**DYSPEPSIA MANAGEMENT**

The potential role of acid suppression in functional dyspepsia: the BOND, OPERA, PILOT, and ENCORE studies

N J Talley, K Lauritsen

Dyspepsia is a common condition in the general population but data are lacking on the benefits of effective acid inhibition with proton pump inhibitors in functional dyspepsia. The results of the large, randomised, double blind clinical trials, BOND and OPERA, the Scandinavian PILOT study, and a follow up study, ENCORE, are reviewed. BOND, OPERA, and PILOT aimed to address the question of whether effective acid inhibition with the proton pump inhibitor omeprazole relieves symptoms in patients with functional dyspepsia. ENCORE followed on from this, addressing the consequences of relieving symptoms in patients with functional dyspepsia once they are off therapy.

**SUMMARY**

Data are lacking on the benefits of effective acid inhibition with proton pump inhibitors in functional dyspepsia. In two large, double blind, multicentre clinical trials, BOND and OPERA, patients (n=1262) with functional dyspepsia were randomised to four weeks of treatment with omeprazole 20 mg or 10 mg once daily, or placebo. The primary efficacy variable was complete absence of symptoms. In the ENCORE study, patients from the OPERA study (n=567) were followed for three months after cessation of therapy. The BOND but not the OPERA trial showed a significant benefit of omeprazole over placebo. Pooling the BOND and OPERA trials, complete relief of symptoms was achieved in 38.2% of the 20 mg omeprazole group (p=0.002) and in 36.0% of the 10 mg omeprazole group (p=0.02) compared with 28.2% in the placebo group. In patients with ulcer-like and reflux-like dyspepsia, respectively, complete relief of symptoms was achieved in 40% and 54% of the 20 mg omeprazole group (p=0.05) and in 35% and 45% of the 10 mg omeprazole group (p=0.08 and p=0.05, respectively) compared with 27% and 23% in the placebo group in pooled analyses. There was no difference between treatment groups in dysmotility-like dyspepsia. The therapeutic response may be influenced by *Helicobacter pylori* status although the observed proportion of responders was not significantly different. Complete relief of symptoms regardless of therapy resulted in fewer days on medication, fewer clinic visits, and higher quality of life scores, which translated into reduced costs compared with persistent symptoms during the three month follow up. Thus acid suppression appears to be superior to placebo in relieving symptoms in patients with ulcer-like but not dysmotility-like functional dyspepsia. Inducing a remission with omeprazole or placebo reduces the subsequent costs and has a positive impact on patient quality of life over a three month period after cessation of treatment.

**INTRODUCTION**

Dyspepsia is a common condition in the general population. The majority of patients have functional (or non-ulcer) dyspepsia in that they do not have any underlying structural explanation for their symptoms, such as peptic ulcer disease or reflux oesophagitis. However, given the significant morbidity and absence from work associated with the condition, patients with functional dyspepsia still require effective management. Indeed, the majority of patients in the community are taking long term $H_2$ receptor antagonist therapy for functional dyspepsia or gastro-oesophageal reflux disease (GORD) rather than for peptic ulcer disease. The superior efficacy of proton pump inhibitors compared with the $H_2$ receptor antagonists in controlling gastric acid secretion is well established but data are lacking on their potential benefits in functional dyspepsia. A number of studies have shown that omeprazole is more effective than placebo, antacid-alginate, and $H_2$ receptor antagonists in relieving symptoms in patients with uninvestigated dyspepsia, and lansoprazole has also been shown to be more effective than ranitidine in these patients (see Jones in...
Acid inhibition in functional dyspepsia

Table 1 Percentage of patients with complete relief of dyspeptic symptoms at four weeks, shown as the percentage of all patients in each treatment arm (All) and also divided according to type of investigator

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients with complete relief of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOND (n=642)</td>
</tr>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>Omeprazole 20 mg once daily</td>
<td>42%</td>
</tr>
<tr>
<td>Omeprazole 10 mg once daily</td>
<td>43%</td>
</tr>
<tr>
<td>Placebo</td>
<td>26%</td>
</tr>
</tbody>
</table>

