INAHTA Briefs

INAHTA

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Technology Assessment

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INAHTA Briefs

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

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

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Introduction

The International Network of Agencies for Health Technology Assessment (INAHTA) is a global network linking 46 non-profit, governmental institutions from 24 countries (2008).

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, Asia, and Australasia. The Secretariat is located at SBU in Sweden.

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

Title **Teriparatide and Bisphosphonates for Treatment of Osteoporosis in Women: A Clinical and Economic Analysis**

Agency **CADTH, Canadian Agency for Drugs and Technologies in Health**
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Reference CADTH Technology Report, Issue 70. October 2006.
ISBN 1-897257-56-2 (print), 1-897257-57-0 (electronic)

Aim

To assess the clinical and cost effectiveness of teriparatide relative to the bisphosphonates for the primary and secondary prevention of osteoporotic fractures in postmenopausal women.

Conclusions and results

Evidence indicates that the main benefits of bisphosphonate therapy, relative to placebo, lie in the secondary prevention of osteoporotic fractures. Etidronate is associated with a reduction in vertebral fractures. Risedronate reduces vertebral, hip, and nonvertebral fractures. Alendronate was associated with reductions in vertebral, nonvertebral, hip, and wrist fractures. Etidronate, risedronate, and teriparatide were more costly and less effective than alendronate. Etidronate was more costly and less effective than both drug and no drug therapy options in all scenarios. Compared to no drug therapy, alendronate costs an additional 169 600 Canadian dollars per quality-adjusted life year (QALY) for a 65-year-old woman. In a 90-year-old, alendronate therapy is less costly and more effective than no drug therapy.

Recommendations

Not applicable.

Methods

The clinical literature was systematically reviewed to compare teriparatide to bisphosphonates or placebo. Net health impact was estimated using a decision-analytic model in terms of QALYs. An economic evaluation compared teriparatide to bisphosphonates, or no drug therapy. The base-case for this analysis was an 80-year-old woman with at least one previous osteoporotic fracture. The budget impact of funding teriparatide and bisphosphonates in public drug plans was also assessed.

Written by Coyle D, Hadj Tahar A, Murphy G, Perras C, Skidmore B, Boucher M, and Husereau D, CADTH, Canada

Title **Sevelamer in Patients with End-Stage Renal Disease: A Systematic Review and Economic Evaluation**

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Reference CADTH Technology Report, Issue 71. November 2006.
ISBN 1-897257-58-9 (print), 1-897257-59-7 (electronic)

Aim

To systematically review the efficacy and harm of sevelamer, and to conduct a primary economic evaluation and budget impact analysis of its use when compared with calcium-based phosphate binders in patients with end-stage renal disease (ESRD) who are on dialysis.

Conclusions and results

There was no convincing evidence that substituting sevelamer for calcium based binders reduced all-cause mortality, cardiovascular mortality, hospitalization, or the frequency of symptomatic bone disease, and no evidence that sevelamer improved quality of life. Sevelamer therapy results in a smaller decrease in phosphate levels, and fewer episodes of hypercalcemia of unknown clinical significance, compared with calcium-based phosphate binders. Even if sevelamer is assumed to be more effective than calcium-based phosphate binders, it is associated with a cost per quality-adjusted life year gained ranging from 127 000 to 278 100 Canadian dollars. It is possible that sevelamer use, restricted to patients ≥65 years of age, might be more economically efficient, but improved effectiveness in this group requires confirmation from future studies.

Recommendations

Not applicable.

Methods

Using two search terms, sevelamer and Renagel, we conducted a comprehensive search to identify all relevant studies of sevelamer use. We assessed the study quality of randomized controlled trials (RCTs), using a condensed version of the Chalmers Index, and a standard data extraction method to record the data elements of interest into a database. We assessed the following outcomes: mortality (all-cause, and cardiovascular); cardiovascular events; hospitalizations; quality of life; levels of serum phosphate, calcium, parathyroid hormone (PTH), bicarbonate, calcium-phosphate product; and occurrence of adverse events. Because of the differences expected between trials, we decided *a priori* to combine results in a conservative fashion using a random effects model.

Written by Manns B, Tonelli M, Shrive F, Wiebe N, Klarenbach S, Lee H, and Culleton B, CADTH, Canada

Title **Point-of-Care Monitoring Devices for Long-Term Oral Anticoagulation Therapy: Clinical and Cost Effectiveness**

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Reference CADTH Technology Report, Issue 72. February 2007.
ISBN 1-897257-64-3 (print), 1-897257-65-1 (electronic)

Aim

To assess the clinical and economic implications of point-of-care (POC) devices for monitoring long-term oral anticoagulation therapy (OAT).

Conclusions and results

Using POC devices to manage OAT results in significantly fewer deaths, fewer thromboembolic events, and better international normalized ration (INR) control than conventional laboratory testing, with no significant difference in hemorrhagic events. Compared to laboratory testing, using POC devices in anticoagulation clinics saves costs compared with conventional testing for healthcare payers. It is also cost effective if society is willing to pay 50 000 Canadian dollars for a quality-adjusted life-year (QALY). Self testing by patients compared to laboratory testing does not seem to be cost effective from a publicly funded healthcare perspective.

Recommendations

Not applicable.

Methods

We systematically reviewed the clinical and economic literature. For the clinical review, multiple databases were searched. Two reviewers independently assessed quality after extracting data from the 16 eligible articles. A meta-analysis was conducted. Seven articles describing six unique studies were reviewed and used in the primary economic evaluation.

Written by Brown A, Wells P, Jaffey J, McGahan L, Poon M-C, Cimon K, and Campbell K, CADTH, Canada

Title **Human Alpha1-Proteinase Inhibitor for Patients with Alpha1-Antitrypsin Deficiency**

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Reference CADTH Technology Report, Issue 74. February 2007.
ISBN 1-897257-06-6 (print), 1-897257-07-4 (electronic)

Aim

To assess the clinical and cost effectiveness of α1-proteinase inhibitor (α1-PI) compared with no human α1-PI in patients with ATT (antitrypsin) deficiency, and to determine the status of public funding for α1-PI in Canada and other countries.

Conclusions and results

In controlled trials, augmentation therapy has not shown reduced lung function impairment in patients with AAT deficiency and chronic obstructive pulmonary disease (COPD), compared with normal care. Conversely, in observational studies, α1-PI is associated with outcomes suggestive of therapeutic benefit in patients with severe AAT deficiency and moderate airflow obstruction. Severe adverse events from treatment have been reported in ~1% of study populations. No evidence was found evaluating the use of α1-PIs in patients with AAT deficiency and no lung function impairment.

Based on the only cost-utility analysis conducted, lifetime costs could average almost 1 million US dollars (USD) to produce 2.57 quality-adjusted life-years (QALYs) (from 4.62 with standard care to 7.19) resulting in a ratio of USD 333 349 per QALY. It is anticipated that Canadian costs would be similar. Public funding of α1-PI varies across Canada, and although the product is marketed in several European countries where funding is provided, the funding details are not known.

Recommendations

Not applicable.

Methods

We systematically reviewed the clinical and economic literature. Information regarding funding and delivery in Canada and similar public health systems was collected and synthesized.

Written by Chen S, Farahati F, Marciniuk D, Mayers I, Boudreau R, and Keating T, CADTH, Canada

Title **Adjunctive Hyperbaric Oxygen Therapy for Diabetic Foot Ulcer: An Economic Analysis**

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Reference CADTH Technology Report, Issue 75. March 2007.
ISBN 1-897257-38-4 (print), 1-897257-39-2 (electronic)

Aim

To determine if adjunctive hyperbaric oxygen therapy (HBOT) is a cost-effective option compared to standard care in treating patients with diabetic foot ulcers (DFU) in Canada.

Conclusions and results

Results from the clinical review corroborate findings in previous assessments that adjunctive HBOT for DFU is more effective than standard care, although the evidence remains limited. The proportion of major lower extremity amputation (LEAs) can decrease from 32% in patients receiving standard care to 11% in those receiving adjunctive HBOT. There was a decrease in the proportion of unhealed wounds with HBOT, but the reverse was true for minor LEAs. Based on the available data, the economic evaluation showed that adjunctive HBOT for DFU was cost effective compared to standard care. The 12-year cost for a patient receiving HBOT was 40 695 Canadian dollars (CAD) compared to CAD 49 786 for standard care alone, with an associated increase of 0.63 quality-adjusted life-years (QALYs) (3.01 QALYs for standard care to 3.64 QALYs for those receiving HBOT). The use of HBOT will require additional resources and planning.

Recommendations

Not applicable.

Methods

Controlled studies that compared adjunctive HBOT for DFU with standard wound care in patients of all ages were identified through a literature search. Summary estimates were derived for proportions of major and minor LEAs and healed ulcers in patients who received adjunctive HBOT and those who received standard care only. Using a decision model, the cost effectiveness of adjunctive HBOT was compared with that of standard care alone in treating 65-year-old patients. A health services budget impact analysis was conducted using prevalence data from the literature and utilization data from Alberta and Canada.

Further research/reviews required

Good quality studies are needed to confirm the comparative benefits of this technology in Canadian health care.

Written by Hailey D, Jacobs P, Perry DC, Chuck A, Morrison A, and Boudreau R, CADTH, Canada

Title	**Triptans for Acute Migraine: Comparative Clinical Effectiveness and Cost Effectiveness**
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Reference	CADTH Technology Report, Issue 76. March 2007. ISBN 1-897257-72-4 (print), 1-897257-73-2 (electronic)

Aim

To assess the comparative clinical and cost effectiveness of the following serotonin (5-HT1) receptor agonists (triptans) in patients with acute migraine: almotriptan, eletriptan, naratriptan, sumatriptan succinate/hemisulfate, rizatriptan, and zolmitriptan.

Conclusions and results

The evidence of differences in benefit between some triptans from unreplicated randomized controlled trials is judged to be of fair quality. Good-quality evidence suggests that there are no demonstrated differences in the harmful effects associated with oral triptans. Since no head-to-head trials were found, it was not possible to draw reliable conclusions about the comparative effectiveness of triptans in adolescents. In adults, evidence from several long-term placebo-controlled trials suggests that oral sumatriptan recipients consistently experience more headache relief. In adolescents, only nasal sumatriptan has been shown to improve pain relief while also demonstrating side effects, most commonly, taste disturbance. Most of the literature evaluating the cost effectiveness of triptans is of a limited utility to healthcare decision makers because of poor quality. Most economic studies do not compare all available triptans.

Recommendations

Not applicable.

Methods

A systematic review was summarized and appraised to compare triptans in adults. The clinical literature was systematically reviewed to compare triptans in adolescents. Economic evaluations were systematically reviewed to identify the primary influential factors determining the cost effectiveness of therapy and to identify compelling evidence of cost effectiveness in a Canadian population.

Further research/reviews required

More comparisons among triptans other than sumatriptan are needed, and better evidence regarding the effectiveness of triptans for early and mild migraines should be considered.

Written by Membe S, McGahan L, Cimon K, Gawel M, Giammarco R, and Mierzwinski-Urban M, CADTH, Canada

Title **Implantable Cardiac Defibrillators for Primary Prevention of Sudden Cardiac Death in High Risk Patients: A Meta-Analysis of Clinical Efficacy, and a Review of Cost Effectiveness and Psychosocial Issues**

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Reference CADTH Technology Report, Issue 81. March 2007. ISBN 1-897257-66-X (print)

Aim

To inform healthcare decision makers and others involved in planning and delivering implantable cardiac defibrillator (ICD) services about evidence on the clinical and cost effectiveness of ICD therapy compared to conventional treatment in primary prevention of sudden cardiac death and to examine the ethical and psychosocial issues related to its use.

Conclusions and results

Implantable cardiac defibrillators (ICDs), with optimal pharmacologic therapy, significantly reduce sudden cardiac death (SCD) and all-cause death in patients at high risk. ICDs are effective in reducing SCD in patients with ischemic and non-ischemic heart disease. ICD therapy is expensive, but some reviewed studies showed that ICDs are cost effective if the willingness to pay is 50 000 Canadian dollars per quality-adjusted life-year (QALY). More study with a broader target population is warranted. Poor psychosocial outcomes in ICD patients may occur as a result of their underlying cardiac condition, rather than as a direct response to ICDs.

Recommendations

Not applicable.

Methods

Randomized controlled trials (RCTs) reporting clinical outcomes for ICDs in primary prevention were systematically reviewed. Psychosocial and ethical issues, and the cost effectiveness of ICD treatment, were examined, and a budget impact analysis was performed.

Written by Ho C, Li H, Noorani H, Cimon K, Campbell K, Tang A, and Birnie D, CADTH, Canada

Title **Pegylated Interferon Combined With Ribavirin for Chronic Hepatitis C Virus Infection: An Economic Evaluation**

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Reference CADTH Technology Report, Issue 82. March 2007.
ISBN 1-897257-84-8 (print), 1-897257-85-6 (electronic)

Aim

To assess the cost effectiveness of treating Canadian adults who have chronic hepatitis C (CHC) with Peg-IFN+RBV (Pegetron™ and Pegasys RBV®) compared to standard (non-Peg) IFN plus RBV, and no antiviral therapy (AVT).

Conclusions and results

No detectable difference was found between PegIFN+RBV and IFN+RBV in all-cause mortality or withdrawals due to adverse effects. However, treatment with PegIFN+RBV was associated with a significantly higher rate of non-fatal serious adverse events during 48 weeks of therapy and 24 weeks of followup and had a higher overall sustained virological response rate than IFN+RBV. Based on our economic analyses, initial treatment with PegIFN+RBV, for patients with CHC and elevated ALT levels, could improve health outcomes and is associated with a lower incremental cost-effectiveness ratio (ICER) compared with IFN+RBV.

Recommendations

Not applicable.

Methods

Clinical data on beneficial and adverse outcomes of antiviral therapy were extracted from randomized controlled trials and a previous CADTH systematic review. The net health impact was estimated using a decision-analytic model in terms of quality-adjusted life-years (QALYs) and life-years (LYs) saved, from the perspective of Canadian ministries of health. The analysis compared PegIFN+RBV to IFN+RBV, and to no antiviral therapy. The simulated population (base case) had an average age of 43 years, with a mix of liver disease states, hepatitis C virus genotypes, and sex, consistent with the Canadian CHC population.

Written by Brady B, Siebert U, Sroczynski G, Murphy G, Husereau D, Sherman M, Wong W, and Mensinkai S, CADTH, Canada

Title **Long-Acting ß2-agonists (LABA) Plus Corticosteroids Versus LABA Alone for Chronic Obstructive Pulmonary Disease**

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Reference CADTH Technology Report, Issue 83. March 2007.
ISBN 1-897257-54-6 (print), 1-897257-55-4 (electronic)

Aim

To determine, using Canadian evidence, the cost effectiveness of inhaled long-acting ß2-agonists (LABA) combined with an inhaled corticosteroid (ICS), known as combined therapy (CT), versus administration of LABA alone as a first-line agent in chronic obstructive pulmonary disease (COPD); and to measure the global economic impact of introducing CT versus LABA in Canada.

Conclusions and results

Available evidence suggests that CT results in fewer overall exacerbations and improved quality of life measures compared with treatment by LABA alone. No evidence suggests that mortality differs with different strategies. The lifetime cost of using a LABA (discounted at 5%) is 9636 Canadian dollars (CAD) per COPD patient. Adding an ICS for the most severe patients (Strategy 2) results in an increase of CAD 93 per patient; Strategy 3 increases costs by CAD 321; and Strategy 4 increases costs by CAD 3120. Each strategy is associated with an additional increase of 0.01 quality-adjusted life-year (QALY) per patient. Those who are prepared to pay up to CAD 50 000 for a QALY may perceive Strategies 2 and 3 as cost effective.

Recommendations

Not applicable.

Methods

Three relevant randomized controlled trials were identified through a systematic literature review. Estimates of changes in exacerbation, serious adverse events, and mortality rates were then derived. Using a Markov model, the 3-year and lifetime cost effectiveness of combination therapy (CT) compared with LABA alone was estimated for 4 disease management strategies. With Strategy 1 (base case), all patients were treated with LABA. With Strategy 2, in addition to the base case, ICS was given to patients with stage-3 disease only. With Strategy 3, in addition to the base case, ICS was given to patients with stage-2 and stage-3 disease only. With Strategy 4, in addition to the base case, ICS was given to all patients. The calculated budget impact of switching patients from LABA to CT was based on Alberta utilization data.

Written by Mayers I, Jacobs P, Marciniuk DD, Chuck A, and Varney J, CADTH, Canada

Title **Infliximab and Etanercept in Rheumatoid Arthritis: Systematic Review of Long-Term Clinical Effectiveness, Safety, and Cost Effectiveness**

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Reference CADTH Technology Report, Issue 85. March 2007.
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Aim

To review the available data on the long-term effectiveness, safety, and cost effectiveness of infliximab (IFX) and etanercept (ETN) in treating patients with rheumatoid arthritis (RA).

Conclusions and results

Randomized controlled trials (RCTs) of >1 year duration showed that anti-TNF agents have a small to moderate effect in clinical outcomes. A clinical and significant improvement in American College of Rheumatology improvement criteria (ACR50) and Disease Activity Scores (DAS28) was observed for IFX+methotrexate (MTX) and ETN+MTX, compared with MTX alone. A statistically significant pooled result was observed for the Short Form 36 (SF-36) physical component with IFX 3 mg/kg every 8 weeks, but the effect was not clinically meaningful (1.77, with an effect size of 0.15). The beneficial effects of anti-TNF agents were revealed on radiological progression: Significant differences were observed between the treatment and control groups, even when the clinical differences were not significant. ETN alone did not offer a clear benefit over MTX alone, but ETN+MTX was better than MTX alone. Anti-TNF agents are well tolerated in the short term (generally ≤6 months), but there are concerns about their longer-term safety. Economic evidence suggests that treatment with ETN and IFX, each used concomitantly with MTX, is only cost effective in treating RA after the failure of other disease-modifying anti-rheumatic drugs (DMARDs), and if a high threshold for cost effectiveness is used (>100 000 Canadian dollars per quality-adjusted life-year (QALY)).

Recommendations

Not applicable.

Methods

The literature was systematically reviewed to compare IFX and ETN at recommended dosages with placebo or other therapies. Outcome measures included American College of Rheumatology improvement criteria (ACR-50: 50% improvement in the number of swollen and tender joints, and 50% in at least 3 of the other 5 core set measures), Disease Activity Scores, functional status, and radiological progression. A meta-analysis was performed to synthesize and combine the results of RCTs. Data from observational studies were synthesized, but not combined. For the review of cost effectiveness, we included all studies reporting costs and outcomes.

Written by Suarez-Almazor M, Ortiz Z, Lopez-Olivo M, Moffett M, Pak C, Skidmore B, Kimmel B, Kallen M, and Cox V, CADTH, Canada

Title **Short-Acting Insulin Analogues for Diabetes Mellitus: Meta-Analysis of Clinical Outcomes and Assessment of Cost Effectiveness**

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Reference CADTH Technology Report, Issue 87. March 2007.
ISBN 1-897257-90-2 (print), 1-897257-91-0 (electronic)

Aim

To evaluate the clinical and economic implications of short-acting insulin analogues (insulin lispro (ILis), insulin aspart (IAsp), and insulin glulisine (IGlu)) in treating type 1, type 2, and gestational diabetes mellitus (DM).

Conclusions and results

In type 1 DM patients, treatment with ILis or IAsp significantly reduced HbA1c levels, compared to human insulin (HI). The occurrence of overall and severe hypoglycemia was similar for both treatments, but nocturnal hypoglycemia was less frequent with ILis compared with HI. In type 2 DM patients, HbA1c levels, occurrences of hypoglycemia, and quality of life were similar between those using HI and those using short-acting insulin analogues (SAIAs). SAIAs did not result in significant reductions in hypoglycemic episodes. Uncertainty remains regarding the use of short-acting insulin analogues in gestational DM patients and pregnant women with diabetes. If users of HI switch to the more expensive insulin analogues, further increases in drug plan expenditures can be anticipated. Evidence suggests that these additional costs can be offset by reductions in other healthcare expenditures in a 12-month horizon. These findings are limited to study settings in the United States. The economic evidence also showed that patients preferred ILis to HI or Mix25 to HI 30/70.

Recommendations

Not applicable.

Methods

A systematic review and a meta-analysis were undertaken to evaluate the clinical and economic implications of using SAIAs in treating diabetes mellitus, relative to human insulin and to oral anti-diabetic agents. SAIAs included insulin lispro (ILis), insulin aspart (IAsp) and insulin glulisine (IGlu).

Further research/reviews required

High-quality long-term studies are needed to determine the benefit and harm of short-acting insulin analogues, compared to conventional insulin. Data on patient mortality and quality of life are lacking. The impact on healthcare costs beyond 12 months is unknown.

Written by Banerjee S, Tran K, Li H, Cimon K, Daneman D, Simpson S, and Campbell K, CADTH, Canada

Title **Tandem Mass Spectrometry and Neonatal Blood Screening in Quebec: Summary Report**

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Reference 07-03. ISBN 978-2-550-48905-4 (print, French), 978-2-550-49399-0 (English summary).
www.aetmis.gouv.qc.ca/site/en_publications_2007.phtml

Aim

To evaluate whether it would be pertinent to use tandem mass spectrometry (MS/MS) for neonatal blood screening in Quebec and to: 1) examine the relevance of replacing current screening methods for phenylketonuria (PKU) and tyrosinemia type 1 (TT1) by MS/MS and introducing neonatal screening for medium-chain acyl-CoA dehydrogenase deficiency (MCADD); and 2) analyze the main ethical, social, economic, and organizational issues.

Conclusions and results

This report was prepared at the request of the Quebec Health and Social Services Ministry in the context of scientific debates and pressure in favor of adopting MS/MS for neonatal blood screening of inborn errors of metabolism. The review confirms the importance of a case-by-case analysis for each inborn error of metabolism. Available options depend on the specific characteristics and state of knowledge for each disease, and the applicability of the technological developments to these diseases. Even though there are gaps in the data, evidence supports the clinical utility of neonatal screening for the 3 diseases in question. As for the appropriateness of implementing MS/MS-based screening in Quebec, the situation differs according to the disease. For MCADD, MS/MS is the only technology available for neonatal screening, and its performance is one of the best for this particular condition. For PKU, the literature suggests that MS/MS yields fewer false positives than the current technology, but compared to the results observed in Quebec, this advantage would not be substantial. However, if MS/MS were used for MCADD screening, the technology transfer for PKU would avoid a duplication of analytical steps and would be efficient, according to the health economics literature examined. For TT1, MS/MS-based neonatal screening relying on both tyrosine and succinylacetone assays seems promising, but needs further validation. Furthermore, the judiciousness of a technology transfer and its optimal timing depend on several ethical, social, legal, economic, and organizational issues in addition to the scientific and technical considerations.

Recommendations

Three separate scenarios are proposed for consideration by policy-makers: 1) conducting a pilot study; 2) postponing the introduction of MS/MS until after the necessary validation studies for TT1 screening have been completed; and 3) introducing MS/MS for PKU and MCADD screening, while, either undertaking gradual technology replacement for TT1, or maintaining the current methods until the results of the validation studies are available. Whichever option is chosen, MS/MS must not be implemented hastily, since other issues (ethical, economic, and organizational) first need to be resolved.

Methods

Critical review of the scientific literature, of epidemiological data in Quebec, and of the grey literature; cost analyses; analysis of some ethical, social, legal, economic, and organizational issues.

Written by Héla Makni, Carole St-Hilaire, Laura Robb, Katy Larouche, and Ingeborg Blancquaert, AETMIS, Canada

Title **Adefovir Dipivoxil and Pegylated Interferon Alfa-2a for the Treatment of Chronic Hepatitis B: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2006;10(28). August 2006.
www.hta.ac.uk/execsumm/summ1028.htm

Aim

To assess the clinical and cost effectiveness of adefovir dipivoxil (ADV) and pegylated interferon alfa-2a (PEG) in treating adults with chronic hepatitis B (CHB) infection.

Conclusions and results

The results showed that ADV was significantly more effective than placebo. For patients resistant to lamivudine (LAM), response rates were significantly higher for those treated with ADV in addition to ongoing LAM than those who continued on LAM with placebo. All studies reported significant alanine aminotransferase (ALT) reductions to normal levels. For treatment-naïve patients, seroconversion rates were statistically significant, rates were higher for LAM-resistant patients who received ADV in addition to on-going LAM than those who continued on LAM with placebo, and rates were higher for LAM-resistant patients who switched to ADV than those who continued on LAM with placebo. HBsAg loss or seroconversion was observed in less than 5% of patients taking ADV. Histological improvement and necroinflammatory activity/fibrosis scores were significantly for ADV than placebo. Dose discontinuations for safety reasons were low for patients receiving ADV. With the exception of headache, the most commonly reported adverse events were often seen in the placebo groups in similar proportions to the ADV groups (different trials reported conflicting results). PEG/LAM dual therapy and PEG monotherapy were similar in effect on HBV DNA and ALT levels, and both were significantly superior to LAM monotherapy. Response rates were higher for HBeAg-negative patients than for HBeAg-positive patients. HBeAg seroconversion rates at followup were significantly higher in PEG monotherapy than in either a combination of PEG and LAM or LAM monotherapy. Comparing PEG and IFN-2a showed a significant difference in combined outcome of ALT normalization, HBV DNA response, and HBeAg seroconversion at followup. No statistically significant difference was found in histological improvement between PEG monotherapy groups, LAM monotherapy groups, and dual therapy groups. Health-related quality of life (HRQoL) decreased during treatment, but returned at followup. For HBeAg-positive patients, there were no significant differences in scores between treatment groups. Dose discontinuations for safety reasons were significantly higher for patients receiving PEG than those receiving LAM monotherapy. Adverse events in the PEG studies were headache, pyrexia, fatigue, myalgia, and alopecia. Our model estimated incremental cost per QALY at GBP 5994 for IFN compared with best supportive care, GBP 6119 for PEG compared with IFN, GBP 3685 for LAM compared with best supportive care, and GBP 16 569 for ADV compared with LAM.

Recommendations

ADV and PEG improve several biochemical, virological, and histological outcomes in HBeAg-positive and -negative patients. In a small proportion of patients this is associated with resolution of infection. For another proportion it leads to remission and reduced risk of progressing to cirrhosis, hepatocellular carcinoma, liver transplant, and death. For others who do not respond or who relapse, retreatment with another agent is necessary. Our cost-effectiveness analysis shows that incremental costs per QALY fall within the range the NHS considers as good value.

Methods

Electronic databases were searched, a model was developed to estimate cost effectiveness, a Markov state transition model was constructed, and changes in HRQoL were estimated. (See executive summary link above.)

Further research/reviews required

Further RCT evidence of the effectiveness of anti-viral treatment is required, particularly for subgroups of patients with different genotypes, patients with cirrhosis, patients from different ethnic groups, patients with co-infections (eg, HIV, HCV) and comorbidities, liver transplant patients, and children and adolescents.

Written by Mr Jonathan Shepherd, University of Southampton, United Kingdom

Title **Etanercept and Infliximab for the Treatment of Psoriatic Arthritis: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2006;10(31). September 2006.
www.hta.ac.uk/execsumm/summ1031.htm

Aim

To evaluate the clinical effectiveness, safety, tolerability, and cost effectiveness of etanercept and infliximab in treating active and progressive psoriatic arthritis (PsA) in patients with inadequate response to standard treatment, including disease-modifying antirheumatic drug (DMARD) therapy.

Conclusions and results

Across the two trials, at 12 weeks, around 65% of patients treated with etanercept achieved an American College of Rheumatology (ACR) 20, showing basic efficacy in terms of arthritis-related symptoms, with around 45% of patients achieving an ACR 50, and around 12% achieving an ACR 70. Subgroup analyses in one trial revealed that the effect of etanercept was not dependent on patients' concomitant use of methotrexate. Almost 85% of patients treated with etanercept achieved PsA Response Criteria (PsARC). The Health Assessment Questionnaire (HAQ) score with etanercept compared with placebo indicates a beneficial effect of etanercept on function. Uncontrolled followup of patients indicates that treatment benefit may be maintained for at least 50 weeks. At 16 weeks, 65% of patients treated with infliximab achieved an ACR 20, showing basic efficacy in terms of arthritis-related symptoms. This was not dependent on patients' concomitant use of methotrexate. Almost half the patients treated with infliximab achieved an ACR 50, and over 25% achieved an ACR 70 versus none in the placebo group, demonstrating a good level of efficacy. In addition, 75% of patients treated with infliximab achieved a PsARC. The beneficial effect on psoriasis was statistically significant with a mean difference in percentage change from baseline in PASI of −5, as was the percentage improvement from baseline in HAQ score with infliximab versus placebo, indicating a beneficial effect of infliximab on functional status. Using the York cost-effectiveness model, infliximab was consistently dominated by etanercept because of its higher costs without superior effectiveness. The incremental cost per QALY gained of etanercept compared with palliative care ranged from GBP 14 818 (females, 40-year time horizon) to GBP 49 374 (males, 1-year time horizon) assuming that when patients eventually fail on biological therapy, their disability (HAQ score) deteriorates by the same amount as it improved when they initially respond to treatment. Results for etanercept ranged from GBP 25 443 (females, 40-year time horizon) to GBP 49 441 (males, 1-year time horizon) per QALY gained, assuming that when patients fail on therapy, their disability level returns to what it would have been had they never responded.

Recommendations

Limited data indicated that etanercept and infliximab are efficacious in treating PsA, with beneficial effects on joint and psoriasis symptoms and functional status. No controlled data indicate that infliximab can delay joint disease progression. Treatment with both etanercept and infliximab for 12 weeks demonstrated a significant degree of efficacy, with no statistically significant difference between them. Adverse events, mainly mild injection/infusion reactions, were common for both drugs. The York model indicated that etanercept is more cost effective than infliximab. The cost effectiveness of etanercept is also sensitive to assumptions regarding the extent of disease progression when patients are responding to therapy.

Methods

A systematic review based on literature searches (2004) evaluated the clinical efficacy and adverse effects of etanercept and infliximab. The efficacy of DMARDs in treating PsA was also reviewed and, where data allowed, treatments were compared utilizing Bayesian evidence synthesis methods. Economic evaluations of etanercept and infliximab in psoriatic arthritis were assessed, and a new economic model was developed (York Model).

Further research/reviews required

Further research should include long-term controlled trials to confirm benefits, review adverse events, and explore further the implications of biologic therapy.

Written by Dr Nerys F Woolacott, University of York, United Kingdom

Title **Computerized Cognitive Behavior Therapy for Depression and Anxiety Update: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2006;10(33). September 2006.
www.hta.ac.uk/execsumm/summ1033.htm

Aim

To evaluate computerized cognitive behavior therapy (CCBT) in treating anxiety, depression, phobias, panic, and obsessive-compulsive behavior (OCD). Software packages to be considered include Beating the Blues (BtB), Overcoming Depression: a five areas approach, FearFighter (FF), Cope, and BT Steps.

Conclusions and results

Twenty studies were identified in the clinical effectiveness review. Analysis of these results showed some evidence that CCBT is as effective as therapist-led cognitive behavior therapy (TCBT) in treating depression/anxiety and phobia/panic and is more effective than treatment as usual (TAU) in treating depression/anxiety. CCBT also appears to reduce therapist time compared to TCBT.

In reviewing cost-effectiveness studies, only one published economic evaluation of CCBT was found. This was an economic evaluation of the depression software BtB alongside a randomized controlled trial (RCT), which found that BtB was cost effective against TAU in terms of cost per quality-adjusted life-year (QALY) (less than GBP 2000). However, it contained weaknesses that were then addressed in the cost-effectiveness model developed for the study.

For the depression software packages the incremental cost per QALY compared with TAU (and the chance of being cost effective at GBP 30 000 per QALY) were GBP 1801 (86.8%) for BtB, GBP 7139 (62.6%) for Cope, and GBP 5391 (54.4%) for Overcoming Depression. The strength of the BtB software being that it has been evaluated in the context of an RCT with a control group. Subgroup analysis found no differences across severity groupings. For phobia/panic software, the model showed an incremental cost per QALY of FF over relaxation of GBP 2380. Its position compared with TCBT is less clear. For OCD packages, a practice-level license cost for BT Steps was dominated by TCBT, which had significantly better outcomes and was cheaper. However, the cheaper PCT level license resulted in the incremental cost effectiveness of BT Steps over relaxation being GBP 15 581 and TCBT over BT Steps being GBP 22 484.

Recommendations

Evidence based on randomized controlled trial supports the effectiveness of BtB and FF. BtB and FF would appear to be cost effective. The cost effectiveness of the two other depression packages and the package for OCD is less certain.

Methods

A systematic review was performed to identify all studies describing trials of CCBT. The cost-effectiveness assessment includes a review of the literature and the evidence submitted by sponsors for each of the products. A series of cost-effectiveness models was developed and run by the project team for the 5 CCBT products across the 3 mental health conditions.

Further research/reviews required

Research is needed to compare CCBT with other therapies that reduce therapist time, in particular bibliotherapy, and to explore the use of CCBT via the Internet. Independent research is needed, particularly RCTs, that examine areas such as patient preference and therapist involvement within primary care.

Written by Dr Eva Kaltenthaler, University of Sheffield, United Kingdom

Title **Psychological Therapies Including Dialectical Behavior Therapy for Borderline Personality Disorder: A Systematic Review and Preliminary Economic Evaluation**

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Reference Health Technol Assess 2006;10(35). Sept 2006. www.hta.ac.uk/execsumm/summ1035.htm

Aim

To summarize the available evidence on the clinical and cost effectiveness of psychological therapies including dialectical behavior therapy (DBT) for borderline personality disorder (BPD).

Conclusions and results

Nine randomized controlled trials (RCTs) and one non-RCT of moderate to poor quality were identified in the clinical effectiveness review. They provided some evidence that DBT is more effective than treatment as usual (TAU) in treating chronically parasuicidal and drug-dependent borderline women; that DBT-orientated therapy is more effective than client-centered therapy (CCT) in treating BPD; and that DBT is as effective as comprehensive validation therapy plus 12-Step in treating opioid-dependent borderline women. Some evidence also showed that partial hospitalization is more effective than TAU in treating BPD, good evidence that manual-assisted cognitive behavioral therapy (MACT) is no more effective than TAU in treating BPD, and some evidence that interpersonal group therapy is no more effective than individual mentalization-based partial hospitalization (MBT) in treating BPD. However, these results should be interpreted with caution as not all studies were primarily targeted to borderline symptoms, and considerable differences were found between the studies. Assessment of cost effectiveness revealed a mix of results in the 4 trials of DBT, along with high levels of uncertainty and limitations in the analyses. The findings do not support the cost effectiveness of DBT, although they suggest it has the potential to be cost effective. The results for MBT are promising, but again surrounded by a high degree of uncertainty. Analysis of MACT suggests that the intervention is unlikely to be cost effective.

Recommendations

The overall efficacy of psychological therapies is promising, but the evidence is inconclusive. Six RCTs examined the cost effectiveness of the intervention, but did not find support for the cost effectiveness of DBT although the potential is suggested. Considerable research is needed in this area.

Methods

Relevant studies were assessed using standard checklists. Two reviewers abstracted data by using standardized forms. Separate economic evaluations were undertaken for 6 selected RCTs. Cost effectiveness was assessed in terms of cost per parasuicide event avoided in all 6 trials and cost per quality-adjusted life-year (QALY) in 4 of them. All results reflect 2003–2004 prices and 12 months of followup.

Further research/reviews required

Further research should involve appropriately powered head-to-head RCTs of psychological therapies; a survey of current practice and the use of the full range of services by people with BPD to inform future economic analyses; full resource-use data collected in the context of pragmatic clinical trials; psychometric assessment of the validity of EQ-5D or other generic and condition-specific preference-based measures in BPD; and the development of a more formal cost-effectiveness model using the above data.

Written by Professor John Brazier, University of Sheffield, United Kingdom

INAHTA Briefs

Issue 2007/70

Title **The Clinical and Cost Effectiveness of Oxaliplatin and Capecitabine for the Adjuvant Treatment of Colon Cancer: Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2006;10(41). Nov 2006. www.hta.ac.uk/execsumm/summ1041.htm

Aim

To assess the clinical and cost effectiveness of oxaliplatin combined with 5-fluorouracil/leucovorin (5-FU/LV) and capecitabine monotherapy as adjuvant therapies in treating patients with Stage III (Dukes' C) colon cancer after complete surgical resection of the primary tumor, versus adjuvant chemotherapy with an established fluorouracil-containing regimen.

Conclusions and results

The review included 3 randomized controlled trials. The MOSAIC trial and NSABP C-07 study considered the addition of oxaliplatin to adjuvant treatment, and the X-ACT study compared oral capecitabine with bolus 5-FU/LV alone. The evidence indicated that in patients with Stage III colon cancer, oxaliplatin combined with an infusional de Gramont schedule of 5-FU/LV (FOLFOX4) was more effective in preventing and delaying disease recurrence than infusional 5-FU/LV alone (de Gramont regimen). Serious adverse events and treatment discontinuations due to toxicity were more evident with oxaliplatin-based regimens (FOLFOX4 and FLOX) than infusional or bolus 5-FU/LV alone (de Gramont and Roswell Park). Oral capecitabine was at least equivalent in disease-free survival to the bolus Mayo Clinic 5-FU/LV regimen for patients with resected Stage III colon cancer. Capecitabine was superior to the Mayo Clinic 5-FU/LV regimen regarding safety and tolerability, but other less toxic 5-FU/LV regimens were not compared. Cost-effectiveness analysis indicated that capecitabine was dominating and saved about GBP 3320 per patient compared to the Mayo Clinic 5-FU/LV regimen, while adding 0.98 quality-adjusted life years (QALYs) over a 50-year model time horizon. Oxaliplatin combined with 5-FU/LV (FOLFOX4) is estimated to cost an additional GBP 2970 per QALY gained compared to the de Gramont 5-FU/LV regimen and demonstrated superior survival outcomes at marginal costs. Uncertainty analysis suggests that both interventions may be cost effective at thresholds of GBP 20 000 and GBP 30 000. Indirect comparison suggests that use of FOLFOX4 in place of the Mayo Clinic 5-FU/LV regimen would cost an additional GBP 5777 per QALY gained. An incremental cost-effectiveness ratio (ICER) is estimated to be about GBP 13 000 per QALY gained from treatment with FOLFOX4 compared to capecitabine. If the Mayo Clinic and de Gramont 5-FU/LV regimens are assumed to be equivalent in effectiveness, the ICER of FOLFOX4 in comparison with capecitabine may be greater than GBP 30 000 per QALY.

Recommendations

The evidence suggests that both capecitabine and FOLFOX4 are clinically effective and likely to be considered cost effective in comparison with 5-FU/LV regimens (Mayo Clinic and de Gramont schedules).

Methods

The search included 10 electronic databases (inception to January 2005) supplemented by hand searching relevant articles, sponsor and other submissions of evidence to the National Institute of Health and Clinical Excellence, and conference proceedings. A systematic review and meta-analysis of clinical efficacy evidence and cost-effectiveness review and economic modeling was undertaken. A new model was developed to assess the costs of the alternative treatments, the differential mean survival duration, and the impact on health-related quality of life. Probabilistic sensitivity analysis addressed the likelihood that each of the interventions was optimal.

Further research/reviews required

Further research is suggested into the effectiveness, tolerability, patient acceptability, and costs of different oxaliplatin/fluoropyrimidine schedules in the adjuvant setting; effects of treatment duration on efficacy, adverse events, resource data collection, and reporting; subgroups benefiting most from adjuvant chemotherapy; and methods of estimating mean survival.

Written by Mr Abdullah Pandor, University of Sheffield, United Kingdom

INAHTA Briefs

Issue 2007/71

Title **A Systematic Review of the Effectiveness of Adalimumab, Etanercept, and Infliximab for the Treatment of Rheumatoid Arthritis in Adults and an Economic Evaluation of their Cost Effectiveness**

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Reference Health Technol Assess 2006;10(42). Nov 2006. www.hta.ac.uk/execsumm/summ1042.htm

Aim

To review the clinical and cost effectiveness of adalimumab, etanercept, and infliximab – agents that inhibit tumor necrosis factor-alpha (TNF-alpha) – in treating rheumatoid arthritis (RA) in adults.

Conclusions and results

Twenty-nine randomized controlled trials (RCTs), most of high quality, were included. The only head-to-head comparisons were against methotrexate. In patients with short disease duration who were naïve to methotrexate, adalimumab was marginally less and etanercept was marginally more effective than methotrexate in reducing symptoms of RA. Etanercept was better tolerated than methotrexate. Both adalimumab and etanercept were more effective than methotrexate in slowing radiographic joint damage. Etanercept was also marginally more effective and better tolerated than methotrexate in patients with longer disease durations who had not failed methotrexate treatment. Infliximab is only licensed for use with methotrexate. All 3 agents, alone or in combination with ongoing disease-modifying antirheumatic drugs (DMARDs), were effective in reducing symptoms and signs of RA in patients with established disease. In patients who were naïve to methotrexate, or who had not previously failed methotrexate treatment, a TNF inhibitor combined with methotrexate was significantly more effective than methotrexate alone. Infliximab combined with methotrexate increased the risk of serious infections. All 10 published economic evaluations met standard criteria for quality, but the incremental cost-effectiveness ratios (ICERs) were very high in some instances. For use in accordance with NICE guidance as the third in a sequence of DMARDs, the base-case ICER was around GBP 30 000 per QALY in early RA and GBP 50 000 per QALY in late RA. TNF inhibitors are most cost effective when used last. The ICER for etanercept used last is GBP 24 000 per QALY, substantially lower than for adalimumab or infliximab. First line use as monotherapy generates ICERs around GBP 50 000 per QALY for adalimumab and etanercept. Using the combination of methotrexate and a TNF inhibitor as first line treatment generates much higher ICERs, as it precludes subsequent use of methotrexate, which is cheap. The ICERs for sequential use are of the same order as using the TNF inhibitor alone.

Recommendations

Adalimumab, etanercept, and infliximab are effective treatments compared with placebo for RA patients who are not well controlled by conventional DMARDs. The combination of a TNF inhibitor with methotrexate was more effective than methotrexate alone in early RA, but clinical relevance of this additional benefit is yet to be established. An increased risk of serious infection cannot be ruled out in combining methotrexate with adalimumab or infliximab. TNF inhibitors are most cost effective when used as last active therapy. In this analysis, other things being equal, etanercept may be the TNF inhibitor of choice, but this may depend on patient preference as to route of administration. The next most cost-effective use of TNF inhibitors is third line, as recommended in the 2002 NICE guidance.

Methods

Systematic reviews of the literature on effectiveness and cost effectiveness were undertaken. Many databases were searched up to February 2005, information was sought from researchers and industry, and industry submissions to NICE were reviewed. Meta-analyses of effectiveness data were undertaken for each agent. A simulation model (BRAM) was further developed and used to produce an incremental cost-effectiveness analysis.

Further research/reviews required

Direct comparative RCTs of TNF inhibitors against each other and against other DMARDs, and sequential use in patients who have failed a previous TNF inhibitor, are needed. Longer-term studies of the quality of life in patients with RA and the impact of DMARDs on this are needed, as are longer studies that directly assess effects on joint replacement, other morbidity, and mortality.

Written by Dr Amanda Burls, University of Birmingham, United Kingdom

Title **Clinical Effectiveness and Cost Effectiveness of Laparoscopic Surgery for Colorectal Cancer: Systematic Reviews and Economic Evaluation**

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Reference Health Technol Assess 2006;10(45). November 2006.
www.hta.ac.uk/execsumm/summ1045.htm

Aim

To determine the clinical and cost effectiveness of laparoscopic, laparoscopically assisted (hereafter together described as laparoscopic surgery), and hand-assisted laparoscopic surgery (HALS) compared to open surgery in treating colorectal cancer.

Conclusions and results

A review of clinical effectiveness included 46 reports on 19 randomized controlled trials (RCTs) and 1 individual patient data (IPD) meta-analysis. The laparoscopic and open surgery trials included 2429 and 2139 participants, respectively. A systematic review of 4 papers suggested that laparoscopic surgery is more costly than open surgery. It showed a higher incremental cost per life-year, but was no more effective than open surgery. Data were sparse on incremental cost per QALY for laparoscopic versus open surgery. Results of the base-case analysis indicate a 40% chance that laparoscopic surgery is the more cost-effective intervention at a willingness-to-pay threshold of GBP 30 000 per QALY. A second analysis assuming equal mortality and disease-free survival found a 50% likelihood at a similar threshold value. Similar results were found in the sensitivity analyses. A threshold analysis examined the magnitude of QALY gain associated with quicker recovery after laparoscopic surgery required to provide an incremental cost per QALY of GBP 30 000. The implied number of additional QALYs required would be 0.009 to 0.010 compared with open surgery.

Recommendations

Laparoscopic resection showed faster recovery, but no difference in mortality or disease-free survival up to 3 years after surgery. However, operation times are longer, and many procedures initiated laparoscopically may need to be converted to open surgery. Conversion may depend on experience in patient selection and in using the technique. Laparoscopic resection appears to be more costly than open resection (about GBP 250 to GBP 300 per patient). In relative cost effectiveness, laparoscopic resection is associated with a modest additional cost, short-term benefits from faster recovery, and similar long-term outcomes in survival and cure rates up to 3 years. Assuming equivalence of long-term outcomes, a judgment is required as to whether the benefits of earlier recovery are worth the extra cost.

Methods

Electronic databases were searched from 2000 to May 2005. Data from selected studies were extracted and assessed. Dichotomous outcome data from individual trials were combined using the relative risk method, and continuous outcomes were combined using the Mantel-Haenszel weighted mean difference method. Results from individual patient data (IPD) meta-analyses were summarized. A Markov model incorporated data from the systematic review in an economic evaluation. A balance sheet compared surgical techniques and was used to estimate cost effectiveness in terms of incremental cost per life-year gained and per quality-adjusted life-year (QALY).

Further research/reviews required

Long-term followup of the RCT cohorts would be useful, and the data should be used in a wider IPD meta-analysis. Data on long-term complications of surgery and differences in outcomes would be valuable. New data on costs and utilities should be included in an updated model. Data are needed from methodologically sound RCTs. Possible variations in the balance of advantages and disadvantages of laparoscopic surgery in subgroups (different stages and locations of disease) should be studied. The effect of experience on performance also requires further research.

Written by Dr Alison Murray, University of Aberdeen, United Kingdom

Title **A Systematic Review and Economic Model of the Clinical Effectiveness and Cost Effectiveness of Docetaxel in Combination with Prednisone or Prednisolone for the Treatment of Hormone-Refractory Metastatic Prostate Cancer**

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Reference Health Technol Assess 2007;11(2). Jan 2007. www.hta.ac.uk/execsumm/summ1102.htm

Aim

To evaluate the clinical and cost effectiveness of docetaxel (Taxotere®, Sanofi-Aventis) in combination with prednisone/prednisolone in treating metastatic hormone-refractory prostate cancer (mHRPC).

Conclusions and results

Seven randomized controlled trials were identified that met the inclusion criteria. A direct comparison of docetaxel plus prednisone versus mitoxantrone plus prednisone in an open-label randomized trial showed improved outcomes for docetaxel plus prednisone in terms of overall survival, quality of life, pain, and prostate specific antigen (PSA) decline. Two other chemotherapy regimens that included docetaxel: docetaxel plus estramustine and docetaxel plus prednisone plus estramustine, also showed improved outcomes in comparison with mitoxantrone plus prednisone. Indirect comparison suggested that docetaxel plus prednisone was superior to corticosteroids alone in terms of overall survival. Conclusions on cost effectiveness were primarily informed by the results of the in-house model. This indicated that mitoxantrone plus a corticosteroid may be cheaper and more effective than corticosteroid alone. Compared with mitoxantrone plus prednisone/prednisolone, the use of docetaxel plus prednisone/prednisolone (3-weekly) appears cost effective only if the NHS is prepared to pay GBP 33 000 per quality-adjusted life-year (QALY). The incremental cost-effectiveness ratio associated with docetaxel plus prednisone (3-weekly) remained fairly robust to these variations with estimates ranging from GBP 28 000 to GBP 33 000 per QALY. Value of information analysis revealed that further research is potentially valuable. Given a maximum acceptable ratio of GBP 30 000 per QALY, the expected value of information was estimated to be approximately GBP 13 million.

Recommendations

Our review of the data suggests that docetaxel plus prednisone seems to be the most effective treatment for men with mHRPC. The results from the assessment group model suggest that treatment with docetaxel plus prednisone/prednisolone is cost effective in patients with mHRPC as long as the health service is willing to pay GBP 33 000 per additional QALY.

Methods

Twenty-one resources (including MEDLINE, EMBASE, and the Cochrane Library) were searched to April 2005. Two reviewers independently assessed studies for inclusion. Data from included studies were extracted and quality assessed. Where appropriate, outcomes were synthesized using formal analytic approaches. A new economic model was developed to establish the cost effectiveness of docetaxel compared to a range of potential comparators. A separate review identified sources of utility data required to estimate QALYs. Sensitivity analyses explored the robustness of the main analysis in alternative assumptions related to quality of life. Monte Carlo simulation was used to propagate uncertainty in input parameters through the model. The impact of uncertainty in the decision was established using value of information and implementation approaches.

