

ECONOMIC ANALYSIS OF TREATMENT OF FUNCTIONAL DYSPEPSIA

An Assessment of the Quality of Published Studies

Anna García-Altés

Catalan Agency for Health Technology Assessment and Research (CAHTA)

Esther Jovell

Consorci Sanitari de Terrassa

Abstract

Objectives: The objective of this study was to assess the quality of economic analysis studies published in the medical and economical literature assessing the clinical management of functional dyspepsia.

Methods: Bibliographic search in the main biomedical databases, in articles from bibliographic references, health technology assessment reports, and in gray literature. A specific protocol with economic and clinical items was designed for the evaluation.

Results: Overall, 18 of 162 studies met the inclusion criteria for the assessment. The compared treatment options were very diverse. The main methodologic deficiencies were in perspective of analysis, inclusion of indirect costs, and sources of clinical information.

Conclusions: Specific checklists with clinical and economical items may help to better assess the quality of economic analysis in the field of functional dyspepsia. The methodologic rigor in the application of economic analysis techniques, as well as the use of appropriate clinical outcome measures, is essential to guarantee the reproducibility of the studies.

Keywords: Functional dyspepsia, Economic analysis, Outcome measure, Scientific evidence

The aim of economic analysis in health care is to identify, measure, and compare competing alternatives that can be applied to the prevention, detection, diagnosis, treatment, care, and rehabilitation of clinical conditions in order to assess their relative efficiency. The results of economic analyses can be used in healthcare decision making at all levels from clinical practice to healthcare policy. Scarce health resources promote the adoption of those healthcare interventions proven to be more cost-effective among available alternatives. Therefore, economic analysis allows choosing, given equal effectiveness or clinical benefit,

The authors thank Joan M. V. Pons, Mercè Barenys, and Albert J. Jovell for their help in the review of a previous version of this manuscript, Antoni Parada for his support in the bibliographic search, and Alejandro Lorenzo for the review of a previous English version.

those medical interventions with lower cost or, at equal costs, those resulting in higher effectiveness or clinical benefit for patients.

The broad range of diseases presenting symptoms of functional dyspepsia, and the large number of diagnostic and therapeutic management options, each one with different costs and effectiveness, have urged the need to design economic analysis studies on this clinical condition. It is thus very doubtful that a single most effective or least expensive strategy could ever be developed for application to all patients alike (42).

Functional dyspepsia is a common disorder, with reported prevalence ranging from 13% to 40% (12). The definition of functional dyspepsia may vary between studies as well. An international working party defined functional dyspepsia as "upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting, or other symptom considered to be referable to the proximal alimentary tract" (10) without organic findings. Therefore, patients with functional dyspepsia may vary in terms of possible etiologic symptoms, pattern, course, and demographic characteristics.

The objective of this study was to assess the quality of economic analysis studies published in the medical and economical literature assessing the clinical management of functional dyspepsia, by means of the design and application of a specific checklist. The obtained results would allow making recommendations about the efficiency of alternative management strategies of functional dyspepsia and about the realization of future economic analysis studies in this clinical condition.

METHODS

A bibliographic search was carried out in the main biomedical databases (MEDLINE, HealthStar, The Cochrane Library, Índice Médico Español, and National Health Service Economic Evaluation Database) from February 1988 to October 1998, including articles from bibliographic references, health technology assessment reports, and gray literature, using the descriptors related to economic analysis and dyspepsia. From the bibliographic search performed, economic analysis studies written in English, French, or Spanish comparing alternative management strategies for functional dyspepsia were selected, excluding abstracts, editorials, and letters. Since the main interest of the study was functional dyspepsia, those studies related to gastric ulcer, duodenal ulcer, peptic ulcer, gastroesophageal reflux disease, gastric cancer, and other organic gastrointestinal diseases were rejected.

