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.

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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.

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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.

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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

neuropsychological dysfunction in this French study had cognitive impairments prior to hospital admission. Presumably, a large percentage of them developed neuropsychological dysfunction because of factors related to hospitalisation, such as depressive symptomatology, use of psychotropic medications (e.g. benzodiazepines), or sleep disturbance.

We assessed cognitive functioning with a shortened version of the MMSE (Breakhus *et al*, 1992) in 49 community-dwelling elderly people with fall-related fractures two months after a fall accident. Our sample consisted of 22 patients with ankle or wrist fractures and 27 with a broken hip. They had been admitted to a hospital, but were all discharged at time of testing. Mean (s.d.) age was 73.9 (8.5) years. In contrast with the results of Jabourian *et al* (1994), only 10 patients (20.4%) scored below the cut-off for cognitive impairments on the shortened version of the MMSE (normal value, >9). Sample differences may account for the discrepancy between the two studies (the patients in the French study were somewhat older). However, it might also be that several of the patients studied by Jabourian *et al* suffered from neuropsychological dysfunction due to factors related to hospitalisation.

From reading the letter by Jabourian *et al* (1994) one could (erroneously) get the impression that almost 90% of serious fall incidents are co-determined by cognitive dysfunction. King & Tinetti (1995) published a review of the literature on risk factors for fall injury and identified several risk factors for falls besides cognitive impairments. They made a distinction between intrinsic factors (e.g. medication use, certain chronic diseases, impairments in muscle strength, balance and gait) and extrinsic factors (e.g. poor lighting and slippery floor). According to King & Tinetti older persons are at increased risk for a serious fall when multiple intrinsic and extrinsic factors are present.

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Clozapine-induced hypersalivation

Sir: In a previous letter (Szabadi, 1996), I argued that the troublesome side-effect of increased salivation seen in patients taking clozapine was unlikely to be due to the blockade of alpha-2 adrenoceptors, as had been suggested by others (Corrigan *et al*, 1995). I concluded that "the way in which clozapine causes hypersalivation remains an enigma". Since then, a paper has come to my attention which may shed some light on the mechanism underlying clozapine-induced hypersalivation. Zorn *et al* (1994) have shown that clozapine, in a cellular preparation expressing all five subtypes (M_1–M_5) of muscarinic cholinoceptors, has a potent full agonistic effect at M_4 receptors, while having antagonistic properties at the other four subtypes. While M_3 is the predominant muscarinic receptor subtype in salivary glands (Leahy *et al*, 1997), there is evidence that M_4 receptors are also expressed in this tissue (Zorn *et al*, 1994). Therefore, it is possible that the net effect of clozapine on salivation reflects the relationship between M_3 receptor blockade, leading to a decrease in salivation, and M_4 receptor stimulation, leading to an increase in salivary output. In some patients taking clozapine, the effects of M_4 receptor stimulation may exceed those of M_3 receptor blockade, resulting in hypersalivation. Thus, clozapine-induced hypersalivation may reflect the subtype-selective agonistic effect of clozapine at M_4 muscarinic receptors (Zorn *et al*, 1994).

This mechanism may also underlie the clinical effectiveness of the antimuscarinic drug pirenzepine in relieving clozapine-induced hypersalivation (see Szabadi, 1996). Pirenzepine, apart from having the ability to block M_1 receptors, is also a potent antagonist of M_4 receptors (Caulfield, 1993).

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Clozapine, Chinese and blood

Sir: Despite the availability of clozapine and its efficacy in treatment-resistant schizophrenia, it has been difficult to persuade Chinese patients in our practice in Singapore to go on a trial of this drug. The reservation in many instances was often not due to the cost of the drug or the risk of agranulocytosis but the mandatory blood monitoring required. In a review on the experience of using clozapine in China, Potter *et al* (1989) reported that the doctors had to make "considerable effort to overcome many patients' concerns and superstitions about having blood drawn".

The traditional Chinese notion of blood differs very much from that in the West. Blood to the Chinese is an extremely precious commodity, as is summed up by the Chinese saying that "one hundred grains of rice make one drop of blood". This has led to a fear of losing even a small amount of blood – a fear that would seem disproportionate to a Western observer. Reassurance that such monitoring would not have any detrimental effect is usually met with disbelief and scepticism. In their belief in the need to make good the blood loss, many would ask for "tonics", which are a traditional Chinese treatment for anaemia. These tonics are usually in the form of extracts, wines, herbs, food containing high-quality proteins and, in a syncretism of traditional Chinese concepts with Western medicine, vitamin tablets (Koo, 1984). We find that the judicious prescription of vitamin tablets goes a long way in allaying this fear of losing too much of this precious fluid in many of our Chinese patients.

Koo, L. C. (1984) The use of food to treat and prevent diseases in Chinese culture. *Social Science and Medicine*, **187**, 55–66.

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