# Commentary: Meta-analysis of trials comparing antidepressants with active placebos†

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This attempt to establish treatment effect sizes follows a tradition, which dates back over 20 years, of assessing the effects of antidepressant treatment under 'blinder conditions'. The method adopted by Moncrieff *et al* has some merit but involves a recourse to studies, many of which are over 30 years old. While the studies may not be seriously flawed, it is difficult to have much confidence in them. None appears to have included what the authors describe as an 'inert' placebo, which strictly speaking would be a non-drug arm to the study. The number of studies is small. The dose of drugs used, which might be expected to have some influence on outcomes, is not mentioned. Finally, as experience with studies in obsessive–compulsive disorder indicates, treatment effect sizes can vary substantially from one decade to another – most probably because different individuals are recruited although all may apparently meet the same diagnostic criteria.

## MAGIC BULLET *V.* THERAPEUTIC PRINCIPLES

More importantly, the authors of this meta-analysis appear to have been caught on the hook of an ideology which I suspect they are keen to discredit. This is the 'magic bullet' ideology of pharmacotherapy, which, in brief, states that there is a biological lesion, either in the catecholamine or serotonergic system, in depression and that the appropriate remedy is therefore biological and that in due course biological treatments will correct the defect with something approaching maximal effect size. They will do so regardless of the psychosocial situation in which the person finds themself, much in the way that specific antibiotics correct a life-threatening infection, regardless of the bedside manner of the treating doctor. It has been very clear for a long time that the 'antidepressants' neither have an effect size nor a specificity to depression that is consistent with such a position; but the ideologically committed presume that future generations of antidepressants will improve on current treatment effect sizes. Moncrieff and colleagues, by reminding us of how small the current effect sizes are, appear to be arguing against a magic bullet point of view (assuming they are not arguing for an absolute inefficacy of tricyclic antidepressants) but, in engaging in this debate at all, they arguably concede the point by implying that effect size matters, and by apparently accepting a specificity of antidepressants to depression.

An alternative to the magic bullet approach is a therapeutic principle framework. According to this, the original tricyclic agents embodied a number of anti-nervousness active principles through their actions on catecholamine, serotonergic, dopaminergic, sigma, histaminergic and cholinergic systems, among others (Healy & McMonagle, 1997). Imipramine, desipramine, clomipramine, trimipramine and opipramol, for instance, are now known to differ to such an extent in terms of their actions on combinations of these systems that it is meaningless to lump them together as one tricyclic group. A relatively selective action on the serotonin system, it is now clear, provides a therapeutic principle in the treatment of some depressive disorders, as may an action that is relatively selective to the catecholamine system. Given that there is no evidence for distinct serotonergic and noradrenergic depressions, these actions must be therapeutic by virtue of distinguishable functional changes that they respectively bring about. An action on the serotonin system broadly speaking appears more anxiolytic (or anti-irritability) in nature, and activity on the catecholamine system more anti-anergic; in both cases the systems on which these drugs act can be presumed to be working normally (Healy & McMonagle, 1997). One might expect that such actions (therapeutic principles) would cut across psychiatric syndromes, and this is what is found, with the SSRIs showing efficacy in a range of disorders and not just in depression, to the extent that calling them antidepressants is all but mislabelling.

This being the case, however, one would not expect the treatment effect size in any one syndrome to be particularly great. The situation is not dissimilar to that for neuroleptics or benzodiazepines, both of which can act as therapeutic principles for a range of disorders from anxiety states and depressive disorders through to frank psychoses (Healy, 1997), with varying treatment effect sizes none of which is particularly great. In the case of the antidepressants, a single action on one neurotransmitter system is likely to be less efficacious against what may be a heterogenous group of depressive disorders than actions on more than one system, in part by virtue of the fact that fewer therapeutic principles are being used. There would appear to be a growing body of evidence that this is the case, from the Danish University's Antidepressant Group studies (Healy, 1997) and more recent studies in which milnacipram and mirtazapine have been shown to have a superior efficacy to fluoxetine. The mirtazapine study interestingly brings out two interpretations of treatment effect; a greater treatment response may indicate that one drug produced a greater improvement in responders than the other or, like mirtazapine, that it may produce a significantly greater number of responders (Wheatley *et al*, 1998). These possibilities have not been distinguished by the authors. An alternative reading of this recent series of studies is that actions on the catecholamine system are particularly useful in older people or those with melancholic features. In contrast, there seems to be emerging evidence that the older tricyclics at least have not been shown to have any efficacy in adolescent depressions, whereas the selective serotonin reuptake inhibitors (SSRIs) appear to have some efficacy in these disorders (British Association of Psychopharmacology, 1997).

## ABSOLUTE *V.* RELATIVE TREATMENT EFFECT SIZES

Two points stem from the above argument. First, on a therapeutic principle basis, treatment effect sizes cannot be calculated

†See pp. 227–231 this issue.

as an absolute value. They can only stand with reference to particular populations. For instance, if childhood depressions were being studied, the treatment effect size of tricyclic antidepressants would be zero, while the treatment effect size for SSRIs may not be as great in older populations. The populations in the studies considered here are poorly characterised but appear to be a heterogenous mix, in which case the number of studies is probably too small to draw any conclusions with confidence.

