Clinical Issues in Long-Term Treatment With Antidepressants

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Historically, the emphasis in treating depression has been focused on the acute phase of treatment, with few published data on the continuation and maintenance phases of treatment. Yet the risk of depression increases with each episode, with a 50% to 90% chance of developing another episode after 1 or 2 prior episodes of depression. Moreover, subsequent episodes of depression are often of longer duration, more severe, and less responsive to treatment. Most patients with major depression require some form of long-term antidepressant treatment, and many need lifelong treatment. Optimizing efficacy and minimizing side effects are essential during both the acute and long-term phases of antidepressant treatment. Antidepressant side effects, including insomnia or somnolence, weight gain, asthenia, and sexual dysfunction, can significantly decrease patient compliance with long-term treatment for depression. Identification and management of side effects, combined with early and ongoing educational messages to the patient about treatment issues and the importance of sustaining illness remission, help improve compliance and reduce the potential for premature discontinuation of an otherwise optimal antidepressant.
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Over the last few decades, an increasing number of effective pharmacologic and nonpharmacologic treatments for depression have become available, including antidepressants, electroconvulsive therapy (ECT), and time-limited psychotherapies. The efficacy of these treatment modalities, particularly the use of antidepressants, for the acute, continuation, and maintenance phases of treatment has been well established in the literature. Historically, the emphasis in treating depression has been on the acute phase of treatment, with a paucity of data on the continuation and maintenance phases of treatment. However, studies suggest that the risk of depression increases with each past episode and that there is between a 50% to 90% chance of developing another episode following 1 or 2 prior depressions.[1–4] Subsequent episodes often occur sooner, are of longer duration, are more severe, and are less responsive to treatment.[2,5–7] There are increasing recognition and acceptance that depression may be a chronic or recurrent medical illness, and a greater understanding of the importance of long-term treatment is needed.

TREATMENT OF MAJOR DEPRESSION

All patients with major depression require adequate treatment during the acute (12 weeks), continuation (4–9 months), and maintenance (1 year or more) phases.[3] The duration of maintenance treatment should be individualized for each patient and may require "extended" or lifelong treatment for many patients. Indications for extended maintenance antidepressant treatment include greater than 2 episodes, chronic depression, double depression, severe depressive episode (i.e., psychosis, suicidality), poor recovery between episodes, and other medical, psychiatric, or psychosocial variables that may exacerbate recurrence or relapse.[3,7–10]

The goals of acute treatment should be to achieve a remission of symptoms and to optimize safety, side effects, and compliance. The goals of long-term or continuation and maintenance treatment should include reducing the likelihood of relapse and recurrence, restoring psychosocial function, reducing the risk of suicide, and optimizing safety, side effects, and overall compliance.

Long-term treatment should be discussed with the patient early in the course of treatment. Relapse during long-term antidepressant treatment has been reported to be as high as 57%[11] and may be the result of a number of overlapping factors, including inadequate response during acute treatment, inadequate treatment, comorbid medical or psychiatric illness, psychosocial factors, and poor com-

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Table 1. Some of the Most Common Reasons for Discontinuation of Antidepressant Treatment[a]

Reason for Discontinuation	Early Quitters, %	Late Quitters, %
Disliked side effects	62	67
Did not need medication	56	46
Felt better	50	44
Felt medication was not working	32	52
Ran out of pills	11	0

[a]Adapted from Lin et al.,[16] with permission.

Table 2. Specific Educational Messages Associated With Better Compliance During the First Month of Antidepressant Treatment[a]

Take antidepressant daily
Antidepressant must be taken for 2 to 4 weeks for noticeable effect
Continue to take medication even if feeling better
Do not stop taking medication without checking with the physician
Resolve questions about antidepressants

[a]Based on Lin et al.[16]

pliance. Failure to achieve a full remission of depressive symptoms during the acute treatment phase may increase the likelihood of relapse.[7,12] Studies suggest that long-term treatment should include maintaining the same dose of antidepressant that was used to achieve the remission during the acute phase.[3,13] New-onset or undiagnosed comorbid medical and psychiatric illnesses should be considered in a patient who relapses during long-term antidepressant treatment. Common comorbid psychiatric disorders include substance use disorders, anxiety disorders, bipolar disorder, psychotic disorders, eating disorders, and personality disorders. Finally, poor compliance with treatment should be considered as a potential cause for relapse during apparent antidepressant treatment.

