Limitations of Contemporary Antidepressants: Tolerability

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Antidepressant side effects are common and persistent. They can contribute to discomfort, distress, disability, morbidity, and mortality and can compromise the efficacy of treatments. Reducing the side effect burden, either by developing treatments that have a lower incidence of side effects or by using treatment strategies that alleviate side effects, would improve the standard of care for mood and anxiety disorders. In this article, the rates of common adverse events among the newer (posttricyclic era) antidepressants are compared with those among the selective serotonin reuptake inhibitors, the most popular, contemporary first-line treatments for depression.

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Side effects can occur at varying times during treatment of mood or anxiety disorders with antidepressants. When they appear early during treatment, side effects can contribute to additional patient discomfort and distress as well as compromise efficacy. Long-term side effects can result in discomfort and distress and delay the restoration of psychosocial functioning, as well as contribute to increased morbidity, mortality, and a loss of therapeutic gains.

ACUTE AND LONG-TERM SIDE EFFECTS

Side effects present during the acute phase of pharmacotherapy for depression are both common and persistent. Hu et al.[1] studied 401 patients with depression who were prescribed a selective serotonin reuptake inhibitor (SSRI). Following 75 to 105 days of treatment, 86% of patients reported 1 side effect or more, 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 the same side effect 75 to 105 days later.

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In addition, discrepancies existed in the timing of certain side effects (e.g., acute versus long term), but not in others.[1] For instance, a high percentage of patients (82%) 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 (29% to 59%). However, insomnia, drowsiness, and sexual dysfunction began early and persisted (approximately 64% to 69%, 56% to 69%, and 62% to 83%, respectively).[1] Thus, even though antidepressant side effects have traditionally been divided into short-term and long-term categories, this division appears to be mostly artificial (Figure 1).

Side effects present during the acute phase of treatment of depression may add to patient suffering and distress, contribute to a delay in attaining an effective or optimal antidepressant dose, and contribute to poor or intermittent compliance or noncompliance altogether. Lin et al.[2] studied adherence to antidepressant therapy in a naturalistic sample of 155 patients starting a new prescription with a tricyclic antidepressant (TCA), trazodone, or fluoxetine. At 2 weeks, 20.6% of patients had discontinued treatment, and at 4 months, 51.2% had discontinued treatment. Side effects were cited as the reason for discontinuation by 62.2% of those who discontinued treatment within the first 30 days and by 66.7% of patients who discontinued treatment between days 31 and 90. Although this study found that the greatest drop in adherence occurred within the first 2 weeks of treatment, the majority of patients who discontinued treatment later did so because of intolerable side effects. These results challenge the traditional belief that, if patients endure side effects initially, then the rate of discontinuation due to side effects will decrease.

A variety of side effects may also occur during the long-term treatment of depression, which may contribute to distress, a delay or failure in restoring psychosocial

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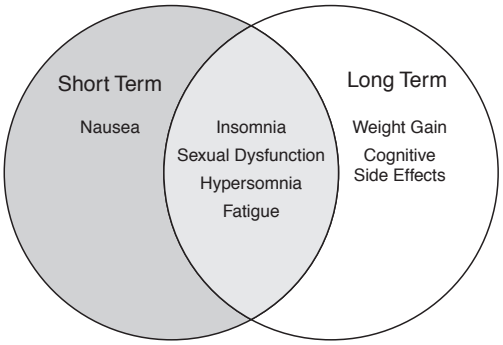
Figure 1. Short- and Long-Term Side Effects Associated With Antidepressant Medication



functioning (e.g., excessive daytime somnolence, fatigue, and cognitive side effects and their effects on work productivity), increased morbidity and mortality (e.g., obesity and vascular illness, lethargy and motor vehicle accidents, falls, and fractures), and a loss of therapeutic gains due to poor compliance, noncompliance, or a need to reduce the antidepressant dose.

