In Debate

Are Antidepressants as Effective as Claimed? No, They Are Not Effective at All

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Antidepressant drugs are claimed to have specific effects on depressive symptoms. It is assumed that they do this by acting on an abnormal brain state that gives rise to depression. In contrast, I suggest that there is no evidence for this position. The effects of antidepressants seen in depression trials can easily be accounted for by nonspecific pharmacologic and psychological actions.

Short-Term Studies

There are thousands of randomized controlled trials (RCTs) comparing antidepressants with placebo, using various measures of depression. Metaanalyses of these have generally come to the conclusion that, overall, they show a small advantage for antidepressants. However, this obscures enormous heterogeneity among published study results, with many trials finding no difference between antidepressant medication and placebo. In addition, we know that negative trials are less likely to be published than positive ones and that positive outcomes are selectively reported within trials. A recent metaanalysis that included unpublished studies found that the difference between antidepressants and placebo amounted to less than 2 points on the Hamilton Depression Rating Scale (HDRS).[1]

There are 2 reasons why the small difference found in this and other recent metaanalyses does not necessarily imply that antidepressants have a truly "antidepressant" effect. First, all rating scales contain items—such as sleeping difficulties, anxiety, and agitation—that are not specific to depression and that are likely to respond to nonspecific sedative effects associated with many antidepressants. For example, the HDRS contains 6 such items; these can score a total of 16 points (a score of 19 to 20 points indicates severe depression as defined by the American Psychiatric Association). Therefore, improvements according to rating scales may simply reflect nonspecific effects and do not necessarily imply any change in mood, per se. Second, antidepressants are active drugs and, as such, produce a range of physiological effects when ingested. These effects may indicate to assessors or trial participants whether they are taking the antidepressant or the placebo; thus, the double-blind design is often penetrated in trials of antidepressants and other psychotropic agents. This is especially likely to happen in contemporary trials in which subjects are forewarned in detail about the randomized design, the use of placebo, and the nature of likely side effects. Patients on antidepressants may therefore experience an amplified placebo effect as a consequence of suspecting that they are taking the active drug. Similarly, raters may inflate ratings for individuals they suspect to be taking the active drugs on the basis of reported side effects. This amplified placebo effect is difficult to demonstrate empirically, but several metaanalyses have found that trials with more rigorously blind conditions demonstrated lower medication effects, compared with placebo, than other trials.[2,3] These metaanalyses have been criticized with some justification, partly owing to the low quality of the included trials. Nevertheless, although critics are right to point out that the effects of placebo amplification have not been conclusively demonstrated, neither have they been refuted.

Therefore, the clinical significance of small differences in rating scale scores in RCTs comparing antidepressants with placebo is unclear. These differences could easily be accounted for by nonspecific pharmacologic effects, such as sedation, or by amplified placebo effects. Evidence from other sources does not suggest that antidepressants have a beneficial impact on the outcome of depression. Naturalistic studies indicate that people treated with antidepressants do less well than people who are not treated with them, even after controlling for the severity of the original condition.[4] Despite the enormous increase in antidepressant prescribing in the West over the last decade and a half, epidemiologic evidence suggests that the prevalence of depressive episodes is higher than ever.[5] Evidence on suicide and absence due to sickness does not suggest that antidepressant use has contributed to reducing the consequences of depression. Despite some claims that antidepressants have contributed to falling suicide rates, there is abundant evidence that suicide trends are long-standing and independent of patterns of antidepressant use. [6] Rates of

sickness absence due to depression increased substantially in the United Kingdom during the 1990s, when antidepressant prescribing was soaring.

Long-Term Studies

The fact that many people appear to relapse after discontinuing long-term maintenance treatment with antidepressants for recurrent depression is often perceived as strong evidence for the efficacy of antidepressants. However, the evidence does not warrant this conclusion. Studies of maintenance or long-term treatment are effectively discontinuation studies. They take a group of individuals who have improved on antidepressants and randomize some of them to have the antidepressant withdrawn and replaced by placebo, usually quite rapidly. Thus the placebo group is really an antidepressant discontinuation group. It is now well recognized that antidepressants are associated with a discontinuation syndrome, but this was not widely acknowledged when most maintenance studies were done. Discontinuation symptoms potentially invalidate maintenance trials, first, because they may be mistaken for early signs of relapse in their own right and, second, because they may unblind participants, making them more vulnerable to relapse through a "nocebo effect"—the inverse of the placebo effect—wherein negative expectations cause physical illness or psychological distress. Negative expectations are likely in participants in maintenance trials, given that by definition they initially "responded" to antidepressants and are therefore likely to believe in their efficacy.

