included, reviewers should discuss the effect of including data from these sources. Any data discrepancies identified across sources in TARs should be highlighted and their impact discussed in the review. In addition, there is a need to carry out, eg, a sensitivity analysis with and without abstract/presentation data in the analysis.

Methods

Evidence for this research was obtained from a survey of TAR groups, an audit of published TARs, and case studies of selected TARs. Analyses of the survey and audit results are summarized in a descriptive and tabular format. Data from the case studies are presented descriptively and quantitatively. Sensitivity analyses compared the effect of inclusion of data from abstracts and presentations on the meta-analysis pooled effect estimates by including data from both abstracts/presentations and full papers, and data from only full publications, included in the original TAR. These analyses were then compared with meta-analysis of data from trials that have been published in full.

Further research/reviews required

Research is needed on the development of search strategies to identify studies available as conference abstracts and presentations in TARs. Since case studies in this report are limited, analyses should be repeated as more TARs accrue, or include the work of other international HTA groups.

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

Title **The Clinical Effectiveness and Cost Effectiveness of Newer Drugs for Children with Epilepsy. A Systematic Review**

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Reference Health Technol Assess 2006;10(7). March 2006.
www.hta.ac.uk/execsumm/summ1007.htm

Aim

To examine the clinical and cost effectiveness of newer antiepileptic drugs (AEDs) for epilepsy in children: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and vigabatrin.

Conclusions and results

The quality of the randomized controlled trial (RCT) data was generally poor. For each of the epilepsy subtypes considered in RCTs identified for this review (partial epilepsy with or without secondary generalization, Lennox-Gastaut syndrome, infantile spasms, absence epilepsy, and benign epilepsy with centrotemporal spikes), placebo-controlled trials provide some evidence that the newer agents tested are of some value in treating these conditions. Where active controls have been used, the limited evidence available does not indicate a difference in effectiveness between newer and older drugs. The data are not sufficient to inform a prescribing strategy for any of the newer agents in any of these conditions. No clinical evidence suggests that the newer agents should be considered as first-choice treatment in any form of epilepsy in children. Annual drug costs of the newer agents range from around 400 to 1200 British pounds (GBP), depending on age and concomitant medications. An AED that is ineffective or has intolerable side effects will only be used for a short period, and many patients achieving seizure freedom will successfully withdraw from drug treatment without relapsing. The results of the decision-analytic model do not suggest that the use of the newer agents in any of the scenarios considered is clearly cost effective but, similarly, do not indicate that they are clearly not cost effective.

Recommendations

The prognosis for children diagnosed with epilepsy is generally good, with a large proportion responding well to the first treatment. However, for those not responding well to treatment the clinical goal is to find an optimal balance between the benefits and side effects of treatment. For the newly, or recently, diagnosed population, the key question for the newer drugs is how soon they should be tried. The cost effectiveness of using these agents early, in place of older agents, will depend on the effectiveness and tolerability of these agents compared with the older agents. Evidence from the available trial data suggests that the newer agents are no more effective, but may be somewhat better tolerated than the older agents. Hence, the cost effectiveness for early use will depend on the trade off between effectiveness and tolerability, both in terms of overall (long-term) treatment retention and overall utility associated with effects on seizure rate and side effects. The date are insufficient available to estimate accurately the nature of this trade-off, either in terms of long-term treatment retention or utility. Better information is required from RCTs before any rational evidence-based prescribing strategy could be developed.

Methods

Studies were assessed for inclusion according to pre-defined criteria. Data extraction and quality assessment were also undertaken. A decision-analytic model was constructed to estimate the cost effectiveness of the newer agents in children with partial seizures, the only condition where there were sufficient trial data to inform a model.

Further research/reviews required

Diagnosis-specific decision-analytic models are required. Further research may be required to inform parameter values adequately with respect to epidemiology and clinical practice.

Written by Dr Josie Sandercock, Public Health & Epidemiology, University of Birmingham, United Kingdom

Title **Surveillance of Barrett's Esophagus: Exploring the Uncertainty Through Systematic Review, Expert Workshop, and Economic Modeling**

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Reference Health Technol Assess 2006;10(8). March 2006.
www.hta.ac.uk/execsumm/summ1008.htm

Aim

To assess what is known about the effectiveness, safety, affordability, cost effectiveness, and organizational impact of endoscopic surveillance in preventing morbidity and mortality from adenocarcinoma in patients with Barrett's esophagus.

Conclusions and results

No randomized controlled trials (RCTs) or well-designed nonrandomized controlled studies were identified, although two comparative studies and numerous case series were found. Reaching clear conclusions from these studies was impossible owing to lack of evidence supported by RCTs. Three cost-utility analyses of surveillance of Barrett's esophagus were identified, one of which built on a previous study by the same group. Both sets of authors used Markov modeling and confined their analysis to 50- or 55-year-old white men with gastroesophageal reflux disease (GORD) symptoms. As the models are American, there are almost certainly differences in practice from the UK. In a workshop, experts identified several key areas of uncertainty that need to be addressed. Our Markov model suggests that the base case scenario of endoscopic surveillance of Barrett's esophagus at 3-year intervals, with low-grade dysplasia surveyed yearly and high-grade dysplasia at 3-month intervals, does more harm than good when compared with no surveillance. Surveillance produces fewer quality-adjusted life-years (QALYs) for higher cost than no surveillance. Probabilistic analyses suggest it is unlikely that surveillance will be cost effective, even at relatively high levels of willingness to pay. A simulation showed that nonsurveillance continued to cost less and result in better quality of life than surveillance.

Recommendations

Current evidence is insufficient to assess the clinical effectiveness of surveillance programs of Barrett's esophagus. A lack of RCT data is the major deficiency. Available models and analyses of cost effectiveness suggest that surveillance programs either do more harm than good compared to no surveillance, or are unlikely to be cost effective at usual levels of willingness to pay.

Methods

Three strands of enquiry were used to address the aims of this report:

1. Systematic review of the effectiveness of endoscopic surveillance of Barrett's esophagus.
2. Workshop on surveillance of Barrett's esophagus.
3. Markov model to assess the cost effectiveness of a surveillance program compared with no surveillance and to quantify important areas of uncertainty.

Further research/reviews required

Future research should target the overall effectiveness of surveillance and the individual elements that contribute to a surveillance program, particularly the performance of the test and the effectiveness of treatment for Barrett's esophagus and adenocarcinoma of the esophagus. Of particular importance is to clarify the natural history of Barrett's esophagus.

Written by Ms Ruth Garside, Peninsula TA Group, University of Exeter, United Kingdom

Title **Systematic Review of the Effectiveness and Cost Effectiveness of 'HealOzone' for the Treatment of Occlusal Pit/Fissure Caries and Root Caries**

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Reference Health Technol Assess 2006;10(16). May 2006. www.hta.ac.uk/execsumm/summ1016.htm

Aim

To assess the effectiveness and cost effectiveness of HealOzone® (CurOzone USA Inc, Ontario, Canada) in managing pit and fissure caries, and root caries.

Conclusions and results

The complete HealOzone procedure involves direct application of ozone gas to the caries lesion on the tooth surface, the use of a remineralizing solution immediately after application of ozone, and the supply of a 'patient kit', which consists of toothpaste, oral rinse, and oral spray all containing fluoride. Five full-text reports and 5 studies published as abstracts met the inclusion criteria. The 5 full-text reports consisted of 2 randomized controlled trials (RCTs) assessing the use of HealOzone in managing primary root caries, of which only 1 was published in a journal, and 2 doctoral theses of 3 unpublished randomized trials assessing the use of HealOzone in managing occlusal caries. Of the abstracts, 4 assessed the effects of HealOzone in managing occlusal caries and 1 the effects of HealOzone in managing root caries. Overall, the quality of the studies was modest. In particular, there were concerns about the choice of statistical analyses. In most of the full-text studies, analyses were at the lesion level, ignoring the clustering of lesions within patients. The methodological concerns were sufficient to raise doubts about the validity of the findings. Evidence from RCTs was insufficient to judge the effectiveness of ozone in managing both occlusal and root caries. It was not possible to measure health benefits in terms of quality-adjusted life-years, due to uncertainties about the evidence of clinical effectiveness and the transient nature of the adverse events avoided. A model was designed, but owing to the limitations of the economic analysis, results are regarded as speculative.

Recommendations

Any treatment that preserves teeth and avoids fillings is welcome. However, the evidence on HealOzone is insufficient to conclude that it is an effective addition to the management and treatment of occlusal and root caries.

The economic analysis was constrained by the uncertainty over clinical effectiveness, and was done merely to illustrate the key factors involved in economic modeling. The long-term effects of HealOzone are unknown, and the assumption that reversed caries remains inactive may not be reliable.

Methods

A systematic review studied the effectiveness of HealOzone in managing tooth decay. A systematic review of economic evaluations of ozone for dental caries was also planned, but no suitable studies were identified. The economic evaluation included in the industry submission was critically appraised and summarized. An economic model was constructed to illustrate the possible cost-effectiveness aspects of HealOzone when used in addition to current management of dental caries.

Further research/reviews required

To make a decision on whether HealOzone is a cost-effective alternative to current preventive methods in managing dental caries, further research into its clinical effectiveness is required. Independent RCTs of the effectiveness and cost effectiveness of HealOzone in managing occlusal caries and root caries need to be properly conducted with adequate design, outcome measures, and methods for statistical analyses.

Written by Ms Miriam Brazzelli, Department of Clinical Neurosciences, University of Edinburgh, United Kingdom

Title **Methods of Treating Chronic Pain. A Systematic Review**

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Reference SBU Report 177/1+2, 2006. ISBN 91-85413-08-9, 91-85413-09-7.
Full text report in Swedish and summary and conclusions in English are available on www.sbu.se

Aim

This report presents the results of a systematic review of the scientific literature on methods for treating chronic pain. The review proceeded from the following questions:

- What methods are effective for treating patients with chronic pain?
- What is it like to live with chronic pain, and how does it affect day-to-day living?
- What health economic considerations are involved in treating patients with chronic pain?

Conclusions and results

The report concludes that effective treatment methods are available. However, the effect is often moderate, and symptoms reappear when treatment is discontinued. Scientific evidence supports multidisciplinary rehabilitation programs for chronic pain of musculoskeletal origin. Physical activity/training under the guidance of, eg, a physiotherapist, is also effective. Combination with cognitive and/or behavioral therapies will further enhance the effect. For neuropathic pain, there is evidence for the use of anticonvulsants, potent opioids, and topical capsaicin. Pharmacotherapy is often accompanied by negative side effects.

The societal costs of chronic pain are high. Some evidence suggests that multidisciplinary rehabilitation and physical activity/training are cost effective. However, further research is needed.

Recommendations

No recommendations.

Methods

Literature searches were performed in MEDLINE, the Cochrane Library, Cinahl, and PsychInfo. The report is a systematic review of randomized controlled trials on the effects and cost effectiveness of methods used in treating chronic pain conditions. Observational studies were also considered in assessing side effects and complications from treatment. Qualitative research was assessed regarding patients' experience of living with chronic pain. A chapter on ethical considerations is included.

Further research/reviews required

Areas identified as particularly important for future research include:

- long-term effects of chronic pain therapies
- impact of pain therapies on cost effectiveness and quality of life
- role of the patient in treatment
- potential value of tailoring special rehabilitation measures to specific groups of patients
- significance of the care setting as regards patient experiences, treatment outcomes, and the health economic considerations involved.

Written by Susanna Axelsson, SBU, Sweden

Title **Outcomes of Electrically Stimulated Gracilis Neosphincter Surgery**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
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Reference Health Technol Assess 2005;9(28). July 2005.
www.hta.ac.uk/execsumm/summ928.htm

Aim

To test the hypotheses:

1. That electrically stimulated gracilis neosphincter surgery (ESGNS) leads to a better quality of life (QoL) than continued medical management of anal incontinence, or the formation of a permanent stoma.
2. That the long-term costs of patient care following ESGNS are less than the costs of alternative management options, or are justifiable in terms of improved patient quality of life.

Conclusions and results

At 3 years after surgery, this third-party evaluation observed that nearly three fourths of all patients had a functioning neosphincter and nearly two thirds had a satisfactory continence outcome. However, half of those with satisfactory continence had ongoing bowel evacuatory difficulties, and many experienced continuing leg and groin pain.

Bowel-related QoL and continence, measured between 1 and 3 years after surgery improved significantly and in excess of 20% when compared with preoperative status in nearly two thirds of patients. These improvements in quality of life and symptoms were maintained in the smaller cohort of patients who reached 4 and 5 years of followup, although by then the success rate had fallen somewhat. Generic measures of QoL demonstrated small improvements at 2 years of followup and moderate and significant improvements at 3 years. Patients in the comparison arm of the study experienced no significant changes in symptoms, QoL, anxiety, or depression over a 2-year followup period. Addition of cross-sectional data from patients who underwent ESGNS at 3 other UK centers confirmed that findings for the patient-based and clinical outcome measures were consistent across all centers, although surgical techniques differed. Length of hospital stays and hospital costs were substantially greater at RLH than at any of 3 other centers, which may be explained by differences in surgical techniques and differences in case-mix.

Costs modeled over 25 years of followup suggested that for patients with prior fecal incontinence the decision to refer to ESGNS at RLH resulted in a cost-effectiveness ratio of about 40 000 British pounds (GBP) per quality adjusted life year (QALY) gained. Using inpatient care costs based on the 3 other UK centers, this value reduced to around GBP 30 000 per QALY gained. The choice of stoma for these patients resulted in a slightly higher cost than ESGNS.

For patients with prior stoma, referral to ESGNS at RLH resulted in a cost-effectiveness ratio of around GBP 15 000 per QALY gained, reducing to GBP 5000 per QALY gained when inpatient costs were based on the 3 other UK ESGNS centers. Cost-effectiveness ratios of around GBP 30 000 per QALY gained or less are generally regarded to be reasonably attractive in the UK NHS context.

Recommendations

One view of ESGNS is that negative outcomes and costs outweigh the improved continence achieved in two thirds of patients. An alternative view is that ESGNS deserves consideration as an option for patients who face a permanent stoma or must continue to live with a debilitating, socially disabling disorder. In any case, ESGNS should not be performed outside of experienced, multidisciplinary, specialist centers able to give life-long followup.

Methods

See Executive Summary link above.

Further research/reviews required

1. Independent study of long-term patient-based outcomes of sacral nerve stimulation.
2. Audit of centers performing artificial bowel sphincter (ABS) operations within the UK.
3. Further study of the effects of different surgical techniques on ESGNS outcomes.
4. Research into the reasons and possible treatment for disordered evacuation and groin and leg pain following ESGNS.

Written by Professor Roger Feldman, Emeritus Professor of Clinical Epidemiology, United Kingdom

Title **Longer Term Clinical and Economic Benefits of Offering Acupuncture Care to Patients with Chronic Low Back Pain**

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Reference Health Technol Assess 2005;9(32). August 2005.
www.hta.ac.uk/execsumm/summ932.htm

Aim

To test the hypothesis that patients with persistent non-specific low back pain (LBP), when offered traditional acupuncture care alongside conventional primary care, gained more long-term pain relief than those offered conventional care only, for equal or less cost; and to monitor safety and acceptability of acupuncture and to assess the evidence for an 'acupuncturist effect'.

Conclusions and results

The trial included 159 patients in the *acupuncture* arm and 80 in the *usual care* arm. Patients randomized to acupuncture received 8 treatments (average). Analysis of covariance, adjusting for baseline score, found an effect size of 5.6 points on the SF-36 Pain dimension in favor of the acupuncture group at 12 months, and 8.0 points at 24 months. No evidence of heterogeneity of effect was found for different acupuncturists. Sixteen patients dropped out of acupuncture treatment. No significant treatment effect was found for any of the SF-36 dimensions other than Pain, or the Present Pain Index, or the Oswestry Pain Disability Questionnaire. The acupuncture group reported a significantly greater reduction in worry about back pain at 12 and 24 months compared to the usual care group. At 24 months, the acupuncture group was significantly more likely to report that they had been pain free for the past 12 months and less likely to report use of medication for pain relief in the past month. Over 2 years, the direct NHS costs (discounted) were greater in the acupuncture group. However, acupuncture was found to be cost effective at 24 months.

Recommendations

Traditional acupuncture delivered in a primary care setting is safe and acceptable to patients with non-specific LBP. Acupuncture and usual care both showed clinically significant improvement at 12- and 24-month followup. Acupuncture is significantly more effective in reducing pain than usual care at 24 months. General practitioner (GP) referral to traditional acupuncture care offers a cost-effective intervention for reducing LBP over a 2-year period. Commissioners of musculoskeletal services would be justified in considering making GP referral to a short course of traditional acupuncture care available for a typical primary care population with persistent non-specific LBP.

Methods

The study was a pragmatic, two parallel group, randomized controlled trial (n=241) involving 3 non-NHS acupuncture clinics, with referrals from 39 GPs in York, UK.

Further research/reviews required

- Assess the impact of traditional acupuncture on the persistence and recurrence of LBP compared with other short-term care delivered for non-acute LBP.
- Investigate the optimum timing of acupuncture treatment for LBP, and assess the value of repeated courses of acupuncture.
- Explore the underlying causes and mechanisms for continued improvement of patients with LBP receiving a short course of traditional acupuncture.
- Distill a protocol for traditional acupuncture for LBP that allows delivery of individualized treatment while defining care that represents value for money, reliability, and safety.
- Compare cost effectiveness of different modes of short-term acupuncture for non-acute LBP, eg, acupuncture by physiotherapists in a primary care setting.
- (See full report for additional items).

Written by Professor Kate Thomas, University of Leeds, United Kingdom

Title **A Systematic Review of the Effectiveness and Cost-Effectiveness of Neuroimaging Assessments Used to Visualize the Seizure Focus in People with Refractory Epilepsy Being Considered for Surgery**

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Reference Health Technol Assess 2006;10(04). Feb 2006. www.hta.ac.uk/execsumm/summ1004.htm

Aim

To review: the effectiveness and/or accuracy of different methods to image the cerebral cortex to visualize the seizure focus in people with refractory epilepsy being considered for surgery; the ability of different neuroimaging techniques to predict post-surgical outcomes; and the cost effectiveness of imaging the cerebral cortex to visualize the seizure focus in people with refractory epilepsy being considered for surgery.

Conclusions and results

No RCTs were identified. Most studies evaluated the diagnostic accuracy of various imaging techniques in localizing epileptic seizure foci and were generally of poor quality. The included studies investigated the following imaging techniques: SPECT (39 studies, 68 evaluations); MRI (30 studies, 40 evaluations); PET (18 studies, 25 evaluations); SISCOM (7 studies, 11 evaluations); MRS (6 studies); CT (5 studies); NIRS (1 study); combinations of more than one test (3 studies). We found no studies evaluating fMRI or diffusion tensor imaging. It was difficult to draw any overall conclusions regarding the accuracy of any imaging technique due to the differences between studies. Test performance was more promising in studies restricted to patients with temporal lobe epilepsy. Ictal SPECT generally had more correctly localizing and fewer non-localizing scans than other techniques evaluated. Results for CT and inter-ictal SPECT suggest that these tests are relatively poor at localizing the seizure focus. Results for volumetric MRI and PET appear promising, but have been assessed in fewer studies than ictal SPECT. SISCOM and MRS have been assessed in fewer studies, but results are less promising than ictal SPECT. T2 relaxometry was reported in only one small study with inconclusive results.

Nine studies used multivariate analysis to investigate the association of various imaging techniques with the outcome following surgery. The imaging techniques evaluated included MRI (7 studies), MRS and volumetric MRI (1 study), PET (3 studies), SPECT (1 study) and SISCOM (3 studies). There was a trend for positive localization of abnormalities to be associated with a beneficial outcome.

Recommendations

Due to the limitations of the included studies, the results of this review do little to inform clinical practice. Studies investigating the prognostic importance of imaging results for the outcome following epilepsy surgery suggest that abnormalities on imaging are associated with a better clinical outcome. However, the data do not allow an accurate prediction for patient outcome.

Methods

A systematic review was undertaken according to published guidelines. Studies were identified by searching electronic databases, Internet searches, handsearching, scanning reference lists of included papers, and consultation with experts. Two reviewers screened titles and abstracts for relevance. Full papers of potentially relevant studies were obtained and assessed for inclusion by one reviewer and checked by a second. Published and unpublished studies in any language were eligible for inclusion. Data extraction and quality assessment were performed by one reviewer and checked by a second.

Further research/reviews required

- Investigate the utility of imaging techniques in the workup for epilepsy surgery.
- RCTs to examine the influence of single tests or combinations of tests on patient outcomes. Health economic data could be collected in parallel, allowing a thorough examination of cost effectiveness.
- We suggest that it is important that clinicians, patient groups, policy makers and healthcare/research funders meet and debate the most appropriate way to investigate these technologies.

Written by Dr Carol Forbes, CRD, United Kingdom

Title **Screening for Thrombophilia in High-Risk Situations: Systematic Review and Cost-Effectiveness Analysis**

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Reference Health Technol Assess 2006;10(11). April 2006.
www.hta.ac.uk/execsumm/summ1011.htm

Aim

- To assess the risk of clinical complications associated with thrombophilia in 3 high-risk patient groups: 1) women who are prescribed oral estrogen preparations, 2) pregnancy and the puerperium, 3) patients undergoing major orthopedic surgery.
- To assess the effectiveness of prophylactic treatments in preventing venous thromboembolism (VTE) and adverse pregnancy outcomes in women with thrombophilia during pregnancy and VTE events in patients with thrombophilia undergoing major orthopedic surgery.
- To evaluate the cost effectiveness of universal and selective VTE history-based screening for thrombophilia compared with no screening.

Conclusions and results

Four screening scenarios were assessed: 1) testing women prior to prescribing combined oral contraceptives and restricting prescribing to those tested negative for thrombophilia; 2) testing women prior to prescribing hormone replacement therapy and restricting prescribing to those tested negative for thrombophilia; 3) testing women at the onset of pregnancy and prescribing prophylaxis to those tested positive for thrombophilia; 4) testing all patients prior to major orthopedic surgery and prescribing extended thromboprophylaxis to those tested positive for thrombophilia.

Thrombophilia is associated with increased risks of VTE in women taking oral estrogen preparations, patients undergoing major elective orthopedic surgery, and adverse outcomes in pregnancy. There is considerable difference in the magnitude of the risks among different patient groups with different thrombophilic defects. Findings from this study show that selective screening based on prior VTE history is more cost effective than universal screening.

Irrespective of patient groups, selective screening based on the presence of previous personal or family history of VTE prevented fewer cases of adverse clinical complications, but was more cost effective than universal screening in all 4 screening scenarios.

Recommendations

Universal thrombophilia screening in women prior to prescribing oral estrogen preparations, in women during pregnancy, and in patients undergoing major orthopedic surgery should not be advocated. Findings from this study show that selective screening based on prior VTE history is more cost effective than universal screening.

Methods

Systematic review and meta-analyses were conducted to:

1. Establish the risk of clinical complications associated with thrombophilia in women who use oral estrogen therapy, women who are pregnant, and patients undergoing major orthopedic surgery.
2. Assess the effectiveness of prophylactic treatments in preventing VTE and adverse pregnancy outcomes in women with thrombophilia during pregnancy and VTE events in patients with thrombophilia undergoing major orthopedic surgery.

An incremental cost-effectiveness analysis was conducted, from the perspective of the NHS in the UK. A decision analytical model was developed to simulate the clinical consequences of four thrombophilia screening scenarios.

Further research/reviews required

- Refine the risks and establish the associations of thrombophilias with VTE among hormone users and inpatients undergoing orthopedic surgery.
- Establish the relative value of a thrombophilia screening program to other healthcare programs.

Written by Professor Ian A Greer, University of Glasgow, United Kingdom

Title **Randomized Clinical Trial, Observational Study and Assessment of Cost-Effectiveness of the Treatment of Varicose Veins (REACTIV Trial)**

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Reference Health Technol Assess 2006;10(13). May 2006.
www.hta.ac.uk/execsumm/summ1013.htm

Aim

To establish the cost effectiveness of surgery and sclerotherapy in treating varicose veins.

Conclusions and results

Of the randomized controlled trials (RCTs), only the Group 3 trial was large enough to provide clear results. This showed that surgical treatment produced better results than conservative treatment in terms of quality of life, symptomatic relief, anatomical extent, and patient satisfaction. The observational study showed no significant differences in outcomes from the RCTs, with no major complications from sclerotherapy and a complication rate of 1.7% following surgery. Clinical outcomes of surgery and sclerotherapy showed significant improvement in the extent of varicose veins, symptomatic, and quality of life parameters.

Cost-effectiveness analysis based on the Group 3 trial showed that the surgery produced an estimated discounted benefit of 0.054 QALY over a 2-year period, with an additional discounted cost of 387.45 British pounds (GBP), giving an incremental cost effectiveness ratio (ICER) of GBP 7175 per QALY. Economic modeling suggested that surgery produced a still greater benefit when considered with a 10-year time horizon, with an ICER of GBP 1936 per QALY. Injection sclerotherapy produced an incremental benefit of approximately 0.044 QALY at a cost of GBP 155 when compared to conservative treatment, giving an ICER of GBP 3500 per QALY. When surgery was compared with sclerotherapy, surgery produced greater benefit with a lower ICER (showing extended dominance). These findings were robust over a range of univariate and multivariate sensitivity analyses, covering different assumptions, and estimates of probabilities, costs, and outcomes.