All studies were reviewed according to alternatives compared, methodologic characteristics, outcome measures used, and results obtained. A specific protocol with economic and clinical items has been designed for the evaluation and applied to each of the selected studies by two independent evaluators. For the economic part, the protocol was constructed taking as a basis the checklist of Drummond et al. (13); for the clinical part, we added specific questions. The protocol is available to the researchers that request it. Discrepancies between evaluators were dealt by consensus. The results of this review were presented as evidence tables.

The clinical characteristics related to the outcome measure were compared alternatives, clinical design of the effectiveness data, and results obtained. The characteristics related to economic analysis methods were type of study, perspective of analysis, included costs, cost calculation method, time-horizon, discount rate, cost-effectiveness ratios used, and realization of incremental and sensitivity analysis.

RESULTS

Overall, 18 of 162 studies met the inclusion criteria for the assessment (5;6;8;14;17;18;20;23;24;25;27;28;29;33;36;40;41;45). The rest of the studies were rejected according to the

Table 1. Results of the Review of Economic analysis Studies of Functional Dyspepsia

	n	Reference no.
<i>Type of economic analysis</i>		
Cost analysis, cost-minimization analysis	10	5;6;8;20;24;25;27;28;36;40
Cost-benefit analysis	1	41
Cost-effectiveness analysis	7	14;17;18;23;29;33;45
Cost-utility analysis	1	14
Decision analysis	10	5;14;17;18;23;29;33;40;41;45
<i>Study perspective</i>		
Society	1	23
Third-party payer	9	5;14;17;18;24;28;29;40;45
Provider	1	27
Not explicit	7	6;8;20;25;33;36;41
<i>Time horizon</i>		
Less 1 year	14	8;14;17;18;20;23;24;25;28;29;33;36;40;45
More 1 year	3	5;27;33
Not explicit	2	6;41
<i>Cost calculation method</i>		
Costs	2	23;24
Prices	11	5;14;18;20;23;24;27;28;33;40;45
Reimbursement payments	10	5;14;17;18;20;25;29;36;41;45
Not explicit	2	6;8
<i>Type of costs included</i>		
Direct	17	5;6;8;14;17;18;20;24;25;27;28;29;33;36;40;41;45
Indirect	3	6;20;23
<i>Sensitivity analysis</i>		
One-way	6	5;23;24;27;33;40
Multiple-way	7	14;17;18;28;29;41;45
Not performed	5	6;8;20;25;36
<i>Incremental analysis</i>		
Yes	3	23;33;45
No	4	14;17;18;29
Not applicable	11	5;6;8;20;24;25;27;28;36;40;41
<i>Source of effectiveness measure</i>		
Randomized controlled trial	4	7;20;23;25
Nonrandomized controlled trial	1	6
Systematic review	4	14;17;18;28
Nonsystematic review	7	5;24;29;33;40;41;45
Others	3	20;27;36

Some of the reviewed studies had two or more characteristics at the same time (i.e., two time horizons), which is why the values of some categories add up to more than 18.

inclusion criteria because they dealt with organic dyspepsia, did not perform an economic analysis, or were abstracts, editorials, or letters. The results of the review are displayed in Table 1 and Table 2.

Most of the studies ($n = 10$) performed some kind of cost analysis or cost-minimization analysis (see results and references in Table 1). Some of them performed a cost-effectiveness analysis ($n = 7$), and only one performed a cost-benefit analysis and one a cost-utility analysis. Ten studies performed the analysis through decision analysis techniques. According to the quality of the effectiveness outcome, the sources of clinical information were randomized controlled trials ($n = 4$), nonrandomized controlled trials ($n = 1$), systematic reviews ($n = 4$), nonsystematic reviews ($n = 7$), and others ($n = 3$) such as specific questionnaires, medical databases, observational data, and expert data.

