Correspondence

EDITED BY TOM FAHY

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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.

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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

https://doi.org/10.1192/S0007125000147282 Published online by Cambridge University Press

crude drop-out rates from randomised controlled trials (RCTs) have their limitations as outcome measures. We have stated elsewhere (Hotopf *et al*, 1996*a*,*b*) that the important question of comparable tolerability and cost-effectiveness of SSRIs and tricyclics will not be resolved without a large primary-care-based RCT.

We deliberately did not subdivide reason for drop-out according to lack of efficacy or side-effects. This was because we believe drop-out from RCTs depends upon multiple factors and that the usual simple classification between side-effects and lack of efficacy is an over-simplification which may be especially subject to observer bias (Hotopf *et al*, 1996*a*).

We have addressed some of Lynch & Curran's points in another paper (Hotopf *et al*, 1997, in press), in which we assessed methodology of the RCTs. Dosages of tricyclics are often inadequately reported in trials: while some studies allow as wide a range of dosages of tricyclics as 75–300 mg in their protocols, approximately one-quarter did not report a mean or median dose attained. Similarly, while the point at which drop-out takes place is important, it is also frequently not reported. Lynch & Curran also mention the duration of studies as another source of heterogeneity. We believe this is less important since two-thirds of studies were of six weeks' duration.

Anderson & Mortimore flatter us by suggesting our paper may be sufficiently widely read to bring evidence-based medicine into disrepute. Their comments mainly concern our decision to classify RCTs according to the 'generation' of tricyclic used. Evidence-based medicine aims to apply research findings to practical clinical problems. The tendency of most trials to use the oldest TCAs is of limited clinical relevance (at least in primary care) as these are not very widely used. It is more relevant to compare current commonly prescribed alternatives, and this was our rationale for the subdivision. Before new (and relatively expensive) drugs such as the SSRIs are widely prescribed, a clear advantage must be demonstrated over the older medications. The absence of any evidence that the newer TCAs have lower drop-out rates than SSRIs is, therefore, important. It is possible, perhaps even likely, that the newer TCAs do have higher drop-out rates. We mentioned the lack of power and gave confidence intervals so readers could make up their own minds, so Anderson & Mortimore's comments regarding "statistical sophistry or naïvety" are unfounded.

Anderson & Mortimore's third comment appears to contradict their other points. The analysis according to type of antidepressant shows that significant heterogeneity remained for the old tricyclics, but not for the other two groups, suggesting that while other sources of heterogeneity exist in the older tricyclics, they do not for the other drugs. This seems to support our classification rather than to refute it. There will always be uncertainty regarding the investigation of heterogeneity (Thompson, 1994) and there may be more than one feasible explanation for any given meta-analysis.

Hotopf, M. H., Lewis, G. & Normand, C. (1996*a*) *The Treatment of Depression: Evaluation and Cost-Effectiveness.* London: London School of Hygiene and Tropical Medicine.

—, — & — (1996*b*) Are SSRIs a cost-effective alternative to tricyclics? *British Journal of Psychiatry*, **168**, 404–409.

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Thompson, S. G. (1994) Why sources of heterogeneity in meta-analysis should be investigated. *British Medical Journal*, **309**, 1351–1355.

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Cost-effectiveness of antidepressant treatment

Sir: We read with interest Woods & Rizzo's (1997) re-examination of Jönsson & Bebbington's (1994) model for comparing the cost-effectiveness of antidepressants. They concluded that tricyclic antidepressants (TCAs) are more cost-effective than selective serotonin reuptake inhibitors (SSRIs) as initial treatment for depression. Neither of these papers, nor the recent review in this journal by Hotopf *et al* (1996), included the costs associated with antidepressant overdose in their comparisons. We believe that while some attention has been paid to the mortality associated with TCA overdose there has been little consideration of its morbidity and the consequent costs.

In an audit of 404 cases of deliberate self-harm presenting to the accident and emergency department at Addenbrooke's Hospital, Cambridge, in the six-month period between 1 January and 30 June 1996 there were 75 cases of deliberate self-poisoning with antidepressants. There were 35 cases of deliberate self-poisoning with TCAs and 40 cases of SSRI overdose. In one case the antidepressant was not identified, one case was of deliberate self-poisoning with trazodone and in two cases an SSRI was taken with a TCA. Thirty of the 35 cases of TCA overdose were admitted to Addenbrooke's Hospital, including six who were admitted to the intensive therapy unit (ITU) and three admitted to the cardiac monitoring unit (CMU). One of these patients died in ITU. Of the subgroup of 16 cases involving newer TCAs (lofepramine and dothiepin), 13 were admitted to Addenbrooke's including two admitted to ITU and one admitted to CMU. Twenty-five of the 40 cases of SSRI overdose were admitted to Addenbrooke's and none of these was admitted to ITU or CMU.

The Addenbrooke's Hospital NHS Trust has recently costed a bed in ITU for one day at £1530 and a bed in CMU at £340. These figures represent costs approximately 15 times and three times, respectively, those of a bed on a general ward. This audit indicates that the cost of treating antidepressant overdoses is considerably greater for TCAs than for SSRIs.

Hotopf, M., Lewis, G. & Normand, C. (1996) Are SSRIs a cost-effective alternative to tricyclics? *British Journal of Psychiatry*, **168**, 404–409.

Jönsson, B. & Bebbington, P. E. (1994) What price depression? The cost of depression and cost-effectiveness of pharmacological treatment. *British Journal of Psychiatry*, **164**, 665–673.

Woods, S. W. & Rizzo, J. A. (1997) Cost-effectiveness of antidepressant treatment reassessed. *British Journal of Psychiatry*, **170**, 257–263.

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Cognitive function and fall-related fractures

Sir: Jabourian *et al* (1994) found a high prevalence of cognitive dysfunction in 120 patients admitted to a hospital exclusively because of fall-related fractures; only 12% of their sample had a normal score on the Mini-Mental State Examination (MMSE; Folstein *et al*, 1975). Based on these findings, Jabourian *et al* argued that cognitive impairments are a major risk factor for falls. It is questionable whether all patients with

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