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Editor: Ian Pullen

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The ethics of prophylactic trials of depression

SIR: For over twenty years psychiatrists have been aware of the importance of continuation therapy with antidepressive agents for prevention of relapse of unipolar depressive illness. Over a dozen studies of continuation therapy have shown a significant advantage for antidepressants over placebo. Montgomery *et al* (1988), dissatisfied with poor definition of relapse versus recurrence, have now reported a multicentre prophylactic study which seems better controlled and executed than any other to date. They have shown that patients who had been recovering for four months from major unipolar illness had a lower relapse rate (20%) continuing for a year on fluoxetine than a control group (54%) maintained for the same period on placebo. Fluoxetine, a relatively new drug, is the only one studied in this way so far. However, even before Dr Montgomery *et al*'s work it was apparent from the literature that the risk of relapse in the first year after recovery amounted to about 50% of placebo users and 20% in those who seemed to have kept up their medication. The serious implications of relapse for the lives of patients are apparent. Despite this knowledge, depression is notoriously badly managed in medical and, possibly, in psychiatric practice. This may be because many patients will not follow good advice or (perish the thought) because good advice is not given.

From Dr Montgomery *et al*'s own review of literature it would appear that no well-controlled study of prophylaxis or continuation has failed to show superiority of drug over placebo, irrespective of the type of antidepressant studied. It follows that subjects recruited into prophylactic trials of the Montgomery type (difficult and lengthy undertakings) should be advised that they are being asked to accept a very high risk of depressive morbidity if they consent to participate. The extent of this risk is difficult to estimate since no published accounts are available on the outcome of placebo relapsed depressives with renewed treatment. Furthermore, the fate of drop-outs is seldom fully reported in follow-up studies. It is noteworthy that the exact wording of 'informed consent' forms is seldom reproduced in the text of published papers. This poses the question of whether subjects of trials such as that of Dr Montgomery *et al* really understand the extent of risk that they are being asked to undergo.

Is the distinction between relapse of the original episode and true recurrence after recovery (insisted upon by Dr Montgomery *et al*) of sufficient importance to justify one year placebo-controlled trials? To the patients, the distinction may appear as mere academic hair-splitting. We already know that these illnesses get worse, not better, over time and that relapse rates rise throughout life. Every psychiatrist should reflect on whether he/she would encourage his/her close relatives to be enrolled in prophylactic studies of the type described. It is conceivable that many will think (as I do) that the price to be paid for more prophylactic trials of classic, placebo-controlled design is unacceptable.

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Reference

MONTGOMERY, S. A., DUFOUR, H., BRION, S., *et al* (1988) The prophylactic efficacy of fluoxetine in unipolar depression. *British Journal of Psychiatry*, **153** (suppl. 3), 69–76.

SIR: There is consistent support from many placebo-controlled studies that in the period following recovery on an antidepressant, further treatment is needed