Recommendations

Standard surgical treatment of varicose veins by high ligation, stripping, and multiple phlebectomies is an effective and cost-effective treatment for varicose veins, with an ICER well below the threshold of about GBP 25 000 to GBP 35 000 per QALY normally considered appropriate for funding of treatments within the NHS. Injection sclerotherapy would also appear to be cost effective, but produces less overall benefit, with a higher ICER than surgery for patients with superficial venous reflux. In minor varicose veins without reflux, sclerotherapy is likely to provide a small average benefit with acceptable cost effectiveness.

Methods

Randomized controlled trials have been done of conservative treatment, sclerotherapy, and surgery for varicose veins, supplemented by observational data collection in those patients who had exclusion criteria or declined participation in the RCTs. An economic analysis was carried out alongside the randomized trial. Additional data were collected via an observational study for those patients who had exclusion criteria or declined participation in the RCTs. Economic modeling was undertaken based upon the primary data collection and a literature review.

Further research/reviews required

One of the key issues in calculating cost effectiveness is the difficulty in evaluating the potential utility benefit of successful treatment in this condition. Research is needed into the methodology for producing accurate and acceptable utility evaluations for conditions with relatively minor effect on quality of life. The study demonstrates the difficulty of large RCTs in this area. It is suggested that economic modeling combined with the collection of observational data may provide a useful approach in assessing the potential of new treatments for this condition.

Written by Professor J A Michaels, Sheffield Vascular Institute, United Kingdom

Title **Measurement of the Clinical and Cost Effectiveness of Non-Invasive Diagnostic Testing Strategies for Deep Vein Thrombosis**

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Reference Health Technol Assess 2006;10(15). May 2006.
www.hta.ac.uk/execsumm/summ1015.htm

Aim

- To estimate the diagnostic accuracy of non-invasive tests for proximal deep vein thrombosis (DVT) and isolated calf DVT in patients with suspected DVT or high-risk asymptomatic patients, and identify factors associated with diagnostic variations.
- To identify practical diagnostic algorithms for DVT, and estimate their diagnostic accuracy, clinical effectiveness, and cost effectiveness.

Conclusions and results

Individual clinical features are of limited diagnostic value, with most likelihood ratios being close to one. Wells clinical probability score stratifies proximal, but not distal, DVT into high, intermediate, and low risk. Unstructured clinical assessment by experienced clinicians may have similar performance to Wells score. In patients with clinically suspected DVT, D-dimer has 90% sensitivity and 55% specificity for DVT, although performance varies. D-dimer specificity depends on pretest clinical probability, being higher in patients with a low clinical probability of DVT. Plethysmography and rheography techniques have modest sensitivity for proximal DVT, poor sensitivity for distal DVT, and modest specificity. Ultrasound has 95% sensitivity for proximal DVT, 65% sensitivity for distal DVT, and specificity of 94%. CT scanning has sensitivity of 95% for all DVT (proximal and distal combined) and specificity of 97%. MRI scanning has sensitivity of 92% for all DVT and specificity of 95%. The diagnostic performance of all tests is worse in asymptomatic patients.

The most cost-effective algorithm discharged patients with a low Wells score and negative D-dimer without further testing, and then used plethysmography alongside ultrasound to diagnose the remaining patients. The cost effectiveness of this algorithm depended on certain assumptions. Plethysmography and venography are limited in the UK, so implementation would involve reorganizing services.

Two algorithms offered high net benefit and would be feasible in most hospitals, without substantial reorganization. Both involved a combination of Wells score, D-dimer, and above-knee ultrasound. For willingness-to-pay thresholds of GBP 10 000 or 20 000 the optimal strategy involved discharging patients with a low or intermediate Wells score and negative D-dimer, ultrasound for those with a high score or positive D-dimer, and repeat scanning for those with positive D-dimer and a high Wells score but negative initial scan. A similar strategy, but repeat ultrasound after a negative initial scan, was optimal at thresholds of GBP 30 000 and above.

Recommendations

Diagnostic algorithms based on a combination of Wells score, D-dimer, and ultrasound (with repeat if negative) are cost effective and feasible. Use of repeat scanning depends upon our threshold for willingness-to-pay for health gain. Further diagnostic testing of patients with a low Wells score and negative D-dimer is unlikely to be cost effective.

Methods

Diagnostic test data and diagnostic algorithms were sought from electronic database searches, 1966–2004; diagnostic test data were sought from bibliographies and manufacturers of assays and instruments; and a postal survey of UK hospitals identified current practice, test availability, and additional diagnostic algorithms. (See full report for details).

Further research/reviews required

1. Evaluate costs and outcomes of using the optimal diagnostic algorithms in routine practice.
2. Develop and evaluate algorithms for specific patient groups with suspected DVT.
3. Evaluate the role of plethysmography.
4. Methodological research on incorporating meta-analytic data into decision-analysis modeling.

Written by Dr Steve Goodacre, University of Sheffield, United Kingdom

Title **Diagnostic Tests and Algorithms Used in the Investigation of Hematuria: Systematic Reviews and Economic Evaluation**

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Reference Health Technol Assess 2006;10(18). June 2006.
www.hta.ac.uk/execsumm/summ1018.htm

Aim

To determine most effective diagnostic strategy to investigate microscopic and macroscopic hematuria in adults.

Conclusions and results

No studies of effectiveness of diagnostic tests or algorithms were identified.

Diagnostic accuracy studies: *Detection of hematuria;* 18 studies evaluated dipsticks. These are moderately useful in detecting, but cannot be used to rule-out, hematuria. *Hematuria as a test for the presence of a disease;* 6 studies indicated that detection of microhematuria alone is not useful either to rule-in or rule-out underlying pathology. *Further investigation to establish the underlying cause of hematuria;* 48 studies addressed localization of bleeding to a glomerular or non-glomerular source.

Our model for detecting hematuria found that immediate microscopy following a positive dipstick improved diagnostic efficiency. Modeling upper tract imaging indicated that ultrasound (U/S) detects more tumors than IVU at one-third cost and fewer false results. For any cause, CT had a mean incremental cost-effectiveness ratio of 9939 British pounds (GBP) compared to U/S. U/S followed by CT (negative results and persistent hematuria) dominates CT alone (saving of GBP 235 000 for 1000 patients). Immediate cystoscopy could be avoided in some patients undergoing lower tract investigations by using tumor markers/cytology, with cystoscopy for followup patients with persistent hematuria, saving GBP 491 000. Except for imaging strategies, the results were generally robust to sensitivity analyses. Delayed detection was not evaluated.

Recommendations

The data are insufficient to derive an evidence-based algorithm of the diagnostic pathway for hematuria. An algorithm based on opinion and practice of clinical experts in review teams, other published algorithms, and results of economic modeling, is presented. The ideas contained in this algorithm and specific questions outlined should form the basis of future research.

Methods

This systematic review followed published guidelines. Decision analytic modeling was undertaken. Studies were identified through searches of electronic databases and handsearching. Two reviewers independently screened titles/abstracts for relevance. Relevant papers were assessed by one reviewer and checked by a second. Published and unpublished studies in any language were eligible. Separate inclusion criteria were derived for each objective, and data were extracted using standardized forms. A second reviewer checked diagnostic accuracy studies. Quality was evaluated using published checklists and criteria. Results were analyzed according to test grouping and clinical aim of studies. (See full report for detailed description of the analysis.)

Further research/reviews required

Future studies should follow the STARD guidelines for reporting of diagnostic accuracy studies. Questions for future research include: Is screening for hematuria effective? Is investigation of the cause of hematuria effective? Which patients with asymptomatic macrohematuria need full investigation? Is there a subset of patients who require fewer or no further investigations? (See full report for other questions.) Areas where further research may be useful are: accuracy of dipstick tests in detecting hematuria; factors that affect the performance of urine cytology; diagnostic accuracy of tumor markers; and the cumulative diagnostic effect of imaging studies.

Written by Mr Mark Rodgers, University of York, United Kingdom

Title **CT and MRI for Selected Clinical Disorders: A Systematic Review of Economic Evaluations**

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Reference CADTH Technology Report, Issue 68, August 2006. ISBN 1-894978-88-9 (print).
Full text available: www.cadth.ca/media/pdf/350_diagnostic_imaging_tr_e_FINAL_Full.pdf

Aim

To summarize the evidence on the cost effectiveness of CT and MRI in investigating specific clinical conditions of the chest, cardiovascular, neurological, and urological systems.

Conclusions and results

The studies included in this review suggest that CT or MRI are effective for some conditions (especially for peripheral vascular disease and stroke), but they are not necessarily more effective or cost effective than traditional alternatives (for peripheral vascular disease). For other conditions, the evidence of cost effectiveness appears positive, but limited (renal artery stenosis and mild head injuries). The evidence for effectiveness or cost effectiveness of CT or MRI for lung cancer screening, pulmonary embolism, carotid artery disease, and cerebral aneurysms is equivocal or conflicting.

Recommendations

Not applicable.

Methods

Published economic evaluations were systematic identified by searching multiple databases using a defined strategy and selection criteria. Of 423 potentially relevant economic evaluations, 21 studies of 8 clinical conditions were identified: peripheral vascular disease, renal artery stenosis, lung cancer screening, pulmonary embolism, carotid artery disease, cerebral aneurysms, head injuries, and stroke. No economic studies addressed coronary artery disease, headaches, seizures, arteriovenous malformations, or urinary tract calculi screening.

Further research/reviews required

The indications for CT and MRI, and their performance compared with earlier generations of the same technologies, are advancing faster than the available literature. Hence, this report could be dated in some areas. Years after CT and MRI techniques have come into use it remains difficult to find high-quality studies that address their use. No studies were found that addressed the cost effectiveness of CT and MRI for coronary artery disease, headaches, seizures, arteriovenous malformations, or urinary tract calculi screening.

Written by Murtagh J, Warburton RN, Foerster V, Lentle BC, Wood RJ, Mensinkai S, and Husereau D, CADTH, Canada

Title **Bioengineered Skin Substitutes for the Management of Burns: A Systematic Review**

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

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Reference ASERNIP-S Report Number 46. ISBN 0-909844-75-5.

Full text available: www.surgeons.org/asernip-s/ (publications page)

Aim

To assess the safety and efficacy of bioengineered skin substitutes (BSS) compared to biological skin replacements and/or standard dressing methods in managing burns.

Conclusions and results

This review included 20 randomized controlled trials (RCTs). Due to the diversity of skin substitutes, methods, etc, it was not possible to study the effectiveness of BSS in partial thickness vs full thickness burns, in pediatric patients vs adult patients, and for total burn surface area (TBSA). However, we could draw some conclusions on the different BSS reviewed.

For partial thickness burns (<15% TBSA), Biobrane® and TransCyte® appear to be more effective than silver sulfadiazine. Biobrane® may offer cost advantages over other BSS.

For burns between 20% and 50% TBSA, allogeneic cultured skin and Apligraf® combined with autograft both appear to be effective. Dermagraft® was also found to be effective for these burns (as effective as allograft), but the validity of this comparison is questionable.

No major complications were reported with BSS in managing burns or donor sites. The mortality rate was relatively high; however, it was unclear whether these deaths were due to the BSS or the actual burn injury. The evidence did not show the long-term safety of BSS as regards viral infection and prion disease. Hence, autograft remains the gold standard for excised burns.

Recommendations

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

Evidence rating: Average.

Safety: BSS, namely Biobrane®, TransCyte®, Dermagraft®, Apligraf®, autologous cultured skin, and allogeneic cultured skin, are at least as safe as biological skin replacements or topical agents/wound dressings. The safety of Integra® could not be determined, nor could the long-term safety of BSS with respect to viral infection and prion disease.

Efficacy: In managing partial thickness burns, BSS, namely Biobrane®, TransCyte®, Dermagraft®, and allogeneic cultured skin, are at least as efficacious as topical agents/wound dressings or allograft. Apligraf® combined with autograft is at least as efficacious as autograft alone. In managing full thickness burns, the efficacy of autologous cultured skin could not be determined, nor could the efficacy of Integra®.

Methods

Search strategy: MEDLINE, EMBASE, the Cochrane Library, Science Citation Index and Current Contents were searched from inception to April 2006. Other electronic databases were searched in April 2006.

Study selection: Only RTCs in humans were included for review. Efficacy outcomes included wound infection, wound closure, wound healing time, and wound exudate. Patient-related outcomes included pain and cosmesis. Safety outcomes included complications and mortality.

Data collection and analysis: Data were extracted by one researcher using standardized data extraction tables developed *a priori* and checked by a second researcher. Statistical pooling was not appropriate due to the study and result heterogeneity.

Further research/reviews required

Rigorous RCTs would strengthen the evidence base, but RCTs are unlikely of patients with large, deep burns. Therefore, RCTs of patients with smaller burns should be undertaken. Studies should evaluate the long-term safety of BSS, and future studies should define and document outcomes for partial and full thickness burns separately. RCTs are also needed on cultured epithelial autograft, in particular cultured epithelial autograft suspensions.

Written by Ms Clara Pham et al, ASERNIP-S, Australia

Title **Self-Expanding Metallic Stents for Relieving Malignant Colorectal Obstruction: A Systematic Review**

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

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Reference ASERNIP-S Report Number 49. ISBN 0-909844-73-9.

Full text available: www.surgeons.org/asernip-s/ (publications page)

Aim

To make recommendations on the safety and efficacy of self-expanding metallic stents (SEMS) for relieving malignant colorectal obstructions.

Conclusions and results

SEMS were compared to surgical procedures to relieve colorectal obstruction, and were also assessed in isolation. The review included 15 comparative studies and 73 case series. Nine studies compared SEMS vs surgery (2 were randomized controlled trials, RCTs), 3 compared elective surgery after decompression with SEMS vs emergency surgery, and 2 compared covered vs uncovered stents.

The quality and quantity of evidence limited the review. Many studies lacked methodological rigor, which made assessing the validity of the data difficult. Despite a poor-quality evidence base, the data suggested that SEMS was safe and effective in overcoming left-sided malignant colorectal obstructions, regardless of the indication for stent placement or underlying disease.

SEMS had positive outcomes compared to surgery, including overall shorter hospital stays and a lower rate of serious adverse events. Postoperative mortality appeared comparable between the two. Combining SEMS with elective surgery appeared safer and more effective than emergency surgery. However, the small sample sizes limited the validity of the findings.

Recommendations

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

Evidence rating: Poor.

Safety: The safety of SEMS placement compared to surgery cannot be determined. However, considered in isolation, the evidence suggests that SEMS is safe in relieving left-sided colorectal obstructions.

Efficacy: The efficacy of SEMS placement compared to surgery cannot be determined. However, considered in isolation, the evidence suggests that SEMS is effective in relieving left-sided colorectal obstructions, with high levels of technical and clinical success.

Methods

Search strategy: Studies were identified by searching MEDLINE, EMBASE, CINAHL, Current Contents, Science Citation Index, PubMed and the NHS Centre for Reviews and Dissemination Database in April 2005. Other databases were searched in April 2005 and February 2006.

Study selection: RCTs, historical and/or nonrandomized comparative studies, case series, and case reports on complications were included. Comparative studies concerned surgical intervention or any internal comparison of different types of stent. Efficacy outcomes included technical and clinical success, duration of patency, progression to surgery, and rates of re-intervention, anastomosis, and colostomy. Safety outcomes included complications, eg, perforation.

Data collection and analysis: Data were extracted by one researcher using standardized data extraction tables developed *a priori* and checked by a second researcher. Statistical pooling was inappropriate for this data set, but narrative pooling was used where appropriate. Data were stratified where possible by intent of stent placement and patient population.

Further research/reviews required

A multicenter RCT of stent placement as a bridge-to-surgery is feasible and desirable. However, the difficulties inherent in randomizing patients seeking palliative treatment may preclude the possibility of conducting an RCT of palliative stent placement.

Written by Ms Amber Watt et al, ASERNIP-S, Australia

Title **Bioengineered Skin Substitutes for the Management of Wounds: A 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 52. ISBN 0-909844-72-0.

Full text available: www.surgeons.org/asernip-s/ (publications page)

Aim

To make recommendations on the safety and efficacy of bioengineered skin substitutes for managing wounds.

Conclusions and results

Bioengineered skin substitutes (BSS) – epidermal, dermal, or both – were compared to standard care/dressings or autografts. The review included 23 RCTs (8 on venous leg ulcers, 6 on diabetic foot ulcers, and 9 on other wounds). Success was defined as complete wound closure across all studies. Other outcomes were not consistently reported, making comparisons difficult.

In venous leg ulcers, Apligraf®, cryopreserved cultured allografts, cultured keratinocyte allografts, Dermagraft®, EpiDex™, OASIS™ Wound Matrix, and Promogran™, were comparable with standard treatment in wound healing time, wound closure, and decreased ulcer area. No difference was found in pain, recurrence, and wound infection.

In diabetic foot ulcers, BSS showed an advantage over standard care. Wound healing time appeared to be better overall with BSS (Apligraf®, Dermagraft®, GraftJacket®, Hyalograft™ and Laserskin™, OrCel™ and Promogran™), and wound closure appeared to be favorable with Apligraf®, GraftJacket®, and OrCel™. Infection rates were lower, and where reported, there was no difference in recurrence.

Healing across different wounds was no better with BSS than the relevant comparator, although pain might be lower. The evidence suggested that Apligraf® for micrographic and postexcisional wounds produced similar results to standard therapy, and Biobrane® for donor sites was inferior to standard therapy. Evidence on Promogran™ in treating pressure sores suggested it equaled standard therapy, and cultured epidermal allografts were superior to standard therapy for wound healing time and pain, but in several studies the small samples may limit the validity of the conclusions.

Recommendations

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

Evidence rating: Average. Limited by small samples, short followup, and lack of rigor.

Safety: BSS are at least as safe as standard therapies for venous leg ulcers, diabetic foot ulcers, and other wounds.

Efficacy: Could not be determined based on the available evidence.

Methods

Search strategy: Studies were identified by searching MEDLINE, EMBASE, Cochrane Library, Science Citation Index, and Current Contents from inception to April 2006. Other electronic databases were searched in April 2006.

Study selection: Only RCTs in humans and only studies comparing a BSS as a physical layer that would integrate into the wound (not lysate) were included.

Data collection and analysis: Data were extracted by one researcher using standardized data extraction tables developed *a priori* and checked by a second researcher. Statistical pooling was not appropriate due to the study and result heterogeneity.

Further research/reviews required

- Additional RCTs with longer followup periods of BSS, particularly in terms of recurrence.
- Development of standard outcome measures for consistent reporting of primary outcomes.
- Cost-effectiveness studies in an Australian health-care context.

Written by Ms Christine Barber et al, ASERNIP-S, Australia

Title **Surgical Simulation: A Systematic Review (Update and Re-Appraisal)**

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

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Reference ASERNIP-S Report Number 53. ISBN 0-909844-71-2.
Full text available: www.surgeons.org/asernip-s/ (publications page)

Aim

To evaluate the effectiveness of surgical simulators, in comparison to each other, no training, or other methods of surgical training.

Conclusions and results

Thirty-one randomized controlled trials (RCTs) with 806 participants were included, but the quality of the RCTs was often poor. Computer simulation generally showed better results than no training, but was not convincingly superior to standard training (eg, surgical drills) or video simulation. Video simulation did not show better results than groups with no training, and the data were inadequate to determine if video simulation was better than standard training or the use of models. Model simulation may have been better than standard training, and cadaver training may have been better than model training. None of the RCTs compared computer simulation and model training.

Recommendations

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

Evidence rating: Poor. The evidence was insufficient since most of the RCTs were flawed, and outcomes were often not comparable across studies.

Safety: Not applicable for this review.

Efficacy: Efficacy cannot be determined. The inconclusive outcome of this review may be related to small sample sizes and the validity and reliability of outcome measurements.

Methods

Search strategy: MEDLINE, EMBASE, PreMEDLINE, Current Contents, the Cochrane Library (issue 2, 2005), scholar.google.com, metaRegister of Controlled Trials, National Research Register (UK), and NHS Centre for Research and Dissemination (UK) were last searched in April 2005. PsycINFO, CINAHL, Science Citation Index were searched on March 25, 2003. Additional articles were identified through the reference sections of the studies retrieved.

Study selection: The review included RCTs assessing any training technique of surgical simulation and any other methods of surgical training, or no surgical training. Included articles must have contained information on at least one of the following outcomes: measures of surgical task performance, whether objective or subjective, and measures of satisfaction with training techniques.

Data collection and analysis: Data were extracted by one researcher using standardized data extraction tables developed *a priori* and checked by a second researcher. It was not appropriate to pool results across studies since outcomes were not comparable. Relative risks for dichotomous outcome measures or weighted mean differences, for continuous outcome measures with 95% confidence intervals were calculated for some outcomes in RCTs where it would aid in interpreting the results.

Further research/reviews required

Further research must be done in the context of training to particular performance standards. Ideally, studies should be multicenter trials with standardized approaches, and with sufficient participants. The skills evaluated should be part of a standard surgical skills training course, not stand-alone technical skills. Once efficacy has been determined economic analyses could be attempted.

Written by Dr Jim Wang et al, ASERNIP-S, Australia

Title **Endoscopic Treatments for Gastroesophageal Reflux Disease: An Accelerated Systematic Review**

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

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Reference ASERNIP-S Report Number 54. ISBN 0-909844-7-47.

Full text available: www.surgeons.org/asernip-s/ (publications page)

Aim

To assess the safety and efficacy of the following endoscopic anti-reflux treatments currently used for treating gastroesophageal reflux disease (GORD).

- Radiofrequency energy ablation (Stretta® Procedure).
- Endoluminal gastroplication (Bard® EndoCinch™, Wilson-Cook Endoscopic Suturing Device and NDO Plicator™).
- Injection/implantation techniques (Enteryx®, Gatekeeper™ Reflux Repair System and Plexiglas®).

Conclusions and results

Limited evidence suggested that in a select group of patients the *Stretta Procedure* improved symptoms and quality of life comparable to laparoscopic fundoplication (LF) and superior to sham treatment. Up to 10% of patients require further intervention after 2 years. The Stretta Procedure has fewer serious complications than LF, and rarely requires general anesthetic.

A single randomized controlled trial (RCT) comparing *EndoCinch* to sham treatment showed a significant placebo effect, but EndoCinch reduced esophageal exposure and medication use more than the sham procedure. Three small nonrandomized comparative studies suggested that EndoCinch provided the same, or slightly inferior, results compared to LF. Although EndoCinch was associated with a reintervention rate of up to 55% within 2 years, patients had fewer serious adverse events following EndoCinch than LF.

Two small case series studies on the *NDO Plicator* noted a positive effect on symptom and quality-of-life scores and medication use between 6 and 12 months after treatment.

A small RCT suggested that *Enteryx* has a substantial placebo effect. The manufacturer recalled Enteryx in 2005 after serious adverse events and 1 death were reported.

One case series reported improved symptoms, quality of life, and medication use 6 months after treatment with the *Gatekeeper Reflux Repair System*. Evidence for *Plexiglas* was sketchy. Both procedures were relatively safe.

Recommendations

The scope, applicability, efficacy, and cost effectiveness of endoscopic anti-reflux therapies in treating GORD are not established. These procedures may provide an alternative treatment for selected patients with mild to moderate GORD who are dependent on medication and are reluctant or unable to undergo surgery.

While the endoscopic anti-reflux procedures are relatively safe in a clinical trial setting, their use in routine practice should be closely monitored. Guidance from professional bodies on the minimum training requirements for performing these procedures would be helpful.

Methods

Search strategy: MEDLINE, EMBASE, CINAHL, PubMed, the Cochrane Library, Science Citation Index, the York Centre for Reviews and Dissemination, Clinicaltrials.gov, the National Research Register, relevant online journals, and the Internet were systematically searched without language restriction to May 2006.

Study selection: Systematic reviews, RCTs, and nonrandomized comparative studies with at least 10 patients in each study arm, and case series studies of at least 10 patients examining the efficacy and safety of the various endoscopic procedures were included for review.

Data collection and analysis: Data were extracted by one researcher and checked by a second using standardized data extraction tables developed *a priori*. The data were not suitable for statistical pooling, and a meta-analysis was not performed.

Written by Ms P Mc Loughlin et al, ASERNIP-S, Australia

Title **Radiofrequency Ablation of Liver Tumors (Update and Re-Appraisal): A Systematic Review**

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

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Reference ASERNIP-S Report Number 56. ISBN 0-9098-44-78-X.

Full text available: www.surgeons.org/asernip-s/ (publications page)

Aim

To update the ASERNIP-S review on radiofrequency ablation (RFA) for liver tumors (October 2002) and assess new studies on the safety and efficacy of RFA compared to other surgical and nonsurgical methods.

Conclusions and results

The original ASERNIP-S review included 12 studies, and this updated review adds 12 more. However, the limitations are much the same, ie, small sample sizes, short followup times, and a lack of comparability in outcome measures. Still, RFA generally showed larger, more complete areas of ablation and higher survival rates compared to other ablative techniques. Surgical resection showed a lower recurrence rate and increased time to recurrence compared to RFA. The two procedures are usually performed on different patient groups, with RFA being performed on patients unable to undergo surgical resection.

The conclusions regarding safety and efficacy of RFA remain largely unchanged, and the results are still inconclusive as regards RFA in treating hepatocellular carcinoma and colorectal metastases. Further studies on both forms of cancer need to contain adequate patient numbers and a focus on long-term local and overall recurrence and safety outcomes. Standardization of outcome measures across studies would benefit any analysis.

Recommendations

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

Evidence: Average.

Safety: RFA is at least as safe as other treatments for liver tumors.

Efficacy: From the data, the efficacy of RFA cannot be determined in relation to other ablation techniques.

