Tolerability of Modern Antidepressants

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Antidepressant side effects may have implications with regard to patient safety as well as the overall tolerability of treatment. Side effects relevant to patient safety can contribute to an increased risk of morbidity and mortality, but may or may not result in patient distress or discomfort. In contrast, side effects related to tolerability can contribute to patient discomfort but are not associated with an immediate increase in risk of morbidity or mortality. Common tolerability-related side effects of modern antidepressants include nausea, insomnia, somnolence, fatigue, sexual dysfunction, and weight gain. Because these side effects can result in patient discomfort and distress, they can lead to poor compliance or noncompliance with treatment that, in turn, may result in an increased risk of depressive relapse or recurrence. Modern antidepressants have varying tolerability profiles, and clinicians should be vigilant about balancing treatment efficacy with side effects when choosing antidepressants. This article compares the rates of common tolerability-related side effects among the newer (post-tricyclic era) antidepressants with the selective serotonin reuptake inhibitors, the most popular contemporary first-line treatment for depression. *(J Clin Psychiatry 2008;69[suppl E1]:8–13)*

Adverse events are unwanted events, whether expected or unexpected, that occur during a period of observation. When the period of observation coincides with treatment, they are referred to as treatment-emergent adverse events. When, in the setting of a randomized, double-blind clinical trial, it can be demonstrated that a treatment-emergent adverse event is statistically more likely to occur during the administration of an antidepressant than an inactive pill, these events are then referred to as "side effects" (as opposed to nonspecific, nocebo-type phenomena). Side effects can contribute to patient discomfort as well as an increased risk of morbidity and mortality. Side effects that increase the immediate risk of morbidity or mortality are referred to as safety-related. In contrast, tolerability-related side effects predominantly result in patient discomfort but not an increased risk of morbidity/mortality.

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TOLERABILITY-RELATED SIDE EFFECTS: PREVALENCE AND IMPACT ON TREATMENT

Side effects associated with antidepressant treatment are both common and persistent. Hu and colleagues[1] studied 401 patients with depression prescribed a selective serotonin reuptake inhibitor (SSRI). Following 75 to 105 days of treatment, 86% of patients reported 1 or more side effect, while 55% reported at least 1 side effect they considered bothersome. In addition, while most side effects first appeared during the initial 2 weeks of treatment, the majority of patients continued to experience side effects that emerged during those first 2 weeks as long as 75 to 105 days later. Discrepancies in the timing of several side effects (i.e., whether they occurred during acute versus long-term treatment) were also noted in that study. For instance, 82% of patients experienced nausea following 2 weeks of treatment, but, by 3 months, only 32% of those patients continued to complain of nausea. In contrast, the percentage of patients who experienced weight gain increased over time (from 29% during the first 2 weeks to 59% during the 3-month follow-up period), while insomnia, drowsiness, and sexual dysfunction appeared early on and persisted throughout treatment. Thus, even though antidepressant side effects have traditionally been divided into short-term and long-term categories, this division appears to be mostly artificial.

Antidepressant side effects can adversely impact the treatment of major depressive disorder (MDD) by adding to patient suffering and distress, contributing to a delay or failure to attain an effective or optimal antidepressant dose, and increasing the risk of intermittent compliance or noncompliance with therapy. Lin and colleagues,[2] for

instance, studied adherence to antidepressant therapy in a naturalistic sample of 155 patients who were prescribed a tricyclic antidepressant (TCA), trazodone, or an SSRI. At week 2, 20.6% of patients had discontinued treatment, and, at 4 months, 51.2% had discontinued treatment. Side effects were cited as the reason for antidepressant discontinuation by 62.2% of patients who discontinued treatment within the first 30 days and by 66.7% of patients who discontinued treatment between days 31 and 90. Thus, although the highest rate of premature discontinuation of antidepressant therapy was observed during the first 2 weeks of treatment, the majority of patients who discontinued treatment later on cited intolerable side effects as the reason for doing so. Such findings challenge the traditional belief that, if patients can "endure" side effects initially, then the tolerability of an antidepressant will gradually improve, leading to a decrease in the rate of premature treatment discontinuation owing to intolerance.