PCP, primary care physician; SG, specialist gastroenterologist.
The split in patients between PCP and SG was 34% and 66% in the BOND study compared with 8% and 92% in the OPERA study. The difference in treatment response between the two studies was statistically significant when comparing active treatment (omeprazole 20 mg and 20 mg) with placebo (p=0.006) as well as when comparing each active drug with placebo (omeprazole 20 mg, p=0.04; omeprazole 10 mg, p=0.003). When adjusting for the type of investigator however, the difference in treatment response was not statistically significant.

this supplement [see page iv42]). However, studies of uninvestigated dyspepsia inherently include patients with underlying acid related diseases, such as peptic ulcer disease and reflux oesophagitis, which would be expected to respond to proton pump inhibitors. What are lacking are data on the efficacy of proton pump inhibitor therapy specifically in patients with functional dyspepsia.

Here we review the results of the large, randomised, double blind clinical trials, BOND and OPERA, the Scandinavian PILOT study,13 and a follow up study, ENCORE.14 BOND, OPERA, and PILOT aimed to address the question of whether effective acid inhibition with the proton pump inhibitor omeprazole relieves symptoms in patients with functional dyspepsia. In BOND and OPERA, a further question was whether the subgrouping of patients, based on their predominant symptom, can predict a response to therapy. The studies also provide some insight into whether the therapeutic response is affected by the H pylori status of the patient. ENCORE followed on from this, addressing the question of the consequences of relieving symptoms in patients with functional dyspepsia once they are off therapy.

PATIENTS AND METHODS

The BOND and OPERA studies

Patients (n=1262) with a clinical diagnosis of functional dyspepsia entered the BOND and OPERA studies, which were of an identical parallel group, double blind, randomised, placebo controlled design and had identical study protocols. They were both multicentre studies conducted in primary care and specialist gastroenterology centres in a total of 13 European countries and Canada.

Patients were eligible if they had persistent or recurrent epigastric pain and/or discomfort on at least one of the three days prior to randomisation, had a history of these symptoms for at least one month, and had a normal upper endoscopy. Patients with a history of documented peptic ulcer disease or GORD were excluded. Patients with classic heartburn or regurgitation as their only symptom without an epigastric component were also excluded in an effort to reduce the inclusion of patients with undiagnosed GORD. However, while patients had to have epigastric pain to be included, and were diagnosed as functional dyspepsia, patients could have concomitant reflux symptoms, as these commonly overlap with upper abdominal pain or discomfort. Patients were also excluded if they had “alarm symptoms”, irritable bowel syndrome, or a history of oesophageal or gastrointestinal surgery.

Patients were randomised to four weeks of treatment with omeprazole 20 mg once daily, omeprazole 10 mg once daily, or placebo. Symptoms were assessed by the investigator at baseline and after four weeks according to a validated four point Likert scale (none, mild, moderate, severe). The primary efficacy variable was complete absence of symptoms (epigastric pain and discomfort) on each of the last three days prior to the final clinic visit at the end of treatment. A secondary measure of efficacy was the patient’s response after four weeks to the question, “Does the study medication give sufficient control of your symptoms?” The gastrointestinal symptom rating scale (GSRS) was also used. Quality of life was assessed using the psychological general well being (PGWB) index. Baseline H pylori status was determined using the 13C urea breath test.

Efficacy of therapy was also investigated in subgroups of patients, divided according to their most bothersome symptom (MBS) on interview. Each patient was subgrouped as having either ulcer-like (MBS: epigastric pain), reflux-like (MBS: heartburn or acid regurgitation), dysmotility-like (MBS: postprandial fullness, early satiety, bloating, or belching), or other (MBS: nausea or flatus) functional dyspepsia.

Differences in the primary variable between treatment groups were analysed using the Mantel-Haenzel χ² test with stratification based on countries. The significance level was adjusted for two comparisons (each of the two omeprazole doses versus placebo) using the Bonferroni rule. All data given are from the intention to treat (ITT) analyses.

