Augmentation Strategies to Increase Antidepressant Tolerability

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The goal of antidepressant treatment is full remission, but adverse events prevent many patients from reaching and sustaining this goal. Differential diagnosis should be made between antidepressant side effects and adverse events that are related to other causes. Antidepressant side effects may be transient or persistent and may occur early or later in treatment. Pharmacologic and nonpharmacologic strategies can be used to improve the tolerability of antidepressants, resulting in a greater probability of achieving and sustaining remission. *(J Clin Psychiatry 2007;68[suppl 10]:23–27)*

While the goal of treating depression includes achieving and sustaining remission, it also includes minimizing adverse events and addressing the safety and tolerability issues of treatment. Adverse events that occur during treatment can result in failure to achieve and sustain remission; for example, adverse events can result in failure to reach a therapeutic dose of an antidepressant, and premature discontinuation of treatment for side effects, and can themselves be misconstrued as side effects when they may be secondary to another modifiable cause.

Establishing a therapeutic alliance with the patient early in treatment is important so that clinicians can address tolerability issues and encourage adherence to treatment. The long-term chronic nature of depression makes documenting signs, symptoms, and psychosocial functioning vital before starting treatment and throughout treatment. This documentation provides a resource to monitor improvement, assess residual symptoms, and ascertain the etiology of adverse events that occur in the course of treatment.[1]

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DIFFERENTIAL DIAGNOSIS OF ADVERSE EVENTS

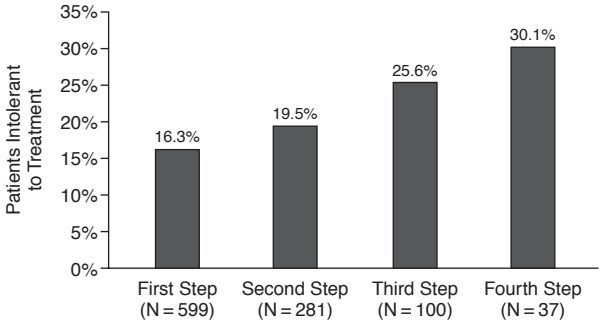
Not all adverse events are due to the side effect burden of antidepressant medication. It is important to distinguish between symptoms arising from antidepressant treatment intolerance and symptoms arising from other causes such as nonadherence, antidepressant syndrome,[2–4] underdosing,[5] other medications, medication interaction, worsening depression due to life stressors or natural course of illness, residual depression,[5] psychiatric and medical comorbidities (e.g., undiagnosed bipolar disorder), or use of alcohol or illicit substances.[3] Clinicians should look for all possible modifiable factors that can be followed up by an intervention.

ANTIDEPRESSANT SIDE EFFECTS

The primary reason people stop antidepressant therapy, during both acute and long-term treatment phases, is side effects.[3] Recent data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial[6] suggest that intolerance to treatment increases over time with each new treatment level (Figure 1).

Antidepressants vary in their side effects, safety, and tolerability,[7–10] and side effects can be short-lived or persistent. While the newer antidepressants in the last decade have demonstrated better overall safety and tolerability compared with tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), these older generation treatments are still viable options to treat depression, and managing side effects may allow optimal dosing and long-term tolerability. The TCAs can be associated with acute and long-term side effects that are linked to muscarinic blockade (e.g., dry mouth, constipation, blurred vision, memory problems, sexual dysfunction, and tachycardia), histaminic blockade (e.g., sedation,

Figure 1. Treatment Intolerance at Each Treatment Level of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study[a]



[a]Data from Rush et al.[6] Participants were considered to have intolerable side effects if they left the treatment level prior to 4 weeks for any reason or left thereafter citing treatment intolerance as the reason.

increased appetite, and weight gain) or α-adrenergic blockade (e.g., sexual dysfunction, orthostatic blood pressure changes, and reflex tachycardia).[1,11] In addition to the dietary and medication restrictions associated with the use of MAOIs, common side effects can include orthostatic hypotension and reflex tachycardia, insomnia, sexual dysfunction, and weight gain.

Both new- and old-generation antidepressant side effects can be divided into early-onset and late-onset side effects. Early-onset side effects may be either transient, including nausea, insomnia, diarrhea, and anxiety, or persistent, including weight gain, sedation, and sexual dysfunction. Late-onset side effects may include sexual side effects, asthenia, and weight gain. Clinicians should treat early-onset side effects but also remain vigilant for late-onset side effects that may require management even when patients have fully remitted.