RELATIVE PREVALENCE OF SIDE EFFECTS WITH VARIOUS ANTIDEPRESSANTS

In a study by Hu et al.,[1] patients were asked to rank which side effects they believed to be most bothersome. Sexual dysfunction was most frequently rated (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 side effects among the newer (post-TCA era) antidepressants. When available, data from meta-analyses of randomized, controlled trials will be used as an estimate of the relative likelihood of developing a given side effect during treatment with various antidepressant agents. In the absence of data from meta-analyses, data from individual randomized, controlled trials will be presented instead. Since most antidepressant comparator trials involve the use of an SSRI in the post-TCA era, the prevalence of side effects during treatment with other newer antidepressants compared to the SSRIs will be related.

Nausea

The SSRIs appear to be associated with equivalent or higher rates of nausea when compared with most non-SSRI medications. Specifically, treatment with the SSRIs appears to result in higher rates of nausea than bupropion,[3] moclobemide,[4] reboxetine (G.I.P.; J. C. Nelson, M.D.; S. Kasper, M.D.; et al., manuscript submitted), and mirtazapine.[5] However, comparative studies of SSRIs and trazodone,[6–9] nefazodone,[10–14] and duloxetine[15–20] have found that nausea rates were roughly equivalent. Venlafaxine appears to have a higher incidence of nausea than SSRIs.[21–26] 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 extended release and paroxetine controlled release).[26]

Insomnia

Treatment with the SSRIs appears to result in higher rates of insomnia than mirtazapine,[5] trazodone,[6,7] and nefazodone.[13,14] Equivalent rates of insomnia have been found among the SSRIs and bupropion,[3] moclobemide,[4] duloxetine,[16–19] and venlafaxine.[21–25,27–39] Finally, reboxetine was found to have a higher rate of insomnia compared with SSRIs (G.I.P.; J. C. Nelson, M.D.; S. Kasper, M.D.; et al., manuscript submitted and reference 40).

Somnolence and Fatigue

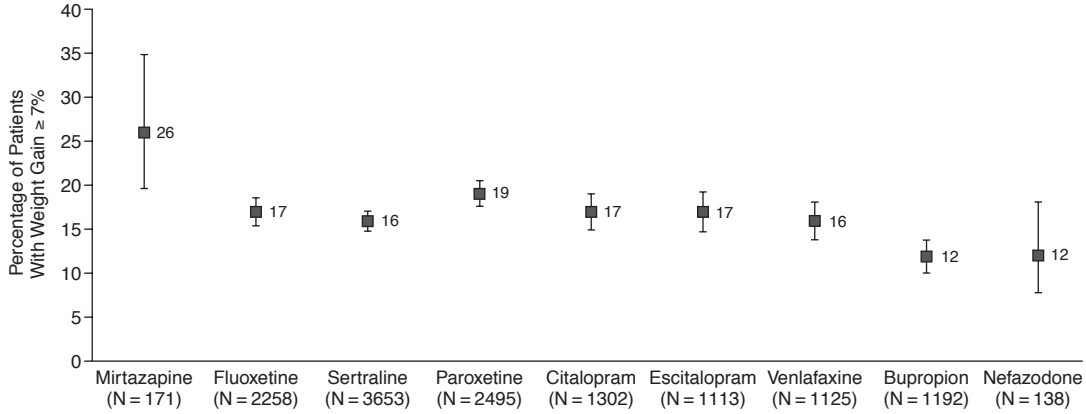
Somnolence and fatigue are also common side effects associated with antidepressant use. Treatment with SSRIs has been found to result in a higher rate of somnolence and fatigue than bupropion[3,41] and reboxetine (G.I.P.; J. C. Nelson, M.D.; S. Kasper, M.D.; et al., manuscript submitted). Moclobemide,[4] nefazodone,[10–13] venlafaxine,[21–25,27–30,32,33,36,37] and duloxetine[15–19] were all found to have rates of somnolence and fatigue equivalent to those of the SSRIs. Finally, treatment with mirtazapine[5] and trazodone[6] appeared to result in greater rates of somnolence and fatigue than SSRI treatment.