The relationship between antidepressant side effects and premature discontinuation of treatment exemplified in the aforementioned study by Lin and colleagues[2] was recently confirmed in a separate study. Specifically, Hunot and colleagues[3] followed 178 patients who were prescribed an antidepressant who were then followed for a total of 6 months. Approximately 50% of patients enrolled in the study had discontinued treatment over the 6-month period. Remarkably, only about 11% of patients who had prematurely discontinued treatment had informed their prescribing clinician of their decision. Concern regarding side effects was found to be a strong predictor of treatment discontinuation in that study, along with preference for a different treatment and a general worry about taking an antidepressant.

Nonadherence to antidepressant therapy is, of course, a major concern for clinicians due to the associated risk of depressive relapse or recurrence. A meta-analysis[4] by Geddes and colleagues, for example, compared relapse rates among depressed patients who had experienced symptom improvement during antidepressant therapy who then went on to either continue or discontinue their antidepressant treatment. Among patients who discontinued treatment, 41% relapsed, while only 18% of those who continued treatment relapsed ($p < .00001$).

Partial adherence to antidepressant therapy has also been linked to an increased risk of depressive relapse. Specifically, Papakostas and colleagues[5] conducted a meta-analysis examining relapse rates among antidepressant remitters who continued antidepressant therapy at the original dose versus antidepressant remitters whose antidepressant dose was reduced by half. A difference in relapse rates between the 2 treatment groups was observed, with a relapse rate of 15.1% for patients who continued on the original dose versus a 25.3% relapse rate for patients who continued on the reduced dose ($p = .001$).

Importance of Tolerability in Antidepressant Selection

Given the relationship between side effects, premature discontinuation of treatment, and an increased risk of depressive relapse, it is no surprise that, among the factors considered by psychiatrists when choosing an antidepressant, side effect profile is one of the most important considerations. Zimmerman and colleagues,[6] for instance, surveyed psychiatrists who had recently prescribed antidepressants regarding factors that influenced their decision-making when choosing one pharmacologic agent over another. The factors most frequently considered by clinicians included the presence of a specific symptom of depression (52.3%), a wish to avoid a specific side effect (48.7%), the presence of a comorbid condition (45.6%), and treatment history including a prior nonresponse during treatment with a particular medication (25.9%). Thus, the results of this survey suggest that psychiatrists are likely to choose a well tolerated medication even in the presence of past treatment failure with that agent, a finding that underscores the importance of tolerability in treatment decision-making to patients as well as clinicians.

RELATIVE TOLERABILITY PROFILES OF MODERN ANTIDEPRESSANTS

In light of the relationship between antidepressant side effect burden and the risk of premature treatment discontinuation and illness recurrence in MDD, it is becoming increasingly clear that, in order to maximize the likelihood of long-term adherence to treatment, clinicians should be vigilant when balancing treatment efficacy with side effects when choosing antidepressants. In the aforementioned study by Hu and colleagues,[1] patients were asked to rank which side effects they experienced as most bothersome. Sexual dysfunction was rated as most bothersome (16.7%), followed by drowsiness/fatigue (16.5%), weight gain (11.5%), and insomnia (11.2%). Nausea was also reported as bothersome by 5.7% of patients. The remainder of this article will focus on describing the relative prevalence of these 5 tolerability-related side effects among newer (post-TCA) antidepressants using SSRIs as a comparator.

