Amoxicillin for acute lower respiratory tract infection in primary care: subgroup analysis of potential high-risk groups

INTRODUCTION
Acute uncomplicated lower respiratory tract infection (LRTI) is common in primary care practice. Most patients still receive antibiotics for LRTI,1–4 despite the recommendations of most guidelines for limited prescribing.5–7 The updated Cochrane review suggests some benefits from antibiotics; with a number needed to treat (NNT) of 6 for cough, nearly halving the number not improving, and no significant short-term harms.8 However, the primary analysis of the largest trial to date, the genomics to combat resistance against antibiotics in community-acquired lower respiratory tract infections (GRACE) project (http://www.grace-lrti.org) European multicentre placebo controlled trial of amoxicillin,9 found that antibiotics did not meaningfully alter important outcomes; either symptom severity or duration of more severe symptoms. The development of new or worsening symptoms was, however, significantly different between groups, but the NNT was high (30) and was roughly equivalent to the number needed to harm. The key question for clinicians and patients is whether the ‘average’ benefit from previous trials is meaningful, that is, whether the benefit or lack of benefit applies to all major clinical subgroups. Current guidelines recommend antibiotics in some situations, for instance older people and those with significant comorbidity,7 and there is a suggestion from observational data that antibiotics confer some protection against pneumonia in older people.3 However, prescribing is not limited to the identified at-risk groups.8 Attempts to explain continued prescribing despite the recommendations of guidelines highlight key clinical factors that drive prescribing: abnormal chest sounds, fever, coloured sputum, and reported breathlessness,10,11 in addition to non-medical reasons,12,13 and perceived patient pressure.14 Thus the debate continues: clinicians and patients need to know whether antibiotics help in some subgroups, despite the average lack of benefit overall. This can only be addressed robustly by data from large trials, or, alternatively, by individual patient data meta-analyses. This secondary analysis of the GRACE trial aims to provide estimates of the benefits and harms of antibiotics for the pre-specified subgroups at risk listed below. Following external referee, an additional subgroup of interest was identified: those with abnormal lung signs.

M Moore, MRCP, FRCP, reader, B Stuart, PhD, research fellow; P Little, FRCP, professor of primary care research, University of Southampton, Southampton, UK. TJM Verheij, MRCP, professor of general practice, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands. CC Butler, FRCGP, professor of primary care, University of Oxford and Cardiff University, Cochrane Institutes of Primary Care and Public Health, School of Medicine, Cardiff University, Cardiff, UK. S Coenen, DMSc, professor and head of the Centre for General Practice, H Goossens, professor of medical microbiology, Laboratory of Medical Microbiology, Vaccine and Infectious Disease Institute (VAXINFECTIO), University of Antwerp, Belgium.

Address for correspondence
Michael Moore, Primary Medical Care, Alderwood Medical Centre, Alderwood Close, Southampton, SO16 5ST, UK.
E-mail: mmm1986@soton.ac.uk
©British Journal of General Practice
This is the full-length article (published online 27 Jan 2014) of an abridged version published in print. Cite this article as: Br J Gen Pract 2014; 10.3399/bjgp14X677121

Abstract
Background
Antibiotics are of limited overall clinical benefit for uncomplicated lower respiratory tract infection (LRTI) but there is uncertainty about their effectiveness for patients with features associated with higher levels of antibiotic prescribing.

Aim
To estimate the benefits and harms of antibiotics for acute LRTI among those producing coloured sputum, smokers, those with fever or prior chest symptoms, and longer duration of prior illness.

Design and setting
Secondary analysis of a randomised controlled trial of antibiotic placebo for acute LRTI in primary care.

Method
Two thousand and sixty-one adults with acute LRTI, where pneumonia was not suspected clinically, were given amoxicillin or matching placebo. The duration of symptoms, rated moderately bad or worse (primary outcome), symptom severity in the first four days (0–6 scale), and the development of new or worsening symptoms were analysed in pre-specified subgroups of interest. Evidence of differential treatment effectiveness was assessed by interaction terms.

