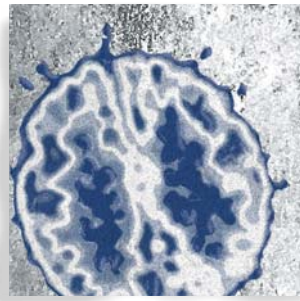


Toward achieving optimal response: understanding and managing antidepressant side effects

Karen Kelly, MD; Michael Posternak, MD; Jonathan E. Alpert, MD, PhD



The safety and tolerability of antidepressants have improved considerably over the past two decades. Nevertheless, antidepressant side effects are still common and problematic. The majority of patients treated with contemporary agents experience one or more bothersome side effects. These side effects often create barriers to achieving depressive remission, as well as to preventing relapse and recurrence. Clinicians tend to underestimate the prevalence of side effects, and as many as one quarter of patients discontinue their antidepressants because of difficult-to-tolerate side effects; others may continue on antidepressant therapy but experience diminished quality of life related to troublesome side effects. This article reviews the prevalence of side effects, the impact of side effects on treatment adherence, and methodological issues including the challenge of distinguishing side effects from residual depressive symptoms, discontinuation effects, and general medical problems. In addition, we address the most common side effects such as sexual dysfunction, gastrointestinal problems, sleep disturbance, apathy, and fatigue, and offer strategies for management that may help patients achieve optimal response to pharmacotherapy.

© 2008, LLS SAS

Dialogues Clin Neurosci. 2008;10:409-418.

Despite advances over the past two decades in the tolerability and safety of antidepressant treatment with the development of the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and other agents, antidepressant side effects continue to pose considerable challenges to treatment. Side effects sometimes exacerbate or masquerade as residual depressive symptoms, and often precipitate premature discontinuation or the use of subtherapeutic doses of antidepressants. In the following review we describe the scope of antidepressant side effects and their impact on treatment adherence, methodological issues concerning the study of side effects, and the most common side effects and approaches to management. Anticipating, recognizing, and vigorously managing antidepressant side effects are crucial avenues for achieving remission in depression as well as preventing relapse and recurrence.

Prevalence and impact of side effects

Despite considerable improvements in side-effect profiles, antidepressants continue to be associated with a significant burden of side effects that affect treatment adherence and quality of life. Hu et al¹ studied 401 patients with depression who had recently been prescribed an SSRI, and found that after 75 to 105 days of

Keywords: *antidepressant; side effect; remission; selective serotonin reuptake inhibitor; depression*

Author affiliations: Department of Family Medicine, Boston University, Boston, Massachusetts, USA (Karen Kelly); Depression Clinical and Research Program, Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts, USA (Karen Kelly; Michael Posternak, Jonathan E. Alpert); Harvard Medical School, Boston, Massachusetts, USA (Michael Posternak, Jonathan E. Alpert)

Address for correspondence: Jonathan Alpert, MD, Depression Clinical and Research Program, 50 Staniford St. Suite 401, Boston, MA 02114, USA (e-mail: jalpert@partners.org)

Translational research

treatment, 86% of patients reported at least one side effect, and 55% experienced one or more bothersome side effects. Interestingly, physicians appear to underestimate the rate of side effects with antidepressants. In a survey of physicians and the patients to whom they had prescribed SSRIs,² physicians underestimated the overall rate of side effects as well as the frequency of specific side effects such as dry mouth, dizziness, drowsiness, headache, insomnia, rash or itching, blurred vision, diarrhea, and weight loss when compared with the actual rate reported by their patients. That clinicians underestimate the prevalence of side effects likely contributes to inadequate communication before and during prescription of antidepressants.

The impact of side effects on achieving depressive remission and on therapy adherence is great. In a study by Demyttenaere et al³ of 272 outpatients receiving antidepressant therapy, 53% had discontinued treatment by the end of the 6-month study. Of these patients, 23% cited “adverse events” as the reason for their discontinuation. In a similar study, Hu et al¹ found that 33% of patients had discontinued their treatment by the end of a 105-day period, with the most often-cited reason being adverse effects (36%). This study found that the presence of multiple side effects or the presence of side effects deemed extremely bothersome by patients significantly increased the odds of discontinuation. In addition to disrupting the goal of achieving a minimally adequate course of antidepressant treatment for achieving remission and preventing relapse and recurrence, side effects frequently impede adequate dose titration, necessary for delivering a full therapeutic dose. Although precise estimates are difficult to find, it is a frequent clinical observation that patients struggling with side effects often remain on lower-than-optimal doses for long periods of time, during which their depression is inadequately treated. In addition, bothersome side effects such as somnolence or sexual dysfunction, even when they do not lead to premature drug discontinuation or inadequate dosing, clearly compromise quality of life.

Methodological issues

There are considerable methodological challenges related to the study and clinical management of side effects. When evaluating side-effect data, it is important to consider whether the information was obtained by spontaneous report, self-report checklists, or responses

to direct questioning. Spontaneous reporting of side effects following an open-ended question (eg, “any change since last visit?”) typically yields a lower incidence of adverse events than itemized self-report checklists (eg, the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) Scale⁴) or direct questioning about specific side effects (The Systematic Assessment for Treatment Emergent Events-Specific Inquiry [SAFE-TEE-SI]⁵). The reporting of certain side effects, particularly sexual dysfunction, may also be influenced by the degree of comfort the patient/subject has with the subject area and with the questioner; this may be affected by gender, culture, and other factors. Side-effect rates presented for an antidepressant in isolation tend to be of somewhat limited benefit, as common experiences such as headache or rhinitis inevitably figure prominently, even if they bear no specific relationship to the agent. Hence, side effects presented as placebo-adjusted rates are often more informative. So too are comparative rates of specific side effects across a number of antidepressant agents, which allow clinicians and patients to make informed choices about the relative risks of side effects of greatest concern to the patient.