COMPLIANCE WITH ANTIDEPRESSANT TREATMENT

Problems with compliance remain one of the most common and significant obstacles to acute and long-term antidepressant treatment. Studies suggest that up to 70% of patients taking antidepressants are noncompliant, either as a result of missed doses, premature discontinuation, or both.[14,15] Lin et al.[16] reported several common reasons why patients prematurely discontinued their antidepressant either early or later in treatment, with the most common reason being side effects in both early and late discontinuations (Table 1). Additionally, these patients reported that specific educational messages improved compliance with antidepressants. Educational messages presented early in treatment were associated with better compliance with antidepressants (Table 2).

Side Effects

The impact of side effects on treatment compliance should be considered with all patients who are treated with antidepressants during acute and long-term treatment. Discussion with patients and management of potential early (during acute treatment) and persistent or late-onset side effects should enhance compliance during all treatment phases. The development of the newer antidepressants within the last several years has presented safer and more tolerable treatment options during acute and long-term treatment. Early-onset side effects, such as nausea, anxiety, insomnia, and somnolence, associated with some of these newer antidepressants frequently abate within the first few weeks of treatment and/or are easily managed with dose adjustments or other pharmacologic intervention.

The recognition and management of persistent and late-onset antidepressant side effects are gaining increased attention given the established need for long-term treatment. Common persistent and late-onset side effects associated with some of the newer antidepressants that may impact optimal long-term treatment outcome include insomnia, somnolence, weight gain, asthenia, and sexual side effects. Similar to early-onset antidepressant side effects, most persistent and late-onset side effects can be managed effectively.

The development of new-onset side effects that appear later in the course of antidepressant treatment should give rise to a careful differential diagnosis of the etiology of the symptoms before attributing them to a direct side effect of the medication. The differential diagnosis should include considering the symptom(s) as a residual symptom of the depression, reemergence of the depression, comorbid disorders (i.e., bipolar disorder, substance use disorders/withdrawal, other medical illness), other concomitant medication, and antidepressant discontinuation syndrome.

Antidepressant Discontinuation Syndrome

An antidepressant discontinuation syndrome may occur as a result of missed doses, abrupt dose reduction, and/or the abrupt discontinuation of some antidepressants.[17] The symptoms(s) of antidepressant discontinuation syndrome can occur as early as 1 day after the medication is reduced or discontinued and can last for variable periods of time. Common symptoms include anxiety, agitation, insomnia, light-headedness, dizziness, vertigo, fatigue, nausea, flu-like symptoms, myalgia, sensory disturbances (e.g., numbness/tingling), and depressive symptoms. The antidepressant discontinuation syndrome has been reported with tricyclic antidepressants (TCAs), short half-life selective serotonin reuptake inhibitors (SSRIs), and venlafaxine.[17] There is little or no evidence of an antidepressant discontinuation syndrome reported with bupropion, fluoxetine, mirtazapine, or nefazodone.[17,18] A high index of suspicion of potential antidepressant discontinuation syndrome should be considered when such symptoms emerge later in treatment.

Table 3. Insomnia Management

Rule out
Depressive symptom
Mania/hypomania
Primary sleep disorder (eg, sleep apnea)
Altered sleep cycle
Other drug use
Decrease total daily dose
Try pharmacologic treatment
Trazodone
Mirtazapine[a]
Benzodiazepines
Zolpidem, zaleplon
Sedating antihistamine
Other
Switch antidepressants

[a]Administered with tricyclic antidepressants, selective serotonin reuptake inhibitors, or venlafaxine.

