Strategies for Switching Antidepressants to Achieve Maximum Efficacy

James W. Jefferson, M.D.

If a patient with major depressive disorder has not responded after an adequate trial of an antidepressant medication, switching to another antidepressant of the same class or a different class may help. When choosing an alternative antidepressant, clinicians should consider the patient's symptoms, drug preferences, and psychiatric and medical comorbidities, as well as drug tolerability, interactions, mechanisms of action, and cost. A wide range of antidepressants is available from a variety of classes, including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, norepinephrine and dopamine reuptake inhibitors, tricyclics, and monoamine oxidase inhibitors (MAOIs). From current evidence, it appears that a switch within or between any class is legitimate. When switching between antidepressants, an appropriate switching strategy should be used. Although a sufficient washout period is essential when switching to or from an MAOI, in switches between other classes of antidepressant, no single strategy has proven benefit over another. The direct approach to switching, the crossover approach, the moderate approach, and the conservative approach are all commonly used in clinical practice. Each switch strategy has advantages and disadvantages, and the choice should be made based on the patient, the patient's illness, the medications involved, and clinical judgment.
(J Clin Psychiatry 2008;69[suppl E1]:14–18)

For many reasons, patients with major depressive disorder (MDD) may not improve after taking an antidepressant, despite an adequate trial of medication and adherence to treatment. Switching to a different antidepressant is often necessary. A wide range of antidepressant drugs is available, and different switching strategies may be used depending on the individual patient and the drugs that the clinician is switching between.

From Healthcare Technology Systems, Inc., Madison Institute of Medicine and the University of Wisconsin School of Medicine and Public Health, Madison.

This article was derived from the planning teleconference series "Maximizing Efficacy of Antidepressants: Beyond SSRIs" that was held in November and December 2007 and supported by an educational grant from GlaxoSmithKline Services Unlimited.

Dr. Jefferson is a consultant for GlaxoSmithKline; has received grant/research support from Bristol-Myers Squibb, Forest, GlaxoSmithKline, Janssen, Eli Lilly, Novartis, Organon, Pfizer, Roche, Solvay, UCB Pharma, and Wyeth; has received lecture honoraria from Abbott, AstraZeneca, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Eli Lilly, Pfizer, UCB Pharma, Shire, and Wyeth; is a stock shareholder of Bristol-Myers Squibb, GlaxoSmithKline, and SciClone; is principal of Healthcare Technology Systems, Inc.; and has received other financial or material support from the pharmaceutical companies listed above.

Corresponding author and reprints: James W. Jefferson, M.D., Healthcare Technology Systems, 7617 Mineral Point Road, Suite 300, Madison, WI 53717 (e-mail: jjefferson@healthtechsys.com).

CRITERIA TO CONSIDER BEFORE SWITCHING ANTIDEPRESSANTS

If a patient does not respond to an antidepressant, clinicians should check that the following criteria have been met before switching to another medication:

- Diagnosis is accurate
- Dose is optimal
- Patient is taking the medication as prescribed
- Patient has tried the medication for at least 6 weeks, but 8 to 10 weeks is preferred

First, clinicians should check that the diagnosis is correct because patients are unlikely to respond well if the medication is not appropriate for the illness.[1] Next, the dose should be maximized, and clinicians should check that the patient is adhering to the treatment. If patients do not take the medication, or do not take it regularly, treatment is doomed to fail. Finally, treatment duration should be examined to ensure that the medication has been given an adequate trial.

According to Nemeroff,[1] if a patient has had a partial response to the medication in the first 4 to 6 weeks, then a full response may develop within another 4 to 6 weeks. Generally, clinicians consider making some kind of change if the medication has no effect after 3 or 4 weeks.

The change could be an increase in dose, augmentation, or a switch to a different medication.

Lack of adherence to antidepressant medication is an underappreciated problem in patients treated by primary care physicians or by psychiatrists. At least one fourth to one third of patients stop taking their antidepressant within the first month.[2,3] More than 40% of patients stop taking the medication within 3 months.[3,4] Clinicians may think they know whether their patients are taking antidepressants, but studies in a variety of medical areas have found that physicians and even patients themselves overestimate their degree of compliance with recommended therapy.[5–7] Among those who discontinue antidepressant treatment altogether, about 25% have not told their clinician about doing so.[8]

REASONS TO SWITCH MEDICATION

A switch to another medication may be indicated for many reasons. The medication may not work well enough, patients may not be able to tolerate the side effects, or they may develop other illnesses during the course of treatment that make it inappropriate to continue a particular medication because of drug interactions. Cost can also be a problem because a patient may not be able to afford the drug, and even if he or she is provided with free samples, when the patient has to pay for a prescription after the samples run out, he or she may discontinue that treatment.