MANAGEMENT AND AUGMENTATION STRATEGIES TO IMPROVE TOLERABILITY

Clinicians can educate patients about the usual time until the effects of medication are noticeable and the importance of continuing medication even if they feel better and consulting the physician before discontinuing medication. Providing clear instructions about daily dosing regimens, inviting questions, and providing office contacts are also helpful.[3] It is important to discuss realistic treatment expectations with patients and explain that remission is the goal. Adherence to long-term therapies should be regularly assessed and reinforced. A relapse prevention program, including extra visits, telephone monitoring, and patient education, can promote adherence, reduce depressive symptoms, and help minimize dropout rates for reasons of intolerance.[12]

When patients respond to antidepressant treatments and then experience side effects, strategies are available to help them tolerate the medication rather than switch treatment (Table 1).[1,13–15] For patients who have shown a good response to treatment but still have residual symptoms of depression or a comorbid psychiatric illness and side effects, an augmentation strategy to both improve efficacy and manage the side effect can be used. For example, management strategies for common side effects of TCAs include bethanechol for urinary retention; bulk laxatives for constipation; artificial saliva for dry mouth and artificial tears for dry eyes, or pilocarpine to treat both; changes in diet and exercise for increased appetite and weight gain; night dosing for sedation; and salt tablets, fluids, and support hose for orthostatic hypotension. Orthostatic hypotension is among the most clinically significant side effects of MAOIs, but because these agents may be the endpoint of pharmacologic treatment for a patient with major depressive disorder, treating a side effect such as low blood pressure may be preferable to switching medication and denying the patient a potentially effective treatment.

Early in treatment, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) can cause nausea, which is thought to be due to the acute increase of serotonin and the effect on the serotonin-3 receptors.[16] Physicians can encourage patients to endure this transient early-onset symptom, or they can lower the dosage. An attempt should be made to increase the dose again later if warranted by lack of full efficacy. Blocking the serotonin-3 receptor for several weeks with an agent such as mirtazapine or ondansetron is an alternate augmentation strategy.

SSRIs, SNRIs, and bupropion may be associated with transient early-onset activating side effects, which may be a result of over-activation of the serotonin-2 receptor or acute indirect effects on the norepinephrine receptor. A dose reduction and gradual increase of dose over time may be considered, alone or in combination with a pharmacologic augmentation. The atypical antipsychotics or low doses of nefazodone or trazodone can block the serotonin-2 receptors. Benzodiazepines may also be used to manage early- or late-onset anxiety associated with the treatment of depression.

Many of the augmentation strategies used to treat side effects are also antidepressant potentiation strategies. Stimulants and modafinil may be used for improving focus, concentration, and fatigue; similarly, methylfolate is potentially helpful for cognitive effects.[1] Combination or augmentation strategies should be tailored to the individual patient and his or her symptoms. A synergistic or an enhanced pharmacologic profile should be chosen; for example, a noradrenergic or dopaminergic agent such as atomoxetine, stimulants, or bupropion should be combined with SSRIs.[1]

MANAGING LATE-ONSET OR PERSISTENT SIDE EFFECTS

Sexual Dysfunction

The etiology of sexual dysfunction and dissatisfaction in the depressed population may be multifactorial.[13,14,17] It is important to obtain baseline information for all patients in order to differentiate between antidepressant side effects and long-standing primary sexual dysfunction. After ruling out causes of sexual dysfunction other than the antidepressant, management of this side effect includes several options. Clinicians can recommend waiting for adaptation to occur, but patients may not tolerate waiting. The antidepressant dose can be lowered, provided it is not done at the cost of losing efficacy. Pharmacologic antidotes may be used, or as a last resort, switching antidepressants is an option. Treatment should be tailored to the individual patient, who should be involved in the treatment selection process.

