Undergraduate preparation for prescribing: the views of 2413 UK medical students and recent graduates

Amy Heaton, David J. Webb & Simon R. J. Maxwell

Clinical Research Centre, University of Edinburgh, Western General Hospital, Edinburgh, UK

WHAT IS ALREADY KNOWN ON THIS SUBJECT

- Adverse drug events are common in National Health Service (NHS) hospitals where junior doctors take responsibility for most of the prescribing.
- Safe and effective prescribing of drugs is a core competency expected of all medical graduates.
- There is a perception from some of those who supervise the prescribing of drugs in the NHS that undergraduate teaching in this area may be deficient, although this view is contested.

WHAT THIS STUDY ADDS

- Our study suggests that a large proportion of medical students and recent graduates from UK medical schools who responded also believe that their teaching and assessment in this area was inadequate.
- This result implies that those responsible for overseeing undergraduate education should urgently review teaching and assessment of competency in relation to prescribing in all UK medical schools.

Correspondence

Dr Simon Maxwell, MD, PhD, FRCP, FRCPE, Clinical Research Centre, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU, UK.

Tel: + 44 0131 242 9214

Fax: + 44 242 9125

E-mail: s.maxwell@ed.ac.uk

S.R.J.M. conceived the idea for the study. S.R.J.M. and A.H. developed the study design and survey website. A.H. took responsibility for promoting the survey to medical students and recent graduates from UK medical schools with support from D.J.W. and S.R.J.M. All authors were involved in writing and approving the final manuscript.

Keywords

drug, education, patient safety, prescribing, undergraduate

Received

30 July 2007

Accepted

1 April 2008

Published OnlineEarly

19 May 2008

AIMS

To gather opinions from UK medical students and recent graduates about their undergraduate training to prescribe and their confidence about meeting the relevant competencies identified by the General Medical Council (GMC).

METHODS

We designed a web-based survey that was distributed to UK medical students and first year Foundation doctors (graduation years 2006–2008) via medical schools and postgraduate networks.

RESULTS

Analysis was restricted to 2413 responses from students graduating in 2006–2008 from the 25 UK medical schools (mean 96.5 per school) with a complete undergraduate curriculum. Distinct courses and assessments in 'clinical pharmacology & therapeutics (or equivalent)' were identified by 17% and 13%, respectively, with mode of learning described most commonly as 'opportunistic learning during clinical attachments' (41%). Only 38% felt 'confident' about prescription writing and only a minority (35%) had filled in a hospital prescription chart more than three times during training. The majority (74%) felt that the amount of teaching in this area was 'too little' or 'far too little', and most tended to disagree or disagreed that their assessment 'thoroughly tested knowledge and skills' (56%). When asked if they were confident that they would be able to achieve the prescribing competencies set out by the GMC, 42% disagreed or tended to disagree, whereas only 29% agreed or tended to agree.

CONCLUSIONS

Many respondents clearly perceived a lack of learning opportunities and assessment related to the safe and effective use of drugs and had little confidence that they would meet the competencies identified by the GMC. There is an urgent need to review undergraduate training in this area.

Introduction

The ability to prescribe commonly used drugs safely and effectively is a core competency of the newly qualified doctor. New graduates are typically required to prescribe many times each day in the hospital drug chart and write the majority of hospital prescriptions. The demands of this task have increased in recent years because of several trends that include an expanding national formulary, increased number of drugs per patient (polypharmacy), higher patient throughput, older, more vulnerable patients, more complicated therapeutic regimens, greater demand from patients for information and the increased threat of litigation.

Prescribing errors are common in UK hospitals. One study from a London teaching hospital detected 135 errors each week, one-quarter of which were potentially serious, with most made by junior or senior house officers [1]. The National Patient Safety Agency database receives >50 000 reports annually of medication incidents from acute and general hospitals [2]. An Audit Commission report has suggested that adverse medication events were responsible for the death of 1100 hospital patients in 2001 in the UK, a fivefold increase over the previous 10 years [3]. There is evidence that inadequate training is often a contributory factor in such events [4, 5]. An analysis of 88 serious medication errors in a UK hospital has suggested that deficits in 'skills and knowledge' were a factor in 60% of cases [4]. Several studies have suggested that the delivery of targeted education can improve prescribing performance and reduce prescription errors [6–9].