MANAGEMENT OF ANTIDEPRESSANT SIDE EFFECTS

General Guidelines

After other causes of new-onset symptoms have been ruled out, and the symptom is attributed to a side effect of the antidepressant, several treatment strategies can be employed. Informing the patient that the symptom is a common side effect to the antidepressant and that it will eventually improve over time may reassure the patient and increase the likelihood that the patient will remain on effective therapy. Since many side effects are dose related, attempting to lower the dose may be helpful, as long as this does not come at the cost of losing efficacy. Switching the time of medication administration or dividing the doses may also be helpful for some side effects such as somnolence, anxiety, and insomnia. Pharmacologic antidotes may also be useful; however, periodic discontinuation of the antidote should be attempted to observe whether the side effect has subsided over time. Finally, switching to another medication may be necessary if side effects are severe, intolerable, or jeopardize compliance or if other interventions have failed to improve the complaint. However, always consider the risk of discontinuing an effective antidepressant in a patient whose depression has remitted.

Management of Insomnia Associated With Antidepressants

The differential diagnosis of insomnia during the use of antidepressants includes a residual symptom of the depression, insomnia as a symptom of mania or hypomania in a bipolar disorder uncovered by the antidepressant, a primary sleep disorder, altered sleep cycle, caffeine use close to bedtime, concomitant medication, and substance use disorders or withdrawal. Dosing the antidepressant earlier in the day or decreasing the dose are possible early interventions. Potential pharmacologic antidotes include trazodone, mirtazapine (with TCAs, SSRIs, and venlafaxine), benzodiazepines, zolpidem, zaleplon, and sedating antihistamines. Finally, switching antidepressants is a later option to consider (Table 3).

Management of Somnolence Associated With Antidepressants

The differential diagnosis of somnolence as a persistent or new-onset symptom during long-term antidepressant treatment should include a residual symptom of the depression, comorbid medical illness (e.g., hypothyroid), disruption of the nocturnal sleep cycle, concomitant medications (e.g., benzodiazepines, antihypertensive agents, antipsychotics, thymoleptics), and substance use disorders. Management of this side effect includes switching most of the medication to evenings or nighttime and using pharmacologic antidotes (e.g., stimulant potentiation or other dopamine agonist agents). With most of the newer antidepressants such as mirtazapine, somnolence is frequently a short-term side effect. There is increasing evidence that increasing the dose of mirtazapine may prevent or manage any potential transient daytime somnolence for this specific antidepressant. This strategy is based on clinical experience and is thought to be based on the notion that higher doses of mirtazapine (via increased norepinephrine activity) may actually "override" the sedating antihistamine effects.

Management of Weight Gain and Increased Appetite With Antidepressants

While increased appetite (often for carbohydrates) may play a role as a potential causative effect for the weight gain observed in some patients taking traditional antidepressants, weight increase has also been reported in patients who exercise and carefully monitor food intake. This can be a difficult challenge, as many patients prematurely discontinue their medication as a result of increased appetite or weight gain. It is essential to rule out other potential causes, such as onset or worsening of a comorbid disorder (e.g., hypothyroidism).

Several introductory and educational messages need to be emphasized during the acute treatment, including encouraging the patients to increase their physical activity while lowering caloric intake to a reasonable portion. These patients may benefit from nutritional consultation. Clinicians should always instruct these patients on how to "wait to feel full" after a meal. Furthermore, the side effects generally dissipate over time. Consumption of fluids, fruit, and pasta (without the calories from high-fat sauces) can also be helpful. It is critical that the clinician work closely with the patient, since patients may misperceive pressure from outside significant relationships, causing unnecessary distress about their weight.

Pharmacologic agents have proved useful for managing some weight and appetite issues associated with antidepres-

sants, including stimulants (methylphenidate, amphetamine, and others). Topiramate, a new anticonvulsive agent for which preliminary data demonstrate mood stabilization in refractory mood disorders, has been associated with weight reduction properties, and therefore should be considered, especially when a bipolar component exists.

There are pilot studies assessing the potential benefits of using histamine-2 gastrointestinal blockers (e.g., famotidine, 20 mg b.i.d.) to manage increased appetite and weight gain associated with psychotropic medications. When all other options fail, consideration should be given to switching antidepressants, as long as this is not at the cost of loss of efficacy.