The second point is that it is not clear that atropine, when used in particular depressed populations, might not also offer a therapeutic principle. This has never been adequately tested, because no pharmaceutical company has had an interest to do so. Atropine was originally assumed not to be an antidepressant because it was not a tricyclic. The evolution of antidepressants, however, has indicated that selective actions by non-tricyclic agents on both the noradrenergic and serotonergic systems may provide therapeutic principles, which raises the question of whether selective actions on cholinergic, histaminergic or sigma systems might also provide anti-nervousness principles. There is some evidence in favour of each of these possibilities. The treatment effect size of any cholinergic principle would need to be investigated in a range of depressive/nervous conditions, age groups and psychosocial settings in order to establish what effects, if any, atropine might have been having in the studies cited in this analysis. While Moncrieff *et al* have conceded this possibility, one small negative study of one anticholinergic agent does not secure their position, given that the active principles in mandragora (mandrake), which was used for millennia for nervous conditions, appear to be anticholinergic in nature. The evidence in favour of the therapeutic possibilities of anticholinergic effects is sufficiently great to obviate any ethical difficulties in using such agents in treatment trials.

## INTENTION-TO-TREAT ANALYSIS

Moncrieff *et al* adopt an intention-to-treat analysis. It is not clear that this is appropriate; the use of such an analysis for this purpose is a matter on which opinions differ. There are two different questions that can validly be addressed. One is the size of a treatment effect in those who take a particular compound. This question is of interest to drug companies and regulators and possibly the original investigators in the studies cited here. A quite different question has to do with the question of outcomes on antidepressant treatments in naturalistic settings. When attempting to answer the first question, it is arguably more appropriate to analyse data from those who adhere to the protocol. Otherwise the analysis drags into the account a range of other factors such as aspects of the relationship between prescribers and subjects. This latter question may be of interest to third parties (purchasers, for instance) or it might be of interest to the individual when the comparison is between a sugar pill or a psychotherapeutic procedure and treatment with an active drug principle. In these latter contexts an intention-to-treat analysis has its merits, but surely not in a comparison between two compounds with prominent anticholinergic effects.

An intention-to-treat analysis, it might be argued, could compensate for the physician-centredness of the outcome measures adopted in the studies reviewed. This is possible, but methodologically weak. Such issues would be better settled by incorporating self-ratings as well as assessments of quality of life or social functioning in trial protocols. The treatment effect sizes of many antidepressants using quality of life assessments as an outcome measure, from what studies have been done, are alarmingly small even when an intention-to-treat analysis is not used. Such instruments may give good indications as to what antidepressants are *not* doing and it is of interest that very little has been published in this area. If companies interpret the recent amnesty on undeclared clinical trials to include the unpublished results on quality of life and social functioning scales that were administered in otherwise published studies, Moncrieff *et al* might have even more interesting meta-analytic possibilities. Rating scales cannot now be built into studies done 30 years ago but it is not clear that an intention-to-treat analysis is the appropriate remedy for the defects in methodology of trials done then, for the simple reason that it gives no indication as to what was going on and accordingly it deprives the reader of an opportunity to decide for themselves whether or not they wish to take certain factors into account.

An alternative method to approach the same goal as Moncrieff *et al* appear to be aiming for was proposed by Greenberg *et al* (1992) who analysed studies in which tricyclic antidepressants were compared with newer antidepressants. Their rationale was that as, in such trials, the tricyclic antidepressant was not the drug on which the expectations of the investigator are focused, any investigator bias to bump up the apparent effects of treatment would thereby be minimised. Reviewing studies that appeared during the 1980s they calculated on this basis that the treatment effect size of tricyclic antidepressants was "exceedingly fragile". However, more recently, Anderson has meta-analysed a 101 studies involving comparisons of SSRIs and a range of tricyclic antidepressants (I. M. Anderson, personal communication, 1997). These are studies that have been sponsored almost exclusively by companies producing SSRIs and, in the circumstances, many of the biases that are inevitable in such studies will have been operating in favour of the SSRIs. From this analysis, some of the tricyclic antidepressants emerge with a greater effect size than the SSRIs.

## WHO ARE THE STAKEHOLDERS?

Moncrieff *et al* end their analysis by suggesting that it would be of interest to compare some of the newer antidepressants with an 'active' placebo. This begs the question of who has an interest to undertake or insist on such a study. The regulatory authorities have no interest. Drug companies had no interest, until it recently became clear that using people with severe depression, drugs not selective for the serotonin system could be shown to 'beat' the SSRIs. The independent academic investigator, who conducted studies like these in the 1960s, has ceased to exist in great part because it is now clear that the treatment effect sizes of antidepressants are so small that only multi-centred studies can answer questions of relevance. The only people likely to be interested today are the third parties who pay for the drugs, but they are much more likely to be interested in studies in which two active agents are compared rather than studies incorporating an agent of uncertain standing such as atropine. On the basis of an apparent superior efficacy for some agents over others, these new stakeholders in mental health may then be tempted to restrict the availability of

compounds to formularies, at which point the task for academics may be to argue for the retention of agents with apparently weaker antidepressant effects on the basis that we still have no real idea of what it is that we are treating and in such circumstances maintaining the maximum number of therapeutic principles, even if some are of weaker effect for particular conditions than others, is the rational option.

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