1994). As predicted, effect sizes for outcome ratings were significantly correlated with the percentage of patients reporting side-effects in each study. Outcome ratings became better as the number of drug-treated patients experiencing side-effects increased. This reinforces the suspicion that information leaked by side-effects may be leading to biased outcome ratings.

At the least, the data provided by Moncrieff *et al*, as well as extensive information summarised in our own publications, suggest a need for confirming blindness in published reports and acknowledgement that the true magnitude of antidepressant effectiveness is currently uncertain.

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Sir: Apologising for failing to make a silk purse out of a sow's ear does not alter the fact that such a task is impossible. Attempts at objectivity aside (i.e. "the short duration of most of these studies should be noted" (p. 230, col. 3)) Moncrieff *et al*'s (1998) conclusion that "unblinding effects may inflate the efficacy of antidepressants in trials using inert placebos" (p. 227, col. 1) is misleading.

Moncrieff *et al* attempt to assess the effect size of antidepressants in studies using an active placebo. Their meta-analysis includes nine studies, seven completed when investigators were merely learning how to conduct an effective trial of antidepressants. These studies are flawed by the design shortcomings of the 1960s. Moncrieff *et al*'s statements suggest that valid conclusions may be drawn from these studies, viz. "despite the age of most of the trials their quality was judged to be reasonable" (p. 230, col. 1) and "Methodological concerns that have only recently had widespread publicity, such as randomisation and blinding, were addressed in these studies" (p. 230, col. 3). The authors should have followed their own advice, that "the results of a meta-analysis are only as good as the trials on which it is based" (p. 230, col. 3). Virtually all of these trials violate at least one basic psychopharmcological tenet of depression: antidepressant dose is critical; and a four-week antidepressant trial duration underestimates drug efficacy. Studies demonstrating that 300 mg imipramine or its equivalent is superior to 150 mg within a patient sample, as well as others which demonstrate equal import of dose effects for monoamine oxidase inhibitors (Watt *et al*, 1972; Ravaris *et al*, 1976; Simpson *et al*, 1976; Tyrer *et al*, 1980), establish the importance of adequate dose. Further, two studies report a statistically significant improvement in the benefit of drug *v.* placebo between four and six weeks on a fixed dose (Quitkin *et al*, 1984; Donovan *et al*, 1994).

The studies included in this meta-analysis all failed to meet these criteria, thus minimising drug effect. Trials reported by Uhlenuth & Park (1963), Weintraub & Aronson (1963), Hollister *et al* (1964) and Friedman *et al* (1966) all lasted four weeks or less. Daneman (1961) and Friedman (1975) used inadequate antidepressant doses. Wilson *et al* (1963) is hopelessly flawed because six patients were included in each treatment. The Murphy *et al* (1984) study is uninterpretable since all the patients had either cognitive therapy, cognitive therapy plus active placebo, tricyclic antidepressant or tricyclic antidepressant plus cognitive therapy. Hussain (1970) is a three-paragraph letter to the *British Medical Journal* which does not give drug dose or study duration. Given these design shortcomings, that the majority of these studies showed a positive effect size, albeit weak, is miraculous.

Knocking down an antidepressant "straw man" does not communicate much about the value, or the effect size, of these drugs, nor does it establish the utility of an active placebo. If side-effects elicit bias or benefits, it is surprising that in studies of putative new agents, at least half are no more effective than inactive placebo (Dimasi, 1995).

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Sir: Moncrieff *et al* (1998) raise some important issues in their meta-analysis of

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