Managing the Adverse Effects of Antidepressants

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Most, if not all, antidepressants can cause bothersome adverse effects. These are described here along with strategies to help patients cope.

Primum non nocere

—Hippocratic Oath

Antidepressants are among the most widely prescribed drugs. Both in Europe and the US, 6% to 10% of the population are treated with antidepressant medications. Most, if not all, antidepressants can cause bothersome adverse effects in a substantial number of patients, with nonadherence as a likely consequence. Nonadherence rates are high, estimated to be between 31% and 60%, and are probably governed by a trade-off between perceived benefits and drawbacks. Adverse effects are dramatically underestimated by the prescribing physicians: more than 80% of patients experience at least one and, on average, patients experience 4 different adverse effects, most of which pose substantial bother, sometimes to the extent that the patient’s daily functioning is affected. Not surprisingly, for about 20% of (primary care) patients, the benefits of antidepressants do not outweigh the adverse effects.

Modern antidepressants held the promise of reducing the adverse-effect burden of the older TCAs. This did not, however, prove to be true. The burden might have changed, but it did not diminish. The most frequently experienced adverse effects, according to a recent survey in 225 primary care patients using different types of antidepressants, are shown in the Figure. Patients seem to be bothered the most by GI complaints, dizziness, weight gain, and decreased libido.

**Jitteriness syndrome**

Jitteriness is a poorly defined syndrome of early worsening of anxiety, agitation, and irritability. It is estimated to occur in up to 65% of patients immediately after starting therapy with a serotonergic or noradrenergic antidepressant. Its importance lies in the fact that it might cause patients to discontinue treatment if they become convinced that it will worsen their condition. A slower titration, especially in patients with anxiety symptoms, might prevent the syndrome. Since jitteriness is time-limited, waiting for tolerance to develop or temporarily combining the antidepressant with a benzodiazepine or propranolol may be helpful.

**CASE VIGNETTE**

Peter is 36, is depressed, and suffers from panic attacks. He is referred by his primary care physician because “things got worse” after starting therapy with escitalopram. He reports having had occasional panic attacks before he started taking the medication, but after beginning the treatment, he was “freaking out all day, couldn’t sit still, and felt restless all the time. It made everything worse.” Even after his physician explained that these effects were likely temporary, Peter refused to continue taking the medication. Eventually he consented to try another SSRI, which was started at the lowest dose and slowly titrated.

**Other adverse effects**

**GI problems.** Complaints such as nausea emerge in about 25% of patients, soon after initiating modern antidepressants. Such complaints are more frequent with venlafaxine and SSRIs than with bupropion, mirtazapine, or reboxetine. In most cases, nausea wanes after 2 or 3 weeks, but it persists in about one-third of patients. Dividing doses, taking medication with some food, or administering more of the dose at bedtime can help; ginger may be beneficial when taking ranitidine or omeprazole. Adding low-dose mirtazapine to the antidepressant regimen may also help.

Diarrhea develops in about 15% of patients. Antidiarrheal agents may be helpful, although in patients in whom diarrhea persists, a switch to another agent should be considered. Constipation, an adverse effect described as bothersome in about 5% of patients, can be managed by physical activity, fluid and fiber intake, or laxatives.

**Weight gain.** Another frequent adverse effect of long-term antidepressant treatment is weight gain.
Several antidepressants cause an initial but transient weight loss, followed by weight gain during maintenance treatment. The majority of antidepressants cause only slight weight gain, except for mirtazapine, amitriptyline, and paroxetine. Bupropion is the only antidepressant that induces weight loss.

Various strategies are suggested, such as nutritional counseling and physical exercise, but most often, antidepressants need to be switched. If a switch is not an option, the addition of bupropion or a psychostimulant can be considered. In any case, patients with a high risk of weight gain should be advised to avoid low-volume, high-calorie foods when they begin treatment with an antidepressant. 

**Sweating.** As many as 20% of patients taking antidepressants experience excessive sweating. It is commonly prominent in the scalp, face, neck, and chest and usually occurs with episodic bursts, often persisting throughout treatment. Reboxetine, venlafaxine, and bupropion increase susceptibility, whereas paroxetine and mirtazapine might decrease susceptibility. Several agents have been proposed to treat excessive sweating, based on hypotheses about its pathophysiology: serotonin antagonists, such as cyproheptadine; antiadrenergic agents, such as clonidine; and anticholinergic agents, such as benztrapine and glycopyrrolate.