The PILOT study

The Scandinavian PILOT study was a double blind, randomised, placebo controlled trial that evaluated the effect of gastric acid inhibition using omeprazole 20 mg twice daily in patients recruited from gastroenterology practices in Sweden and Denmark.13 Patients were excluded if they had a known gastrointestinal disorder, predominant symptoms indicating GORD, or the irritable bowel syndrome, as were patients with heartburn/regurgitation as their only symptom. The results of H pylori testing1 and 24 hour intraoesophageal pH monitoring performed before randomisation13 were blinded and used as explanatory variables.

The ENCORE study

Patients from the OPERA study (n=567) went forward to the ENCORE study for follow up over a three month period during which time treatment was given at the discretion of the investigator.14 Blinding of the treatment received in the previous study was maintained. After three months, gastrointestinal symptoms were assessed, together with healthcare consumption (clinic visits and medication due to dyspepsia), hours absent from work, and quality of life, assessed using the PGWB index and the GSRS. In addition, healthcare consumption and absence from work were converted into costs.

DOES EFFECTIVE ACID INHIBITION RELIEVE SYMPTOMS?

The BOND and OPERA studies, despite being identical in design, showed disparate results (table 1). In the pooled
analyses, omeprazole 20 mg and 10 mg once daily were superior to placebo in terms of the primary end point, complete absence of symptoms at four weeks, although the effect sizes were modest (fig 1A). By ITT analysis (n=1248), complete relief of symptoms was achieved in 38.2% of patients treated with omeprazole 20 mg once daily, and 36.0% of those who received omeprazole 10 mg once daily compared with 28.2% of patients given placebo.

Similar gains over placebo were seen with omeprazole in the secondary endpoint, sufficient control of symptoms in the pooled analyses (fig 1B). Not surprisingly, this secondary end point was achieved in a greater proportion of patients than the more stringent primary end point. Sufficient control of symptoms was achieved in 61% and 59% of patients with omeprazole 20 mg and 10 mg once daily, respectively, compared with 51% of patients treated with placebo. Patient diary cards also confirmed this hierarchy of efficacy with a mean proportion of symptom free days of 52% in patients treated with omeprazole 20 mg once daily (p=0.002 v placebo) and 50% in those who received omeprazole 10 mg once daily (p=0.03 v placebo) compared with 45% in the placebo group.

When the pooled data were analysed, the overall GSRS score was improved in patients treated with omeprazole 20 mg once daily (p=0.02) but not with omeprazole 10 mg once daily compared with placebo. There was no significant difference between treatment groups in the PGWB index. This is perhaps not surprising given the modest difference in symptom relief between treatments in the total patient population, coupled with the fact that the PGWB index is a broad measure of general well being and not a disease specific index.

Weaknesses in study design and execution have been a considerable limitation of studies in functional dyspepsia to date which has been confirmed in a recent systematic review of 32 published, randomised, controlled trials. The BOND and OPERA studies were designed to avoid the pitfalls of previous trials in functional dyspepsia by using validated outcome measures, maintaining strict blinding, including an adequate placebo control, and ensuring sufficient study power. The primary outcome measure in these studies, complete relief of epigastric pain and discomfort, is particularly rigorous but all the symptom measures improved in parallel, with both doses of omeprazole being superior to placebo. The results are therefore likely to be accurate and relevant to clinical practice.

The PILOT study included 197 patients with functional dyspepsia; complete symptom relief (no symptoms on the last day based on diary cards) at two weeks was achieved in 32% of patients treated with omeprazole 20 mg once daily compared with 14% of patients given placebo.

There are very few other data available on the efficacy of proton pump inhibitors in the treatment of functional dyspepsia. In a German multicentre study with different primary end points, there was no significant difference between omeprazole and placebo at two weeks. However, when an end point of complete symptom relief similar to that used in the BOND and OPERA studies was applied in the German study, omeprazole was superior to placebo.