In both research and clinical contexts, an important challenge is presented by the phenomenological overlap between side effects and residual symptoms of depression. Thus, fatigue, cognitive impairment, apathy, jitteriness and irritability, and sleep and appetite changes are core features of depression, but may also be related to antidepressant treatment. In a small study of 43 depressed inpatients,⁶ which investigated the rate of somatic symptoms and complaints that were present before and after treatment, many symptoms often considered to be side effects of drugs were also present prior to treatment, including dry mouth, lightheadedness, sweating, tremors, and constipation. The distinction between residual symptoms and side effects is crucial, as they call for very different responses. In the latter case, a dose increase or pharmacological or other augmentation of treatment may be required. In the former case, a dose reduction or use of a pharmacological antidote would be important initial considerations. A careful delineation of depressive symptoms prior to the initiation of antidepressant treatment, such as with the use of a structured rating scale such as the Inventory for Depressive Symptomatology,⁷ is particularly helpful as a supplement to clinical judgment to determine which adverse events are truly treatment-emergent and which may reflect per-

sisting, inadequately responsive symptoms of depression. Conversely, in some instances, an experience recorded as an adverse event may have been related to depressive improvement; this is particularly true in an individual whose increased weight following a period of anorexia related to depression might be more accurately construed as normalization than weight gain.

An additional, frequently overlooked factor that may confound interpretation of apparent adverse events has to do with discontinuation-emergent effects of antidepressants, which can resemble antidepressant side effects and/or residual symptoms. Thus, for example, a patient with intermittent noncompliance on antidepressants such as venlafaxine or paroxetine that are associated with common discontinuation-related syndromes may experience malaise or nausea after a day or two off medication without being aware of their relationship to abrupt drug discontinuation. Fortunately, when patient history raises the possibility that apparent side effects or residual symptoms are attributable to inconsistent dosing, the hypothesis can be simply tested if the patient is willing to commit to more regular dosing. In the case of forgetful patients, daily pillboxes or newer technologies such as electronic caps that remind the patient of skipped doses are often helpful. In other patients, education about discontinuation effects and/or efforts to address possible ambivalence about use of medications may reduce instances of medication cessation.

Side effects most likely to cause drug discontinuation

An understanding of which side effects occur most frequently and which of these are most likely to lead to patient nonadherence enhances one's ability to choose a drug and counsel patients. The most common side effects reported by patients in the study by Hu et al¹ of 401 outpatients taking SSRIs were drowsiness (38%), dry mouth (34%), and sexual dysfunction (34%). This study, which was conducted in 1999-2000, questioned patients about side effects via phone interviews within 75 to 105 days of starting antidepressant therapy. The side effects deemed most bothersome were sexual dysfunction (17%), drowsiness (17%), and weight gain (11%). While these were the most common, Lin et al⁸ looked at which side effects were most likely to lead to discontinuation in their naturalistic study of 155 outpatients on antidepressant therapy (a tricyclic antidepressant, tra-

zodone, or fluoxetine). They found that severe daytime sleepiness showed a significant association with early discontinuation, and if experienced to a degree deemed severe by patients, fatigue, blurred vision, insomnia, anxiety, appetite changes, and weight gain were all significantly associated with discontinuation in months two and three of treatment.

Time period of side effects

To further understand side effects and their impact on patients' quality of life and compliance, it is also important to be aware of the time when certain side effects present. While there is common belief that side effects can be classified as acute or chronic, a review by Papakostas⁹ challenged this idea. In it, he cites Hu et al's¹ study that shows that although certain side effects may present early or later in the course of treatment, many of those that are considered acute persist to a point that they should be considered chronic. In this study, SSRI-induced side effects such as insomnia, sexual dysfunction, and drowsiness that are often considered acute persisted at 3 months. On the other hand, some side effects such as nausea do start early in the course of treatment and then usually improve, while others such as weight gain are not present initially but emerge over time. Another naturalistic study by Demyttenaere et al³ of 272 outpatients on an SSRI, trazodone, venlafaxine, or moclobemide looked at the time period that patients discontinue treatment secondary to side effects, and found that patients who cited side effects as their reason for discontinuation dropped out of treatment at a mean period of 6.5 weeks. This study showed that side effects and lack of efficacy led to the earliest discontinuation of antidepressants (at 6.5 weeks and 7 weeks respectively), followed by other reasons such as "fear of drug dependence" and "feeling better" that occurred at 8 weeks and later. Reinforcing the conclusion that side effects often account for early discontinuation, Bull et al¹⁰ found that significantly more patients discontinued or switched their SSRI because of an adverse effect within the first 3 months of treatment compared with the second 3 months.