Many antidotes exist for antidepressant-induced sexual dysfunction[13,17,18]; however, few controlled trials exist for these antidotes. Numerous variables can play a role in sexual dysfunction. Some of the more common augmentation strategies include buspirone, bupropion, mirtazapine, and nefazodone, as well as the agents that are used to treat erectile dysfunction and are thought to be effective in both men and women due to increased blood flow.[13,17,18] Yohimbine is another possible augmentation agent; however, caution is needed in patients with anxiety because yohimbine can be anxiogenic.[13,18]

With SSRIs, when serotonin is increased selectively, norepinephrine and dopamine are potentially lowered in a compensatory effect, which can lead to orgasm dysfunction.[13,18] As a result, augmenting with stimulants and even amantadine shows some benefit in treating the various phases of sexual dysfunction caused by SSRIs.[13,17,18] With MAOIs, TCAs, SSRIs, and venlafaxine, augmenting with cyproheptadine can be useful because of the

Table 1. Strategies to Improve Tolerability of Antidepressant Side Effects[a]

Side Effect	Possible Strategies
Activating effects (eg, increased anxiety, agitation, restlessness)	Lower dose of antidepressant Wait for adaptation Benzodiazepine Atypical antipsychotic β-Blockers Switch antidepressant
Asthenia (eg, restricted range of emotions, feeling "dulled," fatigue, apathy, amotivation)	Lower dose of antidepressant Dose later in day Augmentation Stimulants Modafinil Bupropion Methylfolate Atomoxetine Switch antidepressant
Blurred vision	Lower dose of antidepressant If secondary to anticholinergic effects (eg, TCAs) Pilocarpine Bethanechol Switch antidepressant
Cognitive impairment	Lower dose of antidepressant Augmentation Stimulants Atomoxetine Methylfolate Acetylcholinesterase inhibitors Switch antidepressant
Constipation	Lower dose Bulk laxative and increase fluid intake Stool softeners Bethanechol
Dry mouth	Lower dose Artificial saliva Mouth rinses to promote saliva Sugarless candy/gum Bethanechol
Insomnia	Lower dose Wait for adaptation Morning dosing Sedative/hypnotics (zolpidem, zaleplon, eszopiclone, ramelteon) Trazodone Sedating antihistamines Atypical antipsychotics Benzodiazepines Switch antidepressant
Nausea	Wait for adaptation Lower dose or split up dose Take with food (high protein) Augmentation (short-term) Mirtazapine Ondansetron
Orthostatic hypotension	Reduce dose of antidepressant Split dose of antidepressant Increase fluid intake Increase salt intake or give enteric-coated salt tablets Support-hose stockings Fludrocortisone Switch antidepressant
Psychotic symptoms	Remove potential cause (eg, stimulants, dopamine agonists, bupropion) Add an antipsychotic If possible mania Discontinue or reduce antidepressant Add antipsychotic and/or mood stabilizer Consider electroconvulsive therapy

continued

Table 1. Strategies to Improve Tolerability of Antidepressant Side Effects[a] (cont.)

Side Effect	Possible Strategies
Sedation/somnolence	Split up dose or dose later in day Reduce dose of antidepressant Augmentation Modafinil Stimulants Bupropion Atomoxetine Switch antidepressant
Sexual side effects (eg, decreased libido, arousal, delayed orgasm, anorgasmia)	Wait for adaptation Lower dose of antidepressant Switch antidepressant Augmentation (tailor to suspected mechanism causing the side effect, type of side effect, and compatibility with the current antidepressant) Agents that directly modulate dopamine and/or norepinephrine Amantadine Bupropion Stimulants Pramipexole Agents that antagonize the 5-HT_2/5-HT_3 receptor Cyproheptadine Nefazodone Mirtazapine Atypical antipsychotics Granisetron Agents that modulate cholinergic receptors Bethanechol Agents that modulate α-adrenergic receptors Trazodone Yohimbine Phosphodiesterase inhibitors Tadalafil Sildenafil Vardenafil
Sweating	Increase or decrease dose of antidepressant Terazosin Switch antidepressant
Urinary retention/hesitancy	Lower dose of antidepressant (eg, SNRI) Bethanechol (eg, TCAs)
Weight gain/ increased appetite	Diet/exercise "Wait for satiation" after meals/portion control Structured weight loss programs (eg, Weight Watchers) Augmentation Stimulants Topiramate Orlistat Amantadine Metformin Switch antidepressant

[a]Based on Zajecka and Goldstein,[1] Zajecka,[13,14] and Papakostas and Schwartz.[15]
Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor, TCA = tricyclic antidepressant.