Sexual Dysfunction

Antidepressant treatment may also result in a variety of sexual side effects ranging from decreased libido, arousal dysfunction (i.e., inhibited sexual excitement, diminished genital sensation, erectile dysfunction, and failure to achieve or maintain vaginal lubrication), and orgasm disorders (i.e., delayed orgasm and partial or complete anorgasmia).[42] Sexual side effects are notoriously underreported by patients, and physicians must often ask about such bothersome adverse events. Montejo-Gonzalez et al.,[43] for instance, studied 344 patients prescribed fluoxetine, fluvoxamine, paroxetine, and sertraline and found that sexual dysfunction was reported by 58% of patients when physicians *directly inquired* about such side effects, compared with a mere 14% of patients who *spontaneously reported* sexual side effects.

Clayton et al.[44] investigated the prevalence of sexual dysfunction with a number of newer agents, including the SSRIs, bupropion, mirtazapine, nefazodone, and venlafaxine, prescribed to more than 6000 patients. The treatments with the lowest rate of sexual dysfunction were bupropion immediate release (22% to 25%) and nefazodone (28%).

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



[a]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.

The prevalence of sexual dysfunction following treatment with the remaining agents ranged from 36% to 43%.

Randomized controlled trials that employed a scale to specifically measure sexual dysfunction reported that SSRI treatment resulted in significantly higher rates of sexual side effects than bupropion,[3,42,45–50] reboxetine,[51–53] and nefazodone.[11] Studies comparing mirtazapine with an SSRI demonstrated mixed results, with some studies[54,55] showing higher rates of sexual dysfunction with SSRIs than with mirtazapine, and other studies[56–58] showing no difference between the 2 treatment groups. Of more than 40 randomized, controlled trials that compared SSRIs with venlafaxine, only 1 study[33] employed a measurement of sexual dysfunction. No difference in the prevalence of sexual dysfunction between the 2 treatments was observed in that trial. Studies comparing duloxetine with an SSRI[16–19] suggested no difference in sexual side effect rates between the 2 groups, although recent research[15,59] suggested that sexual dysfunction is more likely to occur with paroxetine than with duloxetine treatment.

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 (data on file, GlaxoSmithKline, Brentford, Middlesex, U.K.) based on the General Electric Medical Records Database* involving patients treated for a unipolar depressive episode with antidepressant monotherapy for at least 1 year suggested differences in the proportion of patients who gained 7% or more 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%).[16] Bupropion and nefazodone demonstrated the lowest rates of weight gain (12%).

Only a subset of all randomized, long-term, controlled studies of antidepressants have reported weight data. Of the newer antidepressants, long-term, randomized, controlled trials confirm that treatment with mirtazapine is associated with significant weight gain. For example, in a double-blind, randomized, placebo-substitution trial[60] involving the treatment of mirtazapine remitters with major depressive disorder (MDD) treated with either continued mirtazapine or placebo for a total of 40 weeks, mirtazapine-treated patients gained an average of 1.42 kg while patients taking placebo lost an average of 1.67 kg ($p < .001$). However, in a double-blind extension study[61] involving the treatment of MDD with the TCA amitriptyline, mirtazapine, or placebo, amitriptyline was associated with higher rates of weight gain (22%) than mirtazapine (12.7%) or placebo (2.6%).

Several studies suggest that long-term weight change with the SSRIs fluoxetine and escitalopram was similar to that with placebo.[62–65] However, paroxetine was associated with a significantly higher rate of weight gain (25.5%) than sertraline (4.2%; $p = .003$) or fluoxetine (6.8%; $p = .016$).[66] Reports focusing on duloxetine showed mixed findings, with 1 long-term study[67] showing no difference in weight change versus placebo following treatment with 60 mg/day of duloxetine, and other long-term studies[15,68] demonstrating higher rates of 7% or greater

*General Electric Medical Records Database: A database containing patient information from a consortium of 5000 physicians using General Electric Healthcare's CPO Electronic Medical Records, which documents care for about 4 million patients.

weight gain with duloxetine (80 or 120 mg/day) than placebo. However, it is also important to point out that many long-term, placebo-controlled studies of SSRIs[69–84] and venlafaxine[85] report no weight data. This lack of research data makes it difficult to accurately estimate weight change during the long-term treatment of depression with these agents.