Table 4. Pharmacologic Antidotes for Antidepressant-Associated Sexual Dysfunction[a]

Antidote	Dosage	Comments	Reported Effects[b]
Stimulants			
Methylphenidate	5–40 mg/d	For SSRIs or venlafaxine	Libido, arousal, orgasm
Dextroamphetamine	5–40 mg/d	Avoid night dosing (insomnia)	
Pemoline	18.75–75 mg/d	Check liver function	
Ginkgo biloba extract	180–240 mg/d, tid divided doses	Potential increased clotting time, possible flatulence	Libido, arousal, orgasm
Cholinergic enhancers			
Bethanechol	10–50 mg prn	Used for antidepressants with anticholinergic side effect, TCAs, paroxetine	Arousal
Neostigmine	1 hour before sex or 50–200 mg/d, tid divided doses	Cholinergic side effects	
Estrogen creams or lubricants	As needed	For vaginal dryness, atrophy of vaginal tissue	Arousal
Amantadine	100 mg bid	Caution in patients predisposed to psychosis	Orgasm
Cyproheptadine	4–12 mg qhs	MAOIs, TCAs, SSRIs, venlafaxine; watch for reemergence of depressive symptoms; sedating	Orgasm
Buspirone	30–60 mg/d, bid divided doses		Libido, orgasm
Bupropion	75–150 mg/d, qd or bid divided doses	For SSRIs or venlafaxine; fluoxetine may raise bupropion levels; usual precautionary measures for bupropion	Libido, arousal, orgasm
Mirtazapine	15–45 mg/d	For SSRIs, venlafaxine	Orgasm
Nefazodone	Start 50 mg/d, up to 150 mg/d	SSRIs, venlafaxine	Orgasm
Granisetron	1 mg prn	? Use of other 5-HT_3 antagonists	Orgasm
Sildenafil	50–100 mg/d	Contraindicated with nitrates	Libido, arousal, orgasm
Yohimbine	5.4 mg tid	Can be anxiogenic; ? safety with MAOIs	Libido, arousal, orgasm

[a]Abbreviations: 5-HT_3 = serotonin-3, MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.
[b]The sexual phases that the antidote is reportedly effective in treating, out of 3 possible phases that may be affected by the antidepressant.

Management of Asthenia With Antidepressants

The development of asthenia can frequently be a bothersome side effect associated with some antidepressants. Symptoms of asthenia may present subtly during the long-term phases of treatment and are associated with complaints of feeling apathetic, amotivational, mentally dull, and/or fatigued despite being euthymic. Patients tend to be more aware of asthenia symptoms when they are not physically or mentally active. The differential diagnosis should include inadequate resolution or recurrence of depressive symptoms, concomitant medications, potential drug interaction effects, and other comorbid illness. Theoretically, asthenia is thought to be secondary to an increase of serotonin in the central nervous system, which may result in a secondary effect of lowered norepinephrine or dopamine activity in the frontal lobes, resulting in the apathetic symptoms. This may explain why the overselectivity of increasing serotonin with some antidepressants (i.e., SSRIs) may be associated with more complaints of asthenia compared with antidepressants that increase either other neurotransmitters or a broader range of neurotransmitters (e.g., mirtazapine, bupropion).

Symptoms of asthenia appear to be dose related, and, therefore, attempts should be made to lower the dose of the antidepressant, but not at the cost of losing efficacy. Evening dosing rather than morning dosing may be helpful in some patients, particularly when they report a consistent morning or afternoon onset of symptoms. Possible pharmacologic antidotes (to be used with SSRIs, venlafaxine, or nefazodone) include the use of agents that increase norepinephrine and/or dopamine levels, such as stimulants (methylphenidate or amphetamine, 5–20 mg b.i.d.), bupropion, or bromocriptine. The management of asthenia needs to be tailored to the individual patient and should take into account the possibility of switching antidepressants.

Management of Sexual Dysfunction and Dissatisfaction Associated With Antidepressants

Sexual dysfunction and dissatisfaction are common complaints during long-term treatment with antidepressants. Apparent sexual side effects are a common cause for poor compliance to long-term treatment with antidepressants, especially after the patient achieves remission of depression. Clinicians are encouraged to inquire about potential sexual side effects in all patients treated with antidepressants, since studies show that patients do not commonly spontaneously report these complaints and that such complaints may impact long-term outcome. Discussing the

possibility of sexual side effects during the acute and continuation phases of antidepressant treatment, even in the patient who does not have a sexual partner or has a diminished libido as a result of the depression, may provide for a more open dialogue between the patient and clinician if sexual side effects occur later in treatment. Furthermore, obtaining a baseline of sexual function and satisfaction should be routine in all depressed patients prior to initiating antidepressants, not only as a means to assess a common symptom of depression, but also to provide potentially useful information later in treatment regarding the emergence of persistent or new-onset complaints.