Lack of full response to an antidepressant is a problem that affects the majority of patients with MDD. For example, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) program[9] was an effectiveness study among 2876 outpatients with MDD in a real-world setting. In this study, adequate dosing and duration of treatment were ensured, and remission was the primary goal of treatment. However, the remission rate at level 1 was only 28%.

CRITERIA TO CONSIDER WHEN SWITCHING ANTIDEPRESSANTS

A series of considerations have to be taken into account in deciding which antidepressant to switch to when the first is ineffective. These include patient symptoms, drug tolerability, patient and clinician drug preferences, psychiatric and medical comorbidities, drug interaction potential, cost, and drug mechanisms of action.

The patient's symptoms and lack of tolerance for side effects need to be assessed. For example, a patient might experience sexual dysfunction after taking a medication and want to switch to a drug less likely to cause this particular side effect.

Patients, like clinicians, may have drug preferences. Patient preferences are important in whether or not they accept the physician's preferred medication.[10] Preferences may be based on a variety of information sources including scientific evidence, television, the Internet, or the experience of a relative.[11]

Both psychiatric and medical comorbidities need to be considered when choosing a second antidepressant. For example, a patient may have an anxiety disorder or attention-deficit/hyperactivity disorder for which a particular new drug would be appropriate, or a medical comorbidity that a new medication might affect adversely. The potential for drug interactions should also be investigated, bearing in mind that many people take more than one medication whether by prescription, over-the-counter, or borrowed from a friend or relative.

As already mentioned, the patient's ability to pay for the medication cannot be ignored. Insurance coverage, if available at all, varies by patient and may change over time for the same patient.

Various classes of antidepressants are purported to have different mechanisms of action. Many clinicians believe that if an antidepressant from one class does not work, a better result might be obtained from a switch to an antidepressant from another class than to one with the same mechanism of action; however, this notion is not well established.

SWITCHING AFTER NONRESPONSE TO A SELECTIVE SEROTONIN REUPTAKE INHIBITOR

Clinicians may wonder whether a patient who has no response or partial response to a selective serotonin reuptake inhibitor (SSRI) should be switched to another SSRI or to a drug in another class. Drugs with different mechanisms of action than SSRIs include serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine and dopamine reuptake inhibitors (NDRIs), tricyclics, and monoamine oxidase inhibitors (MAOIs).

A study by Fredman and colleagues[12] examined the next-step choice of 432 clinicians when treating a patient with MDD who did not respond or responded suboptimally to an adequate course of an SSRI. When treating patients who did not respond after 8 weeks of treatment, 61% of participants chose to switch the patient to a different medication, 27% chose to raise the dose, and 12% chose to augment with another medication. When respondents who said they would switch a nonresponsive patient were asked what medication they would switch to, 72% selected a non-SSRI while 28% chose another SSRI. However, in the case of a patient with partial response after 8 weeks of adequate SSRI treatment, the most common choice (82%) was to increase the dose, and only 4% said they would switch to a different drug (two thirds of whom said they would choose a non-SSRI).

An examination[13] of switch studies in patients with MDD who had insufficient response to a first SSRI compared results from 8 randomized controlled trials and 23

open studies and included 3 of the STAR*D[14–16] switch studies. Studies of patients who did not respond to an SSRI and who were switched to another medication of any class showed a wide range of response rates (12% to 86%); similarly, remission rates varied between 7% and 82%. The ranges indicate that the studies were heterogeneous and varied considerably in quality of design. Venlafaxine was the most commonly studied medication used in the switch studies examined, but its clinical benefit over SSRIs was deemed to be "modest and clinically equivocal." The evidence did not justify recommendation of distinct next-step strategies. Overall, Ruhé and colleagues[13] concluded that, after nonresponse to a first SSRI, any switch within or between classes of antidepressant appears legitimate because no unequivocal evidence proved an advantage of a switch between classes.

