

Review

Cost Effectiveness of Natural Health Products: A Systematic Review of Randomized Clinical Trials

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Health care spending in North America is consuming an ever-increasing share of Gross Domestic Product (GDP). A large proportion of alternative health care is consumed in the form of natural health products (NHPs). The question of whether or not NHPs may provide a cost-effective choice in the treatment of disease is important for patients, physicians and policy makers. The objective of this study was to conduct a systematic review of the literature in order to find, appraise and summarize high-quality studies that explore the cost effectiveness of NHPs as compared to conventional medicine. The following databases were searched independently in duplicate from inception to January 1, 2006: EMBASE, MEDLINE, CINAHL, BioethicsLine, Wilson General Science abstracts, EconLit, Cochrane Library, ABI/Inform and SciSearch. To be included in the review, trials had to be randomized, assessed for some measure of cost effectiveness and include the use of NHPs as defined by the Natural Health Products Directorate. Studies dealing with diseases due to malnutrition were excluded from appraisal. The pooled searches unveiled nine articles that fit the inclusion/exclusion criteria. The conditions assessed by the studies included three on postoperative complications, two on cardiovascular disease, two on gastrointestinal disorders, one on critically ill patients and one on urinary tract infections. Heterogeneity between the studies was too great to allow for meta-analysis of the results. The use of NHPs shows evidence of cost effectiveness in relation to postoperative surgery but not with respect to the other conditions assessed. In conclusion, NHPs may be of use in preventing complications associated with surgery. The cost effectiveness of some NHPs is encouraging in certain areas but needs confirmation from further research.

Keywords: CAM—complementary and alternative medicine—cost effectiveness—natural health products—NHPs

Introduction

Consumers in North America are increasingly spending more on complementary and alternative medicine (CAM) and natural health products (NHPs). There are a number of studies that have investigated the cost effectiveness of CAM in terms of the different modalities that are usually

associated with CAM, such as acupuncture, Feldenkrais, chiropractic and massage therapy as examples (1,2). In reviewing the cost effectiveness of CAM, NHPs were often also included. However, there are no studies that reviewed the cost effectiveness of just NHPs specifically. With this review we focused on the cost effectiveness of NHPs.

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Healthcare Spending: Conventional and Complementary

Health care spending in the US reached almost \$2 trillion [\$2.6 trillion 2004 CAD (all currency conversion were

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based on the currency conversion factor for that year as published by the Bank of Canada. Available URL: http://www.bankofcanada.ca/en/rates/exchange_avg_pdf.html. Accessed April 28, 2006)] in 2004 (3), up from \$1.4 trillion (\$2.07 trillion 2000 CAD) in 2000. This represents a \$500 billion increase in just 4 years. In Canada, health care spending reached \$130 billion in that same year (4). Prescription costs account for some of the highest rates of increase in health care spending as evidenced by a growth rate of 8.2% in drug costs in the US between 2003 and 2004 (3). In Canada, an estimated \$18.0 billion was spent on prescription of drugs in 2004 and \$16.3 billion in 2003 representing an increase of 10.4% in 1 year (4).

Health care spending is increasing, both from a government and a private standpoint. As people make health care choices to empower themselves (5) and make their own treatment choices, they are also seeking the assistance of CAM practitioners. In a 2003 survey, conducted by Statistics Canada, 12.4% of Canadians over the age of 12 years indicated that they had contact with alternative health care providers in the past 12 months (6). This was up from an estimated 7.6% in 1999(7). According to the 2003 survey, alternative health care providers included: 'massage therapists, acupuncturists, homeopaths, naturopaths, Feldenkrais or Alexander teachers, relaxation therapists, biofeedback teachers, rolfers, herbalists, reflexologists, spiritual healers, religious healers, etc.' (6). A 2002 US National Health Interview Survey conducted by the Center for Disease Control and Prevention's National Center for Health Statistics (NCHS) found that 62% of US adults had used some form of CAM in the past 12 months (8).