Nausea

Nausea is a fairly common side effect of antidepressant treatment that can have serious implications in terms of premature discontinuation of treatment. The prevalence of nausea during treatment with an SSRI was reported as high as 21% in 1 pooled analysis, while 14% of patients administered placebo reported nausea as a side effect in that study.[7] Treatment with the norepinephrine-dopamine reuptake inhibitor (NDRI) bupropion appears to be associated with lower rates of nausea compared to SSRI treatment,[7] as does treatment with the monoamine oxidase

inhibitor moclobemide, the norepinephrine reuptake inhibitor (NRI) reboxetine, and the serotonin-norepinephrine receptor antagonist mirtazapine.[8] Studies comparing SSRIs with either the serotonin receptor antagonists trazodone and nefazodone or the serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine have, generally, reported comparable rates of nausea among these agents.[8] Treatment with the SNRI venlafaxine, especially in immediate-release form, appears to result in higher rates of nausea than SSRI treatment.[8] Finally, it is worth noting that nausea resulting from the use of either venlafaxine or paroxetine may be reduced by using controlled-release formulations rather than immediate-release formulations of these 2 agents (i.e., venlafaxine XR and paroxetine CR).[8]

Insomnia

Insomnia is another common antidepressant side effect. Insomnia frequently appears early on during the course of treatment and, left untreated, often persists for the full duration of treatment. The results of 1 pooled analysis of randomized, double-blind clinical trials suggest rates of insomnia among SSRI-treated patients with MDD of approximately 16% compared with about 7% for placebo.[7] Rates of insomnia appear to be lower during treatment with several antidepressants including mirtazapine, trazodone, and nefazodone than during SSRI treatment.[8] Treatment of MDD with bupropion, moclobemide, duloxetine, and venlafaxine appears to result in rates of insomnia similar to those reported during SSRI treatment, while treatment with reboxetine appears to result in higher rates of insomnia than SSRI treatment.[8]

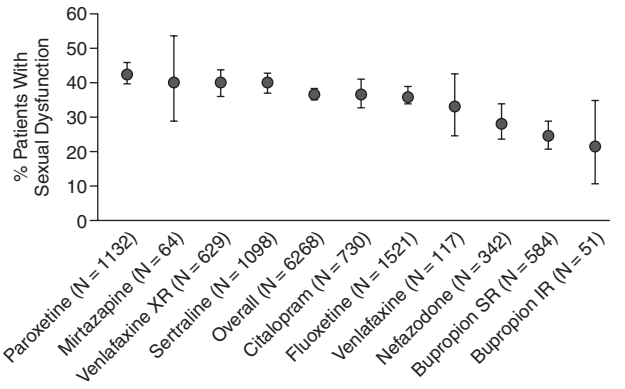
Somnolence and Fatigue

A pooled analysis of randomized, double-blind clinical trials has estimated the prevalence of somnolence and fatigue during treatment with SSRIs as approximately 12% (5% for placebo, $p < .05$).[7] Treatment of MDD with the NDRI bupropion or the NRI reboxetine appears to be associated with lower rates of somnolence and fatigue than SSRI treatment, while rates of somnolence and fatigue reported during treatment with agents including moclobemide, nefazodone, venlafaxine, and duloxetine appear to be similar to those reported during SSRI treatment.[8] Finally, treatment with mirtazapine and trazodone appears to result in higher rates of somnolence and fatigue than SSRI treatment.[8]

Sexual Dysfunction

Several types of sexual dysfunction can be associated with antidepressant treatment, including disturbances in desire, arousal, and orgasm.[9] Of all common antidepressant side effects, sexual dysfunction is most often underreported by patients. For example, Montejo-Gonzalez and colleagues[10] surveyed 344 patients taking antidepressants about sexual dysfunction and found that only 14% of patients spontaneously reported sexual dysfunction, whereas as many as 58% of patients endorsed sexual dysfunction when elicited by direct questioning.

