Antidepressant Drugs: Disturbing and Potentially Dangerous Adverse Effects

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Adverse effects associated with antidepressant drug therapy rarely cause significant morbidity or mortality. Nevertheless, the successful management of patients with depression requires recognition of potential adverse effects that have serious consequences, which include the discontinuation of otherwise effective therapy. The aim of this overview is to highlight the more common and potentially deleterious adverse effects of both older and newer classes of antidepressant drugs. Major adverse effects attributed to the tricyclic antidepressant drugs (TCAs) include conduction defects and lethal overdose. Most worrisome with the selective serotonin reuptake inhibitor drugs (SSRIs) is the serotonin syndrome. Although rare, this syndrome can be insidious and lethal. Recent trends toward the use of medication combinations and augmentation therapies significantly enhance the risk of serotonin syndrome. Cognitive impairment also may occur, especially with the TCAs. Apathy is occasionally a problem with SSRI therapy. The syndrome of inappropriate antidiuretic hormone (SIADH) has been reported with most antidepressant drugs but appears to be more common with serotonergic agents and in elderly patients. Although seizures are uncommon in patients receiving antidepressant therapy, the risk must be understood by both the patient and the clinician. Adverse effects related to sexual function are common, especially with TCAs, SSRIs, and venlafaxine. Sexual dysfunction often leads to noncompliance and self-discontinuation of therapy. Sleep disturbances are common in patients with depression, and recent data illustrate how crucial sleep regulation is to mood. Antidepressant drugs vary in their sleep effects. Although antidepressant drugs can cause a variety of adverse effects, these drugs save lives and their benefits far exceed their risks.

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Doctors pour drugs of which they know little, to cure diseases of which they know less, into human beings of whom they know nothing. —Voltaire

The list of adverse effects reported in patients receiving antidepressant drug therapy is almost endless. Most serious adverse effects, however, are idiosyncratic in nature and occur rarely. As such, they likely will never be observed during the professional lifetime of the vast majority of clinicians. This overview will focus on the more disturbing as well as serious types of complications that can occur with both the newer and older classes of antidepressant drugs. Greater awareness of these adverse effects by clinician and patient may increase recognition of the potential association and, in turn, decrease morbidity.

Overall, the antidepressant drugs are quite safe. Perhaps the greatest risk with these drugs is their lack of use in therapy. Depression is a serious disease that often goes undiagnosed and, consequently, antidepressant drugs are underutilized. A relatively high incidence of suicide among patients with recurrent mood illness, both bipolar and unipolar, has been observed in many studies.[1,2] Therefore, because depression can be a lethal disease, the low risk of significant adverse effects with antidepressant drugs is greatly outweighed by the benefits of their use.

UNDERUTILIZATION OF ANTIDEPRESSANT DRUGS

The benefits of antidepressant therapy can be illustrated by examining the relationship between suicide victims and forensic examination of blood and tissues. In 5 studies[3–7] in which more than 10,000 deaths by suicide were examined, 84% to 85% of patients had no evidence of antidepressant drugs in their bodies. It can be assumed from the cause of death that at least one half of these patients were depressed. Yet, very few of them (about 16%) were being treated with antidepressant drugs. In addition,

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only 4% to 5% of the more than 10,000 subjects had lethal plasma concentrations of antidepressant drugs, and nearly all of the 4% to 5% with lethal antidepressant drug levels also had lethal plasma concentrations of at least 1 other drug as well.

It would appear from these data that undertreatment with antidepressant drugs is a greater concern than overdose, and that greater use of antidepressants would decrease the risk of suicides. Indeed, Coppen[8] demonstrated that long-term use of lithium clearly reduced the suicide rate from 7.3 suicides per 1000 patient-years in patients not receiving long-term lithium treatment to 1.3 suicides per 1000 patient-years in patients receiving long-term lithium treatment.

It is logical to assume that more aggressive, more frequent, and greater use of maintenance therapy with antidepressant drugs also would reduce suicide rates. This has been difficult to document due to problems inherent in following an adequate number of patients for a long enough period of time. However, Isacsson and colleagues[5] concluded that the large decline in suicides recently cited in Sweden is the direct result of greater use of antidepressant medications.