Regarding the issue of cost, Eisenberg *et al.* (9) conservatively estimated that the total annual out-of-pocket spending, in the United States, on all complementary therapies was in the region of \$27 billion USD (\$37 billion 1997 CAD) in 1997. The estimated total out-of-pocket spending by Canadians on CAM was \$3.8 billion CAD in 1997 (10). An Australian 2000 survey estimated that the annual expenditure on CAM was \$AU621 million (\$536 million 2000 CAD) (11).

NHPs are defined by Health Canada's Natural Health Products Directorate (NHPD) as: vitamins and minerals, herbal remedies, homeopathic medicines, traditional medicines such as traditional Chinese medicines and other products including probiotics, amino acids and essential fatty acids. Recent regulations created by the NHPD require that NHPs are safe for public consumption as over-the-counter products, be available for self-care and self-selection and not require a prescription to be sold (12). These products are available and sold over the counter in pharmacies, grocery stores and health food stores. Consumers either self-select NHPs or may be prescribed these products by naturopathic doctors, chiropractors, herbalists and staff at health food stores.

In 1997, it was estimated that the gross income for the NHP industry in Canada was between 1.5 and 2 billion dollars and that the annual growth would be 10 to 15% per annum (8). The estimated annual out of pocket expenditures on NHPs in 2005 was 3.6 billion dollars CAD (13).

The Nonprescription Drug Manufacturers Association of Canada's (NDMAC) Health Vision 1999/2000 publication on consumer attitudes and behaviors found that in 1999, 26% of respondents had used herbal and/or homeopathic remedies (14). This number had increased to 41% by the year 2000 (14). A March 2005 survey of Canadians by IPSOS Reid indicated that reported NHP usage among Canadians is high, with seven out of ten Canadians reporting that they have used a NHP (12). It appears as if more and more Canadians are incorporating NHPs into their health care choices.

This trend is not only evident in North America but is also occurring in other countries. The 2000 Australian survey estimated that annual expenditure on CAM was \$AU1671 million (\$1.442 billion 2000 CAD) (11). This represents a 120% increase since 1993, a time during which inflation in Australia increased by an average of 3.2% per annum (11).

Who is Using NHPs?

The IPSOS Reid survey indicates that NHP users were, by far, more women than men, likely to be better educated and have higher household income (12). This demographic is consistent with the demographics that were found in the Australian survey on alternative medicine (11).

The desire of Canadians to empower themselves in their health care choices is evident in the reasons why they choose NHPs. In the IPSOS Reid survey, 52% indicated that they chose an NHP because of the desire to control or influence their personal health (12). A further 21% did so to help maintain and promote their health and prevent illness (12).

Economic Evaluation

Economic evaluation is the systematic appraisal of costs and benefits of projects, or alternative ways of achieving the same outcomes, undertaken to determine the economic effectiveness of the alternatives (1,15). There are a number of different methods employed in an economic evaluation, each with its own purpose for the analysis. The information for this section was obtained in part from the National Information Center on Health Services Research and Health Care Technology's (NICHSR) Health Economics Information Resources program developed by Moira Napper and Jean Newland (15).

Cost-Benefit Analysis (CBA)

'A CBA is an economic evaluation in which all costs and consequences of a program are expressed in the same units, usually money. CBA is used to determine allocative efficiency; i.e., comparison of costs and benefits across programs serving different patient groups. Even if some items of resource or benefit cannot be measured in the common unit of account; i.e., money, they should not be excluded from the analysis' (15). Herman (1) identifies the challenge of CBA in that its analysis requires putting a monetary value on all health outcomes and ultimately on life. There is inherent difficulty with this type of analysis and as a result very few true CBAs have yet been performed (15).

Cost-Effectiveness Analysis (CEA)

'A CEA is an economic evaluation in which the costs and consequences of alternative interventions are expressed as costs per unit of health outcome. CEA is used to determine technical efficiency; i.e., comparison of costs and consequences of competing interventions for a given patient group within a given budget' (15). The result will be a comparison of cost per unit of improvement between examined treatments (15). Comparison of multiple outcomes is not possible with this type of analysis (1); however, the analysis does help answer urgent questions, such as how much it would cost to reduce hip fractures in osteoporotic women (1).