Figure 1. Prevalence of Sexual Dysfunction: Overall Clinical Population[a]

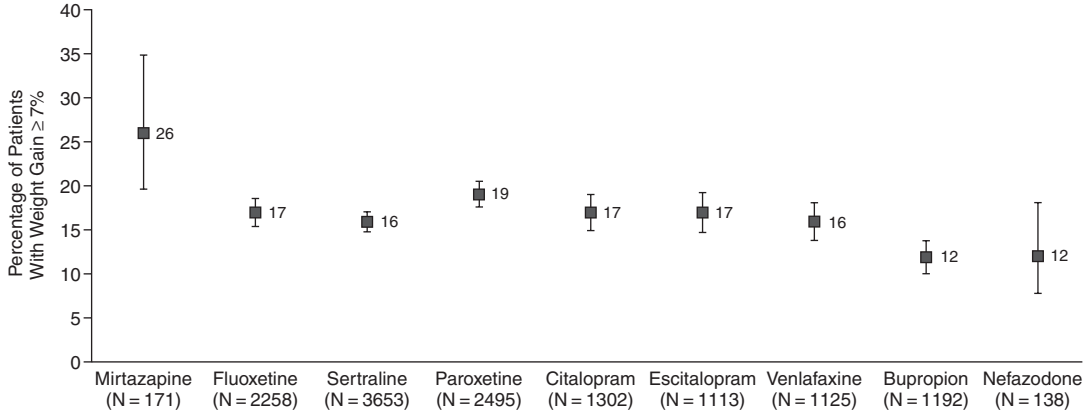


[a]Reprinted with permission from Clayton et al.[11] Sexual dysfunction is defined as a Changes in Sexual Functioning Questionnaire score at or below the gender-specific threshold total score. Bars represent the 95% CI.
Abbreviations: IR = immediate release, SR = sustained release, XR = extended release.

The prevalence of sexual dysfunction appears to vary across antidepressants. Clayton and colleagues[11] conducted a cross-sectional, observational study of over 6000 patients who had been prescribed newer antidepressants. The highest prevalence of sexual dysfunction was found among patients taking an SSRI, mirtazapine, or venlafaxine, while the lowest prevalence was among patients taking nefazodone and bupropion (Figure 1).[11]

The results of randomized, double-blind studies that employ a scale specifically designed to measure sexual dysfunction have confirmed that robust differences exist among antidepressants with regard to their ability to contribute to sexual dysfunction in MDD. Such studies suggest SSRI treatment to result in significantly higher rates of sexual side effects than treatment with either reboxetine[12,13] or nefazodone.[8] Studies comparing rates of sexual dysfunction during treatment with mirtazapine versus an SSRI report inconsistent results, with some studies[14,15] showing higher rates of sexual dysfunction during SSRI treatment and other studies[16–18] showing no difference between the 2 treatment groups. Of more than 40 randomized, controlled trials that compared SSRIs with the SNRI venlafaxine (see reference 8 for review), only 1 study[19] appears to have employed a measurement of sexual dysfunction. No difference in the prevalence of sexual dysfunction between the 2 treatments was observed in that trial. Treatment with the SNRI duloxetine appears to result in somewhat lower rates of sexual dysfunction than treatment with the SSRI paroxetine,[20] or the SSRI escitalopram.[21]

Figure 2. Weight Gain Following 1 Year of Treatment (95% CI)[a]



[a]Reprinted with permission from Papakostas.[8] Data on file, GlaxoSmithKline, Brentford, Middlesex, U.K. Proportion of patients with weight gain and 95% CIs depicted in the General Electric Medical Records Database.

Finally, a pooled analysis of 5 clinical trials conducted by Thase and colleagues[7] examined the relative prevalence of sexual dysfunction during treatment with several SSRIs (fluoxetine, sertraline, and paroxetine) versus the NDRI bupropion. Orgasm dysfunction, sexual arousal disorder, and sexual desire disorder were more likely to occur during treatment with the SSRIs than with bupropion or placebo. Rates of sexual dysfunction for bupropion versus placebo were not statistically different. More recently, reports have also demonstrated lower rates of sexual dysfunction during treatment of MDD with bupropion than with the SSRI escitalopram.[22,23]