Side effects as predictors of response

Although there are no systematic studies to our knowledge that address specific treatment-emergent adverse effects as predictors of response, we are aware that opti-

Translational research

mistic colleagues sometimes look for certain early side effects, such as activation or insomnia, as favorable prognosticators. Emerging biomarkers, such as quantitative electroencephalography¹¹ or neuroimaging,¹² alone or in conjunction with clinical features at baseline and during treatment, represent an important area of current research. Nevertheless, while the presence of particular side effects has no known prognostic significance, when patients have no side effects and minimal response despite full doses of an antidepressant, it is reasonable to re-evaluate medication adherence as well as to consider the possibility of drug-drug interactions (particularly metabolic induction) and genetic polymorphism that might call for higher doses to achieve an optimal outcome.

Common side effects and their management

Given the impact of side effects on treatment adherence, response, and quality of life, an understanding of the management of common side effects is imperative for optimal management of depressed outpatients. Successful management of side effects enhances adherence, permits adequate dosing, improves patient comfort and function, and prevents premature discontinuation of therapy. Appropriate management includes thoughtful drug selection, the anticipation of common and rare but serious side effects with patients, and striving for the lowest effective dose and simplest drug regimens consistent with appropriately vigorous treatment. It also includes the addition of appropriate adjunctive therapies to manage emergent complaints.

Fatigue and somnolence

Fatigue or drowsiness is a common side effect experienced by 10% to 38% of antidepressant-treated outpatients.^{1,13} In one study of 401 outpatients,¹ 70% of people who experienced fatigue had it by 2 weeks, and 63% continued to experience it at 3 months. In comparative studies, SSRIs had a higher rate of sleepiness than bupropion¹⁴ and the noradrenergic reuptake inhibitor, reboxetine,¹⁵ and equivalent rates as nefazodone,¹⁶⁻¹⁸ venlafaxine,¹⁹⁻²¹ and duloxetine²²⁻²³ and the reversible monoamine oxidase inhibitor moclobemide.²⁴ Mirtazapine²⁵ and trazodone²⁶ are associated with greater rates of somnolence and fatigue than SSRIs. The differential of drowsiness should include residual symptoms of

depression, a primary sleep disorder such as obstructive sleep apnea or restless leg syndrome or altered sleep cycle, and substance-use disorders. Management of drowsiness includes careful evaluation of sleep patterns and counseling on sleep hygiene measures (such as avoidance of daytime napping), changes in antidepressant dosing schedule such as a shift from morning to nighttime administration, divided dosing or use of a slower release preparation, as well as pharmacological management with psychostimulants, modafinil, bupropion, reboxetine, or protriptyline, or consideration of alternative remedies such as methylfolate or S-adenosylmethionine. For some patients, a graduated increase in exercise may also help reduce fatigue.

Sexual dysfunction

Sexual dysfunction is a common long-term problem on antidepressants. Medication side effects typically affect libido, arousal, orgasm, and ejaculation,²⁷ and may affect lubrication and erection. These side effects have traditionally been greatly underreported, largely related to patients' and clinicians' reticence to address this topic. In a study of 344 patients by Montejo-Gonzalez et al,²⁸ 58% of patients reported sexual dysfunction when physicians directly inquired, compared with only 14% of those who spontaneously reported sexual dysfunction. In a naturalistic study that directly inquired about side effects through closed-ended questions,¹ 34% of patients reported sexual dysfunction, with half of these patients (17% of the overall group) deeming it bothersome. Seventy percent of patients who experienced sexual dysfunction did so by 2 weeks, with 80% experiencing it at 3 months.

There are clear differences among antidepressant agents in rates of sexual dysfunction. Bupropion immediate-release and nefazodone were found to have the lowest rate of sexual dysfunction in a study of more than 6000 individuals on SSRIs, bupropion, mirtazapine, nefazodone, reboxetine, and venlafaxine.²⁹ Studies comparing SSRIs with mirtazapine are inconclusive, some showing higher rates of sexual dysfunction with SSRIs and others with mirtazapine.³⁰⁻³⁵ Among the SSRIs, paroxetine has been found to have the highest rates of sexual dysfunction.³⁵

Management of sexual dysfunction, like all side effects, begins with a thorough assessment during the initial evaluation to establish a baseline, including discussion

of whether the patient is sexually active and the degree of satisfaction with sexual function prior to treatment, and to discuss concerns about possible sexual dysfunction related to anticipated treatment. It is important to reassess sexual function periodically during the course of therapy, and also to recognize that sexual function may become increasingly important to patients as their depressive symptoms improve.³⁶ Prior to the introduction of sildenafil and similar agents, many methods and medications were used in an attempt to treat the sexual side effects of antidepressants. These included dose reduction, timing of sexual activity toward the end of a dosing interval, several days' drug holiday,³⁷ and antidote therapy with medicine such as psychostimulants³⁸ and dopamine (DA) agonists such as amantadine, pramipexole and Dexedrine, norepinephrine (NE)/DA agents such as bupropion, serotonin (5-HT)₂ receptor antagonists such as nefazodone, and α_2 -adrenergic receptor antagonists such as yohimbine.³⁹⁻⁴⁰ As sildenafil has proven effective in placebo-controlled trials in the treatment of sexual performance,⁴¹ this agent and related phosphodiesterase V inhibitors have become the mainstay of management of sexual function. A recent trial⁴² also demonstrated that sildenafil is effective at decreasing adverse sexual effects in women taking SSRIs, including improvement in desire, arousal-sensation, arousal-lubrication, orgasm, and enjoyment. Nevertheless, many patients do not respond sufficiently well to sildenafil and related agents or other attempted antidotes, and efforts to identify other remedies continue. These include complementary and alternative treatments such as maca root, arginine-containing compounds, and ginkgo biloba. When sexual dysfunction persists despite efforts at dose adjustments and antidote therapy, the principal option is to consider switching to agents with lesser degrees of sexual dysfunction, typically bupropion, or, where available, reboxetine. Nefazodone is another option, though its use has been limited by risk of rare but serious hepatotoxicity.

