Management of Nonresponse and Intolerance: Switching Strategies

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Approximately 29% to 46% of depressed patients show only partial or no response to treatment with antidepressants, with intolerance a frequent cause of treatment failure or discontinuation. Clinicians frequently switch to other antidepressants patients who have failed to tolerate or to respond to antidepressant treatment. The switching strategy involves substitution of another agent for the agent that has either caused intolerable side effects or has failed to induce a response. Fredman and colleagues have recently surveyed 402 psychiatrists from various parts of the country and asked them what steps they would take for patients who fail to respond to 8 weeks or more of an adequate dose of a selective serotonin reuptake inhibitor (SSRI). Interestingly, switching to a non-SSRI agent was the most popular choice indicated by psychiatrists (44% of respondents), with dual-acting agents and bupropion being the next most commonly chosen agents. Even though there are no controlled trials of switching strategies in the literature to date, clinicians often choose this course of action. This article will review some of the currently available studies on switching strategies.

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WHY SWITCH TO ANOTHER ANTIDEPRESSANT?

Approximately 29% to 46% of depressed patients respond only partially or not at all to antidepressants, with intolerance a frequent cause of treatment failure or discontinuation.[1] Clinicians typically switch depressed patients from one antidepressant to another either to provide relief from certain side effects during the acute phase (i.e., insomnia, agitation) or the long-term phase (i.e., sexual dysfunction, weight gain) of antidepressant treatment or to improve outcome in both partial responders and nonresponders, or both. Depressed patients are switched from one antidepressant to another of a different class mostly to obtain a different neurochemical effect (e.g., going from a relatively selective agent to a dual-action agent). In addition, patients who cannot tolerate a certain agent may better tolerate an alternative drug with a different side effect profile. Fredman and colleagues[2] have recently surveyed 402 psychiatrists from various parts of the country and asked them what steps they would take for patients who fail to respond to 8 weeks or more of an adequate dose of a selective serotonin reuptake inhibitor (SSRI). Interestingly, switching to a non-SSRI agent was the most popular choice indicated by psychiatrists (44% of respondents), with dual-acting agents and bupropion being the next most commonly chosen agents. Even though this survey showed that switching from one SSRI to another was the first choice for only 18% of the respondents,[2] there are several reasons to justify such an approach, including the fact (1) that patients intolerant to one SSRI may tolerate another SSRI,[3,4] (2) that nonresponders to one SSRI may respond to another SSRI,[3,4] and (3) that there may be significant differences in pharmacologic or pharmacokinetic (i.e., reduced chance of drug-drug interactions) properties across agents in the same class.

Switching antidepressants is a user-friendly approach, perhaps more acceptable to patients than polypharmacy. The use of a single agent may enhance compliance, is generally less costly than polypharmacy itself, and may be quite appealing to patients, especially when the alternative drug has a more acceptable side effect profile (e.g., lower risk of sexual dysfunction). The main disadvantages of switching are related to the fact that the side effects from the alternative agent may be different but not necessarily better. Also, in the case of partial responders, there is a potential for loss of partial benefit. A significant issue that has arisen in studies on the efficacy of switching strategies is the occurrence of discontinuation-emergent adverse events (particularly with short-acting SSRIs such as paroxetine as well as the serotonin-norepinephrine reuptake inhibitor venlafaxine in its immediate- and extended-release prepa-

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rations) that may be attributed to the drug to which patients have been switched. The significant psychological and somatic symptoms reported in more than 50% of patients discontinuing antidepressants such as paroxetine and venlafaxine[5,6] may contribute to the lack of tolerance of the switch itself. Therefore, clinicians should be quite careful when they switch patients from agents frequently associated with these phenomena.

Switching to MAOIs and TCAs

Switching to monoamine oxidase inhibitors (MAOIs) is a very effective strategy for refractory depression. This strategy was popular in the 70s and 80s but today is typically considered only at the end of a treatment algorithm, primarily because of the dietary restrictions and the risk of hypertensive crises. Nevertheless, these agents may be particularly effective in patients with atypical unipolar depression[7] and anergic bipolar depression who have failed to respond to standard antidepressants.[8] Although the switch to tricyclic antidepressants (TCAs) has also been shown to be effective among SSRI nonresponders,[9] the popularity of this strategy has declined because of the improved safety profile of the newer agents.