Cost-Minimization Analysis (CMA)

'A CMA is an economic evaluation in which consequences of competing interventions are the same and in which only inputs, that is, costs are taken into consideration. The aim is to decide the least costly way of achieving the same outcome' (15).

Cost-Utility Analysis (CUA)

'A CUA is a form of economic study design in which interventions which produce different consequences, in terms of both quantity and quality of life, are expressed as "utilities". These are measures that comprise both length of life and subjective levels of wellbeing. The best-known utility measure is the "quality adjusted life year" or QALY. In this case, competing interventions are compared in terms of cost per utility (cost per QALY)' (15). Health outcomes are assigned a value based on their contribution to quality of life (1). Since CUA analysis provides for summary measures of quality of life, short-term changes, such as those in acute situations, and discrete changes, such as blood pressure control, are not easily identifiable (1).

Perspective of the Economic Analysis

Regardless of the type of analysis performed, the perspective of the economic analysis is another consideration. Is the perspective that of the patient, insurance company or health care system? Determination of the perspective will determine what costs are collected and measured in the analysis.

Classification of Outcomes—ECHO Model

Another component of economic evaluation involves the classification of the outcomes that are assessed. Gunter (16) puts forth the point of view that 'It is essential to measure a balance of outcomes, in the analysis, to ensure that no one outcome is being maximized to the detriment of another.' Kozma *et al.* (17) put forth the Economic, Clinical and Humanistic Outcomes (ECHO) model which recognizes that the outcome of medical care would be along three dimensions—economic, clinical and humanistic outcomes. Outcomes that occur as a result of disease or treatment are classified as clinical outcomes. Direct, indirect and intangible costs are considered economic outcomes and consequences of disease or treatment on patient functional status or quality of life are considered as humanistic outcomes (17).

In this review, we have systematically searched the literature for randomized clinical trials (RCTs) that collected data regarding the cost effectiveness of NHPs in comparison to conventional therapies. Our review is limited to RCTs as they provide the highest-level evidence with the least bias, an issue with special relevance in the study of evidence on CAM wherein different therapies are often combined. Such combinations make it very difficult to ascertain both quality of evidence and causality due to any single treatment component (i.e. NHP). Findings of this review should be of interest to the public, health care professionals and policy makers involved in health care.

Data Sources

The following databases were searched independently by D.A.K. and J.H. in duplicate from inception to January 1, 2006: EMBASE, MEDLINE, CINAHL, BioethicsLine, Wilson General Science abstracts, EconLit, Cochrane Library, ABI/Inform and SciSearch.

Review Methods

To be included in the review, trials had to be randomized, assessed for some measure of cost evaluation (either CBA, CEA, CMA or CUA) and include the use of a NHP as defined by the NHPD. Manuscripts dealing with conditions of disease solely due to malnutrition were excluded from appraisal, since supplementation