Weight Gain

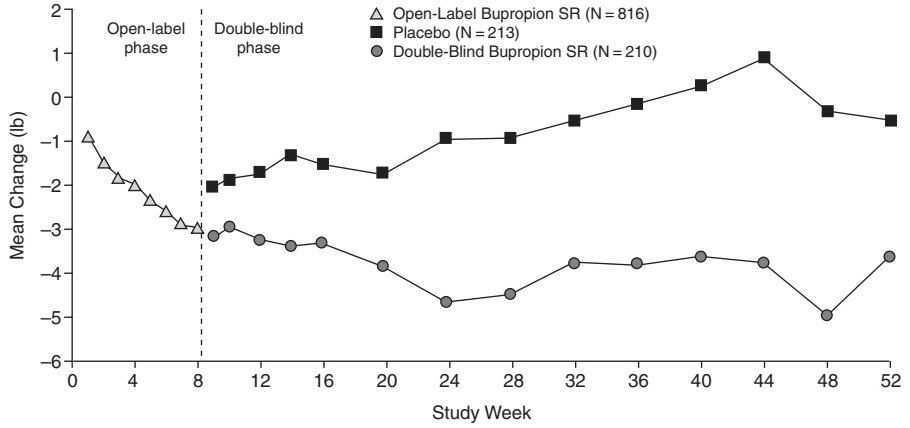
Patients may experience weight gain during antidepressant treatment. Weight gain in antidepressant trials is most often reported either as a change in weight from baseline or as the proportion of patients who gain more than 7% of their body weight compared to baseline. The results of a large, cross-sectional study[8] based on the General Electric Medical Records Database involving patients treated for a unipolar depressive episode with an antidepressant monotherapy for at least 1 year suggested differences among antidepressants in the proportion of patients who gained at least 7% of their body weight during treatment (Figure 2). Mirtazapine was associated with the highest percentage of patients with weight gain (26%), followed by the SSRIs and venlafaxine (from 16% to 19%).[20] Bupropion and nefazodone demonstrated the lowest rates of weight gain (12%). Unfortunately, only a small subset of randomized, double-blind, placebo-controlled studies report on the prevalence of weight gain during the long-term treatment of MDD.

Mirtazapine. A double-blind, randomized clinical trial focusing on the treatment of MDD patients over the course of 20 weeks reported weight gain in approximately 22% of patients treated with the TCA amitriptyline compared to 12.7% for mirtazapine-treated patients and 2.6% for placebo-treated patients.[24] This study underscores that TCAs have the highest incidence of weight gain of available antidepressants, but also demonstrated significant weight gain during long-term mirtazapine treatment in MDD.

That long-term treatment with mirtazapine can result in significant weight gain has been confirmed in a more recent study conducted by Thase and colleagues.[25] Specifically, over the course of 40 weeks of double-blind treatment with either mirtazapine or placebo, mirtazapine-treated patients experienced a mean gain in weight of 1.42 kg. Conversely, patients treated with placebo experienced a mean weight loss of 1.67 kg, a difference that was statistically significant ($p < .001$).

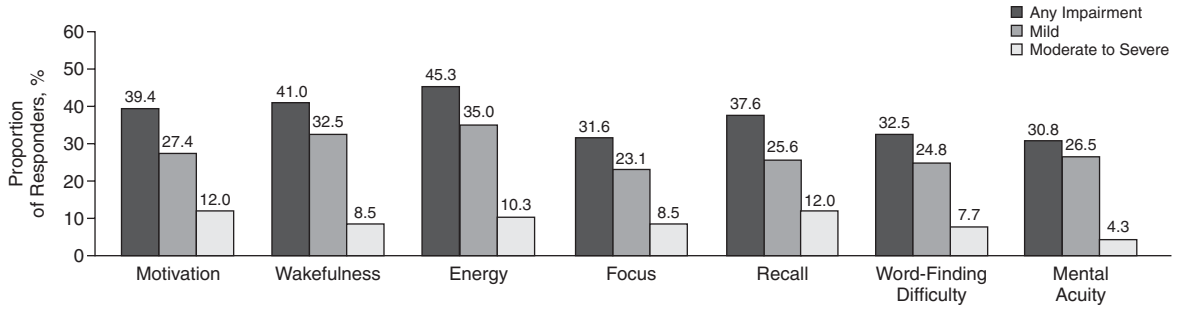
SSRIs. Studies examining weight gain during long-term SSRI treatment report inconsistent results. On one hand, a 52-week study by Kornstein and colleagues[26] found no statistically significant difference in change in weight over the course of treatment among patients treated with escitalopram versus placebo. However, a 34-week clinical trial[27] comparing the SNRI duloxetine (40–120 mg/day) with the SSRI paroxetine (20 mg/day) and placebo reported that both paroxetine and duloxetine treatment were more likely to result in weight gain than placebo. The incidence of ≥ 7% body weight gain was 3.1% among placebo-treated patients, 10.8% among duloxetine-treated patients, and 13.8% among paroxetine-treated patients. Thus, it appears that there may be differences among SSRIs in the risk for weight gain during long-term treatment. In fact, a study[28] involving the treatment of MDD with the SSRIs paroxetine, fluoxetine, or sertraline reported weight gain of 7% or greater by 25.5% of patients taking paroxetine for 26 to 32