Gastrointestinal problems

Nausea and stomach upset

Nausea and stomach upset are also common side effects of antidepressant treatment, present in 17% to 26% of patients taking it,^{1,13} 83% of whom experienced it by 2 weeks, and 32 % of whom continued to experience it at

3 months. Treatment with SSRIs was associated with a higher rate of nausea than bupropion,⁴³ moclobemide,²⁴ mirtazapine,²⁵ and reboxetine.¹⁵ Equivalent rates were found between SSRIs and trazodone,^{26,44} nefazodone,¹⁶⁻¹⁸ and duloxetine.²²⁻²³ Venlafaxine has been found to have a higher incidence of nausea than SSRIs.⁹ Some studies have found that nausea from venlafaxine and paroxetine may be reduced using controlled-release formulations.⁴⁵ The management of nausea and vomiting includes the use of divided dosing or taking medications with a small amount of food, such as crackers or toast. Some patients benefit from ginger-containing foods and beverages, histamine 2 antagonists such as ranitidine,⁴⁶ or proton pump inhibitors such as omeprazole. Adjunctive promethazine, prochlorperazine, or ondansetron also have been shown to be beneficial, as has mirtazapine because of its 5-HT₃ receptor antagonistic properties.

Diarrhea

Diarrhea may also occur as a side effect of antidepressant treatment. As with the other gastrointestinal side effects of antidepressants, it may be a transient effect and resolve within weeks, but it also may persist in some patients. A meta-analysis of 84 trials¹³ found that overall, 16% of patients taking SSRIs experienced diarrhea. Hu et al¹ found a rate of 15% of patients who experienced diarrhea, 78% of whom experienced it at 2 weeks and 45% of whom still experienced it at 3 months. Management of diarrhea can include antidiarrheal agents such as loperamide, or diphenoxylate hydrochloride. Cyproheptadine, Lactobacillus acidophilus culture, and psyllium may also be helpful.

Constipation

Constipation may emerge during antidepressant therapy. Of the SSRIs, paroxetine has been associated with the highest rates of constipation, presumably secondary to its high affinity for muscarinic receptors.⁴⁷ Overall, the rate of constipation has been found to be 11% to 12.5%,^{1,13} with 4.7% of patients describing it as a bothersome side effect.¹ Constipation can often be controlled with adequate activity, fluid, and fiber intake. When pharmacological management is required, bulk-forming laxatives, stool softeners, osmotic agents, bethanechol, and cholinesterase inhibitors may be used.⁴⁶

Translational research

Weight gain

Another bothersome effect of antidepressant treatment that may interfere with treatment adherence and general health is weight gain. This is also an effect that is often difficult to study because it can be a sign of improvement in patients who have weight loss as a symptom of depression, a residual symptom in patients who overeat when depressed, or something independent of depression or its treatment. For this reason, it is important to look at placebo rates of weight gain when evaluating these rates in patients. There are various ways that weight gain is studied and reported, including as the percentage of weight gain from baseline or as rate of weight gain greater than 7% from baseline. Although complaints of weight gain often emerge late in treatment, there are relatively few studies that have systematically assessed this side effect on long-term treatment and fewer that have had the opportunity to compare weight gain on active treatment with that on placebo.⁴⁸ Many of the long-term studies show no difference between SSRIs and placebo, except for paroxetine, showing a significant difference from placebo.^{49,50} There was no drug/placebo difference in weight gain in a study looking at fluoxetine over 26 weeks of continuation treatment⁵¹ or in a 6-month duration study of citalopram.⁵² In a study comparing the rate of weight gain on antidepressants,⁹ mirtazapine was associated with the highest percentage of patients with weight gain (26%), followed by SSRIs and venlafaxine (16% to 19%). Nefazodone,⁵³ bupropion,⁵⁴ and reboxetine⁵⁵ result in the lowest rates of weight gain during treatment. Among tricyclic antidepressants, the secondary amine tricyclics, such as desipramine, nortriptyline, and protriptyline, have generally been associated with lower weight gain than the tertiary amine agents such as imipramine, amitriptyline, and clomipramine.

The management of antidepressant-associated weight gain is challenging and should begin with the choice of drug. Clinicians should try to identify patients who are at risk for weight gain based on medical history and lifestyle, and these patients should be targeted for dietary and physical activity interventions. The addition of bupropion, topiramate, zonisamide, or sibutramine may also be considered. As weight gain may not be dose-dependent, at least within the therapeutic range of doses, a modest dose reduction is often ineffective. In the setting of unacceptable weight gain that is not responsive to dietary and behavioral modifica-

tions, a switch to an agent with a lower propensity for weight gain is a primary consideration.