DIFFERENCES BETWEEN PRIMARY CARE AND SPECIALIST CENTRES

Omeprazole had a modest but significant benefit on symptoms compared with placebo in the analysis of the combined BOND and OPERA studies. However, in the two individual analyses, while this effect was evident in the BOND study, there was no significant benefit with omeprazole in the OPERA study. Of note was the difference in response depending on the treatment setting (table 1). A more marked therapeutic gain was observed with omeprazole 20 mg once daily compared with placebo in primary care centres in both the BOND and OPERA studies. When the data from primary care centres in both studies were combined, complete symptom relief was achieved in 38% of patients treated with omeprazole 20 mg once daily compared with only 13% of those given placebo. However, the observed benefit was greatly reduced in the specialist centres due to an increased placebo response. In the analysis of the combined studies, in contrast with the results in primary care centres, while the response to omeprazole 20 mg once daily in patients treated by specialist gastroenterologists was still 38%, the placebo response rose to 32%.

A definite explanation for the differential response in patients seeing primary care physicians and specialists is not available although it is likely that different types of patients are seen in these settings with a possible filtering of patients occurring in the referral process. In addition, patients may undergo more extensive investigation in the specialist setting, possibly resulting in greater reassurance and hence higher placebo responses.

In the overall analysis of the combined studies, only 21% of patients were treated by primary care physicians. However, a considerably greater proportion of patients in the BOND study (34%) were treated in primary care centres compared with the OPERA study (8%). An analysis has been performed which takes both this difference and the differences in observed treatment effect between primary and secondary care centres into consideration. This showed that the overall difference in therapeutic gain between the studies might be fully explained by the observed differences between primary and secondary care but the impact of unknown factors or chance cannot be excluded.

DOES THE SUBGROUPING OF PATIENTS PREDICT THE THERAPEUTIC RESPONSE TO OMEPRAZOLE?

When the combined data from the BOND and OPERA studies were analysed according to the subtype of dyspepsia, more marked differences were revealed than in the patient population as a whole. Complete relief of symptoms was significantly greater with omeprazole than with placebo in the subgroups of patients with ulcer-like and reflux-like dyspepsia while, as might be expected, there was no indication of benefit with omeprazole in patients with dysmotility-like dyspepsia (fig 2).

Patients with ulcer-like dyspepsia formed the largest subgroup (n=708) and in these patients complete relief of symptoms was achieved at four weeks in 40% of those treated with omeprazole 20 mg once daily; in 35% of those who received omeprazole 10 mg once daily, and in 27% of those given placebo. The advantage with omeprazole was yet more marked in patients with reflux-like dyspepsia (n=143). Of these patients, 54% and 45% of those treated with omeprazole 20 mg and 10 mg once daily, respectively, experienced...
complete relief of symptoms compared with 23% of those given placebo. Presumably, many of these patients did not have functional dyspepsia but symptomatic GORD that was misclassified by the enrolling physicians. The corresponding values in the subgroup with dysmotility-like dyspepsia (n=247) were 32%, 37%, and 31%, with no significant difference between treatments. In the remaining group of patients, in which the MBS was nausea or flatus (n=106), the corresponding values for omeprazole 20 mg and 10 mg once daily, and placebo were 28%, 18%, and 22%, respectively, for nausea, and 14%, 58%, and 73% for flatus.

Patients with functional dyspepsia do not always fall neatly into single symptom subgroups. Rather, patients usually have clusters of symptoms that frequently overlap, and because of this overlap attempts to subgroup patients based on clusters of symptoms have failed in clinical practice.1 11 The BOND and OPERA studies differ in that patients were subgrouped according to symptom predominance, and the current data suggest that the predominant symptom diagnosed in patients with functional dyspepsia may have clinical utility in predicting the response to acid suppression. The role of acid and hence the efficacy of proton pump inhibition in peptic ulcer disease and GORD are well established. The subgroup analyses in the BOND and OPERA studies suggest that in patients with predominantly ulcer-like symptoms, their condition is also, at least in part, acid related.

**IS A BENEFIT OF 10–15% WORTHWHILE?**

The new treatment data suggest that acid pump inhibition by omeprazole is superior to placebo in functional dyspepsia. The results indicate that a subgroup of patients are responsive to acid suppression, and the findings are applicable in clinical practice. Hence omeprazole may be a useful diagnostic tool, and a dose of 20 mg once daily seems optimal for this purpose.