Table 2. Evidence Table of Economic Analysis Studies of Functional Dyspepsia

Check list	Vakil et al. (45)	Laheij et al. (23)	Brignoli et al. (6)	Ebell et al. (14)	Laheij et al. (24)	McIntyre et al. (27)	Ofman (28)	Briggs et al. (5)	Fendrick et al. (17)
Type of study	CEA DA	CEA DA	CA	CEA CUA DA	CMA	CMA	CMA	CA DA	CEA DA
Perspective of analysis Alternatives	Explicit Payer H ₂ A Eradication treat. Endoscopy Biopsy Hp testing	Explicit Society PPI Eradication treat. Endoscopy Hp testing	Not explicit Society Prokinetics PPI H ₂ A Endoscopy	Explicit Payer Eradication treat. Endoscopy Hp testing	Explicit Payer PPI Endoscopy Eradication treat.	Explicit Hospital H ₂ A Eradication treat. Endoscopy Hp testing	Explicit Payer Eradication treat. Endoscopy Hp testing	Explicit Payer H ₂ A Eradication treat. Hp testing	Explicit Payer PPI H ₂ A Eradication treat. Endoscopy Biopsy Hp testing Systematic review
Clinical design	Nonsystematic review	RCT	Nonrandomized controlled trial	Systematic review	Nonsystematic review	Observational data Expert data Questionnaire	Systematic review	Nonsystematic review	Systematic review
Clinical outcomes	Symptom relief	Days free of symptoms Quality of life Absenteeism	—	Ulcer healed Death	Symptom relief	Hp eradication	Symptom relief	Days free of symptoms	Ulcer healed Patient treated
Included costs	Direct	Indirect	Direct Indirect	Direct	Direct	Direct	Direct	Direct	Direct
Measure of costs	Prices Reimbursement payments Less 1 year	Accountability Prices Less 1 year	Not explicit	Prices Reimbursement payments Less 1 year	Cost database Prices Less 1 year	Prices Life expectancy 5%	Prices Less 1 year	Prices Reimbursement payments 10 years 6%	Reimbursement payments Less 1 year
Time horizon	Less 1 year	Less 1 year	Not explicit	Less 1 year	Less 1 year	5 years Life expectancy 5%	Less 1 year	10 years 6%	Less 1 year
Discount rate	—	—	Not explicit	—	—	—	—	—	—
Cost-effic. ratios	Yes	Yes	—	Yes	—	—	—	—	Yes
Incremental analysis	Yes	Yes	—	No	—	—	—	—	No
Sensitivity analysis	Multiple way	One way	No	Multiple way	One way	One way	Multiple way	One way	Multiple way

Results	Noninvasive testing and treatment of Hp can be cost-effective in highly prevalent infected populations	Empirical drug treatment strategy has lower costs and equal effectiveness	Selective endoscopy is cheaper than mandatory endoscopy	Hp testing and eradication is more efficient than empiric treatment, or invasive management strategies	Empirical PPI treatment is more efficient than endoscopy guided treatment	Hp eradication results in cost savings	Initial Hp eradication treatment is the most cost-effective alternative for dyspeptic patients	Testing for and eradication of Hp is more expensive than healing and maintenance doses of cimetidine	Empiric treatment with antisecretory therapy is better than endoscopy and biopsy
Type of study	CEA	CMA	CBA	CEA	CA	CA	CA	CA	CEA
Perspective of analysis	DA	DA	DA	DA	Not explicit	Not explicit	Not explicit	Not explicit	DA
Alternatives	Explicit Payer	Explicit Payer	Not explicit	Explicit Payer	Hospital	Payer	Payer	Society	Not explicit Hospital
	PPI	H ₂ A	—	PPI	H ₂ A	PPI	Antacids	H ₂ A	Prokinetics
	H ₂ A	Eradication treat.	Hp testing	H ₂ A	Endoscopy	Anti-cholinergic	Anti-emetics	Not determined	Antacids
	Eradication treat.	Endoscopy	Hp testing	Eradication treat.	Endoscopy	H ₂ A	H ₂ A	Endoscopy	H ₂ A
	Biopsy	Biopsy	Biopsy	Endoscopy	Biopsy	H ₂ A	Endoscopy	Barium meal	Endoscopy
	Hp testing	Hp testing	Hp testing	Biopsy	Hp testing	Medical databases	Barium meal	Barium meal	Barium meal
Clinical design	Nonsystematic review	Nonsystematic review	Nonsystematic review	Systematic review	RCT	Medical databases	RCT	RCT	Nonsystematic review
Clinical outcomes	Ulcer healed	—	Monetary terms	Ulcer healed	—	—	—	Questionnaire	Change of
	Patient treated			Eradication Treatment compliance					premature death
Included costs	Direct	Direct	Direct	Direct	Direct	Direct	Direct	Direct	Weeks of pain
Measure of costs	Reimbursement payments	Prices	Reimbursement payments	Prices	Not explicit	Reimbursement payments	Reimbursement payments	Prices	% symptomatic patients
Time horizon	Less 1 year	Less 1 year	Not explicit	Less 1 year	Less 1 year	Less 1 year	Less 1 year	Less 1 year	Direct
Discount rate	—	—	Not explicit	—	—	—	—	—	Less 1 year
									8 years
									Not explicit