Further research/reviews required

Future research should include the direct assessment of quality of life and utility gain associated with different treatments, including the effect of adverse events of treatment, using generic instruments, which are suitable in cost-effectiveness analyses.

Written by Ms Ros Collins, CRD, United Kingdom

Title **Obstructive Sleep Apnea Syndrome – Report of a Joint Nordic Project. A Systematic Literature Review**

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Reference SBU Report 184E, 2007. ISBN 978-91-85413-16-4. Full text report in English and summary and conclusions in Swedish are available at www.sbu.se/published

Aim

To investigate:

- Consequences of obstructive sleep apnea syndrome (OSAS) on cardiovascular morbidity, diabetes mellitus, death, and traffic accidents
- How to diagnose OSAS
- Effects of various treatment modalities, including compliance and adverse effects.

Conclusions and results

Cardiovascular complications, diabetes mellitus, and death: OSAS covaries with cardiovascular disease, including stroke and early death in men, but evidence on women is insufficient. Scientific evidence is insufficient on a relationship between OSAS and arterial hypertension or diabetes mellitus.

Traffic accidents: OSAS covaries with traffic accidents independent of daytime sleepiness and driving exposure among men.

Diagnostic procedures: The apnea-hypopnea index (AHI) shows good agreement between 2 nights of polysomnographic recordings. Manually scored portable devices during one night of sleep have high sensitivity and specificity to identify a pathologic AHI compared with polysomnography. Automatic scoring of the results of portable devices has high sensitivity and identifies most patients with a pathologic AHI, but specificity is low. Automatic scoring programs cannot score sleep time and it is unclear whether these programs can differentiate obstructive from central apneas. Pulse oximetry with results from the oxygen desaturation index is insufficient to identify a pathologic AHI, and there is a high risk that patients with sleep apnea syndrome will be incorrectly classified as normal.

A global impression from a case history and a physical examination alone are insufficient to identify or to rule out OSAS.

Treatments: Strong evidence shows that *continuous positive airway pressure (CPAP)* therapy reduces daytime sleepiness regardless of the severity of OSAS and is effective in reducing obstructive sleep apneas. Scientific evidence is contradictory on the effect of CPAP on quality of life or arterial blood pressure. Tolerance and compliance with CPAP is good. Mild to moderate discomfort from the CPAP mask are common adverse effects. Custom-made *mandibular repositioning appliances (MRAs)* reduce daytime sleepiness in patients with mild to moderate sleep apnea syndrome. They reduce apnea frequency, but to a lesser extent than CPAP. Most patients experience mild adverse effects, eg, discomfort in the teeth, during the first few months. There is insufficient scientific evidence for the effect of any *surgical modality* on daytime sleepiness or quality of life.

No studies meeting the inclusion criteria show that *other treatments and lifestyle modifications* (eg, weight reduction programs, drugs, pacemakers) have any effect on OSAS.

Methods

Systematic literature review including meta analyses.

Further research/reviews required

Controlled trials for efficacy and long-term followup for adverse effects are required if surgery for OSAS or snoring is to be considered in the future. Covariation between cardiovascular disease and OSAS needs further study. The effects of CPAP and/or MRAs on traffic accidents, morbidity, and mortality remain unknown. Effects of lifestyle changes are important issues since patients with OSAS often have other risk factors for conditions such as obesity.

Written by Nina Rehnqvist, SBU, Sweden

Title **Rapid Assessment: Cardiovascular Primary Prevention in Belgian General Practice**

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Reference Report no 52A, legal depot: D/200710.273/03.
Report available in English with Dutch and French executive summary

Aim

To assess and compare the current European guideline and the draft Belgian general practice guideline; to assess the practical application of cardiovascular primary prevention (CVP) guidelines in Belgian general practice and identify interventions to enhance this; and to assess the evidence for the effectiveness and cost effectiveness of primary prevention interventions in target populations.

Conclusions and results

The current CVP guideline from the European Task Force and the draft general practice guideline present only a few important differences, the most important of which is the absolute risk threshold for defining high-risk individuals. Regarding dietary interventions, there is only evidence for the benefits of a sustained diet low in saturated fats. In primary prevention, statin therapy is not cost effective in most target populations when compared to the alternative interventions of smoking cessation and low-dose aspirin treatment. Belgian general practitioners (GPs) do not systematically apply the current guidelines and tools for risk assessment.

Recommendations

For pharmaceutical interventions in primary prevention, the focus should be on individuals having the highest cardiovascular risk who can benefit most from such intervention. For smokers, smoking cessation is the most effective and also the most cost-effective intervention. Regarding dietary interventions, the only hard evidence is for sustained diets low in saturated fats.

Methods

We analyzed and compared the current guideline from the European task force and the draft guideline developed by a Belgian GP organization. We also performed a rapid assessment of available evidence on dietary interventions and on statin use in primary prevention. The economic literature on primary CVP was searched and assessed. Barriers against and facilitators for the implementation of CVP guidelines in general practice were investigated via a telephone survey of 286 Belgian GPs, a literature review of implementation research, and group discussions with GPs.

Further research/reviews required

Currently, there is no hard evidence to show which interventions are most appropriate in Belgium to encourage GPs to apply CVP guidelines in daily practice.

Written by De Laet C, Neyt M, Van Brabandt H, and Ramaekers D, KCE, Belgium, in collaboration with Domus Medica

Title **Methods of Promoting Physical Activity. A Systematic Review**

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Reference SBU Report 181, 2007. ISBN 978-91-85413-12-6.
Full text report in Swedish and summary and conclusions in English are available at www.sbu.se/published

Aim

To assess the effectiveness and cost implications for the healthcare system of various methods for promoting physical activity.

Conclusions and results

Among others:

- Advice/counseling in routine clinical practice was consistently shown to increase physical activity by 12% to 50%. No study reported a reduced level of physical activity, and followup at 6 months or longer showed that counseling clearly boosted such activity (Evidence Grade 1).
- Physical exercise in groups leads to greater activity among cardiovascular patients. Such sessions are most effective if they are initially monitored, last between 45 and 60 minutes 2 or 3 times a week, have the proper level of intensity to improve general fitness, and continue for at least 6 months (Evidence Grade 3).
- Interventions that include a patient's general lifestyle, focusing on diet and stress management and physical activity, accelerate the increase in activity. That may be due to many different factors, including the magnitude of the intervention (Evidence Grade 3).
- Interventions that focus on improving the content of the physical education curriculum increase activity by 5% to 25% during class periods in children aged 7 to 14 years – even more so for boys than for girls (Evidence Grade 1).

Methods

The Cochrane Library databases were searched, followed by PubMed, PsycINFO, Eric, SportDiscus, and the Campbell Collaboration Library. Bibliographies of relevant publications were also checked to identify additional studies. For a study to be considered as scientific evidence in addressing the various questions under consideration, it had to meet the following criteria:

- The purpose of the study was to examine the efficacy of methods of promoting physical activity.
- A relevant control group was treated with another intervention, or no intervention.
- The outcome measure was a change in physical activity or, secondarily, physical performance.
- The followup period was at least 6 months from the start of the intervention.

Further research/reviews required

Major gaps exist in our knowledge about the long-term effectiveness of various methods for promoting physical activity. These gaps emerge not only in the content and design of the methods, but in how and by whom they should be used to achieve the desired short-term and long-term results for various patients and groups of patients. Future research should be designed to enable long-term followup of both the effectiveness and cost of various methods, while considering ethical and social aspects, including those related to gender and ethnic background. The project identified several particularly urgent areas for future research.

Written by Ingemar Eckerlund, SBU, Sweden

Title **Methods of Early Prenatal Diagnosis**

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Reference SBU Report 182, 2006. ISBN 978-91-85413-13-3.
Full text report in Swedish and summary and conclusions in English are available at www.sbu.se/published

Aim

To systematically review the literature with the intent of examining the scientific evidence for methods currently used, or about to be adopted, in prenatal diagnosis to detect fetal chromosomal and structural abnormalities.

Conclusions and results

Among others:

- A combined test of nuchal translucency measurement, ultrasonography, and maternal serum biochemistry (biochemical screening) in early pregnancy (10–14 gestational weeks), along with maternal age, is the clinically evaluated method to assess the probability of fetal Down syndrome that strikes the best balance between the percentage of detected cases and false-positive results (Evidence Grade 1).
- All methods (nuchal translucency measurement, maternal serum biochemistry in the second trimester, and the combined test) for assessing the probability of fetal Down syndrome examined by this report and evaluated in clinical practice strike a better balance between the percentage of detected cases and false-positive results than maternal age alone. Thus, the use of these methods requires fewer amniocenteses and chorionic villus samplings per detected cases of Down syndrome than maternal age alone (Evidence Grade 1).
- Most pregnant women want to be notified early and prefer screening in the first trimester (Evidence Grade 1).

Methods

The project analyzed medical, social, psychological, ethical, health economic, quality assurance, and safety aspects of early prenatal diagnosis. Literature searches were performed in electronic databases such as Cochrane Library and PubMed/MEDLINE. A search for health economic studies was also conducted in the National Health Service Economic Evaluation Database (NHS EED). Bibliographies were examined and members of the project team followed various areas of current research. Based on predetermined criteria, the identified literature was systematically selected and quality assessed.

Further research/reviews required

Among others:

- The clinical value of nasal bone ultrasonography, ultrasonographic soft markers, Doppler ultrasonography, 3D ultrasonography, or MRI as screening or prenatal diagnostic methods in the first or second trimester remains unclear.
- There is insufficient knowledge concerning which models are most suitable for informing pregnant women and their partners, or how information should be formulated to satisfy the needs of particular ethnic and cultural groups.

Written by Ingemar Eckerlund, SBU, Sweden

Title **A Randomized Controlled Comparison of Alternative Strategies in Stroke Care**

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Reference Health Technol Assess 2005;9(18). May 2005.
www.hta.ac.uk/execsumm/summ918.htm

Aim

To compare outcomes of stroke patients managed in different settings; to derive prognostic variables to identify patients suitable for management at home and in hospital; to describe organizational aspects of stroke care strategies; to evaluate the acceptability of strategies to patients and professionals; and to perform an economic evaluation.

Conclusions and results

Of the 457 patients randomized, 152 patients were allocated to the stroke unit, 152 patients to stroke team, and 153 patients to domiciliary stroke care (average age 76 years, 48% women). The groups were well matched for baseline characteristics, stroke type and severity, level of impairment, and initial disability. Fifty-one (34%) patients in the domiciliary group were admitted to hospital after randomization. Mortality and institutionalization at 1 year were lower on the stroke unit compared with stroke team or domiciliary care. Significantly fewer patients on the stroke unit died compared with those managed by the stroke team. The proportion of patients alive without severe disability at 1 year was also significantly higher on the stroke unit compared with stroke team or domiciliary care. These differences were present at 3 and 6 months after stroke. Survivors managed on the stroke unit showed greater improvement on basic activities of daily living compared with other strategies. Care strategy did not influence achievement of higher levels of function. Quality of life at 3 months was significantly better in stroke unit and domiciliary care patients. Dissatisfaction with care was greater on general wards compared with stroke unit or domiciliary care. Poor outcome with domiciliary care and on general wards was associated with Barthel Index <5, incontinence and, on general wards, age over 75 years. Total costs of stroke per patient over the 12-month period were GBP 11 450 for stroke unit, GBP 9527 for stroke team, and GBP 6840 for home care. However, the mean costs per day alive for stroke unit patients were significantly less than those for the specialist stroke team patients, but no different from domiciliary care patients. Costs for the domiciliary group were significantly less than for those managed by the specialist stroke team on general wards.

Recommendations

Stroke units were found to be more effective than a specialist stroke team or specialist domiciliary care in reducing mortality, institutionalization, and dependence after stroke. This study does not support specialist domiciliary services for acute stroke nor management of stroke patients on general medical wards, even with specialist team input. The stroke unit is the more cost-effective intervention.

Methods

A prospective, pragmatic RCT was undertaken in patients recruited from a community-based stroke register. The study was conducted in a suburban district in south-east England, where a co-terminus hospital trust, a community health trust, a family heath services authority, and social services provided for health and social needs. The stroke unit provided 24-hour care from a specialist multidisciplinary team based on guidelines for acute care, prevention of complications, rehabilitation, and secondary prevention. The stroke team involved management on general wards with specialist team support. The team undertook stroke assessments and advised ward-based nursing and therapy staff on acute care, secondary prevention, and rehabilitation aspects. Domiciliary care managed patients at home (maximum of 3 months) under the supervision of a GP and stroke specialist with support from specialist team and community services.

Further research/reviews required

Research is needed on processes contributing to reducing mortality on stroke units, to determine the generalizability of these results, and to determine factors that will influence the implementation of findings from this study.

Written by Professor Lalit Kalra, King's College London School of Medicine, United Kingdom

Title **A Series of Systematic Reviews to Inform a Decision Analysis for Sampling and Treating Infected Diabetic Foot Ulcers**

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Reference Health Technol Assess 2006;10(12). April 2006.
www.hta.ac.uk/execsumm/summ1012.htm

Aim

To systematically review the evidence on diagnosing and treating infection in diabetic foot ulcers (DFU) and to use findings from the systematic reviews to create a decision analysis model.

Conclusions and results

We found three studies on diagnostic tests in chronic wound populations (including DFU). These studies indicated that:

- Single items on a clinical examination checklist are not reliable for identifying infection in chronic wounds
- Wound swabs perform poorly against wound biopsies in detecting infection in chronic wounds
- Semi-quantitative analysis of wound swabs may indicate the presence of infection in chronic wounds.

We found 21 RCTs and 2 CCTs examining the effect of antimicrobials on DFU. Most trials were too small to detect clinically important differences in outcomes as statistically significant. There is no strong evidence for recommending any particular antimicrobial agent for preventing amputation, resolving infection, or healing ulcers. Topical pexiganan cream may be as effective as oral antibiotic treatment with ofloxacin for resolution of infection. Findings, each from one small study, indicated that a growth factor (GCSF) was less costly than standard care, cadexomer iodine dressings may be less costly than standard care (daily dressings), and a combination of ampicillin and sulbactam was less costly than imipenem and cilastatin.

A decision analytic model was derived for people for whom diagnostic testing would inform treatment. Information was insufficient to populate aspects of the model with transition probabilities, and hence to inform the most effective diagnostic and treatment strategy.

Recommendations

Clinical assessment of the presence of infection and wound swabbing perform poorly in diagnosing infection in chronic wounds, and their performance in DFU is unknown. Semi-quantitative analysis may be useful in quantitative analysis of wound swabs. The evidence does not allow us to determine whether any particular antimicrobial agent is more effective than either another antimicrobial agent or standard care. An (unlicensed) antimicrobial cream may be as effective as oral antibiotics at resolving infection, but the impact on healing is unknown. Small, single studies indicate that lower treatment costs might be associated with GCSF vs standard care, cadexomoer iodine vs daily gauze dressings, and ampicillin and sulbactam vs imipenem and cilastatin.

Methods

Systematic reviews of the diagnostic, effectiveness, and cost-effectiveness literature with decision analytic modeling were used.

Further research/reviews required

1. To investigate the characteristics of infection in people with DFU which influence healing and amputation outcomes, eg, examining the importance of critical colonization on healing, cell density, and biofilm formation on healing and amputation.
2. To determine if detecting infection prior to treatment yields benefits over empirical therapy and, if so, to identify the most effective and cost-effective methods for detecting infection.
3. To determine the relative effectiveness and cost effectiveness of antimicrobial interventions for DFU infection.

Written by Dr E Andrea Nelson, University of Leeds, United Kingdom

Title **An Evaluation of the Clinical and Cost Effectiveness of Pulmonary Artery Catheters in Patient Management in Intensive Care: A Systematic Review and A Randomized Controlled Trial**

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Reference Health Technol Assess 2006;10(29). Sept 2006. www.hta.ac.uk/execsumm/summ1029.htm

Aim

To test the hypothesis that hospital mortality is significantly decreased in critically ill patients managed with a pulmonary artery catheter (PAC) in adult intensive care units (ICUs) compared with those who are not; and to identify any difference in the expected costs and outcomes of patients treated with and without a PAC.

Conclusions and results

The systematic review identified 11 RCTs. Of these, 3 were of general ICU patients managed with a PAC. The remaining 8 studies were of high-risk surgery patients of which 5 included preoperative optimization of hemodynamics using a PAC in the intervention and 3 did not. A meta-analysis of the 3 studies of general ICU patients found no difference (pooled OR 0.97, 95 % CI 0.74 to 1.26). Separate meta-analyses, which included only those studies of high-risk surgery patients, found no difference between the 2 treatment groups either where preoperative optimization was part of the intervention (5 studies: pooled odds ratio (OR) 0.98, 95% confidence interval (CI) 0.72 to 1.33), or where it was not (3 studies: pooled odds ratio (OR) 1.10 (0.13 to 9.06).

The RCT found no difference in hospital mortality for patients managed with a PAC (68.4%) compared to those managed without (65.7%). The adjusted hazard ratio (PAC vs No PAC) was 1.09 (95% CI 0.94 to 1.27). There was no difference in the ICU length of stay, hospital length of stay, or organ-days of support in ICU between the two groups.

The economic evaluation found that the expected cost per QALY gained from the withdrawal of PAC was GBP 2985. The expected cost per life gained from the withdrawal of PAC was GBP 22 038.

Recommendations

Evidence from this pragmatic RCT has shown that PACs, as currently used in UK critical care, do not confer benefit to patients. The economic evaluation indicates that withdrawal of the PAC from routine clinical practice in the NHS would be considered cost effective in the current decision-making climate.

Methods

A systematic review of the evidence from all randomized controlled trials (RCTs) where patients were randomized to be managed with a PAC (of any type) in one arm and without a PAC in another arm (control). Studies were eligible for inclusion if more than 50% of participants were adult and if the PAC was placed in an ICU or was placed during a surgical procedure leading to ICU admission. Studies were excluded if participants had been declared brain dead, with a PAC being placed solely for organ support prior to donation.

A multicenter, open, RCT with an economic evaluation (cost utility and cost effectiveness analysis). Patients deemed by the treating clinician to require management with a PAC were eligible for inclusion, unless: they were less than 16 years of age; were admitted to the critical care unit electively prior to surgery for preoperative optimization; had a PAC already in situ on admission to the ICU; had previously been entered into the trial; or were brain dead with a PAC being placed for organ support prior to donation.

Further research/reviews required

Efficacy studies are urgently needed to determine optimal management protocols and patient groups who could gain from PAC use.

Written by Dr Kathy Rowan, Intensive Care National Audit & Research Centre, United Kingdom

Title **Telemedicine in Dermatology: A Randomized Controlled Trial**

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Reference Health Technol Assess 2006;10(43). November 2006.
www.hta.ac.uk/execsumm/summ1043.htm

Aim

The project comprises two related, though distinct studies, with different objectives:

1. To assess the equivalence of store-and-forward teledermatology with conventional face-to-face consultation in setting a management plan for new, adult outpatient referrals.
2. To assess the equivalence of digital photography and dermoscopy with conventional face-to-face consultation in managing suspected cases of malignant melanoma (MM) or squamous cell carcinoma (SCC).

Conclusions and results

1. The study failed to recruit the number of patients required by the sample size calculations (208 recruited, number needed 892). The loss of control cases (26%) was greater than intervention cases (17%): difference 8% (95% CI: –3% to 19%, p=0.18). A statistically significant difference in ages between the two groups completing the study may have introduced a bias between the two groups. Another possible source of bias is the greater delay between the telemedicine opinion and the second opinion, whereas control cases usually received their second opinion on the same day as their outpatient appointment. In 55% (51/92) of telemedicine cases, and 78% (57/73) of control cases the diagnosis concurred (difference –23% 95% CI: –36% to –8%; p=0.002) with the second opinion. In 55% (51/92) of telemedicine cases, and 84% (61/73) of control cases, the management plan concurred with the second opinion (difference –28% 95% CI: –40 to –14%; p=0.0001). Of the 92 telemedicine cases, 53 (58% 95% CI: 47% to 67%) were judged also to require a face-to-face consultation, mainly to establish a diagnosis and treatment plan.
2. An unexpectedly high proportion (33%, 85/256) of referrals proved to have a malignancy or a severely dysplastic lesion, with almost 22% having MM or SCC, possibly reflecting the rise in incidence of skin cancers reported elsewhere. When both standard and dermoscopic images were employed, diagnostic concordance was modest (68%). The approach was highly sensitive (98%, 95% CI: 92 to 99%), at the expense of specificity (43%, 95% CI: 36 to 51%). Overall, 30% of cases would not have needed to be seen face to face, but 2 SCCs would have been missed. If the highest thresholds of clinician confidence had been applied, no cancers would have been missed, but only 20% of patients would have avoided an outpatient appointment.

Recommendations

1. In view of the recruitment difficulties and the potential biases introduced by selective loss of patients and the delay in obtaining a valid second opinion in the study group, no valid conclusions can be drawn regarding the clinical performance of this model of store-and-forward telemedicine.
2. It is unlikely that digital photography with dermoscopy can dramatically reduce the need for conventional clinical consultations, while still maintaining clinical safety.

Methods

1. *Randomized controlled trial.* Patients in the telemedicine intervention group were referred to the consultant and managed, as far as possible, using one or more digital still images and a structured, electronic referral and reply. The control group was managed by conventional hospital outpatient consultation.
2. *Case series.* Patients referred under the Government's 2-week-wait for suspected skin cancer were photographed immediately prior to their outpatient appointment. Both standard and dermoscopic images were obtained if possible. A second opinion, based on photographs and referral forms was compared with the opinion of the consultant who saw the patient in clinic.

Written by Dr Ian Bowns, University of Sheffield, United Kingdom

Title **Amniocentesis Results: Investigation of Anxiety. The ARIA Trial**

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Reference Health Technol Assess 2006;10(50). December 2006.
www.hta.ac.uk/execsumm/summ1050.htm

Aim

The ARIA trial tested two hypotheses:

1. That giving amniocentesis results out on a prespecified fixed date alters maternal anxiety during the waiting period, compared with a policy of telling parents that the result will be issued 'when available' (ie, on a variable date).
2. That issuing early results from a rapid molecular test alters maternal anxiety during the waiting period, compared with not receiving any results prior to the karyotype.

The effects of the interventions on anxiety 1 month after receiving the full karyotype results were also examined.

Conclusions and results

1. There was no evidence that giving out karyotype results on a fixed or on a variable date altered maternal anxiety during the waiting period. However, the trial only had sufficient power to detect a moderate-to-large effect.
2. Issuing early results from a partial but rapid test reduced maternal anxiety during the waiting period, compared to receiving only the full karyotype results.

In addition:

- Group differences in recalled anxiety closely reflected the differences in anxiety women had experienced while waiting for results.

One month after receiving normal karyotype results, anxiety was low in all groups, but women who had been given rapid test results were more anxious than those who had not. This was a small-to-moderate effect.

Recommendations

1. Since there are no clear advantages in anxiety terms of issuing karyotype results as soon as they become available, or on a fixed date, women could be given a choice between them.
2. Rapid testing was a beneficial *addition* to karyotyping, at least in the short term. This does not necessarily imply that early results would be preferred to comprehensive ones if women had to choose between them.

Methods

The trial used a multicenter, randomized, controlled, open fixed sample, 2 x 2 factorial design trial, with equal randomization.

Further research/reviews required

1. There should be further research, including more qualitative studies, into the causes, characteristics, and consequences of anxiety associated with prenatal testing.
2. The effects of different testing regimes on short- and longer-term anxiety, on the preferences of women, and on the relationship between anxiety and preference should be investigated.
3. More research is needed on the ways in which information might be used to minimize anxiety in different testing regimes.
4. Further research is required into the policy implications of incorporating individual preferences for different testing regimes into prenatal testing programs.

Written by Professor Jenny Hewison, University of Leeds, United Kingdom

Title **A Systematic Review of Rapid Diagnostic Tests for the Detection of Tuberculosis Infection**

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Reference Health Technol Assess 2007;11(3). January 2007.
www.hta.ac.uk/execsumm/summ1103.htm

Aim

To evaluate the effectiveness of available rapid diagnostic tests to identify tuberculosis infection.

Conclusions and results

Tests for active tuberculosis (TB): The review included 212 studies providing 368 datasets, plus 19 studies assessing fully automated liquid culture. Nucleic acid amplification test (NAAT) accuracy was far superior when applied to respiratory samples vs other body fluids. For pulmonary TB, although better-quality, in-house studies, were better at ruling out TB than the commercial tests, they were less good at ruling it in, but it is not possible to recommend any one over another.

NAAT specificity was high when applied to body fluids, eg, for TB meningitis and pleural TB, but sensitivity was poor, indicating that these tests cannot reliably rule out TB. High specificity estimates suggest that NAATs should be the first-line test to rule in TB meningitis, but they need to be combined with other tests to rule out disease.

No evidence supports adenosine deaminase tests in diagnosing pulmonary TB, but considerable evidence supports their use to diagnose pleural TB and TB meningitis. Anti-TB antibody tests performed poorly, regardless of TB type. More research is needed to establish the accuracy of these tests in other forms of TB and for tests such as phage tests. Speed and precision of fully automated liquid culture methods were superior to culture on solid media.

Tests for latent TB infection (LTBI): The review included 13 studies. Assays based on RD1-specific antigens, ESAT-6 or CFP-10, correlate better with intensity of exposure and are more likely to accurately detect LTBI, than TST/PPD based assays. They are also more likely to be independent of BCG vaccination status and HIV status.

Recommendations

NAATs are a reliable way to increase specificity in diagnosing pulmonary TB, but sensitivity is too poor to rule out disease especially in smear-negative disease where clinical diagnosis is equivocal and clinical need greatest.

For pleural TB and TB meningitis, adenosine deaminase tests have high sensitivity, but limited specificity. NAATs have high specificity and could be used alongside ADA to increase overall sensitivity and specificity.

RD1 antigen based assays are more accurate than TST and PPD based assays in diagnosing LTBI in low prevalence countries.

Methods

Literature was identified from electronic databases and other sources. All databases were searched from 1975 to August 2003 for tests for active TB and to March 2004 for tests for LTBI. Reference lists of studies and relevant review articles were also scanned. (For more details see Executive Summary link above.)

Further research/reviews required

For active TB, large, prospective, well-designed studies are needed to assess the incremental value of test combinations, particularly for samples of biological fluids. For pulmonary TB, NAAT tests should be evaluated in clinically equivocal smear-negative patients. The place of ADA, IFN-gamma, and lysozyme in diagnosing pleural TB needs further investigation. The place of ADA in diagnosing TB meningitis needs to be established. *For latent TB infection,* research is needed in different settings, including countries with a high prevalence of TB, of NTM, in populations with high BCG coverage, and in immunosuppressed populations. Head-to-head comparisons of the main existing commercial assays are needed.

Written by Ms Jacqueline Dinnes, University of Southampton, United Kingdom

Title **A Systematic Review of Quantitative and Qualitative Research on the Role and Effectiveness of Written Information Available to Patients About Individual Medicines**

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Reference Health Technol Assess 2007;11(5). Feb 2007. www.hta.ac.uk/execsumm/summ1105.htm

Aim

To assess the role and value of written information (info) available to patients about individual medicines.

Conclusions and results

From over 50 000 citations, 413 were considered. Of these, 64 papers reporting 70 studies were included (36 papers reporting 43 RCTs in effectiveness; 28 in role and value).

Most people do not value written medicines info (WMI) they receive. The poor quality of many leaflets tested may reflect the finding that provision did not increase knowledge. We found no robust evidence that info affected patient satisfaction or compliance. Qualitative evidence shows patients do not see improving compliance as a function of patient info leaflets (PILs); an informed decision not to take a medicine is an acceptable outcome. This contrasts with some professionals' view that increasing compliance was a prime PIL function. We found consistent evidence that the way risk descriptor info is portrayed has important effects on side-effect knowledge. Delivering risk info numerically, rather than as verbal descriptors, ensures a more accurate estimation of probability and likelihood of a side effect and risk to health. Readability of WMI is important to patients. Patients value idea of tailored info and a balance of benefit and harm info. Few studies addressed either issue. Most patients wanted to know about side effects. Some patients question credibility of pharmaceutical industry info, although the required PIL is written according to strict regulations. Patients would like WMI to help decision making about whether or not to take a medicine, and for managing medicines and interpreting symptoms. Patients did not want WMI to substitute for spoken info from prescribers. There was evidence of professional ambivalence about WMI.

Recommendations

The authors suggest that regulators and producers of WMI consider the following: involve patients at all stages of the process, use findings on info design and content to improve quality and usefulness, present risk info numerically rather than using verbal descriptors, spoken info remains the priority but should be closely linked to written info so it does not substitute for discussion, encourage patients to use WMI, and welcome questions.

Methods

The authors searched full text and bibliographic databases for research on the role, value, and effectiveness of WMI (up to late 2004). Citation and hand searches were done. Six experts in information design were asked to cite relevant key references, and stakeholder workshops were held. (For more details see Executive Summary link above.)

Further research/reviews required

Apply recognized standards to trial design and conduct, recruit more older people, have longer followup and more use of naturalistic settings, develop, validate, and standardize patient-focused outcome measures, find how to better integrate patient input in info research, and ensure the study of role and value alongside effectiveness in future trials. Determine the content, layout, delivery method, and timing of statutory medicine leaflets that best meets patients' needs, find how to better incorporate individualized benefit and risk info, and introduce more lay experience into the PIL development process. (For more details see Executive Summary link above.)

Written by Professor Theo Raynor, University of Leeds, United Kingdom

Title **Glucocorticoid-Induced Osteoporosis: A Systematic Review and Cost-Utility Analysis**

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Reference Health Technol Assess 2007;11(7). March 2007.
www.hta.ac.uk/execsumm/summ1107.htm

Aim

To examine the evidence for efficacy in glucocorticoid induced osteoporosis (GIO), model cost effectiveness, and develop a case finding strategy.

Conclusions and results

Various agents are available to treat osteoporosis, and several are licensed for use in preventing and treating GIO. Evidence was found that the bisphosphonate risedronate and calcidiol reduced the incidence of vertebral fracture. The risk of nonvertebral fractures was not decreased. Antifracture efficacy was comparable to the larger experience of bisphosphonates in postmenopausal osteoporosis, and the latter was used for the purposes of health economic modeling. Previous glucocorticoid use was associated with a significantly increased risk of fracture, even after adjusting for bone mineral density (BMD) and prior fracture. In sensitivity analysis, important determinants of cost effectiveness included age and cost of intervention. Cost effectiveness improved markedly by selecting patients according to BMD. The following strategy was considered appropriate in patients receiving long-term glucocorticoids. Patients with a prior fragility fracture would be eligible for treatment, as would individuals aged 75 years or older, irrespective of BMD. At other ages, patients without prior fractures would be eligible for treatment contingent upon a BMD threshold with a T-score of <–2.0 SD. The strategy would demand BMD testing in 73% of patients and identify 47% for treatment.

Recommendations

An assessment algorithm has been devised for case finding in GIO. The algorithm proposed is conservative because of the conservative nature of some of the assumptions that have been made.

Methods

Systematic reviews were undertaken of all randomized controlled studies in which fracture was measured as an outcome. The risk of an osteoporotic fracture in the presence of a prior osteoporotic fracture was computed from a published meta-analysis of the relationship between prior occurrence of fracture and the risk of future fracture. The additional risk due to exposure to glucocorticoids was determined by meta-analysis of prospectively studied, population-based cohorts. This information was used to populate an individual patient-based health economics model.

Further research/reviews required

Intervention thresholds differ substantially from diagnostic thresholds, and should be based on the absolute fracture probability that depends not only on BMD, but also on other independent risk factors. Health economic assessment based on probability of fracture is an important area for further research. Further areas of research arise from gaps in the empirical knowledge on utilities and side effects.

Written by Professor John Anthony Kanis, University of Sheffield, United Kingdom

Title **Epidemiological, Social, Diagnostic, and Economic Evaluation of Population-Based Chlamydia Screening**

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Reference Health Technol Assess 2007;11(8). March 2007.
www.hta.ac.uk/execsumm/summ1108.htm

Aim

1. To determine the coverage and uptake of postal chlamydia screening and chlamydia prevalence in the general population.
2. To examine the social, emotional, and psychological effects of screening and partner notification for chlamydia.
3. To determine the best test/specimen to use for chlamydia screening.
4. To determine the most effective method of partner notification for chlamydia.
5. To identify criteria for targeted screening.
6. To determine how cost effectiveness of chlamydia screening can be maximized.

Conclusions and results

1. Screening invitations reached 73% (14 382/19 773) of those aged 16 to 39 years. Uptake of the invitation to provide a home-collected specimen was 39.5% (95% CI 37.7, 40.8%) in women and 29.5% (95% CI 28.0, 31.0%) in men aged 16 to 39 years. Chlamydia prevalence in those aged 16 to 24 years was 6.2% (95% CI 4.9, 7.8%) in women, 5.3% (95% CI 4.4, 6.3%) in men, and below 1% in men aged over 24 and women aged over 29 years.
2. Screening did not adversely affect anxiety, depression, or self-esteem. Participants welcomed the convenience and privacy of home-sampling.
3. Relative sensitivity of nucleic acid amplification test: 100% on male urine specimens, 91.8% on female urine, and 97.3% on vulvovaginal swabs.
4. 140 people (74% of eligible) participated in a randomized trial of partner notification methods. Compared with referral to a genitourinary medicine clinic, partner notification by practice nurses resulted in 12.4% more patients with at least one partner treated and 22.0% more patients with all partners treated.
5. The case-control study did not identify any additional factors that would help target screening.
6. Health service and patient costs (2005 prices) of home-based postal chlamydia screening were GBP 21.47 per invitation and GBP 28.56 per accepted offer (similar to the national pilot studies). Preliminary modeling found an incremental cost-effectiveness ratio (2003 prices) comparing annual screening to no screening in the base case of GBP 27 000/major outcome averted at 8 years. If screening uptake and pelvic inflammatory disease incidence were increased, the cost-effectiveness ratio fell to GBP 3700/major outcome averted.

Recommendations

Proactive screening for chlamydia using home-collected specimens is feasible and acceptable to the target population. Nucleic acid amplification tests can be used on mailed home-collected first-catch urine specimens and vulvovaginal swabs. Using empirical estimates of uptake and incidence of complications, proactive chlamydia screening was not cost effective.

Methods

A multicenter multidisciplinary series of linked studies was conducted. For details see Executive Summary link above.

Further research/reviews required

Needed research includes: a large multicenter RCT of chlamydia screening to determine whether reducing female reproductive tract morbidity and chlamydia transmission are achievable long term goals at reasonable cost; research on the effects of chlamydia screening on inequalities in sexual health; a systematic review of studies comparing performance of female urine/vulvovaginal specimens for *C trachomatis* diagnosis. (For more information see Executive Summary link above.)

Written by Dr Nicola Low, University of Berne, Switzerland

Title **Exercise Evaluation Randomized Trial (EXERT): A Randomized Trial Comparing GP Referral for Leisure Center-Based Exercise, Community-Based Walking, and Advice Only**

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Reference Health Technol Assess 2007;11(10). Apr 2007. www.hta.ac.uk/execsumm/summ1110.htm

Aim

To evaluate and compare the effectiveness and cost effectiveness of a leisure-center-based exercise program, an instructor-led walking program, and advice only in GP-referred patients.

Conclusions and results

Followup rates were 66% of those eligible at the 10-week assessment, 60% at 6 months, and 50% at 1 year. Primary outcomes were analyzed by intention to treat.

By 10 weeks, all 3 study groups had increased their duration of activity (at least moderate intensity). By 6 months, the duration of at least moderate activity was significantly higher than at baseline. At 1 year, both leisure center and walking groups maintained significant increases compared with baseline. There was no significant difference between the increases in duration of at least moderate activity in the 3 study groups at any assessment point.

There was a net increase in the share of participants achieving at least 150 minutes per week of at least moderate activity in the sport/leisure and walking categories in all 3 study groups. Systolic and diastolic blood pressure were significantly reduced in all groups at each assessment. There were significant, sustained improvements in cardiorespiratory fitness, leg extensor power, and small reductions in total and LDL cholesterol in all groups, but no consistent differences between the groups for any parameter over time. All 3 groups showed improvement in HADS anxiety and SF-36 mental well-being scores 6 months after the trial started. Leisure center and walking groups maintained this improvement at 1 year.

Costs to the participants were GBP 100 for the leisure center scheme and GBP 84 for the walking scheme. Provider costs were GBP 186 and GBP 92 respectively. Changes in overall SF-36 scores were small, and advice only appeared to be the most cost-effective intervention.

Recommendations

Referral for tailored advice supported by written material and supplemented by detailed assessments, may be effective in increasing physical activity. Inclusion of a 10-week program of supervised exercise classes or walks may not be more effective than providing information about their availability. On cost-effectiveness grounds, assessment and advice alone from an exercise specialist may be appropriate to initiate action. Walking seems to be as effective as leisure center classes and is cheaper.

Methods

Single center, parallel group, RCT, consisting of 3 arms, with the primary comparison at 6 months. The 2 structured exercise groups were followed for a further 6 months, while subjects in the control arm were re-randomized to one of the other trial arms and followed for a further year.

Further research/reviews required

- Updated meta-analysis of published exercise interventions
- Standardized methods for measuring and presenting outcomes
- Supplement physical activity questionnaires with objective measurements
- Identify components of interventions that benefit particular target groups and compare with minimal intervention
- Compare effectiveness and cost-effectiveness of opportunistic referral by GPs and practice nurses vs proactive 'cold calling' of at-risk individuals
- Compare strategies for involving groups underrepresented in present schemes
- Qualitative research with referring clinicians and participants to determine reasons for success and failure.

Written by Dr Anthony Isaacs, Middlesex University, United Kingdom

Title **Jet Injectors in the Administration of Medicines and Vaccines: A Rapid Review**

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Reference FinOHTA Rapid review 1/2007. Pasternack I, Saijonkari M, Mäkelä M.
ISBN 978-951-33-1174-2. Full text in Finnish available at http://finohta.stakes.fi

Aim

To summarize the published scientific evidence relating to the clinical effectiveness and safety of jet injectors and to describe the current practice, potential target groups, and estimated costs of the technology in Finland.

Conclusions and results

No benefits can be achieved by using jet injectors instead of needles and syringes in routine use, eg, in vaccination programs or in self-administration of insulin. The reviewed literature indicates that the absorption of growth hormone, insulin, and vaccines after a jet injection is equivalent to or better than absorption after needle injection. Jet injection is not less painful than the needle injection. There are more adverse effects (eg, minor tissue reactions) in jet injector users than in needle users. The direct costs (equipment and needle waste disposal) of the jet injections are approximately 10 times higher, compared to needle injections.

Recommendations

The jet injector can be an option for patients with fear of needles.

Methods

The assessment was based on a British review, published by the National Horizon Scanning Centre in July 2001. In addition, Cochrane Library and MEDLINE were searched from January 2000 to June 2006. We restricted our search to studies on vaccines, local anesthesia, insulin, and growth hormone administration only. We included controlled trials for effectiveness assessment, and other study types that reported harms and user preferences. A Finnish trader and two suppliers of consumables were consulted for cost information.

Written by Iris Pasternack, FinOHTA, Finland

Title **Diagnostic and Prognostic Value of the Detection of Antibodies Against Keratin and Cyclic Citrullinated Peptides in Rheumatoid Arthritis**

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Reference September 2006.
www.has-sante.fr/portail/display.jsp?id=c_473846

Aim

To assess the diagnostic and prognostic value of the antikeratin (AKA) and anticyclic citrullinated peptide (ACCP) tests in rheumatoid arthritis to advise French National Health Insurance (NHI) on reimbursement.

Conclusions and results

The sensitivity of the AKA test was 9% to 61%, and specificity was 92% to 96% (5 case series). No relationship was found between initial detection of AKA and radiographic damage after 2 and 5 years of followup (2 case series). The sensitivity of the ACCP test was 41% to 77%, and specificity was 94% to 98% (7 case series). The initial detection of ACCP was a predictive factor for radiographic damage at 2 and 5 years of followup (4 case series). ACCP detection can lead to earlier disease management and/or to more aggressive treatment (expert opinion).

Recommendations

Unlike the AKA test, the ACCP test is indicated for the diagnosis and the prognostic evaluation of rheumatoid arthritis. HAS (French National Authority for Health) has advised NHI to reimburse the ACCP test and to cease reimbursement of the AKA test.

Methods

We reviewed published data on the safety and efficacy of the above tests and their contribution to treatment strategy. We selected 14 case series (11 prospective and 3 retrospective case series). The review was discussed by a 15-member multidisciplinary working group before submission to the HAS Committee for Assessment of Medical and Surgical Procedures for their opinion.

Further research/reviews required

Studies are required to evaluate:

- the impact of the initial detection of ACCP on patient treatment and disease progression
- the value of the ACCP test in monitoring disease progression after anti-TNFα treatment.

Written by Fabienne Quentin, HAS, France

Title **Value of Mutation Detection and of the Activated Protein C Resistance Assay in Inherited Thrombophilia**

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Reference September 2006.
www.has-sante.fr/portail/display.jsp?id=c_474527

Aim

To assess the diagnostic value of the activated protein C resistance (APCr) test to advise French National Health Insurance (NHI) on reimbursement.

Conclusions and results

We selected 5 studies on the diagnostic performance of the APCr test (2155 patients), 7 guidelines on mutation testing, and 1 impact study. We found no study addressing the direct impact of testing on morbidity and mortality. Sensitivity of the APCr test was 100%, and specificity was 68% to 100%. In 3 studies, the positivity threshold was defined *post hoc* for 100% sensitivity. According to the working group, the diagnostic performance of marketed APCr tests varies. In clinical practice, mutation detection either replaces or follows the APCr test. The indications for mutation testing are: (a) in men and women under 50: unexplained or recurrent deep vein thrombosis or pulmonary embolism, (b) in pregnant women: an episode of venous thrombosis, or a personal or proven family history of venous thrombosis.

Recommendations

In the opinion of HAS (French National Authority for Health), mutation testing should replace the APCr test. Both genetic tests should be reimbursed by NHI.

Methods

We reviewed published data on (a) the diagnostic benefit of the tests (safety, efficacy, and contribution to treatment strategy), and (b) their public health benefit (impact on morbidity and mortality). The review was discussed by a working group of 8 hematologists and then submitted to the HAS Committee for Assessment of Medical and Surgical Procedures for their opinion.

Further research/reviews required

The following are required:

- additional data on benefits and risks
- a list of the APC resistance tests with good diagnostic performance.

Written by Céline Moty-Monnereau, HAS, France

Title **Value of Intensity-Modulated Radiation Therapy**

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Reference December 2006.
www.has-sante.fr/portail/display.jsp?id=c_490516

Aim

To assess the clinical value of intensity-modulated radiation therapy (IMRT) to advise French National Health Insurance (NHI) on reimbursement.

Conclusions and results

We selected 20 studies (1406 patients): 1 phase I study, 1 randomized dosimetric study (phase III), 2 nonrandomized controlled studies, 16 case series, and 18 dosimetric studies. They concerned mainly tumors of the head and neck (13 studies, 973 patients), skull base (2 studies, 60 patients), and prostate (3 studies, 315 patients). No cases of grade 3 to 4 xerostomy were found in 6 of the 7 studies reporting complications. There was no difference in efficacy or survival between IMRT and 3D-conformal therapy. The working group proposed further indications not backed up by published evidence.

Recommendations

HAS advised:

- reimbursement of IMRT for total body irradiation and treatment of the following tumors: head and neck, skull base and vault, spinal cord, and prostate;
- conditional coverage for the following tumors: craniospinal tumors and total medullar irradiation, multiple bone metastases, retroperitoneal tumors, tumors of the limbs and lungs, and pediatric tumors.

Methods

We reviewed published data on the safety and efficacy of IMRT and its contribution to treatment strategy. The review was discussed by an 11-member multidisciplinary working group before submission to the HAS Committee for Assessment of Medical and Surgical Procedures for their opinion.

Further research/reviews required

The following are required:

- long-term followup (particularly in pediatrics) because of the potential risk of radio-induced cancer
- confirmation of safety and efficacy in indications with a conditional coverage
- assessment of the impact on quality of life and the public health system (both in terms of health economics and care organization) for all indications.

Written by Céline Moty-Monnereau, HAS, France

Title **Value of Extra-Cranial Stereotactic Radiotherapy**

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Reference December 2006.
www.has-sante.fr/portail/display.jsp?id=c_490533

Aim

To assess the clinical value of extracranial stereotactic radiotherapy (ESR) to advise French National Health Insurance (NHI) on reimbursement.

Conclusions and results

According to the 42 selected studies (11 prospective, 31 retrospective):

1. *spinal and paraspinal tumors* (15 studies, 467 patients, median followup 8 to 25 months): pain was decreased in 25% to 100% of patients (8 studies), there were fewer symptoms in 42% to 100% of patients (4 studies), and the local control rate was 87% to 100% (7 studies). No toxicity was observed (9 studies).
2. *bronchopulmonary tumors* (16 studies, 659 patients, median followup 8 to 36 months): the overall control rate was 72% to 100% (13 studies), the 1-year actuarial control rate was 76% to 100% (6 studies), and the 1-year survival rate was 48% to 100% (8 studies). Grade ≥3 complications were observed in 0% to 16% of patients (14 studies).
3. *hepatic tumors* (4 studies, 109 patients; median followup 7 to 12 months): the local control rate was 72% to 95%. No grade 3 toxicity was observed.

The working group also discussed further indications.

Recommendations

The opinion of HAS (French National Authority for Health) is that NHI should reimburse ESR for spinal tumors, primary T1, T2, N0, M0 bronchopulmonary tumors, and slow-growing bronchopulmonary metastases when the primary tumor is under control. It advised conditional coverage of ESR for hepatic tumors.

Methods

We reviewed published data on the safety and efficacy of ESR and its contribution to treatment strategy. The review was discussed by an 11-member multidisciplinary working group before submission to the HAS Committee for Assessment of Medical and Surgical Procedures.

Further research/reviews required

The following are required:

- long-term followup
- further information on the type, volume, and topography of the tumor
- information on therapeutic use compared to other treatments
- health economic assessment in France
- confirmation of the safety and efficacy in indications with conditional coverage.

Written by Céline Moty-Monnereau, HAS, France

Title **Assessment of the Indications and Risks of ICSI (Intracytoplasmic Sperm Injection) to Children Born as a Result of ICSI**

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Reference HAS report, December 2006.
www.has-sante.fr/portail/display.jsp?id=c_500307

Aim

To assess the indications and efficacy of intracytoplasmic sperm injection (ICSI) and the risks to children born as a result of ICSI.

Conclusions and results

The literature reports efficacy for each indication, mainly in fertilization or pregnancy rates, using several denominators, and rarely in terms of birth rates. The main results have been reported per cycle. The fertilization rate/cycle ranged from 43% for bilateral absence of the vas deferens to 62.5% for obstructive azoospermia, and the pregnancy rate/cycle from 21.4% for in vitro fertilization (IVF) failures in cases of non-male infertility to 49.5% for bilateral absence of the vas deferens. Current indications for ICSI are:

- first-line indications, when there is no alternative to ICSI or after failed IVF, ie, azoospermia and oligo-astheno-teratozoospermia, total failure of IVF and reduced (≤20%) fertilization, antisperm antibody levels ≥80%, and technical indications in cases of viral infection or preimplantation genetic diagnosis (PGD)
- second-line indications, when poor sperm quality persists despite previous optimal first-line treatment (medical, surgical, sperm collection, etc) and prevents natural conception, assisted insemination by husband, or IVF, ie, acquired azoospermia of the seminal ducts, hypogonadotrophic hypogonadism, spermatic varicocele, and ejaculation disorders. The working group defined poor sperm quality as either fewer than 500 000 motile spermatozoa after preparation, or more than 500 000 motile spermatozoa after preparation if morphology and/or survival were not normal.

The increasing number of ICSI interventions performed in recent years seems to be due to a wider range of indications and earlier use in moderate azoospermia.

No conclusion could be drawn as to whether the risk to the next generation differs between IVF and ICSI pregnancies. The main risk, as for naturally conceived children, is mortality and morbidity associated with multiple pregnancies. For singleton pregnancies, rates of premature birth, low birth weight, and major congenital malformations were significantly higher in ICSI children than in naturally conceived children. The frequency of chromosomal anomalies passed on to children born as a result of ICSI was significantly higher than that observed for naturally conceived children. Five-year followup studies revealed no significant difference in physical, cognitive, or psychological development between children conceived through ICSI and those conceived naturally. No conclusions may be drawn from available data regarding the occurrence of epigenetic anomalies, oncological events, or existence of specific risks in ICSI connected with either the technique itself or the use of surgically collected spermatozoa.

Methods

Assessment was based on an analysis of literature published between 1995 and 2006 (388 publications examined, including 120 on efficacy, whereof 9 were economic studies, and 71 on risks) and on expert opinion of an 18-member multidisciplinary working group and 16 peer reviewers.

