LETTERS TO THE EDITOR

Cost effectiveness of treatment for gastro-oesophageal reflux disease in clinical practice

EDITOR,—I was interested to read the paper by Eggleston *et al* (*Gut* 1998;42:13-16) purporting to show that a "step up" approach using prokinetics and H₂ receptor antagonists in the management of gastro-oesophageal reflux disease (GORD) is more cost effective than omeprazole in a general practice setting. I do not think the conclusions drawn are supported by data presented.

The MediPlus database does not permit systematic evaluation of the severity of GORD symptoms and so there is no certainty that the three patient groups (who received omeprazole, ranitidine or cisapride) were comparable. Patients were excluded from the study if they had initially been referred to hospital (<13%) because they were regarded as suffering from "more complicated GORD". No evidence is presented for this assertion. It is well recognised that there is no correlation between the severity of a patient's symptoms and the extent of any oesophagitis.¹⁻³ The fact that patients on omeprazole received more prescriptions in the six month study period (2.96) than those on cisapride (1.85) is further evidence that the groups were not clinically comparable. Cisapride is known to be relatively ineffective⁴ in the treatment of GORD symptoms.

The paper makes no evaluation of clinical success, basing the evaluation entirely on cost with the implicit assumption of equivalence in clinical efficacy between omeprazole, ranitidine and cisapride, which many other controlled studies have shown not to be the case.

The conclusions drawn by the authors are also flawed. They have provided no evidence that the "stepped approach" is appropriate in GORD. Many studies have confirmed that omeprazole is more cost effective.⁵⁻⁹ The recent reduction in the price of omeprazole makes this cost advantage even greater.

The conclusion, "such chronic dependence on drug therapy appears to be a particular problem with... omeprazole and represents a further argument in favour of a step up approach aimed at initially targeting prescribing of this powerful drug on a highly selected patient group", is not supported by the evidence from the study nor by references. Moreover, the keenness of patients to take omeprazole is a reflection of its effectiveness. Given the central role of gastric acid in GORD reducing oesophageal exposure to this corrosive agent is a rational approach to the management of this disease. Antacid/alginate combinations provide short lived symptom relief. The H₂ receptor antagonists and cisapride have some efficacy in treating GORD but there is now abundant evidence in the literature to show that proton pump inhibitors are the most effective agents in this disease.

Unlike the H₂ receptor antagonists, proton pump inhibition does not suffer from the drawback of tolerance, and omeprazole heals regardless of the grade of oesophagitis on entry. Symptom resolution with omeprazole is a better indicator of healing of any underlying

ing oesophagitis than with H₂ receptor antagonists.

In conclusion, treatment with proton pump inhibitors provides cost effective management across the GORD spectrum, resolves patients symptoms, improves their quality of life and heals the underlying pathology, preventing the development of complications such as stricture, and reducing hospital referrals.

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Cost effectiveness of treatment for gastro-oesophageal reflux

EDITOR,—Eggleston *et al* (*Gut* 1998;42:13-16) concluded from their observational study that the "step up" approach, starting with a prokinetic or H₂ receptor antagonist, represents the most cost effective initial therapeutic strategy for the treatment of patients with a diagnosis of uncomplicated gastro-oesophageal reflux disease (GORD). In studies of the effects of treatments, non-randomised comparisons can be affected by confounding factors¹ and in our opinion this has resulted in the wrong conclusions being drawn from this study. Therapeutic interventions are commonly prompted by an indication. Primary care physicians selectively treat patients exhibiting more severe GORD with omeprazole and less severe symptoms with cisapride or ranitidine. Thus, by the very rationality of the decision to intervene, treatment differs between patients with GORD with respect to the outcome criterion in efficacy assessment.²

The authors minimised confounding by indication by excluding 511 of 790 patients with a diagnosis of dysphagia or complicated GORD or whose condition was sufficiently complex to require immediate specialist referral. Restricting subject selection indeed prevents confounding by indication, but introduces a change in the magnitude of the effect measured, which is called effect modification. By only evaluating patients with uncomplicated GORD, the difference in the effect measured between cisapride, ranitidine and omeprazole treatment will decrease. Many randomised clinical trials have shown that in patients with GORD omeprazole pro-

vides more rapid and complete healing of associated symptoms than ranitidine or cisapride.³ Therefore, it is misleading to minimise confounding by restricting subject selection, unless it can be assumed that there are no differences in treatment effect between patients. To control for confounding by indication, several other options are available. However, even when confounding factors are taken into account, the validity of findings on drug benefits in non-randomised studies may still be questionable.¹