Methods

Search strategy: Studies were identified by searching MEDLINE, EMBASE, Current Contents, Cochrane Library, and Science Citation Index, from May 18, 2002 to April 14, 2006. Further electronic databases were searched in April 2006. This was supplemented by hand-searching recent conference proceedings and the Internet. Additional articles were found in the references of retrieved studies.

Study selection: Randomized controlled trials (RCTs), quasi-RCTs, and nonrandomized comparative studies assessing patients treated with RFA and one or more comparative invention(s) were included. Patient safety outcomes and efficacy were assessed.

Data collection and analysis: Data were extracted by a researcher using standardized tables developed *a priori* and checked by a second researcher. Data were not pooled. Relative risks, weighted mean differences, or odds ratios and the 95% confidence intervals were calculated individually for the same outcomes in the RCTs and the quasi-RCT.

Further research/reviews required

- Conclusively determine the advantages and disadvantages of RFA for primary hepatocellular carcinoma or metastatic colorectal liver carcinoma over other ablative techniques.
- Compare the safety and efficacy of percutaneous, laparoscopic, and open approaches to RFA.
- Study the relationship of patient safety and efficacy outcomes and tumor size.
- Cancer registries should incorporate data related to treatment outcomes of ablative techniques for hepatocellular carcinoma and metastatic colorectal liver carcinoma.

Written by Mr Nicholas Marlow et al, ASERNIP-S, Australia

Title **Efficacy of Patient Isolation for the Control of Airborne Infections in Hospitals**

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Reference Nasjonalt kunnskapssenter for helsetjenesten. Report number 1-2006.
ISBN 82-8121-081-8. Full text report in Norwegian is available on www.nokc.no

Aim

To review the evidence for the effectiveness of isolation measures in reducing the incidence of some important airborne infections in hospitals.

Conclusions and results

Most studies were observational studies, few with a prospective design.

Tuberculosis: The risk of tuberculosis infection is higher among healthcare workers compared to the general population, but implementation of control measures, including isolation, shows significant reduction.

Methicillin resistant Staphylococcus aureus (MRSA): Implementation of control measures, including isolation, shows reduction of cases.

Severe Acute Respiratory Syndrome (SARS): Implementation of strict control measures protect against transmission of the SARS virus. Procedures like resuscitation or intubation of patients increases the incidence of SARS among healthcare workers.

Most of the studies identified included multiple simultaneous interventions, and it was not possible to assess the relative contribution of individual measures. However, intensive concerted interventions including isolation were shown to reduce nosocomial infection of the various diseases. In addition, a higher incidence of diseases like tuberculosis, measles, and SARS was found among healthcare workers than in the general population.

Methods

The report consists of a systematic review of studies published from 1966 to July 2005. Relevant databases searched were the Cochrane Library, Database of Abstracts of Reviews of Effectiveness (DARE), International Network of Agencies of Health Technology Assessment (INAHTA) database, Ovid CINAHL, National Guidelines Clearinghouse, MEDLINE, and EMBASE. In total, 293 potentially relevant studies were assessed, whereof 60 were included.

Further research/reviews required

Most studies included in the report were observational studies, few with a prospective design. Randomized controlled studies are not suitable for this topic, so such a design will be difficult to obtain. However, studies with a prospective design will give stronger evidence on the issues described.

Written by Ellen M Nilsen et al, NOKC, Norway

Title **Tumor Necrosis Factor (TNF) Inhibitors for Patients with Rheumatic Diseases**

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Reference NOKC report, part 1, Issue 12-2006. ISBN 82-8121-101-6, ISSN 1503-9544.
www.kunnskapssenteret.no/filer/TNF.pdf

Aim

To assess the efficacy and safety of the TNF inhibitors adalimumab, etanercept, and infliximab in treating rheumatoid arthritis (RA), ankylosing spondylitis, and psoriatic arthritis.

Conclusions and results

Forty randomized controlled trials (RCTs) were included in this systematic review. The analysis compared the individual TNF inhibitor with placebo, or with methotrexate. Compared to placebo, or other active treatment (methotrexate), adalimumab, etanercept, and infliximab (alone or in combination with methotrexate) are effective in terms of reducing disease activity in RA, ankylosing spondylitis, and psoriatic arthritis. The analysis failed to find any evidence that either treatment is more effective.

Recommendations

Not applicable.

Methods

Published systematic reviews and randomized controlled trials of adalimumab, etanercept, and infliximab were identified through a comprehensive literature search and included for further analysis if the patients met the criteria for RA, ankylosing spondylitis, or psoriatic arthritis. Data on study characteristics were abstracted, and the expert group assessed study quality. Studies were pooled, and meta-analysis was performed only if approved doses for use in Norway were used. Disease activity, functional, radiological, and clinical outcomes were assessed.

Further research/reviews required

More long-term RCTs and studies based on registers that include more patients are needed to support these findings. This will determine the benefit-to-harm ratio, including potentially rare or delayed adverse events, and the sustainability of the treatments with TNF inhibitors.

Written by Arentz-Hansen H, Granum L, Gulseth H-C, Idsø N, Knudsrød O, Koldingsnes W, Monsbakken J, Mørk N-J, Nordvåg B-Y, Odgaard-Jensen J, Palm Ø, and Wallenius M, NOKC, Norway

INAHTA Briefs

Issue 2006/131

Title **Age Evaluation of Adolescent Refugees**

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Reference June 2006. ISBN 82-8121-104-0.
www.kunnskapssenteret.no/filer/Rapport13_06_aldersvurdering.pdf

Aim

To evaluate the two methods used in Norway to estimate age when assessing whether an asylum seeker of unknown age is above or below 18 years of age, and to evaluate the accuracy of the methods in estimating the chronological age of individuals in the age range between 16 and 20 years.

Conclusions and results

The age of refugees immigrating to Western countries may be unknown or unreliable, and European countries use different methods to assess the age of asylum seekers. This systematic review includes 29 articles that met the inclusion criteria out of 922 articles identified in the search. Skeletal age could be determined with a mean standard deviation of 11.8 months for girls and 14.8 months for boys. These standard deviations are similar to the deviations used in Norwegian practice (12 months for girls and 14 months for boys). In most cases, skeletal age was advanced compared to the reference standard. When considering the difference between skeletal age and chronological age, the differences were significant among several ethnic populations. Their skeletal maturation could be both accelerated and retarded compared to the Caucasian population that forms the reference for age estimation. Factors such as differences in study design, purpose of the x-ray images taken, number of observers, and socioeconomic status might have influenced the results. The dental methods used in Norway are not widely used in age estimation research. Heterogeneity of methods, study designs, outcomes, and presentation of results made it difficult to compare the results of different studies. In determining whether an individual is below 18 years of age, the method used to estimate skeletal age yields a specificity below 80%. In contrast, dental methods yield high specificity, but very low sensitivity. Combining both methods increases specificity, but reduces sensitivity. The implication in using these methods is that an adolescent determined by skeletal and dental examinations to be aged 19 years has an 8% to 12% probability of actually being a minor.

Recommendations

Not applicable.

Methods

For this systematic review, MEDLINE, EMBASE, ISI, Cinahl, and the Cochrane Library were searched for literature published between January 1980 and April 2006. Two reviewers independently selected articles based on defined criteria and study quality.

Further research/reviews required

More research is needed to evaluate the accuracy of the dental methods used in Norwegian practices of age evaluation.

Written by Bjørn Anton Graff, Matthijs ten Have, Bjørn Hofmann, and Inger Natvig Norderhaug, NOKC, Norway

INAHTA Briefs

Issue 2006/132

Title **Effect of Replacing Amalgam Fillings on the Suspicion of Adverse Health Effects from Amalgam**

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Reference Report no 10-2006

Aim

To assess the health effects of replacing amalgam fillings in persons with suspected adverse effects from amalgams.

Conclusions and results

The Norwegian Directorate for Health and Social Affaires requested the Norwegian Knowledge Centre for the Health Service (NOKC) to perform this health technology assessment (HTA). This HTA report will be one of 3 documents used in working on guidelines for physicians and dentists.

Quality is low in the identified studies that address the effects of amalgam removal on health problems. The main findings from the synthesis of study results are:

- Most oral lichenoid lesions in contact with amalgam fillings completely heal or improve after removal of amalgam fillings.
- Lesions extending beyond the contact area, or not in contact with amalgam fillings, show little or no effect on healing after removal of the amalgam fillings.
- The intensity of oral and general symptoms associated with amalgam fillings was reduced after removal of fillings, but remained above the level observed in a representative control group. After removing the amalgam fillings the mercury level in urine and blood temporarily increased before being reduced to an acceptable level. Amalgam removal in healthy subjects was shown not to affect the kidneys as measured by the glomerular filtration rate.
- No studies of sufficiently good scientific quality were found that reported a reduction in signs and symptoms of general disorders after removal of amalgam fillings.

Methods

A review team of external professionals carried out the HTA. The systematic literature search and evaluation was performed in accordance with general HTA principles. In all, 1647 abstracts were reviewed by NOKC professionals at step 1. The review team evaluated full-text publications in pairs, reading 157 studies at step 2. Forty-six studies remained for internal and external validation assessment at step 3. In total, 17 studies were found to be relevant and of sufficient quality according to checklists and were included in the evidence base for evaluating the health effects of removing amalgam fillings.

Written by Lund Håheim L, Dalen K, Eide R, Karlsson S, Bentung Lygre G, Lyngstadaas S P, and Nordmo A-M, NOKC, Norway

Title **Stabilized Hyaluronic Acid in the Treatment of Osteoarthritis**

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www.juntadeandalucia.es/salud/orgdep/aetsa/

Reference Report number 10/2006. ISBN 84-689-8329-2.
Link to full text report: www.juntadeandalucia.es/salud/orgdep/aetsa/descarga.asp?id=58

Aim

To compile the most relevant documents and summarize their conclusions to provide information on the effectiveness and safety of stabilized hyaluronic acid in treating osteoarthritis.

Conclusions and results

Five documents were selected, but only one controlled, double-blind randomized trial was retrieved comparing efficacy and safety of non-animal stabilized hyaluronic acid (NASHA) against placebo in patients with osteoarthritis of the knee (either associated with other affected joints or not). Many limitations in methodology in the remaining selected publications made it impossible to draw conclusions on efficacy.

No significant differences were found in the clinical trial between the placebo and intervention arms for the following endpoints: number of patients responding to treatment, assessment of the overall status of the patient, quality of life scale, and WOMAC pain score.

Greater response to NASHA treatment was reported in the subgroup of patients with osteoarthritis confined to one or both knees. This, however, must be interpreted with caution due to the low number of patients in this subgroup, and in view of the fact that no analysis was conducted to adjust for variables that might potentially influence the response to treatment.

The incidence of adverse effects ranged between 5% and 13% in osteoarthritis of knee (8% in the placebo group) and 29% in hip involvement.

Evidence is still insufficient to prove the superiority, in terms of efficacy, of stabilized hyaluronic acid versus placebo or conventional preparations in treating osteoarthritis.

Methods

Reference databases such as MEDLINE, EMBASE, INAHTA, Cochrane Library, EuroScan, NICE, and the Technology Evaluation Center (TEC) were used. Moreover, a hand search was done in Google Scholar and Medscape, and a secondary review was conducted of the references in the articles found. Systematic and narrative reviews, full documents, and original articles were searched. The articles were read and a qualitative summary was prepared, which evaluated the methodologies used in the different studies.

Written by Leda Ojeda, AETSA, Spain

INAHTA Briefs

Issue 2006/134

Title **Cost Effectiveness of Palivizumab in the Prevention of Hospital Admissions for Syncytial Respiratory Virus in Pre-Term Babies Born at 32 to 35 Weeks**

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Reference Report number 14/2006. www.juntadeandalucia.es/salud/orgdep/aetsa/descarga.asp?id=49

Aim

To determine whether the use of palivizumab is cost effective in preventing hospitalization, morbidity, and mortality due to syncytial respiratory virus (SRV) infection in premature infants born at 32 to 35 weeks gestational age.

Conclusions and results

Results: Of the 416 articles retrieved in the search, only 2 meeting the inclusion criteria were selected, namely, a controlled clinical trial and a cohort study, both with sound internal validity. Only 1 of the studies records the number of deaths, although these were unrelated to palivizumab. Both studies measure the frequency of hospitalization and length of stay for SRV-induced respiratory infection, although only the cohort study provides data on absolute risk reduction specifically for the premature population born at 32 to 25 weeks. According to this study, the absolute risk reduction for SRV-induced hospitalization is 3.9% (2.7% intervention group vs 6.6% control group). The estimate of cost effectiveness of administering palivizumab in pre-term babies born at 32 to 25 weeks of pregnancy ranges between 42 761 and 68 104 euros (EUR) per admission avoided (the first figure according to the sensitivity testing performed). The impact on the annual budget in Andalusia would amount to between EUR 2 693 931 and EUR 2 860 367.

Conclusions: In the population of 32- to 35-week gestational age infants, palivizumab is effective as prophylaxis for SRV infection, but it is not cost effective.

Methods

A systematic review of the literature was performed, running database searches in MEDLINE, EMBASE, Cochrane Library (the Cochrane Database of Systematic Reviews and Controlled Trials Register), and CRD (Centre for Reviews and Dissemination). The Registry of the Andalusian Regional Clinical Trials Committee and related webpages were also consulted. The inclusion criteria for the articles were as follows: design (controlled clinical trials or observational studies with a control group), the population characteristics (pre-term babies born at 32 to 25 weeks gestational age), the intervention (preventive use of palivizumab), and outcomes (rates of hospitalization due to SRV infection and related morbidity and mortality indicators, and costs based on the original populations). The studies were assessed using the Jadad and CASP scales for clinical trials and a list of criteria devised ad hoc for cohort studies. The summary of outcomes is qualitative. Both a cost-effectiveness study and an assessment of the budgetary impact of the prophylactic use of palivizumab in the population of pre-term babies born at 32 to 25 weeks in Andalusia were also performed. A sensitivity study was conducted within our economic assessment using a greater reduction in the risk of hospitalization with palivizumab, a longer mean hospital stay due to SRV, and a higher cost per day of hospitalization than in the original economic analysis.

Written by Leda Ojeda Florido, AETSA, Spain

INAHTA Briefs

Issue 2007/01

Title **Diagnostic Value of Natriuretic Peptides in Patients with Suspected Heart Failure**

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Reference December 2005. KCE Reports vol 24A. Ref D/2005/10.273/34.
http://kce.fgov.be/index_nl.aspx?ID=0&SGREF=5264&CREF=4361

Aim

To address the clinical and cost effectiveness of natriuretic peptides (NPs) as a diagnostic aid for physicians in the initial diagnostic work-up of patients with signs and symptoms suggestive of heart failure (HF).

Conclusions and results

Plasma NP measurement has been established as a helpful aid in diagnosing HF. It is best used as a rule-out test for suspected cases of new HF in breathless patients. This has best been documented in the emergency department (ED) setting. It can be particularly helpful to improve the diagnostic performance of non-cardiologists who are less skilled in clinical examination and electrocardiography than ED physicians are. A cut-off level of 100 pg/ml for BNP or 125 pg/ml for NT-proBNP (450 pg/ml in patients aged >75 years) identifies patients who are unlikely to have acutely decompensated HF, or acute worsening chronic HF.

Recommendations

1. Measurement of natriuretic peptides is useful as a rule-out test of heart failure (HF) in patients presenting with recent onset dyspnea in primary care and in the emergency department.
2. No formal recommendation has been formulated as regards a reimbursement strategy. Three possible options are discussed for financing NP testing in patients with new onset dyspnea: no reimbursement, restricted reimbursement in primary and acute care, and restricted reimbursement in acute care and no reimbursement in primary care.
3. The reimbursement of NP measurement should be accompanied by an information campaign on the evidence-based use of this test.

Methods

A systematic search was limited to the literature published from July 1, 2004 onward, since previously published HTAs had covered the literature until the end of 2004. An initial search was performed in August 2005 and repeated at the end of October 2005. Selection was limited to systematic reviews, HTA reports, and randomized trials in which the reference test was a clinical diagnosis of HF. We searched papers in the CRD database, MEDLINE, EMBASE (keywords: "heart failure" and "natriuretic peptides") and in the Cochrane Library. We used the same MeSH and textword terms for the MEDLINE search as those described in the papers by Doust et al.

Further research/reviews required

1. Current cut-off values are relatively crude and need further refinement in the future.
2. The performance of the test in primary care is less well documented. It can be useful in ruling out HF in this setting, provided that GPs are well informed on the indications and limitations of the test and make use of them accordingly.

Written by Hans Van Brabandt, Dirk Van den Steen, and Irina Cleemput, KCE, Belgium

Title **Effects and Costs of Pneumococcal Conjugate Vaccination of Belgian Children**

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Reference 2006. KCE reports 33C (D/2006/10.273/21), legal depot D/2006/10.273/54.
Report in English. Also available with Dutch (33A) or French (33B) executive summary.
Free download from www.kenniscentrum.fgov.be

Aim

To determine the cost effectiveness of universal vaccination in young children (under 2 years of age) with the currently available 7-valent conjugated pneumococcal vaccine (PCV7), taking into account direct benefits for the immunized children and indirect benefits (herd immunity effects) for the population at large; and to determine the optimal vaccination schedule to achieve those benefits cost-effectively.

Conclusions and results

We conclude the following from our baseline calculations:

- At 9869 euros (EUR) per quality-adjusted life-year (QALY) gained in the baseline, PCV7 vaccination using a 2+1 schedule with injections at 2, 3, and 15 months of age is cost effective compared to other widely accepted interventions in Belgian health care.
- At EUR 155 619 per QALY gained in the baseline (using already more pessimistic assumptions for the 2+1 than the 3+1 schedule), the incremental cost effectiveness of a 3+1 schedule (2, 3, 4, and 15 months) versus a 2+1 schedule (2, 3, and 15 months) compares unfavorably to other widely accepted interventions in Belgian health care.

Recommendations

Based on those results, the KCE recommends the introduction of universal childhood vaccination in Belgium with the 7-valent conjugated pneumococcal vaccine using a 2+1 vaccination schedule with injections at 2, 3, and 15 months.

Methods

We have reviewed the international published and unpublished literature, and collected and analyzed a wide range of Belgian epidemiological and cost data. A simulation model was developed, parameterized, and fitted by using scientifically validated data, as much as possible from Belgian sources. Simulations were performed to estimate how effective, and cost effective, universal PCV7 vaccination of Belgian children would be.

Further research/reviews required

Not explicitly stated/future evaluation of vaccination program.

Written by Beutels P, Van Damme P, Oosterhuis-Kafeja F, and edited by De Laet C, KCE, Belgium

INAHTA Briefs

Issue 2007/03

Title **Trastuzumab in Early Stage Breast Cancer**

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Reference KCE reports 34C (D/2006/10.273/25).
http://kce.fgov.be/index_en.aspx?ID=0&SGREF=5211&CREF=7198

Aim

To estimate the cost effectiveness and budget impact from a payer perspective of reimbursing trastuzumab in early stage breast cancer (ESBC).

Conclusions and results

Clinical conclusions:

- Trastuzumab reduces distant recurrence and improves 2 or 3 year disease free survival (DFS) from 75%–78% to 86%–89% in women with ESBC.
- Postanthracycline trastuzumab also causes severe congestive heart failure.
- When administered after anthracyclines, the pooled efficacy data of 1 year of trastuzumab in terms of DFS in ESBC seem weaker when trastuzumab is started sequentially after taxane treatment compared concurrently with a taxane.
- Preanthracycline administration of 9 weeks of trastuzumab proved efficacious in a recently published smaller trial.
- Trastuzumab may not prevent the development of brain metastases.
- In patients over 70 years of age trastuzumab has not been studied sufficiently.

Health-economic conclusions:

- Trastuzumab administered postanthracycline proved effective in most patient subgroups, while the preanthracycline regimen was effective in all subgroups studied. Trastuzumab was more effective in younger women and in women with more advanced disease.
- When the postanthracycline regimen was modeled on patients with a borderline cardiac function, trastuzumab treatment reduces life expectancy in stage I–II patients older than 50.
- Preanthracycline trastuzumab is more cost effective than the postanthracycline options, can lead to cost savings, and reaches 20% more women in need of treatment for cancer.
- 597 and 491 patients are eligible for pre- and postanthracycline trastuzumab, respectively, and would cost the healthcare payer 5.17 and 19.96 million euros, respectively.

Recommendations

- Unused trastuzumab can be reduced by marketing smaller vials. This should be discussed with the manufacturer.
- Reimbursement should be conditional on strict inclusion and exclusion criteria and embedding in the quality procedures of the oncology programs in Belgian Hospitals. During treatment cardiac function should be monitored.
- A cancer registry is essential to follow up women treated with trastuzumab in Belgium. This report presents several variables that are needed or useful for this purpose.
- A clinical trial comparing 9 weeks of trastuzumab preanthracycline with the 52-week postchemotherapy regimen should be started without delay.
- See full report for additional recommendations.

Methods

The results in this report are based on published information on efficacy and safety, and epidemiological and costing data, some of which are specific for Belgium. A systematic review of the existing literature was performed. The economic evaluation of trastuzumab was based on a cost-effectiveness analysis and an evaluation of the budget impact from a healthcare payer perspective.

Written by Michel Huybrechts, Frank Hulstaert, Mattias Neyt, France Vrijens, and Dirk Ramaekers, KCE, Belgium

Title **HTA Magnetic Resonance Imaging (MRI)**

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Reference 2006. KCE reports 37A (D/2006/10.273/32).
http://kce.fgov.be/index_nl.aspx?ID=0&SGREF=5269&CREF=7368

Aim

- To evaluate the effectiveness of MRI and the possibilities to substitute CT for MRI.
- To analyze the pros and cons of MRI and CT reimbursement systems and compare MRI reimbursement systems in other European countries with the Belgian system.
- To evaluate the feasibility of implementing mobile MRI units in Belgium.

Conclusions and results

Technical improvements in MRI have led to an increase in potential indications for MRI, but quantitative assessments of the clinical effect of MRI in large case series or controlled trials are missing. The high quality and wide use of MRI make such studies difficult. Hence, the evidence is often limited to "diagnostic accuracy".

Belgium has many CT units. The ratio of CT/MRI examinations is among the highest reported. Financing of MRI and CT differs considerably without a clear explanation.

In Belgium, mobile MRI is used as a temporary solution when a fixed MRI is down or being rebuilt.

Recommendations

A biennial update of referral guidelines regarding indications for which MRI or CT should be used, and the optimal imaging technique for each indication, is recommended. A computing system incorporating the referral guidelines would be helpful for prescribers. Appropriate use of medical imaging should be a priority in basic and continuing medical education.

For quality assurance, different measures could be taken, eg, regular MRI and CT site visits by a commission, training and support by experienced radiologists, regular conferences between providers and prescribers of CT and MRI examinations, regulation of MRI installations, and limiting certain exams to expert centers.

Financing mechanisms for CT and MRI should be harmonized, and reimbursement of certain medical imaging procedures revised. The current fee-for-service system for radiologists and lack of financial responsibility of prescribers preclude development of incentive mechanisms to stimulate appropriate use and discourage inappropriate use of medical imaging procedures.

Evidence is insufficient to conclude that the advantages of mobile MRI in Belgium outweigh the disadvantages or otherwise.

Methods

MEDLINE, EMBASE, the HTA Database, NHS EED, CINAHL, and DARE were searched. Study quality was assessed using the QUADAS quality assessment tool for diagnostic research. The level of evidence for diagnostic efficacy was identified for each indication. Information on financing systems in other countries was obtained by a survey of INAHTA members and a literature review. Manufacturers and users of mobile MRI units were contacted.

Further research/reviews required

Biennial updating of the referral guidelines for medical imaging procedures requires regular review of new evidence. In the Belgian context more research is needed on possible financing systems for CT and MRI.

Written by Demaerel P, Hermans R, Verstraete K, Bogaert J, van Goethem M, Deblaere K et al, KCE, Belgium

Title **Cervical Cancer Screening and HPV Testing**

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Reference Health Technology Assessment (HTA). 2006. KCE reports 38C (D/2006/10.273/37). http://kce.fgov.be/index_nl.aspx?ID=0&SGREF=5264&CREF=7764

Aim

To document the effectiveness of cervical cancer screening, in particular the role of human papillomavirus (HPV) testing.

Conclusions and results

Conventional Pap cytology or a validated LBC system remains the cornerstone of cervical cancer screening. Validated HPV testing is currently indicated only for ASC-US triage in women 25 to 64 years of age and in neoplasia treatment followup. HPV and cytology findings (using Bethesda standard) should be mentioned separately, but interpreted together in a single pathology report.

The knowledge of women about HPV is generally poor. Testing positive for HPV may cause anxiety, and upset the woman and her partner. Awaiting the results from large ongoing trials, nonselective testing for HPV cannot be justified. Offering information tools with pretest information, eg, information leaflets on cervical cancer screening and HPV, must be encouraged.

Cervical cancer screening in Belgium is mainly opportunistic and not well organized. Three-year Pap screening coverage in women 25 to 64 years old is only 59%, and many of the women screened are overscreened (annual Pap test). In the UK and the Nordic countries where organized screening was implemented, coverage of at least 80% was reached. Beyond the appropriate introduction of HPV testing, greater screening coverage of the target population and quality improvement in the different steps of the screening process can be expected to improve health in a much larger population.

