Correspondence

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The antidepressant debate continues

In her March 2002 editorial, Dr Moncrieff raises doubts about the efficacy of antidepressant drugs, and argues that side-effects of the active drug may explain some of the differences owing to the associated increased expectancy of a positive effect. Our 24-week study (Malt *et al*, 1999) comparing the efficacy of empathic primary-care counselling and support combined with placebo, a selective serotonin reuptake inhibitor (sertraline) or an α_2/5-$HT_{2/3}$ antagonist (mianserin) in 372 subjects with depressed mood does not support her arguments.

In our study the general practitioners were required to systematically explore possible side-effects. This method yields a greater prevalence of side-effects than when only spontaneously reported side-effects are considered. The mean numbers of baseline-corrected UKU-elicited side-effects (Lingjaerde *et al*, 1987) during the study were 7.11, 6.51 and 6.45 after 8 weeks of treatment with sertraline, mianserin and placebo, respectively, and 3.16, 3.09 and 3.02 after 24 weeks of treatment (NS). This means that prevalence of side-effects is unlikely to explain the difference in response.

Another observation arguing against the hypothesis that non-specific side-effects may explain differences between active drug and placebo is the fact that we obtained differences in response over time among the three treatment arms. As would be expected by the pharmacodynamic profiles of the drugs, mianserin induced a faster initial response, while sertraline demonstrated an advantage in the long run explained by better efficacy among subjects with high neuroticism. At the end of the study, the physicians were not able to identify reliably the treatment given to each of their patients.

Furthermore, differences in effect size between the treatments (see Table 1) clearly demonstrated the advantage of antidepressant drugs on core symptoms of depression. These differences are well beyond the estimated mean effect size of 0.27 reported for active placebo.

Table 1 Differences in effect size on item levels measured on the Montgomery–Åsberg Depression Rating Scale between three forms of treatment in a 24-week randomised treatment trial of patients with depression (n=372) in primary care. Intention-to-treat data obtained from Malt *et al*. (1999)

	Sertraline *v.* placebo	Mianserin *v.* placebo
Observed sadness	0.04	0.19
Reported sadness	0.47	0.39
Anxiety	0.34	0.22
Insomnia	0.59	0.36
Appetite	−0.09	0.05
Concentration problems	0.08	−0.15
Lassitude	0.36	0.24
Inability to feel	0.10	0.22
Pessimistic thoughts[1]	0.54	0.45
Suicidal ideation[1]	0.13	0.04

1. Patients with psychotic ideation or active suicide plans were excluded from the study.

Instead of questioning the efficacy of antidepressant drugs in depression, attention should be directed at the critical question regarding the characteristics of those patients who will benefit from receiving antidepressant drugs in addition to psychological intervention.

Lingjaerde, O., Ahlfors, U. G., Bech, P., *et al* (1987) The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects on neuroleptic-treated patients. *Acta Psychiatrica Scandinavica Supplementum*, **334**, 1–100.

Malt, U. F., Robak, O. H., Madsbru, H.-P., *et al* (1999) The Norwegian naturalistic treatment study of depression in general practice (NORDEP) – I: Randomised, double-blind study. *BMJ*, **318**, 1180–1184.

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Author's reply: Professor Malt feels that his study of the use of antidepressants establishes the utility of antidepressants in mild or moderate depression in primary care and contradicts the notion that unblinding may have biased results. He reports that there was no difference in rates of side-effects in any of the treatment groups. However, patients may be able to guess whether they are taking active drugs without necessarily reporting side-effects. Taking an active drug may lead to a physiological experience, which reveals the nature of the treatment but may not be construed as unpleasant, and therefore may not be reported as a side-effect. Without specifically asking patients to guess whether they are taking active drugs or placebo it is not possible to know whether or not this effect may be occurring. In addition, the fact that Professor Malt reports that the active drugs were substantially more effective than placebo for insomnia suggests that the drugs had a sedative effect which may have been independent of the proposed antidepressant effect and may have suggested to patients that they were taking an active medication.

It is also worth pointing out that although this trial found statistically significant differences between active drugs and placebo, these differences were very small and of doubtful clinical relevance. The difference in the reduction of scores on the Montgomery–Åsberg Depression Rating Scale (MADRS) between the active drugs and placebo consisted of a maximum of 3 points. The MADRS scale has a total of 60 points and mean baseline values in this study were 27. In subjects in whom depression was characterised as severe or major depression, the differences were smaller still, and were not statistically significant.

It is arguable that treatment of mild depression in primary care with antidepressants is the worst case of the inappropriate medicalisation of misery and social problems. This may be harmful to the individuals concerned by encouraging reliance on physical treatments, and to society by masking the social conditions that are the sources of modern discontent.

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