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.

Greenberg, R. P., Bornstein, R. F., Zborowski, M. J., et al (1994) A meta-analysis of fluoxetine outcome in the treatment of depression. *Journal of Nervous and Mental Disease*, **182**, 547–551.

__ & Fisher, S. (1989) Examining antidepressant effectiveness: Findings, ambiguities, and some vexing puzzles. In *The Limits of Biological Treatments for Psychological Distress: Comparisons with Psychotherapy and Placebo* (eds S. Fisher & R. P. Greenberg), pp. 1–37. Hillsdale, NJ: Erlbaum.

__ & __ (1997) Mood-mending medicines: probing drug, psychotherapy, and placebo solutions. In *From Placebo to Panacea: Putting Psychiatric Drugs to the Test* (eds S. Fisher & R. P. Greenberg), pp. 115–172. New York: Wiley.

Healy, D. (1998) Commentary: Meta-analysis of trials comparing antidepressants with active placebos. *British Journal of Psychiatry*, **172**, 232–234.

Moncrieff, J., Wessely, S. & Hardy, R. (1998) Meta-analysis of trials comparing antidepressants with active placebos. *British Journal of Psychiatry*, **172**, 227–231.

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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).

Daneman, E. A. (1961) Imipramine in office management of depressive reactions. *Diseases of the Nervous System*, **22**, 213–217.

Dimasi, J. A. (1995) Success rates for new drugs entering clinical testing in the United States. *Clinical Pharmacology and Therapeutics*, **58**, 1–14.

Donovan, S. J., Quitkin, F. M., Stewart, J. S., et al (1994) Duration of antidepressant trials: clinical and research implications. *Journal of Clinical Psychopharmacology*, **14**, 64–66.

Friedman, A. S. (1975) Interaction of drug therapy with marital therapy in depressive patients. *Archives of General Psychiatry*, **32**, 619–637.

__, Granick, S., Cohen, H. W., et al (1966) Imipramine (tofranil) vs. placebo in hospitalized psychotic depressives. *Journal of Psychiatric Research*, **4**, 13–36.

Hollister, L. E., Overall, J. E., Johnson, M., et al (1964) Controlled comparison of imipramine, amitriptyline and placebo in hospitalized depressed patients. *Journal of Nervous and Mental Disease*, **139**, 370–375.

Hussain, Z. (1970) Drugs in depressive illness. *British Medical Journal*, *ii*, 482.

Moncrieff, J., Wessely, S. & Hardy, R. (1998) Meta-analysis of trials comparing antidepressants with active placebos. *British Journal of Psychiatry*, **172**, 227–231.

Murphy, G. E., Simons, A. D., Wetzel, R. D., et al (1984) Cognitive therapy and pharmacotherapy. *Archives of General Psychiatry*, **41**, 33–41.

Quitkin, F. M., Rabkin, J. G., Ross, D., et al (1984) Duration of antidepressant drug treatment: What is an adequate trial? *Archives of General Psychiatry*, **41**, 238–245.

Ravaris, C. L., Nies, A., Robinson, E., et al (1976) A multiple dose controlled study of phenelzine in depression–anxiety states. *Archives of General Psychiatry*, **33**, 347–350.

Simpson, G. M., Lee, J. H., Cuculica, A., et al (1976) Two dosages of imipramine in hospitalized endogenous and neurotic depressives. *Archives of General Psychiatry*, **33**, 1093–1102.

Tyrer, P., Garnder, M., Lambourn, J., et al (1980) Clinical and pharmacokinetic factors affecting response to phenelzine. *British Journal of Psychiatry*, **136**, 359–365.

Uhlenthuth, E. H. & Park, L. C. (1963) The influence of medication (imipramine) and doctor in relieving depressed psychoneurotic outpatients. *Journal of Psychiatric Research*, **2**, 101–122.

Watt, D. C., Crammer, J. L. & Elkes, A. (1972) Metabolism, anticholinergic effects and therapeutic effects on outcome of desmethylimipramine in depressive illness. *Psychological Medicine*, **2**, 397–405.

Weintraub, W. & Aronson, H. (1963) Clinical judgement in psychopharmacological research. *Journal of Neuropsychiatry*, **5**, 65–70.

Wilson, I. C., Vernon, J. T., Guin, T., et al (1963) A controlled study of treatments of depression. *Journal of Neuropsychiatry*, **4**, 331–337.

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

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antidepressants against active placebos but their conclusions go beyond the data, an issue I have discussed elsewhere (Anderson, 1997). They are right to be concerned about the reality of blindness in randomised controlled trials but interpretation of their results is very much a matter of opinion, particularly as there are methodological limitations in terms of the number and quality of studies they were able to analyse. This means that the actual values of the pooled effect sizes they obtained have to be regarded with great caution.

In effect, the situation is the old chestnut of whether a glass is perceived as half full or half empty. It is reassuring that antidepressants are more effective than active placebos and this study is a confirmation of their efficacy. If we do accept their effect size of about 0.4, it is worth pointing out that this is identical to those that we found for both selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) against placebo in our meta-analysis of comparative trials which also included a placebo arm (Anderson & Tomenson, 1994; SSRIs: 0.41 (0.32–0.50); TCAs: 0.40 (0.31–0.50)). In other words, studies against active placebo give results in line with those against ordinary placebo and therefore the clinical implications outlined by the authors seem to go beyond the data. There is, in fact, little evidence that active placebos provide useful additional information and so we can be reassured (although perhaps not complacent) about standard practice.