Insomnia

Rates of insomnia have been found to be 12% to 22% (antidepressants administered to outpatients with MDD, enrolled in clinical trials who report insomnia as a treatment emergent side effect),^{1,13} with 11% of patients deeming it bothersome. Sixty-four percent of patients who experienced insomnia experienced it by 2 weeks, and 56% continued to experience it at 3 months.¹ In a review of antidepressant-induced side effects, Papakostas⁹ cites higher rates of insomnia with SSRIs than with mirtazapine, trazodone, and nefazodone, and equivalent rates between SSRIs and bupropion, moclobemide, duloxetine, and venlafaxine. Reboxetine was found to have a higher rate of insomnia than SSRIs. It is particularly important to rule out primary sleep disorders or concomitant alcohol and other substance abuse when evaluating and managing insomnia. Management of antidepressant-induced insomnia includes educating patients on behavior techniques and sleep hygiene, modification of use of caffeine and common sympathomimetic agents, changing the timing of doses, and adding adjunctive medications including sparing use of benzodiazepines, zolpidem, eszopiclone, melatonin, trazodone, mirtazapine, and/or low doses of anticonvulsants, and atypical antipsychotics.

Tremor

Fine and rapid tremors of the extremities can occur as a side effect of antidepressants. Rates of tremor of SSRIs and venlafaxine are 3 to 5 times higher than placebo, whereas the rate of tremor in nefazodone and mirtazapine therapy is only 2 to 2.5 times higher than placebo.⁵⁶ It is important to consider other agents or causes when assessing a tremor, including caffeine intake and anxiety as well as common antidepressant adjuncts such as the atypical antipsychotics. Decreasing caffeine intake and the use of benzodiazepines and β -blockers can be helpful in the treatment of tremor.

Apathy

The development of apathy or indifference can be a bothersome side effect associated with antidepressant medication. Symptoms that can include amotivation or

dullness often develop slowly, and although the mechanism of this effect is unclear, it may be secondary to an inhibition of dopamine by serotonergic medications.⁵⁷ Apathy is a challenging and elusive complaint to evaluate and may be secondary to drug treatment, a residual symptom, or may herald relapse. Some, but not all, patients are able to point to a distinction between the comfortable detachment they feel when experiencing antidepressant-related apathy in the setting of an otherwise satisfactory response to treatment compared with the more anguished or far-reaching anhedonia and motivational impairment they experience when depressed. If a relapse or residual symptoms are not suspected, management strategies include dose reduction, switching to a different drug or class, typically toward less serotonergic agents, or the addition of a stimulant or dopaminergic drug. Pharmacologic options include methylphenidate or dextroamphetamine, bupropion, amantadine, ropinirole, pramipexole, modafinil, or pergolide.

Discontinuation syndrome

Abrupt discontinuation of SSRIs, nefazodone, venlafaxine, and mirtazapine may precipitate a discontinuation syndrome that can occur hours to days following the termination of medication. The syndrome often includes flu-like symptoms such as malaise, myalgias, nausea, dizziness, and headache, and may even include neurologic symptoms such as unsteady gait, dysesthesias such as unusual shock-like sensations, tremulousness, or vertigo.⁴⁶ Risk factors for discontinuation syndrome include abrupt cessation of short-acting agents and/or agents at a high dose. Indeed, in some patients, some of the features of discontinuation syndrome simply from an abrupt dose reduction rather than actual cessation. As previously noted in this review, discontinuation symptoms may masquerade as side effects of treatment. Discontinuation syndrome may be minimized with the use of a gradual taper schedule. Patient education about the risk of discontinuation symptoms is crucial whenever an antidepressant likely to be associated with discontinuation emergent symptoms is prescribed. Substituting a longer-acting antidepressant, most notably fluoxetine, for a shorter-acting one may also decrease the risk of withdrawal syndrome.⁵⁸ This is particularly helpful for patients who have already demonstrated problems tapering another antidepressant because of discontinuation emergent adverse events. The addition of benzodiazepines for irritability, anxiety, or

sleep disturbance related to discontinuation or nonsteroidal anti-inflammatory agents for pain may improve patient experience. Communication with patients about the short duration of withdrawal symptoms may help patients cope with these typically self-limited symptoms.

Other management techniques for preventing relapse or discontinuation due to side effects

Patient education

A critical component to side-effect management is education of patients prior to prescribing an antidepressant. This should include discussion of common side effects and when they would be most likely to emerge. It is important to discuss with patients which side effects require a prompt evaluation (eg, rash, agitation, worsening suicidality) and which side effects are likely to be self-limiting (eg, mild nausea or jitteriness). Patients may assign a different value to certain side effects than their clinician; given the large number of agents available it is important to reach agreement on how the anticipated risks and benefits of treatment will factor into choice of agent. Patients may harbor certain preconceptions about side effects which can be addressed at this time. Examples of this would include the mistaken belief that side effects necessarily indicate toxicity or indicate that the medication is a poor match for the patient. It is often helpful to let patients know that antidepressants are associated with a range of side effects that typically do not indicate a safety concern nor predict poor response. Patients are often reassured also to learn about the availability of strategies to address most side effects including dose changes, pharmacological antidotes, and the option to switch to other medications.

Some clinicians are reluctant to discuss side effects in advance because of a concern that it will make patients anxious and may magnify side effect concerns. The literature offers some support of this in a naturalistic study showing that patients who recalled being informed of potential adverse events by their physicians were 55% more likely to report experiencing mild or moderate adverse effects.¹⁰ Although these patients were more likely to report side effects, this same study, as well as a naturalistic study done by Bull et al,² found that discussing adverse effects with patients during treatment was associated with the same or less premature discon-

Translational research

tinuation and with a higher rate of switching medications. Switching medications in this instance may represent a positive alternative to discontinuing treatment.

