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## Disclosures

GMG is an Emeritus NIHR senior investigator; the views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

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Antidepressants; what's the beef?

Do antidepressants, and specifically SSRIs, do more harm than good? The acrimonious debate between colleagues in the wake of yet another meta-analysis, this time by Jakobsen et al (1), suggests we don't know (2, 3). Or rather, we don't know how to interpret the facts that randomized clinical trials provide for us to reach a conclusion that everyone can and perhaps should accept.

What are the facts? Jakobsen et al demonstrated that the effect at the end of treatment (usually 6-8 weeks) was a mean difference of  $-1.94$  HDRS points (95% CI  $-2.50$  to  $-1.37$ ;  $P < 0.00001$ ) in favour of antidepressants compared with placebo. This confirms what others have reported from similar analyses, of various selections of the same and other trials, published and unpublished. They appear to have made a number of errors in extracting and analyzing the data (2), but with little impact on the central result (4).

So the question is not whether antidepressants do any good at all, it is what this difference means? NICE suggested in 2006 that, in clinical trials comparing antidepressant and placebo, a difference on the 17 item Hamilton rating scale should be 3 for an effect to be clinically meaningful. Jakobsen et al make much of this. Unfortunately, how that number was derived is a mystery. It is not based on a correlation between this symptomatic improvement and some superior measure of ecological benefit. Indeed, there are no convincing data which directly relate the change on a rating scale to some agreed gold standard measure of recovery. Most psychiatrists are happy, in principle, with the extrapolation of early reductions in symptoms to eventual recovery because they see it in their patients. However a difference of 3 points at 6 weeks has no intuitive meaning.

In fact, the mean change in symptom scores, while it is the usual metric, is itself potentially misleading because a more detailed examination of response profiles suggests that the distribution of HRSD scores after 6 weeks is better described as bimodal; there are already responders and non-responders. In 5 trials of escitalopram versus placebo, Michael Thase and colleagues showed that a bimodal model captured over 60% of the variance, a unimodal only 6%! (5) This suggests that a more intelligent analysis of individual patient data would give a more useful prediction of treatment response and the argument about 3, the magic number, would probably evaporate. In the case of the escitalopram trials, the mean change in HRSD was 3.23, but the probability of response (50% reduction in baseline symptom score) was increased by 19%. This approach had also been taken in a reassessment by the European regulators of their database (1984-2003). They found around an average 16% greater response rate following active treatment than placebo for newer antidepressants (which included SSRIs) (6)

Another approach offers an alternative to worrying about the HRSD scales. It suggests that many items on these scales are insensitive to short term changes and /or not present at baseline. In either case, scoring them adds nothing to our understanding of drug action. A meta-analysis of the effect of SSRIs on HRSD items in regulatory trials, showed that depressed mood itself was the most sensitive. The effect size for the whole scale was 0.27, while that for mood per se was 0.4 (7).

The bottom line is that SSRIs improve symptoms in major depression and that there can be little doubt around that conclusion. The number needed to treat (NNT) in studies with a mean drug-placebo difference on the HDRS scale of around 3 is between 5 and 7 and this effect size compares reasonably with most drugs used in medicine (8). Finally, analysis of the long-term efficacy of antidepressants shows that in terms of protecting patients against a subsequent relapse to depression these medicines have an NNT of less than 3 (9), which is a remarkable efficacy for any form of treatment.

The key issue is how this trades off against 'harms'. Jacobsen et al make much of the 'serious adverse effects' recorded in trials comparing antidepressants with placebo. 239/8242 (2.7%) participants prescribed an antidepressant experienced a 'serious adverse event' compared with 106/4956 (2.1%) for placebo. This difference does not correct for increased exposure times in active treatment arms (patients tend to drop out of placebo arms due to lack of efficacy), so the absolute increase in risk may be substantially less than 0.6%. Indeed, a 23% reduction in the exposure in the placebo compared with active arms would obliterate the difference completely. We suspect that such an effect explains the difference in the clinical trials, although we should not be complacent about rare complications in vulnerable groups. Such effects would not be detected in short term trials but might emerge from cohort studies in much larger populations.

Much the most common harms are the direct adverse reactions – the 'side effects' – of taking a drug. These are recorded either by spontaneous report or systematic questioning. Absolute numbers are always higher when elicited by the latter method. In the case of the SSRIs, the most common are abdominal queasiness (at worse nausea and vomiting), and changes in sexual function. These symptoms are relatively common at some level of severity. Clinical experience suggests that these adverse reactions are sometimes but not often an important reason why patients do not take their medicines. But they are not irreversible harms. Indeed, they are trivial compared with the adverse effects that some drugs can directly cause. And they are normally easily reversible.

Whether benefits outweigh harms is not answered by counting large numbers of subjective complaints. The best approach is probably to look at patient behavior. Drop out rate is the key metric recommended in the most recent meta-analysis by Cipriani et al (10). This is the net effect of benefit, which will

motivate patients to take a tablet, and cost (the trouble of taking an ineffective treatment and /or its adverse effects). The trials themselves show that acceptability of all SSRI antidepressants is positive (Cipriani et al. Fig 3b) (10). For no SSRI is the drop out rate statistically higher than placebo, which is what the literal interpretation of doing more harm than good would require.

In conclusion, in our view, Jacobsen et al down play the benefits of SSRIs and they inflate the harms. Their argument about efficacy can be answered to show that the clinical trials support an average effect that is fully comparable with drugs used for physical disorders. Moreover, subgroups and individuals probably benefit substantially more. How many people in trials do not actually take the pills they are prescribed, for example? The challenge is to personalize treatment choice and amplify treatment effects with psychotherapy or neurostimulation. Jacobsen et al's emphasis on serious harms is probably spurious, when based on the trial data. The excess of more trivial harms – adverse reactions – is certainly real but it does not lead to high rates of drug discontinuation. Their management is part of clinical practice.

No one suggests the efficacy of SSRIs is better than moderate. The glass is half full but it is not empty, the challenge is to move on and fill it further.

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