The three trials (BOND, OPERA, and PILOT) used a rigorous end point, namely absence of epigastric pain or discomfort, rather than relying on an arbitrary symptom score that may not translate into a clinically meaningful number (see Veldhuyzen van Zanten in this supplement [see page iv23]). Importantly, all symptom measures improved in parallel and all three doses of omeprazole 10 mg or 20 mg once daily and 20 mg twice daily were superior to placebo in different studies. The observed therapeutic gain with omeprazole therefore appears real and clinically meaningful, albeit modest. In planning these trials, the sample sizes had been calculated to detect differences of this order of magnitude, as these were considered clinically relevant by the investigators.

The observed therapeutic benefit was most consistent with omeprazole 20–40 mg daily. However, higher doses of omeprazole (for example, 40 mg twice daily) were not tested and more potent acid suppression might conceivably increase the therapeutic gain.

**IS THE THERAPEUTIC RESPONSE AFFECTED BY H PYLORI STATUS?**

A total of 41% of patients were H pylori positive when they entered the BOND and OPERA studies, evenly distributed between treatment arms. There was no significant difference in complete absence of symptoms at four weeks between H pylori positive and H pylori negative patients in any of the treatment arms (fig 3). In total, symptoms were absent in 37% of H pylori positive patients and in 32% of H pylori negative patients on omeprazole. In addition, there was no significant difference in complete absence of symptoms at four weeks between H pylori positive and H pylori negative patients in the ulcer-like, reflux-like, or dysmotility-like subgroups in any of the treatment arms but these were exploratory analyses (table 2). Although H pylori status did not significantly influence the response to omeprazole, this does not exclude the possibility of a small true difference between H pylori positive and H pylori negative patients in the effect of acid inhibition on functional dyspepsia.

It has previously been suggested that a subset of functional dyspeptic patients who are infected with H pylori have acid dysregulation10 which may therefore respond to acid inhibition with a proton pump inhibitor. However, H pylori status did not predict a response to omeprazole in the BOND and OPERA or PILOT studies.

**DOES UNRECOGNISED REFLUX DISEASE PREDICT WHO WILL RESPOND TO TREATMENT?**

In the PILOT study, oesophageal acid exposure did not significantly influence the response to therapy.11 However, in exploratory analyses it appeared that complete resolution of dyspeptic symptoms during treatment with omeprazole was confined to a group of patients who, before randomisation, described in a self administered structured questionnaire their main discomfort as “a burning feeling rising from the stomach or lower chest up towards the neck” (42% of cases).12 This symptom pattern may best be described as heartburn. Hence it is likely that a subset of patients labelled as having functional dyspepsia actually have GORD.

**BY WHICH MECHANISM IS A PROTON PUMP INHIBITOR EFFICACIOUS IN FUNCTIONAL DYSPESIA?**

If acid pump inhibitors are efficacious in some patients with functional dyspepsia, by what mechanism do they reduce symptoms? Modulation of gastric acid is one consideration.
Table 2 Proportion of patients with complete relief of dyspeptic symptoms by dyspeptic group, *Helicobacter pylori* status, and treatment (all patients in the intention to treat population who answered the question about their “most bothersome symptom” and whose *H pylori* status was known)

<table>
<thead>
<tr>
<th>Dyspepsia subgroup</th>
<th><em>H pylori</em> status</th>
<th>Omeprazole 20 mg once daily</th>
<th>Omeprazole 10 mg once daily</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysmotility-like</td>
<td><em>H pylori</em>−</td>
<td>27% (18/67)</td>
<td>41% (30/73)</td>
<td>27% (15/56)</td>
</tr>
<tr>
<td></td>
<td><em>H pylori</em>+</td>
<td>35% (19/55)</td>
<td>25% (12/48)</td>
<td>39% (19/49)</td>
</tr>
<tr>
<td>Reflux-like</td>
<td><em>H pylori</em>−</td>
<td>60% (15/25)</td>
<td>35% (7/20)</td>
<td>12% (3/26)</td>
</tr>
<tr>
<td></td>
<td><em>H pylori</em>+</td>
<td>52% (7/14)</td>
<td>52% (7/14)</td>
<td>33% (9/27)</td>
</tr>
<tr>
<td>Ulcer-like</td>
<td><em>H pylori</em>−</td>
<td>35% (53/152)</td>
<td>33% (41/124)</td>
<td>24% (34/141)</td>
</tr>
<tr>
<td></td>
<td><em>H pylori</em>+</td>
<td>47% (40/85)</td>
<td>38% (32/85)</td>
<td>31% (32/104)</td>
</tr>
</tbody>
</table>


Basal and peak acid outputs do not differ in patients with functional dyspepsia compared with controls, however, the acid response to gastrin releasing peptide, which is considered to reflect the postprandial state, may be abnormal in up to 50% of *H pylori* infected patients with functional dyspepsia, and in this group the disturbance is similar to that found in patients with duodenal ulcer.