Recommendations

- Well-organized cervical cancer screening (instead of the current opportunistic screening) with the necessary quality assurance should be introduced if policy makers want to reduce cervical cancer mortality.
- The introduction of a comprehensive and mandatory registry is essential.
- Awaiting the results of ongoing trials, HPV tests currently have no proven utility in primary screening. Women must be correctly informed about the HPV test to prevent possible psychological problems. HPV complements cytology-based screening in ASC-US triage (estimated at maximum 3% of screened cases) and in neoplasia treatment followup.
- The annual Belgian health insurance budget used for covering medical activities directly linked to cervical cancer screening can be used more efficiently. Activities associated with overscreening (annual Pap test) should not be financed by the health insurance plan.
- Actual and forthcoming screening activities should be integrated and coordinated across the different cancer screening programs and among all authorities concerned.

Methods

Literature review. Surveys to assess local situation.

Further research/reviews required

Large trials are ongoing to assess the role of primary HPV screening.

Written by Frank Hulstaert, KCE, Belgium

Title **A Framework for the Assessment of Emerging Medical Devices**

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Reference 2006. KCE reports 44A (D/2006/10.273/32).
http://kce.fgov.be/index_nl.aspx?ID=0&SGREF=5264&CREF=7935

Aim

To establish a transparent, scientifically valid procedure in Belgium for early evaluation of medical devices.

Conclusions and results

The KCE in collaboration with the Belgian Health Insurance (RIZIV/INAMI) elaborated a procedure for early evaluation of medical devices. The procedure combines a process of managed uptake, limiting the budgetary risks with the production of solid and impartial evidence on clinical and cost effectiveness.

Implementation of the new procedure will help policy makers reach informed and well-balanced decisions. For the manufacturers that produce innovative devices with 'added value', the procedure allows the gradual and controllable introduction of an emerging device on the market, preventing inappropriate use and operator problems. Moreover, such a procedure guarantees a (partially or fully) government-supported clinical trial and a health technology assessment that presents conclusions on effectiveness, costs and possibly cost-effectiveness, and organizational and patient issues. The framework also assures patients that the emerging interventional technologies are introduced in a state-of-the-art research setting and reviewed to protect their safety.

Recommendations

A transparent registration and vigilance system should be developed. This can lead to more readily accessible information about existing products, procedures, and potentially major safety issues.

Methods

The first part of the report gives a general description of key concepts and provides an overview of the regulatory context for medical devices in developed countries at the European and international levels. The available literature was identified through a search in MEDLINE and the CRD HTA database.

Furthermore, existing procedures to identify, assess, and monitor emerging medical devices were described. Information was collected from national and/or local governmental agencies, and from private agencies when relevant. To validate or add to this information, contact was made with one or more experts in the specific country.

Written by Vinck I, Neyt M, Thiry N, Louagie M, Ghinet D, and Cleemput I, KCE, Belgium

Title **HTA Colorectal Cancer Screening: Scientific State-of-the-Art and Budget Impact for Belgium**

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Reference 2006. KCE reports 45C (D/2006/10.273/57).
Free download from www.kenniscentrum.fgov.be

Aim

To evaluate whether, and under which conditions, colorectal cancer (CRC) screening could become an effective and cost-effective method to reduce the burden of CRC in Belgium.

Conclusions and results

This HTA report shows that CRC screening using biennial guaiac fecal occult blood test (FOBT) screening, followed by colonoscopy in case of a positive FOBT, in individuals aged 50 years and older can be a cost-effective mass screening program when properly organized.

Recommendations

To introduce a CRC screening program in Belgium. However, before such a program can be successfully implemented, several key issues need to be addressed and resolved. We recommend the implementation of a few pilot screening programs to investigate these issues.

Methods

We analyzed and evaluated the available evidence about CRC screening. We also evaluated the uncertainties surrounding CRC screening and identified areas where specific additional data are necessary before such a program can be successfully implemented in this country. To evaluate the financial consequences of implementing a biennial gFOBT-based screening program in Belgium, we conducted a budget impact analysis.

Further research/reviews required

Pilot screening programs are needed to investigate uncertainties for Belgium, mainly concerning screening participation, positivity and cancer detections rates, and organizational aspects.

Written by De Laet C, Neyt M, Vinck I, Lona M, Cleemput I, and Van De Sande S, KCE, Belgium

Title **Acticoat™ for the Treatment of Severe Burns**

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Reference Report prepared for AETMIS (AETMIS 06-08). Internet access to full French text.
ISBN 978-2-550-48230-7 (print), 978-2-550-48231-4 (PDF),
978-2-550-48744-9 (English summary, PDF)

Aim

To consider the medical context for the use of Acticoat, a continuous-release silver dressing, and to analyze published scientific studies on its effectiveness with respect to pain relief, reduction of infection, and healing.

Conclusion and results

The report concludes that Acticoat can reduce pain, especially during dressing removal, when compared to dressings with 1% silver sulphadiazine or 0.5% silver nitrate. This benefit can be enhanced even more by the possibility of less frequent dressing changes offered by this product. According to the clinicians consulted, this feature could contribute to a decrease in workload for nursing staff. Furthermore, according to the results of in vitro and in vivo analyses, Acticoat is effective in reducing colonization and preventing contamination by microorganisms. However, clinical studies have not established that Acticoat's ability to control infection and improve healing is superior, in statistically significant terms, to that of other topical silver agents, such as 0.5% silver nitrate solution and 1% silver sulphadiazine cream. Nevertheless, the observed effects are promising. Current published literature does not demonstrate Acticoat's potential for reducing hospital costs, but quicker discharge from hospital appears to be possible for children treated with Acticoat for medium-sized burns.

Given these results and the lack of studies comparing Acticoat with similar silver-based dressings, AETMIS concludes that Acticoat is a therapeutic option for treating severed burns. The rationale for its use is nonetheless based more on empirical results observed in the clinical setting than on published scientific evidence.

Methods

Analysis of scientific studies published between 1990 and 2006. Studies which addressed cost outcomes were also considered, but an economic evaluation was not conducted.

Further research/reviews required

Burn care is an emerging field of research, and its development paves the way for additional, better-designed clinical studies capable of demonstrating the potential benefit of this dressing

Written by Guylaine Rouleau and Lonny James Erickson, AETMIS, Canada

INAHTA Briefs

Issue 2007/09

Title **Health Technology Assessment: Polysomnography and Home Monitoring of Infants in Prevention of Sudden Infant Death Syndrome**

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Reference 2006. KCE reports 46 (vol 46A with Dutch executive and vol 46B with French executive) (D/2006/10273/59). http://kce.fgov.be/index_fr.aspx?SGREF=3228&CREF=8540

Aim

To assess the value of overnight polysomnographies (PSG) and home monitoring in infants (<1 year of age), particularly in preventing sudden infant death syndrome (SIDS); and to study the utilization of polysomnographies and home monitoring for infants in Belgium and their cost to the social security program.

Conclusions and results

Literature Review: Validated reference values are lacking for polysomnographies and home monitoring in infants. We did not find sufficient evidence-based findings to determine the interaction between cardiorespiratory (CR) events, psychomotor development, and the role of PSG and home monitors. We did not find data to confirm (or dismiss) the usefulness of PSG in clarifying the underlying diagnosis in children who experienced an apparent life-threatening event (ALTE). The usefulness of PSG in infants with other medical conditions (eg, neuromuscular conditions) is generally accepted despite little evidence. The literature, based on large-scale observational cohort studies, clearly shows that the PSG cannot predict SIDS. Large-scale observational cohort studies did not show a decline in SIDS incidence after introducing home monitoring. There are few evaluations of the cost effectiveness of PSG and home monitoring in preventing a sudden unexplained infant death. The literature is of low quality.

Data Analysis: Despite the decrease in PSGs in recent years, polysomnographic examinations in infants are still widely performed in Belgium. Medical practices vary widely. Most PSG stays relate to an indication that is vague, raising suspicions that mainly healthy infants are being tested. A disproportionate use of PSG testing will probably result in a higher utilization of monitoring devices. Belgian healthcare professionals do not seem to propagate PSG as a screening tool, but parents are not always contradicted in their belief that PSG is a sound safety measure. Our research points to inappropriate use of PSG in Belgium at a considerable cost to social security.

Recommendations

To improve the appropriateness of polysomnographies performed in infants in Belgium:

- Offer better information to the public, particularly to young parents, through authorized bodies
- Reinforce the role of healthcare workers and daytime baby minders
- Reform current regulations by limiting the number of hospitals that perform PSGs in infants and require systematic referral to a pediatrician specialized in PSG assessment.

Methods

Literature Review: Critical appraisal of the clinical and economic scientific literature.

Data Analysis: Analysis of relevant observational data (hospital stays, billing codes, health insurer data) and exploratory qualitative study among health professionals and the parents of infants undergoing PSG.

Further research/reviews required

The scientific literature lacks studies of good quality, particularly concerning the effect that CR events in infants have on further psychomotor development.

Written by Marijke Eyssen, Laurence Kohn, Marie-Laurence Lambert, and Dirk Van den Steen, KCE, Belgium

Title **Psychosocial Aspects of Genetic Screening of Pregnant Women and Newborns: A Systematic Review**

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Reference Health Technol Assess 2004;8(33). August 2004.
www.hta.ac.uk/execsumm/summ833.htm

Aim

To investigate how screening programs are likely to be experienced by recipients, and to learn lessons from psychosocial aspects of past screening programs to inform genetic screening in the future.

Conclusions and results

The review was structured around key questions, including: How well informed are screening program participants, and what factors are associated with different levels of knowledge/understanding? What are the aspects of screening programs that are associated with high/low levels of anxiety?

Knowledge: Levels of knowledge adequate for decision making are not being achieved. Information leaflets and videos have some effect, but large gaps in knowledge usually remain. Procedural aspects of testing are better understood than material related to the meaning of risk calculations. Substantial social and cultural inequalities exist in knowledge about testing. These findings probably underestimate the extent of the problem, since only limited aspects of knowledge have been studied. Also: *Knowledge is not the same as understanding*; public understanding of the basic concepts associated with screening is poor. *Knowledge that is only superficially acquired may not be retained*; informed consent for neonatal screening has not been well studied.

Anxiety: Studies that have succeeded in increasing knowledge have not observed a corresponding increase in anxiety. Anxiety is raised in women receiving positive screening results, but evidence is lacking of a beneficial (ie, reassuring) effect of a negative result. Anxiety in screen positive women falls on receipt of subsequent reassuring results, but some residual anxiety may remain. The way in which carrier screening is offered may affect anxiety in screen negative women. See full report for additional findings.

Recommendations

Levels of knowledge adequate for decision making are not being achieved. Substantial social and cultural inequalities exist in knowledge on testing. Considerations of efficiency that limit the time available to inform women may be misguided if achieved levels of understanding are inadequate. Anxiety is often an appropriate response. Much inappropriate anxiety can be traced to poor communication. Knowledge that improves decision making may not be the same as that which reduces anxiety.

Methods

See Executive Summary link above.

Further research/reviews required

As different genetic tests are introduced, the cumulative knowledge demands become substantial, increasing the possibility of inadequate or incorrect understanding.

More complicated testing scenarios may amplify inequalities in understanding, especially if time constraints mean leaflets are used as substitutes for face-to-face explanations. Future research needs to tackle these challenges, focusing particularly on: defining necessary and sufficient levels of knowledge, the needs of people with false positive results, the needs of male partners, and the resource requirements of providing satisfactory service. Policy developments and technological advances are likely to add new components to existing programs, eg, new conditions, new client groups, and new testing modalities. Research needs to incorporate these topics in mainstream work.

Written by Dr Josephine Green, University of Leeds, United Kingdom

INAHTA Briefs

Issue 2007/11

Title **An Evaluation of the Costs, Effectiveness and Quality of Renal Replacement Therapy Provision in Renal Satellite Units in England and Wales**

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Reference Health Technol Assess 2005;9(24). July 2005. www.ncchta.org/execsumm/summ924.htm

Aim

To survey the structure, processes, and organization of renal satellite units (RSUs) in England and Wales *(Phase 1)*, and to compare the effectiveness, acceptability, accessibility, and economic impact of chronic hemodialysis performed in main renal units (MRUs) compared to RSUs *(Phase 2)*.

Conclusions and results

Renal replacement therapy (RRT) has grown significantly in recent decades. Patients now being treated are older with more comorbidity. Given a shortage of kidneys for transplantation, the expansion of RRT has largely been in hospital hemodialysis, increasingly delivered in RSUs. Generally, these are nurse-run units providing only chronic hemodialysis. They are linked to MRUs (with nephrologists, inpatient services, and interventional facilities), but are more accessible for patients. Data on the effectiveness and cost of RSUs and on patients' experience are limited.

Phase 1: 74/80 (93%) of RSUs responded. The data showed, eg: 2600 patients were being treated, 42% were over 65 years of age, and 12% were diabetic; most RSUs were on acute hospital sites; unit size varied substantially with a median of 8 hemodialysis (HD) stations (range 3–31); a quarter of the RSUs were privately owned; and most had no daily medical input. Positive aspects included: improved accessibility, better environment for chronic HD patients, and expanding RRT capacity. Concerns included: the level of medical cover, use of nonacute hospital sites, and potential isolation of nurses.

Phase 2: 82% of eligible patients participated, 394 patients in the 12 RSUs and 342 in the parent MRUs. The response rates were similar. Mean age in the RSU group was 63 years, 18% were diabetic, 33% were 'high risk', and 34% depended on assistance. The MRU group had similar comorbidity scores and dependency, but a lower mean age (57). There were no significant differences in processes of hemodialysis or clinical outcomes, but a few parameters were statistically significantly different – notably the proportion achieving Renal Association Standards for adequacy of dialysis was higher in the RSU patients. The proportion of patients previously hospitalized was less in the RSU patients, but total and mean length of stay were comparable.

RSUs are an effective alternative to MRUs for many HD patients. They improve geographic access and are generally more acceptable to patients. There does not seem to be an adverse impact of care in the RSUs, but comparative long-term prospective data are lacking. The cost-effectiveness of RSUs compared to MRUs is uncertain.

Recommendations

Satellite development could be successfully expanded. No single model can be recommended, but key factors include local geography, catchment population, and type of patients to be treated. Appropriate RSU policies are needed to address medical emergencies, patient transfers, management protocols for common clinical problems, and communication links with the MRU.

Methods

See Executive Summary link above.

Further research/reviews required

1. Cost-effectiveness of RSUs
2. Patient safety: comparison of adverse events with longer duration and larger numbers to identify severe events
3. Characteristics and size of the HD population judged to be unsuitable for RSU care
4. Carer perspectives: possible differences between RSUs and MRUs
5. Nursing perspectives: attitudes of nursing staff given the increased responsibility and autonomy of senior staff in RSUs.

Written by Dr Paul Roderick, University of Southampton, United Kingdom

INAHTA Briefs

Issue 2007/12

Title **Systematic Review on Urine Albumin Testing for Early Detection of Diabetic Complications**

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Reference Health Technol Assess 2005;9(30). August 2005.
www.hta.ac.uk/execsumm/summ930.htm

Aim

To assess the evidence on microalbuminuria (MA) as an independent prognostic factor for diabetic complications in patients with type 1 or type 2 diabetes mellitus (DM); and, in subjects with type 1 or type 2 DM and MA, assess whether improved control of glycemia or blood pressure influences diabetic complications more than in patients without MA.

Conclusions and results

The complications assessed were: mortality, the development and progression of retinopathy, and development of renal failure. Patients with type 1 or type 2 DM and MA have a relative risk (RR) of all-cause mortality of 1.8 (see report for confidence intervals) and 1.9 respectively. Similar RR's were found for other mortality endpoints, with age of cohort being inversely related to the RR in type 2 DM. In patients with type 1 DM, there is evidence that MA or raised albumin excretion rate has only weak, if any, independent prognostic significance for the incidence of retinopathy and no evidence that it predicts progression of retinopathy, although evidence is strong for the independent prognostic significance of MA or raised albumin excretion rate in the development of proliferative retinopathy. For type 2 DM, there is no evidence of any independent prognostic significance for the incidence of retinopathy and little, if any, prognostic relationship between MA and the progression of retinopathy or development of proliferative retinopathy. In patients with type 1 DM and MA there is an RR of developing end-stage renal disease (ESRD) of 4.8 and a higher RR (7.5) of developing clinical proteinuria, with a significantly greater fall in glomerular filtration rate (GFR) in patients with MA. In patients with type 2 DM, similar RR's were observed. In adults with type 1 or type 2 DM and MA at baseline, the numbers progressing to clinical proteinuria and those regressing to normoalbuminuria did not differ significantly. In children with type 1 DM, regression was significantly more frequent than progression. In patients with type 1 or type 2 DM and MA, there is scarce evidence as to whether improved glycemic control has any effect on the incidence of cardiovascular disease (CVD), the incidence or progression of retinopathy, or the development of renal complications. However, among patients not stratified by albuminuria, improved glycemic control benefits retinal and renal complications and may benefit CVD. In the effects of angiotensin-converting enzyme (ACE) inhibitors on GFR in normotensive MA patients with type 1 DM, there was no evidence of a consistent treatment effect. There is strong evidence from 11 trials in normotensive type 1 patients with MA of a beneficial effect of ACE inhibitor treatment on the risk of developing clinical proteinuria and on the risk of regression to normoalbuminuria. Patients with type 2 DM and MA may gain additional cardiovascular benefit from an ACE inhibitor, and there may be a beneficial effect on the development of retinopathy in normotensive patients irrespective of albuminuria. (See full report for additional findings.)

Recommendations

See Executive Summary link above.

Methods

See Executive Summary link above.

Further research/reviews required

Recommendations for microalbuminuria research include: determining rate and predictors of development and factors involved in regression; carrying out economic evaluations of different screening strategies; investigating the effects of screening on patients; standardizing screening tests to enable use of common reference ranges; evaluating the effects of lipid-lowering therapy; and using to modulate antihypertensive therapy.

Written by Dr Martin Mattock, Formerly of St Helier Hospital NHS Trust, United Kingdom

INAHTA Briefs

Issue 2007/13

Title **Randomized Controlled Trials of Conventional Antipsychotic Versus New Atypical Drugs, and New Atypical Drugs Versus Clozapine, in People With Schizophrenia Responding Poorly to, or Intolerant of, Current Drug Treatment**

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Reference Health Technol Assess 2006;10(17). June 2006. www.hta.ac.uk/execsumm/summ1017.htm

Aim

To determine the clinical and cost effectiveness of different classes of antipsychotic drug treatment in people with schizophrenia responding inadequately to, or having unacceptable side effects from, their current medication.

Conclusions and results

In people with schizophrenia whose medication was being changed because of intolerance or inadequate response, there was no disadvantage in quality of life or symptoms over one year in commencing conventional antipsychotic drugs rather than new atypical drugs. On the quality of life scale (QLS) and symptom measures, participants in the conventional arm showed a trend toward greater improvement. Participants reported no clear preference for either class of drug. Net costs of care over the year varied widely with a mean of GBP 18 800 in the conventional drug group and GBP 20 100 in the new atypicals group, not a statistically significant difference.

New atypicals compared with clozapine in people with more narrowly-defined treatment resistance showed an advantage for commencing clozapine in QLS at trend level ($p=0.08$) and in symptoms (PANSS), that was statistically significant ($p=0.01$), at one year. Clozapine showed approximately a 5-point advantage on PANSS total score. Participants reported at 12 weeks that their mental health was significantly better with clozapine than with new atypicals ($p<0.05$). Net costs of care varied widely, with a mean of GBP 33 800 in the clozapine group and GBP 28 500 in the new atypical group, not a statistically significant difference. Of these costs, 4.0% and 3.3% respectively were due to antipsychotic drug costs. The increased costs in the clozapine group appeared to reflect the licensing requirement for inpatient admission for commencing the drug.

Recommendations

In people with schizophrenia whose medication is being changed because of intolerance or inadequate response, there is no disadvantage in terms of quality of life and symptoms, or associated costs of care, over one year in commencing conventional antipsychotic drugs rather than new atypical drugs.

In people with schizophrenia whose medication is being changed because of narrowly defined treatment resistance, there is a statistically significant advantage in terms of symptoms, but not quality of life, over one year in commencing clozapine rather than new atypical drugs.

Methods

Two pragmatic, randomized, controlled trials (RCTs) were undertaken. The first compared the class of older, inexpensive conventional drugs to the class of new atypical drugs in people with schizophrenic disorders, whose current antipsychotic drug treatment was being changed either because of inadequate clinical response, or due to side effects. The second RCT compared the new (non-clozapine) atypical drugs with clozapine in people whose medication was being changed because of poor clinical response to two or more antipsychotic drugs. Both RCTs were 4-center trials with concealed randomization and 3 followup assessments over one year, blind to treatment.

Further research/reviews required

- Randomized trial of NICE antipsychotic treatment guidance using atypical versus conventional drugs in the context of careful management of schizophrenia outlined in this document
- Randomized trial of antipsychotic drug maintenance vs early drug withdrawal plus psychological treatment after the first episode of schizophrenia
- Development of a valid measures of utility in serious mental illness
- Randomized trial of low dose "conventional" vs new atypical in first episode schizophrenia
- Randomized trial of sodium valproate plus antipsychotic drug treatment in acute schizophrenia.

Written by Professor Shon Lewis, University of Manchester, United Kingdom

INAHTA Briefs

Issue 2007/14

Title **Health Benefits of Antiviral Therapy for Mild Chronic Hepatitis C: Randomized Control Trial and Economic Evaluation**

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Reference Health Technol Assess 2006;10(21). June 2006.
www.hta.ac.uk/execsumm/summ1021.htm

Aim

To determine whether the combination of interferon alpha and ribavirin is more effective than no treatment for mild chronic hepatitis C virus (HCV) infection.

Conclusions and results

Virology: In the treatment group, 32 of 98 (33%) patients achieved a sustained viral response (SVR). Patients infected with genotype 1 had a lower SVR than those infected with genotype non-1. No patients who failed to achieve a 2-log drop in viral load at 12 weeks achieved a SVR.

HRQOL: Compared to baseline values, health-related quality of life (HRQOL) fell during treatment and rose with treatment cessation. Patients having a SVR showed modest improvements in HRQOL at 6 months post treatment.

Cost effectiveness: The gain in HRQOL for patients with mild hepatitis C, who were treated and had a SVR, offset the HRQOL reduction during treatment. The overall lifetime cost per QALY gained for treatment compared to no treatment for mild hepatitis C was approximately GBP 20 000 per QALY. The mean cost per QALY gained for patients aged 40 years with genotype non-1 was GBP 5000. For patients aged 40 years with genotype 1, treatment at a mild stage reduced QALYs (-0.05) and was not cost effective. Cost effectiveness improves for those who begin treatment at a younger age; treatment was cost effective for patients with genotype 1 who were aged 20 years at treatment. The intervention was not cost effective for patients aged 65 years or over, irrespective of genotype.

Using viral kinetics to determine early cessation of treatment improved the cost effectiveness of treatment for mild hepatitis C, but the intervention was still only cost effective for patients with genotype non-1.

The model used efficacy estimates from the literature to estimate the cost effectiveness of treating mild patients with pegylated interferon alpha and ribavirin, and demonstrated that this treatment would be cost effective at a mild stage for all hepatitis C patients with genotype non-1 and those with mild hepatitis, due to hepatitis C genotype 1, aged <65 years.

Recommendations

For patients with mild hepatitis C and viral genotype non-1 (genotypes 2 or 3), interferon alpha and ribavirin treatment is effective and cost effective at the cost per QALY threshold used by NHS policymakers. Using viral kinetic data to target treatment at likely SVR cases further improves cost effectiveness. For patients aged <65 years with genotype non-1 and those with genotype 1, the most cost-effective strategy is to treat patients with mild disease. Using liver biopsy to assess disease severity no longer appears justified.

For hepatitis C patients aged >65 years with mild hepatitis due to genotype 1 infection, the low SVR following antiviral treatment means that the cost of intervention is not justified. In these patients it is more cost effective to monitor mild disease, and treat only patients who progress to moderately severe hepatitis C. Patients aged >65 years with genotype 1 infection should be offered liver biopsy to identify moderate or severe disease, which should be treated. Patients in this age group with mild disease should not be treated.

Methods

See Executive Summary link above.

Further research/reviews required

- Long-term HRQOL for patients who have had a SVR
- Impact of pegylated interferon alpha and ribavirin on SVRs HRQOL and health service costs
- Use of predictive tests based on pharmacogenomics to target therapy to those most likely to respond
- Results of not using liver biopsy before treatment in patients with genotype non-1 and younger patients with genotype 1 (<65 years), and the impact of this strategy on costs and outcomes
- Role of noninvasive tests to identify those in the >65 year old group with genotype 1 infection, with more advanced fibrotic disease (> stage 2), who need treatment.

Written by Professor Howard Thomas, St Mary's Hospital Campus, Imperial College, London, United Kingdom

INAHTA Briefs

Issue 2007/15

Title **Pressure Relieving Support Surfaces: A Randomized Evaluation**

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Reference Health Technol Assess 2006;10(22). June 2006.
www.hta.ac.uk/execsumm/summ1022.htm

Aim

To determine any differences between alternating pressure overlays and alternating pressure replacement mattresses with respect to development of new pressure ulcers, healing of existing pressure ulcers, patient acceptability, and cost effectiveness of different pressure relieving surfaces; and to investigate the specific additional impact of pressure ulcers on patients' wellbeing.