Nondrug therapy

Other successful techniques that have been shown to improve patient adherence to medication include the use of cognitive behavioral therapy and the participation in other concurrent nondrug therapy,¹⁰ particularly when care is closely coordinated between the clinician prescribing medication and the clinician providing psychotherapy when these roles are separate. In another area of medical treatment, Safren et al^{59,60} have shown that in HIV-positive patients, an intervention called Life-Steps, which is a single-session intervention utilizing cognitive-behavioral, motivational interviewing, and problem-solving techniques, improves adherence to HIV antiretroviral therapy. Further study should be directed at specific psychotherapeutic interventions similar to these that support treatment adherence in the pharmacotherapy of depression.

REFERENCES

1. Hu XH, Bull SA, Hunkeler EM, et al. Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for depression: patient report versus physician estimate. *J Clin Psychiatry*. 2004;65:959-965.
2. Bull SA, Hu XU, Hunkeler EM, et al. Discontinuation of use and switching of antidepressants: influence of patient-physician communication. *JAMA*. 2002;288:1403-1409.
3. Demyttenaere K, Enzlin P, Dewe W, et al. Compliance with antidepressants in a primary care setting I: beyond lack of efficacy and adverse events. *J Clin Psychiatry*. 2001;62(suppl 22):30-33.
4. Wisniewski SR, Rush AJ, Balasubramani GK, Trivedi MH, Nierenberg AA. Self-rated global measure of the frequency, intensity and burden of side effects. *J Psychiatr Pract*. 2006;12:71-79.
5. Clyde DJ. SAFTEE: data system for side effect assessment scale. *Psychopharmacol Bull*. 1986;22:287.
6. Nelson JC, Jatlow P, Quinlan DM. Subjective side effects during desipramine treatment. *Arch Gen Psychiatry*. 1984;41:55-59.
7. Rush AJ, Giles DE, Schlessler MA, Fulton CL, Weissenburger J, Burns C. The Inventory for Depressive Symptomatology (IDS): preliminary findings. *Psychiatry Res*. 1986;18:65-87.
8. Lin EHB, Von Korff M, Katon W, et al. The role of the primary care physician in patients' adherence to antidepressant therapy. *Med Care*. 1995;33:67-74.
9. Papakostas, GI. Limitations of contemporary antidepressants: tolerability. *J Clin Psychiatry*. 2007;68(suppl 10):11-17.
10. Bull SA, Hunkeler EM, Lee JY, et al. Discontinuation or switching selective serotonin-reuptake inhibitors. *Ann Pharmacother*. 2002;36:578-584.
11. Hunter AM, Cook IA, Leuchter AF. The promise of the quantitative electroencephalogram as a predictor of antidepressant treatment outcomes in major depressive disorder. [122 refs] *Psych Clin N Am*. 2007;30:105-124. Review.

Conclusion

Antidepressant side effects are a common clinical challenge, often jeopardizing treatment adherence and quality of life. Physicians may underestimate the prevalence of side effects and may be reticent to address them proactively out of a mistaken concern that their impact will be magnified. The successful management of side effects begins with adequate communication and patient education prior to and throughout treatment with antidepressants. In addition, it involves thoughtful differentiation of treatment-emergent side effects from residual depressive symptoms, relapse and recurrence, discontinuation related adverse events, and intercurrent general medical problems. Finally, optimal management of side effects involves drawing upon a full array of strategies including dose reduction, changes in the timing of doses or the drug preparation, behavioral strategies, pharmacological antidotes, and willingness to consider switching to other agents. Sound and resourceful management of side effects is an important component in achieving depressive remission and enhancing patient safety and quality of life. □

12. Iosifescu DV, Renshaw PF, Lyoo IK, et al. Brain white-matter hyperintensities and treatment outcome in major depressive disorder. *Br J Psychiatry*. 2006;188:180-185.
13. Trindade D, Menon D, Topfer L, Coloma C. Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. *CMAJ-JAMC*. 1998;159:1245-1252.
14. Papakostas GI, Nutt DJ, Hallett LA, et al. Resolution of sleepiness and fatigue in major depressive disorder: a comparison of bupropion and the selective serotonin reuptake inhibitors. *Biol Psychiatry*. 2006;60:1350-1355.
15. Papakostas GI, Nelson JC, Kasper S, Moller HJ. A meta-analysis of clinical trials comparing reboxetine, a norepinephrine reuptake inhibitor with selective serotonin reuptake inhibitors for the treatment of major depressive disorder. *Eur Neuropsychopharmacol*. 2008;18:122-127.
16. Baldwin DS, Hawley CJ, Abed RT, et al. A multicenter double-blind comparison of nefazodone and paroxetine in the treatment of outpatients with moderate-to-severe depression. *J Clin Psychiatry*. 1996;58(suppl 2):46-52.
17. Feiger A, Kiev A, Shrivastava RK, et al. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. *J Clin Psychiatry*. 1996;57(suppl 2):53-62.
18. Berlanga C, Arechavaleta B, Heinze G, et al. A double-blind comparison of nefazodone and fluoxetine in the treatment of depressed outpatients. *Salud Mental*. 1997;20:1-8.
19. Montgomery SA, Huusom AK, Bothmer J. A randomized study comparing escitalopram with venlafaxine XR in primary care patients with major depressive disorder. *Neuropsychobiology*. 2004;50:57-64.
20. Bielski RJ, Ventura D, Chang CC. A double-blind comparison of escitalopram and venlafaxine extended release in the treatment of major depressive disorder. *J Clin Psychiatry*. 2004;65:1190-1196.
21. Schatzberg A, Roose S. A double-blind, placebo-controlled study of venlafaxine and fluoxetine in geriatric outpatients with major depression. *Am J Geriatr Psychiatry*. 2006;14:361-370.