Further, in contrast to studies in which response rates to different classes of medication are compared in patients who have failed to respond to medication, a meta-analysis[17] by Papakostas and colleagues compared response rates for 2 classes of antidepressant in patients with MDD who were not treatment resistant. Response rates for antidepressants that combined serotonin and norepinephrine mechanisms (i.e., venlafaxine, duloxetine, milnacipran, mirtazapine, mianserin, or moclobemide) were compared with SSRI response rates. The meta-analysis included 93 double-blind randomized trials involving 17,036 patients. A "modest efficacy advantage" was found for SNRIs over the SSRIs, but the number needed to treat (NNT) to have 1 additional responder was high (NNT = 24), thus raising the issue of clinical relevance.

In the STAR*D program,[14–16] trials of adequate duration and adequate dose compared remission rates for different classes of medication in adult outpatients with nonpsychotic MDD. In level 1, all participants were treated with the SSRI citalopram. Seven hundred twenty-seven patients who did not remit or who did not tolerate citalopram chose to switch to a different antidepressant.[14] The options available were bupropion sustained release (SR), an NDRI; sertraline, an SSRI; or venlafaxine extended-release (XR), an SNRI. Remission rates were as follows: bupropion SR, 21.3%; sertraline, 17.6%; and venlafaxine XR, 24.8%. No statistically significant difference was found among the 3 treatments in either remission rate or side effect burden.

Participants (N = 235) in level 3 of the STAR*D program[15] whose depression had failed to respond to or who were unable to tolerate the 2 previous trials of medication (first, citalopram, and second, either another antidepressant as described above or augmentation of citalopram with bupropion or buspirone) could choose a different augmentation strategy or a switch to a different agent. Those who selected to switch (N = 235) were randomly assigned to either mirtazapine or nortriptyline, drugs with dual effects on norepinephrine and serotonin. Remission rates were 19.8% for nortriptyline and 12.3% for mirtazapine, a difference that was not statistically significant. Dropout rates with side effects were not statistically significant, but were substantial (36.2% for nortriptyline vs. 34.2% for mirtazapine).

At level 4 of the STAR*D program,[16] patients who had not achieved remission or had been intolerant in 3 previous levels of the study were randomly assigned to receive either the MAOI tranylcypromine (N = 58) or venlafaxine XR plus mirtazapine (N = 51). Remission rates were 13.7% for the combination versus 6.9% for tranylcypromine, but the difference was not statistically significant. Dropout rates due to intolerable side effects, however, were significantly higher ($p < .05$) in the tranylcypromine group compared with the venlafaxine and mirtazapine group (41.4% vs. 21.6%). Overall, the STAR*D trial results did not provide convincing support for switching antidepressant medication based on mechanism of action.

SWITCH STRATEGIES

Having decided that a switch in antidepressant treatment is necessary, clinicians must determine which switch technique to use. Four strategies (or their variations) are common. With the direct switch, drug A is stopped and drug B is started the next day. With the crossover switch, drug A is tapered and drug B is titrated up simultaneously. In the moderate approach, drug A is tapered, a brief washout period is used, and drug B is started at a low dose after the washout phase. When the conservative switch is employed, drug A is tapered and discontinued, a 4 to 5 half-life washout is used, and then drug B is started. Unless switching to and from MAOIs, in which the conservative approach should be used, no switching strategy has well-established benefits over another, and the choice of strategy should be based on patient characteristics, the drugs involved, and clinical judgment.

The Direct Switch

When the direct switch approach is employed, the patient's current antidepressant is stopped one day and the new antidepressant is started the next day. The advantages of this method are that it is quick and simple. However, discontinuation symptoms and drug interactions can be a concern. Clinicians may have difficulty determining whether an adverse event is a discontinuation symptom, a side effect of the second drug, or an interaction between the 2 drugs.