Results
No subgroups were identified that were significantly more likely to benefit from antibiotics in terms of symptom duration or the development of new or worsening symptoms. Those with a history of significant comorbidities experienced a significantly greater reduction in symptom severity between days 2 and 4 (interaction term –0.28, P = 0.003; estimated effect of antibiotics >0.44 to –0.11, P = 0.001), equivalent to three people in ten rating symptoms equivalently to the number needed to harm.

Conclusion
There is no clear evidence of clinically meaningful benefit from antibiotics in subgroups of patients with uncomplicated LRTI where prescribing is highest. Any possible benefit must be balanced against the side-effects and longer-term effects on antibiotic resistance.

Keywords
antibiotics; primary health care; randomised controlled trial; respiratory infections.
• smokers;
• those with green sputum;
• those with fever at baseline;
• those with previous lung disease and/or significant other comorbidities;
• those with a longer prior duration of illness; and
• those with abnormal lung signs.

METHOD
Settings and patients
The study details are reported fully elsewhere.9 In summary, participants were recruited between November 2007 and April 2010 by primary care practices in 16 networks from 12 European countries (Belgium, England, France, Germany, Italy, the Netherlands, Poland, Spain, Slovakia, Slovenia, Sweden, and Wales).

Inclusion criteria
Participants were aged ≥18 years, with their first consultation with an acute cough (up to and including 28 days’ duration) as the main symptom and where non-infective diagnoses were judged to be very unlikely (see exclusions), or alternatively where cough was not the most prominent symptom (for example, fever or malaise), but where the clinician considered acute LRTI was the main presenting diagnosis.

Exclusions
The following patients were excluded: those with a clinical diagnosis of community-acquired pneumonia,15 based on focal chest signs (focal crepitations or bronchial breathing) and systemic features (high fever, vomiting, severe diarrhoea); those with a prior history of antibiotic use in the previous month; those with penicillin allergy; those who were pregnant; and those with immunological deficiencies. Prior diagnosis of asthma, chronic obstructive pulmonary disease (COPD), or other comorbid conditions were not exclusion criteria.

How this fits in
In acute cough illness in primary care antibiotics confer little overall benefit. Secondary analysis of a large randomised trial failed to identify any subgroup with a clinically meaningful response to antibiotics.

Intervention
Patients who agreed to randomisation were allocated to receive either antibiotic (amoxicillin 1 g) or placebo three times a day for 7 days, by the clinician dispensing sequentially numbered pre-prepared randomised containers.

Data collection
All outcome data were collected blind to treatment allocation, comorbidities, clinical signs, and the severity of baseline symptoms reported by the patient (rating each symptom ‘no problem’, ‘mild problem’, a ‘moderate problem’, or a ‘severe problem’). Participants completed a symptom diary daily until their symptoms had settled, up to a maximum of 28 days. The diary items recorded the severity of the following symptoms: cough, phlegm, shortness of breath, wheeze, blocked/runny nose, chest pain, muscle aches, headache, disturbed sleep, feeling generally unwell, fever, and interference with normal activities. Each symptom was scored from 0 to 6 (0 = no problem, 1 = very little problem, 2 = slight problem, 3 = moderately bad, 4 = bad, 5 = very bad, 6 = as bad as it could be). The diary has previously been validated and is sensitive to change.16 Participants were phoned after 4 days and contacted again after 4 weeks if the diary was not returned, to collect key outcomes by a short questionnaire or standardised phone call.

Main outcomes
Symptom duration. The primary outcome was the duration of more severe symptoms (symptoms rated ‘a moderately bad problem’ or worse by patients17) following the initial presentation, as this is easy to conceptualise for both patients and physicians.

Symptom severity. The mean diary score for all symptoms for study days 2–4 following the index consultation was specified, as this time period is when symptoms are rated as the worst problem by patients. Before day 2, antibiotics will have little chance to provide benefit, and after day 4, although some symptoms remain moderately bad or worse, on average, the mean diary scores for all symptoms are rated less than a moderately bad problem.17

New or worsening symptoms. This was defined as a return to the physician with worsening symptoms, new symptoms, new signs, or illness requiring admission to hospital within 4 weeks after the first consultation, determined from a review of the notes. This definition has been
found useful and workable in previous studies of respiratory tract infection in the community.18 Since so few patients required hospital admission, this outcome effectively represents symptom control.

