Psychopharmacology for the Clinician
Psychopharmacologie pratique

The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided.

Optimal use of antidepressants: When to act?

After the initiation of an antidepressant drug to treat major depression, the clinical lore is to wait for about 6 weeks before making any decision about the treatment regimen. At the 6-week point, assuming that a minimal effective dose has been prescribed and taken regularly, about one-third of patients will be in or near remission, one-third will present a notable but insufficient improvement, and the other third will have experienced no significant change or even deterioration. In about two-thirds of patients, an increase in dose will generally be prescribed, with the next dosage adjustment scheduled for 4–6 weeks later. The problem with this conservative approach is that it requires about 3 months, a period during which about 50% of patients are likely to stop their treatment.[1,2] Is this usual treatment optimal? Certainly not — but can it be improved?

The first question to ask: How long should a clinician wait before changing treatment if there has been no improvement? One solution is to, in a given week, examine the percentage of patients without an improvement who would nevertheless become stable responders or remitters at the end of an adequate trial. This has been examined by Szegedi and collaborators[3] in a first study comparing paroxetine and mirtazapine in 212 patients. They considered an improvement of 20% to indicate onset of action. About 30% of unimproved patients at week 1 still achieved a 50% response by the end of the 6-week trial. By week 2, this number fell to less than 10%, and by weeks 3 and 4 it was virtually 0%. In other words, by week 2 about 90% of the unimproved patients have wasted time because they did not respond or remit by the end of the trial. The same group carried out a similar meta-analysis in the 2458 patients enrolled in 12 double-blind studies of selective serotonin reuptake inhibitors and mirtazapine. The negative predictive value of the lack of early improvement for a stable remission was about 80% for moderate depression and 90% for severe depression.

These investigators then prospectively applied this principle to a study of 242 inpatients who received a forced titration within 1 week to 45 mg/day of mirtazapine or 225 mg/day of venlafaxine.[4] Every patient who failed to meet the 20% improvement criterion on mirtazapine by week 2 also failed to remit at week 6, whereas 38% who met this minimal improvement criterion remitted. The corresponding numbers for venlafaxine were 6% and 39%. In a sample of 315 patients, Trivedi and colleagues[5] performed similar analyses examining the predictive value of a 50% response at week 4, yielding results similar to those mentioned earlier.

Taken together, these observations strongly support the 2-week principle. When using a single antidepressant from treatment initiation, something clinically important has to happen every 2 weeks. First, if there is no clinically detectable improvement at week 2, the dose of the medication, if it is well tolerated, should be increased. Second, at week 4 in the absence of a 50% improvement, the dose could be increased further for the next 2 weeks, or drug substitution or addition could already be implemented. In conclusion, the treatment of depression is often suboptimal and can unduly delay remission.

Pierre Blier, MD, PhD
University of Ottawa Institute of Mental Health Research
Royal Ottawa Hospital
Ottawa, Ont.

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