Finally, nefazodone, bupropion, and reboxetine appear to result in the lowest rates of weight gain during treatment. Specifically, a pooled analysis[86] of randomized trials comparing nefazodone with an SSRI reported a 6.9% and 13.8% rate of weight gain, respectively ($p < .01$). Parallel, long-term, double-blind, placebo-controlled studies of bupropion[87] and reboxetine[88] have shown no difference in mean weight change compared with placebo.

Other Adverse Events

A number of other adverse events have been reported during antidepressant treatment. For example, studies have hinted at possible effects such as hyperprolactinemia with fluoxetine,[89] hyponatremia with paroxetine,[90] and problems with motivation, wakefulness, energy, focus, recall, finding words, and mental acuity with antidepressant treatment in general.[91] Unfortunately, these adverse events have been relatively understudied. Studies have suggested that treatment with the TCAs may result in higher rates of abnormal mood elevations (e.g., mania and hypomania) during the treatment of bipolar depression than the SSRIs paroxetine[92] and fluoxetine.[93] There is a paucity of studies comparing this adverse event among the newer agents. Post et al.[94] reported lower rates of switching to mania or hypomania among patients with bipolar depression treated with bupropion or sertraline than venlafaxine. Similarly, Vieta et al.[95] found lower rates of switching to mania or hypomania among paroxetine- than venlafaxine-treated patients with bipolar depression.

Adverse events that rarely occur represent a significant challenge for researchers and clinicians alike. To study rare adverse events, large sample sizes and/or long follow-up times are required. Specifically, during the early 1990s, concerns[96–99] were voiced regarding the potential for the SSRIs to worsen suicidal ideation or contribute to the emergence of suicidal ideation early on during the treatment of depression. These concerns were quickly followed by a number of pooled analyses,[100–102] which suggested that SSRIs were no more likely than placebo to worsen suicidal ideation or result in suicide attempts. Recently, concerns resurfaced regarding the potential for antidepressants to contribute to the emergence or worsening of suicidal ideation during the early phases of treatment (first 2 weeks) among children, adolescents, and adults with MDD. This time, concerns were voiced by drug regulatory authorities in the United States and United Kingdom and were followed by several more pooled analyses.[103–105] These analyses suggest a small increase in suicidal ideation in the proportion of children and adolescents with MDD during the first few weeks of treatment with the SSRIs. An increased risk in suicide during antidepressant treatment was not demonstrated. Pooled analyses of randomized, controlled trials of antidepressants in adults[106–112] found no relationship between an emergence of suicidal ideation, a worsening of suicidal ideation, or an increase in completed suicides during the treatment of MDD compared to placebo. However, a recent study by Thase et al.[113] demonstrated a numerically, but not statistically, higher rate of suicidal behavior among young adults aged 18 to 24 years treated with paroxetine compared with placebo for MDD. Data on venlafaxine, mirtazapine, and sertraline have yet to be published.

Other rare adverse events in need of further research include gastrointestinal bleeding with SSRIs and concomitant administration of nonsteroidal anti-inflammatory drugs[114]; seizure[115] and atopic reactions[116] with bupropion; thrombocytopenia, neutropenia, and bone marrow suppression with mirtazapine[117–119]; hepatotoxicity[120] and priapism[121] with nefazodone; hepatotoxicity,[122] priapism,[123] and cardiac conduction problems[124] with trazodone; cardiac conduction abnormalities[125] with venlafaxine; urinary hesitancy/retention and dysuria[126] with reboxetine; and liver enzyme abnormalities with duloxetine.[127]

CONCLUSION

Antidepressant side effects appear to be common and persistent. They can contribute to discomfort, distress, disability, morbidity, and mortality and can compromise the efficacy of treatments. Reducing the side effect burden, either by developing treatments that have low incidence of side effects or by using treatment strategies that alleviate side effects, would improve the standard of care for mood and anxiety disorders.

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, fluvoxamine, 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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