Conclusions and results

We assessed 6155 patients for eligibility to the trial, and randomized 1972 (990 to alternating pressure overlay and 982 to alternating pressure mattress replacement). Intention-to-treat analysis found no statistically significant difference in the proportions of patients developing a new pressure ulcer of ≥ Grade 2 (10.7% overlay patients, 10.3% mattress replacement patients, a difference of 0.4%, 95% CI: –2.3%, 3.1%, p=0.75). Logistic regression analysis, used to adjust for minimization factors and prespecified baseline covariates, showed no difference between mattresses with respect to the odds of ulceration (odds ratio 0.94, 95% CI: 0.68, 1.29). There was no evidence of a difference between the mattress groups as regards time to healing (p=0.86). The Kaplan-Meier estimate of the median time to healing was 20 days for each intervention. More patients allocated overlays requested mattress changes due to dissatisfaction (23.3%) than did mattress replacement patients (18.9%, p=0.02), with more than a third of patients reporting difficulties moving in bed and getting in/out of bed. There is a higher probability (64%) that alternating mattress replacements save cost; they were associated with lower overall costs (GBP 74.50 per patient on average, mainly due to reduced length of stay) and greater benefits (a delay in time to ulceration of 10.64 days on average). Patients' accounts highlighted that the development of a pressure ulcer could be pivotal in the trajectory from illness to recovery, by preventing full recovery or causing varied impacts on their quality of life.

Recommendations

No difference was found between alternating pressure mattress replacements and overlays in terms of the proportion of patients developing new pressure ulcers. However, alternating pressure mattress replacements are more likely to save cost.

Methods

A multicenter, randomized, controlled, open, fixed-sample, parallel group trial with equal randomization. The main trial design was supplemented with a qualitative study involving a purposive sample of 20 to 30 patients who developed pressure ulcers, to assess the impact of pressure ulcers on well-being. A focus group was carried out with Clinical Research Nurses (CRNs), who participated in the PRESSURE trial to explore their role and observations of pressure area care.

Further research/reviews required

1. RCT comparing alternating pressure mattress replacements and high-specification foam mattresses in patients at moderate to high risk (it may not be possible to answer this question in the UK where alternating pressure surfaces have become the standard for at-risk patients).
2. Trials to measure the time to ulceration as the primary endpoint since this is more informative economically and possibly from a patient and clinical perspective.
3. An accurate costing study to better understand the cost of pressure ulcers to health and social services in the UK.
4. Trials in higher risk groups of patients in whom serious pressure ulcers are more common and the consequences greater (eg, spinal cord injuries).
5. Epidemiological studies to determine whether people with diabetes are at higher risk of heel ulceration.

Written by Professor Nicky Cullum, University of York, United Kingdom

Title **Effectiveness and Cost Effectiveness of Salicylic Acid and Cryotherapy for Cutaneous Warts. An Economic Decision Model**

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Reference Health Technol Assess 2006;10(25). July 2006.
www.hta.ac.uk/execsumm/summ1025.htm

Aim

To estimate the costs of common treatments for cutaneous warts, and the health benefits and risks associated with these treatments; to create an economic decision model to evaluate the cost effectiveness of the treatments; and to comment on whether a randomized controlled trial (RCT) is needed, feasible, and cost effective – and if so, its size and design.

Conclusions and results

Many patients use over-the-counter (OTC) treatments prior to seeing a GP. The most commonly used OTC preparation was salicylic acid (SA), although OTC cryotherapy (Wartner®) is increasingly common. The economic model also included duct tape (Gaffa tape) since a recent RCT of cryotherapy vs duct tape suggested that duct tape might have treatment benefits.

The economic model suggests that the 3 most cost-effective options for treating warts (compared to spontaneous resolution) are duct tape, OTC cryotherapy, and OTC salicylic acid. However, evidence supporting the first two is limited. The model estimates, within a range of uncertainty, incremental cost-effectiveness ratios for these treatments of 0.22, 0.76, and 1.12 respectively.

Of treatments prescribed by a GP, the incremental cost-effectiveness ratios were 2.20 for salicylic acid, or from 1.95 to 7.06 for cryotherapy (depending on frequency of application and mode of delivery). The cost effectiveness of cryotherapy delivered by a nurse could be comparable to SA prescribed by a GP under certain circumstances.

Recommendations

Cryotherapy by a physician in primary care is an expensive way to treat warts. Options such as GP-prescribed SA and nurse-led cryotherapy clinics are more cost effective, but still expensive compared to self-treatment. Since most cutaneous warts are minor and spontaneously resolve in time, a shift toward self-treatment may be warranted. Although duct tape and OTC cryotherapy appear promising self-treatment options, more research is required to confirm the efficacy of these methods. A public awareness campaign may be useful to educate patients about the self-limiting nature of warts and the OTC treatment options available.

Methods

Various primary and secondary data collection methods were used to develop an economic decision model. Primary data collection involved focus groups, structured interviews with patients and health professionals, and observation of practice. These methods aimed to capture the common care pathways and identify important issues. The results were used in designing a postal survey sent to 723 patients who had recently visited their GP for treatment of warts. The data were used to estimate the effectiveness of wart treatments in primary care. These estimates were compared with outcomes reported in the Cochrane review, which were largely obtained from RCTs in secondary care.

Secondary data used in the decision model came from several sources, including the recently updated Cochrane systematic review and published cost and prescribing data. Combining primary and secondary data sources has led to a model that reflects actual practice to the extent possible.

Further research/reviews required

- Head-to-head RCT comparing SA to nurse-led cryotherapy (to provide efficacy data for these two most common treatments and to measure the cost effectiveness of nurse-led clinics).
- Trial comparing OTC salicylic acid, cryotherapy (Wartner®), and duct tape (home treatment might encourage more patients to self-treat warts, reducing the burden on the NHS).

Written by Dr Kim Thomas, Queen's Medical Centre, United Kingdom

INAHTA Briefs

Issue 2007/17

Title **A Systematic Literature Review of the Effectiveness of Non-Pharmacological Interventions to Prevent Wandering in Dementia and Evaluation of the Ethical Implications and Acceptability of Their Use**

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Reference Health Technol Assess 2006;10(26). July 2006. www.hta.ac.uk/execsumm/summ1026.htm

Aim

To determine the effectiveness and cost effectiveness of non-pharmacological interventions in preventing wandering in people with dementia, in comparison to usual care; and to evaluate the acceptability such interventions and identify ethical issues.

Conclusions and results

Effectiveness: Ten studies met the inclusion criteria (3 multisensory environment; 1 music therapy; 1 exercise; 2 special care units; 2 aromatherapy; 1 behavioral intervention). There was no robust evidence to recommend any non-pharmacological intervention to reduce wandering in dementia. There was some evidence (poor quality) for the effectiveness of exercise and multisensory environment.

Cost effectiveness: There were no relevant studies to determine cost effectiveness of the interventions.

Acceptability/ethical issues: Findings from the narrative review and focus groups were comparable. Exercise and music therapy were the most acceptable interventions and raised no ethical concerns. All other interventions, except for physical restraints, were considered acceptable. Considerable ethical concerns exist to the use of electronic tagging, tracking devices, and physical barriers. The literature ignores the perspectives of people with dementia. The small number of participants with dementia expressed caution regarding the use of unfamiliar technology. Balancing risk and risk assessment in the management of wandering was an important theme for all carers.

Recommendations

There is no robust evidence to make any reliable recommendations for clinical practice.

Methods

See Executive Summary link above.

Further research/reviews required

- High-quality studies, preferably RCTs, to determine the clinical and cost effectiveness of non-pharmacological interventions that allow safe wandering and that are considered practically and ethically acceptable by carers and people with dementia.
- Large, long-term cohort studies to evaluate morbidity and mortality associated with wandering in dementia for people in the community and in residential care. Such data would inform long-term cost-effectiveness studies.
- The diversity of "wandering" behaviors, measuring outcomes that reflect: significant consequences of wandering, the physical safety of the person with dementia, the desired quality of life for people with dementia and their carers, and acceptability of the intervention.
- Views of people with dementia on the acceptability of non-pharmacological interventions to reduce wandering. As rapid development of assistive technologies yields a more diverse and sensitive range of electronic devices, research into users' views, acceptability, and feasibility should precede expensive and complex quantitative studies to evaluate effectiveness.
- Risk assessment and management processes used by carers for people with dementia who wander, and the effectiveness and acceptability of specific interventions to promote safe wandering.
- Studies, with all relevant stakeholders, on the boundaries between walking, safe wandering, and unsafe wandering. Such in-depth research would help identify significant consequences of wandering for which relevant, appropriate outcome measures could be determined.

Written by Dr Louise Robinson, University of Newcastle upon Tyne, United Kingdom

INAHTA Briefs

Issue 2007/18

Title **Accurate, Practical, and Cost-Effective Assessment of Carotid Stenosis in the UK**

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Reference Health Technol Assess 2006;10(30). September 2006.
www.hta.ac.uk/execsumm/summ1030.htm

Aim

To assess the cost effectiveness of various imaging strategies to diagnose carotid stenosis in stroke prevention clinics.

Conclusions and results

In 41 included studies (2404 patients, median age 60–65 years), most data were available on 70% to 99% stenosis. Contrast-enhanced magnetic resonance angiography (CEMRA) was the most accurate (sensitivity 0.94, 0.88–0.97; specificity 0.93, 0.89–0.96) compared with ultrasound (U/S), magnetic resonance angiography (MRA), and computed-tomographic angiography (CTA) which were all similar (eg, for U/S: sensitivity 0.89, 0.85–0.92; specificity 0.84, 0.77–0.89). Data for 50% to 69% stenoses and on tests used in combination were too sparse to be reliable. There was heterogeneity between studies for all imaging modalities except CTA, and some evidence of publication bias. The individual patient data (2416 patients) showed that the literature overestimated test accuracy in routine practice, and that tests perform differently in symptomatic and asymptomatic arteries. It provided data on an older and more representative population than did the literature, and information on tests used in combination. In the cost-effectiveness model, strategies allowing more patients to reach endarterectomy quickly, and where those with 50% to 69% stenosis would be offered surgery (as well as the 70–99% group), prevented most strokes and produced the greatest net benefit. This included most strategies with U/S as first or repeat, but generally not those with intra-arterial angiography (IAA). However, the model was sensitive to less-invasive test accuracy, cost, and timing of endarterectomy. In surgery occurring by 80 days or later, strategies relying on U/S were no longer cost effective since patients with lesser degrees of stenosis would not benefit. Hence, in patients investigated late after transient ischemic attack (TIA), accuracy is crucial and CEMRA should be used to identify patients for surgery.

Recommendations

In the UK, less-invasive tests can be used in place of IAA if radiologists trained in carotid imaging are available to perform and interpret them. Imaging should be carefully audited. Stroke prevention clinics should strive to reduce waiting times at all stages to improve speed of access to endarterectomy. Imaging accuracy is very important in patients presenting late, and U/S results should be confirmed by CEMRA, as patients with 50% to 69% or less stenosis are less likely to benefit. Although one U/S alone seemed to provide the greatest net benefit, lack of confidence in, and the operator dependence of this technique mean that at least a second independent U/S should be obtained prior to surgery.

Methods

See Executive Summary link above.

Further research/reviews required

Methodology for evaluating imaging tests needs to improve (blinding, prospective studies, and carefully differentiating the symptomatic from the asymptomatic artery in analyses). More data are required on the accuracy of less-invasive tests. More data are required on all modalities, CTA in particular. Randomized trials should be considered to evaluate less-invasive imaging strategies in stroke prevention prior to endarterectomy. Streamlined methods of collecting routine audit data on less-invasive tests in routine clinical practice are required, as are streamlined and reliable methods for evaluating new technologies. Better cost information is required for stroke care, surgical procedures, outpatient visits, and imaging tests. More information is needed on the effect of secondary prevention drugs in combination. More and better information is needed from stroke epidemiology studies to determine the distribution of carotid disease by age, gender, and TIA/minor stroke type. A more sophisticated model could be developed from the one constructed in this work to include, eg, differences in the risks of endarterectomy between men and women.

Written by Professor Joanna Wardlaw, University of Edinburgh, United Kingdom

INAHTA Briefs

Issue 2007/19

Title **Cost Effectiveness of Using Prognostic Information to Select Women With Breast Cancer for Adjuvant Systemic Therapy**

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Reference Health Technol Assess 2006;10(34). September 2006.
www.hta.ac.uk/execsumm/summ1034.htm

Aim

To examine the evidence for the cost effectiveness of systemic adjuvant therapies of early breast cancer.

Conclusions and results

Prognostic and predictive factors may be used to indicate the status, future behavior, and likelihood of response to various therapies by women with breast cancer. Some systematic attempts have been made to establish guidelines for using prognostic and predictive information in breast cancer. None of these guidelines have examined the cost effectiveness of basing adjuvant systemic therapy on such information.

Quality of prognostic studies: A characteristic was the lack of empirical evidence to support the importance of particular features affecting the reliability of study findings and avoidance of bias. Multiple small and unvalidated studies were common. *Systematic review of studies of prognostic factors:* A few potentially reliable reviews were found for 18 different factors. The lack of good quality systematic reviews and well-conducted studies of prognostic factors in breast cancer was striking. There was clear evidence of a relationship between tumor size, proliferation indices, P53, cathepsin D, and urokinase and its receptors and survival. *Prognostic models:* Few published prognostic models have been independently re-examined. Where validation studies have been done, the samples were often ill-defined and smaller, with short followup and different patient outcomes. Evidence from validation studies support the prognostic value of the Nottingham Prognostic Index (NPI). Improvement of this index depends on finding factors that are as important as, but independent of, lymph node, stage, and pathological grade. Predictive factors ER/PgR and HER2 predict response to hormone and trastuzumab respectively as these drugs require intact receptors. No evidence was found that other factors were useful predictors of response/survival. *Survey of UK practice:* This survey confirmed pathological nodal status, tumor grade, tumor size, and hormone receptor (ER) status as the most clinically important factors when selecting women for adjuvant systemic therapy, but much variation exists. Some centers used NPI-based protocols while others did not use a single index score. Consensus appeared greatest when selecting women for adjuvant hormone therapy, based primarily upon ER/PgR status rather than combinations of factors.

Cost-effectiveness of prognostic models: Only 5 papers were identified, and these varied in quality. By combining methodologies used in determining prognosis with those used in health economic evaluation, it was possible to simulate the effectiveness (survival and quality-adjusted survival) and cost effectiveness associated with the decision to treat individual women or groups of women with different prognostic characteristics. A set of patient data on prognostic factors, treatments, and outcomes of women diagnosed with early breast cancer made it possible to directly estimate a regression-based risk equation. The model showed that effectiveness and cost effectiveness of adjuvant systemic therapy has the potential to vary substantially depending upon prognosis.

Recommendations

For some women, therapy may prove effective and cost effective, whereas for others it may prove detrimental. Outputs from models based on the methods described may be useful at the patient level (where a clinician must determine whether net benefits can be obtained from adjuvant therapy) and at the policy-making level.

Methods

See Executive Summary link above.

Further research/reviews required

Research needed includes: the quality of studies of prognostic and predictive factors and models in general (robust tools to score quality and templates to improve the research quality are likely to be beneficial); the cost-effectiveness of prognostic and predictive factors; and the most effective ways to present data from studies of prognostic and predictive factors.

Written by Dr Christopher Williams, United Bristol Healthcare Trust, United Kingdom

INAHTA Briefs

Issue 2007/20

Title **Clinical Effectiveness and Cost-Effectiveness of Tests for the Diagnosis and Investigation of Urinary Tract Infection in Children: A Systematic Review and Economic Model**

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Reference Health Technol Assess 2006;10(36). Oct 2006. www.hta.ac.uk/execsumm/summ1036.htm

Aim

To determine diagnostic accuracy of tests for detecting urinary tract infection (UTI) in children under 5 years of age; to evaluate the effectiveness of tests used to further investigate children with confirmed UTI, the effectiveness of following up children with UTI, the cost effectiveness of diagnostic and imaging tests for diagnosis and followup UTI in children under 5; and to develop a preliminary diagnostic algorithm for healthcare professionals who manage these patients.

Conclusions and results

Diagnosis of UTI: *Clinical tests;* these studies examined a variety of clinical characteristics, and overall conclusions could not be drawn. *Urine sampling;* there was good agreement between culture of clean voided urine (CVU) and suprapubic aspiration (SPA) urine samples. Limited data suggested bag/pad/nappy samples may be suitable alternatives to SPA. *Dipstick;* there was insufficient info to assess accuracy of dipstick tests for protein or blood. Positive test for nitrite and LE was most accurate for ruling in disease, and negative test for both nitrite and LE was most accurate for ruling out disease. A glucose test, assessed in 3 studies, was more accurate than other dipstick tests, but its usefulness was limited. *Microscopy;* Microscopy positive for pyuria and bacteriuria was best for ruling in disease, and microscopy negative for both pyuria and bacteriuria was best for ruling out disease. *Culture;* dipslide culture was less accurate than combinations of dipstick or microscopy tests.

Further Investigation of UTI: *Localization of UTI;* studies of clinical and lab tests showed poor accuracy. Scintigraphic techniques were the only investigations able to accurately localize UTI. *Detection of reflux;* contrast-enhanced ultrasound was accurate both for ruling in and for ruling out reflux. *Prediction of scarring;* there was insufficient info to assess accuracy of tests to predict scarring. *Detection of scarring;* static renal scintigraphy and dynamic renal imaging were accurate. Ultrasound was reasonable for ruling in, but not for ruling out scarring. *Multiple aims;* accuracies of these studies were generally poor.

Effectiveness of Followup (1 abstract): Routine imaging after initial UTI lead to higher rates of imaging, identification of reflux, and prophylaxis than selected imaging after repeat infection, it did not lead to reduction in recurrent UTIs or renal scarring.

Economic Evaluation: Only 1 study, with several potential limitations for NHS decision making, met inclusion criteria. A decision analytic model was developed from an NHS perspective. This found that optimal diagnostic strategy for children with symptoms of UTI depends on several factors, eg, sex and age, and health service's maximum willingness to pay for additional QALYs.

Recommendations

Results of systematic review were used to derive an algorithm for diagnosing UTI in children under 5 years of age. This represents conclusions of review in terms of practice. Data were insufficient to propose an algorithm for further investigation of UTI in children under age 5.

Methods

See Executive Summary link above.

Further research/reviews required

Future studies should follow the STARD guidelines for reporting of diagnostic accuracy studies, and should consider relevant subgroups, eg, neonates. The following areas require further research for diagnosis of UTI: urine sampling methods in younger children; accuracy of combination dipstick tests for diagnosing UTI; handling of indeterminate nitrite and LE dipstick test results; usefulness of including microscopy in diagnostic work up of UTI; usefulness of universal confirmatory culture; and usefulness of culture to determine antibiotic sensitivities in children with confirmed UTI. (See Executive Summary link above for areas where further research may provide additional useful information.)

Written by Dr Marie Westwood, University of York, United Kingdom

INAHTA Briefs

Issue 2007/21

Title **What Are the Clinical Outcome and Cost Effectiveness of Endoscopy Undertaken by Nurses When Compared with Doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET)**

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Reference Health Technol Assess 2006;10(40). Oct 2006. www.hta.ac.uk/execsumm/summ1040.htm

Aim

To compare the clinical outcome and cost effectiveness of doctors and nurses undertaking upper and lower gastrointestinal endoscopy by measuring the: acceptability to patients; quality of the process; outcome for, and value to patients; resources consumed by the NHS and by patients; and the relative cost effectiveness of nurses and doctors.

Conclusions and results

The two groups were well matched at baseline for administrative, demographic, and clinical characteristics. Significantly more patients were changed from a planned endoscopy by a doctor to a nurse than vice versa, mainly for staffing reasons. No significant difference was found between the two groups in the primary or secondary outcome measures at 1 day, 1 month and 1-year post procedure, with the exception of patient satisfaction. One day after the procedure, patients were significantly more satisfied with nurses. Nurses were more thorough in the examination of the esophagus and stomach, but no different from doctors in the examination of the duodenum and colon. There was no significant difference in costs to the NHS or patients, although there was a trend toward doctors costing slightly more. The quality of life measures also showed a slight improvement in scores in the doctor group. Although this does not reach traditional levels of statistical significance, the economic evaluation, taking account of uncertainty around the results (both cost and quality of life), suggests that doctors are likely to be more cost effective than nurses.

Recommendations

Nurses can undertake diagnostic endoscopy safely and effectively. However, doctors are more likely to be cost effective. If decision makers nevertheless choose to continue the current trend toward diagnostic endoscopy undertaken by nurses rather than doctors, this has implications for human resources, training, and governance. We estimate that 2 nurse endoscopists will be needed per endoscopy unit.

Methods

The study was a pragmatic randomized controlled trial. Zelen's randomization before consent was used to minimize any distortion of existing practice in the participating sites. Primary outcome measure was the Gastrointestinal Symptom Rating Score (GSRQ). Secondary outcome measures were anxiety scores (STAI), SF36, Euroqol (EQ5D), and Gastrointestinal Endoscopy Satisfaction Questionnaire (GESQ). An economic evaluation was conducted alongside the trial, assessing the relative cost effectiveness of nurses and doctors, and estimating the probability that nurse endoscopy is cost effective.

Further research/reviews required

There is a need to evaluate the clinical outcome and cost effectiveness of nurses undertaking the more complicated and expensive procedures of colonoscopy and therapeutic endoscopy, and diagnostic endoscopy in other settings. The cost effectiveness of nurses may change as they become more experienced, and this will need to be re-evaluated in the future. There is also a need to assess the implications of increasing the number of nurse endoscopists on waiting times for patients, and the career implications and opportunities for these professionals.

Finally, the clinical outcome and cost effectiveness of diagnostic endoscopy for all current indications need to be evaluated.

Written by Professor J G Williams, University of Wales Swansea, United Kingdom

INAHTA Briefs

Issue 2007/22

Title **Cost Effectiveness of Cell Salvage and Alternative Methods of Minimizing Perioperative Allogeneic Blood Transfusion: A Systematic Review and Economic Model**

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Reference Health Technol Assess 2006;10(44). Nov 2006. www.hta.ac.uk/execsumm/summ1044.htm

Aim

To compare patient outcomes, resource use, and cost to the NHS associated with cell salvage and alternative methods of minimizing perioperative allogeneic blood transfusion, and to assess the impact of changes in the use of cell salvage on the NHS and the National Blood Service.

Conclusions and results

Preoperative autologous donation (PAD) reduced the risk of allogeneic blood transfusion by 64% (RR=0.36: 95% CI: 0.25, 0.51) for active vs control studies. PAD plus erythropoietin (EPO) reduced exposure to allogeneic blood transfusion by a relative 44% (95% CI 26%–57%) in orthopedic surgery and 64% (95% CI 12%–85%) in cardiac surgery. Fibrin sealants reduced the relative risk of exposure to allogeneic transfusion by a relative 54% (95% CI 32%–68%). EPO alone reduced exposure to allogeneic blood transfusion by a relative 51% (95% CI 36%–62%) in orthopedic surgery and did not significantly reduce exposure to allogeneic blood in cardiac surgery (RR 0.40, 95% CI 0.13, 1.22). Cell salvage reduced the relative risk of exposure to allogeneic blood by a relative 41% (95% CI 27%–52%). Tranexamic acid reduced the relative risk of exposure to allogeneic blood by 34% (95% CI 19%–46%). Acute normovolemic hemodilution (ANH) reduced the relative risk of exposure to allogeneic blood by 31% (95% CI 16%–44%). Aprotinin reduced the relative risk of exposure to allogeneic transfusion by 30% (95% CI 24%–36%). Epsilon aminocaproic acid resulted in a statistically nonsignificant reduction in exposure to allogeneic blood (RR 0.48, 95% CI 0.19, 1.19). The use of a restrictive transfusion threshold reduced exposure to allogeneic and/or autologous blood transfusion by a relative 42% (95% CI 29%–53%) compared to control. Poor methodological quality, significant heterogeneity, and inadequate reporting of long-term clinical outcomes were evident and should be considered when assessing the evidence of effectiveness. Cell salvage was likely to be cost effective compared to all of the alternative transfusion strategies except ANH. The expected cost of cell salvage in the primary analysis was GBP 4930 per person. The incremental saving associated with cell salvage ranged from GBP 28 to GBP 336 per person. ANH and fibrin sealants had lower expected costs than cell salvage. Cell salvage was associated with improved outcomes compared to all the alternative transfusion strategies except PAD. This translated to a small gain in QALYs. The probability that cell salvage is cost effective compared to all the alternative strategies except ANH was more than 50%. ANH was likely to be more cost effective than cell salvage. Washed intraoperative cell salvage was more cost effective than unwashed postoperative cell salvage for cardiac surgery. Unwashed postoperative cell salvage appeared to be more cost effective than washed intra operative cell salvage for orthopedic surgery.

Recommendations

All of the transfusion strategies to minimize the use of perioperative allogeneic blood transfusion significantly reduced exposure to allogeneic blood. Cell salvage appeared to be cost effective in elective surgery compared to all other transfusion strategies except ANH. However, data for the model were generally poor quality, and results of the economic analysis should be treated with caution.

Methods

See Executive Summary link above.

Further research/reviews required

Adequately powered, high-quality RCTs directly comparing the included blood transfusion strategies that report long-term clinical outcomes are needed to assess the clinical value of avoiding allogeneic blood transfusion and receiving autologous blood transfusion. Observational and tracking studies are required to assess the likelihood of adverse events associated with allogeneic and autologous blood transfusion and their impact on mortality, health status, and health-related quality of life.

Written by Ms Linda Mary Davies, University of Manchester, United Kingdom

INAHTA Briefs

Issue 2007/23

Title **Systematic Reviews of Clinical Decision Tools for Acute Abdominal Pain**

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Reference Health Technol Assess 2006;10(47). November 2006.
www.hta.ac.uk/execsumm/summ1047.htm

Aim

To systematically examine the literature on paper- or computer-based decision tools (DTs) for patients with acute abdominal pain (AAP).