Not surprisingly, the General Medical Council (GMC), which regulates undergraduate medical education, has identified knowledge and skills competencies in relation to the use of drugs that are required of all UK medical students at the point of graduation (Table 1) [10]. However, there have been widespread concerns that these objectives are not being met, partly because of recent changes in the medical curriculum that reduce the emphasis on traditional scientific disciplines such as pharmacology and clinical pharmacology and therapeutics (CPT) [11–13]. This viewpoint has been expressed most commonly by those who might be perceived to have a conflict of interest, and has been contested by the GMC [14, 15].

Medical students have a particular interest in this debate, although their views have rarely been heard, except for anecdotal comment by individuals [16] or small studies relating to individual medical schools [17, 18]. The purpose of this study was to survey the opinions of a large cohort of medical students and recent graduates from around the UK about their undergraduate training and assessment in pharmacology and therapeutics, their acquisition of skills relevant to prescribing and their confidence about meeting the outcomes identified by the GMC.

Methods

The study was conducted across all UK Medical Schools and National Health Service trusts. An online questionnaire was designed to ask specific questions regarding undergraduate experience with respect to 'basic pharmacology' (defined as 'what drugs are and how drugs work') and 'clinical pharmacology & therapeutics' (defined as 'using drugs in the clinical setting including prescribing') (Table 2). In addition, the survey asked questions concerning: the style of medical course; whether there were identifiable teachers who coordinated learning; confidence in relevant drug-related skills; experience in writing prescriptions; availability of e-learning resources; evaluation of teaching and assessment in this area; and opinions as to whether this had allowed or was likely to allow them to meet the competencies outlined by the GMC (Table 1). Explanations to questions were provided where appropriate, with opportunity for free text comments. All questions required a response for a successful form submission. Form results were stored within the online website (<http://fs12.formsite.com>) and downloaded in Excel format.

The questionnaire website was highlighted initially within articles in the *BMA News* [19], the *Student BMJ* and the *BMJ* [13]. The survey URL was brought to the attention of students due to graduate in 2007 and 2008 at all medical schools in the UK by e-mails forwarded through student organizations or by highlighting on electronic notice boards. Deaneries and Postgraduate Medical Education Managers enabled the distribution of the survey (through either e-mail, newsletter or notice board posting) to recent

Table 1

Learning outcomes of undergraduate medical education identified by the General Medical Council in *Tomorrow's Doctors* (2003)

Graduates must know and understand the principles of treatment including:

- 'know . . . how errors can happen . . . and principles of managing risks' (item 4)
- 'know and understand principles of treatment . . . and . . . evaluate effectiveness against evidence . . . the effective and safe use of medicines as a basis for prescribing, including side effects, harmful interactions' (item 16)
- 'work out drug dosage . . . write safe prescriptions . . . give IV, IM and SC injections . . . administer oxygen therapy and use a nebuliser correctly' (item 19)
- 'provide enough information . . . to allow patients to make informed decisions' (item 30)