(Continued)

Table 2. (Continued)

	Olson et al. (29)	Silverstein et al. (40)	Sonnenberg (41)	Fendrick et al. (18)	Bytzer et al. (8)	Sena et al. (36)	Longstreth (25)	Goulston et al. (20)	Read et al. (33)
Cost-effec. ratios	—	—	—	Yes	—	—	—	—	Yes
Incremental analysis	No	—	—	No	—	—	—	—	Yes
Sensitivity analysis	Multiple way	One way	Multiple way	Multiple way	No	No	No	No	One way
Results	Empiric antisecretory treatment is more efficient than invasive management strategies	There are slight differences between initial endoscopy, empirical therapy, and testing for Hp	Treating all dyspeptic patients who test positive for Hp cannot be recommended	Noninvasive strategies are more cost-effective than endoscopy guided strategies	Endoscopy is more efficient than empiric H ₂ A treatment	The total yearly cost of treating gastrointestinal disorders exceeds \$290,000 for the Pennsylvania Medicaid program	Endoscopy treatment is cheaper than barium meal treatment	Endoscopy and barium meal are as costly as empiric H ₂ A treatment	High dose antacids or H ₂ A are slightly better than high dose or barium meal strategies

Studies are presented chronologically.

Definition of abbreviations: CA = cost analysis; CMA = cost-minimization analysis; CBA = cost-benefit analysis; CEA = cost-effectiveness analysis; DA = decision analysis; PPI = proton pump inhibitor; H₂A = histamine H₂ antagonist; Eradication treat = eradication treatment; Hp = *Helicobacter pylori*; RCT = randomized controlled trial.

The perspective of analysis was explicit in half of the studies ($n = 11$). These perspectives were the payer perspective ($n = 9$), the provider perspective ($n = 1$), or the society perspective ($n = 1$). In most of the cases, the established time horizon was shorter than or equal to 1 year ($n = 14$). Only two studies included a longer time horizon (5, 8, 10 years, and life expectancy), and two did not make it explicit (Table 1). All of the studies included direct costs such as tests, procedures, drugs, hospitalizations, and physician fees, but only three included indirect costs (that is, productivity losses). Just one of the studies including indirect cost made the perspective of analysis explicit, which was the society perspective.

In relation to the presentation of results, the outcome measures used to calculate cost-effectiveness ratios were—based on the underlying cause of dyspepsia—cost per ulcer healed, cost per patient treated, cost per *Helicobacter pylori* eradication, and cost per symptom relief. Although the starting point of all the reviewed studies was functional dyspepsia, note that three articles included “ulcer healed” as an outcome measure (17;18;29). In these particular cases, the original studies started their research with patients that had dyspepsia symptoms (then susceptible of being included in the review). It was only after the examination and treatment of the patients that doctors realized that dyspepsia symptoms were caused by ulcers.