An essential step in the management of antidepressant-associated sexual side effects is to attempt to determine the etiology of the complaint. A number of possible overlapping factors can impact sexual function and satisfaction during treatment with antidepressants. Some of these factors include residual depressive symptoms, reemergence of depressive symptoms, comorbid illness, substance use disorders, primary sexual dysfunction, psychosocial factors, or other concomitant medications.

TCAs and monoamine oxidase inhibitors commonly affect all 3 phases of the sexual cycle, including libido, arousal, and orgasm. The SSRIs and venlafaxine appear to have less negative impact on the early phases of the sexual cycle; however, they can affect the ability to achieve orgasm in both men and women. Studies suggest a low incidence of sexual dysfunction associated with the use of bupropion, nefazodone, and mirtazapine.[19–21]

There are several ways to manage sexual side effects attributed to antidepressants. The choice of management needs to be tailored to the individual patient and may change throughout the course of treatment. General management strategies include waiting for the side effect to diminish over time if it is mild and/or intermittent, reducing the dose of the antidepressant to a minimal effective dose, using pharmacologic antidotes, or switching to another antidepressant that is not associated with sexual dysfunction.

Pharmacologic antidotes can be a useful strategy to manage sexual side effects during antidepressant treatment (Table 4). There has been a lack of controlled trials regarding the true efficacy and safety of these strategies. Most of the literature is based on case reports or noncontrolled trials. The choice of antidote for a particular patient should take into account several factors, including the overall efficacy of the primary antidepressant, potential medication interactions, potential additive side effects, potential antidepressant-enhancing effects, potential effects on managing any other side effects, cost, and overall adherence to taking additional medication. Daily standing doses are recommended for most of the antidotes, since little is known about how long it takes for them to become effective.[22,23] One exception is sildenafil, which can be prescribed on a p.r.n. basis, similar to prescribing instructions for male erectile disorder.[23] Table 4 reviews specific antidotes that have been reported in the literature for the treatment of each of the 3 possible sexual phases affected by the antidepressant. The types of antidepressants for which each antidote has been reported, dosing, and cautionary comments are included.

Although "drug holidays" have been reported in the literature to be an effective strategy to manage some antidepressant-associated sexual dysfunction, this strategy, if employed, should be done with caution.[24] Recommending that a patient discontinue his or her antidepressant prior to sexual activity may convey the wrong message about the importance of adherence to treatment, particularly during long-term treatment. Also, "drug holidays" may result in an antidepressant discontinuation syndrome, especially with antidepressants commonly associated with this syndrome.

CONCLUSION

The majority of patients treated for depression require some form of long-term antidepressant treatment; many need "extended" or lifelong treatment. Optimizing efficacy and minimizing side effects are essential during acute and long-term phases of antidepressant treatment. When choosing an antidepressant during the acute phase, it is essential to consider early-onset and persistent or late-onset side effects. Early-onset and late-onset side effects can significantly impair compliance and optimal recovery from depression. Identification and management of side effects can avoid potential premature discontinuation of an otherwise optimal antidepressant. Compliance can be enhanced through early and ongoing educational messages to the patient regarding treatment issues, including side effects and the importance of sustaining illness remission.

Drug names: amantadine (Symmetrel and others), bethanechol (Urecholine), bromocriptine (Parlodel and others), bupropion (Wellbutrin), buspirone (BuSpar), cyproheptadine (Periactin), dextroamphetamine (Dexedrine and others), famotidine (Pepcid), fluoxetine (Prozac), granisetron (Kytril), methylphenidate (Ritalin), mirtazapine (Remeron), nefazodone (Serzone), neostigmine (Prostigmin and others), paroxetine (Paxil), pemoline (Cylert), sildenafil (Viagra), topiramate (Topamax), trazodone (Desyrel and others), venlafaxine (Effexor), yohimbine (Yocon and others), zaleplon (Sonata), zolpidem (Ambien).

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