5-HT_2 blockade effect, which results in a quick reversal of orgasm delay.[13,17,18] Atypical antipsychotics can also help reduce the sexual side effect burden of SSRIs, because the serotonin-2 receptor mediates and modulates norepinephrine and dopamine.[1,19]

Asthenia

With SSRIs, the compensatory decrease of both norepinephrine and dopamine may lead to asthenia or cognitive dulling later in treatment.[1,13] The term *asthenia,* used loosely here, refers to tachyphylaxis or "poop-out" as well as cognitive symptoms, for example apathy, amotivation, fatigue, mental dulling (such as word-finding problems), and forgetfulness.[14] Ruling out other causes of these symptoms is important. Residual depressive symptoms, drug interaction effects, and other iatrogenic or medical causes such as folate deficiency or hypothyroidism may be contributing to asthenia. After other causes have been ruled out, management strategies include using pharmacologic intervention to raise dopamine and norepinephrine levels, lowering the SSRI dose (although this should not be done at the cost of losing efficacy), or taking medication in the latter part of the day.[1,13]

Antidepressants with dual-reuptake blockade such as duloxetine or venlafaxine can be considered at the outset of treatment to prevent these late-onset symptoms in some patients.[13,14] However, if patients are already taking SSRIs and experience asthenia, augmentation with dopamine- and norepinephrine-promoting agents such as bupropion, atomoxetine, methylphenidate, amphetamine, or modafinil can be effective in some patients.[1] Methylfolate is a promising augmentation strategy for patients who experience cognitive dysfunction, fatigue, or other symptoms associated with asthenia, although further research is needed, and is also promising in populations that include patients with low red blood cell folate levels or who are at risk for central nervous system folate utilization (due to, for example, comorbid chronic illness, oral diabetic medications, statins, oral contraceptives, some anticonvulsants, smoking, or alcohol use).[20–22]

Weight Gain

Weight gain can be a problem for people taking antidepressants. The H_1 blockade of some antidepressants, such as the TCAs and mirtazapine, may have direct and indirect effects on appetite increase. In the case of SSRIs and venlafaxine, weight gain may be a rare late-onset effect in some patients. Possible causes are regained weight that was lost during the depressive episode, concurrent medications, direct metabolic effects, and receptor effects. As with other

possible side effects, it is important to make a differential diagnosis to rule out such problems as iatrogenic or hypothyroid causes.[13] Augmentation with stimulants or another antidepressant may be helpful for managing weight gain. Routine nonpharmacologic strategies can help, such as encouraging patients to decrease caloric intake and increase activity, switch to low caloric carbohydrates such as fruit or "watered down" fruit juices, ensure adequate hydration since mild dehydration can result in an urge to eat rather than drink, and attend weight loss programs. Finally, switching antidepressants may help combat weight gain problems, but clinicians should ensure that the switch does not interfere with overall treatment efficacy.

CONCLUSION

Although tolerability of antidepressants can be a problem, many short- and long-term factors are modifiable. Initial choice of medication, dose adjustment, augmentation with treatments that enhance efficacy and also treat side effects, and nonpharmacologic strategies can help patients tolerate antidepressants.

Drug names: amantadine (Symmetrel and others), amphetamine (Adderall, Dextroamp, and others), atomoxetine (Strattera), bethanechol (Urecholine, Duvoid, and others), bupropion (Wellbutrin and others), buspirone (BuSpar and others), duloxetine (Cymbalta), eszopiclone (Lunesta), fludrocortisone (Florinef), granisetron (Kytril), metformin (Fortamet, Glumetza, and others), methylfolate (Deplin, Cerefolin NAC), methylphenidate (Ritalin, Concerta, and others), mirtazapine (Remeron and others), modafinil (Provigil), ondansetron (Zofran and others), orlistat (Xenical), pilocarpine (Salagen and others), pramipexole (Mirapex), ramelteon (Rozerem), sildenafil (Revatio, Viagra), tadalafil (Cialis), terazosin (Hytrin), topiramate (Topamax and others), vardenafil (Levitra), venlafaxine (Effexor and others), zaleplon (Sonata), zolpidem (Ambien, Tovalt, and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, amantadine, bethanechol, granisetron, metformin, ondansetron, orlistat, pilocarpine, sildenafil, tadalafil, terazosin, topiramate, vardenafil, and yohimbine are not approved by the U.S. Food and Drug Administration for the management of a psychotropic side effect; and amphetamine, atomoxetine, bupropion, buspirone, methylfolate, methylphenidate, mirtazapine, modafinil, nefazodone, pramipexole, and trazodone are not approved for the management of a psychotropic side effect to augment the efficacy of the combination treatment.

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