Further research/reviews required

Long-term followup studies are needed to evaluate:

- efficacy of ICSI according to relevant criteria (ie, birth rates)
- risks to children conceived via assisted reproduction technology and to their descendents.

Written by Linda Banaei, Cédric Carbonneil, and Stéphanie Barré, HAS, France

Title **The Clinical Effectiveness and Cost Effectiveness of Enzyme Replacement Therapy for Gaucher's Disease: A Systematic Review**

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Reference Health Technol Assess 2006;10(24). July 2006.
www.hta.ac.uk/execsumm/summ1024.htm

Aim

To determine the clinical and cost effectiveness of enzyme replacement therapy (ERT; intravenous imiglucerase) in treating symptomatic Gaucher's disease (GD).

Conclusions and results

Sixty-three studies reporting effects of ERT were included. All studies suggested benefits from ERT, but did not clarify how these effects translate into patient well-being, survival, and need for services and resources. Quality of life (QoL) improvements with ERT were observed, but studies indicate that patients treated with ERT still have reduced health-related quality of life (HRQoL) compared to the general population. We found 31 studies on the natural history of the disease showing GD to be a progressive condition. Some suggested the disease might become more indolent in adulthood. Most disease is diagnosed in adulthood. Patients presenting in childhood have the most severe symptoms and progression. Data suggest that disease progression is likely to slow in adulthood, and genotype may be a useful predictor of clinical expression. QoL data were obtained from GD registries and 5 studies. Clinical characteristics of type I GD have little impact on subjective HRQoL. Hence, in most people with type I GD this may not be a severe condition, but some patients experience immobility and severe pain from skeletal symptoms. The mean cost per patient treated was about GBP 86 000 annually in England and Wales. Cost per patient varied considerably by dose. The 4 economic evaluations found showed a high cost per quality-adjusted life-year (QALY). In a Markov decision model, ERT was assumed to restore patients to full health in the base case. The estimated incremental cost per QALY (ICER) in the base case ranged from ~GBP 380 000 to GBP 476 000 per QALY, depending on genotype. Univariate sensitivity analyses examined ERT not restoring full health, more severe disease progression in the untreated cohort, and only treating the most severely affected patients (for details see executive summary link above).

Recommendations

In treating the 'average' Gaucher's disease patient, ERT exceeds the normal upper threshold for cost effectiveness seen in NHS policy decisions by over 10-fold. Some argue that since orphan drug legislation encourages development of ERTs, and since GD can be defined as an orphan disease, the NHS should provide it, despite its expense. More information is needed to determine the generalizability of the findings. Data from the UK were used when possible, but were very thin. Nonetheless, even large errors in estimates of the distribution of genotype, genotype-phenotype associations, effectiveness, and numbers of patients will not reduce the ICER to anywhere near the upper level of treatments usually considered cost effective.

Methods

Bibliographic databases were searched for studies that informed on the prevalence of GD, the natural history of the disease, the effectiveness of ERT, and the costs, economic evaluation, and modeling of ERT treatment. Data were extracted independently by 2 reviewers and data synthesis achieved by quantitative and descriptive analyses. A Markov decision model was constructed based on patients moving between states defined according to a disease-specific Severity Score Index. Most parameters were derived from the published literature. ERT was assumed to restore patients to full health in the base case.

Further research/reviews required

Further research will be of clinical interest, but it is questionable whether such research in the current pricing environment would have any substantive impact on policy decisions.

Written by Dr David Moore and Dr Martin Connock, University of Birmingham, United Kingdom

Title **Etanercept and Efalizumab for the Treatment of Psoriasis: A Systematic Review**

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Reference Health Technol Assess 2006;10(46). November 2006.
www.hta.ac.uk/execsumm/summ1046.htm

Aim

To evaluate the clinical effectiveness, safety, tolerability, and cost effectiveness of etanercept and efalizumab in treating moderate to severe chronic plaque psoriasis.

Conclusions and results

Three RCTs of etanercept 25 mg twice a week for 12 weeks resulted in 62% of patients achieving PASI 50 on the psoriasis area and severity index (PASI), 33% achieving PASI 75, 11% achieving PASI 90, and 40% were assessed as clear or almost clear. Improvement in the dermatology life quality index (DLQI) was around 59% with etanercept 25 mg twice a week versus 9% with placebo (mean differences were statistically significantly in favor of etanercept). Two RCTs of etanercept 50 mg twice a week for 12 weeks found that 76%, 49%, and 21% of patients achieved PASI 50, 75, and 90 respectively (pooled relative risks were all statistically significantly in favor of etanercept). Five RCTs studied efalizumab (1 mg/kg once a week subcutaneously). Across these trials, 12 weeks of active treatment resulted in an average of 55% of patients achieving PASI 50, 27% PASI 75, 4.3% PASI 90, and 27% clear or minimal psoriasis. A mixed treatment comparison found a higher response rate with etanercept than with efalizumab. Injection site reactions were the most common adverse effects of etanercept, and it seems to be well tolerated in short- and long-term use. Common adverse events with efalizumab include headache, chills, and nausea. Withdrawal rates due to adverse events are low. In primary analysis comparing etanercept, efalizumab, and supportive care, results of the York Model suggest that the biological therapies would only be cost effective for all patients with moderate to severe psoriasis if the NHS were willing to pay over GBP 60 000 per QALY gained. In patients with poor baseline quality of life, efalizumab, etanercept 25 mg (intermittent), etanercept 25 mg (continuous), and etanercept 50 mg (intermittent) would be cost effective in a treatment sequence if the NHS were willing to pay 45 000, 35 000, 45 000, and 65 000 British pounds (GBP) per QALY gained, respectively. In patients at high risk of hospitalization (21 days/year), these therapies would be cost effective in a sequence at 25 000, 20 000, 25 000, and 45 000 GBP per QALY gained, respectively. In a secondary analysis, the York Model found that it would only be cost effective to use etanercept and efalizumab in a sequence after methotrexate, ciclosporin, and Fumaderm.

Recommendations

Clinical trial data indicate that etanercept and efalizumab are efficacious in patients eligible for systemic therapy, but economic evaluation found these biological therapies likely to be cost effective only in patients with poor baseline QoL and who are at risk of hospitalization.

Methods

Efficacy, safety, and economic evaluations of etanercept and efalizumab were systematically reviewed. Electronic databases and Internet resources were searched up to April 2004. A systematic review of other treatments for severe psoriasis was also updated. Economic models supplied by the manufacturers of etanercept and efalizumab were critiqued, and later an economic model was developed on treating moderate to severe chronic plaque psoriasis.

Further research/reviews required

- Efficacy trials in the specific population for which etanercept and efalizumab are licensed
- Long-term comparisons of etanercept and efalizumab with other treatments for moderate to severe psoriasis
- Long-term efficacy trials and safety/tolerability data for patients treated with etanercept or efalizumab
- Trials on the response of specific subtypes of psoriasis to different drugs
- Hospitalization rates for moderate to severe psoriasis and effects of treatment on this rate.

Written by Dr Alison Murray, University of York, United Kingdom

Title **Pemetrexed Disodium for the Treatment of Malignant Pleural Mesothelioma: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2007;11(1). January 2007.
www.hta.ac.uk/execsumm/summ1101.htm

Aim

To assess the clinical and cost effectiveness of pemetrexed disodium combined with cisplatin in treating unresectable pleural mesothelioma in chemotherapy-naïve patients.

Conclusions and results

One randomized controlled trial (448 patients) comparing pemetrexed and cisplatin to cisplatin alone met the inclusion criteria. Pemetrexed combined with cisplatin showed a 2.8-month gain in median survival compared with cisplatin alone in an intention-to-treat (ITT) population. During the trial, increased reporting of severe toxicity in the pemetrexed arm led to a change in the protocol to add folic acid and vitamin B12 supplementation to therapy. For fully supplemented patients (n=331), the hazard ratio for median survival in favor of pemetrexed plus cisplatin was comparable (0.75), but of borderline significance between treatment arms (p=0.051). The inclusion criteria restricted recruitment to those with a Karnofsky performance status of 70 or greater (equivalent to ECOG/WHO 0 or 1 scales more widely used in the UK). Quality of life scores using the Lung Cancer Symptom Scale demonstrated significantly greater improvement for pain and dyspnea for patients in the combination group compared with those in the cisplatin group. In the ITT population, the incidence of serious toxicities with pemetrexed plus cisplatin was higher compared with cisplatin alone. However, the grade 3/4 toxicities of the combination arm, particularly leucopenia, neutropenia, and diarrhea, were found to improve with the addition of vitamin B12 and folic acid. Published economic literature was limited. The economic evaluation conducted by the study (and that submitted by the manufacturer) suggested that pemetrexed is unlikely to be considered cost effective at conventionally accepted thresholds in the UK for all patients, mainly due to the high cost of pemetrexed compared with cisplatin. These findings were better for some patient subgroups, eg, especially for fully supplemented (FS) patients with good performance status (0/1) and advanced disease (AD). The findings seem robust. The estimated cost-effectiveness results were for the FS population, incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) gained = GBP 59 600; for the FS with AD population, ICER per QALY = GBP 47 600; for the FS with performance status 0/1 population, ICER per QALY = GBP 49 800; and for the FS with performance status 0/1 and AD population, ICER per QALY = GBP 36 700.

Recommendations

The new therapy addressed here demonstrates extended life expectancy and palliation. The small gain in absolute benefit must be weighed against the benefits of effective palliative care. Also, the limited benefit was at the expense of considerable toxicity. Economic evaluations suggest that pemetrexed is not cost effective at conventional thresholds in all patients. Cost effectiveness was better in some patient subgroups, eg, patients with good performance status and advanced diseases, where ICER per QALY is estimated at GBP 36 700. Given the few patients with mesothelioma, the budget impact of pemetrexed is unlikely to exceed GBP 5 million per year.

Methods

Electronic databases were searched up to May 2005. The systematic review followed accepted guidelines. Economic information from the manufacturer of pemetrexed was also assessed. This comprised 2 sections, each using an economic model. One of the models was reformulated to separately explore economic performance.

Further research/reviews required

Research is needed into the optimum chemotherapy for patients with mesothelioma and a clear definition of what constitutes best supportive care.

Written by Ms Rumona Dickson, University of Liverpool, United Kingdom

Title **The Clinical Effectiveness and Cost Effectiveness of Strontium Ranelate for the Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women**

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Reference Health Technol Assess 2007;11(4). Feb 2007. www.hta.ac.uk/execsumm/summ1104.htm

Aim

To estimate the clinical and cost effectiveness of strontium ranelate in preventing osteoporotic fractures in postmenopausal women at different levels of absolute fracture risk. This considers secondary prevention in women with previous fracture and primary prevention in women without previous fracture, as women with osteoporosis are asymptomatic prior to fracture.

Conclusions and results

Three trials were identified. Pooled data from 2 studies indicate that strontium ranelate therapy (SRT) reduces the risk of vertebral fracture and nonvertebral fracture. In general, SRT did not seem to increase the risk of adverse events. However, the risk of one rare but serious adverse event, venous thromboembolism (including pulmonary embolism), was found to be significantly higher in patients receiving strontium ranelate compared to placebo. Some nervous system disorders, eg, mental impairment, memory loss, and seizures, were more common in patients randomized to strontium ranelate. SRT provided gains in QALYs compared with no treatment in women with sufficient calcium and vitamin D intakes. The QALY gain for each intervention was strongly related to the absolute risk of fracture. In the algorithm used, SRT appears to be cost effective in women at relatively high risk of osteoporotic fracture. Probabilistic sensitivity analysis, using efficacy data from randomized controlled trials, suggests that it is not as cost effective as alendronate, a comparator intervention from the bisphosphonate class.

Recommendations

Strontium ranelate was shown to be clinically effective in preventing osteoporotic fractures. Scenarios have been found where SRT can be used cost effectively, but in the probabilistic sensitivity analyses conducted, this intervention appears to be less cost effective than the bisphosphonate alendronate.

Methods

A systematic review was used to determine clinical effectiveness. Major bibliographic databases were searched in September 2004 and updated in March 2005, and reference lists of relevant articles and sponsor submissions were handsearched. Data from selected studies were assessed and included in the meta-analyses. An updated Sheffield Health Economic Model for Osteoporosis was used to calculate cost effectiveness ratios. The model calculated the number of fractures that occur and provided as output data the costs associated with osteoporotic fractures, and the quality-adjusted life-years (QALYs) accrued by 100 osteoporotic women. When the intervention costs were included, the incremental cost compared to no treatment was calculated and divided by the gain in QALYs to calculate cost-effectiveness measures. SRT was calculated against a no-treatment option to evaluate whether it could be given cost effectively. An incremental analysis against alendronate estimated the cost effectiveness of SRT relative to a current standard treatment.

Further research/reviews required

Evidence needs to be strengthened on the efficacy of strontium ranelate in fracture prevention; on the T-score by age of the general female population; and on the prevalence of risk factors associated with fracture rates. Until head-to-head comparisons of strontium ranelate and bisphosphonates are undertaken, and decision-maker choices will be based on indirect evidence. Such trials are unlikely given the large number of patients needed to show statistical difference in efficacy between patients, but high-quality observational databases may provide further insight into relative efficacies.

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

Title **Oral Naltrexone as a Treatment for Relapse Prevention in Formerly Opioid-Dependent Drug Users: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2007;11(6). Feb 2007. www.hta.ac.uk/execsumm/summ1106.htm

Aim

To investigate the clinical and cost effectiveness of naltrexone for relapse prevention in detoxified, formerly opioid-dependent, individuals compared to any strategy that uses or does not use naltrexone, including treatment with placebo, other pharmacological treatments, psychosocial interventions, or no treatment.

Conclusions and results

Methodological quality was poor to moderate in the 26 randomized controlled trials (RCTs) that met the inclusion criteria. The results suggest that naltrexone as maintenance therapy may be better than placebo in treatment retention (not statistically significant). A meta-analysis of 7 RCTs gave the relative risk (RR) of loss of retention in treatment in the naltrexone arm as 0.94. The pooled hazard ratio (HR) reported in 5 of the RCTs for treatment retention data followed up to 35 weeks was calculated as 0.90 in favor of naltrexone (not statistically significant). The risk of drug abuse in naltrexone vs placebo, with or without psychological support in both arms, gave a pooled RR of 0.72 in favor of naltrexone (statistically significant). The pooled HR from 3 RCTs for opioid relapse-free rates was significantly different from placebo in favor of naltrexone 0.53, but fell off over time. The RR of reimprisonment while on naltrexone therapy showed results favoring naltrexone in the combined 2 studies of parolees or people on probation (small number of participants). Adverse events data showed no significant difference between naltrexone and placebo. The quality of the 9 RCTs of interventions designed to increase retention with naltrexone was poor to moderate, but all 3 modalities of enhanced care showed some evidence of effectiveness. All contingency management programs used incentive vouchers; mean duration of treatment retention was 7.4 weeks for the contingency management intervention vs 2.3 to 5.6 weeks for naltrexone treatment alone. Patients stayed on naltrexone 84 to 103 days (mean) with additional psychosocial therapy vs 43 to 64 days for the control group. In trials with added pharmacological agents, the RRs of stopping treatment were 1.63 at 6 months and 1.31 at 12 months (favoring naltrexone plus fluoxetine) and was statistically significant at 6 months, but not at 12 months. A meta-analysis of the RR of stopping treatment at week 12 included 6 of the 9 studies. The pooled RR of stopping treatment was 0.81. The intervention groups had 19% fewer patients who stopped treatment compared with the control group (few studies of poor quality). No economic evaluations were identified. The point estimate for the cost effectiveness of naltrexone was GBP 42 500 per QALY. In a sensitivity analysis the incremental cost-effectiveness ratio varied between GBP 34 600 and GBP 42 500 per QALY gained.

Recommendations

Following successful withdrawal from opioids, naltrexone may be administered on a chronic basis to block future effects of opioids. Naltrexone appears to have limited benefit in helping formerly opioid-dependent individuals remain abstinent, but evidence quality is relatively poor and heterogeneous. Oral naltrexone is used infrequently in UK practice, which this review suggests is appropriate.

Methods

Major electronic databases were searched from inception to September 2005. Selected studies were screened and quality assessed. Meta-analyses were carried out as appropriate. A decision-analytic model using Monte Carlo simulation was developed that compared naltrexone as an adjunctive therapy to no naltrexone. It assumed compliance rates that were not enhanced by contingent management rewards. Utility values could not be identified from the literature, but were obtained from the Value of Health Panel.

Further research/reviews required

More information about the quality of life of people who use illicit opioids is needed to inform policy questions about the cost effectiveness of different programs and interventions.

Written by Dr Amanda Burls, University of Birmingham, United Kingdom

Title **Methadone and Buprenorphine for the Management of Opioid Dependence: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2007;11(9). April 2007.
www.hta.ac.uk/execsumm/summ1109.htm

Aim

To assess the clinical and cost effectiveness of buprenorphine maintenance therapy (BMT) and methadone maintenance therapy (MMT) in managing opioid-dependent individuals.

Conclusions and results

Most of the included systematic reviews and randomized controlled trials (RCTs) were of moderate to good quality and focused on short-term outcomes of retention in treatment and level of opiate use (self-report or urinalysis). Most studies compared a fixed-dose strategy of MMT or BMT and included mainly young men who met criteria as opiate-dependent or heroin-dependent users, without significant comorbidities. RCT meta-analyses have shown that a fixed dose of MMT or BMT has superior levels of retention in treatment and opiate use than placebo or no treatment (higher fixed doses being more effective than lower fixed doses). Evidence showed that fixed-dose MMT reduces mortality, HIV risk behavior, and crime levels compared to no therapy. A small RCT found the mortality level with fixed-dose BMT to be significantly less than with placebo. Flexible dosing of MMT and BMT is more reflective of real-world practice. Retention in treatment was superior for flexible MMT than flexible BMT dosing, but there was no significant difference in opiate use. Population cross-sectional studies suggest that mortality with BMT may be lower than with MMT. A pooled RCT analysis showed no significant difference in serious adverse events with MMT vs BMT. Treatment modifier evidence was limited. One company submitted cost-effectiveness evidence based on an economic model and sourced data from a single RCT; the results showed that for MMT vs no drug therapy, the incremental cost-effectiveness ratio (ICER) was GBP 12 584/quality adjusted life year (QALY), for BMT vs no drug therapy, the ICER was GBP 30 048/QALY and in a direct comparison, MMT was found to be slightly more effective and less costly than BMT. The assessment group model found for MMT vs no drug therapy that the ICER was GBP 13 697/QALY, for BMT vs no drug therapy that the ICER was GBP 26 429/QALY, and in direct comparison MMT was slightly more effective and less costly than BMT. Regarding social costs, both MMT and BMT gave more health gain and were less costly than no drug treatment.

Recommendations

Flexible-dose MMT and BMT are more clinically and cost effective than no drug therapy in dependent opiate users. In direct comparison, a flexible dosing strategy with MMT (daily dose equivalent 20–120 mg) was found to be somewhat more effective in maintaining individuals in treatment than flexible-dose BMT (daily dose equivalent 4–16 mg) and therefore associated with a slightly higher health gain and lower costs. This needs to be balanced by the more recent experience of clinicians in using buprenorphine, the possible risk of higher mortality of MMT, and individual opiate-dependent users' preferences.

Methods

Electronic databases were searched to August 2005. Industry submissions to the National Institute for Health and Clinical Excellence were accessed. Assessment of clinical effectiveness was based on a review of reviews and updated search for RCTs. A decision tree with Monte Carlo simulation model was developed to assess the cost effectiveness of BMT and MMT. Retention in treatment and opiate abuse parameters were sourced from the meta-analysis of RCTs directly comparing flexible MMT with flexible dose BMT. Utilities were derived from a panel representing a societal perspective.

Further research/reviews required

Safety and effectiveness of MMT and BMT as it is delivered in the UK; potential safety concerns of methadone and buprenorphine (mortality and key drug interactions); efficacy of substitution medications; uncertainties in cost effectiveness identified by current economic models.

Written by Dr Rod Taylor, Peninsula Medical School, United Kingdom

Title **Mobility Assistance Dogs for Mobility-Impaired People**

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Reference 07-04. ISBN 978-2-550-49503-1 (print, French),
978-2-55050260-9 (PDF, English summary).
www.aetmis.gouv.qc.ca/site/en_publications_2007.phtml

Aim

To gather evidence on the clinical efficacy, safety, and cost of mobility assistance dogs (MADs); give an opinion on the definition of the target clientele and on the advisability of instituting a government MAD placement program; define the procedures for implementing such a program, if applicable.

Conclusions and results

Using a mobility assistance dog can enhance, on a daily basis, the functional independence of a mobility-impaired individual and appears to be safe, both for the users and those around them. In addition, the interest in this specific assistive modality can only increase, since it can replace several technical aids, thus resulting in cost savings for the healthcare system and user. No technical mobility aid can be used to perform as many daily activities and social roles (life habits) as an assistance dog, and at the same time reduce the burden on helpers. The cost of purchasing and maintaining a dog may be an obstacle for mobility-impaired people who might otherwise benefit from canine technical mobility assistance. Coverage of the purchase and annual maintenance costs by the public health insurance plan will improve access to this assistive modality in accordance with the principles of universality, access, and equity, on which the healthcare system is founded. The definition of the eligible clientele could be modeled after that used in the Ministerial Program for Assistance for Daily and Domestic Living and be rounded out with criteria similar to those used by the MIRA Foundation. Clinical placement criteria could be established to improve the rigor and standardization of evaluations of mobility assistance dogs and their users. There does not seem to be any major contraindication to using mobility assistance dogs, and their presence in public places (restaurants, schools, etc) seems to be a given in our society. However, it will be necessary to examine the definition of "public place" given in Section 15 of the Québec Charter of Rights and Freedoms, which seeks to eliminate any restriction on access to public places, and outline the exceptions that could create problematic situations.

Recommendations

Based on these conclusions, AETMIS recommends that mobility assistance dogs be added to the list of technical aids covered by the program administered by the RAMQ *(Régie de l'assurance maladie du Québec)* under the Health Insurance Act, and that the Regulation respecting devices which compensate for a physical deficiency be amended accordingly.

Methods

Literature search focused on scientific, legal, regulatory, and normative information carried by querying general (ie, MEDLINE) and specialized (ie, ABLEDATA) databases and targeted papers published between January 2000 and December 2006. The references in the publications retrieved were manually searched, which yielded papers dating from 1988 to 1999.

Written by Khelia I, Martin M, and Adam S, with the collaboration of Dussault FP, AETMIS, Canada

Title **Three-Wheel and Four-Wheel Scooters: Alternatives to Powered Wheelchairs?**

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Reference 07-05. ISBN 978-2-550-447771-6 (print, French), 978-2-550-50008-7 (PDF, English summary). www.aetmis.gouv.qc.ca/site/en_publications_2007.phtml

Aim

To determine under what circumstances a 4-wheel scooter (FWS) or 3-wheel scooter (TWS) would be of greater benefit than an electric powered wheelchair (EPW), and what stakes are involved by adding scooters to the list of mobility assistance devices offered by the *Régie de l'assurance maladie du Québec* (RAMQ).

Conclusions and results

The findings show that a scooter is of greater benefit than a motorized wheelchair when it meets the user's mobility needs and the user has the ability to operate it. Scooters actually seem to support social integration, mainly because they have a less stigmatizing appearance. Moreover, since their average cost is half that of EPWs, their allocation could represent savings. However, scooters do not necessarily represent an alternative to powered wheelchairs. To transfer the scooter allocation program from the ministry's two fiduciaries to the RAMQ mobility assistance program, regulations will have to be adapted, and scooter performance indicators adopted and incorporated into the approval process. Furthermore, a postallocation evaluation of mobility devices will be essential for program management. This will mean integrating the existing clinical and administrative data of the ministry and RAMQ programs.

Recommendations

1) Allocate a scooter instead of an EPW whenever potential users have the necessary abilities to operate it and provided that the scooter can meet their mobility needs. 2) Review the eligibility criteria of the ministry and the RAMQ programs for the target clientele and the scooter clinical utility criteria. 3) Standardize the assessment methods used by fiduciaries and by the RAMQ. 4) Compare scooters in light of the parameters related to the target clientele, the clinical utility, and the performance of these devices. 5) Adopt the key elements defining the target clientele, the clinical utility, and the scooter performance to compare scooters among themselves and with other mobility assistive devices within the framework of the RAMQ approval process. 6) Form a committee composed of representatives from the ministry, the RAMQ, the fiduciaries, the *Office des personnes handicapées du Québec*, users and other experts involved in the allocation of mobility assistive devices. 7) Implement relational databases to gather data on the target clientele, the clinical utility, and the performance of the devices together with the accident rates and administrative data to link the information for decision-making purposes. 8) Set up a technology watch to monitor the developments in and marketing of mobility devices and keep abreast of the utilization objectives for the new devices.

Methods

Review of the scientific, medical, standards- and regulation-related publications on the topic. Data extracted from 5 other scooter allocation programs were compared to the results of the review of the available literature and the opinion of clinical experts from a group of consultants and other resource persons in the assistive-technology and rehabilitation fields.

Written by Michèle Monette and Imen Khelia, AETMIS, Canada

Title **Viscosupplementation for the Treatment of Osteoarthritis of the Knee**

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Reference 07-06. www.aetmis.gouv.qc.ca/site/en_publications_2007.phtml

Aim

To evaluate the effectiveness, safety, and cost effectiveness of viscosupplementation in treating osteoarthritis (OA) of the knee.

Conclusions and results

A series of meta-analyses and assessment reports on the different types of intra-articular hyaluronic acid viscosupplements available in Canada were analyzed. AETMIS concluded that viscosupplementation compared to placebo offers clinically modest relief of knee OA symptoms over a period that could last up to several weeks. Furthermore, it is a safe short-term treatment. These conclusions are based on secondary analyses studies of several small primary studies of poor methodological quality. Available data did not help distinguish differences in the effectiveness of any one product over the others. It was equally impossible to identify patient subgroups more likely to benefit from this treatment compared with other currently available therapeutic modalities. The cost effectiveness based on economic studies of this treatment compared to placebo could not be established owing to discrepancies in the clinical data used and the methodological limitations of the economic studies examined. Public coverage for this treatment would lead to increased spending of several tens of millions of dollars per year and would command significant professional resources when Quebec's healthcare system experiences a shortage of health resources. Hence, AETMIS considers that it is not currently justified to contemplate funding viscosupplementation for all patients with knee OA. It nonetheless raises the possibility that this product could be offered as a last-resort treatment to patients who do not achieve pain relief from conventional therapies, or for whom these are contraindicated.

Recommendations

Viscosupplementation should not be offered to all patients suffering from knee OA. However, the Ministry of Health and Social Services could examine the possibility of exceptionally offering it to people who have not experienced pain relief from recognized conventional treatments, as do some third-party payers. AETMIS also recommends that granting agencies should encourage universities to pursue clinical research on viscosupplementation as part of the research areas or programs dedicated to musculoskeletal diseases or chronic pain.

Methods

Literature search in medical databases (MEDLINE, EMBASE, etc), HTA (INAHTA), and insurance companies for meta-analysis of randomized trials on effectiveness; safety data from published secondary studies and registries; economic studies and reports (until December 2006).

Written by Pierre Dagenais and Alicia Framarin, AETMIS, Canada

Title **Diagnostic Performance of Imaging Techniques Used for the Preoperative Locoregional Staging of Rectal Cancer: A Systematic Review**

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Reference 07-07. ISBN 978-2-550-50309-5.
www.aetmis.gouv.qc.ca/site/en_publications_2007.phtml

Aim

To examine the current evidence on the diagnostic performance of endoscopic ultrasonography (EUS), magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography/computed tomography (PET/CT) in determining invasion of the muscularis propria, perirectal tissue, adjacent organs, regional lymph nodes, or the circumferential resection margin in patients who have not received neoadjuvant therapy.

Conclusions and results

A search and examination of the relevant literature shows both its paucity and significant methodological weaknesses. Furthermore, comparative studies of the techniques in the same patients are rare. Methodological limitations of the studies point to the need for caution when interpreting the results of this report. It is unlikely that new, well-designed studies exclusively involving patients who have not received any preoperative therapy will be carried out, as this treatment modality has become the practice standard. Based on the available evidence, AETMIS concludes that: 1) EUS and MRI are both valid techniques, but provide complementary information for staging the disease; 2) if used as the only diagnostic test, MRI provides more useful information in choosing treatment than EUS alone, especially in cases requiring total mesorectal excision; 3) in rare cases where T-stage assessment is important for the choice of treatment, performing EUS in addition to MRI should be considered; 4) MRI is the only modality to offer some degree of certainty for evaluating regional lymph nodes and the circumferential resection margin, the two factors most likely to influence patient management, regardless of the T stage; 5) CT alone is not a good tool for staging rectal tumors, and although multidetector technology may improve its performance, evidence of this is insufficient; and 6) the role of PET/CT in staging rectal cancer will need to be monitored in the future, as there appear to be great hopes for this technology (however, its contribution to diagnosing lymph node involvement still needs to be confirmed).

These conclusions, which stem from an evaluation of the diagnostic performance of imaging techniques, are intended to contribute to the development of clinical practice guidelines. This particular activity and subsequent actions will also have to be based on an examination of the associated organizational and economic issues, which is not within the scope of this assessment.

Methods

Systematic review of published primary studies published between January 1996 and September 2006 for EUS and CT, and between January 2000 and September 2006 for MRI and PET/CT.

Written by Cathy Gosselin, AETMIS, Canada

Title **The Implantable Cardioverter Defibrillator: A Health Technology Assessment**

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Reference Report no 58, 2007.
http://kce.fgov.be/index_en.aspx?SGREF=3231&CREF=9495

Aim

To study the use of the implantable cardiac defibrillator (ICD) in primary prevention of sudden cardiac death (SCD) in patients with ischemic or nonischemic cardiomyopathy. (Devices incorporating cardiac resynchronization therapy were not considered.)

Conclusions and results

Clinical evidence for implanting an ICD for primary prevention of SCD is robust in only a small share of high-risk patients, ie, patients with ischemic heart disease and severely depressed left ventricular function with symptomatic heart failure, not worse than NYHA class III. Most patients with an ICD implant never receive an appropriate shock from the device, stressing the need for better preimplant risk stratification. Our economic study, provides a 95% CI for the base-case ICER of EUR 40 600 to EUR 136 000 per QALY and indicates that ICD use in primary prevention of SCD is an inefficient therapy. From our model and a predicted 2000 new ICD patients annually, we conclude that after a stabilization period of 15 years after extending ICD reimbursement to primary prevention, the projected net cost to the health authorities would be extremely high (EUR 154 000 000 per year).

Recommendations

1. Further extension of reimbursement for ICDs in primary prevention of SCD would expand a technology toward an indication with an average ICER of EUR 72 000 per QALY.
2. No evidence shows that ICDs incur more benefit than harm in the very elderly. It is unclear how to implement this into reimbursement criteria and whether an age criterion would be acceptable.
3. ICD longevity is a major determinant to cost effectiveness of ICD therapy, and increasing battery capacity would improve efficiency. ICD longevity should exceed a patient's life, obviating device replacement. Manufacturers should be encouraged to increase device longevity by imposing a longer device warranty period (5 or more years, or lifetime).
4. The Belgian reimbursement procedures and limiting the number of implant centers have prevented unrestrained growth in ICD implants. This should continue to optimize the concentration of expertise and prevent an inappropriate increase in ICD implants.

Methods

Electronic databases were searched for RCTs, systematic reviews and HTAs with the following general limits: English language, from July 1, 2003 to January 8, 2007, humans. We searched MEDLINE (PubMed), EMBASE, Econlit, Cochrane Library, NHS CRD Database (DARE, NHS EED, HTA). Reference lists of retrieved papers were hand searched. Expert slide presentations were consulted online from tctmd.com. ICD manufacturers were contacted.

A cost-effectiveness analysis was performed from the perspective of the Belgian health insurance system. Only the direct costs of medical care are included, excluding patients' out-of pocket payments. Indirect productivity costs were ignored.

Further research/reviews required

Given the increasing use of device therapy in patients with heart failure, the clinical effectiveness and efficiency of cardiac resynchronization therapy (CRT) in these patients and the incremental benefit of combined CRT plus ICD devices need to be critically evaluated.

Written by Van Brabandt H, KCE, Belgium

Title **Negative Pressure Wound Therapy: A Rapid Assessment**

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Reference Report no 61, 2007.
http://kce.fgov.be/index_en.aspx?ID=0&SGREF=9152&CREF=9622

Aim

To synthesize the evidence on the clinical effectiveness, safety, and cost effectiveness of negative pressure wound therapy (NPWT).

Conclusions and results

Thirteen randomized controlled trials (RCTs) were identified, 11 of poor and 2 of moderate quality. Based on the current evidence, the efficacy of NPWT is unproven. Hence, this promising, emerging technology cannot be considered routine practice for treating chronic or acute wounds. Some evidence on the efficacy of NPWT exists only for diabetic foot ulcers and skin grafts. However, restricting NPWT to selected patients seems impossible at present because the evidence cannot clearly define the patients who would benefit most from the technology.

Although NPWT seems to be a safe technology, safety data are scarce. Well-conducted cost-effectiveness analyses are lacking. Hence, no conclusions can be drawn on the cost effectiveness of this technology, which relates in part to the uncertain clinical efficacy of the technology.

Recommendations

Although no strong arguments prohibit this type of treatment (because of believed potential cost saving and because the technology is apparently safe), hospitals should be well informed about the lack of evidence on the clinical efficacy, safety, and cost effectiveness of NPWT and about the manufacturers' profit margin (probably leaving room for further price negotiation).

Well-designed RCTs, conducted for well-defined wound types (eg, diabetic ulcers, pressure ulcers, traumatic wounds, or venous ulcers) are clearly needed as part of the research and development process of an emerging technology.

Methods

The results of this report are based on a systematic review of the literature, first searching for health technology assessments (HTA) and systematic reviews, and subsequently for RCTs not included in the retrieved HTAs and systematic reviews. Cost data were obtained from experts and contacts with the industry.

Written by Vlayen J, KCE, Belgium

Title **Intensity-Modulated Radiotherapy**

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Reference Report no 62C, 2007.
http://kce.fgov.be/index_en.aspx?ID=0&SGREF=9152&CREF=9620

Aim

To assess the clinical efficacy and cost effectiveness of intensity-modulated radiotherapy (IMRT) compared with standard radiotherapy, to discuss the costs of IMRT, and to estimate the potential budget impact of IMRT on Belgian public health insurance.

Conclusions and results

Well-performed IMRT can improve quality of life in head and neck cancer patients compared with standard radiotherapy. IMRT is more difficult to plan and deliver, and still an area of investigation.

IMRT or 3D conformal radiotherapy are recommended for delivering high-dose external radiation in prostate cancer. IMRT may reduce skin complications after radiotherapy in specific breast cancer patients (eg, large breasted), but no improvement in quality of life could be demonstrated, and long-term outcome data are needed.

Minimal set-up cost for a new IMRT-capable radiotherapy department was estimated at EUR 7 100 000 in the reviewed literature and conversion of a 3DCRT unit into an IMRT unit at EUR 750 000. The hypothetical budget impact of having reimbursed all Belgian prostate and head and neck cancer patients treated in 2003 with IMRT was estimated at EUR 5 000 000 or 5.4% of the external radiotherapy operating budget, breaking down as 72.2% of added fee-for-service expenses, 7.4% of investment costs, and 20.4% of operational costs. Extending IMRT reimbursement to all breast cancer patients in 2003 would have raised the impact to 18.7% (EUR 17 000 000).

Recommendations

- Manufacturers and users of IMRT hardware and software should be made more aware of the risk of inducing secondary malignancies, and product improvement is to be stimulated.
- Currently IMRT used in head and neck cancer patients should be restricted to centers with the necessary expertise. More appropriate financing of complex IMRT planning in head and neck cancer shall be considered.
- Long-term studies are required to assess the risk of inducing a secondary tumor in the contralateral breast after IMRT before introduction into common practice. Specific research financing of IMRT in breast cancer should be considered.
- More frequent imaging for guidance of IMRT is expected to improve the efficacy and safety of IMRT, particularly in targets showing internal movement, eg, in case of prostate cancer. Financing of imaging for IMRT should be re-assessed.

Methods

The scientific literature was searched for clinical effectiveness, cost effectiveness, and cost studies through electronic databases. Organizational issues were also retrieved from grey literature. Budgetary simulations were conducted for 2002 to 2006 using international literature, local cancer registration data, legal documents, and results from a survey.

Further research/reviews required

- More long-term data are needed to confirm any survival advantage of IMRT and to assess the increased risk of secondary malignancies in comparison with standard external radiotherapy techniques.
- As no firm conclusion could be drawn on the cost effectiveness of IMRT in comparison to alternative interventions, in particular 3DCRT, cost and utility data would be collected within the wider framework of an RCT. In this respect, further full costing analyses, preferably activity based, at the hospital level are a prerequisite.

Written by Van den Steen D, Hulstaert F, and Camberlin C, KCE, Belgium

Title **Cost-Effectiveness Analysis of Rotavirus Vaccination of Belgian Infants**

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Reference Report no 54C, 2007.
http://kce.fgov.be/index_en.aspx?ID=0&SGREF=9152&CREF=9409

Aim

To estimate the cost effectiveness of universal rotavirus (RV) vaccination in Belgium.

Conclusions and results

Healthcare Payer Perspective

- The incremental cost-effectiveness ratio is influenced by the number of caregivers assumed to impact on health-related quality of life (HRQOL) and the valuation of care for which no healthcare resources are used.
- Based on the most plausible scenario, fully funded universal RV vaccination would cost EUR 50 024 per QALY gained with Rotarix®, and EUR 68 321 per QALY gained with RotaTeq®.
- At an average of EUR 80 709 per QALY gained, the current situation (private RV vaccination with Rotarix or Rotateq at intermediate levels of uptake, partially reimbursed by the National Health Insurance) is less cost effective than a fully funded universal vaccination program.
- Considering all information for both vaccines, fully funded universal vaccination (and probably private vaccination) is more cost effective with Rotarix than with RotaTeq.

Societal Perspective

- On average, a fully funded universal RV vaccination program is more cost effective for society than for the healthcare payer, but the impact of parameter uncertainty on the results is also greater for society than for the healthcare payer. Fully funded universal RV vaccination would be slightly cost-saving with Rotarix, and would cost EUR 29 618 per QALY gained with RotaTeq.
- Multivariate sensitivity analysis showed the cost effectiveness of universal vaccination vs no vaccination depends mainly on the uncertainty about the number of days away from work to care for a child with clinical symptoms of RV infection.
- In line with the healthcare payer perspective, fully funded universal vaccination is more cost effective with Rotarix than with RotaTeq, and universal vaccination is more cost effective than private vaccination.

Recommendations

The current situation in Belgium whereby parents and their insurers pay private market prices for the 2-dose Rotarix vaccine (and recently the 3-dose RotaTeq vaccine) is clearly less preferable than a fully funded universal vaccination program, because it is more expensive and (at best) equally efficacious per vaccinated person, less effective, and less equitable.

Methods

The study includes a review of the international published and unpublished literature, the collection and analysis of a wide range of Belgian epidemiological and cost data, the development of a simulation model, parameterized and fitted by using scientifically validated data.

Further research/reviews required

Sub-analyses of data from recent clinical trials indicated that the instantaneous efficacy of a reduced schedule (ie, one dose of Rotarix or two doses of RotaTeq) would be high. None of these trials were designed to study the long-term efficacy of using fewer doses than currently recommended for either vaccine or the immediate comparison with the schedules currently recommended. Hence, there is insufficient basis for a model-based analysis of reduced schedule options. Clinical efficacy trials should be set up to compare the current schedules of RV vaccines with reduced ones.

Written by Frank Hulstaert, KCE, Belgium

Title **Care Strategy for Carotid Bifurcation Stenoses – Indications for Revascularization Techniques**

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Reference www.has-sante.fr/portail/display.jsp?id=c_554161,
www.has-sante.fr/portail/display.jsp?id=c_555900

Aim

To assess revascularization techniques (carotid surgery, carotid angioplasty, and stenting (CAS)) for carotid bifurcation stenoses; to specify their indications and contribution to the care strategy; to assess the practical procedures for performing CAS; and to assess the economic impact of these revascularization techniques.

Conclusions and results

Symptomatic atherosclerotic carotid stenoses. Surgery is the treatment of choice for tight symptomatic atherosclerotic carotid stenoses. It is indicated for stenoses of 50% to 99% (according to 2 randomized controlled trials (RCTs) – NASCET and ECST). It should be performed as soon as possible (within 2 weeks) in patients with a transient ischemic attack, or with moderate or regressive ischemic stroke.

The results of 2 European multicenter RCTs comparing surgery with CAS (EVA-3S and SPACE) did not demonstrate the non-inferiority of CAS compared with surgery in terms of 30-day mortality and stroke. Consequently, CAS is indicated only as a second-line procedure to be used when the surgeon decides that surgery is contraindicated on technical or anatomical grounds, or when a multidisciplinary group including vascular surgeons and neurologists considers that there is a risk related to the medical and surgical conditions (expert opinion).

Asymptomatic atherosclerotic carotid stenoses. Surgery is not indicated for asymptomatic stenoses of less than 60%. It is an option for stenoses greater than or equal to 60%, depending on several variables (life expectancy, hemodynamic and anatomical variables, and stenosis progression), and for surgical teams whose expected morbidity-mortality rate at 30 days is less than 3%. The benefit of surgery appears only in the long term (2 years) (RCTs ACAS and ACST and expert opinion).

No indication has been established for CAS in asymptomatic atherosclerotic carotid stenoses. Nevertheless, it may be considered in rare cases when carotid revascularization is deemed necessary (asymptomatic stenoses greater than or equal to 60%), once the surgeon has decided that surgery is contraindicated (expert opinion).

Radiation-induced stenoses and postsurgical restenoses of the carotid. Low-evidence-level studies have shown good results in terms of 30-day mortality and stroke for both CAS and surgery. In practice, the choice of treatment must be discussed by a multidisciplinary group including vascular surgeons and neurologists (expert opinion).

Methods

This assessment is based on a critical appraisal of the literature (systematic literature review using MEDLINE and Pascal databases published in French and English between 1997 and 2006) and the expert opinion of an 18-member multidisciplinary working group (neurologists, vascular surgeons, radiologists, cardiologists, anesthetists, vascular physicians, and health economists) and of 22 peer reviewers.

Further research/reviews required

A national register of carotid angioplasty and stenting procedures should be set up.

Written by Jean-François Albucher and Valérie Lindecker, HAS, France

Title **Botulinum Toxin Injection for Axillary Hyperhidrosis**

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Reference HAS report, 2006.
www.has-sante.fr/portail/display.jsp?id=c_520046

Aim

To assess the expected benefit of unilateral or bilateral injection of botulinum toxin A (BTX) into the axillary cavity.

Conclusions and results

This procedure is used to treat hyperhidrosis resistant to local treatment when the psychological and social impact is severe. HAS assessed the expected benefit of this procedure with a view to issuing an opinion regarding its inclusion on the reimbursement list (Social Security Code, article L.162-1-7) and the conditions for its use.

Low-level evidence studies (21 case series) suggested an efficacy of 75% to 90% for BTX on the HDSS score *(Hyperhidrosis Disease Severity Scale)* in treated subjects (n=20–146). BTX injection into the axillary cavity gave rise to few (<5%) and mild to moderate complications. In a series of 146 patients, 3 cases of extra-axillary perspiration were identified, 2 cases of axillary sensitivity to touch, 2 cases of pain at the site of injection, and 1 case of dizziness following injection.

Treatment had a positive impact on the quality of life in 3 studies (n=278 patients).

BTX injection into the axillary cavity is a third-line treatment for severe axillary hyperhidrosis, following antiperspirants and aluminum salt-based topical treatments. Surgery is used as a last resort, or as a complement to BTX injection when other treatments failed (1 guideline based on data from the literature, experts' opinion).

The data indicate that the procedure has therapeutic value.

Recommendations

The expected benefit of BTX injection is sufficient considering its satisfactory risk/benefit ratio.

HAS considered the expected benefit of BTX injection to be adequate and issued a favorable opinion for its inclusion on the list of procedures reimbursed by the National Health Insurance.

Methods

This assessment is based on a critical appraisal of the literature (systematic review of scientific data published in French and English between January 1986 and July 2006) and on the expert opinion of a 10-member multidisciplinary working group (neurologists, dermatologists, ENT specialists, plastic surgeons, and psychiatrist).

Further research/reviews required

Data could be collected on doses to be injected and on the optimal frequency of injections.

Written by Julie Biga, HAS, France

Title **Acupuncture of Chronic Headache Disorders in Primary Care: Randomized Controlled Trial and Economic Analysis**

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Reference Health Technol Assess 2004;8(48). November 2004.
www.hta.ac.uk/execsumm/summ848.htm

Aim

To determine the effects of a policy of "use acupuncture" on headache, health status, medication use, days off sick, and resource use in chronic headache patients as compared to a policy of "avoid acupuncture", and to determine the cost effectiveness of acupuncture.

Conclusions and results

The study randomized 401 patients, and 301 provided headache diaries at one year. Dropout was similar between groups and groups were well balanced at baseline. Headache score at 12 months, the primary endpoint, was lower in the acupuncture group (16.2, SD 13.7, n=161, 34% reduction from baseline) than in controls (22.3, SD 17.0, n=140, 16% reduction from baseline). The adjusted difference between means is 4.6 (95% confidence interval 2.2 to 7.0; p=0.0002). This result is robust to sensitivity analysis incorporating imputation for missing data. Patients in the acupuncture group experienced the equivalent of 22 fewer days of headache per year (8 to 38). SF-36 data favored acupuncture, although differences reached significance only for physical role functioning, energy, and change in health. Compared with controls, patients randomized to acupuncture used 15% less medication (p=0.02), made 25% fewer visits to general practitioners (p=0.10), and took 15% fewer days off sick (p=0.2). Total costs during the 1-year period of the study were on average higher for the acupuncture group (£403; $768; €598) than for controls (£217) because of the acupuncture practitioners' costs. The mean health gain from acupuncture during the 1-year trial was 0.021 QALYs, leading to a base case estimate of GBP 9180 per QALY gained. This result was robust to sensitivity analysis. Cost per QALY dropped substantially when the analysis incorporated likely QALY differences for the years after the trial.

Recommendations

Acupuncture leads to persisting, clinically relevant, benefits for primary care patients with chronic headache, particularly migraine. It is relatively cost effective compared to several other interventions provided by the National Health Service (NHS).

Methods

Patients with chronic headache, predominantly migraine, were recruited for general practices in England and Wales. Patients completed baseline diaries and were allocated using randomized minimization to receive up to 12 acupuncture treatments over 3 months, or to usual care control. Headache and health status diaries were completed at 3 months and 12 months after randomization; resource use diaries were completed every 3 months.

Further research/reviews required

The optimum methods of acupuncture remain unknown and require systematic research. Further studies might examine the duration of acupuncture effects beyond 1 year and the relative benefit to patients with migraine as compared to tension-type headache. Trials are also warranted examining the effectiveness and cost effectiveness of acupuncture in headache patients receiving more aggressive pharmacologic management.

Written by Mr Robert McCarney, The Royal London Homeopathic Hospital, United Kingdom

Title **Virtual Outreach: A Randomized Controlled Trial and Economic Evaluation of Joint Teleconferenced Medical Consultations**

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Reference Health Technol Assess 2004;8(50). December 2004.
www.hta.ac.uk/execsumm/summ850.htm

Aim

Main trial: To test the hypotheses that virtual outreach would:

- reduce offers of hospital followup appointments
- reduce numbers of medical interventions and investigations
- reduce numbers of contacts with the healthcare system, have a positive impact on patient satisfaction and enablement
- lead to improvements in patient health status.

Economic evaluation: To test the hypotheses that virtual outreach would:

- incur no increased costs for the NHS
- reduce the costs incurred by patients attending outpatient appointments
- reduce the time taken off work.

Conclusions and results

Patients in the virtual outreach group were more likely to be offered a followup appointment. Significant differences in effects were observed between the two sites studied. Virtual outreach increased the offers of followup appointments more in Shrewsbury than in London, and more in ENT and orthopedics than in the other specialties. Fewer tests and investigations were ordered in the virtual outreach group, by an average of 0.79 per patient. There were no significant differences overall in number of contacts with general practice, outpatient visits, accident and emergency contacts, inpatient stays, day surgery, and inpatient procedures or prescriptions between the randomized groups. Tests of interaction showed evidence of differences in effects by specialty for number of tests and investigations (p=0.01) and outpatient visits (p=0.007). They indicated that virtual outreach decreased the number of tests and investigations particularly in patients referred to gastroenterology, and increased the number of outpatient visits particularly in those referred to orthopedics. Patient satisfaction was greater after a virtual outreach consultation than after a standard outpatient consultation. However, patient enablement after the index consultation, and the physical and psychological scores of the SF12 for adults and the scores on the Child Health Questionnaire for children under 16, did not differ between the randomized groups at 6-month followup. Six-month NHS costs were greater for the virtual outreach consultations than for conventional outpatients, GBP 724 and GBP 625 per patient respectively. The index consultation accounted for this excess. Cost and time savings to patients were found. Estimated productivity losses were less in the virtual outreach group.

