

# ANTIDEPRESSANTS

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Depression is one of the most common medical conditions in the United States, with a lifetime prevalence of 16.2%.<sup>1</sup> Whereas many treatment strategies are used in the management of depressed patients, pharmacotherapy remains a cornerstone of modern practice. Modern antidepressant therapy hinges on the 50-year-old monoamine hypothesis, which suggests that depressive symptoms are mediated through an imbalance of the dopaminergic, noradrenergic, and serotonergic systems.<sup>1,2</sup> As a result, numerous antidepressant classes have emerged in an attempt to increase synaptic monoamine concentrations.

In the early 1950s, isoniazid and iproniazid were introduced for the treatment of tuberculosis. Shortly after, it was noted that these patients had improved mood, which was attributed to the ability of iproniazid to inhibit monoamine oxidase. Iproniazid, a derivative of isoniazid, subsequently became the first drug marketed specifically as an antidepressant.<sup>3</sup> This led to the advent of other monoamine oxidase inhibitors (MAOIs). In 1956, the antidepressant effect of imipramine, a tricyclic agent, was recognized, and it was marketed the following year.<sup>4</sup> The MAOIs and tricyclic antidepressants (TCAs) became the mainstay for treatment of depression for several decades until the advent of the safer selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

Antidepressant overdose is highly lethal. It accounts for only 3.7% of human exposures reported to U.S. Poison Control Centers but is involved in 10.5% of all poisoning fatalities.<sup>5</sup>

## MONOAMINE OXIDASE INHIBITORS

### Principles of Disease

Monoamine oxidase (MAO) is located on the outer mitochondrial membrane and is responsible for breakdown of cytoplasmic catecholamines. Type A (MAO-A) primarily deaminates serotonin and norepinephrine; type B (MAO-B) primarily deaminates phenylethylamine.<sup>6</sup> Tyramine and dopamine are metabolized equally by both isoenzymes.<sup>3</sup> Whereas most tissues contain both isozymes, MAO-A is primarily found in the placenta, sympathetic nerve terminals, and intestinal mucosa; MAO-B is found primarily in platelets and the basal ganglia.<sup>3</sup>

Drugs targeting the monoamine oxidase system can act as specific or nonspecific inhibitors. The first-generation MAOIs are nonselective and irreversible. Drugs belonging to this class include phenelzine, isocarboxazid, and tranylcypromine. The second-generation MAOIs can preferentially inhibit either MAO-A or MAO-B.

Although MAOIs have fallen out of favor for treatment of depression, their use in treatment of Parkinson's disease is

increasing. Drugs that selectively inhibit MAO-B disproportionately increase dopamine concentrations in the striatum.<sup>7</sup> Selegiline is an irreversible MAO-B inhibitor used in the treatment of Parkinson's disease. Although it is marketed as a selective inhibitor of MAO-B, at high doses its receptor specificity is lost, and it can cause inhibition of MAO-A as well.<sup>8</sup> Rasagiline is also an irreversible inhibitor of MAO-B but appears to be more potent than selegiline.<sup>6</sup> Furthermore, unlike selegiline, which is metabolized to L-methamphetamine, rasagiline is not metabolized to an amphetamine derivative.<sup>6</sup>

In addition to its antibiotic properties, linezolid, an oxazolidinone class antibiotic, is a reversible inhibitor of monoamine oxidase. Specifically, linezolid can produce significant inhibition of MAO-A.

As a class, MAOIs are rapidly absorbed from the gastrointestinal tract and are bound extensively to plasma proteins. With overdose, the MAOIs initially stimulate release of neurotransmitters from the presynaptic neuron but later inhibit their release.

### Clinical Features

Patients have MAOI toxicity as a result of an acute overdose or as a consequence of a food or drug interaction. Depending on the scenarios that lead to toxicity, the clinical presentations may be very different.