Besides confounding by indication and effect modification, the authors misused the term cost effectiveness.⁴ Cost effectiveness analysis is one form of full economic evaluation in which both the cost and consequences of treatments are examined.⁵ Eggleston *et al* assumed equivalence in therapeutic outcome between the cisapride, ranitidine and omeprazole therapies on the basis of retrospective analysis of prescription data. If this assumption is correct then the design of their study should be called a cost minimisation analysis. The term cost effectiveness should be restricted to studies in which the result can be described as having an additional benefit worth the additional cost. To determine which treatment strategy has additional benefit worth the financial effort, more information is required about symptom relief. Furthermore, the claim of substantial differences in cost cannot be verified without the use of statistical testing. Although statistical testing of cost and cost effectiveness ratios is not as obvious as statistical testing of outcomes, methods are currently being developed to overcome these limitations.⁶

In conclusion, the study by Eggleston *et al* has several methodological shortcomings which have led to unfounded and therefore incorrect conclusions. To avoid the limitations of this study, a prospective randomised trial with representative patients⁷ must be carried out to determine which treatment approach, "step up" or "step down", is best for treating patients with GORD and dyspeptic symptoms in general.

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7 Simon G, Wagner E, Vonkorf M. Cost-effectiveness comparisons using "real world" randomised trials: the case of new antidepressant drugs. *J Clin Epidemiol* 1995;48:363-73.

Cost effectiveness of treatment for gastro-oesophageal reflux disease

EDITOR,—A reading of the recent article by Eggleston *et al* (*Gut* 1998;42:13-16) left several unanswered questions and concerns. The first issue was the authors' statement that clinical equivalence between cisapride, ranitidine, and omeprazole had been established for uncomplicated gastro-oesophageal reflux disease (GORD) in standard practice. To my knowledge, there are no published studies which have reported a similar finding of clinical equivalence of omeprazole to either cisapride or ranitidine. A quick review of the literature revealed 11 studies in which omeprazole was statistically significantly better than cisapride or ranitidine in GORD.¹⁻¹¹

In a review of the reference abstract¹² in which the case for clinical equivalence is postulated, the conclusion of equivalence was highly dependent upon the authors' definition of treatment failure. I take exception to the authors' definition that use of medication for longer than three months was a therapy failure. A retrospective database analysis does not have the ability to distinguish between continuing a medication in order to maintain successfully achieved symptom resolution and continued use of medication due to unsuccessful resolution of symptoms. Initiation of maintenance therapy after successful symptom resolution would not require any change in dosage in the case of omeprazole as 20 mg once daily is the recommended dose for healing and maintenance. Defining success as any use of medication for less than three months that did not involve a change in drug also opens up the possibility of misclassification. Those patients who stop using a drug as a result of treatment failure and who do not return for further care would not only be misclassified in this retrospective analysis as a success but could erroneously contribute to a lower economic burden in the therapy group. In the Methods, the authors state that case records for a total of 257 patients were evaluated. However, there is a discrepancy between the abstract and the manuscript on the number of eligible patients. The abstract talks about 279 patients and the manuscript refers to 257 patients. Additionally, why do the authors, with a database like MediPlus™ UK, which has more than one million patients, end up with a sample size of only 257 patients?

In the Discussion, the authors state that if more severely affected patients were selectively treated with omeprazole, one would expect to see increased non-drug resource use in this group. Since this did not occur, the authors consider this as supportive evidence that they had effectively controlled for this selection bias. An alternative explanation for the finding is patients taking omeprazole were more severely ill due to physician selection bias but omeprazole has superior clinical efficacy in GORD compared with ranitidine and cisapride thus the omeprazole patients resource utilisation level is a reflection of a reduction from what would be the case with any other treatment.

The authors do not state whether the general practitioner (GP) consultations attributed to the drug treatment groups were all specifically for GORD. No information was

provided as to how the authors have separated out GORD related GP consultations from visits for other illnesses. Such a process should be accomplished by a reviewer blinded to treatment allocation, if undertaken. The absence of information leads to a conclusion that the count of GP consultations in table 1 represents visits for all health reasons. As treatment would have had a positive effect on reducing GORD related visits only, the possibility of observing any difference between treatment groups would be diminished, resulting in the finding displayed in table 1.

The authors have based their analysis on an assumption of clinical equivalence which, in this case, is beyond the power of retrospective analysis to prove. Even if the three medications were clinically equivalent, there are a number of other unanswered questions from the manuscript that make it difficult for an unqualified acceptance of the authors' conclusions.