Table 2

The study questionnaire

About your medical course I attend(ed) the following Medical School I will be graduating/I graduated in the year The following word(s) describe(s) the style of my medical course (please tick any that apply) Traditional/Integrated/Problem based/Graduate entry/Other, please explain
About your early learning of basic pharmacology (i.e. what drugs are and how drugs work) With regards to early learning in 'basic pharmacology', the following option best describes my course (please circle one option) A distinct course in 'basic pharmacology' (or equivalent)/Learning as part of a 'basic sciences' course (or equivalent)/Integrated learning within a systems based modules (e.g. cardiovascular/respiratory)/Mainly self-directed learning through PBL case discussions/No identifiable early learning in basic pharmacology With regards to 'basic pharmacology', the following option best describes my course assessment (please circle one option) A specific assessment in basic pharmacology (or equivalent)/Forms part of a basic sciences (or equivalent) assessment/Forms part of a broader assessment with other aspects of the course/No identifiable assessment in basic pharmacology
About your later learning of clinical pharmacology & therapeutics (i.e. using drugs in the clinical setting including prescribing) With regards to learning in 'Clinical Pharmacology & Therapeutics' during the later years, the following option best describes my course (please circle one option) Learning mainly by a distinct course(s) in pharmacology & therapeutics (or equivalent)/Mainly integrated learning within systems-based modules/Mainly self directed learning through PBL casework/discussions/Mainly opportunistic learning during clinical attachments With regards to 'Clinical Pharmacology & Therapeutics', the following option best describes my course assessment (please circle one option) A specific assessment(s) in clinical pharmacology & therapeutics/Part of a broader integrated assessment of clinical components of the course I feel confident in the following skills (please tick those that apply to you) Drug history taking/Prescription writing/Drug dosage calculation/Preparing and administering drugs/Accessing high quality information about medicines The number of times I filled in a hospital prescription kardex during my training (so far) is (please circle one option) 0/1-3/4-6/7-9/10+
About your learning and teaching resources Is there a readily identifiable individual teacher(s) who co-ordinates(ed) the Pharmacology, Therapeutics & Prescribing aspects of the course? Yes/No Which of the following group(s) have played a major role in teaching you about drugs and medicines that you will prescribe? (please tick any that apply) Clinicians/General Practitioners/Nurses/Basic Pharmacologists/Clinical Pharmacologists/Pharmacists Is (Was) there a local 'student formulary' that helps to focus learning around a limited group of specified drugs? (please circle) Yes/No Are (Were) there any significant e-learning resources available to reinforce learning in this area? (please circle) Yes/No
Your views on your training so far I feel that the amount of teaching in Pharmacology, Therapeutics & Prescribing during my course is (was) (please tick one option) Far too much/Too much/Just about right/Too little/Far too little I feel that assessments in 'Pharmacology, Therapeutics & Prescribing' during my course thoroughly tested my knowledge and skills in this area (please circle one option) Agree/Tend to Agree/Neutral/Tend to Disagree/Disagree I rate the overall teaching of 'Pharmacology, Therapeutics & Prescribing' during my course to be (please circle one option) Very Good/Good/Average/Poor/Very poor I feel confident that my training will enable me to achieve the prescribing competencies set out by the GMC (please circle one option) Agree/Tend to Agree/Neutral/Tend to Disagree/Disagree
For any other comments please use the space below

graduates from 2006 (current Foundation year 1). Responses were submitted anonymously. From a total of 32 medical schools in the UK, two did not yet have final year clinical students, three managed purely preclinical aspects of the course, and two were partnered with other institutions. The final analysis was restricted to 25 institutions, each randomly allocated a number 1 to 25. The χ^2 test for independence was used to detect statistically significant relations between two categorical variables. All statistical analysis was performed at the 95% significant level. Microsoft Excel Analyse-It package was used to complete all statistical analysis.

Results

A total of 2783 responses were received between 3 August 2006 and 20 February 2007, of which 2413 met the eligibility criteria (the 25 medical schools above, graduation years 2006–2008). The mean number of responses per medical school was 96.5 (range 5–170), and all but two schools provided at least 50 responses. The number of responses (%) from each graduation year from 2006 to 2008 was 453 (18.8), 991 (41.1) and 969 (40.1), respectively. Respondents identified the style of their course as 'integrated' (39%), 'traditional' (19%), 'problem-based' (19%) and

'graduate-entry' (5%), with 17% using a combination of descriptors.

Learning and Assessment in 'Basic Pharmacology' and 'Clinical Pharmacology & Therapeutics'

Respondents identified a variety of styles of learning (Figure 1). Although 25% had a distinct course, the majority (51.2%) learnt 'basic pharmacology' as part of a course in basic sciences or by integrated system-based learning. The majority of respondents reported that 'basic pharmacology' was assessed as part of a broader course assessment, with 19% describing 'a specific assessment' and 11% 'no identifiable assessment'. The learning pattern in CPT was described most commonly as 'opportunistic learning during clinical attachments' (41%), as well as being 'integrated within systems-based modules' (30%), as a 'distinct course' (16.8%), and as 'self-directed learning through problem-based learning (PBL) casework/discussions' (12%). Only 13% of respondents identified a specific assessment in 'CPT (or equivalent)', with the majority stating that this area was included within a 'broader integrated assessment'.

