Response from GlaxoSmithKline: Dr Healy responds to concerns raised by Markowitz (2001) about the potential for misinterpretation of the Donovan *et al* (2000) study. Markowitz points out that the patient populations receiving SSRIs and tricyclic antidepressants were not similar, and accordingly that comparisons of the effects of the two classes of antidepressants on suicide risk are not meaningful. Dr Healy suggests that there are data in the public domain bearing on this issue, citing the meta-analysis performed by Khan *et al* (2000) and data obtained from the US Food and Drug Administration. Khan *et al* found no difference in suicide or suicide attempts with the use of antidepressants compared with placebo. Dr Healy claims that suicides and suicide attempts during 'washout rather than while on placebo' invalidate the results of Dr Khan *et al*'s analysis.

With respect to paroxetine, Dr Healy misstates the scope of the Khan *et al* meta-analysis, and the conclusions he draws lack scientific substantiation. Dr Healy fails to recognise that the exposure time of patients on paroxetine in the clinical studies was substantially different and far greater than that on placebo – under these circumstances an analysis of absolute numbers of patients with no consideration of time of exposure is not meaningful. Furthermore, contrary to Dr Healy's implication, the Khan *et al* report was not limited to randomised, placebo-controlled studies. In the case of paroxetine, the studies covered included open label extensions, studies without placebo arms, and studies that were not randomised. When one considers only the randomised, controlled portions of the placebo-controlled trials (excluding events occurring during placebo run-in) included in the Khan *et al* analysis, there are no statistically significant differences in suicides or suicide attempts between paroxetine and placebo, either in absolute numbers of patients or when adjusted for time of exposure.

Donovan *et al* caution about the conclusions that should be drawn from the study. They point out that physicians are following guidance to prescribe antidepressants that are purportedly 'safer in overdose' to patients who are perceived to be at greater risk of deliberate self-harm. Consistent with Dr Markowitz's comments, this prejudices against SSRIs when associations are made between their use and deliberate self-harm. Donovan *et al* also note that it is problematic attributing the cause of deliberate self-harm to antidepressant treatment when such behaviour occurs as a symptom of depressive illness itself and that establishment of cause and effect is 'almost impossible'.

The 'drug *v.* "true placebo" ' analysis Dr Healy describes is not only scientifically invalid, but also misleading. Major depressive disorder is a potentially very serious illness associated with substantial morbidity, mortality, suicidal ideation, suicide attempts and completed suicide. Unwarranted conclusions about the use and risk of antidepressants, including paroxetine, do a disservice to patients and physicians.

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Is it ethical to use a placebo?

Michelson *et al* (2001) evaluated the efficacy of fluoxetine in panic disorder and reported that fluoxetine was associated with a significantly greater proportion of panic-free patients compared with placebo. We read this double-blind randomised study with interest and wish to raise some concerns about the use of a placebo arm.

The use of placebo arms in randomised controlled trials remains a controversial issue and has been criticised on ethical grounds. In this context, the Declaration of Helsinki demands that individual patients in a study 'be assured of the best proven diagnostic and therapeutic method' even in the control group (Rothman & Michels, 1994). This statement clearly discards the use of a placebo as control when a 'proven' treatment exists. The declaration also directs that a study that violates its precepts should not be accepted for publication.

In addition to this, a trial that aims to establish whether a treatment is better than placebo may be trying to answer the wrong question. After all, even if a new treatment is worse than an existing one, it may still be 'effective' in that it is better than no treatment (placebo). In this regard, Hill (1963) pointed out that the essential medical question at issue is how the new treatment compares with the old one, not whether the new treatment is better than nothing.

As there are many drugs with proven efficacy in panic disorder (i.e. benzodiazepines, tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, reversible inhibitors of monoamine oxidase A and buspirone), we are keen to know why the authors did not try to compare the efficacy of fluoxetine with existing drugs. It appears that they are keen to reflect a drug-specific effect rather than demonstrating the relative efficacy. In this context Cochrane (1989) stated that no new treatments should be introduced into medicine unless they have been shown, in randomised controlled trials, to be superior to existing treatments or equivalent to existing treatments but cheaper or safer.

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Author's reply: Drs Campbell and Jainer touch on an area of controversy in the design and conduct of psychiatric drug efficacy studies, arguing that the Declaration of Helsinki 'clearly discards the use of placebo . . . when a "proven" treatment exists'. We disagree with their interpretation of the Declaration on several grounds, and note the broad support for careful use of placebo in psychiatric trials (Temple & Ellenberg, 2000) (including the support of the multiple independent ethical review boards that approved the protocol for our study). There are abundant data that non-specific interventions can have marked beneficial effects, albeit on average less than active drugs. Non-drug therapies are

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often offered to patients as an alternative to drug therapies, and the absence of risk related to adverse drug effects can offset the potential for lesser efficacy. In our trial, both treatment groups had marked improvement from baseline. In this regard, placebo is not 'no treatment'.

