The cost-effectiveness and budget impact of competing therapies in hepatic encephalopathy: a decision analysis
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Six interventions for the treatment of hepatic encephalopathy (HE) were investigated. These were:

- no HE treatment;
- lactulose monotherapy;
- lactitol monotherapy;
- neomycin monotherapy;
- rifaximin monotherapy; and
- rifaximin salvage, i.e. up-front lactulose with crossover to rifaximin if poor response or intolerance of lactulose.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis and cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of 50-year-old patients with cirrhosis and HE. Excluded from the analysis were patients with hepatic coma, evidence of active gastrointestinal bleeding, tumours, renal insufficiency, respiratory distress, active infection, concomitant psychiatric diseases, or electrolyte abnormalities.

Setting
The study setting was inpatient secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1973 and 2006. The cost data were derived from sources published in 1997 and 2006. The price year was 2006.

Source of effectiveness data
The clinical and epidemiological data used in the economic evaluation were:

the probability of compliance in overt and subclinical encephalopathy;
the probability of improvement in overt and subclinical encephalopathy;

the annual transition probabilities between health states, including no HE to subclinical encephalopathy, and subclinical encephalopathy to overt encephalopathy;

the annual rate of developing complication of cirrhosis;

the probability of developing ascites in cirrhosis;

the probability of developing variceal bleeding in cirrhosis;

the probability of receiving a liver transplant; and

mortality rates after transplantation.

Modelling
A Markov decision analytic model with a lifetime horizon was developed to model the natural history of cirrhosis and hepatic encephalopathy. The health states, cycle length and time-dependent transition probabilities were presented in full in the paper, along with a number of modelling assumptions which were fully justified.

Sources searched to identify primary studies
Data on transition probabilities, effectiveness and compliance were derived from published randomised controlled trials and, when available, meta-analyses. Data on antibiotic-related complications were derived from the authors' assumptions, which were supplemented by evidence from the literature.

Methods used to judge relevance and validity, and for extracting data
The authors reported that a systematic review of MEDLINE was conducted in order to identify relevant studies. In a technical appendix to the published article, the authors reported, by model parameter, the results of the systematic review and the number of included studies. The authors reported that, for articles reporting multiple outcomes in HE, data were abstracted from the most clinically relevant and/or validated outcome measure, such as the PSE sum/index or West Haven criteria. The authors also reported that, when multiple studies supported an individual point estimate, a mean weighted estimate was calculated by study sample.

Measure of benefits used in the economic analysis
The measures of benefits used were the life-years (LYs) and quality-adjusted life-years (QALYs) gained. The utility values were derived from published decision models in chronic liver disease. The health benefits were discounted appropriately at a rate of 3% per annum.

Direct costs
The analysis was conducted from the perspective of a U.S. third-party payer. It incorporated the direct health care costs for a range of therapies, doctor visits, hospital visits, diagnostic tests and complications of cirrhosis and HE. The costs of drug treatments were derived from the 2006 Red Book (Fleming 2006, see ‘Other Publications of Related Interest’ below for bibliographic details). The costs of doctor consultation and diagnostic tests were derived from the 2006 Medicare fee schedule. Cost estimates for cirrhosis and related health states were derived from a published study. The costs were appropriately discounted at an annual rate of 3% and were reported as average costs. In addition, the authors performed a budget-impact analysis and adopted a per-member per-month (PMPM) cost. The authors specifically focused on the incremental PMPM cost of employing each therapeutic strategy in a hypothetical managed care organisation with 1 million covered people.

Statistical analysis of costs
The costs were reported as point estimates (i.e. the data were deterministic).

**Indirect Costs**
Productivity costs were not included in the analysis.

**Currency**
US dollars ($).

**Sensitivity analysis**
In order to test the influence of all variables on the model results and to rank-order the most influential variables, the authors performed a multivariable sensitivity analysis. The results of this were presented as a tornado analysis. In a second stage, a one-way sensitivity analysis was performed on the most influential variables. The authors also conducted a Monte Carlo simulation assuming triangular probability distributions, and plotted the results on cost-effectiveness acceptability curves stratified by willingness-to-pay thresholds.