COMMON ADVERSE EFFECTS OF TRICYCLIC ANTIDEPRESSANT DRUGS

While there is no doubt that the older, tricyclic class of antidepressant drugs are quite effective, they are not very "patient friendly." Tricyclic antidepressant drugs (TCAs) are associated with a number of uncomfortable side effects that often lead to compliance problems. The major types of side effects associated with TCAs include anticholinergic effects (e.g., dry mouth, constipation), cardiovascular effects (e.g., conduction disturbances, hypotension), and weight gain. Weight gain is a problem primarily with long-term therapy and is the most common reason for discontinuation after the acute treatment phase has been completed. These side effects are more troublesome than dangerous. The most serious concern with the TCAs is their extreme lethality in the overdose setting.

OTHER ADVERSE EFFECTS OF ANTIDEPRESSANTS

Cardiovascular Toxicity

Several studies have noted that depressed patients are more likely to develop ischemic heart disease and die from this condition than nondepressed patients.[9] As a corollary, patients with preexisting cardiovascular disease have a much poorer prognosis and higher mortality if they then become depressed.[9] TCAs have effects on cardiac conduction similar to those of class I antiarrhythmic drugs such as quinidine and procainamide.[10] It is now well documented that class I antiarrhythmic drugs increase rather than decrease mortality following a myocardial infarction in patients with ischemic heart disease. Therefore, it seems reasonable to assume that TCAs might pose the same risk for cardiac dysfunction and sudden death in patients with ischemic heart disease, even if silent, prior to treatment. Because the newer antidepressant drugs lack effects on cardiac conduction, they do not appear to carry the same risks for cardiac toxicity.

Thus, patients who have depression are more likely to die from cardiac-related events, although the reason for this is unclear. As a result, clinicians are obligated to treat depression perhaps even more aggressively in patients with underlying heart disease. In these patients, the newer antidepressant agents are preferred over the TCA drugs. The newer agents are far safer for the heart, but it is likely that no drug is perfectly safe. The primary risk with the selective serotonin reuptake inhibitors (SSRIs) is the potential for bradycardia, which has been reported infrequently.[11–13] Bradycardia occurs most often in patients who already are at risk for cardiac disease.[11] In the rare circumstances when bradycardia is severe, it can lead to more serious cardiac events such as atrial fibrillation and supraventricular tachycardia. Another potential cardiovascular side effect with the newer antidepressant drug venlafaxine is a dose-related increase in blood pressure. The manufacturer of venlafaxine recommends regular monitoring of blood pressure throughout therapy,[14] although it is unclear from a practical standpoint whether this is a medicolegal or a clinical issue. Most experts would advise such monitoring only when doses in the higher range are used.

Cognitive Effects

Cognitive impairment is an unavoidable dose-related complication of the older TCAs. The anticholinergic activity of this class of drugs appears to be responsible for the cognitive effects. At lower doses of TCAs, the impairment generally is minimal. As the dose is increased, many patients note subtle cognitive impairment initially, followed by not-so-subtle changes. In addition to being dose-related, the cognitive impairment associated with TCAs appears to correlate with age.

With the newer antidepressant drugs, cognitive impairment is idiosyncratic, unpredictable, and less common. A more common and increasingly appreciated form of cognitive impairment is the syndrome of apathy or lethargy associated with the SSRIs.[15,16] This effect is sometimes thought to resemble frontal lobe dysfunction due to the degree of indifference and apathy involved.[15,16] Apathy has many potential causes. One is frontal cortical hypoactivity associated with diminished dopamine activity. Serotonin exerts significant inhibitory action on dopamine neurons that project to the frontal areas. Through this mechanism, SSRIs can potentially cause this syndrome of apathy and lethargy.[17]

Further support for the hypothesis that antidepressant drugs interact with striatal dopaminergic function are the persistent, albeit infrequent, case reports of extrapyramidal syndromes (EPS) with the SSRIs.[18] EPS are even less common with the other classes of antidepressant drugs, including TCAs. Because the symptoms of EPS (akathisia, parkinsonism, dystonia, and dyskinesia) associated with SSRIs are almost certainly caused by hypoactivity of the dopaminergic systems, the same mechanism that produces EPS may apply to the syndrome of lethargy and apathy.