In order to assess the stability of the results, most of the studies ($n = 13$) performed a one-way or multiple-way sensitivity analyses. Only three of the cost-effectiveness analyses performed an incremental analysis; most of them presented their results as average cost-effectiveness ratios.

As shown in Table 2, compared treatment options were very diverse. Screening alternatives ranged from invasive diagnostic techniques such as endoscopy, biopsy, and urease test on biopsy specimen to noninvasive diagnostic techniques such as *H. pylori* testing with breath test and serology. Therapeutic options included proton pump inhibitors, histamine H₂ antagonists, antacids, anticholinergics, antiemetics, and *H. pylori* eradication treatments.

DISCUSSION

In general terms, the usefulness of economic analysis of health services, and of functional dyspepsia in particular, is beyond doubt. It could be used to define cost-effective alternatives, to evaluate the costs of alternatives, and, indeed, to make decisions complementing other kinds of information. The methodologic rigor in the application of economic analysis techniques is essential to guarantee the replicability of the studies.

Recently, a number of guidelines for economic analysis have appeared (2;9;15;19;30;34). It seems that economists have reached agreement upon a number of important characteristics that would ensure the validity and reliability of the results. Standards for economic analysis should contribute to making the results of analyses relevant and credible for policy making. The use of the society perspective for explicit cost calculation methods and sources of economic information and the performance of sensitivity and incremental analyses are some of their main recommendations.

Unfortunately, this review, as others previously published (4;13;26;35;37;44), showed that in many cases methods and data are not reported in a way that would enable users to make such an assessment. Recently great effort was devoted to quality assessment of economic analysis, with some interesting and promising results (16;31;32;43). But more attention should be paid to efficacy and effectiveness data used in economic analysis studies, because this key factor is usually underreported (43). Specific checklists, especially those including clinical outcome measures as well as economic outcome measures, might help to better assess the quality of economic analysis in the field of functional dyspepsia and in any other clinical condition. Variables included could be outcome measures, clinical study

design, clinical variables that have an economic impact, and specific variables related to each clinical condition.

Some limitations of the study could be pointed out. Common to review studies, there is a probability of missing studies that should be included. In the present case, this probability was minimized using systematic bibliographic search techniques. The main reason for the relatively large number of rejected articles after applying the inclusion criteria was the extensive criteria used in the bibliographic search in order to avoid missing studies for the review.

Second, the variability in compared alternatives made it impossible to identify the most efficient of the reviewed studies, especially in this case in which diagnostic and treatment alternatives were included in the same study or article. Some of the alternatives, as is the case in *H. pylori* eradication treatment, were recently used, and most of the reviewed studies were published after 1990. That could be the reason why there are no studies with long-term outcome measures, which makes it difficult to value the efficiency of the alternatives in the long term and the assessment of induced costs. The development of studies using longer follow-up periods should be emphasized, especially in a clinical condition characterized by its chronic and recurrent nature. Nevertheless, economic analyses could not include long-term outcome measures unless clinical studies assessing the natural history of functional dyspepsia are performed.

Similarly, economic analysis guidelines recommend the use of the society perspective. As seen in the review, this perspective is not commonly used. The use of a broader perspective that includes indirect costs could be highly relevant because gastrointestinal diseases account for substantial productivity costs (1;38) as well as intangible costs in the form of patient discomfort, symptoms, and pain.

Another important point is outcome measure. Most of the studies performed a cost analysis and therefore did not include an outcome measure, which makes it difficult to obtain conclusions on efficiency of the clinical management of functional dyspepsia. According to the sources of information of outcome measures, most of the studies used nonsystematic reviews instead of systematic reviews, randomized controlled trials, or meta-analyses, which have higher levels of methodologic quality (21). The use of appropriate clinical outcome measures based on the best scientific evidence available is the base for economic analysis studies (22).