Buscando la respuesta óptima: comprensión y manejo de los efectos secundarios de los antidepresivos

En las últimas dos décadas la seguridad y tolerabilidad de los antidepresivos ha mejorado considerablemente. Sin embargo, todavía los efectos secundarios de los antidepresivos son frecuentes y problemáticos. La mayoría de los pacientes tratados con los medicamentos actuales experimentan uno o más efectos secundarios significativos. Estos efectos secundarios a menudo crean barreras para alcanzar la remisión de la depresión, al igual que para prevenir recaídas y recurrencias. Los clínicos tienden a subestimar la prevalencia de efectos secundarios y hasta un cuarto de los pacientes discontinúa los antidepresivos por tolerar mal dichos efectos; otros pueden continuar la terapia antidepresiva, pero experimentan una disminución en la calidad de vida relacionada con los molestos efectos secundarios. Este artículo revisa la prevalencia de efectos secundarios, el impacto de ellos en la adherencia al tratamiento y temas metodológicos que incluyen el desafío de distinguir los efectos secundarios de los síntomas depresivos residuales, los efectos de la discontinuación y problemas médicos generales. Además se hace referencia a los efectos secundarios más comunes como la disfunción sexual, problemas gastrointestinales, alteraciones del sueño, apatía y fatiga, y se ofrecen estrategias para el manejo que pueden ayudar a los pacientes a obtener una respuesta óptima a la farmacoterapia.

Vers une réponse optimale : compréhension et prise en charge des effets secondaires des antidépresseurs

L'innocuité et la tolérance des antidépresseurs ont été considérablement améliorées au cours de ces vingt dernières années. Leurs effets secondaires restent néanmoins courants et source de problèmes. La plupart des patients traités par les molécules actuelles souffrent d'un ou plusieurs effets secondaires gênants. Ceux-ci empêchent souvent l'obtention d'une rémission de la dépression ou de la prévention d'une récurrence ou d'une rechute. Les médecins ont tendance à sous-estimer la prévalence des effets secondaires et jusqu'à un quart des patients arrêtent leur traitement antidépresseur car ils ne tolèrent pas ces effets gênants ; les autres continuent leur traitement mais leur qualité de vie en est diminuée. Cet article passe en revue la prévalence des effets secondaires, leur impact sur l'observance du traitement et les questions méthodologiques comme celle de distinguer les effets secondaires des symptômes dépressifs résiduels, des effets dus à l'interruption du traitement et des affections médicales générales. De plus, nous abordons les effets secondaires les plus courants comme les troubles sexuels, gastro-intestinaux, les perturbations du sommeil, l'apathie et la fatigue et nous proposons des stratégies de prise en charge afin d'aider les patients à obtenir une réponse optimale au traitement médicamenteux.

22. Nelson JC, Prtichett YL, Martynov O, et al. The safety and tolerability of duloxetine compared with paroxetine and placebo: a pooled analysis of 4 clinical trials. *Prim Care Companion J Clin Psychiatry*. 2006;8:212-219.
23. Goldstien DJ, Mallinckrodt C, Lu Y, et al. Duloxetine in the treatment of major depressive disorder: a double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2002;63:225-231.
24. Papakostas GI, Fava M. A meta-analysis of clinical trials comparing moclobemide with selective serotonin reuptake inhibitors for the treatment of major depressive disorder. *Can J Psychiatry*. 2006;51:783-790.
25. Papakostas GI, Homberger CH, Fava M. A meta-analysis of clinical trials comparing mirtazapine with a selective serotonin reuptake inhibitor for the treatment of major depressive disorder. *J Psychopharmacol*. In press.
26. Beasley CM Jr, Dornseif BE, Pultz JA, et al. Fluoxetine versus trazodone: efficacy and activating-sedating effects. *J Clin Psychiatry*. 1991;52:294-299.
27. Zajecka J. Strategies for the treatment of antidepressant-related sexual dysfunction. *J Clin Psychiatry*. 2001;62(suppl 3):35-43.
28. Montejo-Gonzalez AL, Llorca G, et al. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J Sex Marital Ther*. 1997;23:176-94.
29. Clayton AH, Pradko JF, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry*. 2002;3:357-366.
30. Benkert O, Szegedi A, Kohlen R. Mirtazapine compared with paroxetine in major depression. *J Clin Psychiatry*. 2000;61:656-663.
31. Behnke K, Sogaard J, Martin S, et al. Mirtazapine orally disintegrating tablet versus sertraline: a prospective onset of action study. *J Clin Psychopharmacol*. 2003;10:305-314.
32. Wade A, Crawford GM, Angus M, et al. A randomized, double-blind, 24-week study comparing the efficacy and tolerability of mirtazapine and paroxetine in depressed patients in primary care. *Int Clin Psychopharmacol*. 2003;18:133-141.
33. Phillip M, Tiller JW, Baier D, et al. Comparison of moclobemide with selective serotonin reuptake inhibitors (SSRIs) on sexual function in depressed adults: the Australian and German Study Groups. *Eur Neuropsychopharmacol*. 2000;10:305-314.
34. Versiani M, Moreno R, Ramakers-van Moorsel CJ, et al. Comparison on the effects of mirtazapine and fluoxetine in severely depressed patients. *CNS Drugs*. 2005;18:133-141.
35. Montejo AL, Llorca G, Izquierdo JA, Rico-Villademoros F. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. *J Clin Psychiatry*. 2001;62(suppl 3):10-21.
36. Rothschild AJ. Sexual side effects of antidepressants. *J Clin Psychiatry*. 2000;61(suppl 11):28-36.