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Reply

EDITOR,—We welcome the quantity and quality of debate generated by our paper and in this respect the paper has fulfilled its prin-

cipal objective. Many of the issues raised in the resulting correspondence, however, relate to methodological limitations of database analyses that were well rehearsed in the original paper and therefore will not be addressed in detail. For example, we recognise the potential difficulties arising from the non-randomised nature of the study but feel that restriction is essential in enabling the analysis to reflect reality more accurately. The paper also explicitly acknowledges the potential for selection bias in the choice of drugs and specifically examines its potential implications for the interpretation of the results obtained. The patient cohorts seemed to be closely similar in both demographic characteristics and gastrointestinal and non-gastrointestinal medical history. In addition, a selection bias would be expected to lead to a greater intensity of health care resource consumption in patients receiving omeprazole. This did not occur and therefore no evidence is available to support the charge of selection bias.

The limitations of the study are difficult if not impossible to overcome with currently available data and should not distract us from the main focus of the paper. This was to undertake an initial comparison of the therapeutic strategies available to clinicians in the treatment of mild to moderate GORD. The data contained in the paper is merely used to illustrate the general principle that optimum decision making in this therapeutic area, as in any other, requires an informed and sensitive balance of the costs and benefits arising from each strategy.

The clinical outcomes underlying the cost analysis have been reported in a separate publication and provide the necessary clinical springboard for our analysis. The analysis simply indicates that for this particular group of patients (first episodes of uncomplicated GORD) the hypothesis of short term outcome equivalence in practice was not disproved by the clinical database analysis. Evaluating long term comparative outcome in practice would require a modelling approach that evaluated in detail quality of life and clinical outcomes together with the long term pattern of resource use for patients following different therapeutic strategies. An extensive and growing literature is available to inform such a model and research in this area is currently under development.

The basis for a clinician's choice between cisapride, ranitidine and omeprazole is in this study, as in all others, unknown given the complex array of factors determining such a choice. It is specifically because of such complex influences, which are not captured in randomised clinical trials, that analyses of prescribing in practice are so important, given that they implicitly incorporate the myriad of factors that influence real life prescribing behaviour. It is important, however, to recognise that evidence generated in clinical trials and observational studies of this nature should be perceived as being mutually supportive in generating evidence to guide clinical decision making. Obviously the same dataset can give rise to many different interpretations and we are not, necessarily, providing the only possible interpretation of the information generated.

The Nijmegen group question the "inappropriate" use of the term "cost effectiveness analysis" which is often used to refer to all forms of economic evaluation. The term, however, more properly refers to a particular type of evaluation in which outcome is defined and measured in natural units and

costs are measured in monetary terms. Our analysis is structured in a manner that facilitates a direct comparison of the costs per patient relieved of symptoms. Such a structure enables outcome variations to be directly incorporated into the analysis as and when such evidence is generated. Information about cost is useful only when considered jointly with information about clinical outcomes and further research concerning the long term cost and outcome of treatment is currently in progress.

The Nijmegen group's reference to "effect modification" and its potential effect of diluting variations between the therapeutic options is irrelevant in the context of our paper. The aim of good prescribing is to segment general patient populations to ensure that the therapeutic requirements of individual patients are optimally met by the prescriber. Obviously, in their day to day workload primary care physicians also frequently encounter patients with recurrent GORD as well as with H_2 refractory and complicated GORD. Cost effectiveness calculations on "undefined" GORD would inevitably favour omeprazole given that it causes the greatest suppression of acid secretion in patients with severe disease. We make no claims concerning the applicability of the analysis to undefined GORD but simply assert that the extent of acid suppression generated by omeprazole may not be necessary for first episodes of uncomplicated GORD. If this is the case, then hard pressed clinicians will be able to conserve their scarce health care resources for investment elsewhere.

Dr Crawley questions the numerical basis for the analysis. Our sample was generated as a random selection from the entire eligible MediPlus database for 1995 using the software random number based sample selection function. The sample chosen was selected on the basis of manageability given that an individual review of each patient record was required. The reduction from 279 to 257 patients was simply to increase the level of patient homogeneity as outlined in the original paper. Both Crawley and Bate also refer to a large body of evidence supporting the clinical and economic superiority of omeprazole. Unfortunately, for our purposes the vast majority of such evidence is irrelevant given that it does not specifically analyse prescribing in practice for new patients presenting at the primary care level with mild to moderate GORD. Dr Crawley's belief in the superiority of omeprazole due to the lack of need for dose titration is puzzling. The British National Formulary's recommendation for GORD is for 20 mg daily for four weeks, followed by 40 mg for four to eight weeks as required, reduced to 10 mg for long term management, increased to 20 mg if symptoms recur. Dr Crawley's further belief that patients may respond to treatment failure by simply doing nothing also is difficult to substantiate. It is reasonable to assume that individual patients exhibit a personal threshold of tolerance to the symptoms of GORD above which they seek professional advice. Such a threshold will vary significantly between patients but is likely to be fairly stable within the same patient. In such circumstances it is difficult to see why a patient would not seek further professional advice in cases where the initial prescription did not reduce symptomatology below their personal threshold.