A review by Haddad[18] noted that short half-life drugs, such as paroxetine and venlafaxine, are more likely to cause discontinuation symptoms. Discontinuation symptoms are less likely to occur when switching within the same class of antidepressant. If patients are educated about what to expect when switching antidepressant

medication, they are often more tolerant of discontinuation symptoms that are annoying but not dangerous. In the STAR*D studies,[14] direct switching was used with one exception and was apparently well tolerated.[15,16] The exception was that when switching to the MAOI tranylcypromine, a 2-week washout period was used.[16]

The tolerability of switching either with or without a washout period was compared in patients switched from fluoxetine, a drug with a long half-life, to paroxetine, an antidepressant in the same class with a shorter half-life.[19] One group switched the next day, and the other group had a 2-week washout phase. Although fewer side effects occurred in the group with the washout period, no significant difference was found in the percentages of participants who dropped out because of adverse experiences (i.e., 5% in the group with the 2-week washout vs. 6.5% with no washout).

In a study by Wohlreich and colleagues,[20] patients with MDD who either had not responded to or did not tolerate an SSRI or venlafaxine (a short half-life drug) were switched directly to duloxetine. Results were compared with currently untreated patients with MDD in whom duloxetine was initiated. There was no significant difference between groups in sustained response or remission rates, but the adverse event dropout rate was significantly lower ($p = .008$) in the switch group (4.5%) versus the initiating group (17.9%). Most recently, a study[21] that compared direct switching from SSRIs to duloxetine, 60 mg/day, ($N = 183$) to starting duloxetine, 60 mg/day, while tapering SSRIs over 2 weeks ($N = 185$) found equivalent response and remission rates. Adverse event dropout rates were 6.6% and 3.8%, respectively.

The Crossover Switch

The crossover approach for switching antidepressants is commonly used in clinical practice. The dose of the first antidepressant is tapered down gradually, and the dose of the new medication is simultaneously built up. Generally, clinicians start with a lower dose of the second drug than usual. The benefits of this strategy are that the patient does not have a break in treatment, and for a period of time the patient has the benefit of combination therapy. Sometimes a patient responds particularly well to the combination, and although polypharmacy has risks as well as increased cost, the clinician and the patient may be happy to continue both medications for a period of time. The risks of polypharmacy include the potential for drug interactions and a greater number of side effects.

The Moderate Switch

The moderate approach is a variation of the crossover switch. The dose of the first medication is tapered and then washed out for a few days. The second drug is then started at a conservative dose. This strategy has some risk of drug interactions and is more time-consuming than the direct or crossover approaches, but it is a safe approach.

Table 1. Washout Period Necessary When Switching to or From an MAOI

Switch From	Switch to	Washout Period
Venlafaxine or nefazodone	MAOI	At least 1 week
MAOI	Another class of antidepressant	At least 2 weeks
MAOIs, bupropion, mirtazapine, TCAs, SSRIs *except* fluoxetine	MAOI	At least 2 weeks
Fluoxetine	MAOI	At least 5 to 6 weeks

Abbreviations: MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

The Conservative Switch

The conservative strategy involves gradual discontinuation of the first medication followed by a washout period of 4 to 5 half-lives before the new antidepressant is started. The benefit of this approach is safety, but the switch is slow and leaves the patient without treatment for some time. Patients who are already discouraged because the first drug did not work can feel demoralized when they have to wait longer for the new treatment.

When switching to and from MAOIs, the conservative strategy must be used because a sufficient washout period is essential. An insufficient washout period can have fatal consequences. All MAOI antidepressants approved for use in the United States (including transdermal selegiline) are irreversible inhibitors and should be switched with extreme caution. For example, a series of case reports[22] highlighted the importance of avoiding the use of fluoxetine and MAOIs in close temporal proximity; of 8 patients described, 7 died.

As shown in Table 1, the washout period required with MAOIs varies depending on the drugs involved in the switch. For example, if a patient is taken off treatment with a drug that has a relatively short half-life, such as venlafaxine or nefazodone, a washout period of at least 1 week is needed. If a patient is switched to an MAOI from any other antidepressant except fluoxetine, at least a 2-week washout is necessary. Similarly, if a patient is switched from an MAOI to another MAOI or to another class of antidepressant, at least 2 weeks of washout is required.