Recommendations

Virtual outreach consultations resulted in significantly higher levels of patient satisfaction than standard outpatient appointments and led to substantial reductions in numbers of tests and investigations. The main hypothesis that virtual outreach would be cost neutral was not supported, but the hypotheses that patient costs and productivity losses would be less were supported. Changes in costs and technological advances may improve the relative position of virtual consultations.

Methods

A randomized controlled trial compared joint teleconsultations between general practitioners (GPs), specialists, and patients with standard outpatient referral. It was accompanied by an economic evaluation.

Further research/reviews required

- Long-term followup of patients in the virtual outreach trial to determine "downstream" outcomes and costs.
- Effectiveness and costs of virtual outreach used for followup appointments rather than first-time referrals.
- Effectiveness and costs of virtual outreach involving joint teleconsultations where a nurse rather than a GP accompanies the patient.

Written by Professor Paul Wallace, Royal Free and University College Medical School, United Kingdom

Title **The Cost Effectiveness of Screening for Oral Cancer in Primary Care**

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Reference Health Technol Assess 2006;10(14). May 2006.
www.hta.ac.uk/execsumm/summ1014.htm

Aim

To investigate:

1. actual costs of screening for oral cancer and precancer in primary care settings
2. actual costs of managing oral precancerous lesions and oral cancer, including costs of recurrent disease, long-term rehabilitation, and palliation
3. screening programs in primary and if they are cost effective in terms of survival (life-years gained) and overall gains in quality-adjusted-life-years (QALYs)
4. future research priorities, specifically the expected value of perfect information (EVPI) for the decision to adopt a screening program and for each of the model inputs.

Conclusions and results

No screening (Strategy A) was always the cheapest option. Strategies B, C, E, and H were never cost effective and were ruled out by dominance or extended dominance. Of the remaining strategies, the incremental cost-effectiveness ratio (ICER) for the total population (aged 40–79 years) ranged from GBP 15 790 to GBP 25 961 per QALY. Modeling a 20% reduction in disease progression always gave the lowest ICERs. Cost-effectiveness acceptability curves showed considerable uncertainty in the optimal decision identified by the ICER, depending on both the maximum amount the NHS may be prepared to pay and the impact of treatment on the annual malignancy transformation rate. Overall, high-risk opportunistic screening by a general dental practitioner (Strategy G) was the most cost effective.

Recommendations

This study suggests that opportunistic high-risk screening, particularly in general dental practice, may be cost effective, especially if targeted at groups aged 40 to 60 years. However, there is considerable uncertainty in the parameters used in the model, particularly malignant transformation rate, disease progression, patterns of self referral, and costs.

Methods

Cost effectiveness of oral cancer screening programs in several primary care environments was simulated using a decision analysis model. Primary data on actual resource use and costs were collected by case note review in 2 hospitals. Additional data needed to inform the model were obtained from published costs, from systematic reviews, and by expert opinion using the Trial Roulette approach. The value of future research was determined using EVPI for the decision to screen and for each of the model inputs.

Further research/reviews required

There is an urgent need to learn more about the natural history of oral cancer and precancer. Studies are needed to determine: the malignant transformation rates of oral potentially malignant lesions; rates of progression of oral cancer; and the outcome of treating oral, potentially malignant, lesions (evidence suggests that intervention has no greater benefit than 'watch and wait', so a randomized controlled trial may be justified).

A less uncertain estimate of cost effectiveness could be determined if the decision model were run on data obtained from sources with less heterogeneity or uncertainty in the data. For example, accurate estimates may be obtained for populations covered by small, well-controlled cancer registries, or where potentially malignant lesions are also registered and monitored.

Written by Professor Paul Speight, University of Sheffield, United Kingdom

Title **Cognitive Behavioral Therapy in Addition to Antispasmodic Therapy for Irritable Bowel Syndrome in Primary Care: A Randomized Controlled Trial**

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Reference Health Technol Assess 2006;10(19). June 2006. www.hta.ac.uk/execsumm/summ1019.htm

Aim

To determine if cognitive behavioral therapy (CBT) developed to treat irritable bowel syndrome (IBS) can be delivered by specially trained generalist nurses working in primary care; if such therapy offers additional benefit over usual general practitioner (GP) care and antispasmodic medication; and if CBT for IBS is cost effective and could identify variables that predict a better outcome in IBS.

Conclusions and results

Both groups improved over time but a considerable difference was noticed on followup in the CBT group. Improvements were significant at the 5% level of probability. Adherence to medication was unaffected and so is unlikely to account for the differences between therapy groups.

For patients allocated to treatment, linear regression showed that male gender, beliefs that IBS had serious consequences, and an external etiology predicted above-average disability at followup. CBT did not reduce costs even when reserved for Rome I positive patients only.

In total, 70% of patients had been diagnosed by a GP without referral to gastroenterology. Most patients referred to the study met the Rome I criteria for IBS. This prevalence was similar whether the patients had been seen only in primary care (85.1%), or also by a gastroenterologist (87.5%). One patient of the 141 tested for celiac serology tested positive. A similar proportion of patients received serology testing for celiac disease prior to referral to the trial, whether or not the patient had been seen only in primary care (11.4%), or also by a gastroenterologist (10.9%).

Recommendations

Patients with IBS who receive CBT improve in several health dimensions. CBT offers additional benefits over mebeverine hydrochloride and GP care alone. These benefits last up to 1 year post cessation of therapy. Therapy does not reduce costs even when reserved for patients with Rome I positive IBS.

Generalist nurses can develop skills in IBS that can be used effectively in the primary care team. Clinical severity is a poor predictor of outcome in IBS, but male gender and a perception that the condition is dangerous or uncontrollable predict a worse outcome.

Methods

Generalist nurses working in UK general practices were recruited and trained to deliver IBS-specific CBT developed by the research team and delivered in a randomized trial of adding CBT to mebeverine in patients referred to the study by GPs. Patients referred to the study had an initial 2 weeks of GP care and were then re-assessed. Patients with moderate or severe IBS then received 4 weeks of mebeverine (270 mgs three times a day) and were reassessed. Patients still reporting moderate or severe IBS were randomized to 6 sessions of CBT plus mebeverine (72 patients) or to mebeverine alone (77 patients). Followup was at the end of therapy and at 3, 6, and 12 months post therapy. The analysis investigated the clinical and economic impact of therapy and identified variables that predict outcome. (Link to Executive Summary above for further details.)

Further research/reviews required

Future research might include:

- the long-term benefit of CBT for IBS and whether it would reduce costs over time, perhaps by reducing referral and surgical intervention
- whether it is more cost effective to use CBT for patients with IBS, or to reserve it for other conditions
- whether availability of CBT can be increased by training nonspecialist health professionals to deliver therapy (either brief, condition-specific training, or more complete and lengthy training).

Written by Dr Tom Kennedy, Guy's Kings and St Thomas' Medical School, United Kingdom

Title **Cognitive Behavioral Therapy in Chronic Fatigue Syndrome: A Randomized Controlled Trial of an Outpatient Group Program**

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Reference Health Technol Assess 2006;10(37). October 2006.
www.hta.ac.uk/execsumm/summ1037.htm

Aim

To assess the efficacy of treating chronic fatigue/myalgic encephalopathy syndrome through cognitive behavioral therapy (CBT) delivered in a group format.

Conclusions and results

No evidence suggested that the physical state of the participants, as measured by the SF36 physical health summary scale, differed between the 3 treatment conditions (see Methods below), and no significant change over time was indicated. The mean scores for all 3 cohorts were slightly higher at 6 and 12 months compared to baseline, but well below the norm for the general population.

In contrast, some differences with respect to mental health were suggested, but the only statistically significant difference was between the CBT and SMC cohorts. Once again, no significant change over time was indicated. The mean scores in all 3 groups increased from baseline, but remained below the norm for the general population.

The Chalder fatigue scale also showed differences between the groups. The least squares mean score was significantly lower for the CBT cohort than for the other 2 cohorts. The HADS anxiety scale showed a trend toward lower scores (reduced anxiety) in the CBT treatment cohort and higher scores in the SMC treatment cohort. The difference across the 3 groups was not statistically significant. Treatment conditions did not impact on the HADS depression scores, or on the HUI3 overall utility score. For these outcomes, no differences between the scores at 6 and 12 months were found, and there were no significant differences between cohorts.

Similar trends were seen with the General Health Questionnaire and the number of shuttles walked, with lower GHQ scores and more shuttles walked in the CBT treatment cohort, higher GHQ scores and fewer shuttles walked in the SMC treatment cohort, and the EAS cohort showing results similar to the SMC group. Overall, across the 3 groups the differences were not statistically significant.

No significant differences in response to the cognitive tests were found across the 3 treatment conditions, with the possible exception of the repeated digits. The results of the economic evaluation were equivocal.

Recommendations

The trial used a broad range of outcome measures. Three demonstrated a statistically significant change in the direction of the research hypothesis. All outcome measures showed a consistent trend in the same direction, and examination of clinical significance was also consistent. In the Whiting review, studies were classified as having an overall effect if they showed an effect for more than one clinical outcome. On this basis, the treatment was clearly effective.

Methods

This was a double blind, randomized controlled trial with 3 research conditions: 1) Group therapy: CBT, 2) Control group: EAS (education and support), and 3) Standard medical care (SMC). Levels of fatigue, functional disability, emotional distress, and physical fitness were taken at baseline, 6, and 12 months. The data were analyzed on the basis of intention to treat.

Further research/reviews required

The question of which patient subgroup this type of intervention is likely to be most effective should be addressed.

Written by Dr Hazel O'Dowd, Frenchay Hospital, United Kingdom

Title **A Systematic Review of the Effectiveness and Cost Effectiveness of Different Models of Community-Based Respite Care for Frail Older People and Their Carers**

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Reference Health Technol Assess 2007;11(15). April 2007. www.hta.ac.uk/execsumm/summ1115.htm

Aim

To systematically identify, appraise, and synthesize the grey and published evidence for the effectiveness and cost effectiveness of different models of community-based respite care for frail older people and their carers.

Conclusions and results

Uncontrolled studies were reviewed since no controlled studies of respite for carers of people with cancer, of host family respite, or of video respite were identified. Effectiveness evidence from the 22 studies reviewed suggests that the consequences of respite on carers and care recipients are generally small, with better-controlled studies finding a small positive effect on carers in terms of burden and mental or physical health. Many studies report high levels of carer satisfaction. The review found no reliable evidence that respite delays entry to residential care, or that respite adversely affects care recipients. The validity of the randomization process was not always clear. All quasiexperimental studies had methodological weaknesses that undermine the reliability of their findings. The uncontrolled studies had methodological weaknesses, which limit their transferability to other people, conditions, and settings. All 5 economic evaluations compared day care to usual care: day care was often associated with higher costs and either similar or a slight increase in benefits, relative to usual care. Most studies assessed health and social service use and cost, but inadequate reporting of the intervention and comparator limits the potential for exploring applicability to the UK setting. No study included generic, health-related quality of life measures, making cost-effectiveness comparisons with other healthcare programs difficult.

Methods

We searched for studies published in any language in or after 1980 that addressed respite interventions for carers of frail elderly people and included evidence of effectiveness or cost effectiveness. For inclusion in the review, effectiveness studies had to be well-controlled, with uncontrolled studies included only in the absence of higher quality evidence. Economic evaluations had to compare 2 or more options and consider both costs and consequences. Studies of day care, in-home respite, host family respite, institutional respite, respite programs and video respite were eligible for inclusion. For the effectiveness and economic studies, one reviewer extracted data and assessed quality, and a second reviewer checked the work. Disagreements were resolved by discussion, with a third reviewer acting as arbiter if necessary. Results of the data extraction and quality assessment were presented in tables and as a summary. Possible effects of study quality on the effectiveness data and review findings were discussed. Where sufficient clinically and statistically similar data were available, data were pooled using appropriate statistical techniques.

Further research/reviews required

Pilot studies are essential to inform full-scale trials of respite in the UK. Studies should: 1) Clarify the objectives of respite services. 2) Focus on specific groups of older people and carers, or be large enough to permit subgroup analysis. 3) Identify essential components of respite services, clarifying boundaries between respite and intermediate care, crisis response, day care, rehabilitation, and palliative care. 4) Target outcomes relevant to both carers and older people, recognizing the joint and separate interests and aspirations of individuals in a caregiving relationship.

Pilot work should then inform methodologically rigorous trials that can establish the effectiveness and cost effectiveness of UK respite services. Given the complexity and intersectoral nature of respite care, a range of methodological approaches will probably be needed.

Written by Mrs Anne Mason, University of York, United Kingdom

Title **A Systematic Review of Duplex Ultrasound, Magnetic Resonance Angiography and Computed Tomography Angiography for the Diagnosis and Assessment of Symptomatic, Lower Limb Peripheral Arterial Disease**

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Reference Health Technol Assess 2007;11(20). May 2007. www.hta.ac.uk/execsumm/summ1120.htm

Aim

To determine the best method, or combination of methods, to diagnose and assess symptomatic lower limb peripheral arterial disease (PAD).

Conclusions and results

The review suggests that contrast-enhanced MRA (CE-MRA) is more accurate than computed tomography angiography (CTA) or duplex ultrasound (DUS), and is preferred by patients over conventional angiography (CA). Where available, CE-MRA may be a viable alternative to CA. The only controlled trial suggested that DUS was comparable to CA in terms of surgical planning and outcome, conflicting with poor estimates of accuracy for DUS compared to CA.

Economic modeling suggests that when the whole leg is assessed, DUS dominates its alternatives, (higher effectiveness, lower cost/QALY). When assessment is limited to above or below knee, results vary, for above-the-knee 2D time-of-flight (TOF) MRA appears most cost effective, followed closely by CE-MRA. For below-the-knee comparisons results were less certain, with results suggesting that DUS could be the more cost-effective option, followed by 2D-TOF MRA.

Recommendations

It is recommended that a patient simulation model, considering the above issues, assess the long-term cost effectiveness of preoperative imaging diagnostic tests for PAD patients.

Methods

See Executive Summary link above.

Further research/reviews required

Questions requiring further research include: What is the relative clinical effectiveness of the available imaging tests, in terms of surgical planning and postoperative outcome? What adverse events result from testing, and what is the relative incidence for the available tests? Which tests do patients prefer? What is the true diagnostic accuracy of DUS in detection of ≥50% stenoses and occlusions, and how is this affected by timing of the test and operator skill? What are the effects of operator skill, etc on measures of test accuracy for the imaging modalities of interest? What is the diagnostic accuracy and clinical effectiveness of tests to image arteries in different areas of the leg, particularly the foot? What is the diagnostic accuracy and clinical effectiveness of tests in particular patient subgroups, eg, diabetes mellitus?

Data on how patients are managed after diagnostic results are obtained are required to populate the economic model. It is unclear whether the prognosis and quality of life of patients who had an inaccurate treatment plan and underwent a change of procedure, would differ significantly from patients that were correctly diagnosed and managed from the outset. Research on these topics is required.

If the allocation of treatment pathway were to be modeled, research would be required to allow these decisions to be captured and accurately represented. Such a model would reflect different treatment plans to be performed according to the specific clinical characteristics of patients obtained by means of the preoperative diagnostic testing. Hence, the model should consider the choice of treatments available and, based on test results, the treatment chosen by the clinicians.

Written by Miss Ros Collins, University of York, United Kingdom

Title **A Systematic Review of the Routine Monitoring of Growth in Children of Primary School Age to Identify Growth-Related Conditions**

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Reference Health Technol Assess 2007;11(22). June 2007.
www.hta.ac.uk/execsumm/summ1122.htm

Aim

To clarify the role of growth monitoring including obesity in school-aged children, and to examine issues that might impact on the effectiveness and cost effectiveness of such programs.

Conclusions and results

The review included 31 studies, none of which were controlled trials of the impact of growth monitoring or studies on diagnostic accuracy of different methods for growth monitoring. Analysis of the studies that presented a 'diagnostic yield' of growth monitoring suggested that one-off screening might identify between 1:545 and 1:1793 new cases of potentially treatable conditions. Obesity studies focused on body mass index (BMI) vs measures of body fat. Several issues relating to human resources of growth monitoring were identified, but data on attitudes to growth monitoring were sparse.

Cost-effectiveness modeling indicated that growth monitoring is cost effective according to accepted willingness to pay thresholds in the UK of GBP 20 000 to 30 000 per QALY. The mean cost per additional QALY was estimated at GBP 9500. The obesity model suggested primary prevention may be cost effective, but the results are uncertain.

Based on current evidence, monitoring for growth disorders including obesity does not meet all of the National Screening Committee (NSC) criteria. Although growth-related disorders are important, and effective treatments exist for some of them, certain criteria regarding the monitoring program have not been met.

Recommendations

There is potential utility and cost effectiveness for growth monitoring in terms of increased detection of stature-related disorders. However, high-quality evidence is lacking on the potential impact of a monitoring program.

Data are lacking on monitoring for obesity. The cost-effectiveness model incorporated much uncertainty. Relative benefits and harms of monitoring have not been determined, and the effectiveness of current treatments is doubtful.

Gaps and uncertainties in the evidence base mean that growth and obesity monitoring do not currently meet all NSC criteria.

Methods

Data sources: Searches of electronic databases up to July 2005, hand searching of journals, scanning reference lists, and consultation with experts.

Study selection: Two reviewers independently screened titles/abstracts for relevance. Potentially relevant studies were assessed for inclusion by one reviewer and checked by a second. Published and unpublished studies in any language were eligible.

Inclusion criteria: Separate inclusion criteria were derived for each objective.

Data extraction and quality assessment: Standardized forms were used. A second reviewer checked data extraction.

Data synthesis: Data were analyzed separately for each phase of the review. Cost-effectiveness models were generated. Growth monitoring was evaluated against NSC criteria.

Further research/reviews required

High-quality evidence is needed on the impact of growth monitoring programs, eg, acceptability and potential harms. Data are needed on the potential impact of monitoring for obesity. Long-term studies of the predictors of obesity-related comorbidities in adulthood are warranted to clarify the role of screenable parameters, eg, BMI, in determining those children most at risk.

Written by Dr Marie Elaine Westwood, University of York, United Kingdom

Title **Systematic Review of the Effectiveness of Preventing and Treating Staphylococcus Aureus Carriage in Reducing Peritoneal Catheter-Related Infections**

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Reference Health Technol Assess 2007;11(23). July 2007. www.hta.ac.uk/execsumm/summ1123.htm

Aim

To determine: 1) clinical and cost effectiveness of alternative strategies to prevent Staphylococcus aureus (S. aureus) carriage in patients on peritoneal dialysis; 2) clinical and cost-effectiveness of alternative strategies to treat S. aureus carriage in patients on peritoneal dialysis.

Conclusions and results

The review of clinical effectiveness included 25 reports describing 22 studies.

Prophylaxis (all patients): When considering all oral antibiotics together, there were fewer cases of peritonitis caused by S. aureus in the groups that received antibiotics, but the difference did not reach statistical significance (RR 0.69, 95% CI 0.28 to 1.72; p=0.43). There were fewer cases of exit site and/or tunnel infections caused by S. aureus (RR 0.27, 95% CI 0.11 to 0.65; p=0.003).

Only one trial compared a topical antibiotic with no antibiotics. No difference was found in the number of patients with peritonitis caused by S.aureus. However, there were fewer exit site and/or tunnel infections in the group allocated to use a topical antibiotic.

Considering all antiseptics together, there was no real difference in peritonitis caused by S. aureus in the groups allocated to antiseptic use (RR 1.08, 95% CI 0.54 to 2.16; p=0.84). However, when considering antiseptic use at the time of catheter insertion, there were fewer cases of peritonitis (1 trial). Fewer cases of exit site and/or tunnel infections caused by S. aureus were found in the groups allocated to antiseptic use (RR 0.43, 95% CI 0.28 to 0.66; p=0.0001).

Treatment of S. aureus carriage: When considering all oral antibiotics together, there were fewer cases of peritonitis caused by S. aureus in the groups that received antibiotics – again this was not statistically significant (RR 0.27, 95% CI 0.05 to 1.35; p=0.11) – and fewer cases of exit site and/or tunnel infections caused by S. aureus (RR 0.60, 95% CI 0.16 to 2.28; p=0.46).

Considering all topical antibiotics together, there were fewer cases of peritonitis caused by S. aureus in the groups that received antibiotics (RR 0.80, 95% CI 0.49 to 1.32; p=0.39), fewer patients requiring catheter removal (RR 0.63, 95% CI 0.29 to 1.39; p=0.26), and fewer cases of exit site and/or tunnel infections caused by S. aureus (RR 0.66, 95% CI 0.36 to 1.20; p=0.17), but no statistical significance.

Evidence on the effectiveness of the alternative interventions to prevent and treat S. aureus carriage was limited. Hence, their use in an economic evaluation would provide no informative data on relative cost effectiveness. Therefore, the hypothetical model required to compare alternative interventions was provided along with a description of its information needs, which served to highlight key areas where data were unavailable.

Recommendations

We conclude that interventions reduce exit site and tunnel infections, but that we cannot say whether they reduce peritonitis.

Methods

See Executive Summary link above.

Further research/reviews required

More primary research is needed in the form of longer, larger trials. More data on the natural history of carriage are also required.

Written by Ms Kirsty McCormack, University of Aberdeen, United Kingdom

Title **The Clinical Effectiveness and Cost of Repetitive Transcranial Magnetic Stimulation Versus Electroconvulsive Therapy in Severe Depression: A Multicenter Pragmatic Randomized Controlled Trial and Economic Analysis**

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Reference Health Technol Assess 2007;11(24). July 2007. www.hta.ac.uk/execsumm/summ1124.htm

Aim

1. To determine whether repetitive transcranial magnetic stimulation (rTMS) is equivalent to electroconvulsive therapy (ECT) in treating major depression.
2. To compare the side-effect profiles of rTMS and ECT.
3. To calculate and compare the costs of courses of rTMS and ECT in treating major depression.

Conclusions and results

Hamilton rating scale for depression (HRSD) scores at end-of-treatment were significantly lower with ECT (p=0.002), with a significantly higher remission rate compared to the rTMS group (59% vs 17%; p=0.005). Similar results were found with self-rated depression scales. Improvement in subjective reports of side effects following ECT correlated with the therapeutic response. No difference was found between the two groups before or after treatment on global measures of cognition. The costs of administering rTMS were similar to those for ECT. Service costs did not differ between the groups in the subsequent 6 months, but the rTMS group incurred more informal care costs. rTMS has a very low probability of being more cost effective than ECT.

Recommendations

This study demonstrated that ECT was significantly more effective than rTMS in treating major depression.

Methods

This study was a pragmatic multicenter, randomized controlled trial to test equivalence of rTMS with ECT in treating major depression.

Further research/reviews required

Further research is needed to:

1. refine the ECT technique to reduce its cognitive side effects while maintaining its clinical effectiveness.
2. identify the optimum treatment parameters for rTMS as a potential treatment for depression.

Written by Professor Declan McLoughlin, Institute of Psychiatry, United Kingdom

Title **A Randomized Controlled Trial and Economic Evaluation of Direct Versus Indirect and Individual Versus Group Modes of Speech and Language Therapy for Children with Primary Language Impairment**

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Reference Health Technol Assess 2007;11(25). July 2007. www.hta.ac.uk/execsumm/summ1125.htm

Aim

To compare the outcomes of direct individual, indirect individual, direct group, and indirect group modes of language therapy for primary school-age children with primary language impairment (PLI) relative to a comparison group receiving community-based speech and language therapy services; to study the evidence for long-term benefits of therapy for such children at 12-month followup; and to compare the 4 approaches in terms of cost.

Conclusions and results

The results from both the intention-to-treat analyses of the outcomes from the 161 children randomized who met the eligibility criteria, and the protocol analyses of the outcomes from the 152 children for whom post-baseline data were available, revealed no significant post-intervention differences between direct and indirect modes of therapy, nor between individual and group modes on any of the primary language outcome measures, after adjusting for the effects of regression to the means. The evidence showed some benefits of direct therapy from a speech and language therapist (SLT) in secondary outcome measures. Parents and teachers were positive about the children's progress and the project. All four intervention modes were acceptable to parents and schools.

Intervention delivered 3 times a week for 30 to 40 minutes over 15 weeks also yielded significant improvements in age-corrected standardized scores for expressive language, but not for receptive language, relative to those receiving community-based SLT services. Children with specific expressive language delay were more likely to improve than those with mixed receptive-expressive difficulties, and non-verbal IQ was not a significant moderating variable.

Within-trial economic evaluation identified indirect therapy, particularly indirect group therapy, as the least costly of the modes investigated, with direct individual therapy as the most costly option. However, these cost differences should not be over-interpreted.

Recommendations

Well-trained, well-supported, and well-motivated speech and language therapy assistants can be effective surrogates for speech and language therapists in delivering services in schools to children with PLI who do not to require the specialist skills of a qualified SLT.

Generalizing the central estimates of the relative cost of different therapy modes observed here to other educational/health systems is possible, but the differences reported in resource use need to be qualified by the level of program intensity and other characteristic features of education and therapy services that may differ from those observed in the trial.

Methods

See Executive Summary link above.

Further research/reviews required

- Identify effective interventions for receptive language problems and investigate the efficacy of the relationship between dose and treatment effect in both expressive and receptive language.
- Investigate models of integrative service delivery, eg, the partnership between SLTs and schools, cluster models of delivery via integrated community schools, and the involvement of class teachers, classroom assistants, and parents/carers.
- Identify characteristics of children who are most likely to succeed with indirect intervention approaches, and evaluate alternative methods of working with those who may benefit from different modes.
- Conduct research to refine the therapy manual.

Written by Mr James Boyle, University of Strathclyde, United Kingdom

Title **Cardioprotection against the Toxic Effects of Anthracyclines Given to Children With Cancer: A Systematic Review**

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Reference Health Technol Assess 2007;11(27). July 2007.
www.hta.ac.uk/execsumm/summ1127.htm

Aim

To evaluate technologies that can potentially reduce anthracycline-induced cardiotoxicity in children, including: a) different dosage schedules, b) different anthracycline derivatives, c) use of cardioprotective agents, eg, dexrazoxane, and d) use of antioxidant protection, eg, probucol or nutritional supplementation with glutamine. To identify markers to quantify cardiotoxicity in children. To refine outcome measures for use in longer term studies. To identify studies evaluating the cost effectiveness of cardioprotection against the toxic effects of anthracyclines given to children with cancer. To identify priorities for future primary research.

Conclusions and results

Four randomized controlled trials (RCTs) on cardioprotective interventions, and one RCT and six cohort studies on the use of cardiac markers, met the inclusion criteria of the review. All studies had methodological limitations.

Two RCTs considered continuous infusion versus bolus (rapid) infusion. One found that continuous infusion of doxorubicin did not offer any cardioprotection over bolus; the other suggested that continuous infusion of daunorubicin had less cardiotoxicity than bolus infusion. Two studies considered cardioprotective agents. One concluded that dexrazoxane prevents or reduces cardiac injury as reflected in levels of a cardiac marker during doxorubicin therapy without compromising anti-leukemic efficacy of doxorubicin. The other reported a protective effect of coenzyme Q_{10} on cardiac function during anthracycline therapy.

One RCT suggests that cardiac troponin T can be used to assess the effectiveness of the cardioprotective agent dexrazoxane. Two cohort studies considering atrial natriuretic peptide and two considering brain (B-type) natriuretic peptide (BNP) suggest that these chemicals are elevated in some subgroups of children treated with anthracyclines for cancer compared with healthy children. NT-pro-BNP levels were significantly elevated in children treated with anthracyclines who had cardiac dysfunction compared with patients who did not have cardiac dysfunction and healthy controls in one cohort study. One cohort study found that serum lipid peroxide was higher in younger children treated with doxorubicin than in children of corresponding age not receiving doxorubicin. No differences in carnitine levels were found in children treated with doxorubicin and a group of healthy children in one cohort study.

Recommendations

Limited evidence makes it difficult to draw conclusions about the effectiveness of technologies to reduce or prevent cardiotoxicity and about the use of cardiac markers in children. The lack of standardization for monitoring and reporting cardiac performance is problematic. Not all studies report effectiveness in terms of cardiac outcomes and event-free survival with supporting statistical analyses. Studies are mostly small and of short duration, making generalization difficult.

Methods

See Executive Summary link above.

Further research/reviews required

RCTs of the methods to reduce or prevent cardiotoxicity in children treated with anthracyclines for cancer with long-term followup are needed to determine whether the technologies influence the development of cardiac damage. Studies will probably require a range of outcomes, the most important being event-free survival in terms of the whole cancer treatment protocol. Other outcomes include cardiac measurements, eg, echocardiographic findings and potential cardiac markers, side effects, and measures of anthracycline anti-tumor efficacy.

Written by Ms Jackie Bryant, University of Southampton, United Kingdom

Title **Clinical Effectiveness and Cost Effectiveness of Bone Morphogenetic Proteins in the Non-Healing of Fractures and Spinal Fusion: A Systematic Review**

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Reference Health Technol Assess 2007;11(30). Aug 2007. www.hta.ac.uk/execsumm/summ1130.htm

Aim

To determine the effectiveness and cost effectiveness of bone morphogenetic protein (BMP) in treating spinal fusions and fracture healing.

Conclusions and results

The review included 8 randomized controlled trials (RCTs) assessing BMP in treating fracture healing and 10 RCTs assessing BMP in treating spinal fusions. BMP is more effective than surgery alone for patients with acute open tibial fractures. BMP is more effective than autograft bone for patients with single-level degenerative disc disease. The evidence was insufficient to determine effectiveness of BMP in other diagnoses. BMP treatment also reduced pain, the number of secondary interventions, and eliminated donor site morbidity for patients with acute fractures. BMP reduced operative time and hospital length of stay, improved clinical outcomes, and eliminated donor site morbidities for patients with spinal fusions.

Only one economic evaluation was included, which suggested that the initial cost of BMP is likely to be offset by the costs of autograft bone grafting, complications, and increased fusion rates.

The modified economic modeling suggests that for fracture healing the cost per QALY ranges from GBP 13 791 to GBP 66 209 and for spinal fusions the cost per QALY is GBP 54 890.

Recommendations

BMP improves union and fusion rates in patients with acute fractures and single-level degenerative disc disease, respectively. Evidence for other diagnoses is weak, and further research is required.

Methods

Data sources included: electronic searches of MEDLINE, EMBASE, Science Citation Index, Cochrane Library and NeLH, default start dates to 2006; handsearches of frequently cited journals, 1995 to 2006; relevant industry; and authors. The searches were not restricted by language or publication status. Because it was anticipated that there would be a limited amount of relevant studies and the BMP treatment would vary considerably including fracture or fusion, degree of fracture or fusion, location, previous failed interventions, dosage, standard of care treatment method, BMP delivery system etc, we included all varying BMP interventions for treatment of fracture or fusion in humans.

Data were extracted by one reviewer and checked by another. Where appropriate, overall event rates were calculated by pooling results from the included studies. Economic evaluations were assessed. Economic models, provided by industry, were assessed and modified to determine the cost effectiveness of BMP compared with standard of care treatments.

Further research/reviews required

1. Large and properly designed RCTs of patients with nonunions are to compare BMP (as primary treatment) and standards of care.
2. RCTs of acute fractures other than tibia fractures to assess BMP effectiveness in other fracture locations.
3. Compare different BMP products (BMP-2 and BMP-7), the combination of BMP-2 and BMP-7, and different doses.
4. Trials that compare BMP and autogenous bone graft for spinal fusion with a control of intensive rehabilitation without surgery.
5. Large, well-designed RCTs on BMP for treating other spinal conditions for which efficacy is not well established, eg, spinal stenosis or spondylolisthesis.
6. Future trials should use more clinically relevant and patient targeted outcomes, and economic evaluation should be an integral part of clinical trials of BMP.

Written by Ms Kimberly Garrison, University of East Anglia, United Kingdom

Title **A Randomized Controlled Trial of Postoperative Radiotherapy following Breast-Conserving Surgery in a Minimum-Risk Older Population. The PRIME Trial**

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Reference Health Technol Assess 2007;11(31). Aug 2007. www.hta.ac.uk/execsumm/summ1131.htm

Aim

To assess whether the omission of postoperative radiotherapy in older women with 'low risk', axillary node negative breast cancer (To-2, No-1, Mo) treated by breast conservation with wide local excision and endocrine therapy: a) improves quality of life; b) is more cost effective.

Conclusions and results

The hypothesized overall improvement in quality of life with the omission of radiotherapy was not seen in the EuroQol assessment, or in the functionality and symptoms summary domains of the EORTC scales. Some differences were apparent within subscales of the EORTC questionnaires, and insights into the impact of treatment were also provided by the qualitative data obtained by open-ended questions. Differences were most apparent shortly after the time of completion of radiotherapy. Radiotherapy was then associated with increased breast symptoms and with greater fatigue, but with less insomnia and endocrine side effects. Patients had significant concerns about the delivery of radiotherapy services, eg, transport, accommodation, and travel costs associated with receiving radiotherapy. By the end of followup, patients receiving radiotherapy were expressing less anxiety about recurrence than those who had not received radiotherapy.

Treatment did not greatly affect functionality. In the RCT, the Barthel Index demonstrated a small but significant fall in functionality with radiotherapy compared to no radiotherapy. Results from nonrandomized patients did not confirm this effect. Cosmetic results were better in those not receiving radiotherapy, but patients did not appear to view this as important. Home-based assessments by a research nurse proved to be effective in obtaining high-quality data.

Costs to the NHS associated with postoperative radiotherapy were calculated at around GBP 2000 per patient. Followup in this study yielded no recurrences, and the quality-of-life utilities from EuroQol were almost identical. Hence, within this time frame, no radiotherapy is the cost-effective choice. In the longer term, cost effectiveness will depend on recurrence rates in patients not receiving radiotherapy and the effect of recurrence on their quality adjusted life years.

Recommendations

Although there are no global differences in quality-of-life scores between the treatment groups, several dimensions exhibit significant differences. Over the first 15 months, radiotherapy for this population is not cost effective. However, the early postoperative outcome does not give a complete answer, and the eventual cost effectiveness will only become clear after long-term followup. Extrapolations suggest that radiotherapy may not be cost effective unless it results in a recurrence rate at least 5% lower in absolute terms.

Methods

See Executive Summary link above.

Further research/reviews required

1. Obtain long-term data on quality of life and clinical outcomes in PRIME or similar trials.
2. Economic modeling on the longer term costs and consequences of omitting radiotherapy.
3. Use of novel methodologies (eg, touch-screen technology) in capturing and grading comorbidity and quality of life at baseline and at clinical followup.
4. Investigate the influence of specific types and degrees of comorbid disease on quality of life.
5. Refine methodologies to integrate the prediction of recurrence rates from breast cancer with the competing effects of mortality from other diseases to improve clinical decision making.
6. Develop a validated questionnaire/scale to assess the impact of access to healthcare services.

Written by Professor Robin Prescott, University of Edinburgh, United Kingdom

Title **Current Practice, Accuracy, Effectiveness and Cost Effectiveness of the School Entry Hearing Screen**

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Reference Health Technol Assess 2007;11(32). August 2007.
www.hta.ac.uk/execsumm/summ1132.htm

Aim

1) What is current practice for the school entry hearing screen (SES) in the UK? 2) What is known about the accuracy of alternative screening tests and the effectiveness of interventions? 3) What is known about costs, and what is the likely cost effectiveness of the SES?

Conclusions and results

1. a) SES is in place in most areas of the UK, b) coverage varies, but is often >90% for children in state schools, c) referral rates vary, with a median of 8%, d) the test used for the screen is the pure tone sweep test but with wide variation in implementation, e) there is no national approach to data collection, audit, and quality assurance, f) screening takes place in non-ideal conditions.

2. a) the prevalence of permanent hearing loss continues to increase through infancy, b) of the 3.47/1000 children with a permanent hearing impairment at school screen age, 1.89/1000 required identification after the newborn screen, c) introducing newborn hearing screening is likely to reduce significantly the yield of SES for permanent bilateral and unilateral hearing impairments, d) just under 20% of permanent moderate or greater bilateral, mild bilateral, and unilateral impairments, remained to be identified at school entry.

3. a) no good-quality, published, comparative trials of alternative screens or tests for school entry hearing screening were identified, b) studies of the relative accuracy of alternative tests are difficult to compare and flawed by differing referral criteria and case definitions; the pure tone sweep test appears to have high sensitivity and specificity for minimal, mild, and greater hearing impairments, better than alternative tests for which evidence was identified, c) evidence is insufficient to draw conclusions on possible harm of the screen, d) no published studies were identified on the possible effects of SES on longer term outcomes.

4. a) no good-quality, published, economic evaluations of school entry screening were identified, b) a screen based on pure tone sweep tests was associated with higher costs and slightly higher QALYs when compared to no screen and to other screen alternatives; the incremental cost-effectiveness ratio (ICER) is around GBP 2500 per QALY gained; the range of expected costs, QALYs and net benefits indicated a considerable degree of uncertainty, c) targeted screening could be more cost effective than universal screening, d) lack of primary data and the wide limits for variables in the modeling mean that any conclusions must be considered indicative and exploratory only.

A national screening program for permanent hearing impairment at school entry meets all but 3 of the criteria for a screening program, but at least 6 criteria are not met for screening for temporary hearing impairment.

Recommendations

The lack of a good quality evidence base to drive change in this area remains a serious problem.

Methods

See Executive Summary link above.

Further research/reviews required

Evaluate an agreed national protocol to enable future comparisons; develop systems to monitor data and QA; confirm prevalence of permanent mild and unilateral hearing impairment in preschoolers; compare options to the screen; conduct prospective controlled studies of effect of the screen on longer term outcomes; characterize the distribution of detection thresholds in the school entry population.

Written by Professor John Michael Bamford, University of Manchester, United Kingdom

Title **HPV Vaccination for the Prevention of Cervical Cancer in Belgium: Health Technology Assessment**

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Reference Report no 64C, 2007

Aim

To provide an updated assessment of current (October 2007) human papillomavirus (HPV) vaccines, with the long-term aim to prevent cervical cancer.

Conclusions and results

HPV vaccination offers partial protection for cervical cancer and can help reduce the number of cervical cases in the future, provided that cervical cancer screening remains at least at current levels. A reduction in screening coverage, due to a false sense of protection by vaccination, might jeopardize any gains due to vaccination and could lead to more cervical cancer cases in the future.

Recommendations

Initially, keep screening at least at current levels, and try to organize screening better. Additionally, a vaccination program for girls at ages preceding sexual initiation (eg, 12 years of age) might be considered. Better organization of screening in Belgium might partly free the budget to cover this vaccination program.

Methods

Economic modeling, cost-effectiveness literature, and literature and information from regulatory authorities were used to assess efficacy and safety.

Further research/reviews required

None.

Written by Thiry N, Lambert M-L, Cleemput I, Huybrechts M, Neyt M, Hulstaert F, and De Laet C, KCE, Belgium

Title **Drug Eluting Stents in Belgium: Health Technology Assessment**

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Reference Report no 66C, 2007

Aim

To summarize current clinical evidence supporting the use of drug eluting stents in treating coronary heart disease.

Conclusions and results

There is no evidence that drug eluting stents (DES) compared to bare metal stents (BMS) reduce the risk of myocardial infarction (MI) or death. In absolute numbers, only a small proportion of patients will suffer from restenosis after stenting with either BMS or DES, and BMS are quite successful in avoiding restenosis. The health benefit from avoiding restenosis is small and lasts for only a short time. Hence, the possible gain expressed as quality adjusted life years (QALYs) is low in absolute numbers when comparing DES to BMS. The combination of a substantial price difference between DES and BMS, with a low QALY gain for a small number of people leads to very high incremental cost effectiveness ratios (ICERs).

Recommendations

Readjusting the health insurance reimbursement price of DES toward the reimbursement levels of BMS should be considered.

Methods

The cost effectiveness of drug eluting stents compared to bare metal stents was assessed by systematically reviewing the literature and constructing an economic model, incorporating Belgian clinical and cost data retrieved from a nationwide comprehensive registry in 2004.

Further research/reviews required

None.

Written by Mattias Neyt, KCE, Belgium

Title **Continuous Renal Replacement Therapy in Adult Patients with Acute Renal Failure: Systematic Review and Economic Evaluation**

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Reference Technology report no 88, 2007

Aim

To conduct a systematic review of the efficacy and harm of continuous renal replacement therapy (CRRT) and intermittent hemodialysis (IHD); and to conduct an economic evaluation and budget impact analysis comparing these strategies in critically ill adult patients with acute renal failure (ARF).

Conclusions and results

Compared to IHD, observed differences in clinical outcomes after CRRT (dialysis dependence at study end, number of hospitalization days) were not statistically significant, but had wide confidence intervals, suggesting that meaningful clinical differences could exist. Available evidence suggests similar rates of mortality between modalities. Given current CRRT usage rates of 26% to 68%, selectively funding IHD when either technology is appropriate would save 2.1 million to 6.1 million Canadian dollars (CAD) in acute care costs. If no improvements in clinical outcomes are obtained with CRRT, its use leads to equal QALYs and an additional cost of 3679 CAD compared with IHD. If IHD leads to reduced mortality, it produces 0.07 QALYs and additional costs of 8541 CAD per patient largely due to the additional downstream costs of more long-term dialysis.

Recommendations

Not applicable.

Methods

We conducted a systematic review of the clinical literature, selecting for review 13 RCTs and large (n≥100) controlled trials comparing CRRT with IHD. We also identified 3 trials comparing the submodalities of IHD and 10 trials comparing the submodalities of CRRT. A cost-utility analysis was conducted from the perspective of a Canadian third-party payer. A Markov model followed a theoretical cohort of Canadian patients for a lifetime.

Further research/reviews required

The cost effectiveness of CRRT should be revisited if future studies suggest that it leads to better clinical outcomes, especially a reduced risk of dialysis dependence among survivors.

Written by Tonelli M, Manns B, Wiebe N, Shrive F, Pannu N, Doig C, and Klarenbach S, CADTH, Canada

Title **Prostaglandin Analogues for Ophthalmic Use: Analysis of Clinical and Cost Effectiveness**

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Reference Technology report no 89, 2007

Aim

To perform a systematic review and economic evaluation of prostaglandin analogues (PGAs) in treating increased intraocular pressure (IOP), using evidence from published and unpublished randomized controlled trials (RCTs).

Conclusions and results

Not all PGAs are the same. Evidence shows that latanoprost and travoprost reduce IOP more effectively than timolol. The same evidence does not exist for bimatoprost. Timolol that is used as a first-line option could represent an optimal use of scarce resources. For appropriate patients, it would be preferable, from a cost-effectiveness standpoint, to start treatment with timolol and reserve the PGAs as an alternative treatment or as add-on therapy for patients not achieving a clinical response with timolol. Compared to dorzolamide, latanoprost is more effective and less costly. Compared to brimonidine, latanoprost is associated with additional costs, at a lower cost per mm Hg reduced. There is no evidence that greater reductions in IOP translate into reductions in visits to a physician or surgical procedures, or an increase in health-related quality of life.

Recommendations

None given.

Methods

A systematic review the clinical literature included 22 RCTs comparing PGAs to alternative therapy in individuals >18 years old with elevated IOP who were treatment-naïve or who experienced appropriate washout before treatment. The cost-effectiveness analysis used the perspective of Canadian ministries of health. A decision-analytic model using a 3-month time horizon calculated the associated costs and consequences of using latanoprost versus timolol, dorzolamide, and brimonidine; and travoprost versus timolol.

Further research/reviews required

Long-term studies are needed.

Written by Hodge WG, Lachaine J, Steffensen I, Murray C, Barnes D, Foerster V, Ducruet T, and Morrison A, CADTH, Canada

Title **Laparoscopic Adjustable Gastric Banding for Weight Loss in Obese Adults: Clinical and Economic Review**

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Reference Technology report no 90, 2007

Aim

To investigate the evidence on the clinical effectiveness and cost effectiveness of laparoscopic adjustable gastric banding (LAGB) as compared to open and laparoscopic Roux-en-Y gastric bypass (RYGB), open and laparoscopic vertical banded gastroplasty (VBG), lifestyle modification, or control groups.

Conclusions and results

Economic research suggests that investment in LAGB may lower the total future healthcare costs by lowering the severity and incidence of obesity-related comorbidities and associated costs. These calculations must consider the initial set-up costs, long-term costs, and costs of surgeons' learning curves. LAGB is shown to produce a significant loss of excess weight while maintaining low rates of short-term complications and reducing obesity-related comorbidities. LAGB may not result in the most weight loss, but it may be an option for bariatric patients who prefer, or who are better suited, to undergo less invasive and reversible surgery with lower perioperative complication rates.

Recommendations

If LAGB is to become a universal benefit, the proper infrastructure (eg, operating rooms, hospital beds, outpatient clinics) must be in place. Training programs are needed to ensure that bariatric surgeons are fully trained to perform surgery, treat the postoperative complications that may arise (eg, band erosion), and perform the surgical conversion that may be required if a patient does not achieve the weight-loss goal.

Methods

Published systematic reviews, health technology assessments, trials (including primary research), and economic studies were obtained by cross-searching online databases. A parallel search was performed on the Cochrane Library (Issue 1, 2007) database. The websites of regulatory agencies, health technology assessment agencies, and related agencies were searched, as were specialized databases. Two external reviewers commented on this report.

Further research/reviews required

Findings from long-term research may become available, permitting adequate assessment of the long-term implications of LAGB as a surgery option on its own and in comparison to other surgeries such as LRYGB.

Written by Boudreau R and Hodgson A, CADTH, Canada

Title **Atypical Antipsychotic Monotherapy for Schizophrenia: Clinical Review and Economic Evaluation of First Year of Treatment**

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Reference Technology report no 91, 2007

Aim

To evaluate the clinical effectiveness of the 4 atypical antipsychotics (AAPs) commercially available in Canada (risperidone, olanzapine, quetiapine, and clozapine), and to evaluate the economic implications of each when used in maintenance treatment of schizophrenia and related psychoses (eg, schizophreniform, delusional, and schizoaffective disorders).

Conclusions and results

The evidence suggests that, compared with risperidone, olanzapine is associated with a lower risk of relapse and of treatment discontinuation, but is less well tolerated. Evidence also shows that clozapine use reduces suicide risk in high-risk patients, compared with olanzapine. Generic and brand-name olanzapine will require a larger investment by drug plans than quetiapine and risperidone. These costs are offset by reduced downstream costs from hospitalization, the largest cost component for treating patients with schizophrenia. The lack of high-quality evidence to inform first-line therapy reimbursement decisions suggests that additional analysis should be undertaken when comparative effectiveness studies are available. The costs associated with polytherapy, long-term treatment, and the role of traditional antipsychotics should be considered.

Recommendations

Not applicable.

Methods

We appraised and summarized the findings from a drug class review on AAPs. A systematic review of economic evaluations was conducted, with a cost analysis from the perspective of a Canadian third-party payer. A deterministic decision tree followed a theoretical cohort of recently diagnosed and already treated patients for 12 months, using observational data from a Canadian setting, and results from the clinical review.

Further research/reviews required

The analysis presented in this study should be replicated when additional comparative effectiveness data are available on patients with a first episode of schizophrenia.

Written by Farahati F, Boucher M, Moulton K, Williams R, Herrmann N, Silverman M, and Skidmore B, CADTH, Canada

Title **Long-Acting Insulin Analogues for Diabetes Mellitus: Meta-Analysis of Clinical Outcomes and Assessment of Cost Effectiveness**

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Reference Technology report no 92, 2007

Aim

To evaluate the clinical efficacy and economic implications of long-acting insulin analogues (LAIAs), specifically insulin glargine (IGlar) and insulin detemir (IDet), in treating diabetes mellitus (DM).

Conclusions and results

The evidence suggests that LAIAs have not demonstrated clinically important differences in glycated hemoglobin, a widely used marker of blood sugar control in types 1 and 2 DM. Evidence also suggests IGlar can reduce the risk of severe hypoglycemia in type 1 DM patients taking human insulin. IGlar reduced the risk of nocturnal, but not severe, hypoglycemia in type 2 DM patients. IDet has demonstrated a reduced risk of severe and nocturnal hypoglycemia in type 1 DM. No reductions in complications with IDet were observed in patients with type 2 DM. Publicly funding LAIAs will require significant additional investment. Economic arguments for this investment are limited, largely because they are based on unproven assumptions about the long-term benefit of therapy.

Methods

A systematic review and a meta-analysis were undertaken to evaluate the clinical and economic implications of using long-acting analogues in treating DM, relative to human insulin and to oral antidiabetic agents. Meta-analysis was performed using trials that completely reported data. The budget impact to publicly funded provincial drug plans was also examined.

Further research/reviews required

Long-term comparative studies of high quality are needed to definitively determine the benefit and harm of long-acting insulin analogues compared with conventional insulins.

Written by Tran K, Banerjee S, Li H, Cimon K, Daneman D, Simpson SH, and Campbell K, CADTH, Canada

Title **Effectiveness of Magnetic Resonance Imaging (MRI) Screening for Women at High Risk of Breast Cancer**

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Reference Technology report no 93, 2007

Aim

To determine the clinical and cost effectiveness of MRI screening compared to film mammography in women with a high risk of breast cancer. A secondary aim is to determine the strength of evidence used to support the American Cancer Society's guidelines regarding MRI screening for woman at high risk of breast cancer.