Figure 1

Learning style for 'basic pharmacology' (a) and 'clinical pharmacology & therapeutics' (b)

'I feel confident in the following skills'

When asked to identify which drug-related skills the respondents could approach with confidence, 94% identified drug history taking. Rather smaller proportions felt confident about accessing high-quality information about medicines (55%), prescription writing (38%), drug dosage calculation (24%), and preparing and administering drugs (15%). When asked how many times they had 'filled in a hospital prescription kardex during training', 90% and 60% of 2008 and 2007 graduates, respectively, reported having undertaken this task three or fewer times. The proportion for those who had already graduated was 23%, with 7% of this group reporting never having done so prior to qualifying.

Learning resources

Overall 56% respondents were able to identify an individual teacher who coordinates this area of the course, although the proportion varied greatly between medical schools. When asked to identify professional group(s) that played a major role in teaching about drugs and medicines, the following groups were identified: clinicians (89%), general practitioners (43%), nurses (10%), basic pharmacologists (21%), clinical pharmacologists (37%) and pharmacists (27%). A number of schools have introduced a limited list of drugs or a 'student formulary' to help to prioritize learning and avoid factual burden [20], but this was identified by only 29% of respondents. Significant e-learning resources to reinforce learning were available to 35% of respondents.

Overall views about training

When asked about the amount of teaching in pharmacology, therapeutics and prescribing during their course, the majority of respondents from all graduation years felt it was 'too little' or 'far too little' (Figure 2). When asked whether the assessments in this area 'thoroughly tested knowledge and skills', 56% responded 'disagree' or 'tend to

Figure 2

Responses to the statement 'I feel that the amount of teaching in Pharmacology, Therapeutics & Prescribing during my course is (was) ...' by year of graduation (Far Too Much, (■); Too Much, (▦); Just About Right, (▥); Too Little, (▤); Far Too Little, (□))

disagree', with a further 25% neutral (Figure 3). In response to the final statement 'I feel confident that my training will enable me to achieve the prescribing competencies set out by the GMC', 42% of students who responded to the survey disagreed or tended to disagree, whereas only 29%

Figure 3

Responses to the statement 'I feel that my assessment(s) in pharmacology, therapeutics and prescribing thoroughly tested my knowledge and skills in this area' (Agree, (■); Tend to Agree, (■); Neutral, (■); Tend to Disagree, (■); Disagree, (■))

tended to agree or agreed (Figure 4a). The likelihood of agreeing or tending to agree rather than any other view was associated with having already graduated (36% vs. 27%, $P < 0.001$), the presence rather than absence of an identifiable course coordinator (37% vs. 17%, $P < 0.001$), learning in CPT based on a distinct course rather than opportunistic learning (47% vs. 17%, $P < 0.001$), the presence rather than absence of a distinct assessment in CPT (46% vs. 26%, $P < 0.001$), agreement rather than disagreement that CPT had been assessed thoroughly (66% vs. 14%, $P < 0.001$), and sole identification of the style of course as 'traditional' rather than 'PBL' (34% vs. 19%, $P < 0.001$). There was also marked variation between medical schools (Figure 4b).

Discussion

The main findings of this study are that (i) a minority of respondents receive distinct courses and assessments in either basic pharmacology or clinical pharmacology, (ii)

Figure 4

Responses to the statement 'I feel confident that my training will enable me to achieve the prescribing competencies set out by the GMC' by year of graduation (a) and by medical school (b)

few felt confident about key skills such as prescribing and calculating drug doses, (iii) prescribing was very rarely practised prior to graduation, (iv) less than one-third of respondents felt that they had met or were likely to meet the standard expected of them in relation to the use of medicines at the point of graduation, and (v) there were marked variations in the responses of students from different medical schools.

There has been a widespread perception that doctors are not as well prepared for prescribing at the outset of their careers as they should be and that this may contribute to prescribing errors and compromise patient safety [4, 21, 22]. Others have countered that there is no firm evidence of underpreparation for prescribing [15] and, indeed, the GMC regularly inspects the quality of education in all UK medical schools. There are two major problems in providing clarity on this issue. First, since few schools now have a distinct assessment in this area of competence, it is difficult to assert with confidence what level of competence is being achieved. Indeed, the majority of respondents in this study felt they had not been thoroughly assessed in this area of study. Second, the required competencies are stated only in very general terms (Table 1), making it difficult to design exit assessments that unequivocally demonstrate the required outcomes. For these reasons, indisputable evidence to resolve this issue is unlikely to emerge in the near future, even though signals of a significant problem persist [23].