Another potential mechanism may relate to the mucosa being more sensitive in patients with functional dyspepsia, and this might be reduced by antisecretory therapy.

Figure 4 [A] Mean number of days on medication, [B] mean number of clinic visits, and [C] patient quality of life measured by the psychological general well being index, during a three month follow up period in patients with either complete relief of symptoms or persistent symptoms after a four week course of therapy (BOND and OPERA); 95% confidence intervals are also shown.

**WHAT ARE THE CONSEQUENCES OF SYMPTOM RELIEF FOLLOWING CESSION OF TREATMENT?**

The ENCORE study provides new information on the effect of symptom resolution on the natural history of functional dyspepsia during a three month follow up period, and suggests that the benefits of fully controlling symptoms continue after cessation of treatment. However, these observations applied to patients who responded to omeprazole or placebo in the OPERA trial.

Compared with patients in whom symptoms still persisted at the end of trial, during the three month follow up, patients with complete absence of symptoms at the end of active or placebo treatment had fewer days on medication (9.2 ± 22.7) and fewer clinic visits (1.5 ± 2.0) (fig 4). Moreover, quality of life scores were significantly better both after initial treatment and after three months of follow up in the group of patients in whom symptoms had been relieved. Costs arising from clinic visits, medication, and absence from work were reduced in patients with complete absence of symptoms in the majority of the six European countries that were involved in the study. Duration of disease and severity of symptoms at baseline were not predictors of outcome.

Evidently, from the ENCORE study the benefits of symptom relief accrue even after therapy has finished. The study suggests that reduced costs and improved quality of life occur over a three month period following cessation of treatment in patients with functional dyspepsia if symptoms have been fully controlled, regardless of the treatment used. Studies with long term follow up are now needed.

**CONCLUSION**

Overall, omeprazole 20 mg or 10 mg once daily appears to be superior to placebo in relieving the symptoms of functional dyspepsia. More specifically, omeprazole was effective in patients with ulcer-like and reflux-like dyspepsia but probably not in those with dysmotility-like dyspepsia. In addition, symptom relief may be unrelated to *H pylori* status. Successful treatment (whether using an active drug or placebo) appears to reduce the subsequent costs and has a positive impact on patient quality of life over a three month period after cessation of treatment. The caveat to these data is that they are only from the studies outlined here, and clearly these observations need further confirmation.

Indeed, while the new data cast valuable light on the management of functional dyspepsia (see Talley in this supplement [see page iv72]), considerable further work is required in this area. An important perspective of the data reported here however is that they provide useful pointers for the way forward for research in this field. The BOND and OPERA
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studies suggest that specific subgroups of patients are more likely to respond to omeprazole therapy but will more sophisticated methods of subdividing patients provide us with more accurate means of predicting those who will respond to effective acid inhibition? Moreover, is there a diagnostic role for higher doses of omeprazole, analogous with the diagnostic benefits that have been demonstrated in reflux disease? In the ENCORE study, patients continued to benefit three months after relief of their symptoms but prolonged follow up is needed to assess how long this benefit lasts. Studies are also needed to determine the long term effects on healthcare costs in relation to the degree of symptom control in empirically treated patients. In addition, we are still ignorant of what role, if any, maintenance or on demand therapy with effective acid suppressants should play in the management of patients with functional dyspepsia, or in specific subgroups of patients.

Authors’ affiliations

N J Talley, Department of Medicine, University of Sydney, Nepean Hospital, Penrith, Australia
K Lauritsen, Department of Medical Gastroenterology, Odense University Hospital, Odense, Denmark

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