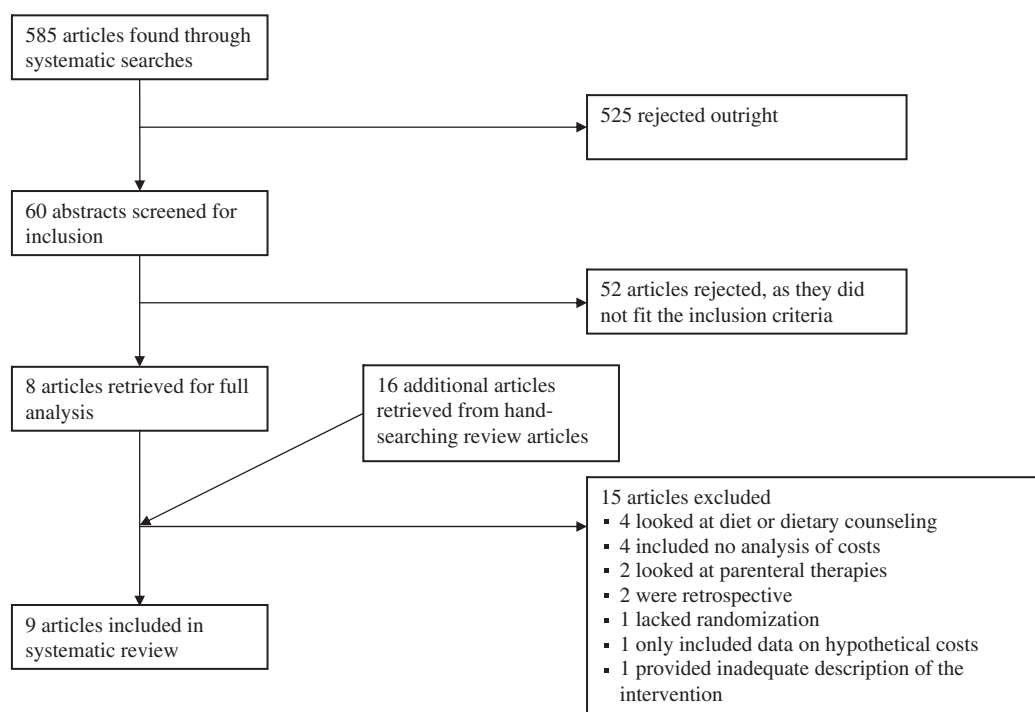


Figure 1. Flow chart of studies excluded and selected for systematic review.

of a frank nutritional deficiency would clearly be cost-effective. Where necessary, authors were contacted for clarification of evidence.

Data extraction sheets were used to collect and compile data on each of the articles included in the review. The extraction sheets were completed independently by D.A.K. and J.H. Primary data points collected included: type of study, costs (direct and indirect), intervention, outcomes measured, adverse effects, type of economic analysis and the principal economic characteristics associated with each study (including the timing of analysis), level of costs analyzed and economic evaluation based on the ECHO model described above.

Results

The pooled searches unveiled 585 original articles. Of these, eight fit our inclusion/exclusion criteria. One additional study was found through hand-searching the bibliographies of relevant manuscripts. The search process is further detailed in Fig. 1. Conditions assessed by the studies included three on postoperative complications (18–20), two on cardiovascular disease (21,22), two on gastrointestinal disorders (23,24), one on critically ill patients (25) and one on urinary tract infections (UTIs) (26).

The results of the analysis revealed that eight of the nine studies demonstrated that when an NHP was included in care, there was a concomitant cost savings with the positive health outcomes demonstrated.

Cost savings in the studies ranged from 3.7 to 73% reduction in costs over the control group. A summary of the studies included in this analysis is presented in Table 1.

NHPs Found to be Cost-Effective

The three studies related to enriched perioperative nutrition and enriched enteral nutrition for the critically ill demonstrated a reduction in postoperative complications and mortality and therefore an overall reduction in hospital-related costs. The two cardiovascular studies showed that while supplementation with NHPs, in this case Vitamin E and n-3 polyunsaturated fatty acids (n-3 PUFA), did improve clinical outcome, costs were not necessarily reduced. The Davey *et al.* (21) study showed that Vitamin E supplementation was cost-effective as compared with control by an average of \$578 USD in improving outcomes post MI (20). However, the Franzosi *et al.* (22) study demonstrated that supplementation with n-3 PUFA's while significantly decreasing negative outcomes post MI, did so with only with an increase in costs (21). The cost increase of \$1030 USD was solely attributed to the cost of the n-3 PUFA supplementation. Regarding the use of NHPs to treat gastrointestinal disorders and UTIs, typically outpatient conditions, the studies demonstrated that NHPs did provide cost savings (ranging from 19 to 73%). Adverse effects were reported but were not quantified in monetary terms, nor taken into consideration in the cost effectiveness analysis.