After an overdose, patients may have symptoms within several hours or may be asymptomatic for up to 24 hours before significant, possibly life-threatening toxicity develops. After this asymptomatic period, hyperadrenergic symptoms, including tachycardia, hypertension, and hyperthermia, can develop. Seizures, rhabdomyolysis, coma, and ultimately cardiovascular collapse can occur once presynaptic catecholamines are depleted. Laboratory abnormalities are nonspecific but can include hyperglycemia, leukocytosis, and elevated creatine kinase.

Patients who take nonselective MAOIs in therapeutic doses are at risk for food-drug interactions. Tyramine is an indirectly acting sympathomimetic amine that is present in aged cheeses, red wine, smoked or pickled and aged meats, and other foods. Usually, tyramine is metabolized in the gut and liver by monoamine oxidase, rarely causing systemic effects. When MAO-A is inhibited, tyramine is absorbed systemically and enters presynaptic vesicles, ultimately causing release of norepinephrine and serotonin into the synapse, leading to a hypertensive crisis.<sup>9</sup> This *tyramine syndrome*, which can occur within minutes to hours of ingestion of foods with high tyramine content, is characterized by headache, hypertension, flushing, and diaphoresis. This syndrome can occur up to 3 weeks after discontinuation of a nonselective MAOI. Although it is theoretically possible, this syndrome is rare with therapeutic use of MAO-B inhibitors.<sup>10</sup>

A drug-drug interaction may result when MAOIs are combined with other agents that have serotonergic effects. A variety of prescription and over-the-counter medications may interact with MAOIs to produce a constellation of symptoms referred to as *serotonin syndrome* (see later section). This syndrome may be life-threatening, so use of medications with serotonin-potentiating activity should be avoided in patients taking MAOIs.

## Diagnostic Strategies

Obtaining a thorough medication history is key to establishment of the diagnosis of MAOI toxicity. After overdose, an asymptomatic period followed by delayed toxicity can be a diagnostic clue. Immunoassay urine drug screens that are commonly used in the emergency department do not detect MAOIs, and even gas chromatography–mass spectroscopy of urine may fail to detect the presence of an MAOI. Patients taking selegiline will test positive for methamphetamine because methamphetamine is a metabolite.

Symptomatic patients presenting after an MAOI overdose should have an electrocardiogram with measurement of serum glucose and electrolytes if they are obtunded (see Chapter 147 for general management).

## Differential Considerations

The differential diagnosis for MAOI toxicity includes drug abuse or other sympathomimetic, anticholinergic, and methylxanthine toxicity. Nontoxicologic causes to consider include environmental hyperthermia, febrile illness, pheochromocytoma, carcinoid syndrome, thyroid storm, meningitis, and hypertensive emergency.

## Management

Even if they are initially asymptomatic, all patients presenting after an MAOI overdose should be admitted or observed in a monitored setting until 24 hours after the ingestion because of the risk of delayed, rapid deterioration. As with most intoxications, supportive care is paramount. Central nervous system (CNS) excitation should be treated with intravenous administration of benzodiazepines, such as lorazepam and diazepam, in usual titrated doses. Hyperthermia should be treated with external cooling. Mild hypertension should not be treated, but severe hypertension is best managed with a rapid, short-acting agent, such as phentolamine or nitroprusside. Hypotension should first be managed by aggressive volume resuscitation. Persistent or severe hypotension requires treatment with infusion of a direct-acting catecholamine, such as norepinephrine or epinephrine. Because hypotension and cardiovascular collapse after MAOI overdose are due to catecholamine depletion, the use of indirect-acting agents, such as dopamine, is not likely to be beneficial. Extracorporeal elimination is also unlikely to be beneficial because of extensive protein binding and large volume of distribution of MAOIs. Because of the potential for intracranial hemorrhage in the setting of severe MAOI-induced hypertension, patients with a seizure or significant neurotoxicity should undergo a non-contrast-enhanced head computed tomography (CT) scan.