CONCLUSION

Switching a patient from one antidepressant to another is often necessary because of nonresponse, intolerability, or cost. Fortunately, many antidepressants are available from which to choose, and the choice can be based on the individual patient's profile. Currently, no clear indicators are available to determine the most appropriate second drug to use when switching, but mechanism of action and clinical experience may provide some guidance. Several switching strategies are commonly used, each with advan-

tages and disadvantages, but no single method is superior in all cases. Choice of switching strategy depends on characteristics of the patient, the drugs involved, and the clinician's best judgment. Patients must be educated so that they know what to expect. Clinicians need to be flexible and approach switching drugs in a way that is tailored to the individual patient.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), selegiline (EMSAM), sertraline (Zoloft and others), tranylcypromine (Parnate and others), venlafaxine (Effexor and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

REFERENCES

1. Nemeroff CB. Augmentation strategies in patients with refractory depression. Depress Anxiety 1996–1997;4:169–181
2. Simon GE, Von Korff M, Wagner EH, et al. Patterns of antidepressant use in community practice. Gen Hosp Psychiatry 1993;15:399–408
3. Lin EH, Von Korff M, Lin E, et al. The role of the primary care physician in patients' adherence to antidepressant therapy. Med Care 1995;33:67–74
4. Katon W, Von Korff M, Lin E, et al. Collaborative management to achieve treatment guidelines: impact on depression in primary care. JAMA 1995;273:1026–1031
5. Parker CS, Chen Z, Price M, et al. Adherence to warfarin assessed by electronic pill caps, clinical assessment, and patient reports: results from the IN-RANGE study. J Gen Intern Med 2007;22:1254–1259
6. Bachmann LH, Stephens J, Richey CM, et al. Measured versus self-reported compliance with doxycycline therapy for chlamydia-associated syndromes: high therapeutic success rates despite poor compliance. Sex Transm Dis 1999;26:272–278
7. Waterhouse DM, Calzone KA, Mele C, et al. Adherence to oral tamoxifen: a comparison of patient self-report, pill counts, and microelectronic monitoring. J Clin Oncol 1993;11:1189–1197
8. Demyttenaere K. Risk factors and predictors of compliance in depression. Eur Neuropsychopharmacol 2003;13(suppl 3):S69–S75
9. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006;163:28–40
10. Hunot VM, Horne R, Leese MN, et al. A cohort study of adherence to antidepressants in primary care: the influence of antidepressant concerns and treatment preferences. Prim Care Companion J Clin Psychiatry 2007;9:91–99
11. Sleath B, Wurst K, Lowery T. Drug information sources and antidepressant adherence. Community Ment Health J 2003;39:359–368
12. Fredman SJ, Fava M, Kienke AS, et al. Partial response, nonresponse and relapse with selective serotonin reuptake inhibitors in major depression: a survey of current "next-step" practice. J Clin Psychiatry 2000;61:403–408
13. Ruhé HG, Huyser J, Swinkels JA, et al. Switching antidepressants after a first selective serotonin reuptake inhibitor in major depressive disorder: a systematic review. J Clin Psychiatry 2006;67:1836–1855
14. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion SR, sertraline, or venlafaxine XR after failure of SSRIs for depression. N Engl J Med 2006;354:1231–1242
15. Fava M, Rush AJ, Wisniewski SR, et al. A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: a STAR*D report. Am J Psychiatry 2006;163: 1161–1172
16. McGrath PJ, Stewart JW, Fava M, et al. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. Am J Psychiatry 2006;163: 1531–1541
17. Papakostas GI, Thase ME, Fava M, et al. Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? a meta-analysis of studies of newer agents. Biol Psychiatry 2007;62:1217–1227
18. Haddad PM. Antidepressant discontinuation syndromes: clinical relevance, prevention and management. Drug Saf 2001;24:183–197
19. Kreider MS, Bushnell WD, Oakes R, et al. A double-blind, randomized study to provide safety information on switching fluoxetine-treated patients to paroxetine without an intervening washout period. J Clin Psychiatry 1995;56:142–145
20. Wohlreich MM, Mallinckrodt CH, Watkin JG, et al. Immediate switching of antidepressant therapy: results from a clinical trial of duloxetine. Ann Clin Psychiatry 2005;17:259–268
21. Perahia DGS, Quail D, Desaiah D, et al. Switching to duloxetine from selective serotonin reuptake inhibitor antidepressants: a multicenter trial comparing 2 switching techniques. J Clin Psychiatry 2008;69:95–105
22. Beasley CM, Masica DN, Heiligenstein JH, et al. Possible monoamine oxidase inhibitor-serotonin uptake inhibitor interaction: fluoxetine clinical data and preclinical findings. J Clin Psychopharmacol 1993;13:312–320