Conclusions and results

Making accurate decisions for patients with acute abdominal pain (AAP) is difficult, because many conditions cause it, and no single clinical finding or test is both specific and sensitive. To avoid missing seriously ill patients, many undergo unnecessary surgery, with negative laparotomy rates of 25%. Delays can lead to perforation rates of 20%. Many paper- or computer-based DTs, that combine two or more clinical or laboratory findings have been developed to help manage patients with AAP. No consensus exists on which of these DTs is most appropriate for clinical use.

Question 1, accuracy review: 32 studies were eligible whereof 13 reported false-positive and false-negative rates for both DTs and unaided doctors' diagnosis, enabling direct comparisons. In random effects meta-analyses of these 13 studies, DTs had significantly lower false-positive rates and may have higher false-negative rates than unaided doctors; significant heterogeneity was present. Two studies compared the diagnostic accuracies of doctors aided by DTs to unaided doctors' performance. Neither study demonstrated evidence of a difference in performance between aided and unaided doctors. Meta-regression of DTs from 32 studies showed association of diagnostic odds ratio with type of data set used ($p<0.001$), year of study ($p<0.001$), and whether study authors evaluated a tool they had themselves developed ($p=0.02$). There was no evidence of an association between disease prevalence and the accuracy of diagnostic DTs ($p=0.96$). None of the other quality indicators tested were significantly associated with the diagnostic odds ratio of DTs in the meta-regression. *Question 2, impact study review:* Only 1 of 15 potentially relevant papers was eligible, showing a clear need to improve the design and implementation of such studies. In the only eligible study, a 4-arm cluster randomized trial showed similar impacts of a structured paper checklist and the computer DT on hospital admission rates, perforation rates, and negative laparotomy rates. *Question 3, usability:* Usage rates of AAP DTs from studies retrieved for the accuracy and impact reviews ranged from 10%–77%. Possible determinants of usability include the reasoning method used, the number of data items to enter, and the output format. *Question 4, cost effectiveness:* A deterministic cost-effectiveness comparison demonstrated that a structured paper checklist is likely to be more cost effective than a computer-based DT, under stated assumptions.

Recommendations

With their significantly lower false-positive rates than doctors, DTs are potentially useful in confirming a diagnosis of acute appendicitis, but not in ruling it out. The clinical use of well-designed paper or computer-based structured checklists is a promising way to improve management of AAP patients, subject to further research.

Methods

See Executive Summary link above.

Further research/reviews required

- Better-designed studies are needed to evaluate the accuracy and impact of AAP decision tools on clinical decisions (eg diagnosis) and patient outcomes.
- Primary studies are needed to assess the usability of such DTs.
- Further research is needed to identify the most accurate AAP DT, whether it is computer-based or paper-based.

Research on decision tools in general should focus more on clinical problems and use accepted biometric methods, whatever the technology.

Written by Professor Jeremy C Wyatt and Dr Joe Liu, University of Dundee, United Kingdom

INAHTA Briefs

Issue 2007/24

Title **Evaluation of the Ventricular Assist Device Program in the UK**

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Reference Health Technol Assess 2006;10(48). November 2006.
www.hta.ac.uk/execsumm/summ1048.htm

Aim

To summarize the effectiveness and cost-effectiveness literature on ventricular assist devices (VADs); collect data on survival, transplantation rates, health-related quality of life (HRQoL), and resource use for VAD and non-VAD transplant candidates in the UK; construct cost-effectiveness and cost-utility models of VADs in a UK context; and investigate the factors that drive costs and survival.

Conclusions and results

Of the 70 VAD patients, 30 (43%) died pre-transplant, 31 (44%) underwent transplantation, and 4 (6%) recovered and had the VAD removed. Five (7%) were still supported for median 279 days at the end of the study. Bridge to transplant/recovery rates were consistent with published rates. Survival from VAD implant was 74% at 30 days and 52% at 12 months. There were 320 non-fatal adverse events in 62 patients during 300 months of VAD support, mostly in the first 30 days after implant. Commonly observed events were bleeding, infection, and respiratory dysfunction. Twenty-nine (41%) patients were discharged from hospital with VAD. For patients successfully bridged to transplant, 1-year survival after transplantation was 84%.

Seventy-one inotrope-dependent and 179 non-inotrope-dependent transplant candidates were listed. Death rates while listed were 10% and 8% and median waiting times were 16 and 87 days. For transplant recipients 1-year survival was 85% and 84%.

Symptom scores were similar in all groups pre-transplant. After transplantation all groups showed a marked and similar improvement in physical and psychosocial function. (See Executive Summary link above.)

Cognitive impairment was not found to be more common in VAD patients than non-VAD patients after transplantation.

Mean VAD implant cost, including device, was GBP 63 830, with costs of VAD support for survivors of GBP 21 696 in month one and GBP 11 312 in month two. Main cost drivers were the device, staffing, ICU stay, initial implant hospital stay and adverse events.

For the base case, extrapolating over the lifetime of the patients mean cost for VAD patients was GBP 173 841, mean survival 5.63 and mean QALYs 3.27 years. Costs for inotrope-dependent patients were GBP 130 905, mean survival 8.62 and mean QALYs 4.99 years. Non inotrope-dependent transplant candidates had similar survival rates to those on inotropes but lower costs. Compared with the worst clinical scenario the lifetime incremental cost-effectiveness ratio (ICER) for VADs was GBP 49 384 per QALY. In sensitivity analyses the mean ICER for the lifetime model, compared with the worst clinical scenario, ranged from GBP 35 121 if the device cost was zero to GBP 49 384. Since neither inotrope-dependent transplant candidates nor the worst-case scenario were considered fair controls we investigated the assumption that, in the absence of VAD technology, we would have a mixture of these situations. For mixtures considered the ICER for VADs ranged from GBP 79 212 per QALY to the non-VAD group being both cheaper and more effective.

Recommendations

Data from the published studies and the current study are insufficient to construct a fair comparison group for VADs. If the worst scenario were plausible, and we can extrapolate results to the lifetime of the patients, VAD recipients can expect improved survival and HRQoL, but VADs would not be cost effective at traditional thresholds.

Methods

See Executive Summary link above.

Further research/reviews required

- Randomized controlled trials in the UK using current second generation devices or subsequent devices (focus on long-term circulatory support or bridge to recovery)
- Modeling of the impact of VADs on the transplant program.

Written by Dr Linda Sharples, MRC Biostatistics Unit & Papworth Hospital NHS Trust, United Kingdom

INAHTA Briefs

Issue 2007/25

Title **Topotecan, Pegylated Liposomal Doxorubicin Hydrochloride and Paclitaxel for Second-Line or Subsequent Treatment of Advanced Ovarian Cancer: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2006;10(9). March 2006. www.hta.ac.uk/execsumm/summ1009.htm

Aim

To examine the clinical effectiveness and cost effectiveness of intravenous formulations of topotecan monotherapy, pegylated liposomal doxorubicin hydorocholoride (PLDH) monotherapy, and paclitaxel alone or in combination with a platinum-based compound for second-line or subsequent treatment of advanced ovarian cancer (AOC).

Conclusions and results

Nine randomized controlled trials (RCTs) were identified. Three trials included participants with both platinum-resistant and platinum-sensitive AOC. Two trials included only participants with platinum-sensitive disease. A further 4 trials were identified. Participants with platinum-resistant disease showed a low probability of response to treatment with PLDH, topotecan, or paclitaxel. Also, little difference was found between the 3 comparators as regards overall survival. Toxicity profiles of the comparators differed considerably. Paclitaxel and platinum combination therapy gave the most favorable survival times and response rates for participants with platinum-sensitive disease. Regarding single-agent compounds, the evidence suggests that PLDH is more effective than topotecan. Another trial that compared PLDH and paclitaxel found no significant difference between these two. The 3 comparators differed significantly in terms of their toxicity profiles across the trials.

Four studies met the inclusion criteria for cost-effectiveness review. Review of the economic evidence found significant limitations in studies assessing the cost effectiveness of PLDH, topotecan, and paclitaxel. Analysis 1 assessed the cost effectiveness of PLDH, topotecan, and paclitaxel as monotherapies. In the base-case results, paclitaxel monotherapy was cheapest. As regards incremental cost-effectiveness ratios (ICERs), topotecan was dominated by PLDH. Hence, the options considered in estimating ICERs were paclitaxel and PLDH. The ICER for PLDH compared with paclitaxel was GBP 7033 per quality-adjusted life-year (QALY) in the overall patient population. The ICER was more favorable in the platinum-sensitive group and less favorable in the platinum-refractory/resistant group. Incorporating the results of the additional trial data resulted in less favorable estimates for the ICER for PLDH versus paclitaxel compared with the base-case results. Analysis 2 explored the cost-effectiveness of the full range of treatment comparators for platinum-sensitive patients. The reliability of these results should be interpreted with caution. Topotecan, paclitaxel monotherapy, and PLDH were all dominated by platinum monotherapy. After excluding these alternatives, platinum monotherapy was the least costly and least effective.

Recommendations

PLDH treatment may be more beneficial than topotecan, but patient and physician choice as to the potential toxicities associated with each of the comparators and the patient's ability and willingness to tolerate these are important. Assuming the NHS is willing to pay GBP 20 000 to GBP 40 000 per additional QALY, PLDH appears to be cost effective compared with topotecan and paclitaxel monotherapy. (See Executive Summary link above.)

Methods

Seventeen databases were searched up to April 2004 for RCTs, systematic reviews of clinical effectiveness, and economic evaluations of the cost-effectiveness of PLDH, topotecan, and paclitaxel. Selected studies were quality assessed and data extracted, as were the 3 company submissions. A new model was developed to assess the costs of alternative treatments, the differential mean survival duration, and the impact of health-related quality of life. Monte-Carlo simulation was used to reflect uncertainty in the cost-effectiveness results.

Further research/reviews required

- Trial to compare paclitaxel in combination with a platinum-based therapy versus single-agent PLDH.

Written by Dr NF Woolacott, University of York, United Kingdom

INAHTA Briefs

Issue 2007/26

Title **A Systematic Review of the Clinical Effectiveness and Cost Effectiveness of Enzyme Replacement Therapies for Fabry's Disease and Mucopolysaccharidosis Type 1**

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Reference Health Technol Assess 2006;10(20). June 2006. www.hta.ac.uk/execsumm/summ1020.htm

Aim

To determine the clinical and cost effectiveness of administering intravenous enzyme replacement therapy (ERT) to symptomatic patients to prevent long-term damage and symptoms in Fabry's disease and mucopolysaccharidosis type 1 (MPS1).

Conclusions and results

Fabry's disease is described as a multisystem, life-threatening disorder particularly involving kidney, heart, and brain with individual patients exhibiting many manifestations. Fragmentary information in 16 reviewed studies relevant to the natural history of clinical manifestations of MPS1 did not generate a coherent picture of disease progression and added little to published narrative reviews. UK MPS1 registry data indicated a birth prevalence of 1.07/100 000 births and median survival of 11.6 years (all MPS1 subtypes combined).

The results suggested beneficial effects of ERT for Fabry's disease on measures of pain, cardiovascular function, and some endpoints reflecting neurosensory function. Renal function appeared to be stabilized by ERT.

No published evidence reporting an economic evaluation of ERT for Fabry's disease was identified. A dynamic decision model was constructed based on a birth cohort of male patients followed up until death, but many assumptions had to be applied. The estimated incremental cost-effectiveness ratio (ICER) was GBP 252 000 per QALY (agalsidase beta). Univariate sensitivity analyses around the key assumptions produced ICERs ranging from GBP 602 000 to 241 000. The unit cost of ERT was taken as GBP 65.1/mg based on the cost of agalsidase beta. The unit cost would have had to be reduced to GBP 9 to obtain an ICER of GBP 30 000 per QALY.

Minimal evidence is published on the impact of ERT on the severity and rate of change of clinical manifestations of MPS. Information on the effect of ERT on mortality is also lacking owing to the relatively short time that the treatment has been available. We found no published economic evaluation of ERT for MPS1 or any study that reported the quality of life of MPS1 patients within a utility format. Given the lack of data, it was not possible to develop a cost-effectiveness model of ERT for MPS1. The mean cost of treating an MPS1 child (20 kg) with ERT (England, Wales) is approximately GBP 95 000 per annum, and the corresponding cost for an adult (70 kg) around GBP 335 000. The cost per patient varies considerably by dose.

Recommendations

The cost effectiveness of ERT treatment for an 'average' patient with Fabry's disease exceeds the normal upper threshold seen in NHS policy decisions by over 6-fold. Even large errors in assumptions made will not reduce the ICER to anywhere near the upper level usually considered cost effective. The cost effectiveness of ERT for MPS1 is likely to be similar to that for Fabry's disease. Some clinicians, and the manufacturers of ERT, argue that since these diseases have special status as orphan diseases, the NHS has little option but to provide ERT. The opportunity costs forgone under such a policy will mount as more ERTs become licensed for increasing numbers of the rare genetic storage disorders.

Methods

Relevant published studies were identified and assessed using recommended quality criteria. Data were sought via disease registries and contact with experts. Evidence was synthesized and reported in narrative review.

Further research/reviews required

- Establishment of disease-specific data registries to facilitate technology assessment and improve patient care through better knowledge of the disease progression and the effectiveness of potential treatments (should include longitudinal data on clinically relevant problems of all affected patients in the UK, interventions received, and quality of life in a utility format).

Written by Dr Martin Connock, University of Birmingham, United Kingdom

INAHTA Briefs

Issue 2007/27

Title **A Systematic Review and Economic Model of the Effectiveness and Cost Effectiveness of Methylphenidate, Dexamfetamine, and Atomoxetine for the Treatment of Attention Deficit Hyperactivity Disorder in Children and Adolescents**

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Reference Health Technol Assess 2006;10(23). July 2006. www.hta.ac.uk/execsumm/summ1023.htm

Aim

To assess the clinical and cost effectiveness of oral methylphenidate hydrochloride (MPH), dexamfetamine sulphate (DEX), and atomoxetine (ATX) in children and adolescents diagnosed with attention deficit hyperactivity disorder (ADHD), including hyperkinetic disorder.

Conclusions and results

Sixty-five papers met the inclusion criteria. The results suggest that MPH and DEX are effective at reducing hyperactivity and improving quality of life (QoL), as determined by Clinical Global Impression, in children. However, the reliability of the MPH study is unknown, and there were few DEX studies. Consistently, ATX was superior to placebo for hyperactivity and Clinical Global Impression. Studies on ATX more often reported the study methodology well, and the results were likely to be reliable. Few studies made direct head-to-head comparisons. Adequate and informative data regarding the potential adverse effects of the drugs were also lacking. Results of the economic evaluation clearly identified an optimal treatment strategy of DEX first-line, followed by IR (immediate release)-MPH for treatment failures, followed by ATX for repeat treatment failures. Where DEX is unsuitable as a first-line therapy, the optimal strategy is IR-MPH first-line, followed by DEX and then ATX. For patients contraindicated to stimulants, ATX is preferred to no treatment. For patients in whom a midday dose of medication is unworkable, ER (extended release)-MPH is preferred to ATX, and ER-MPH12 appears more cost effective than ER-MPH8. As identified in the clinical effectiveness review, the reporting of studies was poor, which should be borne in mind when interpreting the model results.

Recommendations

Drug therapy seems to be superior to no drug therapy, no significant differences between the various drugs in terms of efficacy or side effects were found, mainly owing to lack of evidence, and the additional benefits from behavioral therapy (in combination with drug therapy) are uncertain. Given the lack of evidence for any differences in effectiveness between the drugs, the economic model tended to be driven by drug costs, which differed considerably.

Methods

Selected studies were assessed using modified criteria based on CRD Report No 4. Clinical effectiveness data were reported separately for each drug and by type of comparison. Data for MPH were analyzed separately based on whether it was administered as an immediate release or extended release formulation. For all drugs, the data were examined by dose. Data for the core outcomes of hyperactivity, Clinical Global Impression, and adverse events were reported. For crossover studies, the mean and standard deviation (SD) for each outcome were data extracted for end of trial data. For parallel studies, change scores were reported where given, otherwise means and SDs were presented for end of trial data. Mean differences with 95% confidence intervals were calculated for each study. For adverse events, self-ratings or parent reports were used. Percentages of participants reporting adverse events were used to calculate numbers of events in each treatment arm. All clinical effectiveness data and economic evaluations included in the company submissions were assessed. A new model was developed to assess the cost effectiveness of the alternative treatments in terms of cost per quality-adjusted life-year, using a mixed treatment comparison model to estimate the differential mean response rates. Monte Carlo simulation was used to reflect uncertainty in the cost-effectiveness results.

Further research/reviews required

- Trials of MPH, DEX, and ATX that prioritize assessment of tolerability and safety
- Longer-term followup of individuals participating in trials
- Research on whether somatic complaints are related to drug treatment or to the disorder itself.

Written by Dr Rob Riemsma, Kleijnen Systematic Reviews, United Kingdom

INAHTA Briefs

Issue 2007/28

Title **The Cost Effectiveness of Testing for Hepatitis C (HCV) in Former Injecting Drug Users**

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Reference Health Technol Assess 2006;10(32). September 2006.
www.hta.ac.uk/execsumm/summ1032.htm

Aim

To evaluate the effectiveness and cost effectiveness of testing for hepatitis C virus (HCV) among former injecting drug users.

Conclusions and results

Case finding for HCV is likely to prevent, for 1000 people approached, 3 cases of decompensated cirrhosis, 3 deaths due to HCV, and 1 case of hepatocellular cancer (at 30 years). Twenty-five additional people are likely to undergo combination therapy as a result of initial case finding. One liver transplant is likely to be prevented for 10 000 people included in case finding. Case finding is likely to cost around GBP 760 000 more than a policy of no case finding. The total cost of either strategy is high and driven mainly by the cost of combination therapy. Systematically offering testing to 1000 people would cost around GBP 70 000. Case finding is likely to result in an additional life-year gained at a cost of GBP 20 084. The cost-utility of case finding is estimated at GBP 16 514 per QALY. If NHS policy makers view GBP 30 000 per QALY as an acceptable return on investment, there is a 74% probability that case finding for HCV would be considered cost effective (at GBP 20 000 per QALY the probability is 64%). All analyses showed a high probability of case finding being considered cost effective at GBP 30 000 per QALY. Case finding in drug services is likely to be the most expensive. Correspondingly, benefits are highest for this strategy, and cost effectiveness is similar to the general case. Case finding in general practice by offering testing to the whole population aged 30 to 54 years is estimated to be the least expensive option since few people accept the offer, and HCV prevalence in this group is much higher than in the general population. Two approaches to case finding in prison were considered. These differed substantially in the prevalence of cases identified in the tested populations. Subgroup analyses based on duration of infection show that case finding is likely to be most cost effective in people whose infection is more long-standing. In people infected more than 20 years previously, case finding yields benefits at around GBP 15 000 per QALY. Treatment effectiveness was modeled using estimates from randomized controlled trials, and lower rates of viral response may be seen in practice. However, estimates of cost effectiveness remained below GBP 30 000 for all levels of treatment effectiveness above 58% of those shown in the relevant trials. The value of information analysis, assuming that 10 000 people might be eligible for case finding and that programs would run for 15 years, suggests that the maximum value of further research into case finding exceeds GBP 19 million.

Recommendations

Case finding for hepatitis C is likely to be considered cost effective by NHS commissioners. Further improvements in the effectiveness of treatments to slow or halt disease progression are likely to improve the cost effectiveness of case finding. Case finding is likely to be most cost effective if targeted at people whose HCV disease is probably more advanced.

Methods

A decision analytic model was developed to investigate the impact of case finding and treatment on progression of HCV disease in a hypothetical cohort of 1000 people. This was compared with a cohort in whom no systematic case finding is implemented, but spontaneous presentation for testing is allowed to occur. A group of epidemiological and clinical experts informed the structure of the model, which has three main components: testing and diagnosis, treatment, and long-term consequences of infection. A fourth component, case-finding strategies, examines the potential impact of case finding in three settings: prisons, general practice, and drug services.

Further research/reviews required

- Empirical work to specify, in practice, different approaches to case finding in appropriate settings and to evaluate their effectiveness and cost effectiveness directly.

Written by Dr Ken Stein, University of Exeter, United Kingdom

INAHTA Briefs

Issue 2007/29

Title **The Effectiveness and Cost Effectiveness of Computed Tomography Screening for Coronary Artery Disease: Systematic Review**

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Reference Health Technol Assess 2006;10(39). October 2006.
www.hta.ac.uk/execsumm/summ1039.htm

Aim

To assess the clinical and cost effectiveness of computed tomography (CT) screening for asymptomatic coronary artery disease; to establish whether coronary artery calcification (CAC) predicts coronary events and adds anything to risk factor scores; and whether measuring CAC changes treatment.

Conclusions and results

No randomized control trials (RCTs) assessed the value of CT screening in reducing cardiac events. Seven studies assessed the association between CAC scores on CT and cardiac outcomes in asymptomatic people (n=30 599). Six used electron-beam CT. The relative risk of a cardiac event was 4.4 if CAC was present. As CAC score increased, so did the risk of cardiac events. The correlation between CAC and cardiac risk was consistent across studies. CAC scores varied among people with the same Framingham risk factor scores, and within the same Framingham bands people with higher CAC scores had significantly higher cardiac event rates (mainly when the CAC scores exceeded 300). In one study, CAC score was a better predictor of cardiac events than the Framingham risk scores. No studies showed whether the addition of CAC scores to standard risk factor assessment would improve outcomes. Two observational studies showed that lowering of low-density lipoprotein cholesterol to about 3 mmol l^{-1} or below with statin treatment modestly reduced CAC scores, but this was not confirmed in 2 RCTs. In 3 studies on whether knowledge of CAC scores would affect compliance with lifestyle measures, perception of risk was affected, but it did not improve smoking cessation rates, and did increase anxiety. A few economic studies of CT screening for heart disease provided useful data on costs of scans, other investigations, and treatment, but did not provide definitive answers. One modeling study estimated that adding CT screening to risk factor scoring, and only giving statins to those with a CAC score over 100, would save money. However, generic statins have reduced prices, and these savings no longer apply.

Recommendations

CT examination of the coronary arteries can detect calcification indicative of arterial disease in asymptomatic people, many of whom would be at low risk when assessed by traditional risk factors. The higher the CAC score, the higher the risk. Treatment with statins can reduce that risk. However, CT screening would miss many of the most dangerous patches of arterial disease, because they are not yet calcified. Hence, there would be false-negative results: normal CT followed by a heart attack. There would also be false-positive results in that many calcified arteries will have normal blood flow and will not be affected by clinically apparent thrombosis: abnormal CT not followed by a heart attack. For CT screening to be cost effective, it must add value over risk factor scoring by producing sufficient information to change treatment and cardiac outcomes, at an affordable cost per quality-adjusted life-year. The evidence did not support this. Most National Screening Committee (NSC) criteria were not met, or met only in part.

Methods

Screening studies and economic evaluations were systematically reviewed. Studies were included in the review if screening for coronary heart disease was the principal theme and if data were provided that allowed comparison of CT screening with current practice, ie, risk factor scoring. Mismatches between CAC scores and risk factor scoring were of particular interest. The case for screening was reviewed using the NSC criteria for assessing screening programs.

Further research/reviews required

It would be useful to have more data on the distributions of risk scores and CAC scores in asymptomatic people, the level of concordance between risk factor and CAC scores, the risk of cardiac events per annum according to CAC score and risk factor scores, information on the acceptability of CT screening, after information about the radiation dose, and an RCT of adding CT screening to current risk factor-based practice.

Written by Professor Norman Waugh, University of Aberdeen, United Kingdom

Title **The Use of B-type Natriuretic Peptides (BNP and NT-proBNP) in the Investigation of Patients with Heart Failure**

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Reference Craig et al. 2005. Health Technology Assessment Report 6.
ISBN 1-903961-49-1

Aim

- To determine the role of B-type natriuretic peptides (BNP) in diagnosing heart failure.

More specifically, whether or not a normal BNP or NT-proBNP result can reliably 'rule out' heart failure:

- in the primary care setting to inform the decision to refer a patient to a specialist or for echocardiography
- in the admissions setting to inform decisions around treatment and placement of patients.

Conclusions and results

Testing of BNP has similar sensitivity, but greater specificity than electrocardiograms (ECGs) read by cardiologists in selecting patients for referral to echocardiography. The accuracy of BNP testing is greatest in patients with more severe disease and poorest in patients receiving therapy for heart failure.

Modeling results suggested that BNP tests could be cost saving if the specificity of diagnostic tests currently used to inform whether or not to refer patients for echocardiography is less than 50%. The cost-effective use of BNP testing may reduce the number of patients referred inappropriately for further cardiac assessment from general practice, and decrease the length of stay and total treatment costs in the acute setting.

Patients would value avoiding unnecessary anxiety waiting for a diagnosis of heart failure if a more sensitive and relatively noninvasive test can 'rule out' heart failure.

Recommendations

- In the primary care setting, GPs, who do not record ECGs in their own practice or who are not confident in confirming an automated ECG report, should adopt BNP tests.
- In the acute setting, physicians should use BNP tests, in conjunction with other clinical information, for patients in whom there is genuine diagnostic uncertainty after standard evaluation, and no timely access to echocardiography.
- BNP tests should not replace echocardiography for the diagnosis of heart failure.
- Healthcare professionals should explain to patients and carers, in a clear and timely manner, what the diagnosis is and how it was made, and ensure that this is supported by written information.

Methods

Scientific literature was systematically searched to identify evidence. Experts, patient interest groups, and manufacturers were invited to submit evidence. All evidence was critically appraised, and clinical data were pooled to evaluate the accuracy of diagnostic tests in heart failure and left ventricular systolic dysfunction. An economic model was constructed to compare the number and cost of correct test results for heart failure in alternative diagnostic pathways. Patients' needs and preferences and organizational issues were considered.