Table 1. Condition, intervention, outcomes, costs, and adverse effects of each study

Reference	Condition investigated	Interventions compared	Health outcomes/ measurements	Costs control group (USD) A	Costs treat group (USD) B	Cost savings (USD) (A-B)	Percentage of cost reduction $\frac{(A-B)}{A} \times 100$	Adverse effects
Gianotti <i>et al.</i> (19)	Postoperative complications for gastrointestinal cancer	<ul style="list-style-type: none"> ■ Enriched perioperative nutrition ■ Isonitrogenous, isocaloric liquid 	<ul style="list-style-type: none"> ■ Postoperative infections and complications 	17 100 ^a	12 049 ^a	5051	29.5	None reported
Senkal <i>et al.</i> (18)	Postoperative complications post elective upper gastrointestinal surgery	<ul style="list-style-type: none"> ■ Immune enhancing perioperative nutrition ■ Isoenergetic, isonitrogenous perioperative nutrition 	<ul style="list-style-type: none"> ■ Postoperative infectious complications 	1765 ^b	846 ^b	919	52.0	None reported
Smedley <i>et al.</i> (20)	Postoperative complications post lower gastrointestinal surgery	<ul style="list-style-type: none"> ■ Perioperative nutrition ■ Postoperative nutrition ■ Combined post and perioperative nutrition 	<ul style="list-style-type: none"> ■ Postoperative weight loss ■ Postoperative complications 	4767 ^c	4168 ^c	599	12.5	None reported
Jones <i>et al.</i> (25)	Critical illness	<ul style="list-style-type: none"> ■ Glutamine-supplemented enteral nutrition ■ Enteral nutrition 	<ul style="list-style-type: none"> ■ Mortality ■ Morbidity ■ Costs at 6 months post study 	30 900	23 000	7900	25.5	None reported
Davey <i>et al.</i> (21)	Cardiovascular disease	<ul style="list-style-type: none"> ■ Vitamin E 400IU ■ Vitamin E 800IU ■ Placebo 	<ul style="list-style-type: none"> ■ Nonfatal MI ■ CV death ■ Nonfatal AMI 	15 573	14 995	578	3.7	None reported
Franzosi <i>et al.</i> (22)	Cardiovascular disease	<ul style="list-style-type: none"> ■ n-3 PUFA ■ Placebo 	<ul style="list-style-type: none"> ■ Mortality ■ Nonfatal MI ■ Nonfatal stroke 	5558 ^a	6588 ^a	-1030 ^d	-18.5	None reported
Paterson <i>et al.</i> (24)	Dyspepsia	<ul style="list-style-type: none"> ■ Homeopathy and general practitioner care ■ General practitioner care only 	<ul style="list-style-type: none"> ■ Changes in Measure Yourself Medical Outcome Profile (MYMOP) and symptoms of dyspepsia 	134 ^c	108 ^c	26 ^e	19.4	None reported
Passmore <i>et al.</i> (23)	Chronic constipation	<ul style="list-style-type: none"> ■ Lactulose ■ Senna fibre 	<ul style="list-style-type: none"> ■ Frequency of stool ■ Stool consistency ■ Ease of evacuation 	72 ^c	19 ^c	53	73.6	Variety
Stothers <i>et al.</i> (26)	Lower UTIs	<ul style="list-style-type: none"> ■ Cranberry tabs ■ Cranberry Juice ■ Placebo 	<ul style="list-style-type: none"> ■ \$ per UTI prevented 	6.52 ^f	4.20 ^f	2.32	35.5	Reflex, nausea

^aBased on conversion of 1 EUR = 1.26204 USD on April 27, 2006; ^bBased on conversion of 1 DEM = 0.64497 USD on April 27, 2006; ^cBased on conversion of 1 GBP = 1.82148 USD on April 27, 2006; ^dAttributed to the cost of n-3 PUFA; ^eExcludes the cost of homeopathy (\$191); ^fBased on conversion of 1 CAD = 0.8938 USD on April 27, 2006.