Serotonin Syndrome

Serotonin syndrome is a potentially life-threatening complication of any drug with serotonergic activity.[19,20] In addition to the 4 marketed SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline), nefazodone and venlafaxine also have significant serotonergic activity. The serotonin syndrome consists of cognitive (disorientation, confusion), autonomic (fever, shivering, diaphoresis, diarrhea), and neuromuscular (agitation, restlessness, hyperreflexia, myoclonus, ataxia) signs and symptoms.[19] The symptoms associated with serotonin syndrome resemble those of neuroleptic malignant syndrome, sometimes causing confusion in the differential diagnosis. There is an overlap between the typical adverse effects seen with SSRIs and the symptoms of serotonin syndrome; therefore, it is often difficult to distinguish where one leaves off and the other begins. Serotonin syndrome usually is provoked by an increase in the dose of a serotonergic drug or by the combining of serotonergic agents and often occurs within 24 hours of these changes.[20] The most dangerous and potentially lethal combinations are those with an SSRI and a monoamine oxidase inhibitor (MAOI).[19] Other potentially dangerous drug combinations are discussed in more detail in the review by Lane and Baldwin.[19]

The best approach to the management of serotonin syndrome is to avoid the high-risk, or high-dose, serotonergic drug combinations.[19] If serotonin syndrome does develop, the serotonergic agent(s) should be discontinued and supportive care implemented. Supportive care generally includes maintaining hydration and cardiac and renal function, and monitoring for hyperthermia. The use of serotonin antagonists such as cyproheptadine, methysergide, and propranolol have been suggested as antidotes, but their benefits are unproven. Serotonin syndrome usually resolves within 24 hours after discontinuing the offending drug(s).[19]

Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

The syndrome of inappropriate antidiuretic hormone (SIADH) has been reported with nearly all psychotropic drugs, including the antidepressant drugs.[21] It has been reported infrequently with TCAs but more commonly with SSRIs.[21–23] In 1 study,[24] 16.7% of 108 patients taking clomipramine developed hyponatremia (serum sodium less than 135 mmol/L), a significantly ($p < .001$) higher incidence than observed in control subjects (1.1%). SIADH may be mediated through serotonin-2A and serotonin-2C subreceptors, which may explain why this complication is observed more often with the SSRIs.[23] The early symptoms of SIADH generally are nonspecific and, thus, SIADH should be considered in the differential diagnosis for any patient who complains of a change in overall level of functioning. The diagnosis can be easily assessed by obtaining a serum sodium level. Advanced age (≥ 65 years), concomitant use of diuretics, and smoking appear to increase the risk for SIADH associated with antidepressant drugs.[22] Management of SIADH includes discontinuation of the antidepressant and supportive care.[21] Some patients may respond to demeclocycline therapy.

Hematologic Abnormalities

Platelets are embryologically related to neurons and have similar serotonin receptors. In addition, serotonin is intimately involved with platelet function. Therefore, it is not surprising to see some alteration in platelet function in patients who are treated with SSRIs or other drugs possessing serotonergic activity. There are several case reports of bleeding and bruising during treatment with SSRIs as well as with venlafaxine and nefazodone. In a few cases, concomitant thrombocytopenia was present. Bleeding abnormalities and bruising associated with these drugs are rarely clinically important. There are reports of improvement with administration of vitamin C.[25]

Agranulocytosis is an extremely rare event associated with antidepressant drugs.[26–28] During the clinical investigation of mirtazapine, 2 cases of agranulocytosis were reported among a total of 2796 patients who received the drug in clinical trials.[29] The occurrence of agranulocytosis has been closely monitored during postmarketing surveillance and, to date, there have been only 5 subsequent cases in 1 million exposures. In each of these 5 cases, patients were receiving at least 1 concomitant medication that has been associated with agranulocytosis. Therefore, the initial concern regarding agranulocytosis appears to be unnecessary, as clinical experience is quite reassuring.