Patients presenting with a tyramine reaction may have spontaneous resolution of symptoms during 6 hours. Severe hypertension higher than 200 mm Hg systolic with symptoms may be treated with phentolamine or nitroprusside. Patients with persistent severe headache and hypertension should have a head CT scan to look for intracranial hemorrhage. Patients with chest pain should be evaluated for myocardial infarction (see Chapter 26).

Treatment of suspected serotonin syndrome is supportive (see later section).

## Disposition

Patients presenting with an MAOI overdose should be admitted or observed in a monitored setting until 24 hours after ingestion for development of hyperadrenergic symptoms. Asymptomatic patients chronically taking an MAOI who present out of concern for a possible drug-food interaction can be discharged after 6 hours if no signs of toxicity develop.

## TRICYCLIC ANTIDEPRESSANTS

### Principles of Disease

In the 1950s, imipramine became the first tricyclic antidepressant (TCA) used for the treatment of depression. Until the introduction of the SSRIs, TCAs remained the primary agents for treatment of depression. The therapeutic benefit of TCAs results from monoamine reuptake inhibition.<sup>11</sup> Whereas use of TCAs for treatment of depression has waned, use for other conditions, including nocturnal enuresis, attention-deficit/hyperactivity syndrome, trigeminal neuralgia, and migraines, has increased.

### Clinical Features

Cyclic antidepressant toxicity can result from overdose of a TCA or drug-drug interactions. Overdose is more commonly associated with life-threatening toxicity, but toxic effects can also occur when a TCA is combined with drugs that impair its metabolism through cytochrome P450. Tertiary amine TCAs, such as amitriptyline, imipramine, and clomipramine, are substrates of CYP2C19 and CYP1A2. Doxepin is also a substrate for CYP2D6. Drug-induced inhibition of these enzymes as well as genetic polymorphisms can decrease metabolism of these drugs, resulting in unexpectedly high serum concentrations and clinical toxicity.<sup>12</sup> Conversely, inhibition of CYP2D6 and other P<sub>450</sub> enzymes by these TCAs can also lead to increased serum concentrations of other drugs metabolized by the same enzymes. Because desipramine and nortriptyline are only weak CYP2D6 inhibitors, they cause fewer drug-drug interactions. Another drug interaction that occurs with TCAs is the serotonin syndrome, which occasionally results when a TCA is combined with another serotonergic drug, such as MAOI or SSRI.

After an overdose of a TCA, symptoms typically begin within 1 to 2 hours. With smaller ingested amounts, symptoms may be minimal and resolve quickly; patients who take large amounts may deteriorate rapidly soon after ingestion. All seriously poisoned patients have symptoms within 6 hours of an overdose. Early TCA poisoning is characterized primarily by anticholinergic effects. Patients typically present with tachycardia, flushed and dry skin, mydriasis, and altered level of consciousness. They may be alert and confused, severely agitated, mute, hallucinating, or even deeply comatose. Speech is often rapid and mumbling in character. Urinary retention is common. Seizures may occur and are likely to be multifactorial, resulting from increased synaptic monoamines, sodium channel inhibition, and possibly  $\gamma$ -aminobutyric acid (GABA) receptor antagonism. Early hypertension is common from the anticholinergic effects of the TCA and excess norepinephrine in the synapse from blockade of norepinephrine reuptake, but hypotension may also be due to  $\alpha$ -receptor antagonism and also norepinephrine depletion. Later myocardial depression resulting from severe sodium channel antagonism may also lead to hypotension and bradycardia.<sup>13,14</sup> Significant sodium channel blockade is associated with widening of the QRS interval. TCAs also block potassium efflux, which leads to a prolonged QT interval.<sup>15</sup> With severe poisoning, the combined effects of the TCA on various receptors and ion channels lead to

depressed level of consciousness, seizures, hypotension, and wide-complex cardiac arrhythmias.

Chronic toxicity from drug-drug interactions or decreased ability to metabolize the drug because of genetic polymorphism may be manifested in a more subtle fashion. Confusion, urinary retention, and prolonged QTc interval are common. Chronic toxicity presents more gradually and should be considered in any confused patient taking therapeutic doses of a TCA.