Conclusions and results

Cost-effectiveness studies suggest that MRI for breast cancer screening could be cost effective, depending on the willingness to pay and the value attributed to one QALY. Overall, MRI has a higher sensitivity for breast cancer screening compared to mammography. In addition, the number of cancers detected by MRI alone was higher than that detected by mammography alone, although MRI also missed some cancers. These results indicate that some breast cancers would have been missed with mammography screening alone, and the addition of MRI resulted in more cancers being detected. High-risk women, eg, those with BRCA1/2 mutations, those having a first-degree relative with a mutation, or those with a strong family history of breast cancer, seem to benefit most from adding MRI to the screening modality.

The rigor of development of the American Cancer Society's guidelines was found to be low, because the inclusion and exclusion criteria, the external review process, and the process for updating the guidelines were not reported. Editorial independence from the funding body and conflicts of interest were not reported, making the editorial independence score zero. The clarity and presentation were well done, because the recommendations were specific and easily identifiable.

Methods

Published literature was obtained by cross-searching online databases. Health technology assessments, meta-analysis, systematic reviews, clinical studies, clinical guidelines, observational studies, and economic studies were retrieved. The websites of regulatory agencies, health technology assessment agencies, and related agencies were searched, as were specialized databases.

Using the AGREE instrument (Appraisal of Guidelines Research and Evaluation), two independent reviewers assessed the quality of the American Cancer Society's guidelines.

Further research/reviews required

There is a lack of high-level evidence regarding the effectiveness of MRI screening for breast cancer detection. Randomized controlled trials would aid in the evaluation of MRI screening and would provide better evidence for clinical and cost effectiveness.

Written by Dunfield L and Severn M, CADTH, Canada

Title **Comparative Overview of Cancer Control Strategies in Selected Jurisdictions**

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Reference 2007-08. ISBN 978-2-550-50997-4 (print).
www.aetmis.gouv.qc.ca/site/en_publications_2007.phtml

Aim

To provide better knowledge of the choices made by different public administrations regarding priorities, governance models, service organization, quality, and factors of success for implementing change.

Conclusions and results

Although priorities differ, the initiatives recommended in the current strategies overlap and have two main cancer-control objectives: to ensure the ability of the healthcare system to deal with a growing demand for services and to ensure an optimal care pathway for known and suspected cancer patients. We find wide diversity in the means of implementation used, whether for service organization, the governance model, or levers of change.

Two underlying philosophies are identified, depending on whether or not a disease management approach has been developed. While all of the countries and provinces embrace better service integration through oncology networks and programs, the organizational configurations are characterized by the more or less extensive use of dedicated structures and infrastructures to meet quality requirements and the need to coordinate services.

As regards governance, we distinguish 3 approaches according to the degree of authority sharing and the degree to which responsibilities are assigned to central cancer control organizations by the Ministry of Health: 1) authority delegated to one agency (Alberta, British Columbia, Ontario); 2) authority shared with separate dedicated organizations (France, England); and 3) authority distributed within the ministry, which comprises a dedicated ministerial organization (Québec, Nova Scotia).

The variable progress observed in organizational reforms may depend on the complexity of the recommended changes and the coexistence of more global healthcare system reforms, but especially on the levers of change made available. Yet, all countries and provinces are not at the same level in terms of the availability of these levers. Five lessons are drawn from analyzing the main findings: 1) adopt a tailored approach specific to the particular context of a given healthcare system to configure the organizational means required to ensure an optimal patient pathway in that system; 2) obtain a clear commitment from the highest government authorities, an essential condition for implementing a strategy; 3) assess the applicability of an "effective solution" from another country or region to the specific context of the healthcare system before implementing it; 4) go beyond the dichotomous view of "ministry or agency?" to define the conditions for functional governance in which the organizations responsible have sufficient authority and adequate means to carry out their mandates and coordinate to implement change; and 5) bring together all the critical levers – accountability and performance management systems, including evaluation and information gathering/management mechanisms – to ensure the implementation of service organization reforms.

Methods

Comparative overview of cancer control strategies (and programs) in selected countries and Canadian provinces (ie, England, France, Alberta, British Columbia, Nova Scotia, Ontario, and Québec). Detailed search of the gray literature and interviews with key informants.

Written by Lorraine Caron, with the collaboration of
Mirella De Civita, Susan Law, and Isabelle Brault, AETMIS, Canada

INAHTA Briefs

Issue 2007/134

Title **The Practice of Percutaneous Coronary Interventions in Hospitals Without On-Site Cardiac Surgery: Review of Guidelines and Analysis of Quebec Data, 1999–2004**

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Reference 2007-09. ISBN 978-2-550-51310-0. www.aetmis.gouv.qc.ca/site/en_publications_2007.phtml

Aim

To examine the advisability and safety of performing percutaneous coronary intervention at facilities without on-site cardiac surgical support.

Conclusions and results

Percutaneous coronary intervention (PCI) is generally performed in catheterization laboratories in hospitals with on-site cardiac surgery. However, there have been pressures worldwide to perform PCI at facilities without on-site cardiac surgical support. Québec currently has 5 such centers.

This assessment is based on a review of the most recent guidelines and on an analysis of Québec medico-administrative data for PCIs performed from 1999 to 2004. In general, the guidelines urge caution in creating PCI centers without on-site surgical support and stress the need for mentorship by established tertiary cardiology centers, for high institutional and operator volume, for clear protocols on rapid patient transfer when emergency cardiac surgery is required, and for continuous clinical outcome monitoring.

The evidence indicates that clinical outcomes may be slightly less favorable in patients who undergo PCI at centers without on-site cardiac surgery, even in highly controlled conditions with rigorous selection of low-risk patients. The same observation emerges from the analysis of PCI outcomes in Québec, using a first PCI as the index event. Although these results should be considered preliminary, the risk of 1-year, all-cause mortality appears to be significantly higher at centers without on-site cardiac surgery. The relative and absolute increases in this risk are estimated at 29% and 1.4%, respectively, compared to the risk observed in centers with on-site cardiac surgery.

Although opening PCI centers without on-site surgery might be considered as a means to offer primary PCI more widely across Québec to patients with ST-segment elevation myocardial infarction (STEMI) and to treat them more rapidly, two factors temper this rationale: 1) primary PCI accounts for less than one fourth of all PCIs; 2) fibrinolytic therapy is a well-accepted alternative for treating patients with STEMI and is readily available throughout Québec in any healthcare center equipped with an emergency room.

This report highlights the uncertainty regarding the advantages of performing PCI in centers without on-site surgery and leads AETMIS to advise caution in response to the demand to create and expand such centers. Given the considerable resources required to perform PCI and achieve its benefits, and the risks associated with invasive interventions, this assessment emphasizes the importance of interhospital collaboration, the establishment of clear protocols, and commitment to quality-of-care conditions. The report also stresses the need for a high-quality data registry and the monitoring of performance to ensure the most favorable outcomes and optimal allocation of resources.

Methods

Review of international and Canadian practice guidelines and analysis of Québec medico-administrative data; literature search in G-I-N, MEDLINE, the Cochrane Library 2007, Issue 2, HTA Database for primary studies and other scientific documents; review of the grey literature on the Internet and in governmental and corporate websites.

Written by Laurie Lambert, Peter Bogaty, James Brophy, and Lucy J Boothroyd, AETMIS, Canada

Title **Interferon Alfa (Pegylated and Non-Pegylated) and Ribavirin for the Treatment of Mild Chronic Hepatitis C: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2007;11(11). April 2007. www.hta.ac.uk/execsumm/summ1111.htm

Aim

To assess the clinical and cost effectiveness of pegylated interferon alfa (PEG) and nonpegylated interferon alfa (IFN) and ribavirin (RBV) in treating adults with histologically mild chronic hepatitis C infection.

Conclusions and results

Eight randomized controlled trials (RCTs) of antiviral treatment in mild hepatitis C virus (HCV) were identified and included. The RCTs were generally of good quality, and the results suggested that effectiveness (particularly with respect to sustained virological response) was similar in patients with mild disease to the results obtained in patients with moderate/severe disease. This finding was supported by a set of 11 RCTs of patients with mild/moderate/severe HCV which reported the results for mild HCV subgroups. The authors' cost-effectiveness analysis showed that early treatment compared with watchful waiting is associated with quality-adjusted life-year (QALY) gains, but with increased treatment costs. Base-case incremental costs per QALY for 48 weeks of treatment are: watchful waiting with IFN + RBV versus best supportive care (GBP 3097–6585); early treatment with IFN + RBV versus watchful waiting with IFN + RBV (GBP 5043–8092); watchful waiting with PEG 2a + RBV versus best supportive care (GBP 3052); early treatment with PEG 2a + RBV versus watchful waiting with PEG 2a + RBV (GBP 5900); watchful waiting with PEG 2b + RBV versus best supportive care (GBP 2534); and early treatment with PEG 2b + RBV versus watchful waiting with PEG 2b + RBV (GBP 5774). These results were consistent with previous assessments.

Recommendations

This systematic review and economic evaluation show that patients with histologically mild HCV can be successfully treated with both pegylated and nonpegylated interferon alfa. Early treatment and watchful waiting strategies are associated with acceptable cost-per-QALY estimates. Research needs to be directed toward newer, potentially more effective interventions, particularly those that improve treatment response in patients with genotype 1, with minimal adverse effects.

Methods

A systematic review and an economic evaluation were conducted. A sensitive search strategy was designed and applied to several electronic bibliographic databases up to July 2005. Manufacturer and sponsor submissions to NICE were searched. The trials were reviewed in a narrative synthesis, but meta-analysis was not undertaken due to heterogeneity in the interventions and comparators evaluated. A Markov state transition model was developed to estimate the cost effectiveness of treatment strategies for adults with mild chronic HCV, from the perspective of the NHS and personal social services. The model includes 8 health states through which a cohort of patients pass at different rates. A lifetime horizon was employed (1-year cycle). Published quality of life weights were taken from a UK RCT to derive QALYs. Transition rates through the health states were estimated from the literature. Costs and resources were estimated from published literature and clinical opinion. The cost year was 2003/2004. Costs were discounted at 6% and benefits at 1.5%. Uncertainty in assumptions and parameters was investigated through probabilistic and deterministic sensitivity analyses.

Further research/reviews required

Further research is required: on the natural history of HCV (to estimate better the rate of liver disease progression); and on the effectiveness of noninvasive biochemical markers of liver disease (as an alternative to liver biopsy).

Written by Mr Jonathan Shepherd, SHTAC, United Kingdom

Title **Systematic Review and Economic Evaluation of Bevacizumab and Cetuximab for the Treatment of Metastatic Colorectal Cancer**

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Reference Health Technol Assess 2007;11(12). April 2007.
www.hta.ac.uk/execsumm/summ1112.htm

Aim

To assess the clinical and cost effectiveness of bevacizumab and cetuximab in treating metastatic colorectal cancer (CRC).

Conclusions and results

Adding bevacizumab to irinotecan in combination with 5-FU/folic acid (FA) + irinotecan resulted in a statistically significant increase in median overall survival (OS) of 4.7 months. Adding bevacizumab to 5-FU/FA resulted in a nonsignificant increase in median OS of 3.7 months in one study and 7.7 months in another. Adding bevacizumab to irinotecan, fluorouracil, and leucovorin (IFL) resulted in a statistically significant increase in median progression-free survival (PFS) of 4.4 months. Adding bevacizumab to 5-FU/FA resulted in a statistically significant increase in median PFS of 3.7 months, and a statistically significant increase in time to disease progression of 3.8 months. An overall tumor response rate of 44.8% was reported for bevacizumab + IFL compared to 34.8% for IFL + placebo. This improvement in tumor response was statistically significant. Adding bevacizumab to 5-FU/FA resulted in a significant difference in tumor response rate in one study, but not another. Bevacizumab combined with IFL or 5-FU/FA resulted in an increase of grade 3/4 adverse events. Economic assessment suggests that the cost effectiveness of bevacizumab + IFL is unlikely to be better than GBP 46 853 per life-year gained (LYG); the cost-utility of bevacizumab + IFL is unlikely to be better than GBP 62 857 per quality-adjusted life-year (QALY) gained. The cost effectiveness of bevacizumab + 5-FU/FA versus 5-FU/FA is unlikely to be better than GBP 84 607 per LYG; the cost-utility of bevacizumab + 5-FU/FA versus 5-FU/FA is unlikely to be better than GBP 88 658 per QALY gained.

No trials met the inclusion criteria for the systematic review of cetuximab. A Phase II trial reported a median OS duration of 8.6 months for patients receiving cetuximab + irinotecan, and suggested that treatment with cetuximab combined with irinotecan is associated with significantly more adverse events than cetuximab monotherapy. A single arm study of cetuximab + irinotecan reported a median OS duration of 8.4 months, a median time to progression of 2.9 months and a tumor response rate of 15.2%. The cost-effectiveness model suggested that the expected survival duration of patients receiving cetuximab + irinotecan is 0.79 years. For cetuximab + irinotecan to achieve a cost-utility ratio of GBP 30 000 per QALY gained, treatment must provide an additional 0.65 life years over treatment with active/best supportive care.

Recommendations

Trials indicate that bevacizumab combined with 5-FU/FA and bevacizumab combined with IFL are clinically effective in comparison with standard chemotherapy options in first-line treatment of metastatic CRC. Economic analysis suggests that the marginal cost-utility of bevacizumab + IFL versus IFL is unlikely to be better than GBP 62 857 per QALY gained, and the marginal cost-utility of bevacizumab + 5-FU/FA versus 5-FU/FA is unlikely to be better than GBP 88 658 per QALY gained. No evidence shows whether cetuximab combined with irinotecan improves health-related quality of life (HRQoL) or OS in comparison with active/best supportive care or oxaliplatin + 5-FU/FA. Indirect comparisons suggest that the incremental cost-utility of cetuximab + irinotecan is unlikely to be better than GBP 30 000 per QALY gained.

Methods

See Executive Summary link above.

Further research/reviews required

Examples of further research needed:

- clarify the true impact of first-line bevacizumab combined with irinotecan and/or infusional 5-FU/FA on OS in patients with metastatic CRC
- study the optimal role of bevacizumab alongside oxaliplatin, irinotecan and 5-FU/FA
- investigate (RCT) the impact of bevacizumab treatment on HRQoL
- study the resource implications associated with bevacizumab
- compare the impact of cetuximab + irinotecan to active/best supportive care

Written by Mr Paul Tappenden, University of Sheffield, United Kingdom

Title **A Systematic Review and Economic Evaluation of Epoetin Alfa, Epoetin Beta, and Darbepoetin Alfa in Anemia Associated with Cancer, Especially that Attributable to Cancer Treatment**

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Reference Health Technol Assess 2007;11(13). April 2007. www.hta.ac.uk/execsumm/summ1113.htm

Aim

To assess the effectiveness and cost effectiveness of epoetin alfa, epoetin beta, and darbepoetin alfa (referred to collectively here as epo) in anemia associated with cancer, especially that attributable to cancer treatment.

Conclusions and results

Forty-six RCTs were included that compared epo + supportive care for anemia with supportive care for anemia alone. Hematological response (HR), defined as an improvement by 2 g dl–1, had a relative risk of 3.4 with a response rate for epo of 53%. Hemoglobin (Hb) change showed a weighted mean difference of 1.63 g dl–1 in favor of epo. Erythropoietin treatment in patients with cancer-induced anemia reduces the number of patients who receive a red blood cell transfusion (RBCT) by an estimated 18%. A positive effect was observed in favor of an improved HRQoL for patients on epo. Published information on side effects was of poor quality. The previous Cochrane review had suggested a survival advantage for epo, HR 0.84 based on 19 RCTs. The update, based on 28 RCTs, suggests no difference. Although it is difficult to draw firm conclusions, the conclusions are broadly in line with those of a Food and Drug Administration (FDA) safety briefing (recommended, eg, that patients with Hb above 12 g dl–1 should not be treated and the target rate of rise in Hb should not be too great). Five economic evaluations from the literature showed inconsistent results, with estimates ranging from a cost per QALY under GBP 10 000 through to epo being less effective and more costly than standard care.

Recommendations

Epo is effective in improving hematological response and RBCT requirements, and appears to have a positive effect on HRQoL. The incidence of side effects and effects on survival remains highly uncertain. If there is no impact on survival, it seems unlikely that epo would be considered a cost-effective use of healthcare resources.

Methods

Using a recently published Cochrane review as the starting point, a systematic review of recent RCTs comparing epo with best standard was conducted. MEDLINE, EMBASE, the Cochrane Library, and other databases were searched from 2000 (1996 in the case of darbepoetin alfa) to September 2004. Inclusion, quality assessment, and data abstraction were undertaken in duplicate. Where possible, meta-analysis was employed. Economic assessment consisted of a systematic review of past evaluations, assessment of economic models submitted by manufacturers of the 3 epo agents, and development of a new individual sampling model (Birmingham epo model).

Further research/reviews required

Further research should focus on improving estimates of impact on survival, starting with more detailed secondary research, eg, the individual patient data meta-analysis started by the Cochrane group. Further trials may be required, eg, as recommended by the FDA. The Birmingham epo model developed as part of this project has features that are not present in previous models. These features improve its flexibility in exploring different scenarios in the future. Research to resolve uncertainty about other parameters, particularly quality of life and adverse events, should be pursued in parallel with attempts to improve evidence on survival. The rate of normalization was also an important parameter in the model for which no published data source was identified. Hence, further research in this area would be beneficial.

Written by Ms Jayne Wilson, University of Birmingham, United Kingdom

Title **A Systematic Review and Economic Evaluation of Statins for the Prevention of Coronary Events**

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Reference Health Technol Assess 2007;11(14). April 2007.
www.hta.ac.uk/execsumm/summ1114.htm

Aim

To evaluate the use of a group of statins, atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin, in preventing cardiovascular events.

Conclusions and results

Thirty-one randomized studies compared a statin with placebo or with another statin, and reported clinical outcomes. Meta-analysis of data from placebo-controlled studies indicates that in patients with, or at risk of, cardiovascular disease (CVD), statin therapy is associated with reduced relative risk of all-cause mortality, cardiovascular mortality, coronary heart disease (CHD) mortality, and fatal myocardial infarction (MI), but not of fatal stroke. It is also associated with reduced relative risk of morbidity and coronary revascularization. On the evidence available from placebo-controlled trials, it is hardly possible to differentiate between the clinical efficacy of atorvastatin, fluvastatin, pravastatin, and simvastatin. Some evidence from direct comparisons between statins suggests that atorvastatin may be more effective than pravastatin in symptomatic CHD, but evidence on effectiveness in different subgroups is limited. Statins are considered to be well tolerated and have a good safety profile. Increases in creatine kinase and myopathy have been reported, but rhabdomyolysis and hepatotoxicity are rare. Some patients may receive lipid-lowering therapy for up to 50 years, but long-term safety is unknown. In secondary prevention of CHD, the incremental cost-effectiveness ratios (ICERs) increase with age, between GBP 10 000 and GBP 17 000 per QALY for ages 45 and 85 respectively. Sensitivity analyses show these results are robust. ICERs vary substantially by age and risk in primary prevention of CHD. The average ICERs weighted by risk range from GBP 20 000 to GBP 27 500 for men and from GBP 21 000 to GBP 57 000 for women. The results are sensitive to the cost of statins, discount rates, and the modeling timeframe. In the CVD analyses, the average ICER weighted by risk level remains below GBP 20 000 at CHD risk levels down to 0.5%. A key limitation of the analyses is the need to extrapolate well beyond the timeframe of the trials.

Recommendations

The evidence suggests that statin therapy is associated with a statistically significant reduction in the risk of primary and secondary cardiovascular events. The generalizability of these results is limited, and the treatment effect may be reduced in an unselected population. Modeling shows that statin therapy in secondary prevention is likely to be cost effective. In primary prevention, the cost-effectiveness ratios depend on the level of CHD risk and age, but results from CVD analyses support the more aggressive treatment recommendation in recent guidelines in UK.

Methods

A review was undertaken to identify and evaluate all literature relating to the clinical and cost effectiveness of the listed statins in the primary and secondary prevention of CHD and CVD in the UK (electronic databases were searched between November 2003 to April 2004). A Markov model was developed to explore the costs and health outcomes associated with a lifetime of statin treatment.

Further research/reviews required

Additional high-quality evidence on quality of life and compliance and continuance for patients on statins is required. Large outcome studies at lower risk thresholds would be useful to determine whether the relative risk reduction figures remain valid at lower risk levels and to determine the extent to which potential disutility due to statins may become an issue as treatment is extended to a vast proportion of the 'well' population. Future service implementation research is important, particularly on effective policies for targeting low-risk populations. Research is needed on the attitudes of low-risk patients and relatively healthy 45-year-olds towards taking lifetime medication, along with research into the optimal methods of explaining risks and benefits of treatment to patients so they can make informed choices.

Written by Ms Sue Ward, University of Sheffield, United Kingdom

Title **Screening for Type 2 Diabetes: Literature Review and Economic Modeling**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
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Reference Health Technol Assess 2007;11(17). May 2007.
www.hta.ac.uk/execsumm/summ1117.htm

Aim

To reconsider the case for screening for undiagnosed type 2 diabetes, eg, by reviewing choice of screening test, examining the cost effectiveness of screening, and considering higher risk groups at which screening might be targeted.

Conclusions and results

The case for screening for undiagnosed type 2 diabetes does not meet all the criteria of the UK National Screening Committee (NSC), but the case is somewhat stronger than it was at the last review, because of more options for reducing cardiovascular disease, principally through the use of statins, and because of the rising prevalence of overweight and hence type 2 diabetes.

Detecting lesser degrees of glucose intolerance such as impaired glucose tolerance (IGT) is worthwhile, partly because the risk of cardiovascular disease (CVD) can be reduced by treatment to reduce cholesterol levels and blood pressure, and because some diabetes can be prevented. Several trials show that lifestyle measures and pharmacological treatment can reduce the proportion of people with IGT who would otherwise develop diabetes. Screening could be two-stage, starting with the selection of people at higher risk. The second-stage choice of test for blood glucose remains a problem. The best test is the oral glucose tolerance test (OGTT), but it is expensive, inconvenient, and has weak reproducibility. Fasting plasma glucose would miss people with IGT. Glycated hemoglobin does not require fasting, and may be the best compromise. More people might be tested and diagnosed by using the more convenient test, rather than the OGTT. Five economic studies assessed the costs and short-term outcomes of different screening tests, but did not show which test would be best. The choice of cut-off would be a compromise between sensitivity and specificity. Modeling suggests that diabetes screening is cost effective for the 40 to 70 year age band, more so for the older age bands. But even in the group aged 40 through 49 years, the ICER for screening versus no screening is only GBP 10 216 per QALY. Screening is more cost effective for people in the hypertensive and obese subgroups. Although the prevalence of diabetes increases with age, the relative risk of CVD falls, reducing the benefits of screening. Screening for diabetes meets most of the NSC criteria, but fails on three. The issue here is whether all methods of improving lifestyles to reduce obesity and increase exercise have been sufficiently tried. The rise in overweight and obesity suggests that health promotion interventions have not so far been effective.

Methods

See Executive Summary link above.

Further research/reviews required

A key uncertainty concerns the duration of undiagnosed diabetes, and whether the rise in blood glucose levels is linear throughout, or whether a slower initial phase may be followed by acceleration around the time of clinical diagnosis. This has implications for the screening interval. Another uncertainty is the natural history of IGT and what determines progression to diabetes. Other research needs include;

- ways to reduce the prevalence of insulin resistance. What forms and amounts of exercise are required to prevent or reduce insulin resistance?
- How can public health campaigns on lifestyle be more effective? Most cases of type 2 diabetes are preventable. What balance should be struck between the public health, prevention by lifestyle approach, and the more medical model of care focused on the individual?
- If screening were to be introduced, should it be repeated, and, if so, at what interval?

A randomized controlled trial of the type required by NSC criterion 13 is under way, but will not report for about 5 years.

Written by Professor Norman Waugh, University of Aberdeen, United Kingdom

INAHTA Briefs

Issue 2007/140

Title **The Effectiveness and Cost Effectiveness of Cinacalcet for Secondary Hyperparathyroidism in End-Stage Renal Disease Patients on Dialysis: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2007;11(18). May 2007. www.hta.ac.uk/execsumm/summ1118.htm

Aim

To establish the effectiveness and cost effectiveness of cinacalcet in treating secondary hyperparathyroidism (SHPT) for people on dialysis due to end-stage renal disease (ESRD).

Conclusions and results

The systematic review included 7 trials comparing cinacalcet plus standard treatment with placebo plus standard treatment (846 people were randomized to receive cinacalcet). Cinacalcet was more effective at meeting parathyroid hormone (PTH) target levels (40% vs 5% in placebo, p<0.001). In those patients meeting PTH targets, 90% also experienced a reduction in calcium–phosphate product levels, compared to 1% in placebo. Significantly fewer people treated with cinacalcet were hospitalized for cardiovascular events, but no difference was seen in all-cause hospitalization or mortality. Significantly fewer fractures and parathyroidectomies were also seen with cinacalcet. Findings on all patient-based clinical outcomes were based on small numbers. The authors' economic model estimated that, compared to standard treatment alone, cinacalcet in addition to standard care costs an additional GBP 21 167 and confers 0.34 QALYs (or 18 quality-adjusted weeks) per person. The incremental cost-effectiveness ratio (ICER) was GBP 61 890/QALY. In most cases, even extreme adjustments to individual parameters did not result in an ICER below a willingness-to-pay threshold of GBP 30 000/QALY with probabilistic analysis showing only 0.5% of simulations to be cost effective at this threshold. Altering the assumptions in the model by changing the input data sources yielded an ICER range from GBP 39 000 to GBP 92 000/QALY.

Recommendations

Cinacalcet plus standard care is more effective than placebo plus standard care at reducing PTH levels without compromising calcium levels. However, information is limited about the impact of this reduction on patient-relevant clinical outcomes. It is unclear how data should be extrapolated to the long term. This, plus the high drug cost, means that cinacalcet is unlikely to be considered cost effective.

Methods

Electronic databases were searched for relevant literature on the clinical effectiveness of cinacalcet for SHPT in ESRD. Searches were updated in February 2006. Randomized controlled trials were critically appraised for internal and external validity. Relevant data were extracted and a narrative synthesis was carried out.

Electronic databases were searched for relevant literature on the cost effectiveness of cinacalcet for SHPT in ESRD. No studies were identified. Amgen (manufacturer of cinacalcet) submitted an economic evaluation to the National Institute for Health and Clinical Excellence. This was critically appraised and compared with the authors' economic evaluation.

The authors developed a Markov model to compare cinacalcet plus standard treatment with phosphate binders and vitamin D versus standard treatment alone. Incremental costs and quality-adjusted life-years (QALYs) were calculated. Extensive one-way sensitivity analysis and probabilistic sensitivity analysis were undertaken.

Further research/reviews required

Accurate estimates of the multivariate relationship between biochemical disruption in SHPT and long-term clinical outcomes are of paramount importance to model the effectiveness of cinacalcet, or other similar agents. Longer term studies of the maintenance of PTH control in SHPT and of the clinical impact with cinacalcet should examine its impact in subgroups based on age and diabetes. A better understanding of the epidemiology of fractures in SHPT is needed. The impact of fracture, cardiovascular events and uncontrolled PTH levels on quality of life in people with SHPT should be investigated.

Written by Ms Ruth Garside, Peninsula Technology Assessment Group, Peninsula Medical School, United Kingdom

INAHTA Briefs

Issue 2007/141

Title **The Clinical Effectiveness and Cost Effectiveness of Gemcitabine for Metastatic Breast Cancer: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2007;11(19). May 2007.
www.hta.ac.uk/execsumm/summ1119.htm

Aim

To assess the clinical and cost effectiveness of gemcitabine used in combination with paclitaxel as second-line treatment for people with metastatic breast cancer who have relapsed following treatment with anthracycline-based chemotherapy.

Conclusions and results

The systematic review identified one RCT where data were available only in 3 conference abstracts. The methodological quality and quality of reporting of the trial were assessed to be poor, but this may be due to the lack of information in the limited publications rather than being a fair reflection of the trial's quality. This RCT compared gemcitabine and paclitaxel therapy with paclitaxel monotherapy in 529 patients with metastatic breast cancer who had previously received anthracyclines, but no prior chemotherapy for metastatic breast cancer.

Survival at 1 year was statistically significantly better in the gemcitabine/paclitaxel (G/P) group than the paclitaxel group. Approximately 71% of the G/P patients survived for 1 year, versus 61% of the paclitaxel group. The hazard ratio showed a 26% lower chance of survival in the paclitaxel group, and time to progressive disease was also shorter in this group. The overall response rate was higher in the G/P group than in the paclitaxel group. Adverse events, particularly neutropenia, were more common with G/P combination therapy than with paclitaxel therapy alone.

The economic model developed for this review was run for a simulation of 1000 patients, assuming that chemotherapy continued until patients' disease progressed. This base-case analysis found an ICER of GBP 58 876 per QALY gained and GBP 30 117 per life-year gained. In normal practice, patients are likely to receive chemotherapy for a fixed number of cycles, rather than until disease progression. Hence, the model was re-run with treatment restricted to 6 cycles (maximum) per patient, yielding an ICER of GBP 38 699 per QALY gained and GBP 20 021 per life-year gained.

Recommendations

We can draw only tentative conclusions since our review of clinical effectiveness is based on data from a single RCT, which has not yet been fully published. Evidence from the RCT may indicate that treatment with gemcitabine and paclitaxel improves outcome for patients in terms of survival and disease progression, but at the cost of increased toxicity. An economic model developed for this review reflects high costs per QALY for this treatment combination. The base-case analysis shows high ICERs, with costs per QALY gained close to GBP 60 000. Limiting chemotherapy to 6 cycles (max) gives a more favorable cost-effectiveness estimate, but still exceeds the amount usually considered as a cost-effective treatment from an NHS perspective.

Methods

The literature was systematically reviewed, and a model was developed for economic evaluation. Electronic databases were searched from inception to March 2006 and reference lists from retrieved papers were checked for further publications. Clinical advisers were asked about additional studies. Standard criteria developed by the Centre for Reviews and Dissemination were used to assess the quality of RCTs. Study reports were tabulated and synthesized in a narrative summary. A Markov state transition model was developed to estimate the cost effectiveness of gemcitabine with paclitaxel for patients with metastatic breast cancer. The model consisted of 4 states (responsive, stable disease, progressive disease, and death) and applied transition probabilities. Sensitivity analyses were carried out to estimate the effect of treating for a maximum of 6 cycles of chemotherapy.

Further research/reviews required

Further research should include an update of this review in 12 to 18 months, by which time the included RCT should be fully published. It would also be useful to compare gemcitabine with current treatments for metastatic breast cancer, including capecitabine and vinorelbine.

Written by Dr Andrea Takeda, SHTAC, United Kingdom

INAHTA Briefs

Issue 2007/142

Title **Adalimumab, Etanercept, and Infliximab for the Treatment of Ankylosing Spondylitis: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2007;11(28). August 2007.
www.hta.ac.uk/execsumm/summ1128.htm

Aim

To assess the comparative clinical effectiveness and cost effectiveness of adalimumab, etanercept, and infliximab in treating ankylosing spondylitis (AS).

Conclusions and results

The review of clinical effects included 2 studies of adalimumab, 5 of etanercept, and 2 of infliximab in comparison with placebo (along with conventional management). No RCTs directly comparing anti-tumor necrosis factor-a (TNF-a) agents were identified. Meta-analyses were conducted for data on Assessment in Ankylosing Spondylitis (ASAS), mean change in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and mean change in Bath Ankylosing Spondylitis Functional Index (BASFI) at 12 weeks following initiation of anti-TNF-a therapy or placebo for all 3 drugs. Meta-analyses were also conducted at 24 weeks for etanercept and infliximab. Each meta-analysis of anti-TNF-a therapy demonstrated statistically significant advantages over placebo, although there was no significant difference between individual anti-TNF-a agents. At 12 weeks, ASAS 50% responses were 3.6-fold more likely with anti-TNF-a treatment than placebo. Compared with baseline, BASDAI scores were reduced by close to 2 points at 12 weeks. Functional scores (BASFI) were reduced at 12 weeks.

The review included 6 full economic evaluations. Conclusions were mixed, but the evidence in the short term indicates that anti-TNF-a therapies are unlikely to be considered cost effective. Limitations in clinical outcome data restrict the assessment of cost effectiveness. Direct unbiased RCT evidence is only available in the short term. Currently BASDAI and BASFI are the best available assessment tools, but not ideal for economic evaluations. A review of the 3 models identified several inherent flaws and errors. Incremental cost-effectiveness ratios (ICERs) of etanercept and adalimumab were similar, falling below an assumed willingness-to-pay threshold of GBP 30 000. The ICER for infliximab ranged between GBP 40 000 and GBP 50 000 per QALY. The short-term model confirmed large front-loading of costs with a result that none of the 3 anti-TNF-a agents appears cost-effective at the current acceptable threshold, with infliximab yielding much poorer economic results (GBP 57 000–120 000 per QALY). Assumptions of the short-term model were used to explore the cost effectiveness of using anti-TNF-a agents in the long term (far more speculative). Sensitivity analyses show wide variations in long-term cost estimates, but it is unlikely that costs will decrease over time.

Recommendations

The review of clinical data related to the 3 drugs (including conventional treatment) compared with conventional treatment plus placebo indicates that in the short term (12–24 weeks), the 3 treatments are clinically effective in relation to assessment of ASAS, BASDAI, and BASFI. Indirect comparisons of treatments were limited and did not show a significant difference in effectiveness between the 3 agents. The short-term economic assessment indicates that none of the 3 anti-TNF-a agents is likely to be considered cost effective at current acceptability thresholds, with infliximab consistently the least favorable option.

Methods

See Executive Summary link above.

Further research/reviews required

To obtain robust estimates of the longer term clinical and cost effectiveness of anti-TNF-a agents for AS, clinical trials should address several limiting factors related to patients suffering from AS, the disease itself, and its treatment.

Written by Ms Claire McLeod, University of Liverpool, United Kingdom

Title **Role and Positioning of University Outpatient Departments**

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Reference HTA project report 1.
ISSN 1992-0488 (print), 1992-0496 (online)

Aim

To define, from a positioning standpoint, the services of university hospital outpatient clinics in contrast to healthcare services offered by specialized physicians and/or outpatient clinics in peripheral hospitals.

Conclusions and results

Results of literature review: Economic arguments dominate the discussion on the role of outpatient clinics in university hospitals. Cornerstones of the debate include: structural reforms, medical training and research, patient visits and referrals, hospital operation, and documentation of performance.

Results of development of methodology:

- Development of a prototype to analyze outpatient performance data: profiles of 3 different groups of patients determining the profile of services delivered, were defined: 1) complex and interdisciplinary cases/patients vs noncomplex cases; 2) emergency patients vs nonemergent patients; 3) pre- and postinpatient cases and consequent examinations and therapies.
- Development of a matrix to systematically categorize services based on 'depth of care', defined by: 1) technical input/infrastructural need; 2) complexity/interdisciplinarity; 3) specialization/low incidence/rareness/risk. This definition served to differentiate medical services that can be offered only in university clinics from those offered in other settings (group-practices or specialized physicians).

Conclusion: Generation of a profile for outpatient services in university hospitals must be realigned along the following key elements:

- Clinical factors determining the range of services offered defined by infrastructural need; complexity/interdisciplinarity; rareness of indication and need for specialization.
- Factors determining the needs in medical teaching and research are led by the need for 'average' patients and the need for training in unspecific diseases. (Only the extent/the minimum number of 'average' patients is under question.)
- Alternative low threshold institutions for extramural care, especially for the socially disadvantaged who visit outpatient clinics more frequently than specialized physicians.
- Economic rationalities showing that especially care for non-complex patients takes disproportionately more resources – because of additional diagnostic and therapeutic input – than in other settings.

Methods

a. A literature search identified 34 relevant publications on strategic positioning, spectrum of services, function, documentation and quantification of care/medical training and teaching/research, patient access, resource use, and appropriateness in the setting of outpatient clinics in university hospitals. A systematic literature review, complemented by a survey of university hospital managers, summarizes the state of the discussion.

b. A methodology to empirically analyze the data on the performed services was developed as a prototype and probed.

c. A matrix was developed to systematically categorize the services performed, based on 'depth of care'.

Written by Mad P, Langer T, Guba B, Kvas E, Wild C, Reichelt C, and Adlbrecht C, LBI of HTA, Austria

INAHTA Briefs

Issue 2007/144

Avastin for Age-Related Macular Degeneration. Rapid Assessment

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Reference Rapid Assessment LBI-HTA 2

Aim

To clarify the safety risks for age-related macular degeneration (AMD) patients treated with Avastin and to estimate the liability risks for the physicians and institutions providing care.

Conclusions and results

The incidence of neovascular AMD increases rapidly with age. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) have approved the monoclonal antibodies Pegaptanib (Macugen®) and Ranibizumab (Lucentis®) for intravitreal therapy to inhibit vascular endothelial growth factors (VEGF). A third drug, Bevacizumab (Avastin®), has not been approved for this indication. However, because it is 30 times less expensive than Lucentis it is used "off-label" much more in clinical settings than the approved drug Lucentis. Chemically, Ranibizumab, is a fragment of the Bevacizumab protein. Both substances were developed by Genentech laboratories and show similar pharmacodynamics although they have different half-lives.

Analysis of the studies on the safety of intravitreous AMD therapy by Bevacizumab does not provide valid evidence either for or against the use of Avastin. Trials have been methodologically inadequate and insufficient to draw firm conclusions. Specifically, the evaluation of treated and untreated patients, information on diagnoses and AMD stages, incomplete reporting on side effects, and varying numbers of patients in followup limit the validity of the evidence. However, based on preliminary data, administration of Bevacizumab (Avastin) is appraised as promising, since the monitored side effects are of only moderate clinical relevance. Nevertheless, only a comprehensive randomized comparative clinical trial of Bevacizumab and Ranibizumab could produce final, valid results.

Methods

This report is based on a simple literature review, using MEDLINE and EMBASE. Results were selected using inclusion and exclusion criteria, eg, medical indications, clinical trials, interventions, and number of participants. Also, 21 published clinical trials on safety and side effects of Avastin and 56 partially unpublished references concerning the topic have been evaluated.

Written by Adlbrecht C and Wild C, LBI of HTA, Austria

Title **Mammography Screening. Evidence-Based Evaluation of Mammography-Based Breast Cancer Screening Programs**

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Reference HTA project report 7.
ISSN 1992-0488 (print), 1992-0496 (online)

Aim

To provide an evidence-based aid for program evaluation that can help in quality assurance and evaluation of Austrian mammography screening programs (implemented from the outset on the basis of international, evidence-based, high-quality criteria).

Conclusions and results

The regional government of Salzburg requested this report. It summarizes the current situation of mammography screening in Austria and describes in detail the international evidence on methods of evaluation in existing mammography screening programs. In the context of each of the programs, fields of activities are defined and outlined using different quality indicators and degrees of attainment of defined target values.

Quality indicators are grouped in different ways, but clinical parameters serve to build a firm core element. A framework was developed to understand possible correlations between the aspects defining a screening program. Various ways of description and formalization were considered and compared. The report correlates the programs' stakeholders and describes their methods of communication according to the procedural algorithm of screening. It shows that, at times, the quality of "hard" clinical indicators is highly dependant on technical, organizational parameters, or even aspects of data management and marketing. On one hand, these correlations address internal professional structures, while on the other hand they relate screening units to the women attending the screening program.

Conclusion: Clinical and economic parameters and target values are valid tools for evaluation only if they are regularly (re-)defined with regard to indicators in other fields that define a screening program.

Methods

Relevant literature was identified by systematic searches in 4 databases, by personal contact with experts, and by searching the Internet.

Written by Radlberger P, Guba B, and Wild C, LBI of HTA, Austria

Title **Testing for HER2 Positive Breast Cancer. Challenge for Improvement of Current Conditions and Practice**

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Reference HTA project report 8.
ISSN 1992-0488 (print), 1992-0496 (online)

Aim

To address the following questions: Are the resources allocated to treat HER2 patients being used most efficiently? What is the gold standard for diagnosing HER2-positive tumors? Which method is most accurate and reproducible in identifying candidates for potential therapy with monoclonal antibodies, and are the tests reliable for selecting HER2-positive patients? Is it necessary to look closer at specific areas of uncertainty – if so, which areas?

Conclusions and results

The review systematically discusses HER2 testing results of more than 23 000 specimens (in local, central, or reference labs) explored by different testing methods (DNA, RNA, protein levels).

- Many studies are not comparable due to differences in specimen numbers, tissue extraction, specimen histology, and test methods.
- IHC (immunohistochemistry) results show more variability than FISH (fluorescence in situ hybridization) results, particularly in FISH-negative cases. The results of most studies indicate that high-level HER2 amplification and an IHC score of 3+ will identify HER2-positive breast carcinoma; low-level amplification and/or IHC score of 2+ should be carefully interpreted.
- There is agreement that the most (cost-) effective testing strategy is to screen all patients with IHC, followed by FISH for IHC of 2+ (or of 2+ and 3+).
- A challenge in routine practice concerns differences in interpreting probes. There is a need to adhere to guidelines in handling disconcordant results and validation of clinical results.
- Uncertainty exists regarding the clinical significance of low-level gene amplification in the response to trastuzumab.
- Findings concerning different results from local/central labs point to moderate inter-observer and inter-laboratory reliability of test results. A volume/experience relationship is observed.
- Inter-laboratory comparisons and performance evaluations are important in overcoming test limitations. The results of this assessment suggest there are fewer HER2-positive women than generally reported: not 20% to 30%, but 15% to 20% are amplifying HER2 positive in "real-life" settings.

Recommendations

- Due to the high variability between the different IHC tests, we recommend using only standardized and approved tests.
- Due to the consequential costs (non-monetary costs/side effects of therapy and monetary costs), we recommend establishing standard operating procedures.
- Due to high inter-laboratory variability, we recommend using a few central reference centers.
- Due to high inter-laboratory variability, we recommend national and international inter-laboratory exchange on results of diagnostic outcome.

Methods

We searched the literature in several databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Pascal Biomed, and BIOSIS Previews) and included studies (n=75) published after year 2000. The main focus was on issues of validity, standardization and/or calibration of the two most commonly used methods (IHC and FISH), inter-observer and inter-laboratory concordance, and the role of the morphological variables and borderline test results.

Written by Korencan A and Wild C, LBI of HTA, Austria

INAHTA Briefs

Issue 2007/147

Title **Population Screening for Primary Open-Angle Glaucoma**

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Reference 2007-10. ISBN 978-2-550-51116-8 (print).
www.aetmis.gouv.qc.ca/site/en_publications_2007.phtml

Aim

To update the information on glaucoma screening published 11 years ago by the Conseil d'évaluation des technologies de la santé (CETS), the predecessor of AETMIS.

Conclusions and results

Glaucoma is an irreversible eye disease that can lead to blindness. The prevalence of primary open-angle glaucoma (POAG) among the population aged 40 years and older was 1.86% in the United States in 2000. Emergence of new diagnostic technologies has again raised the question of a population screening program for POAG.

New diagnostic techniques lead to earlier and more accurate detection of POAG-related structural and functional defects, but their sensitivity and specificity, taken in isolation, are insufficient for screening. Combinations of diagnostic tests could prove effective for target populations, but few studies have evaluated them. An economic assessment under way in the United Kingdom may shed new light on these aspects.

There is no evidence that screening asymptomatic people reduces the onset of severe complications or major visual impairment, and the criteria to support the introduction of a population screening program are not all met in the case of POAG.

Hence, AETMIS concludes that, presently, it is not justified to recommend introducing a population screening program for glaucoma in Québec. From a broader public health perspective of reducing preventable blindness and improving access to ophthalmology care, AETMIS finds that: 1) opportunistic screening activities are in place, lead to referrals to ophthalmologists, and absorb specialized resources; 2) the extent, effectiveness, and costs of opportunistic screening activities are not known; 3) some patients are at greater risk of a rapidly progressive form of glaucoma, but these risk factors are not fully known; 4) case-finding scenarios (opportunistic screening) targeting at-risk individuals and combining several diagnostic tests achieve good performance in these groups. Some of these issues may be clarified by better understanding current opportunistic screening. Defining criteria for optometrists to refer suspected glaucoma cases to ophthalmologists would contribute to more effective followup and treatment for these patients; it is up to the two professional associations to determine those criteria. Moreover, a literature watch on the performance and cost effectiveness of glaucoma screening (especially studies assessing combinations of screening tests), along with analysis of the results of the UK assessment, should help identify promising avenues for screening at-risk groups. It would be appropriate to verify their applicability to the Québec context to formulate research priorities for Québec.

Methods

Systematic literature review; HTA Database, MEDLINE, Cochrane Library 2007, Issue 3; interviews with ophthalmologists and optometrists associated to examination of data provided by Québec's Health Insurance Board.

Written by Brigitte Côté and Nieves Rodriguez, AETMIS, Canada

Title **Male Infertility: Intracytoplasmic Sperm Injection (ICSI) Using Surgically Retrieved Sperm from the Testis or the Epididymis**

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Reference Report no 7-2007. ISBN 978-82-8121-148-3.
www.kunnskapssenteret.no/filer/rapport7_07_mannlig_infertilitet.pdf

Aim

To identify, in the case of male infertility, the effect of intracytoplasmic sperm injection (ICSI) treatment with sperm retrieved from the epididymis or testis on the risk of spontaneous abortion, chromosome aberrations, growth restriction, malformations, abnormal neurological development, and transmission of reduced sperm quality to subsequent generations.

Conclusions and results

We found no differences in the risk of malformations in ICSI pregnancies when comparing the use of testicular, epididymal, and ejaculated sperm. The risk of spontaneous abortion showed a nonsignificant tendency to be higher for testicular sperm than for epididymal sperm. This finding deserves attention in future research and surveillance.

Methods

Searches for relevant literature were performed using the following databases: Cochrane Library, MEDLINE, EMBASE, and Registry of Current Controlled Trials. The following designs were included in the search: systematic reviews, randomized controlled studies, reports/registry data with well defined comparisons between groups, and cohort and case control studies with relevant comparisons.

Further research/reviews required

There is a need for further research and surveillance related to the use of assisted reproduction technology both in Norway and internationally. Due to the relatively small number of children conceived in Norway using different methods of assisted reproductive technology, international collaboration is needed to initiate followup studies of children beyond pregnancy and birth.

Written by Therese Opsahl Holte, NOKC, Norway

Title	**Centralization of Selected Surgical Procedures: Implications for Australia**
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Reference	Report number 57. ISBN 0-909844-79-8.
	Link to full text report: www.surgeons.org/asernip-s/publications.htm

Aim

To assess the efficacy of centralizing 5 surgical procedures in the Australian setting: abdominal aortic aneurysms, knee arthroplasty, liver resection, esophagectomy, and prostatectomy. (The following Brief addresses 1 of the 5 procedures. For others, see the complete review.)

Conclusions and results

Abdominal aortic aneurysm

Unruptured: The relationship between hospital volume and both patient morbidity and length of stay was inconclusive. The data suggest an inverse relationship between hospital volume and patient mortality rates. None of the studies examined the relationship between surgeon volume and patient morbidity. Limited data support an inverse relationship between surgeon volume and patient mortality. One study reported a statistically significant inverse relationship between surgeon volume and length of stay.

Ruptured: None of the studies examined the relationship between hospital volume and patient morbidity. Limited data suggest a relationship between surgeon volume and patient mortality. Very limited data indicate that hospital volume does not affect length of stay. None of the studies examined the relationship between surgeon volume and patient morbidity. One study reported a statistically significant relationship between surgeon volume and both patient mortality and length of stay.

Recommendations

Classifications, Evidence rating: The evidence for this systematic review is rated as average.

Methods

Search strategy: Two search strategies were used – a broad search in MEDLINE, EMBASE, CINAHL, NHS CRD databases, and Current Contents Connect to identify the range of centralization studies on surgical procedures, followed by a second targeted search that utilized a separate procedure-specific search algorithm in the databases listed above plus Clinical Trials Databases, Current Contents Connect, Current Controlled Trials, National Research Register, PubMed, and the Cochrane Library.

Study selection: Studies were included if they met the inclusion criteria and reported at least one of the following outcome measures: patient mortality, morbidity, and length of stay.

Data collection and analysis: Data were extracted by one researcher and checked by a second researcher using standardized data extraction tables developed *a priori*. When studies reported on overlapping patient groups, we used only the paper with the most complete data set.

Further research/reviews required

Each of the procedures of interest should continue to be monitored for relevant Australian data. Financial analyses should be commissioned to provide a representative assessment of the Australian healthcare system. Future research should utilize common clinical terminology, eg, uniform definitions of mortality and morbidity, to enable more efficacious comparisons. Australian-based research studies across a range of surgical procedures, utilizing common clinical terminology, must be conducted before the impact of centralization in Australia can be definitively assessed. Attention should be given to quality factors that affect skills development and maintenance of surgeons in low- and high-volume hospitals. These studies require nationally representative data from low- and high-volume Australian hospitals to assess standards of care to ensure that centralization is not instituted solely for political or financial reasons.