Sample size calculation
Separating participants into two age bands < and ≥60 years, using the NQuery sample size programme to detect a difference between age groups, it was calculated that 586 people were needed per age band to detect a 7.5% change to the deterioration of illness (15% versus 7.5%, 80% power, α = 0.05, 95% follow-up), and 544 were needed per age band to detect a chance of 0.33 standard deviations for the other two outcomes (80% power, α 0.01, 80% follow-up). The subgroups of interest in this study are of a similar magnitude to this (ranging from 409 in the group of those with green phlegm, to 817 in the group of those with longer duration of prior illness). A variety of abnormal lung signs were recorded: wheeze 305 (14%), rhonchi 281 (14%), crackles 126 (6%), and diminished vesicular breathing 256 (12%). No formal guidance was issued regarding characterisation of abnormal signs, and in a previous observational study in the same networks, variation in labelling of clinical signs between networks was evident.19 Individual signs lacked power for subgroup analysis, so it was decided to combine abnormal physical findings into a new subgroup; ‘abnormal signs’ of similar magnitude to the other subgroups examined, 692 (34%). Since those with a clinical diagnosis of pneumonia were not included in the randomised study, these abnormal signs should be considered ‘non diagnostic of pneumonia’.

Analysis
No interim analysis was performed, and all analyses were performed blind to group allocation, using Stata (version 11). Subgroup analyses were specified in advance. Analysis used linear regression models controlling for the severity of baseline symptoms: Cox regression for the duration of symptoms allowing for censoring; simple linear regression for symptom severity; and logistic regression for deterioration of illness. The interaction between a particular subgroup (for example, smokers) and the intervention (in this case antibiotics) concerns the difference in effectiveness of antibiotics in those in that particular subgroup (smokers), compared to those who are not (non-smokers). The interaction term is the variable introduced into the statistical model to allow estimation of the size of that difference.

RESULTS
Participants
In total, 2061 participants were recruited between 2007 and 2010 and 595 (28%) of the trial population were aged ≥60 years, 310 (15%) had chronic lung disease (asthma or COPD). Deterioration of illness (or no deterioration) was documented in 98%, of whom 18% (356/2027) experienced deterioration; the vast majority of these represent reconsultation with new or worsening symptoms and only three patients required hospital admission (two from the control group and one from the intervention group) in the month following recruitment. Symptom severity and illness duration were documented in 87% and 88% respectively. The groups were well balanced at baseline.

Table 1. Resolution of symptoms rated moderately bad or worse in amoxicillin versus placebo group

<table>
<thead>
<tr>
<th></th>
<th>Median time to resolution of symptoms rated moderately bad (IQR)</th>
<th>Interaction term* (95% CI)</th>
<th>P-value</th>
<th>Hazard ratio for subgroup* (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amoxicillin</td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole cohort (n = 1799)</td>
<td>6 [3–11]</td>
<td>7 [4–14]</td>
<td></td>
<td></td>
<td>1.06 (0.98 to 1.18)</td>
</tr>
<tr>
<td>Green sputum (n = 346)</td>
<td>6 [3–10]</td>
<td>8 [5–14]</td>
<td>1.28 (0.99 to 1.65)</td>
<td>0.059</td>
<td>1.31 (1.05 to 1.65)</td>
</tr>
<tr>
<td>Current smoker (n = 487)</td>
<td>6 [4–10]</td>
<td>7 [6–14]</td>
<td>1.20 (0.95 to 1.51)</td>
<td>0.121</td>
<td>1.23 (1.01 to 1.50)</td>
</tr>
<tr>
<td>Significant past history* (n = 440)</td>
<td>6 [4–16]</td>
<td>8 [5–15]</td>
<td>0.98 (0.78 to 1.25)</td>
<td>0.914</td>
<td>1.04 (0.86 to 1.31)</td>
</tr>
<tr>
<td>Prior duration of illness</td>
<td>6 [4–15]</td>
<td>7 [3–14]</td>
<td>0.81 (0.66 to 0.99)</td>
<td>0.040</td>
<td>0.93 (0.79 to 1.09)</td>
</tr>
<tr>
<td>&gt;7 days (n = 715)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever at baseline (n = 608)</td>
<td>7 [4–14]</td>
<td>7 [4–11]</td>
<td>0.97 (0.78 to 1.20)</td>
<td>0.783</td>
<td>1.04 (0.88 to 1.25)</td>
</tr>
<tr>
<td>Minor chest signs (n = 692)</td>
<td>6 [4–14]</td>
<td>6 [4–15]</td>
<td>0.98 (0.79 to 1.21)</td>
<td>0.832</td>
<td>1.05 (0.88 to 1.24)</td>
</tr>
</tbody>
</table>