## Diagnostic Strategies

After overdose, the electrocardiogram can yield prognostic information. Early anticholinergic effects cause sinus tachycardia, which occurs virtually uniformly before other effects. Whereas the serum tricyclic concentrations are not particularly beneficial in predicting adverse events, the electrocardiogram is prognostic. A QRS duration longer than 100 milliseconds is predictive of seizures, whereas a QRS duration longer than 160 milliseconds is predictive of ventricular dysrhythmias.<sup>16</sup> Additional findings on the electrocardiogram include a rightward shift of the terminal 40 milliseconds of the QRS complex seen as an R wave in aVR longer than 3 milliseconds.<sup>17</sup> QT prolongation is less important clinically than the QRS duration. Urine drug of abuse screens commonly test for the presence of TCAs, but a positive test result suggests only use of a TCA or another xenobiotic that cross-reacts with the screen. Serum tricyclic levels do not correlate with severity of illness.<sup>16</sup> General management (see Chapter 147) suggests other supportive care measures.

## Differential Considerations

Other agents with anticholinergic properties produce a similar early clinical presentation. In addition, sympathomimetic toxicity, serotonin syndrome, and hypoglycemia should be included in the differential diagnosis. Other toxins causing sodium channel blockade, a wide QRS, and subsequently intraventricular conduction delay include Vaughn-Williams class IA antidysrhythmics (e.g., procainamide, disopyramide, quinidine) and class IC antidysrhythmics (e.g., flecainide, encainide, and propafenone), amantadine, carbamazepine, cocaine, diphenhydramine, mesoridazine, and thioridazine. In addition, propoxyphene and propranolol can also cause an intraventricular conduction delay by sodium channel blockade but typically cause a bradycardic rhythm rather than a tachycardic rhythm. The constellation of early anticholinergic symptoms, decreased level of consciousness followed by seizures, wide QRS, and cardiovascular collapse is highly suggestive of acute TCA overdose.

## Management

Ensuring stability of the airway, breathing, and circulation is of primary importance. There are no randomized controlled trials demonstrating improved patient-oriented outcomes (e.g., improved mortality) with activated charcoal in patients with cyclic antidepressant overdose. Nonetheless, because of the high lethality of the acute overdose, a patient who presents within 1 hour after ingestion and who is awake and alert can be given activated charcoal, if it is recommended by the regional poison center consultant and if the patient will readily drink it. It should not be administered to patients who are unwilling or unable to voluntarily consume it and is contraindicated if the patient has any decreased level of consciousness because charcoal aspiration may pose a greater risk to the patient than the benefit, if any, of charcoal administration. There is no role for gastric lavage.

Patients with sinus tachycardia alone do not need specific treatment but should be monitored to detect QRS widening early. Early hypertension should not be treated. Hypotensive patients should

first receive fluid resuscitation with an isotonic crystalloid.<sup>13</sup> Patients who remain hypotensive should be treated with direct-acting vasopressors, such as norepinephrine and epinephrine.<sup>13,14</sup> There are some data that epinephrine may be superior to norepinephrine in this setting.