Written by Marlow N et al, ASERNIP-S, Australia

Title **A Review of Policies and Processes for the Introduction of New Interventional Procedures**

Agency **ASERNIP-S, Australian Safety and Efficacy Register of New Interventional Procedures – Surgical**
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Reference Report number 58. ISBN 0-909844-80-1. www.surgeons.org/asernip-s/publications.htm

Aim

To identify and review Australian and international policies and processes for introducing new interventional procedures into clinical practice, specifically:

1. how decisions on adopting new interventional procedures are made
2. the extent to which evidence-based information, particularly health technology assessment (HTA), is used in the decision-making process.

Conclusions and results

Searches of the published literature revealed only 1 paper outlining relevant policy information. Targeted website searches were more fruitful, and uncovered many relevant policy documents, most of which were from NHS Trusts in the UK. Six policies (2 Australian, 2 Canadian, and 1 each from Denmark and the UK) were selected for this review. Each of these polices contained a clearly defined purpose and an explicit description of the approval process, including the role of relevant clinical governance structures.

Five of the 6 included policies use an application form as part of the approval process, while 1 (Canada) bases its policy decisions largely on recommendations from its Technology Assessment Unit. These HTAs evaluate safety, efficacy, cost effectiveness, and ethical and legal implications. The 5 policies that use application forms in the approval process all required information on clinical outcomes, need, disease burden, the safety, efficacy, and effectiveness of the procedure, and organizational outcomes (eg, cost, training requirements). Both Australian policies required patient information sheets and informed consent forms in the approval process. Similarly, the UK policy also required that patient information and informed consent be addressed, but these issues were not addressed by the Canadian or Danish policies.

Three studies that evaluated the outcomes of specific polices in Australia, Canada, and the UK were found by searching the published literature, while targeted website searches revealed 1 document describing the outcomes of a second Australian policy. These studies have focused largely on the number and type of procedures approved since the implementation of specific policies, and 2 studies provided information on organizational impact.

Searches of the published literature uncovered 3 studies, 2 in Israel and 1 in Denmark, that examined decision-making at the hospital level, while targeted website searches revealed 1 document describing a decision-making processes in New Zealand. The results from these studies have shown that while the safety, efficacy, and clinical and cost effectiveness are important considerations in the decision-making process, other factors also play a role, and decisions are never based solely on the findings of HTAs. A lack of access to relevant and timely HTAs was identified as a barrier to an optimal decision-making process.

Methods

Search strategy: MEDLINE, EMBASE, CINAHL, Current Contents, and PubMed were searched from inception to February 2007. Several relevant journals were hand-searched from 2000 to February 2007. Relevant online sources were also searched.

Study selection: Documents outlining specific policies and processes were included if they evaluated the clinical need, safety, efficacy, effectiveness and/or financial implications of a new intervention. Where outcomes were reported for specific policies, these policies were given preference for inclusion. Studies addressing the use of HTAs in decision-making were also included.

Data collection and analysis: One researcher extracted the data and a second checked it using standardized data extraction tables developed *a priori*. Data for the main outcomes were reported narratively.

Written by Thavaneswaran P et al, ASERNIP-S, Australia

INAHTA Briefs

Issue 2007/151

Title **Scalpel Safety in the Operative Setting**

Agency **ASERNIP-S, Australian Safety and Efficacy Register of New Interventional Procedures – Surgical**
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Reference Report number 59. ISBN 0-909844-81-X.
Link to full text report: www.surgeons.org/asernip-s/publications.htm

Aim

To identify and assess the efficacy and effectiveness of devices and procedures designed to lower the incidence of scalpel injuries in the operative setting.

Conclusions and results

This systematic review included 19 studies: 13 on cut-resistant gloves and glove liners; 3 on the hands-free passing technique; 1 on protective footwear; 1 on the feasibility of sharpless surgery, and 1 on a single-handed scalpel blade remover. Seven of these studies were randomized trials (NHMRC Level II), 3 were non-randomized comparative studies (Level III-2), 2 were comparative studies with historical controls (Level III-3), 1 was a Level IV study, and 7 were experimental studies to which the NHMRC Hierarchy of Evidence could not be applied.

Recommendations

Evidence rating: The evidence base in this review is rated as poor, limited by the quantity and quality of the available evidence. Specific limitations included the diversity of interventions and outcomes considered, the lack of a standard comparator, and differences in clinical settings and experimental environments.

Effectiveness and efficacy: Effectiveness outcomes were considered for interventions undertaken in clinical settings, and efficacy outcomes for those undertaken in laboratory settings:

- *Cut-resistant gloves & glove liners, hands-free passing technique, sharpless surgery, pass tray & single-handed scalpel blade remover.* Based on the published literature, the effectiveness of these devices/methods in the clinical setting cannot be determined.
- *Cut-resistant gloves & glove liners and protective footwear.* Based on the published literature, the efficacy of these devices/methods in experimental settings cannot be determined.

Clinical and research recommendations: Few published studies systematically assess the effectiveness of safety devices in reducing percutaneous injuries, despite the proliferation of such devices. Reports show substantial variation in study methodology and measurement of outcomes. Standardization of these features needs to be considered to compile a clinically relevant and statistically valid body of evidence by which to assess new safety procedures and devices. Randomized controlled trials (RCTs), particularly of cut-resistant gloves and glove liners, are feasible and desirable.

A detailed audit of scalpel injuries would assist in contextualizing the incidence, prevalence, and epidemiology of these injuries in the Australian healthcare setting, allowing targeted interventions where needed. However, a large part of preventing sharps injuries involves creating a culture of safety. To reduce the rates of scalpel injury in the operative setting in the long-term, the concept of 'scalpel safety' must be reinforced through practice and education.

Methods

Search strategy: RCTs, comparative studies, observational studies, surveys, and modeled data reporting outcomes of interest were identified by searching MEDLINE, EMBASE, CINAHL, the Cochrane Library, Current Contents, PubMed and AMI from inception to December 2006. The Clinical Trials Database (US), NHS CRD Database (UK), National Research Register (UK), and Meta Register of Controlled Trials were also searched in January 2007.

Data collection and analysis: Data were extracted by an ASERNIP-S researcher using standardized extraction tables developed *a priori* and checked by a second researcher. Studies that were sufficiently homogeneous were examined by meta-analysis. Heterogeneous studies that did not meet the criteria for meta-analysis were reported qualitatively.

Written by Watt A et al, ASERNIP-S, Australia

INAHTA Briefs

Issue 2007/152

Title **Rapid versus Full Systematic Reviews: An Inventory of Current Methods and Practice in Health Technology Assessment**

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Reference Report number 60. ISBN 0-909844-82-8. www.surgeons.org/asernip-s/publications.htm

Aim

To assess current practice in preparing rapid reviews by HTA organizations nationally and internationally; to examine the evidence base for the methodology of rapid reviews; and to identify any differences in the essential conclusions of rapid and full reviews on the same topic.

Conclusions and results

Survey of HTA organizations: 23 surveys were returned, with 18 agencies reporting the production of 36 rapid review products. The most common reason for conducting a rapid review was in response to political urgency and/or to support decisions. Search strategies varied widely. The components of reviews also varied between product types, with full reviews more likely to report clinical outcomes (100% vs 94%), examine economic factors (92% vs 72%), and consider social issues (85% vs 53%).

Literature on rapid review methodology: 11 relevant studies were identified. None of the included studies detailed guidelines for the methodology of rapid reviews. Authors suggested restricted research questions and truncated search strategies as ways to limit the time taken to complete a review.

Identification and comparison of rapid reviews and full systematic reviews: Full and rapid reviews were compared on the topics of drug eluting stents, lung volume reduction surgery, living donor liver transplantation, and hip resurfacing. Axiomatic differences between the products were identified, but in no instances were the essential conclusions of the different reviews opposed. Full reviews consistently provided deeper information and more detailed recommendations for implementation.

Recommendations

This report shows that rapid review products by HTA agencies are not well defined and vary widely in methodology. It is recommended that rather than developing formalized methods for conducting rapid reviews, which may inappropriate and oversimplified, agencies should increase the transparency of methods used in each review. It would be useful if HTA agencies clearly identified their HTA products with respect to the commissioning group, the purpose of the review, and general details outlining the methods used. Certain parts of a comprehensive systematic review (eg, an independent and complete economic evaluation) might not realistically be completed in a rapid timeframe. Methods need to be developed to incorporate timely advice from expert panels, ensuring that rapid reviews reach appropriate conclusions at clinical and policy levels. A rapid review should be written to answer specific questions rather than as a quick alternative to a full systematic review. Hence, rapid reviews could be used to inform specific policy decisions in a timely manner without losing any of the important information that may be expected from a comprehensive review.

Methods

Three concurrent methods were used: A survey was developed and distributed electronically to 50 HTA agencies identified through INAHTA membership records and Review Group advice. Data were collated via spreadsheet tabulation, discussed, and subjected to simple statistical analysis.

Systematic literature searches of the Cochrane Database of Methodology Reviews, the Cochrane Methodology Register, EMBASE, MEDLINE, and the Australasian Medical Index were undertaken in March 2007 to identify literature pertaining to methodology for undertaking rapid reviews.

Internet sites of 75 international HTA organizations were searched for rapid reviews meeting pre-defined inclusion criteria. For each rapid review identified, a literature search was undertaken utilizing the University of York CRD database to identify full reviews (systematic reviews or HTA reports) published on the same topic within approximately one year of the identified rapid review.

Written by Cameron A et al, ASERNIP-S, Australia

Title **Surgical Simulation for Training: Skills Transfer to the Operating Room**

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Reference Report number 61. ISBN 0-909844-83-6.
Link to full text report: www.surgeons.org/asernip-s/publications.htm

Aim

To assess whether skills acquired via simulation-based training transfer to the operative setting.

Conclusions and results

This review included 12 randomized controlled trials and 2 nonrandomized comparative studies. It looked at simulation as a concept and included studies with various training techniques in the surgical setting. Differences were found in indications, simulation-based training methods, training times, and the amount of guidance and feedback given to trainees. Most simulation-based training was an add-on to normal surgical training programs. Only one study compared simulation-based training with current training methods (patient-based training).

For laparoscopic cholecystectomy, participants who received simulation-based training prior to conducting patient-based assessment generally performed better than their counterparts who did not have this training. This improvement was not universal for all parameters, but the untrained group never outperformed the trained group. Trained groups generally made fewer errors and reported fewer instances of supervising surgeon takeover than the untrained groups did.

For colonoscopy/sigmoidoscopy, simulation-based training prior to patient-based assessment gave participants an advantage over their untrained controls, particularly in the initial stages of learning.

For catheter-based intervention in occlusive vascular disease and TEP hernia repair, participants seemed to benefit from simulation-based training when later conducting patient-based assessment.

For endoscopic sinus surgery, no differences in performance were found between simulator-trained residents vs controls.

The study that compared patient-based training vs simulation-based training for colonoscopy/sigmoidoscopy found that participants trained in the assessment procedure performed better than those trained exclusively on a simulator without any mentoring or supervision.

Recommendations

Evidence rating: The evidence-base in this review is rated as average. Studies varied in quality and did not have comparable simulation-based methods for the same indications, resulting in an inability to draw solid conclusions.

Methods

Search strategy: MEDLINE, EMBASE, CINAHL, the Cochrane Library, and Current Contents were searched from inception to December 2006. The Clinical Trials Database (US), NHS Centre for Research and Dissemination Databases (UK), National Research Register (UK), Meta Register of Controlled Trials, and the Australian Clinical Trials Registry were also searched in December 2006.

Study selection: Only studies that reported on the use of simulation for surgical skills training, and on the transferability of these skills to the patient care setting, were included. The articles must have contained training and/or measures of performance in the simulated setting and measures of performance in the operative setting. Measures of surgical task performance included accuracy of skills, time to complete technique, efficiency of movement, error rates, and achievement of performance to criterion levels.

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 heterogeneity of the included studies.

Further research/reviews required

Research is recommended on the transfer of skills acquired via simulation-based training to the patient setting, eg, the nature and duration of training required for maximum transfer effect, the stage at which trainees benefit most from different forms of simulation, the effect of different levels of mentoring, and changes in staff productivity.

Written by Sturm L et al, ASERNIP-S, Australia

INAHTA Briefs

Issue 2007/154

Title **A Systematic Review of Natural Orifice Translumenal Endoscopic Surgery (NOTES)™ for Intra-Abdominal Surgery**

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

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Reference Report number 62. ISBN 0-909844-84-4. www.surgeons.org/asernip-s/publications.htm

Aim

To assess the safety and efficacy of various intra-abdominal, Natural Orifice Translumenal* Endoscopic Surgery™ (NOTES™) procedures that do not cut the dermis, compared to traditional intra-abdominal surgery which cuts the dermis.

Conclusions and results

The evidence base for this review was limited since there were no comparative studies, and all 22 included studies were conducted in animals to test the feasibility of NOTES. Presently, NOTES does not appear to be as safe or effective as current intra-abdominal surgical techniques, and requires further development before it can be considered in a clinical setting. Although intra-abdominal access via oral, anal, or urethral orifices could be achieved reliably in all cases, the evidence does not indicate the optimal access route and method. Viscerotomy closure could not be achieved reliably in all cases, and risk of peritoneal infection has not been adequately minimized.

Several technical problems with NOTES must be resolved. Many abstracts relating to NOTES suggest that this area of surgery is developing rapidly. The review indicates that NOTES is feasible for some intra-abdominal surgical procedures, but it is too early to tell if these will be comparable to current procedures and if the advantages of NOTES outweigh the disadvantages.

Recommendations

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

Safety: Currently, NOTES for intra-abdominal surgery is less safe than laparoscopic and laparotomic alternatives.

Efficacy: NOTES for intra-abdominal surgery is currently less efficacious than laparoscopic and laparotomic alternatives.

Methods

Search strategy: MEDLINE, EMBASE, CINAHL, Current Contents, the Cochrane Library, and Entrez-PubMed were searched for studies published from 2000 to March 2007. The clinical trials database (US), NHS CRD databases, and the National Research Register (UK) were searched in March 2007, and the SAGES 2006 and 2007 annual meeting abstracts were sourced for information.

Study selection: The review included live-human or animal studies involving surgery in the intra-abdominal region using natural orifice access (cadaver studies were excluded). Studies where the new intervention involved an incision to the dermis were excluded as were studies reporting established endoscopic procedures that are not transluminal, eg, abscess or cyst drainage or debridement.

Data collection and analysis: Data were extracted by one researcher using standard data extraction tables developed *a priori* and checked by a second researcher.

Further research/reviews required

NOTES is in the early stages of development, and more robust technologies are needed to achieve reliable closure and overcome technical challenges. Well-managed human studies are needed to determine the safety and efficacy of NOTES in a clinical setting. This may be approached by performing hybrid NOTES/laparoscopic procedures that may help evaluate safety in a human model before moving to larger trials. NOTES procedures and studies should adhere to strict guidelines, eg, the membership criteria developed by NOSCAR.

* *Translumenal* is used in the trademarked name 'Natural Orifice *Translumenal* Endoscopic Surgery', however *transluminal* is accepted Australian version of the word.

Written by Della Flora E et al, ASERNIP-S, Australia

Title **Hormonal Therapies for Early Breast Cancer: Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2007;11(26). July 2007.
www.hta.ac.uk/execsumm/summ1126.htm

Aim

To establish the clinical and cost effectiveness of aromatase inhibitors (AIs) anastrozole, letrozole, and exemestane compared with tamoxifen in adjuvant treatment of early estrogen receptor-positive breast cancer in postmenopausal women with estrogen receptor-positive early-stage breast cancer.

Conclusions and results

A significant difference in overall survival was found when an unplanned anastrozole switching strategy was compared with 5 years' tamoxifen. Compared with 5 years' tamoxifen, disease-free survival was significantly improved in the primary adjuvant setting with anastrozole and letrozole, and with an exemestane switching strategy. Breast cancer recurrence was significantly improved with primary adjuvant anastrozole and letrozole, anastrozole switching, extended adjuvant anastrozole, or letrozole. AIs and tamoxifen have different side-effect profiles (eg, increases in endometrial cancer with tamoxifen, and increases in osteoporosis with AIs). Absence of tamoxifen treatment also increases the risk of hypercholesterolemia and cardiac events in women of this age.

No significant difference was found in overall health-related quality of life between standard treatment and either primary adjuvant anastrozole and extended adjuvant letrozole strategies. The cost-effectiveness results for AIs compared with tamoxifen in the primary adjuvant setting are estimated at between GBP 21 000 and GBP 32 000 per QALY. Cost-effectiveness for anastrozole and exemestane, compared with tamoxifen in the unplanned switching setting, is estimated to be GBP 23 200 and GBP 19 200 per QALY, respectively. In the extended adjuvant setting, the cost per QALY for letrozole compared with placebo is estimated to be GBP 9800. All these results are considered to be conservative. The base case assumes that the benefits of AIs over tamoxifen or placebo during the therapy period are gradually lost during the following 10 years. An alternative scenario, the 'benefits maintained' scenario, is tested in sensitivity analysis and assumes that the annual recurrence rate in both arms is the same. This reduces the cost-effectiveness ratio by over 50%, to around GBP 10 000 to 12 000, GBP 5000, and GBP 3000 in the primary adjuvant, unplanned switching, and extended adjuvant settings, respectively. Limited evidence of benefits after the therapy period suggests that the 'benefits maintained' scenario may be realistic. Results from the economic analyses in the industry submissions are generally lower than those in the authors' model and are close to or below GBP 12 000 in all 3 settings. The authors' analyses generally produce a lower estimate of QALY gain for AIs, due to the more conservative assumption on benefits, along with differences in the utility values used in the analysis.

Recommendations

Based on current data and indications, AIs can be considered clinically effective compared with standard tamoxifen treatment, but long-term effects are unclear. AIs are likely to be considered cost effective in all 3 settings, assuming that recurrence rates are the same in both arms after therapy is complete. Understanding of the long-term treatment effects on cost effectiveness is, however, incomplete.

Methods

See Executive Summary link above.

Further research/reviews required

Randomization of populations at any point other than the start of treatment programs should be discouraged in future trials. Data on AIs' impact on survival are awaited from most trials to confirm whether or not the benefits seen in disease-free survival and rates of recurrence are translated into overall survival benefit in the medium to long term. Long-term followup data on major adverse events are awaited. Evidence suggests that these adverse events do not unduly impact on the cost-effectiveness ratios. Long-term implications for the costs and benefits of AIs and tamoxifen will need to be reviewed as new information becomes available.

Written by Dr Daniel Hind, ScHARR-TAG, University of Sheffield, United Kingdom

INAHTA Briefs

Issue 2007/156

Title **The Clinical and Cost Effectiveness of Inhaled Insulin in Diabetes Mellitus: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2007;11(33). September 2007.
www.hta.ac.uk/execsumm/summ1133.htm

Aim

To review the clinical effectiveness and cost effectiveness of a new technology, the inhaled insulin, Exubera®.

Conclusions and results

Nine trials of inhaled insulins were found, but only 7 used the Exubera form of inhaled insulin (five trials in type 1 and two in type 2 diabetes). Inhaled insulin is clinically effective. It is as good as short-acting soluble insulin in controlling blood glucose, plus it works slightly more quickly. Most patients in the trials were on combinations of short-acting, and either long- or intermediate-acting insulin, and in most trials, both were changed, making it difficult to assess the effects of only the change from soluble to inhaled insulin. Patient preference was the only significant difference between inhaled and soluble insulin in the trials. Most patients preferred inhaled to injected short-acting insulin. The control groups mostly used syringes and needles, rather than pens. As pens are more convenient, their use might have narrowed the patient satisfaction difference. There were no trials of inhaled insulin vs continuous subcutaneous insulin infusion (CSII). No serious adverse experiences of inhaled insulin in the lung have been observed, but it is too soon to judge long-term effects.

The manufacturer's model appears to be of high quality, although the results depend more on the assumptions fed into the model than on the model itself. Key assumptions are: the size of the gain in quality-of-life utility from inhaling rather than injecting insulin; the effect of having an inhaled option on the willingness to start insulin among people with poor diabetic control on oral drugs; and the effect on glycemic control. We consider that the manufacturer's assumptions make the cost effectiveness appear better than it really would be. The manufacturer's submission assumed utility gains of 0.036 to 0.075 in patients with type 1 diabetes, and 0.027 to 0.067 in those with type 2 diabetes, based on an unpublished utility elicitation study sponsored by the manufacturer. These gains appeared optimistic. However, patients having particular problems with injection sites might have more to gain, although they might also be a group with much to gain from CSII.

A key factor is the cost of inhaled insulin. Much more insulin has to be given by inhaler than by injection. Hence, the cost of inhaled insulin is much higher than injected. The extra cost depends on dosage, but ranges from around GBP 600 to over GBP 1000 per patient per year.

Recommendations

The inhaled insulin, Exubera, appears to be effective and, so far, safe. However, given the considerable incremental cost, it seems unlikely to the authors that it would be cost effective.

Methods

A systematic literature review was conducted and economic modeling carried out. Literature searches were done up to November 2005. The industry model, EAGLE, was used for modeling.

Further research/reviews required

Long-term research is recommended for safety purposes.

Written by Professor Norman Waugh, University of Aberdeen, United Kingdom

INAHTA Briefs

Issue 2007/157

Title **The Effectiveness and Cost Effectiveness of Carmustine Implants and Temozolomide for the Treatment of Newly Diagnosed High Grade Glioma: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2007;11(45). Nov 2007. www.hta.ac.uk/execsumm/summ1145.htm

Aim

To assess the clinical and cost effectiveness of adjuvant carmustine wafers (BCNU-W) and also of adjuvant and concomitant temozolomide (TMZ), compared to surgery with radiotherapy.

Conclusions and results

A large multicenter randomized controlled trial (RCT) suggested a possible survival advantage with BCNU-W among a cohort of patients with grade III and IV tumors, adding a median of 2.3 months. Analysis using per-protocol, unstratified methods shows this difference to be not statistically significant. Long-term followup suggests a significant survival advantage. The cost of surgery and radiotherapy, with followup, treatment of adverse effects, and end-of-life care is estimated to be around GBP 17 000 per patient. Treatment with BCNU-W adds GBP 6600. A modeled cohort of 1000 patients suggests BCNU-W costs an additional GBP 6.6 million and confers an additional 122 quality-adjusted life-years (QALYs). On average, that is GBP 6600 per patient for 0.122 QALYs. The base-case incremental cost-effectiveness ratio (ICER) is GBP 54 500/QALY. In probabilistic sensitivity analyses, BCNU-W was not cost effective in 89% of the simulations, assuming a willingness-to-pay threshold of GBP 30 000/QALY. It is unlikely to be the most cost-effective option at normal levels of willingness to pay.

TMZ provides a small but statistically significant median survival benefit of 2.5 months, giving a hazard ratio (HR) of 0.63. At 2 years, 26.5% of patients treated with TMZ were alive compared to 10.4% of those in the control arm. Median progression-free survival (PFS) is also enhanced with TMZ, giving a median 1.9 months' advantage. A median gain of 6.4 more life-months is seen with TMZ among those with reduced O6-methylguanine-DNA methyltransferase (MGMT), giving an HR of 0.51 ($p<0.007$). PFS is increased by a median of 4.4 months, giving an HR of 0.48 ($p=0.001$). The model shows a cost per patient treated with surgery, radiotherapy, and including adverse effects of treatment and end-of-life care of around GBP 17 000 per patient. TMZ in the adjuvant and concomitant phase adds around GBP 7800. Across the modeled cohort of 1000 patients, use of TMZ costs an additional GBP 7.8 million and confers an additional 217 QALYs. For the average patient this is GBP 7800 for an additional 0.217 QALY. The base-case ICER is GBP 36 000/QALY. Probabilistic sensitivity analysis shows that TMZ was not cost effective in 77% of the simulations. The cost-effectiveness acceptability curve (CEAC) suggests a 23% chance that TMZ is the most cost-effective option at a willingness-to-pay level of GBP 30 000/QALY, rising to be more cost effective than no TMZ at slightly higher levels (50% probability at GBP 35 000/QALY).

Recommendations

BCNU-W has not shown a significant advantage in survival for patients with grade III tumors when treated with the drug, compared to placebo, nor a survival advantage for patients with grade IV tumors. Limited evidence suggests a small (significant) advantage in both overall survival and PFS with TMZ in a mixed population with grade IV and III (7%–8%) tumors. There does appear to be a survival advantage for patients with grade IV tumors. Neither BCNU-W nor TMZ is likely to be considered cost effective by NHS decision makers (based on limited evidence of variable quality).

Methods

See Executive Summary link above.

Further research/reviews required

Future use of genetic and biomarkers may help identify subtypes that will respond, but current licensing indications do not specify these. Further research is suggested into the effectiveness of these drugs and other areas, eg, genetic markers, chemotherapy, and patient and carer quality of life.

Written by Ms Ruth Garside, PenTAG, Peninsula Medical School, United Kingdom

INAHTA Briefs

Issue 2007/158

Title **Drug-Eluting Stents: A Systematic Review and Economic Evaluation**

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Reference Health Technol Assess 2007;11(46). November 2007.
www.hta.ac.uk/execsumm/summ1146.htm

Aim

To assess the effectiveness and cost effectiveness of using drug-eluting coronary artery stents in percutaneous coronary intervention (PCI) in patients with coronary artery disease (CAD).

Conclusions and results

In the 17 randomized controlled trials (RCTs) of drug-eluting stents (DES) versus bare metal stents (BMS), no statistically significant differences in mortality or myocardial infarction (MI) were identified up to 3 years. Significant reductions in repeat revascularizations were determined for DES compared with BMS. This estimated benefit appears to be stable from 1 to 3 years. Binary restenosis and late luminal loss also favored DES. In the 8 RCTs of DES versus DES, no statistically significant differences in mortality or MI were detected between DES designs. In meta-analyses of target lesion revascularization (TLR), target vessel revascularization (TVR), and composite event rate, a marginal improvement in efficacy of Cypher™ over Taxus™ was observed. These results await confirmation beyond 1 year, and differences in study design may have influenced the reporting of outcomes. The review included 10 full economic evaluations, and the balance of evidence indicated that DES are more cost effective in higher risk patients. The review of submitted models confirmed the view that DES may be cost effective only under very limited circumstances when realistic assumptions and data values were used. In the cost-utility analysis of DES versus BMS, the use of DES appears to reduce the rate of repeat revascularizations; benefit estimates used in the economic assessment are defined as 'broad' (ie, cases involving any TLR/TVR irrespective of any other lesions/vessels undergoing revascularization) and 'narrow' (ie, cases involving TLR/TVR only). The incremental benefit to the patient is described as the loss of quality-adjusted life-years (QALYs) avoided by not having to undergo repeat revascularization. Univariate sensitivity analysis and extreme values analysis indicate that the price premium, numbers of stents used in the index procedure, and absolute risk reduction in repeat interventions most significantly influence the cost-effectiveness ratios. Sensitivity analyses also permit a range of values for efficacy and effectiveness to be considered for individual designs of DES. The cost-effectiveness results reveal that (all patients considered together) the calculated cost per QALY ratios are high (GBP 183 000–562 000) and outside the normal range of acceptability. Cost effectiveness is only achieved for those non-elective patients who have undergone a previous coronary artery bypass graft and have small vessels. 'Real-world' data show that patient numbers in this latter group are small.

Recommendations

DES would be best targeted at subgroups of patients with the highest risks of requiring re-intervention, and could be considered cost effective in only a small percentage of such patents. This is similar to the conclusion of our previous assessment. The annual volume of DES purchased by the NHS in England is estimated to range between 35 000 and 42 000 units, costing an additional GBP 21–25 million. If anecdotal evidence of 70% current DES usage is accepted, the estimated total cost of purchasing DES rises to GBP 30–36 million; if 100% DES usage were assumed, the projected cost would be around GBP 42–51 million.

Methods

A systematic literature review of effectiveness focused primarily on RCTs. Full economic evaluations that compared 2 or more options, and considered both costs and consequences, were eligible for inclusion in the economic review. A critique of manufacturer submissions to NICE and an economic evaluation (cost-utility analysis) were carried out.

Further research/reviews required

Further research would be useful in the following areas: trials of DES compared with new generation BMS, trials of DES compared with DES, and evaluation of newer BMS in combination with drug administration.

Written by Ms Rumona Dickson, University of Liverpool, United Kingdom

INAHTA Briefs

Issue 2007/159

Title **The Role of Hyperbaric Oxygen Therapy in the Management of Autism**

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Reference 2007-11. ISBN 978-2-550-51397-1.
www.aetmis.gouv.qc.ca/site/en_publications_2007.phtml

Aim

To present the published scientific data and current studies on the presumed efficacy of hyperbaric oxygen (HBO) therapy in addressing the symptoms of autism.

Conclusions and results

The question about the efficacy of HBO in managing autism is part of the broader mandate given to AETMIS by the Minister of Health and Social Services to update a previous report. That report outlines the indications for which the efficacy of HBO is supported by scientific data. The Minister specifically asked AETMIS to pay special attention to cerebral palsy and autism. The first of these topics was already the subject of an assessment report submitted to the Minister in January 2007.

Despite a thorough literature search of scientific databases, textbooks, and websites dealing with autism or HBO, it must be concluded that there is a lack of evidence. Apart from 2 descriptions of anecdotal cases, the only results available are from a randomized controlled trial and 3 case series studies, 2 of which are described only briefly. These studies seem to indicate a reduction in autism symptoms, but their validity cannot be demonstrated due to the small patient samples and methodological weaknesses.

Five current studies on this subject were also identified. In examining their designs, the oxygen and pressure parameters were found to vary from study to study. Furthermore, the number of subjects enrolled is small, ranging from 10 to 60. Both factors will influence the analysis and interpretation of results when these studies are published.

In light of its assessment, AETMIS concludes that the evidence is insufficient to build a strong case for the efficacy of hyperbaric oxygen therapy in managing autistic disorders. For now, hyperbaric oxygen therapy should be considered an experimental treatment modality in the management of autism. As such, this treatment should be limited to formal research projects.

Methods

Systematic review of scientific publications; search in scientific databases (Biosis, CINAHL, Dissertation Abstracts, Current Contents, the Cochrane Library, Psychological Abstracts, PubMed, EMBASE, and Web of Science); Manual search in recognized journals (Austism, Journal of Autism and Developmental Disorders, and Child Neuropsychology); examination of grey literature in the Web (National Institute of Mental Health, Canadian Autism Intervention Research Network, Autism Society Canada, and Autism Society of America).

Further research/reviews required

A literature watch should be conducted to evaluate the results of the current and future studies.

Written by Khalil Moqadem and Gilles Pineau, AETMIS, Canada

Title **Monitoring Depth of Anesthesia – A Health Technology Assessment**

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Reference 2007; 7(2). ISBN 978-87-7676-517-0. Full text report in Danish and English summary available at www.sst.dk/publ/Publ2007/MTV/Soevndybde/monitorering.pdf

Aim

To evaluate, and consider the economics of, whether the use of anesthetic depth monitors during anesthesia should be recommended to reduce the incidence of awareness and/or to shorten and improve the quality of recovery from anesthesia.

Conclusions and results

None of the monitors can predict response to painful stimulus. However, if sleep index remains stable following the start of surgery, the index may be used to titrate the depth of anesthesia during the procedure. None of the monitors indicate the true level of sleep. Hence, the results of monitoring must be compared with the clinical signs traditionally used to evaluate depth of anesthesia.

It is well documented that Bis-monitoring may reduce the incidence of awareness. It is likely, but not documented, that the other monitors will be similarly efficient in this feature. However, use of anesthesia depth monitors will not reduce recovery time or complications in the immediate postoperative period. Both the CS and AEP-II monitors are cost effective, whereas the Bis- and Entropy monitor cost approximately 80 Danish kroner (DKK) per case. Monitors based on the spontaneous EEG and evoked response seem to be similarly effective.

Recommendations

Because of the documented efficiency of these monitors, we recommend that they shall be used as a minimum for anesthesia of all high-risk cases, and that it should be considered to use them for all cases of general anesthesia. This will reduce the incidence of awareness and likely increase patient satisfaction with anesthesia.

Methods

This medical technology assessment is a systematic literature review.

Written by Birgitte Bonnevie, DACEHTA, Denmark

Title **Hereditary Nonpolyposis Colorectal Cancer in Denmark – A Health Technology Assessment**

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Reference 2007; 7(3). ISBN 97887-7676-450-0. Full text report in Danish and English summary available at www.sst.dk/publ/Publ2007/MTV/HNPCC/HNPCC.pdf

Aim

To review the present situation for patients suspected of having hereditary colorectal carcinoma (CRC) and to provide recommendations for the future.

Conclusions and results

- Families with hereditary CRC (HNPCC) are identified primarily in surgical departments, and HNPCC patients/families are registered at every contact with the healthcare system.
- HNPCC families are also at increased risk for other types of cancer – most frequently, eg, in the uterus, stomach, small intestine, bile tract, upper urinary tract, and brain.
- Notions of individual autonomy and bodily integrity represent core values in established medical ethics. These values are challenged by the concept of prevention (the societal wish to save lives), which in concert with the establishment of the family tree in genetic counseling makes information to family members a concrete possibility.

In conclusion, the fraction of colorectal cancer caused by hereditary factors is unknown. The well-known syndromes of familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) comprise 5% of all patients with colorectal carcinoma. It is estimated that hereditary factors are involved in up to 35% of all cases with CRC, although neither biological mechanisms nor heredity are known. HNPCC is by far the most frequent hereditary syndrome causing CRC.

Recommendations

The recommendations include:

- To establish a national classification system of HNPCC diagnoses as a common database
- To establish nationally uniform guidelines for informed consent to genetic counseling
- To establish higher integration of the different medical specialties: surgery, pathology, clinical genetics, and clinical biochemistry
- To advise families with an increased frequency of stomach or urinary tract cancer to follow a more intensive control program, including gastroscopy.

Methods

Registries have been reviewed and data have been compiled.

Written by Birgitte Bonnevie, DACEHTA, Denmark

Title **Followup Home Visits at Elderly Patients after Discharge from Hospital – A Health Technology Assessment**

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Reference 2007; 7(4). ISBN 978-87-7676-543-9. Full text report in Danish and English summary available at www.sst.dk/publ/Publ2007/MTV/Hjemmebesoeg/opf_hjemmebesoeg_aldre.pdf

Aim

To examine:

- If the chosen system – early, structured, and close followup of elderly patients by their GP and a visiting nurse after discharge from a medical or geriatric department – contributes to better patient treatment.
- The extent to which the chosen system can be implemented according to finances, present actors, and organizational structures.

Conclusions and results

The study documents a positive effect on treatment quality in terms of:

- The GP gains a better overview of the medical treatment of patients. The intervention is shown to reduce the inconsistency between the GP's knowledge and the patient's intake even though many of the intervention patients still take medicine that the GP does not know of, or where the GP provides information about medicine that the patient is not taking
- Better followup of the recommendations in the discharge letter
- Reduced risk for subsequent hospitalization.

Economic analysis indicates that the intervention is cost neutral with a tendency toward socioeconomic gain in favor of patients subjected to increased followup.

If the evaluated model is to be implemented, some basic conditions are necessary, including:

- Central or local procurement of a contractual basis for a system
- Managerial and political support
- Establishment of a fixed framework and agreements regarding the cooperation
- A motivated healthcare staff. They should prioritize the task and show flexibility vis-à-vis arranging joint visits to patients. Time pressure could be an obstacle to followup.

Recommendations

The project group recommends implementation of systems with improved post-discharge followup of elderly patients under medication. Inclusion of joint, focused home visits by the GP and the visiting nurse in the systems and a supplemental followup visit at the patient's GP should be offered. The project group also recommends efforts aimed at selected patient groups in special need of followup. Finally, the group recommends implementation of a register-based evaluation where the effect of the interventions is continuously reviewed.

Methods

The study consists of a randomized, controlled intervention study where data were collected via registration forms, patient interviews, and registers. This was supplemented by a survey and focus group interviews to examine the organizational situation.

The intervention was carried out from November 2003 to June 2005, followed by the organizational study. The project included 331 patients aged 78 years or more, discharged from the medical or geriatric department at Glostrup Hospital after admission of at least 2 days. All 7 municipalities near the hospital and 63% of the GPs in the area were enrolled in the project.

Written by Helle Neel Jakobsen, the Capital Region of Denmark, Denmark

Title **Followup Visits from Nurses after Discharge from Multidisciplinary Pain Center – A Health Technology Assessment**

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Reference 2007; 7(5). ISBN 978-87-7676-546-0. Danish, English summary.
www.sst.dk/publ/Publ2007/MTV/Tvaerfagligt_smertecenter/ss_tvaerfagl_smertecenter.pdf

Aim

To examine whether followup visits to chronic non-malignant pain patients after discharge from a multidisciplinary center could:

- Prevent a drop in the patients' health-related quality of life (HRQoL)
- Reduce patients' use of health services
- Be implemented in a way that is satisfactory to the parties involved.

Conclusions and results

- There was a tendency toward better HRQoL and (slightly) more quality-adjusted life years (QALY) in the intervention group versus the control group. Pain patients with poor physical HRQoL improved most. Opioid use increased markedly in the control group, but not in the intervention group. The nurses noticed symptoms of depression in 80% of the patients who developed depression during the project period and could refer them to early treatment. Patients in the intervention group reduced their use of catastrophizing.
- The intervention reduced the patients' use of health services by 37% over the 2-year intervention period. The savings more than make up for extra expenses incurred by followup visits.
- The applied model for implementation of followup visits is considered relevant and useful by patients, nurses and general practitioners.

The analysis shows that followup nurse visits tend to be a cost-effective service, as (slightly) more QALYs and lower costs to the health system are achieved. It is important to anchor this service in the multidisciplinary pain centers.

Recommendations

The project group recommends that followup visits by nurses to chronic non-malignant pain patients after discharge from a multidisciplinary pain center be implemented. Nurse visits should be offered to those patients who will benefit most from intervention, namely patients with low physical HRQoL, patients who often use catastrophizing, and patients who take opioids.

Methods

A randomized controlled trial (RCT) that enrolled 102 patients investigated the program's health effect on HRQoL. Fifty-two patients were included in the intervention group and 50 in the control group. The intervention group received home visits every fourth month over a 2-year period.

Patients' perceptions of the visits were evaluated by questionnaires and by focus group interviews. Data concerning the use of healthcare resources were collected from administrative registers from the 5 hospitals in the catchment area (HS) and from the primary care service registers in Copenhagen and Frederiksberg municipalities.

Further research/reviews required

Outcomes and costs should be systematically monitored.

Written by Liv Frich and Jette Højsted, Rigshospitalet, and Jan Sørensen, University of Southern Denmark, Denmark

Title **HTA of Computer Assisted Surgery Used in Orthopedic Surgery – Focused on Total Knee Arthroplasties**

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Reference 2007; 7(7). ISBN 978-87-7676-598-9. Full text report in Danish and English summary available at www.sst.dk/publ/Publ2007/MTV/computer-assisteret/CAS_net_final.pdf

Aim

To investigate the evidence concerning the use of computer assisted surgery (CAS) in total knee replacement (TKR) and to assess the consequences of CAS for technology, the patient, the organization, and the economy.

Conclusions and results

- A conservative analysis shows that CAS is more expensive than traditional total knee arthroplasty by approximately 10 000 Danish kroner (DKK).
- CAS provides a possibility for more precise placement of the prosthesis measured on radiographs. The literature shows a reduction in numbers of outliers.
- A clear connection has not been established between a more precisely placed prosthesis and an improved early range of movement.
- CAS technology is advantageous in patients where traditional instrumentation is not possible due to malalignment in the femur or tibia.

Recommendations

Potential applications in knee arthroplasty for CAS could include revision surgery and the further development of minimally invasive surgery (MIS) technology.

Methods

Chapters regarding the technology, patient, and organization consist of systematic literature reviews of all available randomized controlled trials. The chapter on economics consists of a systematic literature review and an independent cost analysis.

Further research/reviews required

It will be necessary to explore the revision rate for CAS beyond 10 years because the use of CAS is expected to diminish the long-term revision rate, compared with traditional knee arthroplasty.

Written by Jensen CM, Rohde T, and Paulsen AW, University Hospital of Herlev, and Hansen BB and Poulsen PB, Muusmann Research and Consulting, Denmark

Title **A Review of Organizational and Patient-Related Assessments in HTAs Published by INAHTA Members**

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Reference 2007; 9(2). ISBN 978-87-7676-504-0.
www.sst.dk/publ/Publ2007/MTV/Litteraturstudie/A_review_of_HTAs.pdf

Aim

1. To describe the extent to which international HTAs include organizational and patient-related assessments.
2. To describe and discuss the content and handling of organizational and patient-related assessments in international HTAs, to describe 'best practice', and to present recommendations for organizational and patient-related assessments in future HTAs.
3. To describe and discuss the methodology used in HTAs to generate and analyze data for assessing organizational and patient-related issues, and to describe the extent to which HTAs report on the methodology used and on the generalizability of organizational and patient-related results in other contexts.

Conclusions and results

Inclusion of organizational and patient-related assessments in HTAs is less common than inclusion of technological/clinical and economic assessments. When organizational assessments are included they mainly concern issues such as: the actors and organizations associated with use of the technology, work flow, staff numbers and skills, physical resources, and legislative structures. Issues related to organizational culture, communication, and physical and psychological work environments are less often included. When patient-related issues are included they mainly concern issues such as: fear and discomfort, impact on the patient's daily life and quality of life, patient acceptance of the technology, and patient information. Issues related to patient involvement in decision-making and how a technology impacts patients' personal economy and their significant others are less often included. While some HTAs include a variety of issues, they are often handled in a restricted and superficial way. More comprehensive assessment of the issues is less often performed. There is room to improve the methodologies applied in assessments since most reports simply describe the methods used to generate and analyze data. Fewer reports discuss the methodological choices made and their consequences.

Recommendations

For an HTA to function as a decision-making tool, it must be comprehensive and take a broad view. Including an assessment of the potential organizational and patient-related issues relevant to the technology under study must be considered. The types of organizational and patient-related issues to include in an HTA, and which assessment methodology to use, depends on the purpose and scope of the HTA and the research questions. HTAs should report not only on the methodological steps taken, but also why these choices were made and their impact on the findings, including the generalizability of the results. This information will enable readers to evaluate the relevance and reliability of the findings.

Methods

Quantitative and qualitative analyses were based on a review of organizational and patient-related assessments found in a random sample of 50 full HTA reports identified from INAHTA members' websites and that included organizational and/or patient-related assessments published in English or a Scandinavian language.

Further research/reviews required

Development of systematic and relevant analytical models or frameworks would enhance the general quality of organizational and patient-related assessments. Further investigation is needed to determine useful ways to report on the generalizability of results from organizational and patient-related assessments.

Written by Lee A and Sinding LS, DACEHTA, Denmark

INAHTA Briefs

Issue 2008/007

Title **Point-of-Care Testing in the Private Sector**

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Reference 08-01. ISBN 978-2-550-51186-1.
www.aetmis.gouv.qc.ca/site/en_publications_2008.phtml

Aim

To perform an exhaustive literature review that would help provide an appropriate definition for point-of-care testing (POCT), draw up a list of Canada-approved kits and instruments, flag the major issues associated with POCT, and identify the quality-control and quality-assurance measures proposed in Canada and worldwide.

Conclusions and results

In light of our assessment based on analysis of the major issues raised by POCT and examination of the different measures in place in other provinces and countries to ensure the quality of this practice, AETMIS has identified the principles and conditions that could guide how this practice should be governed in Québec.

As a general rule, POCT should be performed only when justified by the need for a rapid response and in situations requiring immediate test results. This type of testing seems more appropriate for patient monitoring than for disease screening or diagnosis. Point-of-care testing must remain a complementary adjunct to central laboratory services. In an effort to promote high-quality test results and prevent any harm to people's health, the following conditions must be met: 1) Point-of-care testing must be performed in a secure setting that meets strict quality standards, 2) Each step in the testing procedure must be accurately recorded in the medical file and the source of errors at the different testing stages must be identified, 3) The confidentiality of patients' test results and consultations with the health professionals who order the tests must be safeguarded, 4) Responsibilities must be clearly defined in policies and procedures on the use of the different tests, 5) The appropriateness and frequency of tests must be evaluated, and 6) Manufacturers' recommendations, maintenance programs, and hygiene and waste-disposal measures must be strictly observed.

Any decision on prioritizing these tests must be based on a comprehensive analysis of each test, including an economic component to ensure that its benefits outweigh its disadvantages and costs.

Methods

Literature review (primary scientific studies in MEDLINE, the Cochrane Library 2007, and EMBASE), search with keywords in various websites (laboratories, standards organizations, and provincial Health Ministries), and consultation with experts from the private sector.

Written by Carole St-Hilaire, AETMIS, Canada

INAHTA Briefs

Issue 2008/008

Title **Smoking Cessation in Different Socioeconomic Groups**

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Reference Report no 13-2007. ISBN 978-82-8121-162-9.
www.kunnskapssenteret.no/filer/Sosialulikhetogroyking_nettversjon.pdf

Aim

To determine the effect of interventions to reduce smoking among different socioeconomic groups and in lower socioeconomic groups.

Conclusions and results

We summarized results from 4 reviews and 19 randomized control studies and defined 4 main target groups for smoking cessation interventions. Studies of smoking prevention in schools showed compounded results. Students with technical college and lower academic education had stronger intention to smoke. Free nicotine patches and supporting telephone calls for pregnant women showed only a short-term effect on smoking cessation. High family income and few smoking friends were important factors for smoking cessation. Interventions targeted at adult daily smokers were effective. High socioeconomic status, high motivation to quit, low nicotine dependence, and amount of time spent with non-smokers are important factors for the duration of smoking cessation. Interventions targeted at patients with better social networks have a higher probability of success, ie, quit smoking. Counseling increased smoking cessation among lower socioeconomic groups compared with high socioeconomic groups. Smoking cessation interventions are most efficient in groups with high socioeconomic status. Few studies report separate effects for groups with lower socioeconomic status.

Methods

We conducted a systematic literature search in the following electronic databases: MEDLINE, EMBASE, Cochrane Library, PsycINFO, CINAHL, Social Services Abstracts, Sociological Abstracts, Eric, International Bibliography of the Social Sciences, Social Sciences Citation Index, Social Care Online, C2-SPECTR, SveMed, BiblioMap, Bibsys, and Google Scholar until November 2006. Relevance and study quality are appraised according to the Knowledge Centre's methodological handbook.

Further research/reviews required

Further intervention research is needed in Norway and internationally regarding daily smokers in the lower socioeconomic groups. In effect studies, background data are collected at the outset of the studies (baseline). Hence, many studies report socioeconomic data to appraise whether the groups are comparable. We have identified a need for analyzing socioeconomic differences in existing data. This, however, is a time-consuming process and one that is difficult to accomplish.

Written by Asbjørn Steiro, Geir Smedslund, and Karianne Thune Hammerstrøm, NOKC, Norway

Title **In Vitro Maturation of Oocytes Within Assisted Reproduction**

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Reference Report no 18-2007. ISBN 978-82-8121-167-4. ISSN 1890-1298.
www.kunnskapssenteret.no/filer/IVM_rapport_nettversjon.pdf

Aim

To summarize the documentation of clinical outcomes from in vitro maturation (IVM) cycles and the obstetric, perinatal, and devolopmental outcomes in IVM children.

Conclusions and results

We included 17 relevant publications representing 8 unique datasets. Few studies were controlled, and no randomized controlled trials were identified. These studies documented results from 182 IVM children. Two studies included followup data, but no studies had followed the children more than 2 years.

Reported rates of spontaneous abortion varied between 17% and 63%. Pregnancies per embryo transfer in the studies varied between 0% and 36%. Alhough the included studies reported that IVM children were healthy, and showed normal development, further studies are needed to draw conclusions regarding the impact of IVM on child health and development.

There are no relevant, randomized controlled trials reporting clinical success or safety following IVM in assisted reproduction. Few children are born after IVM, and few studies with short followup time have followed IVM children.

Methods

We systematically searched for litterature in the following databases: Cochrane Library, MEDLINE, and EMBASE for the period 2004–2007.

Further research/reviews required

Further research and surveillance are needed regarding the use of in vitro maturation of oocytes. Due to the small number of children conceived in Norway using different methods of assisted reproductive technology, there is need for international collaboration to initiate followup studies of children.

Written by Therese Opsahl Holte, NOKC, Norway

Title **Dual Diagnoses – Substance Use Disorder and Severe Mental Illness. Accuracy of Screening- and Diagnostic Instruments**

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Reference ISBN 978-82-8121-182-7. ISSN 1890-1298.
www.kunnskapssenteret.no/filer/Rapport_07_21_Dobbeldiagnose.pdf

Aim

To determine which screening or diagnostic tests can better uncover substance use disorder (SUD) in a population with severe mental illness (SMI), and to determine which screening or diagnostic tests can better uncover SMI in a population with SUD.