Viguera et al[7] have suggested that antidepressant withdrawal may increase vulnerability to relapse in its own right, independent of the course of the underlying condition, as is the case for lithium withdrawal. In a metaanalysis of maintenance trials, these authors found that relapses tended to cluster after withdrawal, with declining risk thereafter, suggesting that the event of withdrawal is associated with relapse. In addition, the risk of relapse was constant whether patients had been taking antidepressants for 3 weeks or 4 years. This also suggests a withdrawal-related effect, since a greater length of stability would generally be expected to predict a lower relapse rate if withdrawal were merely revealing the underlying course of the disorder.

An Alternative View of the Action of Antidepressants

Elsewhere, I have suggested that psychiatric drugs should be viewed as acting not by targeting and redressing abnormal biochemical states but by causing abnormal drug-induced states.[8] These drug-induced states, such as the sedation and indifference produced by neuroleptics in acute psychosis, may be useful in some acute psychiatric conditions. Different antidepressants produce a range of drug-induced effects. Tricyclic antidepressants cause profound sedation and cognitive impairment. The effects of selective serotonin reuptake inhibitors are less pronounced, but they appear to cause both mild stimulant and sedating effects. There is no evidence other than that derived from RCTs that antidepressants elevate mood. In volunteer studies, they either cause dysphoria or they have no effect; nor, for reasons spelled out above, do the results of RCTs with patients suffering from depression confirm that antidepressants affect mood in patients either, other than possibly through amplified placebo effects. Although many drugs are known to cause short-term, context-dependent euphoria or mood elevation, there is no evidence that any drugs, including antidepressants, can produce long-term mood elevation.[9] Sedative effects may be useful in the short term in some cases of depression accompanied by agitation, sleep impairment, or anxiety. However, it is difficult to think of any other recognized drug-induced effects that are desirable in depression.

Conclusion

I suggest that the term "antidepressant" is a misnomer. The small advantage that antidepressants have over placebo in RCTs is easily accounted for by nonspecific psychological and pharmacologic effects. Other evidence does not confirm that antidepressants have a clinically significant effect. We have no reason to suppose that any drugs can reverse the diverse problems that are labelled as depression. We need to emphasize other ways of responding to people who seek help from psychiatrists when they are distressed. The quest for the magic bullet for depression may be a wild goose chase.

References

1. Kirsch I, Moore TJ, Scoboria A, et al. 2002. The emperor's new drugs: an analysis of antidepressant medication data submitted to the US Food and Drug Administration. Prevention and Treatment [Internet]. [cited 30 Nov 2006] (1). Available from: www.content.apa.org/journals/pre/5/1/23.
2. Moncrieff J, Wessely S, Hardy R. Meta-analysis of trials comparing antidepressants with active placebos. Br J Psychiatry. 1998;172:227–231.
3. Greenberg RP, Bornstein RF, Greenberg MD, et al. A meta-analysis of antidepressant outcome under "blinder" conditions. J Consult Clin Psychol. 1992;60(5):664–669.
4. Brugha TS, Bebbington PE, MacCarthy B, et al. Antidepressants may not assist recovery in practice: a naturalistic prospective survey. Acta Psychiatr Scand. 1992;86(1):5–11.
5. Patten SB. The impact of antidepressant treatment on population health: synthesis of data from two national data sources in Canada. Popul Health Metr. 2004;2(1):9.
6. Moncrieff J, Kirsch I. Efficacy of antidepressants in adults. BMJ. 2005;331(7509):155–157.
7. Viguera AC, Baldessarini RJ, Friedberg J. Discontinuing antidepressant treatment in major depression. Harv Rev Psychiatry. 1998;5(6):293–306.
8. Moncrieff J, Cohen D. Rethinking models of psychotropic drug action. Psychother Psychosom. 2005;74(3):145–153.
9. Moncrieff J, Cohen D. Do antidepressants cure or create abnormal brain states? PLoS Med. 2006;3(7):e240.

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