The use of decision analysis techniques, despite their methodologic constraints (39), is a useful way to model reality when direct observation of the phenomenon is not available and cannot be performed, and could be useful in trying to understand a complex reality and as an alternative to economic clinical trials (7). However, models involve assumptions and their use emphasizes the need for transparent reporting data, methods, and analyses. Most of the decision analyses reviewed were found to use nonsystematic reviews as the source of clinical data. If models are used when primary clinical data are missing, it is even more important to use clinical data coming from high-quality designs and systematic reviews.

At the same time, there is some uncertainty regarding many aspects of economic analysis of healthcare interventions, such as clinical data, discount rates, or included costs. However, this parameter is often handled inconsistently and unsatisfactorily (3;26). Recently published guidelines should improve this situation.

Finally, it should be mentioned that efforts should be devoted to economic analysis methods and to orient them to decision making. There is little sense in performing an economic analysis if it is going to have no impact on decision making. Its impact on decisions, however, is still unclear (11). A continuing challenge for healthcare economic analysis is to improve the dissemination of the studies and to produce healthcare economic analyses that are timely and relevant to the needs of decision makers.

POLICY IMPLICATIONS

From the reviewed studies, it is not possible to identify the most efficient alternative for the management of functional dyspepsia. This review also allowed us to point out some topics for future study, such as the importance of the methodologic rigor in the application of economic analysis techniques and the quality of clinical outcome measures included in the studies.

Standards for economic analysis should contribute to making the results of analyses relevant and credible for policy making. Adherence to reporting conventions and attention to providing information require understanding, and interpreting study results would improve the relevance and accessibility to economic analyses. The methodologic rigor in the application of economic analysis techniques is essential to guarantee the study reproducibility.

Equally important is the use of clinical outcome measures obtained in study designs of the highest level of evidence, such as randomized controlled trials or meta-analysis of randomized controlled trials. Integration of outcome measures based on the best scientific evidence available in economic assessment studies will allow for a higher quality of the performed analysis. Specific checklists, with clinical and economic outcome measures, might help to better assess the quality of the data. Also, the development of studies using longer follow-up periods should be emphasized, especially in clinical conditions characterized by their chronic and recurrent nature.

Finally, a continuing challenge for healthcare economic analysis is to improve the dissemination of the studies and to produce healthcare economic analyses that are timely and relevant to the needs of decision makers.

REFERENCES

1. Ament A, Evers S. Cost of illness studies in health care: A comparison of two cases. *Health Policy*. 1993;26:29-42.
2. Australia Commonwealth Department of Health, Housing and Community Services. *Guidelines for the pharmaceutical industry on preparation of submissions to the Pharmaceutical Benefits Advisory Committee*. Canberra: Commonwealth Department; 1992.
3. Briggs A, Sculpher M, Buxton M. Uncertainty in the economic evaluation of health care technologies: The role of sensitivity analysis. *Health Econ*. 1994;3:95-104.
4. Briggs AH, Gray AM. Handling uncertainty in economic evaluations of healthcare interventions. *BMJ*. 1999;319:635-638.
5. Briggs AH, Sculpher MJ, Logan RP, et al. Cost effectiveness of screening for and eradication of *Helicobacter pylori* in management of dyspeptic patients under 45 years of age. *BMJ*. 1996;312:1321-1325.
6. Brignoli R, Watkins P, Halter F. The Omega Project. A comparison of two diagnostic strategies for risk- and cost-oriented management of dyspepsia. *Eur J Gastroenterol Hepatol*. 1997;9:337-343.
7. Buxton MJ, Drummond MF, Van Hout BA, et al. Modelling in economic evaluation: An unavoidable fact of life. *Health Econ*. 1997;6:217-227.
8. Bytzer P, Hansen JM, Schaffalitzky de Muckadell OB. Empirical H₂-blocker therapy or prompt endoscopy in management of dyspepsia. *Lancet*. 1994;343:811-816.
9. Canadian Coordinating Office for Health Technology Assessment (CCOHTA). *Guidelines for economic evaluation of pharmaceuticals: Canada*. Ottawa: CCOHTA; 1994.
10. Colin-Jones DG, Bloom B, Bodemar G, et al. Management of dyspepsia: Report of a working party. *Lancet*. 1988;1:576-579.
11. Davies L, Coyle D, Drummond M. Current status of economic appraisal of health technology in the European Community: Report of the network. The EC Network on the Methodology of Economic Appraisal of Health Technology. *Soc Sci Med*. 1994;38:1601-1607.
12. Drossman DA, Li Z, Andruzzi E, et al. US householder survey of functional gastrointestinal disorders: Prevalence, sociodemography, and health impact. *Dig Dis Sci*. 1993;38:1569-1580.