Further research/reviews required

Research is needed to identify relevant cutoffs for different settings and different patient subgroups, particularly the elderly.

Written by Emma Riches, NHS QIS, United Kingdom

Title **The Provision of Alcohol-Based Products to Improve Compliance with Hand Hygiene**

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Reference Ritchie et al. 2005. Health Technology Assessment Report 7.
ISBN 1-903961-51-3

Aim

To review the literature on the effectiveness, costs, and benefits of alcohol-based hand hygiene products; and to assess whether the added benefits of improving hand hygiene are likely to offset the additional costs.

Conclusions and results

This review highlights the weaknesses of the evidence base pertaining to the clinical and cost effectiveness of interventions to improve hand hygiene compliance and reduce hospital-associated infection rates. (The term 'hand hygiene' refers only to handwashing with soap and water and the use of alcohol-based hand hygiene products.) Many of the reviewed studies were not well conducted or reported. They were heterogeneous in terms of study design, interventions used, and outcome measures. Hence, statistical synthesis of results could not be undertaken.

Alcohol-based products were usually part of a broader multi-component strategy of infection control. Other interventions included education sessions, reminders or surveillance, and feedback of infection rates. Most types of interventions generated at least transient improvements in hand hygiene compliance and reductions in infection rates. Successful interventions generally involved several components, long-term interventions, and a range of factors to modify hand hygiene behavior.

The cost of providing alcohol-based hand hygiene products to staff in clinical areas are greatly outweighed by the potential benefits associated with reducing hospital-associated infection. Two economic evaluations showed that if only a 1% reduction in the hospital-associated infection rate were achieved, hand hygiene programs using alcohol-based hand hygiene products would be cost effective.

Recommendations

- Alcohol-based hand hygiene products should be made available to all NHSScotland staff who may come into contact with patients and to all hospital visitors, particularly where handwashing facilities are limited.
- Multi-component strategies to improve local hand hygiene compliance should be implemented as these are more likely to be effective and sustainable than single-component strategies.
- Hospitals should evaluate the effectiveness of any hand hygiene intervention put in place.

Methods

The scientific literature was systematically searched to identify evidence of the clinical and cost effectiveness of alcohol-based hand hygiene products. Experts, professional groups, and other interested parties were invited to submit evidence. All evidence was critically appraised. A survey was undertaken by NHS Quality Improvement Scotland to ascertain the current provision of hand hygiene arrangements in primary and acute care settings across Scotland.

Further research/reviews required

Robust evaluation of any hand hygiene intervention should be carried out. This will require auditing of compliance and/or infection rates before and after the intervention and taking into account the possible influences on these rates. Followup measurements should be made at intervals, and comparator groups included wherever possible. Ideally, cluster randomized trials methodology should be employed.

Written by Emma Riches, NHS QIS, United Kingdom

Title **The use of Epoetin Alfa Before Orthopedic Surgery in Patients with Mild Anemia**

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Reference Craig et al. 2006. Health Technology Assessment Report 8.
ISBN 1-84404-853-5

Aim

To determine whether or not epoetin alfa should be used in patients with mild anemia (Hb<10–13 g/dL) prior to major elective orthopedic surgery to reduce exposure to allogenic blood transfusion.

Conclusions and results

Meta-analysis demonstrated that the likelihood of transfusion was significantly lower for patients receiving epoetin alfa than for those receiving placebo (p=0.007). The patient group receiving epoetin alfa required significantly less blood than that receiving placebo (p<0.0001). One study reported the number of units of blood transfused per transfused patient. This showed that in patients who actually underwent a transfusion, epoetin alfa administration did not reduce the number of units of blood used. None of the studies reported significant differences in length of stay or postoperative infection rates as a result of using epoetin alfa. It is unclear to what extent the clinical effectiveness results can be generalized to Scotland as many of the studies were in settings with different transfusion policies.

The economic model combined the effectiveness data with drug costs, the savings from avoided viral infections, and adverse events and calculated a cost per QALY of over GBP 21 million. Furthermore, the model demonstrated that cost of transfusing a unit of blood would have to rise from the current GBP 230 to over GBP 2750 for the use of epoetin alfa as a blood sparing treatment to become cost effective. Hence, while epoetin alfa is effective in reducing the incidence of transfusion in this patient population, it is not cost effective.

Recommendations

In NHSScotland, administration of epoetin alfa to patients with mild anemia prior to major elective orthopedic surgery, to reduce exposure to allogenic blood transfusion, is not recommended. It should be considered only if the patient cannot receive a blood transfusion for religious reasons, or because suitable blood is unlikely to be available.

Methods

A literature search was undertaken to identify evidence pertaining to the clinical and cost effectiveness of epoetin alfa compared to standard care. Experts, patient interest groups, and the manufacturer also provided evidence. The evidence was critically appraised, and meta-analyses were performed. An economic model was constructed, and the results were tested with sensitivity analyses to ensure extreme changes in parameter values had no effect.

Further research/reviews required

It may be informative to update the analyses at a later date if, eg, the price of epoetin alfa decreases, the risks associated with transfusion increase, or the demand for blood exceeds the supply.

Written by Susan Downie, NHS QIS, United Kingdom

Title **Short Report: Temporal Artery Thermometry in the Postoperative Setting**

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Reference VA Technology Assessment Program Short Report.
December 2006. www.va.gov/vatap

Aim

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

Conclusions and results

The searches yielded 85 citations, including 11 studies comparing TAT to another thermometry device. The best available evidence consists of 2 preliminary studies, with conflicting results, that compare the diagnostic accuracy of TAT to pulmonary artery catheter measurement in mixed adult inpatient populations. No HTA reports or systematic reviews on this topic were identified. The review found a lack of conclusive evidence supporting the clinical use of TAT as an instrument for measuring core temperature in adult inpatient populations, including those in the postoperative setting.

Recommendations

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

Methods

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

Further research/reviews required

Several investigators have called for improved study quality and quality monitoring of new thermometry devices in the appropriate clinical setting, and with a range of suitable patients, to confirm the safe use and clinical value of the devices.

Written by Elizabeth Adams, VATAP, USA

INAHTA Briefs

Issue 2007/34

Title **Diagnosis and Treatment of Obstructive Sleep Apnea – A Health Technology Assessment**

Agency **DACEHTA, Danish Centre for Evaluation and Health Technology Assessment**
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Reference Medicinsk Teknologivurdering – puljeprojekter 2006; 6(5). ISBN 87-7676-312-9 (online): www.sst.dk/publ/Publ2006/CEMTV/Soevnapnoe/Sleepapn_summary.pdf

Aim

To examine the documentation for diagnosing and treating obstructive sleep apnea (OSA); and to evaluate the organizational and economic consequences of different, mainly diagnostic, strategies.

Conclusions and results

The best documented treatment is continuous positive airway pressure (CPAP). Auto-adjusted CPAP is as effective as fixed pressure CPAP. Auto-adjusted CPAP may involve some advantages compared to fixed pressure CPAP: manual titration is eliminated and followup adjustments and controls are probably reduced. CPAP treatments in patients with obstructive sleep apnea increase quality of life and reduce morbidity. Treatment is cost effective due to the reduction in morbidity. Organizational analysis showed that polysomnography (PSG) supervised in hospital was the most expensive method. The costs for ambulatory respiratory polygraphy and oximetry were similar. Seen from a patient-ethical point of view, ambulatory partial polygraphy and auto-adjusted CPAP are preferable in diagnosing and treating uncomplicated obstructive sleep apnea. A health-related economic analysis indicates that diagnosing and CPAP treatment of obstructive sleep apnea is cost effective, even if only morbidity data are included.

Recommendations

It is important to focus on the quality of submissions, visitation, and other evaluation of patients with obstructive sleep apnea. CPAP is a chronic treatment, and relevant organization of followup should be present. A significant proportion of patients with obstructive sleep apnea present major comorbidities, eg, neurological, cardiac, or pulmonary diseases, or suffer from other sleep-related breathing disorders. Patients with other sleep disorders like narcolepsy, motor or behavior disorders during sleep, or nocturnal seizures may share some symptoms similar to sleep apnea. These patients need more extensive evaluation in fully accredited sleep laboratories with extensive diagnostic and treatment procedures, presence of relevant neurological and medical specialties with relevant education of medical and nonmedical staff. From an organizational perspective, a limited number of such high-level clinics should be established in hospitals with relevant specialties and co-diagnostic resources.

Methods

The HTA includes a systematic review of the literature and different studies including: 1) a controlled study of the difference between fixed-pressure CPAP and auto-adjusted CPAP, 2) a study of the influence of CPAP on quality of life, 3) a study of morbidity before and after CPAP treatment, and 4) a questionnaire study of the diagnosis and treatment of obstructive sleep apnea in Denmark involving all relevant clinics and hospitals. Also, a health economic analysis of diagnosis and treatment was performed.

Further research/reviews required

Future health-related economic analysis should include social, professional, and traffic aspects.

Written by Jennum P, Folkersen J, and Andreasen J, DACEHTA, Denmark

INAHTA Briefs

Issue 2007/35

Title **Preventive Health Screenings and Health Consultations in Primary Care – A Health Economic Analysis of "Ebeltoft Health Promotion Project"**

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Reference Medicinsk Teknologivurdering – puljeprojekter 2006; 6(6). ISBN 87-7676-316-1 (online): www.sst.dk/publ/Publ2006/CEMTV/Ebeltoft/ebeltoft_ce_rap.pdf

Aim

To assess whether the implementation of preventive health screenings and health consultations in primary care in Denmark will be cost effective.

Conclusions and results

The intervention groups (health screening plus health consultation, and health screening alone) for men and women combined showed economic dominance compared to the control (questionnaire) group. This is based on the finding that the health effect in the intervention groups is statistically significantly better than the health effect in the control group, yet no significant differences in costs are found, regardless of the cost measure considered (direct healthcare costs, total expenses, or total costs). The health effect of health screening plus health consultation is also significantly better than the health effect of health screening alone, without any significant difference in expenses or costs. Subjects that are offered health screening and health consultation gain on average 0.30 years of life versus 0.16 years for subjects in the control group and 0.24 years for those offered health screening alone. The differences in costs are not statistically significant. When each gender is assessed separately, it appears that in men the health effect of both health screening plus health consultation and health screening alone is significantly better than the health effect for subjects in the control group, while there are no significant differences in costs, regardless of the cost measure examined. In women, the health effect is significantly better for subjects offered health screening and health consultation than for subjects in the control group, again without significant differences in any of the cost measures examined.

To conclude, offering systematic, primary-care-based preventive health screening and health consultation to men and women aged 30 to 49 years is economically advantageous compared to what is offered to the control group. This is implied by the finding that the health effect, in terms of life years gained assessed over a 5-year period, is significantly better in the intervention group offered health screening and health consultation than in the control group, while the costs for the intervention group, assessed over 6 years, were not higher than for the control group.

Methods

The study determined the expenses and costs related to predefined health effect measures for 3 randomized groups, ie, 2 intervention groups (1006 subjects) and 1 control group (501 subjects). Participants were aged 30 to 49 years (as of January 1, 1991), men and women living in the municipality of Ebeltoft, and registered in one of the municipal primary care units. Randomization of subjects into control and intervention groups was stratified by primary care unit, sex, age, body mass index (BMI), and cohabitation status. The participants were randomized among the 4 types of intervention groups.

Written by Rasmussen SR, Kilsmark J, Hvenegaard A, Thomsen JL, Engberg M, Lauritzen T, and Søgaard J, DACEHTA, Denmark

Title **Preventive Health Screenings and Health Consultations in Primary Care – An Analysis of the Psychosocial Impact**

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Reference Medicinsk Teknologivurdering - puljeprojekter 2006; 6(7). ISBN 87-7676-319-6 (online): www.sst.dk/publ/Publ2006/CEMTV/Ebeltoft/ebeltoft_ptpersp.pdf

Aim

To determine if it is recommendable to introduce, to the population, an offer of general health checks and health discussions with one's own general practitioner (GP).

Conclusions and results

The project addressed the patient perspective of offering general health checks and health discussions in general practice, whether the population is interested in being offered general health checks, and whether any ethical, psychological, or social problems can be linked to introducing such a scheme.

The randomized studies, ie, the Ebeltoft Health Promotion Project, do not indicate an association between long-lasting, poor self-assessed health, or poor emotional well being, and being offered or participating in general health checks. Most participants did not experience a negative impact from their participation. On the contrary, many participants reported a positive impact. Nonrandomized followup studies and cross-sectional studies show that some participants are anxious or worry about their health and mental well-being, including depressive symptoms in the short term. There is no evidence that these impacts are long-lasting or permanent. In general, people have been interested in and satisfied with their participation in the studies.

Recommendations

Based solely on our present knowledge about the patient perspective, it is not recommended to offer the population general health checks and health discussions with their own GP as there is no evidence of an improvement in participants' emotional well being, self-assessed health, or other related parameters after participation. However, the decision to offer general health checks and health discussions should not be based on the patient perspective alone. It is also important to consider organizational, economic, and technological effects.

Methods

A systematic literature search was conducted and data were analyzed concerning aspects of the patient perspective from the Ebeltoft Health Promotion Project, a Danish randomized trial investigating the impact of general health checks and health discussions in general practice.

Written by Larsen EL, Thomsen JL, Lauritzen T, and Engberg M, DACEHTA, Denmark

Title **Operation for Vaginal Wall Prolapse in Day Surgery – A Health Technology Assessment**

Agency **DACEHTA, Danish Centre for Evaluation and Health Technology Assessment**
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Reference Medicinsk Teknologivurdering - puljeprojekter 2006; 6(8). ISBN 87-7676-339-0 (online): www.sst.dk/publ/Publ2006/CEMTV/Vaginal_kirurgi/Vaginal_kir.pdf

Aim

To investigate whether surgery for vaginal wall prolapse can be done on an outpatient basis.

Conclusions and results

The result of the health technology assessment (HTA) shows that outpatient treatment can be introduced without changing the already low complication and recurrence rates of the procedure. Furthermore, outpatient treatment can increase the training opportunities for young surgeons, provide high patient-satisfaction, and save healthcare resources. The HTA also shows a need to analyze the existing organization before changing to an outpatient regime, and a need to involve all personnel when implementing the outpatient regime.

There is no increased risk of complications or relapse after day surgery compared to inpatient surgery. Day surgery requires preparation of the patient (eg, good quality information about the process), preparation for the procedure, and precautionary measures following surgery.

The patient is affected by smaller amounts of sedatives and feels ill for a short period after outpatient treatment.

Successful conversion to outpatient treatment requires a deliberate, transparent process, wherein different contributors have ownership and collaborate on the goals defined during the implementation process. Communication throughout the entire process is important.

Day surgery requires less admission time, less surgical time, and less wake-up time, amounting to a reduction of about 1/3 of the expenses of surgery during hospitalization and without significantly increased costs during followup in the primary sector.

Recommendations

Conversion to outpatient treatment affects major parts of the organization. Future changeover to outpatient treatment needs to be preceded by a thorough description of the existing organization, and a model for the new regime must be chosen.

Methods

The HTA included retrospective and prospective investigation of 2 nonrandomized cohorts, structured interviews, questionnaire, collection of data from patient records, decision analysis, and cost minimization analysis.

Written by Axelsen S and Sørensen J, DACEHTA, Denmark

Title **Preventive Outpatient Treatment in Affective Disorders. Results From a Health Technology Assessment (HTA)**

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Reference Medicinsk Teknologivurdering – puljeprojekter 2006; 6(9). ISBN 87-7676-352-8 (online): www.sst.dk/publ/Publ2006/CEMTV/Affektive_lidelser/affektive_lidelser.pdf

Aim

To review the courses of depressive and bipolar disorders and discuss whether prophylactic interventions influence the courses of these disorders.

Conclusions and results

In response to a nationwide questionnaire survey of patients with major affective disorder, undertaken in 2003 in relation to the present HTA, more than half of the patients stated that they would prefer to receive outpatient treatment at a central, specialized treatment facility rather than from their usual therapist.

Little evidence was found regarding how concrete organizational measures can best ensure optimum treatment of patients with major affective disorders. The HTA discusses 2 models of organization. One consists of decentralized outpatient treatment by practicing psychiatrists or general practitioners. In the other model, some patients may also be treated in centralized outpatient clinics offering combination therapy involving pharmacotherapy and psychological treatment.

Based on results from clinical trials, it is estimated that systematic outpatient treatment with prophylactic pharmacotherapy and psychotherapy/psychoeducation can reduce bed days by 20% in patients admitted with depressive disorder and by 40% in patients admitted with bipolar disorder in the first year after discharge, compared to patients who do not receive such systematic treatment.

Bed days must be reduced by at least 10% to 15% in 2 years to cover the cost of centralized outpatient clinics.

Recommendations

Regarding outpatient treatment for patients with depressive or bipolar affective disorder, it is recommended that consideration be given to supplementing the current organization with 5 to 10 specialized clinics. This corresponds to 1 or 2 clinics in each of the coming 5 administrative regions of Denmark.

Methods

The international literature was systematically reviewed. Furthermore, the HTA includes a nation-wide questionnaire survey (autumn 2003) of patients and a nation-wide questionnaire survey (autumn 2003) of head doctors at psychiatric hospitals throughout Denmark. The technology section includes a systematic review of the literature on treatment, including prophylactic pharmacotherapy, and prophylactic combination therapy involving pharmacotherapy and psychological treatment.

Written by Kessing LV, Hansen HV, Hougaard E, Hvenegaard A, and Albæk J, DACEHTA, Denmark

INAHTA Briefs

Issue 2007/39

Title **Cardiac Rehabilitation – A Health Technology Assessment: Evidence From the Literature and the DANREHAB Trial**

Agency **DACEHTA, Danish Centre for Evaluation and Health Technology Assessment**
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Reference Medicinsk Teknologivurdering – puljeprojekter 2006; 6(10). ISBN 87-7676-346-3 (online): www.sst.dk/publ/Publ2006/CEMTV/Hjerterehab/hjerterehabilitering.pdf

Aim

To analyze the prerequisites and consequences of cardiac rehabilitation (CR) focusing on the perspectives of the patient, the technology, the economics, and the organization.

Conclusions and results

This health technology assessment (HTA) shows that CR increases patient satisfaction, and that patients are willing to participate in the service. The assessment identified 49 randomized trials on the effects of CR. A meta-analysis of the trials shows that CR reduces total mortality by 19% (OR 0.81 (95% CI 0.69–0.95)) and cardiac mortality by 26% (OR 0.74 (95% CI 0.61–0.90)). The trials primarily include men below 65 years of age with myocardial infarction, and it is uncertain whether the effect can be extrapolated to a wider target group. The quality of the trials can be questioned, leaving a risk of overestimating the effect of CR. Based on 3 high-quality trials, there is no statistical significant evidence for the effect of CR on total mortality (OR 0.92 (95% CI 0.40–2.14)) or cardiac mortality (OR 0.70 (95% CI 0.35–1.41)). There is no evidence on the effect of CR on reinfarction rates or revascularization rates. CR has a significant effect on cardiac risk factors, ie, blood pressure, lipids, and smoking, and this effect might be due to bias. Some trials show an effect of CR on rehospitalization and total bed days. Regarding quality of life, there is no evidence of CR being superior to usual care. More high-quality trials are needed on this topic. CR reduces acute rehospitalization rates and total bed days spent in the hospital, which raises the potential for reducing total healthcare costs. CR is not fully implemented at hospitals in Denmark. Several organizational challenges exist in the implementation process of CR, but a local study shows that it is possible to implement CR in accordance with the current guidelines in Denmark.

Methods

The HTA is based on a systematic review and meta-analysis of CR trials. Further, the HTA analysis includes results from the Danish CR randomized controlled trial (DANREHAB trial) and cost analysis. The report also presents an organizational analysis on diffusion of CR in Denmark, the translation of the CR concept into clinical practice at a local hospital, and an extensive discussion on the ethical implications of CR.

Further research/reviews required

Detailed knowledge is sparse on how to organize and operate CR. There is a need to gather experiences from existing programs and programs under development. CR must be studied in large, high-quality trials before final conclusions on effects can be drawn.

Written by Zwisler AD, Nissen NK, Madsen M, and the DANREHAB-group, DACEHTA, Denmark

Title **Coherent Monitoring and Followup of Pregnant Women with a Heart Disease – A Health Technology Assessment**

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Reference Medicinsk Teknologivurdering - puljeprojekter 2006; 6(11). ISBN 87-7676-356-0 (online): www.sst.dk/publ/Publ2006/CEMTV/Gravidehjerter/gravidehjerte.pdf

Aim

To assess the Center for Pregnant Women With Heart Disease at Copenhagen University Hospital in Denmark to inform Danish decision makers on the consequences of appropriate distribution of assignments and coordination between sectors and personnel as regards offers to pregnant women with heart disease.

Conclusions and results

The health status of children was found to improve after establishment of the center. Furthermore, the shared care of patients promotes the development of competence among personnel in the center since they gain insight into the different specialty areas. Pregnant women reported greater satisfaction with the level of information after establishment of the center. The center has positive economic consequences for society, the healthcare sector, and the patients.

Both before and after establishment of the center, pregnant women with heart disease have received good and safe monitoring and followup. After establishment of the center, however, the coordination of monitoring and followup of these women has greatly improved. Coordination of patient flow will also make it possible to provide good patient flow as regards pregnant women with heart disease.

The present health technology assessment shows that the purpose of the center has been successfully fulfilled. The center's organizational constellation ensures that pregnant women with heart disease receive the interdisciplinary monitoring and followup necessary to enable optimum management of the mother and the child via safe and coordinated patient flow. The fact that the center is based on changes in the organization and the methods of cooperation illustrates that it is possible, within existing budgets, to improve the quality of treatment compared to the situation prior to the establishment of the center.

The center is a good example of how it is possible to organize, given existing conditions and budgets, to improve cooperation and planning of patient flow without following old traditions and routines.

Methods

The present health technology assessment was designed as a quasiexperimental "before and after" study comparing a prospective cohort of patients in the center with a comparable historic cohort of women with heart disease.

Written by Søndergaard L, Johansen M, Nørrelund A, Palm P, Hedegaard M, Kolbye A, Danø AM, and Poulsen PB, DACEHTA, Denmark

INAHTA Briefs

Issue 2007/41

Title **Treatment and Care as Assessed by Patients and Health Care Professionals – An Analysis Based on Patients Treated for Colorectal Cancer – A Health Technology Assessment**

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Reference www.sst.dk/publ/Publ2006/CEMTV/Patient_sundhedsv/Patient_sundhedsv_Summary.pdf

Aim

To investigate how patients and healthcare professionals (ie, nurses and doctors) assess the technical, interpersonal (ie, psychosocial), and organizational aspects of treatment and care; and to analyze the degree to which their assessments correlate.

Conclusions and results

Analyses of the correlation between patients' and healthcare professionals' responses generally showed that the correlation between the answers to rather factual questions ranged from moderate to nearly perfect ($0.19 \leq \kappa \leq 0.95$). On the other hand, the patients' and the healthcare professionals' answers to more subjective questions only correlated weakly ($-0.01 \leq \kappa \leq 0.22$).

The analyses of whether patients differentiate between various aspects of treatment and care showed that in all cases the patients' assessments of technical quality correlated closely with their interpersonal and organizational experiences during the hospital stay. In most cases the correlations were positive.

In a Danish population undergoing treatment for colorectal cancer, there were significant differences in perceptions of care between patients and health professionals. In particular, health professionals and readers of reports on patient evaluations ought to remember that the patient's perspective is just one source of information to be used in assessing hospital and health care.

Recommendations

The study highlights the necessity of collecting and comparing several types of information, including the assessments of both patients and healthcare professionals, if a complete view of quality in the Danish health service is desired.

Methods

The study included 527 patients and focused on patients operated for colorectal cancer and the healthcare professionals who treated them. Using this patient population enabled researchers to correlate the questionnaire responses to individual patients' disease-specific and diagnosis- and treatment-related information stored in the Danish Colorectal Cancer Database. Information on 336 of the 527 patients (64%) was available in the Danish Colorectal Cancer Database.

Written by Mathiesen TP, Jørgensen T, Freil M, Willaing I, Andreasen AH, and Harling H, DACEHTA, Denmark

INAHTA Briefs

Issue 2007/42

Title **Treatment of Alcohol Abuse – A Health Technology Assessment**

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Reference Medicinsk Teknologivurdering; 2006; 8(2). ISBN 87-7676-357-9
(online): www.sst.dk/publ/Publ2006/CEMTV/Alkoholbeh/MTValkoholbehandling.pdf

Aim

To describe the effect of treatment programs for persons with alcohol dependence and to describe organizational, patient-related, and financially-related health aspects of the treatment.

Conclusions and results

This report is intended to serve as a starting point for the on-going quality improvement of alcohol dependency treatment in Denmark. The report's main conclusion is that several pharmacological and psychosocial treatment programs have positive effects on alcohol dependence. There is little evidence to support the extensive use of disulfiram in Denmark. Treatment with acamprosat and naltrexon is effective in maintaining abstinence and adherence to psychosocial treatment. There is evidence to support targeted cognitive-behavioral therapy compared to standard approaches. Approaches offering both specialized pharmacological and psychosocial treatment have the best results. International cost-effectiveness studies suggest that treatment is cost effective, but the applicability of these results to a Danish setting is uncertain, and Danish cost data are sparse.

The results of this report provide the basis for the individual Danish treatment facilities to review and consider their current treatment options. In addition, the report supplies evidence-based professional input for the preparation of a combined treatment offer for persons with alcohol dependence.