Seizures

Seizures have been closely linked to certain antidepressant drugs, in particular maprotiline and the TCA clomipramine.[30] The seizures were dose related but were a problem even at lower doses. With TCAs in general and the newer antidepressant bupropion, there also appears to be some increased risk of seizures. This risk is primarily related to dose and overaggressive use. If, however, these drugs are used conservatively, seizures generally are not a concern. In a prospective surveillance study, the incidence of seizures was 0.4% (3/765) in closely monitored inpatients receiving TCA therapy for an affective or panic dis-

Table 1. Subjective Sleep Quality Versus Relapse of Major Depression*

Study Group[a]	Relapse Rate[b]
Good sleep quality (N = 10)	10%
Poor sleep quality (N = 9)	67%[c]

*Adapted from reference 34.
[a]Patients > 60 years of age with major depression receiving interpersonal psychotherapy.
[b]Relapse of major depression during 1-year follow-up after discontinuation of antidepressants.
[c]$p < .02$ vs. group with good sleep quality.

Table 2. Insomnia and Suicidality*

Study Group[a]	SADS Suicidal Score (Mean ± SD)[b]
Insomnia (N = 69)	4.4 ± 1.3
No sleep disturbance (N = 24)	2.8 ± 1.2[c]

*Adapted from reference 33.
[a]Inpatients or outpatients with major depression.
[b]Schedule for Affective Disorders and Schizophrenia (SADS) suicide subscale. Patients with a score ≥ 3 were categorized as suicidal.
[c]$p < .05$ vs. group of patients with insomnia.

order.[31] Initial reports with bupropion signaled a high risk of seizures, which delayed initial marketing of this drug. Subsequent prospective surveillance established a seizure rate of 0.4% for bupropion,[32] the same as that noted by Preskorn and Fast[31] for TCAs.

Sleep Impairment

Depression significantly affects sleep parameters such as sleep architecture and sleep quality. Conversely, sleep affects depression.[33,34] It is well known, for example, that sleep deprivation temporarily improves depression in many patients. Erratic sleep patterns, however, clearly worsen mood illness. Many clinicians find that shift working is a difficult clinical management problem in patients with mood disorders. In turn, many clinicians, including the author, feel strongly that sleep regulation will improve mood and enhance the response to antidepressive treatment.

Two studies support these conclusions. In 1 study,[34] patients who were over the age of 60 years and had exhibited good resolution of recurrent major depression after treatment with antidepressant drugs were followed for 1 year. During the 1-year follow-up period, antidepressant therapy was withdrawn and patients were treated with outpatient interpersonal psychotherapy, a form of psychotherapy that is effective in the treatment of patients with depression. The patients were divided into 2 groups based on their quality of sleep. Patients who slept poorly had a significantly, indeed dramatically, higher relapse rate than did those who slept well (Table 1). This finding is not surprising but should serve as a reminder to clinicians that when patients complain of not sleeping well, this is a harbinger of future problems. In addition, it should alert clinicians that patients with sleep disturbances deserve attention and require medical treatment. Hypnotics have an important role in the management of depressed patients with sleep disorders and can be effectively used on an intermittent basis.

Table 3. Qualitative Effect of Antidepressants on Sleep*

	Sleep Effect	
Antidepressant Drug	REM Activity	Efficiency/Continuity
SSRIs	↓	↓
Venlafaxine	↓	↓
Bupropion	↑	?
Nefazodone, trazodone	↑	↑
Mirtazapine	↔	↑

*Abbreviation: SSRIs = selective serotonin reuptake inhibitors.
Symbols: ↑ = increased, ↓ = decreased, ↔ = neither increased nor decreased, ? = effect unknown.