One other implication from this study is that anticholinergics themselves are unlikely to have significant antidepressant activity in support of the single negative controlled study cited by the authors.

Anderson, I. M. & Tomenson, B. M. (1994) The efficacy of selective serotonin reuptake inhibitors in depression: a meta-analysis of studies against tricyclic antidepressants. *Journal of Psychopharmacology*, **8**, 238–249.

— (1997) Psychiatry: evidence-based but still value laden. *British Journal of Psychiatry*, **171**, 226.

Moncrieff, J., Wessely, S. & Hardy, R. (1998) Meta-analysis of trials comparing antidepressants with active placebos. *British Journal of Psychiatry*, **172**, 227–231.

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Aggression and violence in severe mental illness

Sir: Scott *et al* (1998) recently reported results of an interview in a comparatively small community sample of people with psychosis with (n=27) and without (n=65) substance misuse. Although the severity of aggression and offending among this community sample was low, individuals with a dual diagnosis were significantly more likely to report a history of committing an offence or recent hostile behaviour. Surprisingly a substantial proportion of those in the psychosis-only group reported substance-related offences, which might be explained by inadequate assessment of substance use disorders in that group.

High rates of substance misuse and dependence have been recognised as a major problem not only in the USA but also in various European samples of people with schizophrenia (Soyka *et al*, 1993). There is also a broad literature on the violence and delinquency of people with a dual diagnosis of substance use disorder and schizophrenia. In a subsequent analysis of the study on two large samples of people with schizophrenia (Soyka, 1993) it was shown that 25.0% of all people with schizophrenia were found to have been convicted before, basically because of offences against property (19.5%) and traffic offences (4.3%), whereas violent behaviour was comparatively rare (1.8%). Patients with substance misuse had been convicted more often than people with schizophrenia and no substance misuse (40.1 *v.* 13.7%, $P<0.001$).

These data are in line with results of a major epidemiological study focusing on violence/aggression in schizophrenia. Lindquist & Allebeck (1990) in a study on 644 people with schizophrenia did not find a higher crime rate among males with schizophrenia compared with the general population, but reported a four-fold higher rate of *violent* offences among them. Lindquist & Allebeck (1989) also demonstrated the significant role of substance misuse for assaultive behaviour in people with schizophrenia: 14 (38%) of the 38 offenders with schizophrenia misused alcohol and/or drugs and seven others were probable alcohol/drug misusers. Prevalence rates for substance misuse in violent offenders (38%) were significantly higher than in other people with schizophrenia (16%).

The reasons for violence and aggression among people with both schizophrenia and alcohol/drug misuse have not been fully understood. The comparatively high rate of violence and aggression in dual diagnosis schizophrenia might be explained *inter alia* by a more severe psychopathology, a primary antisocial personality and a more pronounced non-compliance with treatment compared with uncomplicated schizophrenia, but the possible role of intoxication should also be considered. Other epidemiological data point in that direction: Boeker & Haefner (1973) not only found that the risk of a patient with schizophrenia acting violently was nine times higher than that of psychiatric patients with other diagnoses, they also reported that 10.4% of violent patients with schizophrenia were intoxicated at the time of their delinquent action.

In conclusion, there is broad clinical and epidemiological evidence for substance misuse being a major problem in people with schizophrenia, which has a significant impact on violence/aggression and delinquency in these patients. Implications of these findings for clinical practice and research have already been addressed by Scott *et al* (1998). I believe that Smith & Hucker (1994) were also right to conclude that *longitudinal* studies are required to facilitate a better understanding of the inter-relationships between substance misuse and violence in schizophrenia.

Boeker, W. & Haefner, H. (1973) *Gewalttaten Geistesgestoerter. Eine Psychiatrische–Epidemiologische Untersuchung in der Bundesrepublik Deutschland*. Berlin: Springer.

Lindquist, P. & Allebeck, P. (1989) Schizophrenia and assaultive behavior: the role of alcohol and drug abuse. *Acta Psychiatrica Scandinavica*, **82**, 191–195.

— & — (1990) Schizophrenia and crime. A longitudinal follow-up of 644 schizophrenics in Stockholm. *British Journal of Psychiatry*, **157**, 345–350.

Scott, H., Johnson, S., Menezes, P., *et al* (1998) Substance misuse and risk of aggression and offending among the severely mentally ill. *British Journal of Psychiatry*, **172**, 345–350.

Smith, J. & Hucker, S. (1994) Schizophrenia and substance abuse. *British Journal of Psychiatry*, **165**, 13–21.

Soyka, M. (1993) Substance abuse and dependency as a risk factor for delinquency and violent behaviour in schizophrenic patients – how strong is the evidence? *Journal of Clinical Forensic Medicine*, **1**, 3–7.

—, Albus, M., Finelli, A., *et al* (1993) Prevalence of alcohol and drug abuse in schizophrenic inpatients. *European Archives of Psychiatry and Clinical Neuroscience*, **242**, 362–372.

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