Conclusions and results

Screening tests for SUD in patients with SMI: According to the evidence, the Chemical Use, Abuse, and Dependence Scale (CAGE) is able to identify alcohol disorder (LR+ 13), both current and lifetime. The Alcohol Use Disorders Identification Test (AUDIT) reports an area under the receiver operating characteristic (ROC) curve of 0.95. This means that the tests' ability to identify patients with alcohol disorder, and not identify those without, is high. The remaining studies did not report the likelihood ratio, or the likelihood was reported as low.

Screening tests for SMI for patients with SUD: The evidence base suggests that the Psychiatric Diagnostic Screening Questionnaire (PDSQ) could identify mania well (SaR+ 21). For depression, psychotic disorders, and personality disorders the evidence base did not report figures that could decide diagnostic accuracy.

Diagnostic tests: The two tests – the Computerized Diagnostic Interview Schedule (C-DIS) and the Minnesota Multiphasic Personality Inventory (MMPI) – both showed low diagnostic accuracy (LR+ below 10) when compared to reference standard (CIDI, LEAD, MINI, SCID, or thorough clinical evaluation). The Psychiatric Research Interview for Substance and Mental Disorders (PRISM) shows good concordance with the reference standard, reporting a kappa between 0.63 and 0.90 (usually considered good) for borderline personality disorders, alcohol dependence, heroin dependence, and severe depression.

Methods

Cochrane Library, MEDLINE, EMBASE, Center for Reviews and Dissemination (CRD), SveMed+, and PsycINFO were searched up to April 2007 with text words and subject headings in combination with search filters for screening and diagnostic tests. Studies were included if the population had SMI and SUD, were older than 16 years, the index test tried to measure SUD or SMI, and the outcomes were SUD or SMI measured by a reference standard (defined as CIDI, SCID, MINI, LEAD, or thorough clinical examination) based on the DSM or ICD criteria. The included studies had to have a cross-sectional design using a reference standard (gold standard) and research methods that enabled calculation of diagnostic accuracy.

Further research/reviews required

This approach delivers a high level of accuracy and considerable precision in results. However, some measurement tools that could be clinically relevant might have been excluded from the review due to the research methodology employed. It would be helpful to have specific reviews on the different tests.

Written by Larun L, Helseth V, Bramness JG, Gråwe RW, Haugerud H, Høie B, Kornør H, Landheim A, Lossius K, Hammerstrøm KT, and Waal H, NOKC, Norway

Title **Effects of Geriatric Care for Elderly Inpatients**

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Reference Report no 14-2006. ISBN 82-8121-134-2.
www.kunnskapssenteret.no/filer/rapport14_06_geriatriske_tiltak.pdf

Aim

To assess whether geriatric evaluation and management of elderly inpatients leads to improved outcomes compared to the provision of ordinary care.

Conclusions and results

This overview includes 13 systematic reviews published between 1993 and 2005. Most of the studies were conducted in the United States, but relatively few in Europe. Most reviews included studies of general multidisciplinary geriatric evaluation and management of elderly patients admitted to hospitals due to acute functional failure, compared to routine care, eg, in a medical department. The results were categorized in two groups:

1. Geriatric evaluation and management in specialized units/departments in the hospital
2. Geriatric consultation services by a team or an individual for departments in the hospital.

Evaluation and management studies in specialized units showed a positive effect on survival and return to the patient's own home versus death or institutionalization. The results were less convincing when mortality was considered alone. Findings were inconsistent for other important outcomes, eg, level of functioning, need for hospitalization, and length of stay. Using multidisciplinary consultation teams in hospitals has not been shown to be effective.

Recommendations

The expected increase in number of elderly citizens indicates that more research is needed to develop and evaluate new, potentially improved, interventions and to identify criteria to identify the elderly patients who are most likely to gain from specialized geriatric management strategies.

Methods

This report is predominantly an overview of reviews, ie, we have searched for, critically appraised, and summarized research from existing systematic reviews of relevant effectiveness studies.

Written by Elisabeth Gjerberg, Arild Bjørndal, and Atle Fretheim, NOKC, Norway

Title	**Overview of Systematic Methodology Reviews of the Design and Conduct of Randomized Trials and Systematic Reviews of Healthcare Interventions**
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Reference	Report no 17-2006. www.kunnskapssenteret.no/filer/rapport17-06_practihc_revidert.pdf

Aim

To support Pragmatic Randomized Controlled Trials in HealthCare (Practihc) guidance for designing pragmatic randomized trials:

- to inform future revisions of the CONSORT guidelines for reporting randomized trials
- to inform guidelines for conducting and reporting systematic reviews
- to inform decisions about priorities for Cochrane methodology reviews.

Conclusions and results

Twenty-eight methodology reviews, covering 16 topics, were included. Thirty-one structured abstracts were prepared for the included reviews, and a commentary was written for each topic area.

Many decisions about the design and reporting of randomized trials and systematic reviews must be based on logical arguments – but often with uncertainty about what empirical evidence is available (due to the lack of a systematic methodology review), or uncertainty about the impact of alternative decisions (due to the lack of empirical evidence).

This uncertainty not only impacts on the use of resources for research, but it has important consequences for the availability of reliable evidence to inform decisions about health care.

Methods

Methodology reviews were compiled by searching the Cochrane Methodology Register, the Cochrane Database of Methodology Reviews, and UK NHS HTA Methodology Reviews. Two reviewers identified potentially relevant reviews. These were retrieved, and the same two reviewers assessed the relevance. A structured abstract and a commentary were prepared for each included methodology review.

Further research/reviews required

In general, relatively few systematic methodology reviews are available, and many of the included methodology reviews found a paucity of empirical evidence. There are many important methodological questions for which no systematic reviews were found.

Written by Elizabeth Paulsen, NOKC, Norway

INAHTA Briefs

Issue 2008/013

Title **Use of Scorecards in Hospitals**

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Reference Report no 19-2007.
www.kunnskapssenteret.no/filer/malstyring_nettversjon.pdf

Aim

To assess whether the implementation of 'scorecards' in hospitals provide better strategies, better management, or better hospital quality.

Conclusions and results

Hospitals have implemented different tools for performing 'evidence based' leadership to meet the challenges of modern hospital management. The Balanced Scorecard (BSC) and EFQM Excellence Model (EFQM) are among such tools. The key mission of these is to provide a system for evaluating the organization from several predefined perspectives.

Results: We retrieved 639 possibly relevant publications, whereof 71 articles were obtained in full text, and 5 studies were finally included. Four studies reported experiences from implementing BSC and one study reported on EFQM.

Included studies described that scorecards may be useful at a local level to define strategic aims, measure quality indicators, define lower levels for quality action, compare departments over time, or evaluate implementation of new treatment options. We found no evidence that implementation of BSC or EFQM influenced hospital management or quality.

- Three studies reported results in different areas after implementing BSC at a hospital department level: emergency unit, anesthesia department, and nephrology department. The studies described development of criteria and indicators for measuring, but could not relate the results to implementation of BSC or EFQM.
- Two studies reported results on an institutional level. One study used EFQM to evaluate the implementation of evidence based treatment processes in an addiction center in the Netherlands. Another study used indicators in the BSC model to compare one hospital in Japan with a Chinese hospital. Both studies assessed the models as useful for measuring quality.

Conclusion: Research on the usefulness of scorecards is especially challenging since scorecards may influence different levels in a hospital and affect different time points.

- There is no evidence that BSC or EFQM influence hospital performance.
- There are descriptive reports on scorecard usefulness for different purposes in local settings.
- Time series with several pre- and post-measurements would add to our understanding of the usefulness of scorecards.
- More research and development of suited methodology are needed.

Methods

A systematic literature review was conducted using a defined search strategy and predefined criteria for selecting studies. Two researchers, independent of each other, assessed quality, extracted data, and summarized the results.

Written by Unni Krogstad, Sari Ormstad, and Inger Norderhaug, NOKC, Norway

Title	**Proton Therapy**
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Reference	Report no 11-2006. ISBN 82-8121-067-2. Full text report: www.kunnskapssenteret.no/filer/rapport11_06_protonterapi.pdf

Aim

To review the documentation on the use of proton therapy in treating cancer.

Conclusions and results

Proton therapy is used in radiation treatment and is an established practice in many countries, but not in Norway. Proton therapy, more than conventional radiation treatment, allows the radiation dose to be limited to within the tumor. This reduces radiation to surrounding normal tissue, potentially yielding fewer complications. Proton therapy also allows delivery of higher radiation doses to the tumor than conventional radiation treatment does. Documentation of the treatment's effect is based mainly on noncontrolled studies. A few randomized controlled studies have been conducted, but only one of these studies has complete data. A significant problem is that studies used different patient groups in comparing proton therapy with other treatments. Also, proton therapy is not fully standardized. Most patients treated with proton therapy have received treatment at basic research laboratories, rather than in established clinical units. This too has limited the research, and may have influenced the studies.

Recommendations

None given.

Methods

A group of Norwegian scientists with expertise in radiation biology, physics, oncology, and method evaluation was asked to conduct a systematic review of scientific documentation on the clinical effects of proton therapy in treating malignant and benign tumors. The group conducted a MEDLINE search and searched for ongoing studies in the Cochrane Library or PDQ, National Cancer Institute and current controlled trials. Several inclusion/exclusion criteria were established, and each study was evaluated against checklists prepared by NOKC.

Further research/reviews required

None of the included studies compared proton therapy with conventional radiant treatment. Hence, it was recommended that randomized controlled studies be conducted to document the clinical utility value of proton therapy, including survival, local tumor control, and complications in normal tissue.

Written by Dag Rune Olsen, Øyvind Bruland, Gunilla Frykholm, and Inger Norderhaug, NOKC, Norway

INAHTA Briefs

Issue 2008/015

Title **Mammography Screening of Women Aged 40 to 49 Years**

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Reference Report no 9-2007. ISBN 978-82-8121-153-7. ISSN 1890-1298.
www.kunnskapssenteret.no/filer/mammografiscreening40_49.pdf

Aim

To summarize evidence on the effect of mammography screening in women between the ages of 40 and 49 years at average risk for breast cancer.

Conclusions and results

Women aged between 40 and 50 years probably have a slightly smaller risk of dying from breast cancer than women who do not follow such a program. We have estimated the relative risk reduction for dying, for women in their 40s who are invited to screening, to be 16% (confidence interval 4–27%) after 13 years of followup. In our judgment, this is an optimistic estimate. Studies of the highest methodological quality show a smaller effect, and some of the effect may be due to screening after 50 years of age. The absolute risk reduction is 0.0003, or approximately 1 in 3000 after 13 years. Potential risks that have been discussed in connection with mammography screening of younger women are overtreatment of certain cancer types (DCIS), radiation-induced breast cancer, greater risk of false negatives, or the psychological effect of false positive mammograms.

Recommendations

Whether or not the benefit outweighs the harm in breast cancer screening is debatable, especially for younger women. Policy makers must also consider ethical issues and the need for resources. At the personal level, womens' own perceptions of risk and individual preferences, informed by balanced information, should be part of the decision-making process.

Methods

Data were gathered from 3 systematic reviews that summarized existing research on the effects of inviting large groups of women to a screening program. Also included was a randomized controlled trial published in 2006.

Further research/reviews required

The balance between benefit and potential harm of mammography screening in women younger than 50 years is delicate. The balance could be shifted by results from research on how to increase sensitivity and specificity of mammography, particularly in women with dense breast tissue. Also, research on how to distinguish between different types of cancers, eg, DCIS, would be important to counteract overtreatment. Lastly, although the risk of radiation-induced breast cancer is considered to be small, the cumulative risk of another 10 years of mammography is unknown. Further research on the improvement of technology would be appropriate.

Written by Arild Bjørndal and Louise Forsetlund, NOKC, Norway

Title	**Efficacy and Safety of Newer Antidepressants in Adults**
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Reference	Report no 17-2007. ISBN 978-82-8121-166-7. www.kunnskapssenteret.no/filer/Rapport_07-17_SSRI.pdf

Aim

To systematically review the literature that compares the effect and safety among different selective serotonin reuptake inhibitors (SSRIs) and other second-generation antidepressants.

Conclusions and results

We included 12 different head-to-head comparisons out of 66 possible. Nine different antidepressants were involved in the comparisons. We did not find any significant differences among the antidepressants as regards effect and safety. The conclusions are based on documentation of medium or low quality.

Methods

We systematically reviewed the literature for effect and safety in head-to-head studies of SSRIs and other second-generation antidepressants used in adults with depression. The literature was identified by a systematic search in MEDLINE, EMBASE, PsychINFO, Cochrane Library, and the CRD databases. We also received literature from the pharmaceutical industry. Relevance and quality were assessed according to our handbook. We used GRADE to assess the documentation for each of the outcomes. Results are presented in tables and in a descriptive summary. Meta-analyses were also performed.

Further research/reviews required

The report shows that the head-to-head studies are few and insufficient. If further research in this area is desired, head-to-head studies with sufficient power to detect differences should be performed.

Written by Ingvil Sæterdal, Eva Pike, Tove Ringerike, and Marianne Klemp Gjertsen, NOKC, Norway

INAHTA Briefs

Issue 2008/017

Title **Laparoscopic and Laparoscopy-Assisted Colectomies**

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Reference www.has-sante.fr/portail/display.jsp?id=c_541177

Aim

To assess the efficacy and safety of 8 laparoscopic colectomy procedures to advise French National Health Insurance on their inclusion on the list of reimbursed procedures: right-sided colectomy (RC) with restoration of intestinal continuity; transverse colectomy (TrC); left-sided colectomy (LC) with restoration of intestinal continuity; total colectomy (TC) without restoration of continuity; TC with ileorectal anastomosis, total coloproctectomy (TCP) without restoration of intestinal continuity, and TCP with ileoanal anastomosis.

Conclusions and results

Laparoscopy is an alternative to open surgery when performing a colectomy. HAS considered the expected benefit to be adequate for all 8 procedures assessed and favors their inclusion on the list of reimbursed procedures.

- *Indications for laparoscopic colectomy:* cancer – RC for cancer of the cecum, ascending colon, colonic hepatic flexure; TrC for cancer of the transverse colon; LC for cancer of the colonic splenic flexure, descending colon, sigmoid colon; TC for hereditary non-polyposis colorectal cancer, multifocal cancer, cancer in patients with familial adenomatous polyposis (FAP), some obstructive colon cancers; TCP for cancer in patients with FAP and chronic inflammatory bowel disease (CIBD) and some non-malignant diseases (RC for Crohn's disease, LC for diverticular sigmoiditis, RC and LC for polyps not suitable for colonoscopic removal, TC and TCP for CIBD and FAP).
- *Laparoscopic TrC:* Not assessed in the literature. In the absence of published negative results and by analogy with other types of laparoscopic colectomy, the working group considered its efficacy and safety to be no different from that of open surgery.
- *Laparoscopic RC and LC:* Published morbidity rates were not much different from those for open surgery; the types of complication differed.
  - *In the short term,* at least as effective as open surgery;
  - *In the long term,* efficacy no different from that of open surgery for cancers (provisional conclusion) and at least equivalent for non-malignant diseases. The working group considered that laparoscopic RC for Crohn's disease provided a significant long-term parietal and cosmetic benefit even though its efficacy has been insufficiently assessed.
- *Laparoscopic TC:* Efficacy and safety were not much different from those for open surgery. The working group considered it a viable alternative in all malignant and non-malignant indications, even though the literature on cancers is inconclusive.
- *Laparoscopic TCP without restoration of intestinal continuity:* A rare intervention; published data inconclusive.
- *Laparoscopic TCP with ileoanal anastomosis:* Efficacy and safety were not much different from those for open surgery; literature on cancers inconclusive. The working group considered that it provides a significant long-term parietal and cosmetic benefit in non-malignant diseases.
- *Cost of laparoscopy:* Higher than that of open surgery. The extra cost may be offset by a shorter hospital stay in non-malignant cases. However, in cancer cases, the acceptability of the extra cost needs to be assessed in relation to the short-term benefits of the procedure.

Methods

Search of main medical and health economics databases (1996–2006); opinion of a working group of 7 gastrointestinal surgeons.

Further research/reviews required

Long-term oncologic results (main end-points for colorectal cancer surgery) have been inadequately assessed. Further data are needed to confirm the conclusions of the current literature review.

Written by Nathalie Bataille, HAS, France

INAHTA Briefs

Issue 2008/018

Title **Heart Surgery With or Without Extracorporeal Circulation: Role of the Second Surgeon**

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Reference www.has-sante.fr/portail/display.jsp?id=c_597156

Aim

To assess the need for a second surgeon during cardiac surgery, ie, extracorporeal circulation (EC) surgery or beating-heart surgery (241 listed procedures).

Conclusions and results

HAS defined the role, conditions for participation, and qualifications of the second surgeon and assessed the safety, clinical, organizational, and economic issues relating to the presence of a second surgeon.

- A second surgeon is usually present in French practice. The formal consensus panel confirmed that their presence is necessary for most cardiac surgery (all EC procedures and 50 beating heart procedures) to enhance safety, to help with technical maneuvers, and to shorten operative time.
- The presence of a second surgeon is customary in 8 of 10 countries (qualification in cardiac surgery in 6 of 10 countries), but is mandatory in California only.
- The second surgeon in France may be a registered qualified surgeon or a surgeon undergoing training under the supervision of the head of department.
- The second surgeon must be present in the operating block throughout EC surgery and throughout the construction of vascular anastomoses during bypass surgery. He/she should not be required to perform any other types of intervention or examination.
- The economic impact should consider the risks and benefits of the absence or presence of a second surgeon (impact on length of stay in resuscitation and/or intensive care, peri- and/or postoperative complications), but could not be assessed.
- The organizational impact of a second surgeon could not be evaluated.

Methods

Databases for English and French publications (MEDLINE, Pascal, HTA database, National guideline clearinghouse, Cochrane Library) were searched for 1996 to 2006, but provided insufficient information. A study of current French practice was therefore undertaken using 3 methods: a) a postal survey of all cardiac or vascular surgery teams with access to EC facilities; b) an analysis of hospital record databases; c) a formal consensus method. To perform comparisons, a questionnaire was mailed to professional societies, experts, and health technology agencies in 10 countries – Australia, Belgium, Germany, Italy, Netherlands, Spain, Switzerland, UK, USA (California), and Canada (Quebec) to obtain information on their practices and views regarding the presence of a second surgeon. The final report was validated by a working group of 20 health professionals and by 2 peer reviewers in health economics.

Further research/reviews required

HAS stressed the need for French surgeons to contribute activity data and morbidity and mortality data relating to heart surgery to the national Epicard registry.

Written by Valérie Lindecker-Cournil and Roselyne Delaveyne, HAS, France

Title **Psychosocial Interventions After Large Accidents and Disasters**

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Reference Report no 8-2006. ISBN 82-8121-123-7. Link to full text report:
www.kunnskapssenteret.no/filer/rapport8_06_psykososiale_tiltak_nettversjon.pdf

Aim

To systematically review the effects of psychosocial interventions after crises, accidents, and disasters.

Conclusions and results

The report included 14 studies: 6 randomized controlled trials (RCTs), 6 controlled before-and-after studies, and 2 cohort studies.

Four RCTs investigated the effects of psychological debriefing (PD) after major traumatic events. Two of these reported reductions in psychological distress after PD, but none of the studies were sufficiently methodologically robust to produce reliable effect estimates.

The remaining 10 studies included various other therapeutic modalities, from specific interventions such as Eye Movement Desensitization and Reprocessing (EMDR) and Experimental Mastery Technique to more general group psychotherapy. No or marginal differences in psychological distress between the intervention and control groups were observed.

A major trend appeared to show that several types of psychosocial interventions could be beneficial. However, the potential effects of these interventions remain uncertain due to poor study quality, low number of studies, small samples and heterogeneity.

Methods

We assembled an external expert panel consisting of 5 persons to assist in the systematic review. It was decided to focus exclusively on interventions after major accidents (transport or industrial accidents) and disasters. We carried out systematic searches in international research databases, using set criteria to select studies, checklists to assess study quality, and summaries based on standardized data collection forms. Results from the included studies were summarized in text only.

Written by Hege Kornør, NOKC, Norway

Title **Pharmacological Therapies for Opiate Dependence**

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Reference Report no 23-2006. ISBN 82-8121-124-5. Link to full text report:
www.kunnskapssenteret.no/filer/rapport2306_opiatavhengighet_nettversjon.pdf

Aim

To evaluate effects of methadone, buprenorphine, and naltrexone.

Conclusions and results

We included 5 systematic reviews and 17 recent single studies from the NICE report on methadone and buprenorphine therapy, and the entire report on naltrexone treatment (1 systematic review and 25 single studies).

Fewer persons treated with methadone, buprenorphine, or naltrexone used illicit opiates than in the control groups. These effects were assessed to be reliable. Further, there were methodological reasons to trust that methadone therapy increases retention rates compared with no pharmacotherapy or with buprenorphine. For naltrexone, no difference was found in retention between intervention and control groups. The results did not give a sufficiently robust basis to claim that pharmacological therapies reduce mortality, that additional psychosocial interventions or higher methadone doses are effective, or that retention rates are higher in specialist services than in primary care. However, the evidence base for these outcomes were of modest to low quality, and more research is needed to draw conclusions.

Several secondary clinical questions on pharmacotherapies for opiate dependence remained unanswered due to gaps in quality research, but it was clear that all 3 agents were effective in reducing illicit opiate use.

Methods

We selected studies from 2 recent reports from National Institute for Health and Clinical Excellence (NICE), and relied on the study quality assessments that had already been carried out. In addition, we used GRADE (Grading of Recommendations Assessment, Development, and Evaluation) to evaluate the reliability of the pooled effect estimates.

Written by Hege Kornør, NOKC, Norway

Title	**Psychosocial Interventions after Crises and Accidents**
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Reference	Report no 14-2007. ISBN 978-82-8121-163-6. Link to full text report: www.kunnskapssenteret.no/filer/Psykososiale_tiltak_ved_kriser_og_ulykker_nettversjon.pdf

Aim

To evaluate the preventive effects of psychosocial interventions delivered within 1 year following accidents and crises on trauma-related psychological disorders, functional impairments, and behavior problems.

Conclusions and results

We included 10 systematic reviews, 29 randomized controlled trials (RCTs) and 10 nonrandomized effect evaluations. The systematic reviews and the nonrandomized studies were accounted for only, while we performed more thorough analyses of the RCTs.

The 29 RCTs were published in 34 different articles. Interventions were:

- Psychological debriefing (PD) delivered in 1 or 2 sessions less than 3 weeks after trauma (7 studies)
- Other 1- or 2-session interventions, such as information, practical assistance and memory structuring therapy (4 studies)
- Cognitive behavior therapy (CBT) delivered in 4 to 14 sessions less than 6 months after trauma (9 studies)
- Other multiple-session interventions, such as group interventions, counseling programs and individual support (4 studies)
- Pharmacological interventions (2 studies)
- Interventions for traumatized children (3 studies)

Meta-analyses showed no effect from PD compared to no intervention. The outcomes were posttraumatic stress disorder (PTSD), posttraumatic stress symptoms, anxiety, and depression after 3 to 6 months and 1 to 3 years.

Meta-analyses also showed that CBT was effective, both in comparison with no intervention and with other interventions. Relative risk for a PTSD diagnosis for CBT versus other interventions was 0.54 after 3 to 6 months, 0.38 after 9 months, and 0.25 after 3 to 4 years.

Conclusions:

- Cognitive behavior therapy for 4 weeks or more may prevent trauma-related psychological disorders.
- There is no evidence of preventive effects of psychological debriefing.
- There is not sufficient research evidence on other types of interventions to draw conclusions about effects.

Methods

We searched international scientific databases, selected studies according to preset criteria, appraised the methodological quality using checklists, and summarized the results narratively, in tables, and in meta-analyses.

Written by Hege Kornør, NOKC, Norway

INAHTA Briefs

Issue 2008/022

Title **Optical Coherence Tomography of the Posterior Segment of the Eye**

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Reference www.has-sante.fr/portail/display.jsp?id=c_569665

Aim

To assess the clinical utility of optical coherence tomography (OCT) in diagnosing diseases of the retinal macula and optical papilla.

Conclusions and results

HAS considered the following indications for OCT (a non-invasive, contact-free imaging technique that uses refraction of laser beams):

1. *Age-related macular degeneration (ARMD):* OCT was found to be highly sensitive (78.6% to 87%) but moderately specific (66% to 89%) in diagnosing choroidal neovessels in patients with ARMD. It is an adjunct to the standard procedure (angiography) in diagnosing retinal or choroidal neovessels. It can be used as an alternative or adjunct to angiography when monitoring ARMD, particularly when assessing treatment effects.
2. *Macular edema and diabetic retinopathy (DR):* OCT was found to be highly sensitive (72.2% to 98.4%) and highly specific (81% to 95%) in diagnosing macular edema (in diabetic and non-diabetic patients). It is a first-line procedure for diagnosing macular edemas and for pre- and post-treatment monitoring of the condition. Color stereophotographic retinography of the fundus oculi can be performed as an alternative or adjunct to OCT during diagnosis.

   OCT can also be used to monitor DR, particularly as an adjunct to the standard procedure (angiography) when diagnosing retinal or choroidal neovessels and as an alternative or adjunct to angiography when monitoring neovessels. OCT is also a first-line procedure when diagnosing and monitoring diabetic macular edemas.
3. *Diseases of the vitreoretinal interface:* OCT is performed as a first-line procedure in diagnosing diseases of the vitreoretinal surface, particularly macular holes, pseudo-holes, lamellar holes and epiretinal membranes, and for pre- and post-treatment monitoring of these conditions.
4. *Severe myopia with choroidal neovessels:* OCT was found to be highly sensitive (78.6% to 87%), but moderately specific (66% to 89%). It is an adjunct to the standard procedure (angiography) during diagnosis and monitoring.
5. *Open-angle glaucoma:* When used to diagnose open-angle glaucoma, OCT was:
   - effective in establishing a diagnosis in patients with suspected glaucoma;
   - very effective in discriminating between eyes with and without glaucoma. Efficacy increased as disease severity increased;
   - effective in discriminating between early, moderate, and severe glaucoma.

OCT can be used as an adjunct to perimetry, tonometry, and gonioscopy in diagnosing and monitoring open-angle glaucoma. It cannot be used alone to screen for open-angle glaucoma.

HAS concluded that the clinical utility of this procedure is sufficient.

Methods

The assessment was based on a critical appraisal of the literature (main medical bibliographical databases; 1996–2007) and the opinion of 4 experts (ophthalmologists).

Further research/reviews required

The experts considered that additional studies comparing OCT with the use of antiangiogenic molecules to treat ARMD were needed and that economic studies on OCT would be of value. HAS did not assess the expected benefit of OCT for the anterior segment of the eye. However, an assessment will probably soon be necessary given the many publications already available.

Written by Cédric Carbonneil, HAS, France

INAHTA Briefs

Issue 2008/023

Title **Baropodometric Gait Analysis**

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Reference www.has-sante.fr/portail/display.jsp?id=c_576173

Aim

To assess the expected benefit of baropodometric gait analysis.

Conclusions and results

The assessment was performed to advise the French National Health Insurance (NHI) on inclusion of the technique on the list of reimbursed procedures. It was requested by UNCAM (French National Union of Health Insurance Funds) and SOFMER *(Société française de médecine physique et de réadaptation,* French society of physical medicine and rehabilitation). HAS examined the indications, efficacy, and safety of the technique and its contribution to the care strategy.

- Baropodometric gait analysis is the only quantitative dynamic method for analyzing the distribution of plantar pressures and supports in patients with neurological, orthopedic, or metabolic diseases or in patients with malformations. It is a second-line procedure used as an adjunct to clinical examination and to other manual or instrumental methods of motor and/or morphostatic assessment.
- Several clinical assessment studies have established the expected benefits of the technique. Baropodometric analysis of the deficiency or disorder in foot function (step orientation; distribution of supports; coordination) is used to:
  - make better therapeutic choices
  - assess treatment efficacy (orthotic devices, drugs, surgery).
- No complications are associated with the technique. However, the examination must be conducted under safe conditions to avoid any risk of the patient falling.

Methods

HAS' method for assessing the expected clinical benefit of medical or surgical procedures is based on a critical appraisal of published scientific data and on the expert opinion of a multidisciplinary working group of healthcare professionals. Several databases (MEDLINE, the Cochrane Library, National Guideline Clearinghouse, HTA Database) were searched (January 1995 to February 2007). Studies assessing a) the technical performance of the equipment (reproducibility and reliability studies, studies comparing systems of analysis) and b) the expected benefits in terms of treatment efficacy and performance were selected for analysis. The results of the analysis were reviewed by the working group (specialists in physical medicine and rehabilitation, neurology, sports medicine and sports traumatology, and orthopedic surgery).

Written by Françoise Saint-Pierre, HAS, France

INAHTA Briefs

Issue 2008/024

Title **Kinematic Gait Analysis**

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Reference www.has-sante.fr/portail/display.jsp?id=c_576204

Aim

To assess the expected benefit of kinematic gait analysis.

Conclusions and results

The assessment was performed to advise the French National Health Insurance (NHI) on inclusion of the technique on the list of reimbursed procedures. It was requested by UNCAM (French National Union of Health Insurance Funds) and SOFMER *(Société française de médecine physique et de réadaptation,* French society of physical medicine and rehabilitation). HAS examined the indications, efficacy, and safety of the technique and its contribution to the care strategy.

- Kinematic gait analysis is the only dynamic method for analyzing kinematic gait variables. It is a second-line procedure used as an adjunct to clinical examination. It assesses the trajectories of multiple joints, their movement, their angles, and the way in which they change over time, as well as linear and angular velocities and accelerations.
- Several clinical assessment studies have established the expected benefits of the technique. Kinematic analysis of the movements of the pelvis, hips, knees, and ankles in individuals suffering from gait disorders caused by neurological, orthopedic or rheumatologic factors, or by malformation provides valuable data on gait that can be used:
  - to help select treatment (surgery, aids, drugs, rehabilitation program)
  - to assess treatment efficacy and adjust the treatment if necessary.

No complications are associated with the technique. The examination must, however, be conducted under safe conditions.

Methods

HAS' method for assessing the expected clinical benefit of medical or surgical procedures is based on a critical appraisal of published scientific data and on the expert opinion of a multidisciplinary working group of health-care professionals. Several databases (MEDLINE, the Cochrane Library, National Guideline Clearinghouse, HTA Database) were searched (January 1995 to February 2007). Studies assessing a) the technical performance of the equipment (reproducibility and reliability studies, studies comparing systems of analysis) and b) the expected benefits in terms of treatment efficacy and performance were selected for analysis. The results of this analysis were reviewed by the working group (specialists in physical medicine and rehabilitation, neurology, sports medicine and sports traumatology, and orthopedic surgery).

Written by Françoise Saint-Pierre, HAS, France

INAHTA Briefs

Issue 2008/025

Title **Static and/or Dynamic Vertical Platform Posturography**

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Reference www.has-sante.fr/portail/display.jsp?id=c_576214

Aim

To assess the expected benefit of analyzing static and/or dynamic vertical postural control on a force platform (forceplate).

Conclusions and results

The assessment will advise the French National Health Insurance (NHI) on including the technique on the list of reimbursed procedures. The assessment was requested by UNCAM (French National Union of Health Insurance Funds) and SOFMER *(Société française de médecine physique et de réadaptation,* French society of physical medicine and rehabilitation). HAS examined the indications, efficacy, and safety of the technique and its contribution to the care strategy.

- Computer-assisted posturography quantifies the balance disorder, documents each of the sensory components (proprioceptive, visual, vestibular) that help maintain postural stability, and analyses postural abnormalities and the risks of falling. It is a second-line procedure used as an adjunct to clinical examination and conventional tests.
- Several clinical assessment studies have established the expected benefits of the technique. The technique should be performed only in individuals with serious, progressive disorders. It is used to:
  - evaluate balance and postural control particularly in patients suffering from vestibular and neurological disorders and in elderly patients. The aim is to select therapy for balance disorders and the prevention of falls.
  - evaluate the benefit of different therapeutic procedures on balance in disabled people.
- No complications are associated with the technique. The examination must, however, be conducted under safe conditions to avoid any risk of the patient falling.

Methods

HAS' method for assessing the expected clinical benefit of medical or surgical procedures is based on a critical appraisal of published scientific data and on the expert opinion of a multidisciplinary working group of healthcare professionals. Several databases (MEDLINE, the Cochrane Library, National Guideline Clearinghouse, HTA Database) were searched (January 1995 to February 2007). Studies assessing a) the technical performance of the equipment (reproducibility studies) and b) the expected benefits in terms of treatment efficacy and performance were selected for analysis. A working group (specialists in physical medicine and rehabilitation, ENT, neurology, sports medicine and sports traumatology, and orthopedic surgery) reviewed the results of this analysis.

Written by Françoise Saint-Pierre, HAS, France

Title **Diagnostic Performance and Cost Effectiveness of Technologies to Measure Bone Mineral Density in Postmenopausal Women**

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Reference Technology report no 94, 2007

Aim

To study the effectiveness of technologies to assess bone mineral density (BMD) in diagnosing osteoporosis.

Conclusions and results

The studies reviewed do not show major differences between central dual-energy x-ray absorptiometry of the hip (DXA) and qualitative ultrasonography (QUS). Quantitative computed tomography (QCT) seems to be at least as effective as DXA. QCT, however, uses more radiation than DXA. Overall, QUS seems to be comparable to DXA for discriminating fractures in postmenopausal women, although this is based on low-quality evidence.

Three studies reported on costs of technologies to measure BMD. A study from Thailand reported the cost-effectiveness ratio in US dollars to be USD 88.42 per fracture prevented for DXA and USD 146.48 per fracture prevented for QUS. A US study found DXA to cost USD 703 000 per 1000 women to prevent 7.8 hip fractures, QUS cost USD 632 000 per 1000 women to prevent 6.7 hip fractures, and sequentially testing by QUS then DXA cost USD 442 000 per 1000 women to prevent 5.7 fractures. A Spanish study found that the total cost per correctly detected case of osteoporosis was EUR 23.85 for DXA and EUR 22.00 for QUS.

Recommendations

None given.

Methods

Published literature was identified by cross searching Biosis, EMBASE, and MEDLINE databases on the OVID search system. Parallel searches were performed in the Cochrane Library (Issue 2, 2007) databases. One reviewer selected articles and extracted data.

Further research/reviews required

Because of the limited availability and the cost implications of DXA devices, an assessment of the effectiveness of alternative devices is needed to determine their usefulness in predicting the fracture risk in postmenopausal women.

Written by Dunfield L, Mierzwinski-Urban M, Hodgson A, and Banks R, CADTH, Canada

INAHTA Briefs

Issue 2008/027

Title **Thiazide Diuretics as First-Line Treatment for Hypertension: Meta-Analysis and Economic Evaluation**

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Reference Technology report no 95, 2007

Aim

To evaluate the evidence for the clinical effects and economic implications of thiazide diuretics (TZDs) when used as first-line treatment for hypertension.

Conclusions and results

This assessment is intended to inform those who must decide on an optimal choice of antihypertensive drug therapy in a patient diagnosed with hypertension for the first time.

TZD-based therapy is superior to placebo or no treatment in reducing the risks of all-cardiovascular (CV) and cerebrovascular (CRV) events in subjects with uncomplicated hypertension. No significant differences for all-CV- and CRV-related morbidity and mortality were found when comparing TZDs with other antihypertensive medications. TZDs, however, were better in reducing the risk of stroke than ACE inhibitors and in reducing the risk of heart failure than calcium channel blockers (CCB).

Economic analysis found little difference between therapies in terms of effectiveness, and found TZD to be the most cost-effective initial therapy for patients in all study populations, unless society is willing to pay more than 400 000 Canadian dollars per QALY gained from the use of CCB. Evidence from a limited number of trials, most of low quality, showed that the intensive lowering of blood pressure below the standard target of 140/190 mm Hg in patients with hypertension did not result in a difference in the risks of all-cause death, death related to cardiovascular events, and renal failure.

Recommendations

None.

Methods

For the clinical review, bibliographic databases and grey literature sources were searched until May 2007. Two reviewers, using defined criteria, selected studies systematically. We also conducted a review of economic evaluations that compared the use of thiazide diuretics to other drug therapies, as a first-line therapy for the treatment of hypertension. No attempt was made to quantitatively synthesize the economic study results. Hence, the review of studies was presented in narrative form.

Further research/reviews required

Systematic reviews should be conducted to examine which agent is suitable as first-line therapy for hypertensive patients with specified comorbidities or diseases.

Written by Tran K, Ho C, Noorani HZ, Cimon K, Hodgson A, Coyle D, Coyle K, Myers MG, and Wright JM, CADTH, Canada

Title **Recombinant Human Growth Hormone for Treatment of Turner Syndrome: Systematic Review and Economic Evaluation**

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Reference Technology report no 96, 2007

Aim

To evaluate the clinical efficacy of recombinant human growth hormone (rhGH) and the economic implications of its use in treating Turner Syndrome (TS).

Conclusions and results

Treatment with rhGH has a demonstrated impact on final height, but its effect on quality of life (QoL) is uncertain. The available evidence suggests that, compared to patients receiving placebo or no treatment, patients who are treated with rhGH experience accelerated growth and improvement in final height. Treatment appears to be safe with no serious adverse events (AEs) and few, if any, AEs reported. QoL data, reported in 2 studies, were variable and inconclusive. For the average patient, rhGH is cost effective if a payer is willing to pay more than 200 000 Canadian dollars (CAD) for a QALY. However, from an ethics perspective, the provision and funding of rhGH could be supported until those with TS reach the lower end of the normal adult height range. Publicly funding rhGH treatment will require additional investment. If it were assumed that all TS patients aged 10 to 15 years were eligible for rhGH therapy, the corresponding annual budget impact for covering ~400 patients across Canada would be CAD 11.3 million. The more likely scenario would be that 40% to 50% of eligible patients would receive treatment, with a proportionate decrease in expenditure.

Recommendations

None given.

Methods

A systematic review was conducted to identify randomized controlled trials (RCTs) and comparative observational studies comparing rhGH with placebo or no treatment in patients with TS. The outcomes analyzed were growth, AEs, and QoL. A meta-analysis was conducted when appropriate. Economic studies comparing rhGH treatment with no treatment were identified through electronic databases, websites, and manufacturers.

Further research/reviews required

Long-term studies of high quality are needed to determine the benefits and drawbacks of rhGH treatment.

Written by Li H, Banerjee S, Dunfield L, Kirby J, Jones M, Hamilton J, Deal C, Hadjiyannakis S, Normandin S, and Tsakonas E, CADTH, Canada

INAHTA Briefs

Issue 2008/029

Title **Adalimumab, Alefacept, Efalizumab, Etanercept, and Infliximab for Severe Psoriasis Vulgaris in Adults: Budget Impact Analysis and Review of Comparative Clinical- and Cost Effectiveness**

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Reference Technology report no 97, 2007

Aim

To facilitate evidence-informed decisions by providing:

- comparative evidence on the clinical and cost effectiveness of adalimumab, alefacept, efalizumab, etanercept, and infliximab (targeted immune modulators)
- budget impact analysis based on these treatments being reimbursed by public drug plans.

Conclusions and results

No comparative conclusions can be made regarding the relative efficacy of targeted immune modulators (TIMs) in treating adults with severe plaque psoriasis. Relative to placebo, each TIM therapy (except adalimumab, no information was retrieved) resulted in the clinical improvement of plaque psoriasis as measured by scores on the PASI, PGA, and DLQI in the short term (up to 24 weeks). Advisory warnings regarding treatment with the TIMs studied here have come from Canadian and international organizations, but no conclusions could be drawn regarding adverse events associated with TIMs for periods longer than one year.

In Canada, treating adult patients with severe plaque psoriasis with a TIM was estimated to cost 30.1 million Canadian dollars annually. This estimate was sensitive to assumptions on Canadian psoriasis prevalence rates and assumptions about the proportion of patients taking an oral systemic who would transfer to a TIM therapy.

Recommendations

None given.

Methods

Published literature was obtained by cross searching several electronic databases. The clinical review included HTAs, systematic reviews (SRs), meta-analyses, RCTs, and observational studies that focused on comparative (head-to-head) evidence, and HTAs, SRs, or meta-analyses comparing more than one TIM on at least one efficacy, clinical effectiveness, or QoL outcome. Reports were included in the economic review if they described the severity of severe psoriasis, the use of TIMs, and the cost or economic analysis between at least 2 TIMs.

Further research/reviews required

Given the potential budget impact of funding TIMs for severe plaque psoriasis, comparative information on long-term benefits, harms, and cost effectiveness should be gathered to support funding decisions.

Written by Boudreau R, Blackhouse G, Goeree R, and Mierzwinski-Urban M, CADTH, Canada

INAHTA Briefs

Issue 2008/030

Title **Subcutaneous Versus Intravenous Immunoglobulin for Primary Immunodeficiencies: Systematic Review and Economic Evaluation**

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Reference Technology report no 98, 2008

Aim

To assess the clinical and cost effectiveness of subcutaneous immunoglobulin (SCIg) compared with intravenous immunoglobulin (IVIg); to investigate the budget impact of switching between therapies; and to investigate the use of immunoglobulin (Ig) in Canadian patients with conditions other than primary immunodeficiencies (PIDs).

Conclusions and results

The clinical evidence suggests similarities between SCIg and IVIg in terms of most outcome measures, except quality of life (QoL), which was higher among SCIg patients. A switch from hospital IVIg to SCIg or home IVIg would save 700 to 1000 Canadian dollars (CAD) per person yearly, given certain assumptions. Home IVIg yields the larger net gain by avoiding hospital and treatment or diagnostic charges. Compared to home IVIg, SCIg is attractive, if decision makers are willing to pay CAD 39 500 for a QALY. Information about the magnitude of initial investment, including training costs and comparative effectiveness, is needed to validate this. The comparison between IVIg and SCIg is based on limited clinical and economic information. SCIg may be considered as a reasonable alternative for patients with contraindications to IVIg and poor venous access.

Recommendations

Until reliable comparative clinical and cost-effectiveness conclusions can be drawn, an option for Canadian decision makers may be to gradually establish SCIg as an alternative for patients who are willing and clinically suitable to switch to SCIg.

Methods

A systematic review of the clinical and economic evidence from published and unpublished literature was conducted using accepted methods for the literature search, article selection, data extraction, and quality assessment. For the clinical review, randomized controlled trials (RCTs) and non-RCTs comparing clinical outcomes and adverse events for IVIg and SCIg were included. For the economic review, non-Canadian comparative cost-minimization studies were summarized. The cost effectiveness of SCIg versus IVIg was examined using two approaches: cost-minimization analysis (CMA) and cost-utility analysis (CUA). The budget impact on the provincial healthcare system if patients were switched between therapies was estimated. Reviews and consensus documents were examined to identify the evidence for the use of Ig in conditions other than PIDs.

Further research/reviews required

Clinical and economic information comparing IVIg and SCIg is limited. High quality RCTs are needed.

Written by Ho C, Membe S, Cimon K, Roifman C, Kanani A, and Morrison A, CADTH, Canada

INAHTA Briefs

Issue 2008/031

Title **Telehealth for Acute Stroke Management (Telestroke): Systematic Review of Analytic Studies and Environmental Scan of Relevant Initiatives**

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Reference Technology report no 99, 2008

Aim

To evaluate the available data on using telehealth to deliver health services to acute stroke patients.

Conclusions and results

Telestroke improves access to thrombolysis treatment, which may in turn reduce mortality and serious morbidity post-stroke. A high level of patient satisfaction has been documented with this service. Conclusions regarding the economic impact and potential harm from telestroke services compared with face-to-face care could not be drawn from the available evidence. The lack of standardized reporting of resources and outcomes precludes comparisons among programs and the determination of best practices. The creation of 2 programs in Canada opens the door to collaborative efforts that could lead to standardized evaluation frameworks, economies of scale for knowledge transfer, and a better understanding of the safety and resource implications of the services that both programs offer.

Recommendations

The emerging telestroke programs, and their financial and political backers, have an opportunity to join efforts that could place Canada at the forefront of telestroke care, while ensuring that Canadians have access to the services that they expect, regardless of where they live.

Methods

This systematic review was based on a search of 5 bibliographic databases completed in mid-December 2006, and a scan of relevant reference lists. It included 22 studies with original data on telestroke modalities assessing health outcomes, cost effectiveness, patient and provider satisfaction, or process of care, published in English in a peer-review journal. Two independent teams of reviewers screened all articles and extracted data by consensus. The environmental scan, which identified 15 organizations (2 in Canada) providing telestroke services, was based on the articles included in the systematic review and a review of 400 hits from Google.

Further research/reviews required

More research is warranted to determine the impact of telehealth on post-stroke care. Our results present weak evidence for telerehabilitation, so no conclusions could be drawn in this area. A focused systematic review might be able to determine its effectiveness.

Written by Deshpande A, Khoja S, McKibbon A, Rizo C, and Jadad AR, CADTH, Canada

Title **Real-Time (Synchronous) Telehealth in Primary Care: Systematic Review of Systematic Reviews**

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Reference Technology report no 100, 2008

Aim

To conduct a systematic review of existing systematic reviews (ie, a meta-review) assessing the impact of real-time telehealth on health outcomes, process of care, resource utilization, and user satisfaction.

Conclusions and results

The results from high-quality reviews indicated that real-time telehealth could be an effective way to improve communication between patients and providers, monitor chronic conditions such as congestive heart failure, and support patients with psychiatric and neurological conditions in remote and under-served communities. Information about cost effectiveness, access to services, resource utilization, process of care, and user satisfaction is lacking. Theoretically, telehomecare could save money by eliminating travel costs and reducing the number of re-admissions to hospital.

Recommendations

With its aging population, vast geographic area, limited healthcare workforce, and rapidly developing telehealth programs, Canada is in a unique position to pave the way for effective and efficient health services that result in equitable, fair, and sustainable healthcare delivery for its citizens. Although weak, the evidence gathered suggests that telehealth could play a role in this process.

Methods

Systematic identification of studies on telehealth modalities published in English in peer-reviewed journals, assessing health outcomes, process of care, resource utilization, and user satisfaction in primary care, yielded 31 publications. Two independent teams of reviewers screened literature, extracted data, and conducted quality assessments. While there was no formal economic analysis, related economic outcomes were extracted from clinical reviews.

Further research/reviews required

Real-time telehealth, with new forms of technology, eg, mobile videoconferencing and multimedia-enabled cellular phones, continues to evolve. Systematic reviews need to be updated regularly to ensure that the knowledge provided is up-to-date and based on new evidence.

Written by Deshpande A, Khoja S, McKibbon A, and Jadad AR, CADTH, Canada

INAHTA Briefs

Issue 2008/033

Title **Asynchronous Telehealth: Systematic Review of Analytic Studies and Environmental Scan of Relevant Initiatives**

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Reference Technology report no 101, 2008

Aim

To critically evaluate the available data concerning the use of clinical applications of asynchronous telehealth.

Conclusions and results

The overall quality of most original studies in asynchronous telehealth is poor. These studies, however, provide consistent evidence suggesting that this telehealth modality could lead to shorter wait times, fewer unnecessary referrals, high levels of patient and provider satisfaction, and equivalent (or better) diagnostic accuracy when compared with face-to-face consultations. In Canada, where the reduction in wait times for health care has become a priority, asynchronous telehealth could be an option to choose for improving access to specialized services. It is unknown, however, whether the benefits demonstrated in small local studies could be realized after wide-scale implementation.

Policy makers could play a role in helping to shape the future of asynchronous telehealth in Canada. By formulating pragmatic objectives with consistent and reasonable outcomes, policy makers and researchers could promote projects, eg, asynchronous telehealth triage services, that could increase the efficiency of the healthcare system and enrich the body of research.

Recommendations

None given.

Methods

We systematically reviewed the literature and used an environmental scan to help synthesize the practices of organizations that provide asynchronous telehealth services. A systematic search was conducted for studies on any modality of asynchronous telehealth. The studies were to be published in English in peer-reviewed journals and assess health outcomes, economic outcomes, and the impact of health services. The environmental scan was based on information available in the articles included in the systematic review, complemented by a scan of 400 hits yielded by an Internet search using the Google search engine. Two independent reviewers screened all articles and extracted data, reaching consensus on the articles and data identified.

Further research/reviews required

Systematic reviews must be updated regularly to ensure that the knowledge is kept up-to-date, based on new evidence.

Written by Deshpande A, Khoja S, Lorca J, McKibbon A, Rizo C, and Jadad AR, CADTH, Canada

Title **Minimally Invasive Arthroplasty in the Management of Hip Arthritic Disease: Systematic Review and Economic Evaluation**

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Reference Technology report no 102, 2008

Aim

To examine the impact of adopting minimally invasive total hip replacement (MI THR) into the Canadian health system.

Conclusions and results

MI THR techniques may have some perioperative advantages (less blood loss and shorter operative time), although these may be of limited clinical significance. Of particular concern is the absence of evidence on the rates of revision after a primary procedure. Single-incision techniques are associated with higher costs (20 400 versus 19 100 Canadian dollars (CAD)) and quality-adjusted life-years (7.48 versus 7.47) compared to standard THR, resulting in an incremental cost per QALY gained of CAD 148 300. The probability that MI THR is more cost effective than standard THR for a decision maker willing to pay CAD 50 000 for a QALY is 47%. These results are most sensitive to the cost of initial hospitalization and patient utility values in the first year post-treatment. Compared to expanding funding for single-incision MI THR, it would be cost effective to spend up to CAD 480M on gathering additional data through field evaluation, to remove uncertainty regarding the effect of MI THRs on revision rates.