Switching From One SSRI to Another SSRI

As mentioned earlier, switching patients from one SSRI to another is not the first choice for the majority of clinicians. However, this strategy—which is probably more commonly used by primary care physicians than psychiatrists—is supported by studies showing response rates from 42% to 71%.[3,4,10,11] It should be pointed out that these studies have several methodological limitations, including the retrospective (and not prospective) determination of nonresponse and the overlap between intolerance and nonresponse.

Switching to Bupropion

Even though switching to bupropion appears to be a very popular strategy among psychiatrists,[2] there is very little literature discussing it. Two small studies, by Goodnick et al.[12] and by Walker et al.,[13] show significant improvement upon switching SSRI-treated patients to bupropion. The main advantage of this strategy is probably the reduced risk of weight gain and sexual dysfunction; in fact, the study by Walker et al.[13] showed improvement in sexual functioning (and depression) upon switching to bupropion among 31 patients who had discontinued fluoxetine because of sexual side effects. Finally, an older study by Stern et al.[14] showed improvement among patients treated with bupropion after failing to respond to TCAs.

Switching to Venlafaxine

A study by Nierenberg et al.[15] showed a 30% to 33% response rate among 84 consecutive treatment-resistant, depressed patients (who had failed at least 3 antidepressant trials). The disadvantage of the strategy is that venlafaxine, acting more on the serotonin than on the norepinephrine system, may work better in TCA nonresponders and MAOI nonresponders than in SSRI nonresponders.[16]

On the other hand, a recent 6-week double-blind study[17] compared the efficacy of venlafaxine (200 to 300 mg/day) with that of paroxetine (30 to 40 mg/day) in 123 patients. These patients presented with major depression resistant to 2 adequate antidepressant trials in the course of an episode of depression of duration not exceeding 8 months. In this study, the percentage of patients presenting with remission was significantly higher in the group receiving venlafaxine (42%) compared with that receiving paroxetine (20%).

Switching to Nefazodone

Thase et al.[18] recently presented results of a multicenter study in which patients with poor response to SSRIs improved on switching to nefazodone. The main disadvantage of the nefazodone switch is that this drug is at times underdosed by clinicians, as it requires a dose escalation. On the other hand, treatment with nefazodone is associated with fewer sexual side effects than the SSRIs.[19]

Switching to Mirtazapine

A study by Catterson and Preskorn[20] found that 59% of 49 amitriptyline nonresponders exhibited good response (defined as a 50% reduction in the 17-item HAM-D score) upon switching to mirtazapine in a crossover phase. We have recently completed a multicenter study[21] that showed a 47% response rate to mirtazapine switch (15 to 45 mg/day) among 103 patients who had failed to tolerate or respond to SSRI treatment. The efficacy of mirtazapine was comparable among SSRI nonresponders (N = 76) and SSRI-intolerant patients (N = 18). Sedation and appetite increase/weight gain were the most common side effects, but an interesting advantage of the switch to mirtazapine was that by switching abruptly from the short-acting SSRI paroxetine to mirtazapine, there were fewer discontinuation-emergent symptoms than would have been the case with a washout period.[21] Similarly, the abrupt switch from SSRIs to mirtazapine was as effective as the switch after a brief washout.[21] In addition, there was a significant improvement in sexual functioning in a substantial proportion of patients with SSRI-induced sexual dysfunction.[21]

CONCLUSION

The switching strategy is a safe and effective approach to refractory or intolerant depressed patients. This strategy typically aims at obtaining a different neurochemical effect or reducing the likelihood of specific side effects (i.e., sexual dysfunction). Washout periods are typically necessary only with MAOIs, so that switches can be carried out

either by immediate substitution—which appears well tolerated when switching within the same class or, in some cases (e.g., when going from SSRIs to mirtazapine), even when switching to a different class—or with the gradual introduction of the new agent while slowly tapering the failed/nontolerated drug. Further studies are clearly needed to evaluate the efficacy and tolerability of this strategy.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), fluoxetine (Prozac), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), venlafaxine (Effexor).

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