Translational research

37. Rothschild AJ. Selective serotonin reuptake inhibitor-induced sexual dysfunction: efficacy of a drug holiday. *Am J Psychiatry*. 1995;152:1514-1516.
38. Bartlik BD, Kaplan P, Kaplan HS. Psychostimulans apparently reverse sexual dysfunction secondary to selective serotonin reuptake inhibitors. *J Sex Marital Ther*. 1995;21:264-271.
39. Herman JB, Brotman AW, Pollack MH, et al. Fluoxetine-induced sexual dysfunction. *J Clin Psychiatry*. 1990;51:25-27.
40. Hsu JH, Shen WW. Male sexual side effects associated with antidepressants: a descriptive clinical study of 32 patients. *Int J Psychiatry Med*. 1995;25:191-201.
41. Nurnberg HG, Hensley PL, Gelenberg AJ, Fava M, Lauriello J, Paine S. Treatment of antidepressant-associated sexual dysfunction with sildenafil. *JAMA*. 2003;289:56-64.
42. Nurnberg HG, Hensley PL, Heiman JR, Croft HA, Debattista C, Paine S. Sildenafil treatment of women with antidepressant-associated sexual dysfunction: a randomized controlled trial. *JAMA*. 2008;300:395-404.
43. Thase ME, Haight BR, Richard N, et al. Remission rates following antidepressant therapy with bupropion or selective serotonin reuptake inhibitors: a meta-analysis of original data from 7 randomized controlled trials. *J Clin Psychiatry*. 2005;66:974-981.
44. Falk WE, Roxenbaum JF, Otto MW, et al. Fluoxetine versus trazodone in depressed geriatric outpatients. *J Geriatr Psychiatry Neurol*. 1989;52:294-299.
45. DeVane CL. Immediate-release versus controlled-release formulations: pharmacokinetics of newer antidepressants in relation to nausea. *J Clin Psychiatry*. 2003;64(suppl 18):14-19.
46. Kinrys G, Simon NM, Farach FJ, Pollack MH. Management of antidepressant-induced side effects. In: Alpert JE, Fava M, eds. *Handbook of Chronic Depression*. New York, NY: Marcel Dekker, Inc; 2004:411-446.
47. Boyer WF, Blumhardt CL. The safety profile of paroxetine. *J Clin Psychiatry*. 1992;53(suppl):61-66.
48. Fava MF. Weight gain and antidepressants. *J Clin Psychiatry*. 2000;61(suppl 11):37-41.
49. Fava M, Roxenbaum JF, Judge RA, et al. Fluoxetine vs. sertraline and paroxetine in major depression: long-term changes in weight. In: New Research Program and abstracts of the 152nd Annual Meeting of the American Psychiatric Association. May 19, 1999; Washington, DC. Abstract NR430:186.
50. Aberg-Wistedt A, Agren H, Ekselius L, et al. Sertraline versus paroxetine in major depressive disorder: changes in weight with long-term treatment. *J Clin Psychopharmacol*. 2000;20:645-652.
51. Michelson D, Amsterdam JD, Quitkin FM, et al. Changes in weight during a 1-year trial of fluoxetine. *Am J Psychiatry*. 1999;156:1170-1176.
52. Mackle M, Kocsis J. Effects on body weight of the SSRI citalopram. Paper presented at; the 37th annual meeting of the American College of Neuropsychopharmacology; Dec 14-18, 1998; Las Croabas, Puerto Rico.
53. Sussman N, Ginsberg DL, Bikoff J, et al. Effects of nefazodone on body weight: a pooled analysis of selective serotonin reuptake inhibitor-and imipramine-controlled trials. *J Clin Psychiatry*. 2001;62:256-260.
54. Weihs KL, Houser TL, Batey SR, et al. Continuation phase treatment with bupropion SR effectively decreases the risk of relapse for depression. *Biol Psychiatry*. 2002;51:753-761.
55. Thase M, Bartlett C. Reboxetine does not cause weight gain during long-term therapy [abstract]. *Eur Neuropsychopharmacol*. 2001;11(suppl 3):S215.
56. Nelson JC. Safety and tolerability of the new antidepressants. *J Clin Psychiatry*. 1997;58(suppl 6):26-31.
57. Hoehn-Saric, Lipey JR, McLeod DR. Apathy and indifference in patients on fluvoxamine and fluoxetine. *J Clin Psychopharmacol*. 1990;10:343-345.
58. Rosenbaum JF, Fava M, Hoog SL et al. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biol Psychiatry*. 1998;44:77-87.
59. Safren SA, Otto MW, Worth JL, et al. Two strategies to increase adherence to HIV antiretroviral medication: Life-Steps and medication monitoring. *Behav Res Ther*. 2001;39:1151-1162.
60. Safren SA, Otto MW, Worth JL. Applying cognitive behavioral therapy to HIV medication adherence. *Cogn Behav Pract*. 1999;6:332-341.