IQR = interquartile range. *Estimates controlled for baseline symptom severity.†Lung disease, heart disease, diabetes, or hospital admission. The apparent anomaly here is that the proportional hazards assumption of hazards being constant over time was violated: the interaction term suggests a slower resolution in those with longer prior duration, whereas the median time to resolution suggests the opposite. The Kaplan–Meier survival curves cross, so although the median suggests a shorter duration, those receiving antibiotics have a group taking longer to resolve (90% of the placebo group recover by 24 days but it takes 28 days for 90% of the antibiotic group to recover).
Subgroup analysis for the three outcomes

No subgroups were identified that were significantly more likely to benefit for the duration of symptoms rated moderately bad or worse (Table 1). For those with green sputum, the interaction term was of borderline significance (interaction term $1.28$, $P = 0.059$; hazard ratio in the subgroup [HR] = 1.31 [95% confidence interval [CI] = 1.05 to 1.65], $P = 0.019$). A Kaplan–Meier survival curve is shown for those with green sputum (Figure 1). Although a separation of the survival curves may be seen, there is a modest impact on the median and interquartile range of symptom duration.

For the symptom severity on days 2–4 (Table 2), those with a history of significant comorbidities (lung disease, heart disease, diabetes, or prior hospital admission) experienced a significantly greater reduction in symptom severity between days 2 and 4 than those without a past history (interaction term $–0.28$, $P = 0.003$; estimated effect of antibiotics among those with a past history $–0.28$ [95% CI = $–0.44$ to $–0.11$], $P = 0.001$). Smokers and those with a longer prior duration of illness appeared significantly less likely to benefit from antibiotics for symptom severity, although the differences were small.

No subgroups were identified that were significantly more likely to develop new or worsening symptoms (Table 3). For those with abnormal lung signs, no benefit of antibiotics was seen in any of the three outcomes examined.

### Table 2. Mean symptom severity score on days 2–4 after consultation, in amoxicillin versus placebo group

<table>
<thead>
<tr>
<th></th>
<th>Amoxicillin</th>
<th>Placebo</th>
<th>Interaction term* (95% CI)</th>
<th>P-value</th>
<th>Difference for subgroup* (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole cohort (n = 1789)</td>
<td>1.62 (0.84)</td>
<td>1.69 (0.84)</td>
<td>$–0.07$ ($–0.15$ to $0.01$)</td>
<td>0.074</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green sputum (n = 343)</td>
<td>1.79 (0.87)</td>
<td>1.91 (0.87)</td>
<td>$–0.12$ ($–0.31$ to $0.06$)</td>
<td>0.196</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker (n = 483)</td>
<td>1.85 (0.84)</td>
<td>1.77 (0.84)</td>
<td>$0.07$ ($0.07$ to $0.23$)</td>
<td>0.314</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant past historya (n = 438)</td>
<td>1.63 (0.87)</td>
<td>1.90 (0.87)</td>
<td>$–0.28$ ($–0.44$ to $–0.11$)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior duration of illness</td>
<td>1.53 (0.77)</td>
<td>1.46 (0.77)</td>
<td>$0.07$ ($0.05$ to $0.18$)</td>
<td>0.253</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;7 days (n = 711)</td>
<td>1.94 (0.92)</td>
<td>2.02 (0.92)</td>
<td>$–0.02$ ($–0.19$ to $0.14$)</td>
<td>0.799</td>
<td>$–0.08$ ($–0.23$ to $0.06$)</td>
<td>0.262</td>
</tr>
<tr>
<td>Fever at baseline (n = 607)</td>
<td>1.94 (0.92)</td>
<td>2.02 (0.92)</td>
<td>$–0.02$ ($–0.19$ to $0.14$)</td>
<td>0.799</td>
<td>$–0.08$ ($–0.23$ to $0.06$)</td>
<td>0.262</td>
</tr>
<tr>
<td>Minor chest signs (n = 692)</td>
<td>1.81 (0.89)</td>
<td>1.89 (0.89)</td>
<td>$–0.03$ ($–0.17$ to $0.17$)</td>
<td>0.791</td>
<td>$–0.08$ ($–0.21$ to $0.06$)</td>
<td>0.288</td>
</tr>
</tbody>
</table>