Comparison of Costs Included in the Studies

A summary of the economic characteristics of each study is presented in Table 2. There were a number of different methods used to derive the costs. In some studies, the actual costs were collected as the data was being collected. Other studies used surrogate measures for cost such as third party payer reimbursements rates at the Diagnosis Related Group (DRG) level. In other studies, the costs were estimated through consultation with medical experts regarding the components of care that would have been required for the usual care of a patient with a given health condition.

The level of the cost analysis is an important consideration since this determines what costs will be collected and included in the analysis. For example, studies that collected cost data at the level of the individual took into consideration: the costs of days of lost work, transportation costs to and from appointments and other identifiable direct and indirect patient costs. There were a number of studies that looked at the costs from the perspective of the hospital, for example, collecting data for medical or nursing care and also costs while in the intensive care unit. These studies did not incorporate costs at the individual patient level. A number of studies were done from the perspective of a national health service, which for outpatient conditions provides for a broader, more policy-based collection of costs; i.e. physician consultations, drugs utilized and diagnostic procedures performed.

Discussion

There is a range of different conditions that are included in our analysis. Some of the conditions that were analyzed are those that are usually treated as outpatient conditions (i.e. dyspepsia, constipation and UTIs), while others relate to reducing complications and hospital care after a nonfatal cardiac event. The studies that were included demonstrate that NHPs do provide a reduction in overall costs for each of the conditions that assessed except for the one study on cardiovascular health (22).

A glance at Table 2 reveals that there is little consistency across the studies that we found regarding economic characteristics. Further, in the evaluation of cost effectiveness of different treatment options, within the health care area, there are as yet, no consistent standards that are employed and a number of issues that still need resolution (27). Direct costs are those costs that can be attributed directly to the patient. For example, most of the studies incorporated direct hospital costs in their analysis, whereas one study by Franzosi *et al.* (22) looked at only the incremental direct costs, i.e. costs that were incurred for a patient beyond what was provided, as a baseline, for all patients in the study (21).

Limitations

A principal limitation to this systematic review is the paucity and variability of the data we were able to find. Given the number of studies, the different NHPs studied, and the variation in conditions of disease, it is impossible to combine our findings statistically in a meta-analysis. This limitation may have been partially alleviated by allowing the inclusion of observational studies, however, this would have come at the cost of reducing the validity of our findings overall.

There is limited evidence regarding the cost effectiveness of NHPs overall both in terms of the numbers of studies that have been conducted and the rigor of the methodologies employed. This may be partially due to the limited research focus on NHPs specifically and also on cost effectiveness studies in general. The inclusion of data points required for a robust cost effectiveness model is required at the design phase of a trial. Considering the lack of use of NHPs in conventional health care, it is no surprise that cost effectiveness issues, of great importance to policy makers, are not standard components of trials that use NHPs. Efficacy and adverse effects are the principal concerns for these types of intervention and as such the issue of cost effectiveness is probably often not considered, especially at the outset.

Economic Evaluation

Economic evaluation and analysis is not new. Analysis of the costs and benefits of alternatives have been performed in the industrial arena for a long time. However, the inclusion of economic evaluation within the health care sector is a relatively new phenomenon in a time where health care costs are ever increasing and administrators are faced with having to do more with less. Table 2 highlights the difficulty that exists due to a lack of standardization in the performance of economic evaluations thus making the comparison of the economic results from one study to the next difficult at best.

