EDITORIAL: PERSPECTIVES ON THE PLACEBO EFFECT

Is the Efficacy of Antidepressants Truly a Myth?

抗抑郁药的效果是否确实堪称神话？

¿Es realmente un mito la eficacia de los antidepresivos?

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Antidepressant drugs are among the most widely prescribed drugs worldwide. Until recently, there was little doubt that such drugs should be considered first-line treatment in depressive patients. However, serious doubts about the efficacy of these drugs have been raised and are increasingly perceived by healthcare professionals and the public. On the previous two pages of this issue of *Global Advances in Health and Medicine*, readers find an interview with Irving Kirsch, who is clearly among the most notable critics of antidepressants. He summarized the most important findings of his longstanding research on the subject in a book[1] that is of great interest to anyone who is involved in the care of patients with depression or who is doing research in the field.

In summary, Kirsch has three main arguments: (1) the published studies overestimate the effects of antidepressants over placebo; (2) the remaining small difference is seen only in trials in patients with very severe depression and is likely due to unblinding as a result of side effects; (3) the theory that depression is due to chemical imbalances in the brain is wrong. Kirsch concludes that the improvement in depression observed in randomized trials and clinical practice is due to a placebo effect. We think that Kirsch's arguments are very interesting, but we are uncertain whether the evidence provided is truly sufficient to advise against prescribing antidepressants to the extent suggested by the interview.

The evidence that published trials give an overly optimistic view of the effects of antidepressants over placebo is convincing indeed. This evidence comes in part from work by Irving Kirsch and colleagues,[2] but the most comprehensive study was published by Turner et al in *The New England Journal of Medicine*.[3] These meta-analyses compared results published in journals with the data submitted to the US Food and Drug Administration (FDA). For the licensing of new drugs, pharmaceutical companies must provide detailed data of all studies relevant to a drug to the FDA, including unpublished studies. The meta-analyses show that trials with negative results are published less often and that trials with ambiguous results are often published in a way that conveys a positive outcome. On average, published data inflated the effect size of the pharmaceuticals over placebo by 32%; if the full FDA dataset was analyzed, effects over placebo were statistically significant but minimally so.

In 2008, Kirsch et al published a meta-analysis investigating the influence of baseline severity on the difference between improvements observed under antidepressant and placebo treatment in 35 trials submitted to the FDA for the licensing of four new-generation antidepressants.[4] They found that drug-placebo differences reached conventional criteria of clinical relevance only at the upper end of the very severely depressed category. Differences decreased as a function of baseline severity with virtually no differences at moderate levels of depression. While this is an important meta-analysis, it still has relevant limitations. First, there was only one trial in which the average baseline score indicates moderate depression severity, which severely limits the conclusiveness for this category. Second, using group means of separate studies for estimating the influence of baseline severity might be subject to confounding. A much better approach to address this question is by an individual patient data meta-analysis in which baseline severity and outcomes are available for each individual participant. At least two such analyses have been performed. While one confirms the findings by Kirsch et al,[5] another more recent and larger analysis found the tested antidepressants similarly effective at different severity levels.[6] In conclusion, while the effects of placebo are small in general, it is unclear whether actual effects over placebo do exist in severely depressed patients only.

Still, the more general part of Kirsch's second argument is that the remaining small differences between drugs and placebo are due to unblinding. Patients find out whether they receive the drug or placebo due to the side effects they experience. This unblinding affects the size of placebo effects and might bias assessments. Indeed, there is some evidence that when antidepressants are compared with active placebos mimicking the side effects of the tested drugs, differences between groups are very small.[7] In his book, Kirsch also claims that the more side effects depressed patients experience while taking the active drug, the more they improve. However, the evidence cited for support of this claim is weak. Kirsch cites a meta-analysis on fluoxetine trials by Greenberg et al. Summarized, it reports a high correlation between the frequency of side effects and improvement as a secondary result.[8] Yet the correlation coefficients are based on summary data from only four and six studies,

respectively. Kirsch finally argues that drug-placebo differences are no longer statistically significant when controlled for side effects. But it is challenging to perform such an analysis adequately, and the cited study is unpublished. Overall, the idea that the residual differences between antidepressant drugs and placebo are due to unblinding is not more than a hypothesis, albeit a good one.

Kirsch's third argument, that the concept of antidepressants lacks both plausibility (as so many different drugs with different mechanisms seem to be effective) and an evidence base, sounds plausible to us, but we do not feel competent to discuss it critically.

In summary, the available data indeed show that most of the improvement seen under antidepressant treatment in clinical trials is also observed under placebo treatment. Improvements are also seen in studies including a no-treatment or wait-list condition, but these changes are much smaller.[9] Based on these data, the possible influence of unblinding, the lack of plausibility of the chemical imbalance theory, and considerations based on placebo research in general, Kirsch concludes that the improvements observed under antidepressant treatment are due to a placebo effect and recommends that patients turn to psychotherapy. While we have sympathy with a lot of Kirsch's arguments, we believe this goes too far.

There can be little doubt that psychological interventions are effective for the treatment of depression. However, also in this field of research, there is evidence for bias and considerable overestimation of treatment effects.[10,11] There is no big industry behind psychotherapy, but there is evidence that personal interests (allegiance bias) of researchers in the field also influence psychotherapy research findings.[12] Whether psychological interventions are truly superior to antidepressants as first-line treatment in routine primary care is far from clear. In many countries, capacities for psychotherapy are still limited, and many patients have to wait several months for treatment. Finally, many family physicians and psychiatrists are convinced of the effectiveness of antidepressants based on their practical experience. While practical experience clearly can be wrong, we also cannot be certain whether effect sizes observed in clinical trials can be directly generalized to clinical practice. The evidence base for antidepressants is not foolproof, and it is important that guidelines take this into account.

In the interview in this issue, Kirsch is cited as saying that guidelines from the United Kingdom National Institute for Health and Clinical Excellence (NICE) discourage prescribing antidepressants except in severe cases. However, this statement does not reflect the differentiated recommendations in the current guideline.[13(pp570-86)] There the recommendation is only to not *routinely* treat persistent subthreshold depressive symptoms or mild depression with antidepressants.[12]

In our opinion, a more critical use of antidepressants is clearly indicated, but unless it is ensured that any depressed patient who needs treatment has access to an effective alternative option as well, radical changes are not warranted.

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