Although the importance of official inspections of curricula and associated assessments cannot be diminished, the views of medical students about their training are also relevant. Our study is by far the largest to explore this specific aspect of the curriculum in detail, and the results are consistent with those of smaller local surveys of opinion [17, 18]. The results describe the prevalence of an integrated style of learning and assessment in an area that was traditionally delivered as a specific discipline within the curriculum. Whatever the pattern of learning, Figure 2 shows that a large majority believes that the overall amount is insufficient. Respondents showed a general lack of confidence about prescribing, a skill that they would be expected to undertake regularly from day one of their career. Although a degree of caution on this point is understandable, this feeling is perhaps not surprising given that many respondents reported having little practice. Figure 4 shows that overall self-rated attainment of competency varied between students of different schools, as previously noted in relation to other core skills [24].

It is clear that learning about drugs poses considerable challenges for students and teachers, but it has previously been suggested that, in any curriculum style, this might happen more effectively with clear leadership, focusing learning around a limited list of commonly used drugs, and with the support of e-learning resources [20, 25]. Only a minority of respondents reported that they had these facilities available.

Our study has a number of methodological limitations, so the results have to be interpreted with some caution. First, it was publicised at a time when there had been adverse comments made about prescribing education in the medical and lay media. Second, the respondents represent only a small proportion of graduates for the years 2006–2008 and cannot necessarily be extrapolated to represent the views of the whole cohort. It is possible that our respondents may have been biased towards those who are generally malcontent or concerned about their educational needs. This might have been clarified by seeking opinions on a 'control' area of undergraduate education. Nevertheless, the findings in relation to prescribing are similar to those of smaller studies [17, 18]. Third, those graduating in 2007 and 2008 had not completed their course and had to base their responses to some of the questions on 70–90% of their complete undergraduate experience. However, most students would be aware of the total content of their studies by this stage. Although there was greater confidence about having met the GMC criteria amongst those who had graduated, this belief was expressed by only one-third of that group. Fourth, it relies entirely on self-rated confidence rather than objective demonstration of knowledge and skills. Finally, since this was an uncontrolled web-based survey, we cannot rule out the fact that some respondents may have been motivated to enter multiple responses.

In conclusion, this is the largest survey so far undertaken of UK medical student opinion concerning preparation for prescribing drugs. In spite of its obvious limitations, our study has shown that, at the very least, a substantial minority of students believe that they are not being adequately prepared for prescribing when they begin their medical careers. We think that the following actions are now required: (i) the requirements in terms of knowledge, attitudes and skills with respect to drugs should be clarified in detail by the GMC as a matter of urgency; (ii) once this task is completed, all medical schools should be required to have robust assessment structures to ensure these outcomes have been met; and (iii) there should be a coordinated effort undertaken by UK medical schools to share best practice and learning materials in this area.

Competing interests

S.R.J.M. and D.J.W. are clinical pharmacologists and members of the British Pharmacological Society.

Postscript

In response to concerns that had been expressed about education for safe prescribing the GMC convened a meeting in January 2007 at which preliminary data from this study, as well as data and opinions from other relevant stakeholders, were presented.

This meeting concluded by setting up a Safe Prescribing Working Group under the auspices of the Medical Schools Council and GMC, which also included representation from the National Health Service, Postgraduate Deans, National Patient Safety Agency, National Prescribing Centre and British Pharmacological Society. A major outcome was an agreed statement of the knowledge and competencies in relation to prescribing that might be expected of a newly qualified doctor in the UK. This statement, as well as a report of the other activities of the Safe Prescribing Working Group can be accessed at <http://www.chms.ac.uk/documents/finalreport.doc>.