13. Drummond MF, O'Brien B, Stoddart GL, et al. *Methods for the economic evaluation of health care programmes*. 2nd ed. New York: Oxford University Press; 1997.
14. Ebell MH, Warbasse L, Brenner C. Evaluation of the dyspeptic patient: A cost-utility study. *J Fam Pract*. 1997;44:545-555.
15. England and Wales Department of Health. *Guidelines on good practice in the conduct of economic evaluation of medicines*. London: Department of Health; 1994.
16. Evers S, Goossens M, van Tulder M, et al. Criteria list for quality assessment of economic evaluation reviews. Proceedings of the 15th Annual Meeting of the International Society of Technology Assessment in Health Care (ISTAHC), June 20–23, 1999; Edinburgh, United Kingdom. Toronto: ISTAHC; 1999:153.
17. Fendrick AM, Chernew ME, Hirth RA, et al. Alternative management strategies for patients with suspected peptic ulcer disease. *Ann Intern Med*. 1995;123:260-268.
18. Fendrick AM, Chernew ME, Hirth RA, et al. Immediate endoscopy or initial *Helicobacter pylori* serological testing for suspected peptic ulcer disease: Estimating cost-effectiveness using decision analysis. *Yale J Biol Med*. 1996;69:187-195.
19. Gold MR, Siegel JE, Russell LB, et al. *Cost-effectiveness in health care and medicine*. New York: Oxford University Press; 1996.
20. Goulston KJ, Dent OF, Mant A, et al. Use of H₂-receptor antagonists in patients with dyspepsia and heartburn: A cost comparison. *Med J Aust*. 1991;155:20-26.
21. Jovell AJ, Jovell E. Evidencia científica y análisis económico: ¿dos conceptos excluyentes? *Revista Española de Farmacología*. 1998;(Junio):23-29.
22. Jovell AJ, Navarro-Rubio MD. Evaluación de la evidencia científica. *Med Clin (Barc)*. 1995;105:740-743.
23. Laheij RJ, Severens JL, Jansen JB, et al. Management in general practice of patients with persistent dyspepsia: A decision analysis. *J Clin Gastroenterol*. 1997;25:563-567.
24. Laheij RJ, Severens JL, van de Lisdonk EH, et al. Randomised controlled trial of omeprazole or endoscopy in patients with persistent dyspepsia: A cost-effective analysis. *Aliment Pharmacol Ther*. 1998;12:1249-1256.
25. Longstreth GF. Long-term costs after gastroenterology consultation with endoscopy versus radiography in dyspepsia. *Gastrointest Endosc*. 1992;38:23-26.
26. Mason J, Drummond M. Reporting guidelines for economic studies. *Health Econ*. 1995;4:85-94.
27. McIntyre A-M, MacGregor S, Malek M, et al. New patients presenting to their GP with dyspepsia: Does *Helicobacter pylori* eradication minimise the cost of managing these patients? *Int J Clin Practice*. 1997;51:276-281.
28. Ofman JJ, Etchason J, Fullerton S, et al. Management strategies for *Helicobacter pylori*-seropositive patients with dyspepsia: Clinical and economic consequences. *Ann Intern Med*. 1997;126:280-291.
29. Olson AD, Fendrick AM, Deutsch D, et al. Evaluation of initial noninvasive therapy in pediatric patients presenting with suspected ulcer disease. *Gastrointest Endosc*. 1996;44:554-561.
30. *Ontario guidelines for economic analysis of pharmaceutical products*. Toronto: Ontario Ministry of Health; 1994.
31. Pang F, Drummond M. Meta-analysis of economic evaluations: A methodological approach and case-study. Proceedings of the 15th Annual Meeting of the International Society of Technology Assessment in Health Care (ISTAHC), June 20–23, 1999; Edinburgh, United Kingdom. Toronto: ISTAHC; 1999:78.
32. Pang F, Tolley K. Developing a quality assessment scoring system for economic evaluations. Proceedings of the 15th Annual Meeting of the International Society of Technology Assessment in Health Care (ISTAHC), June 20–23, 1999; Edinburgh, United Kingdom. Toronto: ISTAHC; 1999:120.
33. Read L, Pass TM, Komoroff AL. Diagnosis and treatment of dyspepsia: A cost-effectiveness analysis. *Med Decis Making*. 1982;2:415-438.
34. Rovira J. Standardizing economic appraisal of health technologies in the European Union. *Soc Sci Med*. 1994;38:1675-1678.
35. Salkeld G, Davey P, Arnolda G. A critical review of health-related economic evaluations in Australia: Implications for health policy. *Health Policy*. 1995;31:111-125.