Figure 3. Mean Change in Weight From Baseline in Patients Treated With Bupropion SR (300 mg/day) vs. Placebo[a]



[a]Reprinted with permission from Weihs et al.[33]

Figure 4. Proportion of Responders With Cognitive and Physical Impairment (N = 117)[a]



[a]Reprinted with permission from Fava et al.[34] Impairment measured according to the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire.

weeks. Conversely, only 6.8% of patients taking fluoxetine and 4.2% of patients taking sertraline experienced clinically significant weight gain in that study.

SNRIs. Until recently, no data on weight change from long-term, placebo-controlled studies focusing on the use of venlafaxine for the treatment of mood or anxiety disorders had been published.[8] Recently, however, the results of a 2-year study comparing venlafaxine with placebo for MDD revealed no difference in weight gain for venlafaxine and placebo-treated patients.[29] Long-term weight gain with duloxetine appears to be similar to placebo at daily doses of 60 mg[30,31] and greater than placebo at daily doses above 60 mg (i.e., 80 mg or 120 mg).[27,31]

Nefazodone. Treatment of MDD with the serotonin receptor antagonist nefazodone appears to carry a very low risk of weight gain in clinical studies. For example, a pooled analysis[32] examining effects on weight of up to 46 weeks of treatment with nefazodone versus an SSRI found that nefazodone treatment was associated with a weight gain of 7% or more in 6.9% of patients, compared with 13.8% of patients treated with SSRIs.

Bupropion. Treatment with bupropion also appears to carry a very low risk of weight gain. In fact, in a 44-week study[33] comparing bupropion (300 mg or SR formulation) versus placebo, no statistically significant difference in the change in weight was observed for bupropion- versus placebo-treated patients with MDD (Figure 3).

Less-Studied Tolerability-Related Side Effects

Besides nausea, insomnia, somnolence, fatigue, sexual dysfunction, and weight gain, other tolerability-related adverse events can also occur during antidepressant treatment including decreased motivation, apathy, difficulties in concentration and focus, and poor short-term memory.

Cognitive and physical side effects of antidepressants are not well understood, although they appear to be fairly common and clinically relevant. In an observational study,[34] Fava and colleagues examined 117 patients taking

antidepressants for MDD who had reached partial or full remission. After at least 3 months of treatment, between 31% and 45% of patients reported some impairment in motivation, wakefulness, energy, focus, recall, word-finding ability, or mental acuity. Between 4% and 12% of patients reported having moderate to severe impairment in these domains (Figure 4). This finding suggests the need for further investigation into these kinds of treatment side effects.

CONCLUSION

Tolerability-related antidepressant side effects appear to be common and persistent. They can contribute to discomfort, as well as an increased risk of premature discontinuation of treatment that, in turn, may result in depressive relapse/recurrence. Therefore, minimizing the side effect burden for patients undergoing antidepressant treatment is vital to improve their standard of care.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, moclobemide and reboxetine are not approved by the U.S. Food and Drug Administration for the treatment of major depressive disorder.

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