*Estimates controlled for baseline symptom severity. aLung disease, heart disease, diabetes, or hospital admission.

### Table 3. Worsening of illness according to subgroup in amoxicillin versus placebo group

<table>
<thead>
<tr>
<th></th>
<th>Amoxicillin</th>
<th>Placebo</th>
<th>Interaction term* (95% CI)</th>
<th>P-value</th>
<th>Odds ratio for subgroup* (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole cohort</td>
<td>162/1021</td>
<td>194/1006</td>
<td>0.79 (0.63 to 0.99)</td>
<td>0.043</td>
<td>0.79 (0.45 to 1.18)</td>
<td>0.202</td>
</tr>
<tr>
<td>Green sputum</td>
<td>40/221</td>
<td>43/185</td>
<td>0.93 (0.53 to 1.61)</td>
<td>0.787</td>
<td>0.91 (0.58,1.42)</td>
<td>0.680</td>
</tr>
<tr>
<td>Current smoker</td>
<td>47/304</td>
<td>45/269</td>
<td>1.21 (0.72 to 2.03)</td>
<td>0.482</td>
<td>0.86 (0.55 to 1.36)</td>
<td>0.520</td>
</tr>
<tr>
<td>Significant past historya</td>
<td>44/257</td>
<td>47/243</td>
<td>1.11 (0.65 to 1.88)</td>
<td>0.692</td>
<td>0.88 (0.61 to 1.26)</td>
<td>0.474</td>
</tr>
<tr>
<td>Prior duration of illness &gt;7 days</td>
<td>70/411</td>
<td>74/390</td>
<td>1.16 (0.73 to 1.86)</td>
<td>0.528</td>
<td>0.82 (0.56 to 1.20)</td>
<td>0.300</td>
</tr>
<tr>
<td>Fever at baseline</td>
<td>59/345</td>
<td>70/347</td>
<td>1.05 (0.65 to 1.69)</td>
<td>0.844</td>
<td>0.75 (0.51 to 1.10)</td>
<td>0.139</td>
</tr>
<tr>
<td>Minor chest signs</td>
<td>57/345</td>
<td>70/334</td>
<td>0.92 (0.57 to 1.49)</td>
<td>0.740</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Estimates controlled for baseline symptom severity. aLung disease, heart disease, diabetes, or hospital admission.
DISCUSSION

Summary
To the authors’ knowledge, this is the largest multicentre randomised placebo-controlled trial of antibiotics for acute uncomplicated LRTI and the first to provide robust estimates of benefit in common subgroups. It found no clear evidence of clinically meaningful selective benefit from antibiotics among key clinical subgroups of patients with uncomplicated LRTI where prescribing is highest.

Strengths and limitations
The findings are made relevant to everyday practice by the broad and pragmatic diagnostic entry criteria in the absence of an agreed definition for uncomplicated LRTI, and by recruiting from multiple networks and countries. These inclusion criteria are consistent with recent pragmatic trials, large cohorts, and observational studies, and with a recent consensus exercise. It is unlikely that poor adherence diminished efficacy, since more than 90% of patients in both groups reported taking study medication by day 5 and data from observational studies suggest antibiotic choice is also unlikely to affect outcome. There is a risk of type 1 error (false-positive result) with multiple comparisons in subgroups and so results should be treated with some caution; although the majority of the subgroups were identified in advance prior to the main analysis, an additional analysis was added at the request of the reviewers. In each instance, a positive result in a subgroup was seen in only one of the outcomes analysed, so it is feasible these findings arose by chance. Although a large trial, the study was not powered to detect rare but serious complications, such as empyema and hospital admission.