**Sexual dysfunction.** Antidepressants can affect every aspect of sexual functioning and cause decreased libido, problems with arousal, ejaculatory delay, anorgasmia, and erectile dysfunction. Prevalence rates up to 80% have been reported. SSRIIs are more likely to cause sexual adverse effects than are noradrenergic drugs. In some patients, sexual adverse effects will disappear spontaneously or improve after dose reduction. Taking a drug holiday, ie, stopping the antidepressant for a few days, has been shown to improve sexual function and satisfaction in approximately half of the patients taking an SSRI with a short half-life, such as sertraline or paroxetine. The addition of sildenafil or tadalafil is an effective strategy for men with antidepressant-induced erectile dysfunction. In women, transdermal testosterone increases the frequency of satisfactory sexual events; adding a higher dose of bupropion (300 mg/d) also seems to improve sexual function. Although generally considered to resolve on cessation of the drug, SSRI- and SNRI-emergent sexual adverse effects may persist after drug discontinuation in some patients. Psychological processes probably play a role in the persistence of these sexual dysfunctions, and they should be addressed.

**Sedation.** Often wanted but frequently annoying, sedation is more commonly associated with TCAs and mirtazapine than with SSRIs and SNRIs. In the event that dose reduction or bedtime dosing does not help, switching to a less sedating alternative, such as bupropion, an SSRI, or an SNRI, can be considered. In the case of excessive sleepiness and fatigue, adjunctive modafinil can be considered to improve wakefulness.

A dose-related and reversible decrease in motivation and emotional responsivity or detachment, also referred to as apathy or emotional blunting, has been reported, mainly in case reports and predominantly associated with the use of SSRIs. In these cases, reducing the dose or switching to another antidepressant, preferably bupropion, may help.

**The discontinuation syndrome**

A final hurdle to overcome is the discontinuation syndrome, which develops in some patients (5% to 86%) 1 to 7 days following dose reduction or discontinuation of an SSRI or SNRI. Typically, patients describe electric shocks in the brain, visual flashes, and headaches. Other symptoms are dizziness, lethargy, light-headedness, insomnia, fatigue, anxiety, agitation, and nausea. This syndrome has been linked to the half-life of a given SSRI; paroxetine has been involved more often than other SSRIs. Tailoring tapering to the individual patient and to the specific antidepressant should reduce the likelihood of experiencing discontinuation symptoms. In some cases, prescribing an SSRI with a longer half-life (eg, fluoxetine) while discontinuing the antidepressant might be helpful.

**CASE VIGNETTE**

Maria, who is 58, was treated for depression and anxiety. She has been referred by her primary care physician because her symptoms relapsed during tapering of venlafaxine. She reports, “Two days after tapering, I felt electrical twitches in my head; I have headaches and feel nervous and agitated. I think I am relapsing and will have to take my pills forever.” Maria is experiencing discontinuation symptoms. Gradual tapering of venlafaxine, taking 37.5 mg every other day, does not prevent severe discontinuation symptoms. Fluoxetine 20 mg/d is prescribed, and venlafaxine is discontinued without any problem. Fluoxetine is then gradually tapered, but about 2 weeks after the final dose, Maria experiences mild discontinuation symptoms (“feeling nervous”). These disappear after another week.
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Serious adverse effects
Apart from the annoying and bothersome adverse effects described above, the clinician should be aware of several serious adverse effects that can be associated with modern antidepressants. In a small subgroup (4% to 14%) of younger patients, suicidal ideation can emerge in the first weeks following treatment initiation and dose adjustments. Even after short-term use of an SSRI or venlafaxine, the risk of upper GI bleeding is slightly higher than with the older TCAs, especially in higher-risk situations such as alcohol use. Although depression is associated with the metabolic syndrome and some antidepressants may induce weight gain, there may not necessarily be a correlation between the two. However, in young adults, long-term antidepressant use may increase the risk of type 2 diabetes mellitus. Although more often associated with TCAs, cardiovascular adverse effects, seizures, and agranulocytosis are also possible adverse effects of other antidepressants. Treatment decisions based on identifying risk factors, carefully reviewing all appropriate antidepressants, and patient preferences, as well as careful monitoring, will help keep adverse effects to a minimum (Table).

Conclusion
Clinicians will be confronted with bothersome and sometimes severe adverse effects in their patients when prescribing antidepressants. Before the initiation of antidepressant treatment, patients should be informed about potential adverse effects and encouraged to contact the physician with any concerns, so that these can be managed adequately. As a rule, begin with an antidepressant that has shown better tolerance at the lowest dose, then titrate slowly. Careful monitoring should focus on tolerance as well as on symptom alleviation. It is important to distinguish adverse effects from depression symptoms, such as fatigue and carbohydrate craving. Should bothersome adverse effects emerge, watchful waiting is often a reasonable option, since most adverse effects diminish over time. Either reducing the dose or adjusting the dosing schedule can be tried before switching to another antidepressant. If this strategy is not successful, the (off-label) addition of other pharmacological agents can be considered.

Disclosures:
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References:


6. Uguz F. Low-dose mirtazapine added to selective serotonin reuptake inhibitors in pregnant women with major depression or panic disorder including symptoms of severe nausea, insomnia and decreased appetite: three cases. *J Matern Fetal Neonatal Med.* 2013;26:1066-1068.


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