

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.

Donovan, S., Clayton, A., Beeharry, M., et al (2000) Deliberate self-harm and antidepressant drugs. Investigation of a possible link. *British Journal of Psychiatry*, **177**, 551–556.

Khan, A., Warner, H. A. & Brown, W. A. (2000) Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials. *Archives of General Psychiatry*, **57**, 311–317.

Markowitz, J. C. (2001) Antidepressants and suicide risk. *British Journal of Psychiatry*, **178**, 477.

F. Rockhold, A. Metz, P. Traber

GlaxoSmithKline, PO Box 13398, Five Moore Drive, Research Triangle Park, NC 27709-3398, USA

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.

Cochrane, A. (1989) Effectiveness and efficacy: random reflections on health services. *BMJ*, **10**, 428–433.

Hill, A. B. (1963) Medical ethics and controlled trials. *BMJ*, **i**, 1043–1049.

Michelson, D., Allgulander, C., Dantendorfer, K., et al (2001) Efficacy of usual antidepressant dosing regimens of fluoxetine in panic disorder. Randomised, placebo-controlled trial. *British Journal of Psychiatry*, **179**, 514–518.

Rothman, K. J. & Michels, K. B. (1994) The continuing unethical use of placebo controls. *New England Journal of Medicine*, **331**, 394–398.

C. Campbell, A. K. Jainer St Michael's Hospital, South Warwickshire Combined Care NHS Trust, St Michael's Road, Warwickshire CV34 5QW, UK

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