Comparison with existing literature
This study supports, to some extent, the approach taken in current guidelines, in that those with a prior history of significant comorbidity (lung disease, heart disease, diabetes, or hospital admission) appear to derive modest symptom benefit from antibiotics (a reduction of 0.28 in symptom score on day 2–4, which approximates to a 15% reduction in severity, or three people in ten rating their symptoms a slight problem rather than a moderately bad problem). However, there was no other benefit in terms of resolution of symptoms rated moderately bad or worse, or worsening of symptoms in this group. In the absence of other benefits, the positive finding may be of limited clinical relevance. Any benefit needs to be balanced against the likely harms from treatment (a number needed to harm of around 20 for rash, nausea, or diarrhoea).

Those with green sputum experienced a small but significant reduction in the duration of moderately bad symptoms but no change in symptom severity after 2–4 days, or likelihood of symptom deterioration. The interaction term was of borderline significance, so this result should be treated with some caution. This finding provides some evidence to back up GPs’ tendency to prescribe for this group. Although statistically significant, the confidence intervals were wide, and in the absence of benefit in other outcomes, the balance between benefit and harm is likely to be marginal and only a modest reduction in the median or interquartile range of symptom severity was observed. This finding must also be put in context with the observational evidence, which showed no benefit for those with coloured sputum. No evidence was found to support greater prescribing in those who currently smoke. No evidence of benefit was found in those with abnormal chest signs (not diagnostic of pneumonia). Since crepitations and reduced breath sounds featured in the diagnostic model for pneumonia, these were also examined as a separate (but small) subgroup (354/2061 [17%]) and the interaction terms were not significant for each of the outcomes.

Given that a small number of patients with LRTIs may benefit from antibiotic treatment, it is unlikely that they can easily be identified from features of the history and clinical examination in primary care.

Implications for practice
A statistically significant reduction in symptom severity between days 2 and 4 was observed in those with pre-existing comorbidities; however, there was no benefit for duration of moderately bad symptoms or worsening of illness. Those with green sputum possibly experienced a small reduction in the duration of moderately bad symptoms. The modest short-term benefits are of questionable clinical significance and must be balanced against the side-effects and the longer-term harm of fostering antibiotic resistance.

Funding
Funding was from the European Commission Framework Programme 6 (LSHM-CT-2005-518226). Eudract-CT 2007-001586-15 UKCRN Portfolio ID 4175 ISRCTN52261229 FWO G.0274.08N. The researchers are independent of all funders. The work in the UK was also supported by the National Institute for Health Research. In Barcelona, the work was supported by: 2009 SGR 911, Ciber de Enfermedades Respiratorias (Ciberes CB06/06/0028), the Ciberes is an initiative of the ISCIII. In Flanders (Belgium), this work was supported by the Research Foundation — Flanders (FWO; G.0274.08N).

Ethical approval
Ethical approval for the UK was granted by Southampton and South West Hampshire Local Research Ethics Committee IB (ref. 07/H0506/104). Competent authority approval for the UK was granted by the Medicines and Healthcare Products Regulatory Agency. The research sites outside of the UK also obtained ethical and competent authority approval from their local organisations. Patients who fulfilled the inclusion criteria were given written and verbal information on the study and asked for informed consent.

Competing interests
The authors have declared no competing interests.

Acknowledgements
Key members of the GRACE consortium trial team whose hard work has made this possible are: Niels Adriaenssens, Zuzana Bielicka, Pascale Bruno, Jo Coast, Patricia Fernandez, Iris Hering, Anna Kowalczyk, Christina Lannering, Marieke Lerniengre, Katherine Loens, Christine Lammens, Greet leven, Bo-Eric Malmvall, Magdalena Mura, Nuria Sanchez Romano, Matteu Serra Prat, Igor Sivab, Richard Smith, Jackie Swain, Paolo Tarsia, Frank Leus, Robert Veen, and Tricia Worby. We are very grateful to all the clinicians and patients who consented to be part of GRACE, without whom this study would simply not have been possible, and the independent GRACE trial steering committee for their help and suggestions (Patrick Bindels, Gordon Taylor, and Mark Woodhead).

Discuss this article
Contribute and read comments about this article: www.bjgp.org/letters
REFERENCES