Drs Campbell and Jainer suggest drawing conclusions about drug efficacy based solely on comparisons of active agents. Unfortunately, in many trials a drug previously shown to be active is not superior to placebo despite adequate powering and the use of standard trial designs. Such trials are often referred to as 'failed' and in anxiety and depression are extremely common. A comparison of a new agent against a drug previously shown to be active without a placebo comparator is uninterpretable unless one agent is superior to the other. Concluding that a drug is efficacious without a placebo comparison can lead to an incorrect assumption of drug-specific effects if neither the investigational drug nor the active drug was, in that trial, any better than placebo would have been if included. Introducing a drug into therapeutic use on the basis of such a trial would expose patients to a compound with no greater benefit than placebo but all the risks of a pharmacological intervention (Temple & Ellenberg, 2000). Placebo is also critical in the assessment of safety, as it provides a base rate for determining which adverse events are truly related to the investigational drug. For these reasons, placebo-controlled trials are almost universally demanded by regulatory bodies to demonstrate efficacy for new pharmacological interventions.

Drs Campbell and Jainer also assert 'no new treatments should be introduced into medicine unless they have been shown . . . to be superior to existing treatments . . . [or] cheaper and safer'. This absolute statement reflects several misconceptions and confounds the investigation of a drug with its introduction into general use. There is no general agreement about how to define or demonstrate equivalent or relative efficacy – precisely the reasons why most regulatory bodies will not consider relative efficacy claims in labelling. Furthermore, clinical trials provide information about group responses. Individual patients may not respond to or tolerate a particular drug, yet benefit from a different drug that is not, on average, more efficacious or safer than the first agent – it is in patients' interest to have several choices. For example, using Campbell and Jainer's procedure, the selective serotonin reuptake inhibitors, now proven to be safer and better tolerated than tricyclic antidepressants, might well not have been introduced into practice.

Finally, price is not an issue of trial design or science, but determined by the value that patients and purchasers put on a drug, based on evidence about the drug and experience with it (effectiveness as well as efficacy). Whether new drugs for panic or other psychiatric disorders should be 'introduced into medicine' and how they should be priced are decisions made on the basis of assessments of data about safety, efficacy and potential place in the therapeutic armementarium – decisions that cannot be made before the data are collected. Campbell and Jainer may feel that the results of this trial do not warrant further investigation of the use of fluoxetine for panic disorder, although we would disagree. It is, however, wrong to suggest that the trial as designed should not have been performed or published.

Declaration of interest

D.M. is an employee of Eli Lilly and Co.

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User-led research and evidence in psychiatry

The editorial by Faulkner & Thomas (2002) raises serious issues, as did another recent paper (Bracken & Thomas, 2001: see van Beinum, 2001). They present a false dichotomy between (morally good) 'users' and (morally irresponsible) researchers, from which flows an unwarranted assumption that somehow psychiatric research rarely has the interests of patients at heart. Their editorial, with its unsubstantiated statements, poor definitions, political banner-waving and lack of understanding of both science and the research process, is the antithesis of considered and evidence-based argument.

There is, however, no doubt that patients and their families should have a substantial voice in helping to set the questions that research attempts to answer, and in establishing mechanisms for ensuring the importance of this process. This does not mean, however, that being a 'user' somehow qualifies a person as a top-notch research scientist. Thus, for example, the user-led research quoted by the authors (Faulkner, 2000) was deeply flawed, in that it did not address the issue of researcher bias and some of the conclusions bore no relation to the evidence presented. User groups have their own political agendas and are not representative of the body of patients as a whole.

There is a difference between asking socially relevant questions and conducting sound research. Good research is difficult to do and is best done by teams of well-trained research scientists. Arguing, as Faulkner and Thomas do, that psychiatrists and funding bodies should give equal weight to research conducted by groups of users and by professional researchers is a travesty. We do patients (and ourselves, for many of us have been, or will become, users) no favours by confounding good research with political correctness, for there is nothing more unethical or wasteful than poor research on vulnerable patients.

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Authors' reply: We are grateful to Dr van Beinum for drawing our attention to the weaknesses of our editorial. In particular, it is good that he has highlighted the issues of researcher bias and the reprehensible wastefulness of 'poor research on vulnerable patients'. Presumably, he assumes that professional research, undertaken by 'teams of well-trained research scientists', is of high quality and free of bias. Is this so? Let us consider by way of example the drug treatment of schizophrenia. Thornley & Adams (1998) examined the quality of 2000 controlled trials for treatment for schizophrenia from the Cochrane Schizophrenia Group's register. They concluded

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