REFERENCES

- 1 Dean B, Schachter M, Vincent C, Barber N. Prescribing errors in hospital inpatients: their incidence and clinical significance. *Qual Saf Health Care* 2002; 11: 340–4.
- 2 National Patient Safety Agency. Quarterly National Reporting and Learning System data summary: Winter 2006/07. Available at <http://www.npsa.nhs.uk/health/resources/NRLSdata> (last accessed: 2 March 2007).
- 3 The Audit Commission. A Spoonful of Sugar: Medicines Management in NHS Hospitals. London: The Audit Commission, 2001.
- 4 Dean B, Schachter M, Vincent C, Barber N. Causes of prescribing errors in hospital inpatients: a prospective study. *Lancet* 2002; 359: 1373–8.
- 5 Leape LL, Bates DW, Cullen DJ, Cooper J, Demonaco HJ, Gallivan T, Hallisey R, Ives J, Laird N, Laffel G. Systems analysis of adverse drug events. ADE Prevention Study Group. *JAMA* 1995; 274: 35–43.
- 6 Scobie SD, Lawson M, Cavell G, Taylor K, Jackson SHD, Roberts TE. Meeting the challenge of prescribing and administering medicines safely: structured teaching and assessment for final year medical students. *Med Educ* 2003; 37: 434–7.
- 7 Garbutt JM, DeFer TM, Highstein G, McNaughton C, Milligan P, Fraser VF. Safe prescribing: an educational intervention for medical students. *Teach Learn Med* 2006; 18: 244–50.
- 8 Langford N, Martin U, Kendall M, Ferner R. Medical errors. Medical schools can teach safe drug prescribing and administration. *BMJ* 2001; 322: 1424.
- 9 Vollebregt JA, Metz JC, de Haan M, Richir MC, Hugtenburg JG, De Vries TP. Curriculum development in pharmacotherapy: testing the ability of preclinical medical students to learn therapeutic problem solving in a randomized controlled trial. *Br J Clin Pharmacol* 2006; 61: 345–51.
- 10 General Medical Council. Tomorrow's doctors: recommendations on undergraduate medical education. London: GMC, February 2003.
- 11 Maxwell S, Walley T, Ferner RE. Using drugs safely. *BMJ* 2002; 324: 930–1.
- 12 Rawlins MD. Making tomorrow's doctors better prescribers. *Br J Clin Pharmacol* 2003; 55: 495.
- 13 Aronson JK, Henderson G, Webb DJ, Rawlins MD. A prescription for better prescribing. *BMJ* 2006; 333: 459–60.
- 14 Rubin P. A prescription for better prescribing: medical education is a continuum. *BMJ* 2006; 333: 601.
- 15 Kmietowicz Z. GMC to gather data on prescribing errors after criticism. *BMJ* 2007; 334: 278–9.
- 16 Ellis A. Prescribing rights: are medical students prepared for them? *BMJ* 2002; 324: 1591.
- 17 Han WH, Maxwell SR. Are medical students adequately trained to prescribe at the point of graduation? Views of first year foundation doctors. *Scott Med J* 2006; 51: 27–32.
- 18 Tobaiqy M, McLay JS, Ross S. Foundation year 1 doctors and clinical pharmacology and therapeutics teaching. A retrospective view in light of experience. *Br J Clin Pharmacol* 2007; 64: 363–72.
- 19 BMA News. Students get their chance to rate their skills in prescribing. 12 August 2006. Available at <http://web.bma.org.uk/nrezine.nsf/wd/GSCT-6VMTBU?OpenDocument&Login&C=12+August+2006> (last accessed: 24 April 2008).
- 20 Maxwell SRJ, Walley T. Teaching prescribing and therapeutics. *Br J Clin Pharmacol* 2003; 55: 496–503.
- 21 Audit Scotland. A Scottish Prescription: Managing the Use of Medicines in Hospitals. Edinburgh: The Scottish Executive, 2005. Available at http://www.audit-scotland.gov.uk/docs/health/2005/nr_050728_managing_medicines_pr.pdf (last accessed: 24 April 2008).
- 22 BMA Science and Education Department. Evidence-Based Prescribing. London: BMA, May, 2007. Available at <http://www.bma.org.uk/ap.nsf/content/evidencebasedprescribing> (last accessed: 24 April 2008).
- 23 South Tees Hospitals NHS Trust. Report from the meeting of the clinical governance committee held on Wednesday 25 October 2006. Available at <http://www.southtees.nhs.uk/trustboardpapers/2006-07/Dec%202006/121700.doc> (last accessed: 24 April 2008).
- 24 Goldacre MJ, Lambert T, Evans J, Turner G. Preregistration house officers' views on whether their experience at medical school prepared them well for their jobs: national questionnaire survey. *BMJ* 2003; 326: 1011–2.
- 25 Maxwell SRJ, McQueen DS, Ellaway R. eDrug: a dynamic interactive electronic drug formulary for medical students. *Br J Clin Pharmacol* 2006; 62: 673–81.