The second study was conducted in a group of inpatients or outpatients with major depression.[33] The presence or absence of a sleep disturbance was ascertained retrospectively. Using the Schedule for Affective Disorders and Schizophrenia (SADS) suicide subscale, a suicidal score was determined for each group of patients. Patients with a score of 3 or higher were categorized as suicidal. The suicide rating was found to be significantly ($p < .05$) higher in patients with a sleep disturbance (Table 2). These findings may correlate with observations that patients who have more agitation are more likely to be suicidal. While this does not prove a direct correlation between insomnia and suicide, the relationship should not be ignored.

The comparative effects of antidepressant drugs on sleep are summarized in Table 3. It is evident that the various antidepressant drugs have different effects on rapid eye movement (REM) sleep and sleep efficiency and continuity. Based on the summary in Table 3, either nefazodone or mirtazapine can be considered as the drug of choice for patients with significant sleeping difficulties, all other factors being equal (which, of course, they never are). Although trazodone is widely used as a hypnotic, it can result in daytime sedation at higher doses and therefore would not be considered first-line therapy in these patients.

Sexual Dysfunction

A variety of sexual disorders have been associated with antidepressant therapy. These include primarily orgasm dysfunction and also decreased libido, decreased arousal and, less commonly, decreased erectile ability. Although sexual side effects have been reported with most antidepressant drugs, there are distinct differences among the various agents. Clomipramine ranks highest in terms of frequency (Table 4). In addition, the SSRIs clearly cause sexual dysfunction, although the precise incidence is unknown. One study found that up to 73% of patients treated with an SSRI may be affected[35]; however, most SSRI studies reveal an incidence of about 40% for sexual difficulties, particularly difficulties with orgasm. Bupropion[35,36]

Table 4. Relative Ranking of Sexual Dysfunction With Antidepressant (From Highest to Lowest)*

Clomipramine
MAOIs
SSRIs
Venlafaxine
Tricyclic antidepressants—tertiary amines
Tricyclic antidepressants—secondary amines
Trazodone (priapism)

*Adapted from references 35–38. Abbreviation: MAOIs = monoamine oxidase inhibitors.

Table 5. Treatment Strategies for Adverse Sexual Effects Caused by Antidepressants

Decrease the dose
Use putative (or proposed) antidotes
Cyproheptadine
Bethanechol (for TCAs)
Yohimbine
Amantadine
Stimulants
Switch to alternative antidepressant therapy
Bupropion
Nefazodone
? Mirtazapine[a]

[a]Data concerning the relationship between mirtzapine and adverse sexual effects are limited.

and nefazodone[37] have been documented to cause very few sexual function side effects. Although data are limited, mirtazapine also appears to be relatively free of these types of side effects.[38] A very troublesome side effect with trazodone is priapism, which has been reported in a small number of men (about 1 in 20,000).

A variety of treatments have been used to alleviate antidepressant drug-associated sexual problems when they occur. Yohimbine is the one most commonly used (Table 5). None of these treatments, including yohimbine, have been demonstrated to work predictably or reliably,[39] and patients generally are reluctant to take a drug to treat the side effects of another drug, especially when dealing with sexual function side effects.

SUMMARY

In summary, although the antidepressant drugs are associated with a variety of adverse effects, most serious effects occur rarely. The most significant adverse effects attributed to the TCAs include cardiac conduction disturbances, especially in the overdose setting. Of greatest concern with the SSRIs and other drugs with serotonergic activity is the serotonin syndrome, which, although rare, can be insidious and lethal. Cognitive impairment, SIADH, sexual dysfunction, and seizures vary in frequency among the different classes of antidepressant drugs. Despite the adverse effects associated with antidepressant therapy, the benefits of such therapy in treating patients with depression greatly outweigh the risks. Successful management of the depressed patient requires recognition of the life-saving effects of antidepressant drugs.

Drug names: amantadine (Symmetrel), bethanechol (Urecholine and others), bupropion (Wellbutrin), clomipramine (Anafranil), cyproheptadine (Periactin and others), demeclocycline (Declomycin), fluoxetine (Prozac), fluvoxamine (Luvox), maprotiline (Ludiomil), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), procainamide (Procanbid and others), propranolol (Inderal and others), quinidine gluconate (Quinaglute), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor), yohimbine (Yocon and others).

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