36. Sena MM, Stoddard ML, Pashko S. Use of non-antacid antiulcer agents in the treatment of heartburn and dyspepsia. *Clin Ther.* 1994;16:103-109.
37. Severens JL, Gert-Jan van der Wilt. Economic evaluation of diagnostic tests. *Int J Technol Assess Health Care.* 1999;15:480-496.
38. Severens JL, Laheij RJ, Jansen JB, et al. Estimating the cost of lost productivity in dyspepsia. *Aliment Pharmacol Ther.* 1998;12:919-923.
39. Sheldon TA. Problems of using modelling in the economic evaluation of health care. *Health Econ.* 1996;5:1-11.
40. Silverstein MD, Petterson T, Talley NJ. Initial endoscopy or empirical therapy with or without testing for *Helicobacter pylori* for dyspepsia: A decision analysis. *Gastroenterology.* 1996;110:72-83.
41. Sonnenberg A. Cost-benefit analysis of testing for *Helicobacter pylori* in dyspeptic subjects. *Am J Gastroenterol.* 1996;91:1773-1777.
42. Sonnenberg A. Economic analysis of dyspepsia. *Eur J Gastroenterol Hepatol.* 1997;9:323-326.
43. Stoykova B, Nixon J, Glanville J, et al. Issues concerning the sources of effectiveness data used in economic evaluations included in the National Health Service Economic Evaluation Database (NHS EED). Proceedings of the 15th Annual Meeting of the International Society of Technology Assessment in Health Care (ISTAHC), June 20–23, 1999; Edinburgh, United Kingdom. Toronto: ISTAHC; 1999:47.
44. Udvarhelyi IS, Colditz GA, Rai A, et al. Cost-effectiveness and cost-benefit analyses in the medical literature. Are the methods being used correctly? *Ann Intern Med.* 1992;116:238-244.
45. Vakil N, Ashorn M. Cost-effectiveness of noninvasive testing and treatment strategies for *H. pylori* infection in children with dyspepsia. *Am J Gastroenterol.* 1998;93:562-568.