Many of the issues raised reflect the fact that many gastroenterologists only come into

Table 1 Risk of admission to hospital with drug induced liver injury in those taking NSAIDs plus one other drug known to cause sporadic liver injury

NSAID	Hepatotoxin	Controls	Cases	Odds ratio	95% CI
—	—	294	7	Reference	
+	—	99	5	2.1	0.6 to 7.0
—	+	67	11	6.9	2.5 to 19.4
+	+	40	11	11.6	4.2 to 32.9

CI, confidence interval.

contact with the tip of the iceberg with regard to GORD. By supporting 95% of patients without recourse to specialist advice, primary care physicians ensure gastroenterologists encounter a very thin slice of reality with regard to the optimal treatment of GORD. The vast majority of treatments are initiated without prior investigation and where empiricism is successful such patients do not come to the attention of gastroenterologists. Although this may be appreciated intellectually by gastroenterologists, our paper provides powerful re-enforcement of the nature of the division of labour between primary care physicians and gastroenterologists in the treatment of reflux disease.

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Diagnostic value of T cell reactivity in drug induced hepatitis

EDITOR,—I read with interest Maria and Victorino's work (*Gut* 1997;41:534–40) on the diagnostic value of specific T cell reactivity to drugs in 95 cases of drug induced liver injury. They are to be congratulated on assembling the largest group of patients with suspected drug induced hepatotoxicity and attempting to assess causality using their lymphocyte test.

In their discussion, when referring to the clinical significance of the presence of prostaglandin producing suppressor cells in vitro, they state that, "patients in which this phenomenon was detected had a less severe disease, as assessed by aminotransferase concentrations and more rapid cure." There is another potential clinical significance to the interpretation of their in vitro results and that is that non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of developing drug induced hepatotoxicity in this unpredictable, hypersensitivity type of liver injury. Gutthann and Rodriguez¹ showed that patients taking an NSAID plus one other drug known to cause sporadic liver injury were at almost twice the risk of being admitted to hospital with biochemical and clinical evidence of liver disease than those taking a potentially hepatotoxic drug alone (table 1).

It would be interesting to know in Maria and Victorino's group of patients how many were taking an NSAID in addition to the suspected hepatotoxin and whether this was

higher than in their control groups or a standard adult population.

Given the large number of patients that consume NSAIDs, even a small increase in the risk of potentiating hypersensitivity reactions to other drugs, including organs other than the liver, could represent a major health issue.

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- 1 Gutthann SP, Rodriguez LAG. The increased risk of hospitalisations for acute liver injury in a population with exposure to multiple drugs. *Epidemiology* 1993;4:496–501.

Reply

EDITOR,—We showed that the in vitro phenomenon of putative prostaglandin producing suppressor cells demonstrated in patients with drug induced hepatitis was significantly associated with a less severe form of disease and a more rapid cure. It is possible to speculate that this in vitro phenomenon could also occur in vivo and play a part in the down regulation of the immune response triggered by the drug or its metabolites.

We think that Dr Bartle's point suggesting that there is another potential clinical significance to the interpretation of our in vitro results, namely that non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of developing drug induced hepatotoxicity, is a very interesting possibility. Our own epidemiological data are consistent with the results of the epidemiological study presented by him, showing that patients taking NSAIDs have an increased risk of developing liver injury induced by other drugs. In fact, we compared the frequency of NSAID consumption in our population with drug induced liver injury with two different adult populations integrated into prospective studies, one consisting of patients admitted to our internal medicine unit in the University Hospital and the other consisting of patients followed in the primary care setting (table 1). Patients with drug induced hepatitis took significantly more NSAIDs than the control populations (χ^2 test, $p < 0.0001$).

Although all epidemiological evidence suggests that NSAIDs increase the risk of hepatotoxicity from other drugs, the possibility that this could have an immunological basis

Table 1 Consumption of NSAIDs by patients with drug induced hepatitis and two control populations

	Patients with drug induced hepatitis	Patients admitted to hospital	Population of a health centre
Number of cases	136	277	1723
Mean age	46.7	63.9	44.6
Number taking NSAIDs	43	40*	206
Percentage	32	14	12

* Took NSAID in the 15 days prior to admission.