

This issue's letters

- Effectiveness of selective serotonin reuptake inhibitors
- A "take with a grain of salt" label for Holiday Review articles
- Health Check program

Effectiveness of selective serotonin reuptake inhibitors

As a family physician I see many patients with mood disorders and selective serotonin reuptake inhibitors are an important therapeutic option for them. I have the clinical impression that drugs in this class can be very effective, and I prescribe them often. I was thus interested to read what the systematic review by Barbui and colleagues revealed about their effectiveness.¹

I was disappointed and puzzled by the bizarre primary outcome measure selected by the authors: the proportion of patients who left a study early for any reason. Consider the ideal situation in which no one in either study arm drops out; it would be impossible for the active treatment to be better than placebo even if all treated subjects went into remission. How can this be a measure of effectiveness?

In my practice, the biggest challenge is persuading patients to persist with therapy through the first few days of unpleasant side effects until the beneficial effects become manifest. I consider early dropout to be a failure of my persuasive powers and not an indication that the therapy is ineffective. I believe that it is important to distinguish between dropout in the first days of treatment, which is a consequence of the predictable and often transitory unpleasant side effects, and delayed dropout, which may reflect treatment failure. The authors failed to stratify their analysis on the time of dropout

and their analysis is thus not informative with respect to dropout for the important end points of treatment failure or persistent side effects.

As a clinician I am primarily interested in the effectiveness of a drug in those who actually take it. It is thus disappointing that the authors gave short shrift to their secondary outcome measures, all of which showed a significant benefit of active treatment.

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Competing interests: None declared.

REFERENCE

1. Barbui C, Furukawa TA, Cipriani A. Effectiveness of paroxetine in the treatment of acute major depression in adults: a systematic re-examination of published and unpublished data from randomized trials. *CMAJ* 2008;178:296-305.

DOI:10.1503/cmaj.1080023

[The authors respond:]

We selected leaving the study early for any reason as the primary outcome for our systematic review¹ because patients frequently stop taking or change their antidepressant medication. In Italy, for example, a recent survey showed that of more than 2800 adults observed for 6 months after receiving their first antidepressant prescription, 60% received only occasional prescriptions after their first one.² We therefore reasoned that treatment adherence might represent a clinically useful outcome measure in meta-analyses of randomized controlled trials, as we thought that under experimental conditions this outcome might integrate patients' and clinicians' judgments of efficacy, safety and tolerability into a global measure of effectiveness and acceptability. Similar reasoning was recently used in a clinical trial of antipsychotic drugs.³

We acknowledge that this outcome measure may only offer a "down-to-earth" evaluation of a drug's effective-

ness and acceptability, but this limitation can be seen as a strength in a field of research where efficacy is typically quantified as a score on a rating scale: in clinical practice, physicians seldom define patient improvement with rating scales.

For patients with moderate to severe major depression, one of the first goals is to keep them on treatment. Therefore, the main clinical question of our systematic review was whether paroxetine is better than placebo at keeping patients on treatment. Staying on treatment can also be seen as a hard measure with little measurement error. In addition, we investigated the effectiveness of paroxetine in those who actually took it and we also used standard measures of depression.

The main clinical message of our analysis is that the effect of antidepressants in patients with moderate to severe depression is modest. Physicians should consider combining pharmacologic and nonpharmacologic treatments such as psychological and psychosocial interventions backed by scientific evidence.^{4,5} Similarly, patients should not receive the message that modifications of thought, mood and behaviour can be achieved by pharmacologic means only.

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Competing interests: None declared for Corrado Barbui and Andrea Cipriani. Toshiaki Furukawa has received research funds and speaker's fees