NHPs are purported to have fewer side-effects than other medical therapies. Therefore, the incorporation of the humanistic outcomes in the cost effectiveness analysis is particularly important for NHPs. Few studies examined the humanistic dimension and therefore some of the potential benefits of NHPs may have been excluded from analysis. These potential benefits could include improvements in quality of life and reductions in drug-induced side-effects that certainly have an economic impact. If these humanistic elements were to be included, it is conceivable that the cost benefits would be greater than reported for these studies regarding NHPs. Possible indirect cost benefits that could arise include a speedier recovery leading to earlier return to employment and changes in dietary habits leading to reduced health care costs in the future. The placebo effect, however, does

Table 2. Principal economic evaluation characteristics of each study

Reference	Economic analysis	Level of costs analyzed	Dimension of outcome (ECHO)	Type of costs included	Comments
Gianotti <i>et al.</i> (19)	Prospective	Hospital	Economic Clinical	Direct costs	Indirect patient costs were not taken into consideration
Senkal <i>et al.</i> (18)	Prospective	Hospital	Economic Clinical	Direct medical cost of postoperative complications	No length of stay nor days in ICU costs were included Indirect patient costs were not taken into consideration.
Smedley <i>et al.</i> (20)	Prospective	Health Service	Economic Clinical	Direct costs excluding cost of surgery	Quality of life measures were performed however, not included in the analysis
Jones <i>et al.</i> (25)	Prospective	Hospital	Economic Clinical	Direct costs	Cost of nutrition not included Costs for 1 year of the study were collected and used as a basis for the costs throughout the study.
Davey <i>et al.</i> (21)	Retrospective cost analysis on study by Stephens <i>et al.</i> , 1996 (28)	Health care system	Economic Clinical	Estimated direct costs	Estimated resources utilized and costs were derived
Franzosi <i>et al.</i> (22)	Retrospective cost analysis on study by Valagussa <i>et al.</i> , 1999 (29)	Third-party payer	Economic Humanistic	Incremental direct health care costs	Costs were estimated using Italian third-party payer reimbursement rates.
Paterson <i>et al.</i> (24)	Prospective	National health service (NHS)	Economic Humanistic	Direct costs	Patient out of pocket expense data was collected but not reported on
Passmore <i>et al.</i> (23)	Prospective	Individual	Economic Clinical	Cost of supplement only	
Stothers <i>et al.</i> (26)	Prospective	Individual	Economic Clinical	Direct and indirect costs	

provide genuine relief to patients and if improved by the use of natural therapies like NHPs, should not be discounted out of hand.

Finally, the preponderance of studies that we found relating to the use of NHPs for postsurgical care with a cost effectiveness component implies that this is an area of real importance with regards to cost savings. It is also indicative of the potential for NHPs to provide benefit in this context. Our findings support this potential and raise the issue of whether policy changes with regards to the inclusion of certain NHPs in postoperative care would not in fact ameliorate conditions for patients, public health care and third-party insurers.

Conclusion

The use of NHPs demonstrated some evidence of cost effectiveness in relation to postoperative surgery, yet is inconclusive in relation to the other conditions assessed. Further clinical research in the postsurgical setting is needed to clearly establish the cost benefits that may be achievable in this and other settings. Another aspect highlighted by this review is the lack of consistency regarding the cost effectiveness analysis. Further work needs to be done to determine a cost effectiveness framework which incorporates humanistic outcomes within which to evaluate NHPs.

