

Do we underestimate the benefits of antidepressants?

In the past 5 years, doubts have been raised about the therapeutic effectiveness of antidepressants in patients with depressive disorders, because of the small differences in symptom improvement between antidepressants and placebo recorded in randomised controlled trials (RCTs). With the recent debates about lowering of disease thresholds in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, and the medicalisation of normal bereavement, this scepticism has increased. For the large group of patients with mild depression, the differences between antidepressants and placebo are not thought to be large enough to be clinically significant—ie, at least three points on the Hamilton Depression Rating Scale, HAMD-17.¹ Therefore, several guidelines^{2,3} no longer recommend antidepressants as first-line treatment for patients with mild and moderate depression, and instead generally favour psychotherapy. We are concerned that scepticism about the benefits of antidepressants goes too far, and risks depriving many patients with depression of effective treatment.

The crucial question for both patients and doctors is how much symptom improvement can a patient expect if he or she tolerates and reliably takes antidepressants, compared with watchful waiting, psychotherapy, or other alternatives? The present approach to estimation of the clinical significance of antidepressants is misleading, for several reasons.⁴ Induction of hope of treatment benefit is an important factor in antidepressant treatment.⁵ In double-masked RCTs, less hope is induced in patients receiving an active drug than in routine care, because patients are left uncertain about which treatment group they belong to; however, more hope is induced in those receiving placebo compared with those who are undergoing watchful waiting, because the pill could be an antidepressant. Both factors together reduce the antidepressant–placebo difference in RCTs compared with the unmasked real-life situation.

Clinical significance of therapeutic effects of antidepressants is estimated on the basis of antidepressant–placebo differences⁶ in improvement of depressive symptoms. In this context, the method of intention-to-treat analysis with last observation carried forward is usually applied. This conservative method is clearly useful to prove efficacy. However, the benefit that a compliant patient can expect from antidepressants in

routine care cannot be estimated from study samples which include early drop outs for various study-related reasons. A better approach to estimate real-life benefit would be to include only those who completed the study.

Patients without health insurance might be motivated to participate in RCTs because of free treatments or other financial advantages. Likewise, study centres might be motivated to recruit many patients in a short period. A likely consequence is the inclusion of a substantial percentage of inappropriate and uncompliant patients, resulting in small effect sizes.⁷

By contrast with the situation in RCTs, antidepressant treatment in routine care allows individual adaptation of the chosen antidepressants and dosage in case of tolerability problems, or application of augmentation or combination strategies in case of insufficient efficacy.

Even when the present approach of measurement of clinical significance is accepted, the effect sizes of antidepressants in RCTs are comparable to many treatments in medicine. A recent qualitative review of drug treatments for common diseases showed a wide variability of effect sizes (eg, 1.39 for proton-pump inhibitors for reflux oesophagitis, and 0.41 for sumatriptan for migraine). Overall, the mean effect size of antidepressants for major depressive disorders was about 0.30 for acute treatment and 0.60 for relapse prevention.⁸ The Kirsch meta-analysis⁶ of data submitted to the US Food and Drug Administration on four new-generation antidepressants, which concluded that antidepressants seem clinically useless in cases other than severe depression, attracted much attention from the academic and popular media. Notably, a recent multi-meta-analysis revisited the Kirsch dataset with a different statistical approach and showed an effect size of antidepressants for depression of 0.34 (comparable to the effect size found by Leucht and colleagues⁹) with no role of baseline symptom severity.⁹ Furthermore, most patients would not agree with the present practice of considering an additional improvement of two points on the HAMD-17 scale as not being clinically significant. Such a difference might indicate, for example, clear improvements in appetite, sleep, or suicidality.

Are there better alternatives to antidepressants? For mild to moderate depression, some guidelines favour psychotherapy over antidepressants. Although the value



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of psychotherapy is undoubted, the evidence base for its effect size is less solid than that for antidepressants.⁴ The main reason for this weaker evidence is the difficulty in definition of valid control groups and the fact that therapists, patients, and often even raters are not masked. Outcome in psychotherapy control groups has even been found to be significantly worse than that in pill placebo groups (the so-called nocebo effect), because patients are fully aware of their study situation.¹⁰ Testing psychotherapy against a nocebo condition could therefore lead to artificially large group differences and effect sizes.

In summary, the present approach to estimation of the benefits of antidepressant treatments is likely to underestimate the clinical significance of antidepressants and overestimate that of psychotherapy. At the same time, we are experiencing an increasing tendency to medicalise individuals who have emotional reactions to difficult life circumstances but without any clinical signs of depression, and to offer them antidepressants or psychotherapy which might not be appropriate to their needs.¹¹ We should be careful not to offer our treatments to the wrong patients, but to provide them consistently to the right patients.

*Mazda Adli, Ulrich Hegerl

Department of Psychiatry and Psychotherapy, Charité-Universitätsmedizin Berlin and Fliedner Klinik Berlin, 10117 Berlin, Germany (MA); and Department of Psychiatry and Psychotherapy, University of Leipzig, Leipzig, Germany (UH)
mazda.adli@charite.de

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Challenges in rolling out interventions for schizophrenia

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The Global Mental Health (GMH) movement has played a pivotal part in bringing to attention the unmet needs of patients with mental disorders, particularly in low-income and middle-income countries.^{1,2} Schizophrenia is of primary concern in view of the high level of associated disability and stigma, and the risk that, without treatment, patients will experience prolonged institutionalisation, neglect, and abuse.^{3–5}

Sudipto Chatterjee and colleagues' multicentre, randomised controlled COMMUNITY care for People with Schizophrenia in India (COPSI) trial,⁶ in *The Lancet*, represents a milestone by showing the benefits of a collaborative community-based care plus facility-based care model compared with conventional

facility-based care alone for treatment of moderate to severe schizophrenia. However, implementation of collaborative community-based care in low-income and middle-income countries has several issues that need further consideration, such as ensuring continuity in supervision of community workers, safeguarding the physical health of patients, and embedding services within the local context and culture.

Collaborative community-based care makes sense: physical facilities (eg, clinics and hospitals) are not needed, demand on professional skills is low, and the family remains the core unit of care. COPSI is the first trial to test collaborative community-based care rigorously in a developing country, India.⁶ 187 participants were