

Why Settle for Silver, When You Can Go for Gold? Response vs. Recovery as the Goal of Antidepressant Therapy

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Issue: *Widespread observations of “apathetic” recovery from depression and “poop-out” of clinical response following antidepressant treatment are prompting emphasis on attaining full remission, not just a response, for patients with depression and anxiety disorders.*

Good News/Bad News in the Treatment of Depression

The good news is that advances in the treatment of depression in the past decade have led to better recognition of those with depression, and also to a reduction in the number of relapses by continuing to treat patients once they have responded to an antidepressant. A plethora of new agents introduced in the past decade have proved to have not only better tolerability than the tricyclic antidepressants that they replaced, but also a broader spectrum of efficacy across affective and anxiety disorders. Furthermore, over half of depressed patients will recover within 6 months of an index episode and more than three fourths will recover by 2 years.¹

The bad news is that even those patients whose depression is recog-

nized and who respond to antidepressants may frequently be inadequately treated. That is, it is not enough to get a response from an antidepressant and to improve functioning—it is necessary to complete the job by aiming for complete recovery, removal of all symptoms, and return to wellness as the goal.

Although over 90% of depressed patients will eventually “respond” to one or a combination of different drugs, up to half of these will never remit, and for those who do, up to 30% do not remain well in the first 18 months following remission.^{1,2}

Response or Remission?

Would a physician treating an infection choose to reduce only half the number of disease-causing organisms? How about only 50% of the number of cancerous cells in a tumor? Then why accept treatment responses of only 50% reduction of symptoms in depression? This standard, set for proving the efficacy of antidepressants by the FDA and by many psychiatric publications, has tended to obscure that the goal of antidepressant treatment is recovery and prevention of relapses, not just diminishing symptoms to a lower level of suffering.

Although existing treatments of psychiatric illnesses such as schizophrenia and Alzheimer’s disease generally cannot achieve remission, but only palliation of symptoms, it is frequently possible to achieve complete “wellness” when antidepressants are used to treat affective and anxiety disorders. However, prescribers may be treating less aggressively when they monitor whether patients are better, not whether they are well. This could increase the likelihood of relapse, poor outcome, future treatment nonresponsiveness, residual disability, and even suicide.

Are All Antidepressants Created Equal?

Antidepressants differ sometimes dramatically in side effect profiles, but it has been very difficult to consistently demonstrate distinctions in overall efficacy for the treatment of depression. Response rates of all antidepressants are repeatedly the same (about 60%–70%), whereas placebo response rates are about 30% to 40%.^{2–9} Remission rates, however, can differ between antidepressants.^{2–9} Also, individual patients can have distinctively different therapeutic reactions to different antidepressants or to combinations

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of antidepressants and augmenting agents. Since the name of the game is remission, not response, striving for this goal requires psychiatrists to explore treatment strategies that help patients achieve this.

Going for Gold

How can response be turned into remission? If one agent generates response but not remission, it is theoretically possible and frequently observed empirically that another agent may do the job. Unfortunately, there is little to guide the rational selection of second-line treatment for a partial responder. One theme to consider is to create dual serotonin and norepinephrine actions for cases in which serotonin actions alone are not adequate, especially if 2 or more serotonergic selective agents have proved less than ideal. This strategy arises from suggestions that 3 dual action antidepressant classes have outperformed single selective action serotonergic agents in several (but certainly not all) studies.⁴⁻⁹ Thus, dual reuptake inhibition tricyclics (especially clomipramine), as well as venlafaxine, and the dual disinhibiting mirtazapine (through α_2 blockade) have sometimes proved superior to one or another of the selective serotonin reuptake inhibitors (SSRIs).

Therefore, when only a response occurs in a patient with adequate dosing and duration of treatment with an SSRI, consider augmenting or switching to a dual action agent. Also, consider adding a more selective agent that provides noradrenergic action to serotonergic action, such as adding bupropion, desipramine, maprotiline, and soon, reboxetine.

Norepinephrine may help boost a patient's apathetic recovery to full remission with energy, zest, and social drive. It is possible that some patients do well with serotonergic

intervention alone, others with noradrenergic intervention alone, and still others require both. Since one cannot know this in advance, it may be best to treat with a dual action agent first.

Conclusion

Whether this strategy is any better than a random rotation through different antidepressants, even of the same pharmacologic class, is unknown. The real issue is to keep going for gold, namely the conversion of response into remission.

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Take-Home Points

- ◆ Some of the most impressive advances that have occurred in the field of depression in recent years include improving the rate of recognition and initial treatment of this illness by medical professionals, and the increased use of maintenance treatment with antidepressants to help prevent relapses.
- ◆ Introduction of almost a dozen new antidepressants with enhanced tolerability in the past decade has led to an emphasis on broadening the population receiving such treatment, but not necessarily demanding complete recovery from such treatments. Thus, symptoms of depression are frequently reduced but not eliminated.
- ◆ Settling for a response (i.e., > 50% reduction of symptoms) but not pushing for remission (i.e., return to normal, or "wellness") can have disturbing consequences, such as increased likelihood of relapse, poor outcome, future treatment nonresponsiveness, residual disability, and even suicide.
- ◆ Incomplete treatment responses should be recognized and treated aggressively by ensuring optimal dosing and duration of antidepressant treatment and perhaps also by exploiting dual serotonin/norepinephrine pharmacologic actions of single drugs or combinations of drugs to get the job completely done.