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References

- Herman PM, Craig BM, Caspi O. Is complementary and alternative medicine (CAM) cost-effective? A systematic review. *BMC Complement Altern Med* 2005;5:11.
- Hulme C, Long AF. Square pegs and round holes? A review of economic evaluation in complementary and alternative medicine. *J Altern Complement Med* 2005;11:179–88.
- Snapshot Health Care Costs 101: Californian HealthCare Foundation, 2006: 24.
- Health Care in Canada 2005: Canadian Institute for Health Information, 2005: 117.
- Canada NDMAo. Canadian Self-Care Industry profile: Nonprescription Drug Manufacturers Association of Canada, 2003.
- Contact with Alternative health care providers, by age group and sex, household population, aged 12 and over, Canada excluding territories, 2003: Statistics Canada, 2004: 5.
- Contact with Alternative Health Care providers, by age group and sex, household population aged 12 and over, Canada excluding territories, 1994/95–1998/99: Statistics Canada, 2002: 5.
- Barnes PM P-GE, McFann K, Nahin RL. *Complementary and Alternative Use Among Adults*, United States, 2002: US Department of Health and Human Services Centers for Disease Control and Prevention National Center for Health Statistics, 2004: 19.
- Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, et al. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. *JAMA* 1998;280:1569–75.
- Ramsay CWM, Alexander J. *Alternative Medicine in Canada: Use and Public Attitudes*. Vancouver: The Fraser Institute, 1999, 31.
- MacLennan AH, Myers SP, Taylor AW. The continuing use of complementary and alternative medicine in South Australia: costs and beliefs in 2004. *Med J Aust* 2006;184:27–31.
- Ipsos/Reid. Baseline Natural Health Products Survey Among Consumers: Health Canada, 2005: 85.
- Canada NDMAo. Self-Care: Making Canadians healthier: Nonprescription Drug Manufacturers Association of Canada, 2005, 9.
- Canada NDMAo. HealthVision 1999/2000: Nonprescription Drug Manufacturers Association of Canada, 1999/2000.
- Napper M, Newland J. *Health Economics Information Resources: A Self-Study Course*. Bethesda: U.S. National Library of Medicine, 2003.
- Gunter MJ. The role of the ECHO model in outcomes research and clinical practice improvement. *Am J Manag Care* 1999;5 (4 Suppl): S217–24.
- Kozma CM, Reeder CE, Schulz RM. Economic, clinical, and humanistic outcomes: a planning model for pharmacoeconomic research. *Clin Ther* 1993;15:1121–32; discussion 1120.
- Senkal M, Zumtobel V, Bauer KH, Marpe B, Wolfram G, Frei A, et al. Outcome and cost-effectiveness of perioperative enteral immunonutrition in patients undergoing elective upper gastrointestinal tract surgery: a prospective randomized study. *Arch Surg* 1999;134:1309–16.
- Gianotti L, Braga M, Frei A, Greiner R, Di Carlo V. Health care resources consumed to treat postoperative infections: cost saving by perioperative immunonutrition. *Shock* 2000;14:325–30.
- Smedley F, Bowling T, James M, Stokes E, Goodger C, O'Connor O, et al. Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care. *Br J Surg* 2004;91:983–90.
- Davey PJ, Schulz M, Gliksmann M, Dobson M, Aristides M, Stephens NG. Cost-effectiveness of vitamin E therapy in the treatment of patients with angiographically proven coronary narrowing (CHAOS trial). Cambridge Heart Antioxidant Study. *Am J Cardiol* 1998;82:414–7.
- Franzosi MG, Brunetti M, Marchioli R, Marfisi RM, Tognoni G, Valagussa F. Cost-effectiveness analysis of n-3 polyunsaturated fatty acids (PUFA) after myocardial infarction: results from Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI)-Prevenzione Trial. *Pharmacoeconomics* 2001;19:411–20.
- Passmore AP, Wilson-Davies K, Stoker C, Scott ME. Chronic constipation in long stay elderly patients: a comparison of lactulose and a senna-fibre combination. *Br Med J* 1993;307:769–71.
- Paterson C, Ewings P, Brazier JE, Britten N. Treating dyspepsia with acupuncture and homeopathy: reflections on a pilot study by researchers, practitioners and participants. *Complement Ther Med* 2003;11:78–84.
- Jones C, Palmer TE, Griffiths RD. Randomized clinical outcome study of critically ill patients given glutamine-supplemented enteral nutrition. *Nutrition* 1999;15:108–15.
- Stothers L. A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. *Can J Urol* 2002;9:1558–62.
- Andrews GJ. Addressing efficiency: economic evaluation and the agenda for CAM researchers. *Complement Ther Clin Pract* 2005;11:253–61.
- Stephens NG, Parsons A, Schofield PM, Kelly F, Cheeseman K, Mitchinson MJ. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge heart antioxidant study (CHAOS). *Lancet* 1996;347:781–6.
- Valagussa, et al. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. *Lancet*. 1999;354:447–55.

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