**Estimated benefits used in the economic analysis**
Only the benefits for the least and most effective interventions were reported.

The do nothing strategy was the least effective, generating 2.8 QALYs and 3.9 LYs gained.

Rifaximin salvage was the most effective strategy, generating 5.3 QALYs and 6.9 LYs gained.

**Cost results**
As with the benefits, only the costs of the least and most costly interventions were reported.

The least costly strategy was lactulose monotherapy, with a cost of $56,967 per patient.

The most costly strategy was rifaximin monotherapy, with a cost of $75,671 per patient.

**Synthesis of costs and benefits**
The costs and benefits were combined using an incremental cost-effectiveness ratio (i.e. the additional cost per LY gained) and an incremental cost-utility ratio (i.e. the additional cost per QALY gained).

Both lactulose monotherapy and rifaximin salvage were found to be dominant over the other four strategies (i.e. they were both more effective and less costly).

Compared with lactulose monotherapy, the use of rifaximin salvage cost an additional $2,315 per QALY gained (2.5th and 97.5th percentiles: 995 and 4,816) and $1,894 per LY gained (2.5th and 97.5th percentiles: 1,111 and 2,614).

The results from the tornado analysis revealed that the model was most sensitive to changes in, by importance: the costs of lactulose, the costs of rifaximin, the costs of liver transplantation, compliance with lactulose and compliance with neomycin.

The results of the Monte Carlo simulation showed that, if the third-party payer were willing to pay $20,000 per additional QALY or $0.10 PMPM for rifaximin salvage therapy, then 100% of patients would fall within the budget.

**Authors’ conclusions**
The use of rifaximin monotherapy was not cost-effective in the treatment of chronic hepatic encephalopathy (HE) at current average wholesale prices. However, a salvage strategy reserving rifaximin for lactulose-refractory patients might
be highly cost-effective.

**CRD COMMENTARY - Selection of comparators**

A justification was given for the comparators used. They represented current practice in the authors’ settings. However, the authors acknowledged in their discussion the limitation of the study that other potential strategies, such as lactulose and rifaximin co-therapy, were not evaluated. You should decide if the comparator used represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**

The parameters were derived from published research in most instances. For those parameters not derived from published research, authors’ assumptions based on the published literature were used. The authors reported that the clinical data were derived either from published meta-analyses, or from meta-analyses performed specifically for this study. The authors reported, in full, both the methods of the search for published evidence and the inclusion criteria. They also stated the outcomes that included studies should, ideally, have reported.

**Validity of estimate of measure of benefit**

The health benefits (LYs and QALYs) were derived appropriately using a Markov model. The use of QALYs ensures the comparability of the results with the benefits of other health care interventions. The benefits were appropriately discounted. The utilities were derived from a number of different decision analytic models in the area of liver disease, but no details of the valuation method were reported.

**Validity of estimate of costs**

The analysis of the costs was performed from the perspective of the third-party payer paying for the health care intervention. Given this perspective, it would appear that all the relevant categories of costs have been included. The cost data were derived from national references (i.e. Red Book and Medicare reimbursements) and from a previous study. In some instances, charges appear to have been used to proxy prices, which was appropriate given the third-party payer perspective of the study. The costs were appropriately discounted as they could be incurred over a lifetime horizon. The price year and the discount rate used were appropriately reported.

**Other issues**

The authors reported that, to their knowledge, this was the first decision analysis to measure the cost-effectiveness of competing agents in HE and, in particular, to consider the health economic implications of rifaximin. The issue of generalisability to other settings was partly addressed in the sensitivity analyses. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis.

The authors acknowledged a number of further limitations to their study. First, the base-estimates were derived from studies of varying design, populations, follow-up and quality. Second, the utility values used might be unreliable because truly encephalopathic patients may be unable to accurately complete utility assessments or questionnaires. Third, the patient exclusion criteria may have limited the generalisability of the study results. Finally, the analysis applies only to a narrow patient population.

**Implications of the study**

The authors recommend that future research should aim to measure prospectively the cost-effectiveness of competing treatment strategies in representative samples of community-based patients with HE, and should also examine the effects of combination therapy in refractory HE.

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