Recommendations

Alcohol dependent citizens constitute a very heterogeneous group. Hence, it is necessary to approach the individual patient and assess what treatment would benefit this person most. Such an assessment presumes, eg, that it is possible to carry out a satisfactory analysis and diagnosis of the severity of the alcohol abuse and its nature, and the possibility of suggesting both pharmacological and psychosocial treatment offers. This type of differentiated, needs-oriented approach can gainfully be supported by development of clinical guidelines and national reference programs in the field of alcohol treatment.

Methods

Systematic literature searches were performed to correspond with the 4 aspects of the health technology assessment (HTA) concept, ie, technology, organization, patient, and finance. The report is primarily based on secondary literature, including HTA reports, meta-analyses and systematic literature examination including Cochrane reviews. Guidelines were also included and, where relevant, supplemented with relatively recent primary studies, especially in areas where no secondary literature could be found. A substantial amount of relevant literature concerning the effect of the treatment programs themselves (the technology) was found while no considerable amount of literature was located concerning the other 3 aspects, ie, organization, patient, and finance.

Written by Nielsen AS, Becker U, Højgaard B, Lassen AB, Willemann M, Søgaard J, and Grønbæk M, DACEHTA, Denmark

INAHTA Briefs

Issue 2007/43

Title **Therapeutic Conversation: the Effectiveness of Intensified Physician–Patient Communication**

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Reference HTA project report no 1.
ISSN 1992-0488, 1992-0496 (online)

Aim

To systematically review the effects of a therapeutic conversation.

Conclusions and results

Results of large patient surveys in different countries suggest that patients expect to receive good counseling, to be extensively informed, and to be given sufficient time and opportunity to communicate their concerns when visiting a physician. In some countries, this has resulted in reimbursing an item called the "therapeutic conversation", which goes beyond the usual consideration of the patient's medical history.

Several outcome parameters were investigated to answer the following question: Does the therapeutic conversation result in improvement of the quality of care offered in physicians' practices? The outcome parameters analyzed were; attainment of therapeutic goals, patients' compliance, participation, self-management, satisfaction, and a reduction in additional healthcare costs.

The report also covers reimbursement regulations in selected countries. Some options for maintaining or extending the coverage are discussed, taking into account the existing study results and the problems of transferring these results to the real care situation in Austria. In Austria, the therapeutic conversation is reimbursed up to a specified limit.

Reasonable evidence was found for the effectiveness of the therapeutic conversation on patients' self-management and satisfaction. For specific diseases/disorders, a reduction in additional healthcare costs was reported. For the remaining outcome parameters, evidence was less convincing.

Methods

Databases used in the systematic review were MEDLINE, EMBASE, Cochrane Central, CINAHL, Pascal Biomed, and the databases of the Centre for Reviews and Dissemination, York. The review included primarily high-quality studies (RCTs and systematic reviews of RCTs). Additionally, cohort studies, observational studies, and several qualitative studies were identified. Overall, 49 publications were considered for the assessment.

Written by Rosemarie Felder-Puig, LBI of HTA, Austria

Title **Horizon Scanning System (HSS). An Overview**

Agency **LBI of HTA, Ludwig Boltzmann Institute of Health Technology Assessment**
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Reference HTA project report no 2.
ISSN 1992-0488, 1992-0496 (online)

Aim

To support the development of transparent criteria for selecting new technologies that will be reported in a European-wide newsletter on emerging technologies.

Conclusions and results

In the European Network for Health Technology Assessment (EUnetHTA), it is the task of Work Package 7 (WP 7), Strand B, to develop a European-wide newsletter on emerging technologies.

The established horizon scanning systems are similar in that they go through the same processes, but they differ in terms of size, resources, operational level, mandate, customers, and organizational embedding. Hence, there are some differences in the methodologies of identification, filtration and prioritization, assessment, dissemination, and monitoring. The most obvious difference is that they serve different target groups and therefore prioritize and select different technologies. Additionally, the weight that is given to expert suggestions and the use of implicit or explicit measures for identifying and selecting technologies are characteristics of the different horizon scanning systems.

Methods

The report is based on a literature review, on unpublished information gathered from the relevant agencies (horizon scanning systems), and on personal email contacts with staff members.

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INAHTA Briefs

Issue 2007/45

Neonatal Care of Low-Risk Newborns. An Approach to Evidence Based Health Care Planning in Styria

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Reference HTA project report no 4.
ISSN 1992-0488, 1992-0496 (online)

Aim

To address the question whether employing 24-hour, on-site pediatricians at hospitals that provide care for low-risk births results in better outcome for newborns than arranging visiting consultants with on-call duties.

Conclusions and results

Internationally, trends in obstetrics are toward "regionalization" and "centralization". The former relates to managing births in hospitals at different levels of care according to pre-defined risks in pregnancy. The latter relates to a general shift toward managing births at larger units supported by the argument that a high volume of births is associated with low neonatal mortality. In Styria, neonatal care is characterized by considerable regionalization with only 2 clinics that provide neonatal units alongside obstetrics. One third of the births take place in these 2 hospitals. In the remaining 8 obstetric units, visiting consultants provide the care for newborns. Generally in Austria, births have increasingly taken place in hospitals with pediatric units. In addition to several obstetric units with over 1000 births/year, there are units with less than 1 or 2 births/day and low rates of difficult births (eg, caesarians, forceps). Studies show higher mortality risks at volumes under 500 births/year. Yet, the question of adequate pediatric staff for the 10% to 12% of newborns requiring neonatal care is barely addressed. Since primary responsibility in birth management lies with the obstetrician, it is common (even in clinics with neonatal care units) that they (or midwives) perform the first examination of the newborn (cutting the umbilical cord, suctioning amniotic fluid, determining the Apgar-Score, determining the acid-base balance). Physicians with experience in neonatology become involved only in cases of serious adaptation problems that may require a transfer to another level of care. In contrast, pediatricians always perform the routine examination of newborns before hospital discharge. No studies were found that address the research question directly. The literature and guidelines mainly address issues of regionalization, centralization (volume), timing of neonatal diagnostics, and required neonatological qualification. According to the guidelines, experience and yearly volume are relevant for adequate diagnostics and care in cases of neonatal problems and for routine examinations. However, no accepted minimum caseload has yet been defined.

Optimal neonatal care is to be seen as a trade-off between maximum centralization with maximum availability of highly experienced staff on one hand, and short distances to hospital but higher risks due to low volumes on the other. Making an additional pediatric unit available would be useful only under a general regional restructuring involving the overall care system and prognostic demographic factors.

Recommendations

1. Improve neonatological education for obstetricians
2. Guarantee neonatological acute care by highly experienced staff in case of adaptation problems
3. If necessary, restructure (centralize, reduce obstetric units) taking into account the overall system of care
4. Conduct further research in the form of primary studies.

Methods

Secondary data of obstetric and neonatal care provision in Styria were analyzed. Information concerning the role of pediatricians in the care of newborns was collected, based on current standards of care. A systematic literature review was performed using well-known databases and complemented by a systematic review of clinical guidelines. Secondary data indicating future needs were collected.

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Title **Use and Performance of Clinical Mammography in Denmark – A Health Technology Assessment**

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Reference Medicinsk Teknologivurdering – puljeprojekter 2006; 6(12). ISBN 87-7676-376-5 (online). www.sst.dk/publ/Publ2006/CEMTV/Klin_mammo/klinisk_mammografi.pdf

Aim

- To evaluate the organization of clinical mammography and breast assessment in Denmark, in particular to evaluate compliance with European (EUSOMA – European Organisation of Mastology) guidelines
- To determine performance of clinical mammography in Denmark in 2000
- To evaluate the use and interactions between clinical mammography, organized mammography screening, and opportunistic screening in Denmark, in particular.

Conclusions and results

EUSOMA guidelines: In 2002, only 44% of the public breast assessment centers met the requirement of 2000 mammograms per year, and only 56% had a radiologist reading at least 1000 mammograms per year. Concerning private mammography clinics, most did not meet the EUSOMA activity volume requirements in 2000.

Within the 2-year followup period, clinical mammography in Denmark in 2000 had a sensitivity of 75%, a specificity of 99%, and accuracy of 98%. The results shows that the overall sensitivity in Denmark is rather high, and only a low proportion of Danish women get a false positive diagnosis. However, the variation in performance among clinics was rather high. Concerning organizational factors, the presence of at least one high-volume-reading radiologist increased accuracy. Clinics with a high-volume-reading radiologist performed better, and they missed fewer cancers without increasing the burden of extra tests and/or operations in healthy women.

Non-attenders in organized mammography screening did not seek mammography outside the programs. A positive policy toward opportunistic screening did not increase the proportion of women using diagnostic mammography.

Recommendations

As the results in the present study showed that the presence in a clinic of a high-volume-reading radiologist increased accuracy in the clinic, action should be taken to increase the radiologist experience in Danish clinics. Future evaluations of clinical mammography in Denmark would benefit greatly by implementing a central register containing data on patient characteristics, radiological data, and followup data on breast cancer.

Methods

The following methods were used: Prospective cohort study, interview-based study, and register-based study with use of individual data from all Danish mammography clinics, the CPR-register, the Danish Cancer Register, the Nation-wide Pathology Register, and from databases covering the organized mammography screening programs in Copenhagen and the county of Fyn.

Written by Jensen A, Vejborg I, and Lynge E, DACEHTA, Denmark

Title **Psychological Aspects, Women's Views, and Expectations Regarding Ultrasound During Pregnancy – A Health Technology Assessment**

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Reference Medicinsk Teknologivurdering – puljeprojekter 2006; 6(13). ISBN 87-7676-421-4 (online). www.sst.dk/publ/Publ2006/CEMTV/Ultralyd/ultrascan.pdf

Aim

To explore 'patient issues', ie, psychological aspects, attitudes, and expectations regarding ultrasound in a low-risk population of pregnant women undergoing screening for fetal abnormalities at different times during pregnancy.

Conclusions and results

Ultrasound in pregnancy is popular among pregnant women. Ninety percent of women wanted ultrasound offered as a nuchal translucency (NT) scan or abnormality scan, while only 10% might accept an offer of invasive testing.

About 40% might accept an invasive test if the risk assessment on Down syndrome were 1:400. If Down syndrome were diagnosed, about 48% might choose abortion. A woman's nationality, age, educational level, and ultrasound in a previous pregnancy were predictive of attitudes toward these matters.

Routine ultrasound (NT or abnormality scan) resulted in an immediate but transient decrease in anxiety level. Anxiety level seemed to be associated with the number of scans. Analyses revealed an association between heightened anxiety in pregnancy at baseline and several potential predictive factors, eg, ethnicity, age, educational level, reproductive history, and ultrasound scan findings in a previous pregnancy.

Methods

A prospective randomized multicenter study on ultrasound screening for fetal abnormalities was used, and women's attitudes and expectations toward this matter were identified by questionnaires (2500 consecutively enrolled, low-risk pregnant women completed postal questionnaires at gestational weeks 8, 22, and 35, and 12 weeks after delivery). Results were associated with clinical and sociodemographic factors.

Further research/reviews required

Identifying subgroups for heightened anxiety may contribute significantly toward anxiety reduction if adequate antenatal counseling, advice, and care can be provided for these particularly vulnerable subgroups of pregnant women. In addition, studies on the association between heightened anxiety in pregnancy and predictive factors are required.

Future research might focus on women's knowledge about ultrasound screening for fetal abnormalities and on attitudes and expectations of health professionals toward some of the qualitative matters to compare with present results.

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Title **Dialysis in Chronic Renal Failure – A Health Technology Assessment**

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Reference Medicinsk Teknologivurdering 2006; 8(3). ISBN 87-7676-394-3 (online).
www.sst.dk/publ/publ2006/CEMTV/Dialyse/dialyse.pdf

Aim

To investigate whether the number of patients with chronic renal failure in outgoing dialysis can be increased with a positive result.

Conclusions and results

The survival rate for Danish peritoneal dialysis (PD) patients appears to be superior for the first 1.5 years except in diabetes patients aged >55 years. There is a potential to increase the number of patients on outgoing dialysis from the present 30% to 45%. This places greater demands on patients having the necessary information and being allowed to help choose the treatment method. However, it is important to emphasize that patients are not to be forced into outgoing dialysis. Clinical contraindications and strong social factors can be reasons for patients preferring chronic hemodialysis (CHD). Furthermore, the report indicates several organizational challenges if the outlined growth in the proportion of patients is to be managed. Additional patients in outgoing treatment may result in a cost-saving potential of approximately 68 million Danish kroner.

Recommendations

- Increased effort to have general practitioners and relevant hospital units refer patients with progressing chronic renal disease in the early stages of the disease
- Improved preparation of the patient for dialysis treatment with clarifying information about dialysis methods
- Guidelines for start of dialysis and subsequent dialysis method
- Better possibilities of assistance at home for automated peritoneal dialysis (APD)
- Clarification of the economic responsibility concerning assisted APD
- Exchange of knowledge and development of holistic nephrologic competence for nurses
- Joint awareness and strategies in the entire nephrologic area
- Prioritize lower time consumption in dialysis and increase freedom and flexibility for patients.

Methods

The analysis comprised literature reviews and interview studies with patients and staff and includes numbers from Danish registries for patients with chronic renal failure. A health economic assessment was performed for the various forms of dialysis and different scenarios in outgoing dialysis.

Written by Bonnevie BM, Nielsen CP, Lee A, Sinding LS, and Olsen J, DACEHTA, Denmark

Title **X-rays of the Lower Back in the 20 to 49 Patient Groups Referred From Primary Section**

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Reference Medicinsk Teknologivurdering 2006; 8(4). ISBN 87-7676-414-1 (online).
www.sst.dk/publ/publ2006/CEMTV/Rtg_laenderyg/rtglaend.pdf

Aim

To identify indications for referral to lumbar spine radiography in patients aged 20 to 49 years; to assess small area variation in utilization of the technology; and to determine the impact of altered utilization on patients and the economy.

Conclusions and results

For patients in the 20 to 49 age group, x-rays of the lower back should be used primarily for "red flag" situations (indicate, eg, fracture, infection, arthritis, tumor).

There is no support for automatically referring a patient with unspecified lower back pain for x-ray after a certain period. A new British clinical randomized study shows that such an approach has no effect. However, 12 of 13 earlier and new guidelines recommend that the patient be referred after a certain period. Similar to the latest guidelines from DSAM (Danish College of General Practitioners), it is recommended that clinicians may refer the patient for x-ray after 6 weeks with unspecified lower back pain.

There is no support for the assumption that the patient's condition (eg, emotional wellbeing) should prevent a change in utilization. From 1998 to 2004, utilization at chiropractors has decreased by 32%, while utilization with referral from GPs has decreased by 12% (reports from 6 counties). From 2003 to 2004 minor increases in utilization were registered, ie, 5% and 3% for chiropractors and GPs respectively. The discrepancy between data extracts from local hospital units (by county) and the Danish National Patient Registry on x-ray of the lower back averages 6%, and for some counties up to 14%.

Some counties probably have unexplained overutilization of x-ray examinations in diagnosing lower back pain. Theoretically, and according to the economic model, this may be interpreted as practice variation. The literature suggests it represents overutilization rather than underutilization.

Subject to the assumptions included in the model, the economic analysis estimated a potential savings of around 1.6 million Danish kroner (DKK) annually. The total cost for x-ray examination of the lower back in patients aged 20 to 49 years referred from the primary sector is around DKK 27 million per year.

Based on foreign cost-effectiveness analyses, the economic cost of patients with lower back pain is generally lower in patient courses without the use of x-ray than in courses including x-ray.

Recommendations

Clinical studies documenting the genuine clinical effect of x-raying patients with lower back pain are needed. The effect of x-raying after 6 weeks of unspecified pain should be further documented. Studies are needed that document patient-related consequences based on primary endpoints. It should also be documented whether information can serve as an equal alternative to x-ray exams. A more uniform and consistent registration practice is required, especially in registering "form of referral", ie, who referred the patient. The increased utilization from 2003 to 2004 shows that a focus on lowering/maintaining utilization is still needed.

Methods

The report uses an evidence-based approach related to national/international HTAs and clinical guidelines, review articles, and recent primary studies not assessed in connection with a systematic followup. Literature was searched and assessed based on an established protocol. Specific search strategies were prepared and are maintained as documentation. The analysis of the organizational and economic perspective is based mainly on data and registry extracts.

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INAHTA Briefs

Issue 2007/50

Title **Capsule Endoscopies of the Small Intestine – A Health Technology Assessment**

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Reference Medicinsk Teknologivurdering – puljeprojekter 2007; 7(1). ISBN 978-87-7676-461-3 (online). www.sst.dk/publ/Publ2007/MTV/Kapselendoskopi/Kapselendoskopi.pdf

Aim

To evaluate the use of capsule endoscopy for obscure gastrointestinal bleeding (OGB) in Denmark.

Conclusions and results

Although patients with OGB account for only a few percent of the patients with gastrointestinal bleeding, these patients often undergo repeated diagnostic investigation. This health technology assessment (HTA) report investigates the use of capsule endoscopy as a diagnostic procedure of the small intestine. The report includes 100 consecutive patients with OGB. Over 90% of the patients are satisfied with the procedure, which is similar to other studies of capsule endoscopy and indicates a higher level of satisfaction than other diagnostic procedures. Approximately one third of the patients state that their health condition improved after capsule endoscopy, and 30 patients report not having had any new endoscopic procedures or blood transfusions.

In general, repeated endoscopy decreased significantly within the first year after capsule endoscopy compared to the year previous. Additionally, only 2 radiological examinations of the small intestine were performed in the 100 patients. Hence, there is a significant overall decline in imaging after capsule endoscopy, most pronounced for standard diagnostic procedures of the small intestine.

Abdominal CT scans after capsule endoscopy have increased after capsule endoscopy. This is either due to directing the diagnostics toward extra intestinal reasons for the anemia, or due to limited access to CT and MR scanning of the small intestine. However, less than 20% of the patients are subjected to additional CT scanning. Average hemoglobin levels were similar prior to and after capsule endoscopy.

Regarding the financial consequences of capsule endoscopy, the diagnostic-related group (DRG) value of the hospital contacts related specifically to examination of OGB were reduced by approximately 50% during the postperiod compared to the preperiod.

In conclusion, patient satisfaction with the procedure is high. The health condition is improved for about 30% of the patients, and another 30% of patients are not subjected to additional diagnostics of the gastrointestinal system. Capsule endoscopy examination significantly reduces endoscopic procedures.

Recommendations

Five years after its introduction, capsule endoscopy has proven to be an important diagnostic tool for patients with OGB. Meta-analysis showed capsule endoscopy to be superior in detecting abnormalities in the small intestine compared to other noninvasive procedures, with an overall diagnostic yield of approximately 50%. As the procedure is easily performed, with minimum patient discomfort and few contraindications and complications, it is recommended internationally that capsule endoscopy be performed as a primary examination of the small intestine in OGB patients without contraindications. This strategy should also be implemented in Denmark based on the significant diagnostic yield, but also to avoid radiation from conventional barium follow-through, which for this group of patients has a diagnostic yield below 10%.

Methods

The following methods were used: quasiexperimental pre-post design, literature reviews, journal reviews, questionnaires regarding patients, questionnaires regarding hospitals, semistructured telephone interviews, and value assessments.

Written by Christensen LA, Dahlerup JF, Poulsen PB, and Thranholm L, DACEHTA, Denmark

Title **Visual Mobility Aids for Patients With Night Blindness**

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Reference 06-09. ISBN 978-2-550-48413-4 (printed French edition),
2-550-48752-4 (English summary, PDF).
www.aetmis.gouv.qc.ca/site/index.php?fr_publications_2006

Aim

To determine whether Night Vision Aids (NVAs) should be included in the Visual Devices Program administered by the provincial public health insurance plan.

Conclusions and results

Night visions devices, such as the wide-angle mobility light (WAML) and NVAs, can, despite certain limitations, effectively help certain individuals with night blindness by making it safer for them to travel in low-illumination conditions. On the other hand, night vision goggles (NVGs) are still in the experimental stage. For these night vision assistive devices to be as useful as possible, they should be allocated and their use monitored by orientation and mobility specialists within the context of a personalized intervention. The intervention should include, eg, a pre-allocation assessment of the needs of the user, appropriate training, a trial period with the device, and regular followup assessments. Problems accessing these different devices in Québec could be resolved with a public program such as the Visual Devices Program. Lastly, this report emphasizes the need to continue efforts to collect and share data to better identify the conditions for optimal night-vision aid utility.

Recommendations

AETMIS recommends that the eligibility requirements of the Visual Devices Program take into account all of the aspects of vision affected by night blindness; that the Ministry of Health and Social Services, after consulting its partners, make NVAs and mobility light accessible to individuals with night blindness and, when the necessary conditions are met, take steps to include these devices in the list of aids available in the Visual Devices program; that the allocation of these devices and the monitoring of their use be supervised by professionals working in Québec rehabilitation facilities; and that these facilities collect data on the clinical utility of night vision devices and draw the necessary conclusions from these data to improve the services offered.

Methods

A scientific literature search was conducted in different databases, including MEDLINE (PubMed) and the INAHTA database. The report provides a complete review of the relevant studies that were selected. In addition, several websites were consulted to identify the commercially available products and the resources available for people with night blindness. Also, interviews were conducted to describe the situation in Québec regarding the use of night vision assistive devices.

Written by Valérie Martin, AETMIS, Canada

Title **Glaucoma: Screening and Early Diagnosis – Problems and Outlook in France**

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Reference HAS report, November 2006

Aim

To summarize and comment on the current status of key clinical and economic data on glaucoma.

Conclusions and results

This report reviews data on the history and epidemiology of glaucoma, problems posed by diagnosis and treatment in France, the relevance of screening, and the expectations of health professionals. Assessing the possible implementation of a national screening program for glaucoma is not relevant in view of the current state of knowledge and medical practice in France. There is no single specific diagnostic test for early-stage glaucoma. Several tests would need to be used, complicating the screening strategy. Furthermore, the value of these tests has not been assessed in either the general population or a targeted population.

Methods

The report was produced in 4 months by a method not previously used by HAS. Studies were selected and reviewed according to the same evidence-based rules as for standard assessments, but the review was restricted to studies having a high level of evidence. Documentary research focused on documents from agencies and/or learned societies, systematic reviews, meta-analyses, and French or European observational studies. The opinion of 11 health professionals from different professional backgrounds and regions of France, who are concerned by glaucoma, was requested in a questionnaire. The report was submitted to members of the *Commission d'évaluation des stratégies de santé*[1] and the HAS Board to establish the issue(s) that the assessment report on glaucoma scheduled for 2007 (HAS' work program) should address.

Further research/reviews required

The following actions are needed according to the data in the present report:

- Carry out an epidemiology study to estimate the prevalence of glaucoma (by type of glaucoma) and raised intraocular pressure in France
- Identify and describe the risk factors (characteristics and threshold values of abnormality) that should be looked for to define a target population (by type of glaucoma) that would benefit from an improved early diagnosis strategy
- Establish and standardize diagnostic and management strategies for glaucoma
- Establish the sequence of tests to be used in the diagnostic strategy and whether they are appropriate for screening.

HAS proposes that guidelines should be developed on the diagnosis and treatment of glaucoma in France. They should also cover followup of patients with either raised intraocular pressure or confirmed glaucoma.

[1] Committee for Healthcare Strategy Assessment

Written by Roselyne Delaveyne and Anne-Isabelle Poullié, HAS, France

INAHTA Briefs

Issue 2007/53

Title **Bisphosphonates for the Primary and Secondary Prevention of Osteoporotic Fractures in Postmenopausal Women: A Meta-Analysis**

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Reference CADTH Technology Report, Issue 69. October 2006. ISBN 1-897257-22-8 (print), 1-897257-23-6 (electronic)

Aim

To assess the clinical effectiveness of etidronate, alendronate, and risedronate in the primary and secondary prevention of osteoporotic fractures in postmenopausal women over a followup period of at least one year.

Conclusions and results

None of the bisphosphonates was found to be effective at reducing hip, wrist, or other nonvertebral fractures. Etidronate had a beneficial effect on reducing vertebral fractures only when used for secondary prevention. The data did not support an effect of etidronate on reducing vertebral fractures when used for primary prevention or reductions in nonvertebral, hip, or wrist fractures if used for primary or secondary prevention. Alendronate reduced the risk of vertebral, nonvertebral, hip, and wrist fractures when used for secondary prevention. There were no statistically significant reductions in the primary prevention of osteoporotic fractures by alendronate, with the exception of vertebral fractures. The data for risedronate supported a beneficial effect in reducing the risk of vertebral, nonvertebral, and hip fractures (but not for wrist), when used for secondary prevention. No estimates were possible regarding the use of risedronate in primary prevention.

Recommendations

Not applicable.

Methods

We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) that compared primary and secondary fractures in women with osteoporosis taking etidronate, alendronate, or risedronate to women receiving placebo.

Further research/reviews required

Whether differences in risk reduction exist across groups of patients with varying degrees of osteoporosis needs further study, as does the impact of bisphosphonates on the RR of nonvertebral fractures in populations without osteoporosis. The role of risedronate in the primary prevention of osteoporotic fractures needs to be clarified. Finally, areas of future research should focus on issues such as whether bisphosphonates reduce nonvertebral fractures in younger women, and if supplemental calcium or combination therapy with other active treatment can significantly increase the effect of these drugs on fractures.

Written by Wells GA, Cranney A, Boucher M, Peterson J, Shea B, Robinson V, Coyle D, and Tugwell P, CADTH, Canada

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