Recommendations

None given

Methods

A comprehensive literature search was conducted involving electronic databases, relevant websites, contact with experts in the field, and the scrutiny of retrieved papers to identify reports of published and ongoing studies. Systematic reviews and selected conference proceedings were also searched. The clinical review adopted the same methods as those in the National Institute for Health Research (NIHR) health technology assessment (HTA) report. A systematic review of economic evaluations was performed, comparing the minimally invasive approach to standard THR. A Markov simulation model was created to estimate long-term costs and quality-adjusted life-years (QALYs) for patients undergoing standard THR and MI THR.

Further research/reviews required

More long-term, high-quality studies are needed.

Written by Coyle D, Coyle K, Vale L, de Verteuil R, Imamura M, Glazener C, and Zhu S, CADTH, Canada

INAHTA Briefs

Issue 2008/035

Title **Evidence-Informed Health Policy: Using Research to Make Health Systems Healthier**

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Reference Report no 1-2008. Moynihan R, Oxman AD, Lavis JN, Paulsen E.
ISBN 978-82-8121-187-2. www.kunnskapssenteret.no/index.php?artikkelid=1032&back=2

Aim

To identify and describe experience of organizations worldwide, especially in low- and middle-income countries, that are successful or innovative in supporting the use of research evidence to develop clinical practice guidelines (CPGs), health technology assessments (HTAs), and health policy.

Conclusions and results

In 2004, country delegations at the Ministerial Summit on Health Research (Mexico City) called for establishing mechanisms to support the use of research evidence in policy and practice. In 2005, the World Health Assembly approved a resolution arising from the Mexico Summit.

Participants regard an evidence-based approach as the greatest strength in the way the organizations conduct their work, but view the time-consuming nature of the approach as its greatest weakness. Researcher–policymaker relationships are desirable, but awareness is lacking about potential tensions and how to manage or resolve them. A lack of financial and human resources challenges many organizations. Conflicts of interest pose a critical issue. Multidisciplinary teams and international networks are desirable, and there is a need to coordinate at an international level to avoid duplication. Dissemination and implementation receive little attention in relation to efforts focused on producing evidence-based materials.

Recommendations

The main implications for those establishing or administering organizations that produce CPGs or HTAs, or organizations supporting the use of research evidence in developing health policy, include:

1. Collaborate with other organizations
2. Establish strong links with policymakers and involve stakeholders
3. Be independent and manage conflicts of interest among those involved
4. Build capacity among those working in the organization
5. Use good methods and be transparent
6. Start small, have a clear audience and scope, and address important questions
7. Be attentive to implementation considerations.

Methods

We convened a reference group to provide feedback on our approach and materials. The project involved 3 phases: a survey, telephone interviews, and case descriptions that drew on site visits. In the second and third phases we focused on a purposive sample of those involved in the previous phase. Many people and organizations worldwide helped in generating a list of organizations to survey. We modified an existing questionnaire, adapted one version for organizations producing CPGs and HTAs and another for organizations supporting the use of research evidence in developing health policy, piloted both versions of the questionnaire, and made final modifications to both versions of the questionnaire. We emailed the questionnaire to 176 organizations and followed up on non-responders by email and phone. We then purposively sampled 25 organizations from among those responding to the survey, and developed and piloted an interview schedule and conducted phone interviews with the director of each organization. Thereafter, we purposively sampled 8 cases of one or more organizations bridging research and policy from among the cases described in the phone interviews and (once) other cases. We developed and piloted a case study data-collection protocol and conducted site visits for each case. Data collection included interviews with 51 key informants and review of publicly available documents. Simple descriptive statistics were developed from survey data. We used a constant comparative method to analyze written survey responses, phone interviews, in-person interviews, and documents. We produced a video documentary about each case study.

Written by Andrew D Oxman, NOKC, Norway

INAHTA Briefs

Issue 2008/036

Title **Organizational and Economic Issues in the Management of Patients with Acute ST-Segment Elevation Myocardial Infarction (STEMI)**

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Reference 2008-02. ISBN 978-2-550-51924-9.
www.aetmis.gouv.qc.ca/site/en_publications_2008.phtml

Aim

To shed light on the scientific, organizational, and contextual issues concerning optimal management of patients suffering from acute myocardial infarction with ST-segment elevation.

Conclusions and results

In Quebec, an estimated 4800 patients are hospitalized each year for acute myocardial infarction with ST-segment elevation (STEMI). The immediate cause of this serious condition is the occlusion of a coronary artery by a thrombus that must be urgently cleared to minimize irreversible damage to the cardiac muscle. Two treatments can be used for this purpose, fibrinolysis and primary percutaneous coronary intervention (PPCI), both of which are recommended in North American and European clinical practice guidelines. According to these guidelines and available evidence, it cannot be affirmed that one of these reperfusion methods is superior to the other for all patients in all clinical situations, at all times of the day. In this context, the best treatment for a particular patient will be that which is clinically appropriate and administered in a timely fashion, ie, within recommended delays. Such management depends on optimal organization and delivery of care and services.

This report examines the applicability of current evidence and clinical guidelines for Québec, by considering the context of care and related issues with respect to organization and resources, and describes approaches that can reduce delays to treatment.

Recommendations

AETMIS recommends that: 1) fibrinolysis and PPCI be recognized as complementary modes of intervention where the choice of treatment depends on a variety of clinical and practical considerations; 2) treatment delays be minimized for both therapies, at each point of care from emergency medical services to the initial receiving hospital and to PCI hospitals that may receive patients for PPCI; 3) recourse to PPCI not be the preferred option when the expected door-to-balloon time exceeds the delay recommended in clinical practice guidelines, and that the initial decision to proceed to fibrinolysis or PPCI be based on an evaluation of the individual patient's risk profile and the anticipated delays to both treatments; 4) performance monitoring of prehospital ECG initiatives be implemented at the local, regional, and provincial levels; 5) pilot projects for the administration of prehospital fibrinolysis be considered, particularly in remote regions, as a strategy to markedly reduce delays to reperfusion; 6) interested and concerned organizations establish protocols of understanding and encourage discussion between the diverse participants in STEMI care and collaboration between hospitals and ambulance services; 7) training in emergency medicine and cardiology include theoretical and practical education on both reperfusion treatments; 8) performance be monitored at the provincial level across the continuum of care and that regular, timely feedback be provided to all caregivers involved; and 9) incentives be introduced to facilitate and reinforce appropriate use of fibrinolysis and PPCI by health professionals and institutions.

Methods

Review of scientific and grey literature, synthesis and qualitative analysis of clinical guidelines, qualitative review of economic issues, and analysis of contextual data.

Further research/reviews required

Economic analysis of STEMI management in Québec.

Written by Bogaty P, Boothroyd LJ, Lambert L, Lance J-M R, and Paquette D, AETMIS, Canada

INAHTA Briefs

Issue 2008/037

Title **Hyperbaric Oxygen Therapy: A Rapid Assessment**

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Reference Report no 74C, 2008

Aim

To gather evidence about the clinical effectiveness of hyperbaric oxygen therapy, to examine its economic aspects, to describe current practice and organization in Belgium, and to make recommendations for the most appropriate use of this therapy.

Conclusions and results

Hyperbaric oxygen therapy (HBOT) has been used for many indications. However, few indications have been subject to rigorous randomized controlled clinical trials. Hence, we have insufficient good-quality data to properly assess this therapeutic modality. Stakeholders and decision makers should have access to evidence-based information when deciding whether or not to support and reimburse the use of HBOT for specific indications. Recommendations that are mainly consensus based cannot be considered good evidence.

Physicians in Belgium provide HBOT for a wide range of indications. But the impact of HBOT on the National Health Insurance budget is minimal, due to restrictive rules that limit reimbursement for the first and second days of treatment.

Evidence is insufficient to simply extend reimbursement of this therapy regardless of indication. If decision makers decide to offer more attractive reimbursement for specific indications, this should be linked to a proper randomized research setting with the explicit goal to collect data on effectiveness and costs.

Recommendations

1. No expansion of HBOT capacity is recommended since capacity is not a problem and geographic distribution appears to be sufficient, given the currently "accepted" indications.
2. HBOT in treating decompression accidents and severe gas embolism is supported by historical empirical evidence and by wide consensus. HBOT in treating carbon monoxide poisoning to avoid long-term neurological sequels is not supported by clinical evidence (low-quality evidence from small RCTs on the clinical non-efficacy of HBOT; no evidence from RCTs on short-term effectiveness for carbon monoxide poisoning).
3. Conditional financing for experimental treatment could be considered and/or research encouraged specifically for indications of sufficient clinical relevance and where some evidence is available. For diabetic ulcers and selected cases of radiation-induced tissue injury, there is low-quality evidence from small RCTs on the clinical efficacy of adjuvant HBOT. For acute deafness that presents early, some evidence shows a beneficial effect although the clinical relevance of this benefit is questionable.
4. HBOT for other indications is not supported due to no, or very low-quality, evidence.
5. For common indications, further research on larger populations could be performed both on a national basis (given the number of Belgian centers and locally available expertise) and internationally. Research on rare indications would require multicenter studies. An initiative at the European level would probably be needed to gather evidence on those indications. Specific research financing sources are unclear, although protocols were developed previously with European support.
6. These recommendations should be revised when newer and better data on efficacy of HBOT become available.

Methods

Systematic review, analysis of Belgian data (questionnaire), and cost analysis.

Further research/reviews required

None.

Written by Mattias Neyt, KCE, Belgium

Title **The Effectiveness of Compulsory, Residential Treatment of Chronic Alcohol or Drug Addiction in Non-Offenders**

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Reference HSAC Report 2008; 1(1). Broadstock M, Brinson D, Weston A.
ISBN 978-0-9582910-0-2. ISSN 1178-5748

Aim

To critically appraise the evidence pertaining to the effectiveness of compulsory detention for residential treatment in people with chronic alcoholism and/or drug addiction.

Conclusions and results

The evidence base identified in this review yields minimal evidence on the effectiveness of compulsory residential treatment of non-offenders alone. However, some weak evidence suggests that at least some people benefit from compulsory treatment. Many studies on compulsory treatment in populations that include offenders appear to report comparatively positive outcomes, and others less so.

Reviewers have concluded that:

- Compulsory treatment has generally demonstrated better outcomes in terms of treatment process (ie, uptake of treatment following referral).
- The offender literature shows longer treatment to be a consistent predictor of positive therapeutic outcomes.
- Some treatment retention studies report lower drop-out rates for clients receiving compulsory treatment versus voluntary treatment.
- The generalizability of these findings to compulsory residential treatment in New Zealand's non-offender population is not known.
- Due to insufficient clinical evidence, it is not possible to assess the cost effectiveness of compulsory residential treatment of alcohol/drug dependence.
- At present, the evidence remains incomplete.

Methods

The literature was searched using the following bibliographic databases: MEDLINE, EMBASE, PsycINFO, CSA social services abstracts, CSA sociological abstracts, various databases within the Cochrane Library, and the National Guideline Clearing House database. Also, bibliographies of included papers were examined for relevant studies. Searches were undertaken in September 2007 and were limited to English-language material. The search strategy identified 1121 citations. After consideration of titles and abstracts using the study selection criteria, 192 full papers were retrieved and scrutinized in detail for possible inclusion in the review. As a result, 4 review publications were eligible for inclusion in the review and were critically appraised.

Further research/reviews required

There is a need for evaluation studies, using well operationalized baseline and outcome variables, which investigate the complex interplay between client and treatment characteristics within the New Zealand civil context.

Written by David Brinson, HSAC, New Zealand

Title **Caries – Diagnosis, Risk Assessment, and Non-Invasive Treatment. A Systematic Review**

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Reference SBU Report 188, 2007. Mejàre I, Axelsson S, Dahlén G, Espelid I, Norlund A, Svensson Å, Tranæus S, Twetman S. ISBN 978-91-85413-21-8. www.sbu.se/published

Aim

To assess the scientific evidence with reference to the following questions:

- How effective are different methods of disclosing the presence of a caries lesion, compared with a reference method? Are there side effects and risks associated with the methods reviewed? Which diagnostic method is the most cost effective?
- How well can caries be predicted?
- Are there effective, non-invasive methods (no removal of tooth substance) to treat early caries lesions on the crown or the root surface of the teeth?

Conclusions and results

Past caries experience is the best single factor for predicting future caries. It is possible to identify children and adolescents at very low risk of developing caries during the next 2 to 3 years. However, it is difficult to determine accurately which individuals are at risk of developing caries.

For caries diagnosis, a combination of visual-tactile and radiographic examination is more reliable than either method used separately. In general, accuracy in excluding the presence of caries is greater than in confirming its presence. The likelihood that radiation-induced cancer will develop because of exposure to dental radiography is considered to be very small, but greater than zero. There are no studies on the cost effectiveness of the various diagnostic methods.

There is insufficient scientific support for any conclusions as to whether early caries lesions can be treated effectively by non-invasive methods.

Recommendations

No recommendations.

Methods

A systematic search of the literature was conducted primarily via electronic data bases (Cochrane Library and PubMed) dating back to 1966. To be included in the systematic review, all articles were required to meet predetermined criteria: the results of the studies should be relevant to the questions posed by the project, ie, have appropriate outcome measures and an appropriate followup period and study design. A model analysis was undertaken which analyzed and compared the cost of diagnosis, prediction, and treatment of early caries lesions. Ethical implications were considered.

Further research/reviews required

Currently, no studies verify that identification of patients at risk leads to better treatment, ie, that the effects of risk assessment and subsequent intervention benefit the patient in terms of improved oral health. The present scientific base is inadequate for drawing conclusions on the efficacy of the various methods of treating early caries lesions.

Studies need to address cost aspects of various methods of caries diagnosis and early treatment and need to evaluate the benefits of risk assessment in preventing the development of the disease.

Written by Susanna Axelsson, SBU, Sweden

Title **Guidelines for Pharmacoeconomic Evaluations in Belgium**

Agency **KCE, Belgian Health Care Knowledge Centre**
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Reference Report no 78C, 2008. Cleemput I, Van Wilder P, Vrijens F, Huybrechts M, Ramaekers D. Joint work by KCE and the Belgian National Sickness and Disability Insurance Institute

Aim

To develop methodological and reporting guidelines for pharmacoeconomic evaluations submitted in the context of a reimbursement request for pharmaceutical products.

Conclusions and results

Twelve guidelines are built around a reference case that defines the recommended methodology for each component of the economic evaluation: literature review, perspective of the evaluation, target population, comparators, analytic technique, study design, calculation of costs, estimation and valuation of outcomes, time horizon, modeling, handling uncertainty, and testing robustness of results and discount rate. Each pharmacoeconomic submission should at least contain a reference case analysis. Additional analyses are allowed, but cannot replace the reference case.

Recommendations

Access to and provision of Belgian resource use data should be facilitated for pharmacoeconomic analyses aimed to serve Belgian pharmaceutical policy.

The Royal Decree of December 21, 2001 may benefit from integration of guideline 2 of the Guideline for Pharmacoeconomic Evaluation. Pharmacoeconomic analyses should include the costs to the healthcare payer, including governmental payers and the patients.

To increase the credibility and usefulness of pharmacoeconomic evaluations for drug reimbursement decisions, both the applicants and RIZIV/INAMI should systematically apply these guidelines.

Methods

The guidelines were developed in two phases:

Phase 1: A set of draft guidelines were developed by 8 health economists from Belgium and abroad, 2 pharmacists, 1 medical doctor with training in health economics, and 1 statistician.

Phase 2: The guidelines were implemented during a 6- to 12-month test period, which led to conclusions concerning their practicality, usefulness, and potential for improvement. The guidelines were adapted and finalized based on the practical experience of 1 company and extensive feedback from about 20 pharmaceutical companies through the organization representing the pharmaceutical industry in Belgium, *Pharma.be.*

Further research/reviews required

The field of economic evaluation in health care is still evolving. Hence, the guidelines will need to be revised regularly to include new insights and improved methods of economic evaluation.

Written by Irina Cleemput, KCE, Belgium

INAHTA Briefs

Issue 2008/041

Title **Subcutaneous Insulin Pump Therapy: Systematic Review Update and Economic Evaluation for the New Zealand Setting**

Agency **HSAC, Health Services Assessment Collaboration**
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Reference HSAC Report 2008; 1(3). February 2008. Campbell S, Suebwongpat A, Standfield L, Weston A. ISBN 978-0-9582910-2-6 (online). ISSN 1178-5748 (online)

Aim

To provide a summary of the recent evidence pertaining to the relative effectiveness, safety, and cost effectiveness of continuous subcutaneous insulin infusion (CSII) in patients with insulin treated diabetes, when compared to optimized multiple daily injections (MDI).

Conclusions and results

Data from literature search (9 randomized controlled trials and 2 systematic reviews) show that CSII results in a modest but potentially worthwhile improvement in glycosylated hemoglobin levels in all patient groups assessed (including adults, children, adolescents, and pregnant women with preexisting diabetes), compared with optimized MDI. Generally, these findings support those of the original NHS assessment report, ie, improvement in glycemic control that is of small magnitude and borderline statistical significance. The short duration of the clinical trials did not enable evaluation of longer term benefits of such a difference in glycosylated hemoglobin levels – but the expectation is that it would be reflected by fewer long-term complications. Although more immediate primary benefits from CSII may be associated with an impact on the incidence of severe hypoglycemic events and improved quality of life, the studies identified offer limited evidence to support this.

Although not supported by the evidence, it is postulated that CSII may reduce the number of severe hypoglycemic attacks a patient experiences compared with MDI. The cost-effectiveness analysis suggests that if every patient who changed from MDI to CSII therapy were able to avoid one severe hypoglycemic attack every 2 years (ie, an improvement of 0.5 events per annum), the incremental cost per severe hypoglycemic event avoided would be approximately 6000 New Zealand dollars (NZD). The total incremental cost associated with the introduction of CSII compared to MDI for a patient with type 1 diabetes is approximately NZD 16 000 over 6 years.

Methods

The systematic review update was based on the NHS technology assessment report (Colquitt et al, 2004), which informed the National Institute for Health and Clinical Excellence (NICE) recommendations on the use of CSII in diabetes. Randomized clinical trials and systematic reviews published since January 2002 were identified using electronic databases and references of relevant articles. One reviewer used predefined criteria to assess the studies for inclusion in the systematic review update. One reviewer, with full tabulation of all eligible studies, extracted the data and assessed quality. Data on clinical effectiveness were tabulated, using meta-analysis where appropriate.

Relevant economic evaluations were identified using electronic databases. An economic analysis was undertaken to examine the cost effectiveness of CSII versus MDI for a patient with Type 1 diabetes. The economic model was based mainly on the method and approach presented in the NHS assessment report (Colquitt et al, 2004), modifying inputs to populate the model with New Zealand data wherever available. Other published economic evaluations informed the cost-effectiveness interpretations.

Written by Dr Suzanne Campbell, HSAC, Australia

INAHTA Briefs

Issue 2008/042

Teleoncology: Applications and Associated Benefits for the Adult Population

Agency IHE, Institute of Health Economics
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Reference January 2007 (English). ISBN 978-1-897443-02-6 (print).
www.ihe.ca/hta/publications.html

Aim

To systematically review teleoncology applications and inform cancer agencies and other organizations involved in providing cancer care services to rural and remote communities.

Conclusions and results

Fifty-four articles met the inclusion criteria for the systematic review. A further 91 publications were used to prepare the overview. The papers providing information on outcomes described 42 clinical and 8 economic studies. Seventeen (40%) of the clinical studies were judged to be of high or good quality. A further 9 (21%) were of fair quality, and the remaining studies were of poorer quality.

Clinical studies. Teleoncology intervention was successful in 18 of the 28 better-quality studies. Success was not achieved in 7 studies, and the outcome was unclear in 3 others. Most of the studies with positive findings showed only small effect sizes, and few projects had proceeded beyond the feasibility stage. The strongest evidence of effectiveness came from 6 studies on psychosocial applications (2 on palliative care and one each on prevention, screening, diagnosis, and treatment). Positive findings from higher-quality studies suggested that telephone-based technology was an effective tool for promoting mammography and coloscopy in specific populations, increasing fruit and vegetable consumption, and providing an effective alternative to in-person support groups for women with breast cancer.

Economic studies. Since the 8 economic studies were limited in quality and scope, it was impossible to determine whether or not teleoncology is a cost-effective alternative to standard cancer care.

Satisfaction studies. Information from 20 papers suggests that patients were generally satisfied with various teleoncology applications, but these findings are of limited significance and generalizability.

Recommendations

Implementation of teleoncology applications in Alberta must take account of the overall healthcare context in the province. The literature suggests some useful possibilities for developing new services using Internet or Web-based, telephone-based, and video-based technologies for cancer patients in rural areas, but it is likely that these applications will need validation with suitable local studies.

Methods

Computerized literature searches from January 1995 to December 2005 identified relevant articles published in English using bibliographic databases, Internet sites of health technology assessment agencies and other relevant organizations, tables of contents of 7 electronic journals, and a Web search engine. Reference lists of retrieved articles were manually searched.

The systematic review included comparative quantitative clinical studies, case series studies (sample size ≥10), qualitative studies, and economic studies of teleoncology services provided to adults across the cancer continuum (prevention, screening, diagnosis and treatment, psychosocial and supportive care, rehabilitation, and palliative care). Study quality and reliability were evaluated using various approaches, depending on study type.

Further research/reviews required

The overview indicated that the literature was rich in examples on the use of communication technologies across the cancer continuum, with gaps in the areas of cancer prevention, screening, and rehabilitation. However, the reviewed literature did not include findings and recommendations that were specific to services for rural and remote communities.

Written by Hailey D, IHE; Paquin M-J, Maciejewski O, Taschuk P and Fields A, Alberta Cancer Board; Harris L, Cross Cancer Institute; and Casebeer A and Fick G, University of Calgary and SEARCH Canada, Canada

INAHTA Briefs

Issue 2008/043

Title **Safety and Efficacy of Inhaled Nitric Oxide in the Management of Hypoxemic Respiratory Failure in Adults with Acute Respiratory Distress Syndrome**

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Reference April 2007 (English). ISBN 978-0-9780024-9-7. www.ihe.ca/hta/publications.html

Aim

To examine the scientific evidence on the safety and efficacy of inhaled nitric oxide (iNO) in managing hypoxemic respiratory failure in adult patients with acute respiratory distress syndrome (ARDS) to ensure the most clinically and economically appropriate application of iNO.

Conclusions and results

One systematic review, 5 randomized controlled trials (RCT), and 1 followup study on the use of iNO in patients with ARDS were identified. The 5 RCTs varied considerably in methodology, making comparisons challenging. In 4 of the primary studies, the manufacturer/supplier of the treatment gas provided funding. Nonetheless, the results indicated that using iNO to treat ARDS does not improve mortality rates, compared to conventional ventilator management, with or without placebo gas. Also, it appears that improvements in supportive care, early treatment, and the use of evidence-based management strategies, eg, lung-protective ventilation, over the past 10 years have dramatically improved overall mortality.

However, iNO is not without complications. Although the incidence of serious adverse effects was not clinically significant in the studies presented, even a slight complication in a critically ill ARDS patient can be dangerous. While iNO has been suggested as a last resort in the most severely refractory hypoxemic patients to obviate the need for more expensive therapeutic options, eg, extracorporeal membrane oxygenation, the degree of benefit has not been established.

Recommendations

People with ARDS resulting from a nonpulmonary infection (eg, sepsis) and those with multiorgan failure or an irreversible underlying condition generally have poor outcomes. Using iNO in these patients does not appear to alter their prognosis. Hence, its use should be reconsidered.

Transient improvement in oxygenation can be expected in about 60% of people receiving iNO early in ARDS (within 72 hours). Any improvement is typically evident within 10 minutes of initiating therapy and may continue up to 48 hours. Beyond this time, continued use should be re-evaluated based on the patient's condition, including an assessment for potential complications.

iNO should be used in concentrations of less than 40 parts per million (ppm), with the best available evidence indicating a range of 5 to 10 ppm as being the most effective (when there is a response to oxygenation). Daily dose assessment or challenges should be conducted throughout iNO administration to re-establish optimal dosing. Stepwise discontinuation of iNO should be conducted if there is no ongoing positive response in oxygenation or intensity of ventilation.

Methods

All relevant systematic reviews and RCTs, published in English, were identified by systematically searching the Cochrane Library, the Centre for Reviews and Dissemination databases (National Health Service Economic Evaluation Database, HTA, Database of Abstracts of Review of Effects), PubMed, EMBASE, CINAHL, and Web of Science, plus relevant practice guidelines, regulatory agencies, and evidence-based resources and other HTA agency-related resources from January 1999 to November 2006. Methodological quality of the included studies was not assessed.

Further research/reviews required

Future studies are needed to determine whether the use of iNO alters the duration and intensity of ventilation, or obviates the need for more expensive therapies.

Written by Gregory Duchscherer, SEARCH Canada Program, and Bing Guo, IHE, Canada

INAHTA Briefs

Issue 2008/044

Title **Risk Assessment Instruments for Predicting Recidivism of Spousal Violence**

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Reference November 2007 (English). ISBN 978-1-897443-15-6 (print), 978-1-897443-16-3 (online). www.ihe.ca/hta/publications.html

Aim

To assess the research evidence on inter-rater reliability and predictive validity of risk assessment instruments used to predict male-to-female spousal violence recidivism and lethality in males who have had contact with the police system.

Conclusions and results

Eight primary studies were found that evaluated the predictive validity of several current instruments: Ontario Domestic Assault Risk Assessment (ODARA), Spousal Assault Risk Assessment (SARA), Danger Assessment (DA), Domestic Violence Screening Instrument (DVSI), Violence Risk Appraisal Guide (VRAG), and Level of Service Inventory-Revised (LSI-R). The characteristics of the male offenders varied considerably across the included studies. Some were arrested, on probation, or in a maximum-security psychiatric facility, whereas others were referred to batterer treatment programs.

Inter-rater reliability was only reported for SARA, ODARA, and VRAG. Limited research indicated good inter-rater reliability for all 3 instruments.

In terms of predictive validity, none of the studies reported any lethal assault during the followup period. The area under the receiver operating characteristic curve (a measure of predictive validity) was less than 0.80 (range 0.59 to 0.77) for all instruments evaluated, suggesting only marginal to moderate improvement over chance in predicting non-lethal recidivism.

Recommendations

All of the instruments evaluated were better than chance in predicting spousal violence recidivism, but no conclusion could be made regarding the superiority of one tool over another, or their ability to predict lethal assault. The decision of which risk assessment instrument (RAI) to use should take into account the available evidence, the population assessed, the intended users of the instrument, and the purpose of the assessment. As research evidence on the predictive validity of RAIs is limited, it is inappropriate to base any decision about an individual's risk of recidivism solely on these instrument scores.

Methods

All original, published systematic reviews or primary cohort studies were identified by systematically searching PubMed, the Centre for Reviews and Dissemination databases (National Health Service Economic Evaluation Database, HTA, Database of Abstracts of Review of Effects), EMBASE, Family & Society Studies Worldwide, Sociological Abstracts, Social Services Abstracts, Social Sciences Abstracts, Academic Search Premier, Web of Science, PsycINFO, and ABI/Inform from January 1995 to May 2007. Relevant library collections and the websites of HTA-related agency resources were also searched. Methodological quality of the included studies was not assessed.

Further research/reviews required

Universal, multidimensional definitions for spousal violence need to be developed that capture multiple domains of aggressive behavior. It would be helpful to correlate RAIs with different categories of recidivism severity, taking into consideration the treatment provided to the abuser. Evaluation of RAIs by independent researchers, rather than the instrument developers, is essential.

The feasibility, utility, and impact of RAIs need to be investigated in different settings. In Alberta, both SARA and ODARA are used. Data gathered from the Provincial Family Violence Treatment Program will allow a direct comparison of the predictive validity of SARA, ODARA, or a combination of both, in male abusers who enter the program.

Written by Bing Guo and Christa Harstall, IHE, Canada

INAHTA Briefs

Issue 2008/045

Using Fetal Fibronectin to Diagnose Preterm Labor

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Reference February 2008 (English). ISBN 978-1-897443-13-2 (print), 978-1-897443-14-9 (online). www.ihe.ca/hta/publications.html

Aim

To evaluate the accuracy and safety of using the TLi™ System (Adeza Biomedical Corporation, Sunnyvale, CA, USA) as a point-of-care test for rapid detection of cervicovaginal fetal fibronectin (fFN) to diagnose preterm labor in symptomatic women.

Conclusions and results

The reviewed evidence confirms that the principal usefulness of the TLi System (referred to here as the rapid fFN assay) lies in its high negative predictive value. The absence of fetal fibronectin in cervicovaginal secretions of symptomatic women is a powerful predictor of the absence of progressive delivery within the next 7 to 10 days. However, the positive predictive value of the rapid fFN assay is a poor predictor of subsequent progressive preterm delivery/birth in symptomatic women with preterm labor, and the clinical importance of a positive test result remains unclear.

Knowledge of a negative rapid fFN assay result may supplement clinical judgment in predicting "false" preterm labor with more accuracy than clinical criteria alone. However, the hypothesis that using the rapid fFN assay will alter clinical management (eg, avoid overdiagnosis and unnecessary intervention) and ultimately improve patient outcomes and reduce healthcare costs remains unproven. Evidence from good-quality randomized controlled trials (RCTs) suggests these effects may be negligible, raising the question of whether the rapid fFN assay offers significant benefit beyond that of good clinical assessment and judgment.

Recommendations

Initial and ongoing education of clinical and laboratory staff, and regular audits of clinical practice, are necessary to ensure optimal use of the rapid fFN assay. Samples must be collected according to manufacturer recommendations and contraindications to specimen collection rigorously observed.

As the rapid fFN assay becomes widely available in Canada, clear protocols and a standardized clinical pathway are needed to guide clinicians in using the results to manage preterm labor in symptomatic women. Implementing the rapid fFN assay may inadvertently increase the use of interventions to prevent preterm delivery/birth if clinicians are unwilling to change their practices on the basis of its results.

Methods

All relevant systematic reviews and RCTs, published in English or French, were identified by systematically searching the Cochrane Library, the Centre for Reviews and Dissemination databases (National Health Service Economic Evaluation Database, HTA, Database of Abstracts of Review of Effects), PubMed, EMBASE, CINAHL, Web of Science, websites of various HTA agencies, research registers, evidence-based resources, and practice guideline clearinghouses from January 1995 to April 2007. Two reviewers, using appraisal tools developed by the Critical Appraisal Skills Programme (UK), independently assessed the methodological quality of the studies.

Further research/reviews required

Information from rapid fFN assay helps resolve uncertainty about whether to transport a woman in preterm labor from a level 1 or 2 healthcare center to a level 2 or 3 center. However, current evidence from good-quality RCTs only addressed the impact of the rapid fFN assay in level 2 and 3 hospitals where admission (or transfer) for care would occur. Further well-designed research is needed to assess the clinical and economic impact of using the test in level 1 hospitals.

Written by Paula Corabian and Christa Harstall, IHE, Canada

Title **Air Ambulance Transportation with Capabilities to Provide Advanced Life Support**

Agency **IHE, Institute of Health Economics**
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Reference February 2008 (English). ISBN 978-1-897443-24-8 (print), 978-1-897443-25-5 (online). www.ihe.ca/hta/publications.html

Aim

To assess the evidence on the efficacy/effectiveness and safety of air ambulance transportation with on-board advanced life support (ALS); to inform policy in Alberta on organizing, providing, and funding air ambulance services and their integration with ground ambulance transport.

Conclusions and results

No studies were found that compared airplane and helicopter transports. Of the 16 studies that compared helicopter with ground ambulance transport, only 1 was prospective. The studies varied in methodological details (eg, setting, sample size, patient demographics, severity of condition), making generalization of the results to a local context challenging.

Patients transported from the scene or between facilities by helicopter were more likely to survive. They reached the healthcare facility or received definitive treatment faster and had better results than patients transferred by ground ambulance. However, these benefits might be more attributable to the expertise, qualifications, and therapeutic options brought to the scene by the helicopter crew than to the mode of transport. Transportation safety was not detailed in the comparative studies.

Although this report did not cover economic analyses, the search identified 2 cost-effectiveness analyses, 1 cost-benefit analysis, 2 comparative studies, and 3 case series studies that provided some costing information.

Recommendations

Access to services and the mix of expertise aboard a transport, rather than the *type* of transport, seem to affect clinical outcomes for trauma and medical patients. Alberta has unique political, geographic, and medical characteristics to consider when planning and evaluating the transportation system. Since April 1995, Alberta has maintained a Trauma Registry on major trauma patients admitted to hospital via air or ground ambulance transport. Expanding this registry to include medical patients would provide more detail on ambulance services to inform provincial policies. Planning for evidence-informed ambulance services needs to be system based and should include input from trauma centers, hospital emergency departments, and emergency transport dispatch centers.

Methods

All relevant studies, published in English, were identified by systematically searching PubMed, EMBASE, HealthSTAR, the Cochrane Library, Science Citation Index, and websites of various HTA agencies, research registers, and guideline clearinghouses from January 2000 to July 2007. Studies with the best evidence were divided into 2 groups (scene and interfacility) and grouped, eg, by patient conditions, trauma, or injury. ALS capability was assumed when explicitly mentioned in the study, or when air and ground ambulances carried qualified staff, eg, paramedic, nurse, or physician. Relevant guidelines and policy papers were included. Methodological quality of the studies was not assessed. The report was externally reviewed.

Further research/reviews required

Controversies about the utility of on-scene aggressive interventions versus basic life support (BLS) focus on increased patient survival and safety outcomes. Definitions differ regarding specific times and intervals relevant to (air) transportation. The relationship between time to definitive care and clinical outcomes, including quality of care, is subject to controversy. It is necessary to establish Canadian training standards and clear definitions for ALS and BLS.

Written by Carmen Moga and Christa Harstall, IHE, Canada

Title **Gamma Knife Radiosurgery**

Agency **MSAC, Medical Services Advisory Committee**
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Reference MSAC Reference 34 Assessment report. ISBN 1-74186-030-X.
Ms Merry Pearson edited the report

Aim

To assess the safety, effectiveness, and cost effectiveness of gamma knife (GK) in treating cerebral metastases, arteriovenous malformations (AVMs), acoustic neuromas, primary malignant lesions, meningiomas, and pituitary adenomas.

Conclusions and results

Safety: Comparative safety evidence was minimal. GK appears to result in a lower rate of medium-term, treatment-related complications and procedural mortality than surgery for acoustic neuroma. Adding stereotactic radiosurgery (SRS) to whole brain radiotherapy (WBRT) for cerebral metastases may slightly increase the risk of serious radiation-related toxicity.

Effectiveness: Evidence from 1 randomized controlled trial (RCT) shows a small increase in survival for patients with single (but not multiple) metastases treated by SRS plus WBRT, versus WBRT alone. One RCT indicated no difference in survival, neurological function, or quality of life for patients with primary lesions treated by SRS in addition to radiotherapy, surgery, and chemotherapy, versus these treatments without SRS. Observational evidence suggests no difference in survival for patients with cerebral metastases or primary malignancies treated by GK versus Linac. GK may be comparable to surgery for controlling progression of acoustic neuroma, and may also improve quality of life, hearing preservation, and facial function in those ineligible for surgery. The evidence shows that patients with residual nonfunctioning pituitary adenoma benefit, in terms of tumor progression, from GK after surgery compared with observation. Conclusions could not be drawn on the comparative effectiveness of GK for meningioma and AVMs.

Cost effectiveness: The base case estimate of the cost-per-treatment for GK was 3757 Australian dollars (AUD) compared to a range of AUD 960 to AUD 3549 for an adapted Linac unit.

Recommendations

Gamma knife radiosurgery is safe, appears to be effective, but is not cost effective when compared with Linac stereotactic radiosurgery. MSAC recommends no change in current funding arrangements. The Minister for Health and Ageing endorsed GK radiosurgery in 2006.

Methods

MSAC conducted a systematic review of the biomedical literature (MEDLINE, EMBASE, Pre-Medline, Current Contents, Cinahl, ACP Journal Club, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, and Cochrane Controlled Trials Register) from 2001 to September 2005 to update its previous assessment of GK. Reference lists and HTA websites were also searched. A partial economic costing was conducted due to the limitations of the evidence for effectiveness.

Further research/reviews required

N/A

Written by MSAC with assistance of Marinovich L, Griffiths A, and Lord S,
NHMRC Clinical Trials Centre, University of Sydney, Australia

Title **Endoscopic Ultrasound for Evaluating Pancreatic, Gastric, Esophageal and Hepatobiliary Neoplasms**

Agency **MSAC, Medical Services Advisory Committee**
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Reference MSAC 1072 Assessment report. ISBN 1-74186-199-3. Ms Ann Jones edited the report

Aim

To evaluate the safety, effectiveness, and cost effectiveness of endoscopic ultrasound (EUS) and endoscopic ultrasound-guided, fine-needle aspiration (EUS-FNA) in diagnosing and staging gastrointestinal neoplasms.

Conclusions and results

Safety: The data suggest that use of EUS + FNA for diagnosing and staging gastrointestinal neoplasms is associated with a low perforation risk and is generally a safe procedure.

Effectiveness: Direct evidence indicated that the potential value of EUS + FNA was not increased survival, but fewer inappropriate surgeries performed. Diagnostic accuracy evidence indicated that EUS + FNA in addition to computed tomography (CT), or CT plus positron emission tomography (PET), increased sensitivity in esophageal, gastric, and pancreatic cancer staging. Increased sensitivity is likely to occur at the expense of a small trade-off in specificity. Compared to current clinical practice, EUS + FNA was found to have greater sensitivity in pancreatic, biliary, and gastric submucosal tumor diagnoses. Patient management studies indicated that EUS + FNA findings contributed to avoiding surgeries and other investigations, which reduced the number of complex procedures performed.

Cost effectiveness: Economic evaluation was undertaken for indications with sufficient clinical evidence. Use of EUS was determined to be cost saving for gastric and pancreatic cancer staging. Compared to current clinical practice, EUS + FNA was associated with an incremental cost for staging esophageal cancer and diagnosing pancreatic tumors. The annual financial impact for the first 3 years following listing was estimated to be 1 098 600 and 2 279 010 Australian dollars for EUS and EUS-FNA, respectively.

Recommendations

MSAC recommended that endoscopic ultrasound should be publicly funded for staging esophageal, gastric, and pancreatic cancer, with or without fine-needle aspiration in diagnosing pancreatic, biliary, and gastric submucosal tumors. The Minister for Health and Ageing endorsed this recommendation in 2007.

Methods

The literature on EUS and EUS-FNA in diagnosing and staging gastrointestinal (esophageal, gastric, pancreatic, and extrahepatic biliary tract) neoplasms was systematically reviewed.

Further research/reviews required

N/A

Written by MSAC with the assistance of Dyer S, Gillespie J, Lynch M, Bevan M, Hutchinson J, Ruth A, and Levison D, Medical Technology Assessment Group, IMS Health, Australia

Breast Magnetic Resonance Imaging

Agency MSAC, Medical Services Advisory Committee
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Reference MSAC Application 1098 Assessment report. ISBN 1-74186-203-5.
Bruce Howarth, PhD, edited the report

Aim

To assess the safety, effectiveness, and cost effectiveness of magnetic resonance imaging (MRI) of the breast as an addition or replacement to mammography, with or without breast ultrasound, in screening asymptomatic, high-risk women under 50 years of age, and in those aged 50 years and older.

Conclusions and results

Safety: Breast MRI is a safe procedure in patients without contraindications to exposure to magnetic fields.

Effectiveness: No randomized controlled trials have assessed MRI in breast screening for evidence of its impact on patient outcomes. Accuracy studies provide strong evidence that MRI is more sensitive and less specific than mammography in detecting breast cancer. Consistent evidence shows that adding MRI to mammography provides a 2.6-fold increase in test sensitivity (MRI + mammography sensitivity 94% (95% CI 86%–98%); mammography sensitivity 36% (95% CI 25%–48%; incremental sensitivity of MRI 58% (95% CI 46%–70%)). Estimates of test specificity using MRI varied, but one study showed a 3-fold increase in the rate of investigations for false positive findings. Evidence showing that mammography has a higher sensitivity in older women suggests the incremental accuracy of MRI is likely to be lower in this age group. There was a lack of clinical evidence to determine the health benefits gained by earlier detection of breast cancer in women at high risk.

Cost effectiveness: Based on modeled estimates of the effects of early detection, MRI may potentially be cost effective for screening very high-risk women such as BRCA1 mutation carriers aged 35 to 54 years, but is unlikely to be cost effective for screening BRCA2 carriers or women with a wider risk or age distribution. The total additional cost of implementing MRI for breast cancer screening will depend on the cost and uptake of the procedure, the sensitivity of standard mammography screening protocols that include the option of performing a screening ultrasound, and patient baseline risk.

Recommendations

When used as part of an organized surveillance program, breast MRI combined with mammography is safe and effective in diagnosing breast cancer in asymptomatic women at high risk. Evidence suggests that breast MRI combined with mammography may be cost effective compared to mammography alone in high-risk women below 50 years of age.

MSAC recommends interim public funding for breast MRI in diagnosing breast cancer in asymptomatic women at high risk of developing breast cancer when used as part of an organized surveillance program. Evidence should be reviewed in not less than 3 years. The Minister for Health and Ageing endorsed this recommendation in 2007.

Methods

MSAC conducted a systematic review of the biomedical literature up to March 2006 to assess the safety and effectiveness of breast MRI. A published evaluation of the cost effectiveness of MRI for screening women at high risk of breast cancer in the United States was used to discuss economic considerations. A secondary economic analysis was based on this model, but excluded indirect costs and applied Australian relative prices.

Further research/reviews required

Evidence should be reviewed in not less than 3 years.

Written by MSAC with the assistance of Lord S, Lei W, Griffiths A, Walleser S, Parker S, and Thongyoo S, NHMRC Clinical Trials Centre, and Eckermann S, Flinders Centre for Clinical Change and Health Care Research, Australia

INAHTA Briefs

Issue 2008/050

Title **Double-Balloon Enteroscopy**

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Reference MSAC Application 1102. ISBN 1-74186-207-8.
Ms Jo Mason edited the report

Aim

To assess the safety, effectiveness, and cost effectiveness of double-balloon enteroscopy (DBE) in obscure gastrointestinal bleeding or suspected small bowel disease relative to laparotomy with or without intraoperative enteroscopy.

Conclusions and results

Safety: Fourteen uncontrolled case series and 4 case reports addressed the safety of DBE. Major complications, eg, perforation and sepsis, were reported in less than 1% of patients. No deaths were reported. Pancreatitis was the most common cause of major complication, most of which was resolved by conservative therapy. Minor complications, eg, abdominal pain and sore throat, were experienced in 7.2% of procedures. No studies comparing the relative safety of DBE against the comparative procedures of laparotomy, with or without intraoperative enteroscopy, were identified. Without direct comparative data, it is not possible to conclude that DBE is as safe as, or safer than, the comparators. However, given DBE's less invasive nature, fewer complications are likely to arise.

Effectiveness: Effectiveness outcomes of DBE were reported in 11 uncontrolled case series. Ten case series reported the success of DBE as a therapeutic intervention, ranging from 77% to 100%, with 6 studies reporting 100% success in the treatments used. All 11 case series reported biopsy or diagnostic yield. Transfusion requirement after DBE was poorly reported, with only 1 study reporting a 70% reduction in the number of patients requiring transfusion after DBE. As no data compared DBE with laparotomy, with or without intraoperative enteroscopy, no conclusions can be drawn on the relative effectiveness of the procedure. Based on the evidence identified, DBE appears to be effective at providing therapies to small bowel lesions.

Cost effectiveness: As there was no comparative evidence on DBE, it was not possible to determine if the procedure was as effective as, or more effective than, the comparators. A financial incidence analysis was performed, which indicated that although DBE would be more costly to the Commonwealth relative to the comparators, there were likely to be savings to the Australian healthcare system overall.

Recommendations

Double-balloon enteroscopy (DBE) is a safe, minimally invasive technique to endoscopically examine the small intestine, concurrently allowing biopsy and certain therapeutic procedures. While there are no direct comparative data, DBE is likely to be safer than the most appropriate alternative, intraoperative enteroscopy. DBE is effective in allowing enteroscopic assessment and some treatment of the entire small intestine. Although more costly to Medicare than intraoperative enteroscopy, DBE can potentially save costs for the entire health funding system. MSAC recommends public funding for DBE to diagnose and treat patients with obscure gastrointestinal bleeding. The Minister for Health and Ageing accepted this recommendation in 2007.

Methods

MEDLINE, EMBASE, the Cochrane Library, other biomedical databases, and HTA and other websites were searched (2001 to May 2006). Specific journals were hand searched and reference lists canvassed. Studies were included in the review using predetermined PICO selection criteria, and reasons for exclusion were documented. Study quality was appraised, data extracted in a standardized manner, and findings synthesized qualitatively.

Further research/reviews required

N/A

Written by Buckley E, Newton S, Hedayati H, Merlin T, Moss J, and Hiller J, AHTA, Australia, on behalf of MSAC

Fetal Fibronectin Test for Preterm Labor

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Reference MSAC Application 1103 Assessment report. ISBN 1-74186-209-4.
Ms Ann Jones edited the report

Aim

To evaluate the safety, effectiveness, and cost effectiveness of fetal fibronectin testing to assess preterm labor and the circumstances under which this test should be publicly funded.

Conclusions and results

Safety: Safety data relating to fetal fibronectin testing were not identified. The risk to patients is considered to be minimal because test samples are obtained during standard speculum examinations.

Effectiveness: Negative test results provide moderate diagnostic value to identify women in suspected preterm labor not at immediate risk of preterm delivery. The evidence was insufficient to support conclusive recommendations about the diagnostic precision of fetal fibronectin testing among asymptomatic pregnant women considered to be at high risk of preterm delivery.

The value of fetal fibronectin testing in clinical decision making in Australia remains uncertain because patient management data are limited. Treatment effectiveness was not examined among women in suspected preterm labor because it was considered unlikely that testing would identify additional patients needing treatment. Treatment effectiveness was not examined among high-risk, asymptomatic women because diagnostic accuracy and patient management data provided insufficient evidence for analysis.

Cost effectiveness: The financial impact of fetal fibronectin testing for women in suspected preterm labor was estimated to cost Medicare Australia between 1.66 million and 3.04 million Australian dollars per year. However, there was some uncertainty about potential savings generated as a result of providing testing for women suspected of preterm labor. The evidence was insufficient to warrant an economic analysis of testing among high-risk, asymptomatic women.

Recommendations

MSAC determined that the test is safe, but effectiveness has not been demonstrated. MSAC does not support public funding for the test at this time. The Minister for Health and Ageing endorsed this recommendation in 2007.

Methods

MSAC conducted a systematic review of the medical literature pertaining to fetal fibronectin testing. Citations that met predefined inclusion criteria were presented in the review of evidence.

Written by MSAC with the assistance of Birinyi-Strachan L, Bevan M, Smala A, and Hutchinson J, M-TAG Pty Ltd, IMS Health, Australia

INAHTA Briefs

Issue 2008/052

Title	**Screening for Phenylketonuria in Newborns in Finland**
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Reference	Rapid HTA report. May 2008

Aim

To evaluate the cost effectiveness of phenylketonuria (PKU) screening in newborns in Finland, especially regarding PKU screening targeted at infants born to non-Finnish parents.

Conclusions and results

Early treatment may prevent irreversible brain damage caused by PKU. Finland does not have a national screening program since PKU incidence is only 1:100 000 to 1:200 000 (ie, significantly lower than elsewhere).

The Guthrie method, fluorometry, or tandem mass spectrometry (MS/MS) are used to screen for PKU, with MS/MS being the most specific method. The Guthrie method and fluorometry were found to be cost effective in many countries. MS/MS was cost effective only when combined with screening of at least one other metabolic disease. In 2000 to 2006, infants born to immigrant parents increased from 2.3% to 3.4% of all newborns. Annual costs for screening would be 96 000 euros for these infants, and 2.7 million euros for screening all infants. Twenty hospitals (representing 80% of all births) screened for PKU in newborns with immigrant parents. A single case of PKU was found by screening, and no other cases were identified in 7 years. The cost effectiveness of both universal and selective PKU screening in Finland is dubious. Targeted screening evokes ethical questions, eg, definition and identification of ethnic origin and acceptability as a public health strategy.

Methods

Assessment strategy:

- Systematic review
- Primary data: The number of infants with immigrant parents in 2000 to 2006 was retrieved from the National Medical Birth Register combined with the Finnish Population Information System. Current screening practice was assessed by a survey of maternity hospitals.

Type of analysis: decision analysis, cost analysis, social/ethical implications consideration.

Data sources: Cochrane, DARE, CRD, HTA, EED, MEDLINE.

Types of studies assessed: all.

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