Correspondence

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Dicontinuation rates of SSRIs and tricyclic antidepressants

Sir: Hotopf *et al* (1997) present a systematic review of the discontinuation rates in randomised controlled trials of selective serotonin reuptake inhibitors (SSRIs) versus tricyclic (TCAs) and heterocyclic antidepressants. Their main conclusion was the same as ours, that, overall, discontinuation rates are a little lower on SSRIs compared with TCAs as a group (Anderson & Tomenson, 1995). They go on to suggest that the poorer tolerability may be accounted for by studies using old TCAs (amitriptyline and imipramine), whereas newer tricyclics have equal tolerability to SSRIs. However, this distinction, and the interpretation of their results, is fraught with difficulties.

First, there is no pharmacological justification for the separation into 'old' and 'newer' TCAs. Examination of receptor binding affinity for individual drugs (presumed to relate to propensity to cause side-effects) shows no good reason to divide them in the way Hotopf *et al* have done (Richelson, 1996); the division may have been 'proposed in advance' but is no less arbitrary for that. Second, in interpreting the results the authors make the fundamental mistake of equating 'no evidence of difference' with 'evidence of no difference' (Oxman, 1994). The results for old TCAs compared with SSRIs do reach statistical significance but those for newer TCAs, with a smaller number of studies and wider confidence intervals, do not. This does not mean that old TCAs are different to SSRIs whereas newer TCAs are not. The odds and risk ratios for old and newer TCA groups differ very little and are certainly not significantly different from each other. It is likely that dividing the TCAs in any way would result in statistical significance for the larger group but not for the smaller group. Therefore, it is statistical sophistry or naïvety to claim that old and newer TCAs differ in their tolerability compared with SSRIs. This is not to deny that there *may* be a difference, but it is not shown by these results and is likely to be extremely small. Third, the authors investigate sources of heterogeneity as a possible indicator of differences between groups of drugs. The overall result does demonstrate statistical heterogeneity. If this is due to differences between the antidepressant groups, then exclusion of these groups should reduce the heterogeneity. In fact the heterogeneity is slightly increased by excluding newer TCAs and heterocyclics, indicating that there must be some other explanation. While some sources of heterogeneity are examined others are not, for example dose of TCA used in the study or the study quality/size.

Therefore Hotopf *et al*'s conclusion that the difference in drop-outs between tricyclics and SSRIs may be explained by the 'old versus newer' TCA distinction is not warranted on the evidence produced. Systematic reviews and meta-analyses are helpful in clarifying the limits of our knowledge but we must be very careful not to go beyond the evidence; otherwise we play into the hands of critics of evidence-based medicine and bring the process into disrepute.

Anderson, I. M. & Tomenson, B. M. (1995) Treatment discontinuation with selective serotonin reuptake inhibitors compared to tricyclic antidepressants: a meta-analysis. *British Medical Journal*, **310**, 1433–1438.

Hotopf, M., Hardy, R. & Lewis, G. (1997) Discontinuation rates of SSRIs and tricyclic antidepressants: a meta-analysis and investigation of heterogeneity. *British Journal of Psychiatry*, **170**, 120–127.

Oxman, A. D. (1994) Checklists for review articles. *British Medical Journal*, **309**, 648–651.

Richelson, E. (1996) Synoptic effects of antidepressants. *Journal of Clinical Psychopharmacology*, **16**(suppl. 2), 1S–9S.

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Sir: We were interested to read the meta-analysis of discontinuation rates of SSRIs and tricyclic antidepressants by Hotopf *et al* (1997). Although the result of the comparison of newer tricyclic agents and SSRIs is not surprising, we were unclear about some methodological points relevant to the conclusions.

In the treatment studies of newer TCAs and SSRIs, patients discontinue treatment for various reasons such as lack of efficacy, adverse events or early treatment response. Also, there may be wider variations in the dosage ranges for some newer tricyclics and SSRIs compared with others, and in the rate of dosage escalation to achieve the *BNF* dosages. We were not clear whether these sources of heterogeneity had been addressed, or if not, whether these would have affected the conclusions reached.

A more serious problem is the method used in the trials to establish lack of efficacy and what constitutes an adverse event. Some studies use different outcome measures and different response criteria on the basis of change in score of these measures. Some studies use different methods to enquire about possible adverse events or adjust for the effects of preceding somatic and cognitive complaints at study entry. These factors may affect the comparability of such studies. Also, we would be interested to know whether there were differences in the time onset of discontinuation (i.e. 'early' or 'late') in these studies.

Another important point is the likely rate of discontinuation of antidepressants after response in the acute phase of illness, that is in the maintenance phase; as the studies referenced mostly appear to have been of short duration. If such information was available this would be of great interest, as some clinicians argue that SSRIs might be more acceptable in maintenance treatment than tricyclics, yet we are not aware of any good evidence that this holds for newer classes of tricyclic antidepressants such as lofepramine.

Hotopf, M. Hardy, R. & Lewis, G. (1997) Discontinuation rates of SSRIs and tricyclic antidepressants: a meta-analysis and investigation of heterogeneity. *British Journal of Psychiatry*, **170**, 120–127.

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Authors' reply: We thank the correspondents for their comments on our paper. Throughout the paper we emphasised that

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