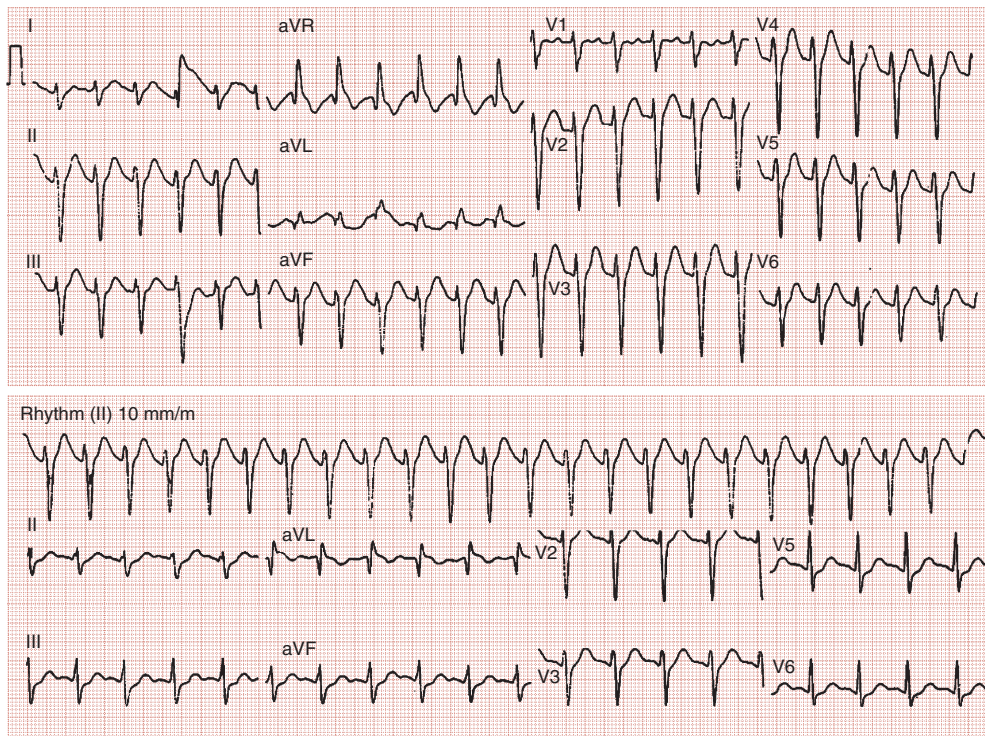
Hypertonic sodium bicarbonate should not be given prophylactically and should be given only to treat specific evidence of sodium channel blockade, such as a wide QRS and ventricular dysrhythmias. Recommendations vary about how to administer this therapy. A conservative approach is to administer a bolus of 1 to 2 mEq/kg hypertonic sodium bicarbonate if the QRS interval exceeds 100 milliseconds. This dose may be repeated in a few minutes if the QRS does not narrow. A sodium bicarbonate infusion can be used to maintain a pH between 7.50 and 7.55.<sup>13</sup> This can be done by administration of 5% dextrose in water with 150 mEq of sodium bicarbonate and 40 mEq of potassium added to each liter of fluid at a rate of twice maintenance starting at 35 mEq/hr and titrating to pH. Alternatively, infusions of 1 mEq sodium bicarbonate per milliliter of fluid may be used if volume overload is a concern. Additional boluses of sodium bicarbonate may be necessary if the QRS widens or if adequate alkalinization is not achieved with infusion alone. [Figure 151-1](#) demonstrates a 12-lead electrocardiogram from a patient poisoned with a TCA before and after sodium bicarbonate therapy. If ventricular dysrhythmias persist despite maximal alkalinization (pH > 7.55), 200 mL of 3% hypertonic saline (in an adult) can be used.<sup>18</sup> Class IA and IC antidysrhythmics can worsen cardiac toxicity and should be avoided.<sup>13</sup> Seizures are treated with lorazepam or diazepam and with phenobarbital if they are refractory to benzodiazepines. Because seizure leads to acidosis and worsens the cardiac status, seizing patients who do not respond quickly should be rapidly paralyzed and intubated if necessary to prevent increasing acidosis.

Asystole has occurred after physostigmine use, and this agent is considered by many experts to be contraindicated in the management of TCA overdose. Whereas physostigmine should not be administered to any patient with QRS or QTc prolongation after TCA overdose, it may be used in patients with delirium of unknown etiology who are therapeutically taking TCAs and in whom chronic toxicity is suspected, but only if their QRS and QTc intervals are normal. Physostigmine should be given with caution in a monitored setting because it may produce seizures and bradycardia, and it is relatively contraindicated in patients with reactive airway diseases.

Intravenous lipid emulsion (ILE) therapy has gained interest recently for reversal of toxicity caused by lipophilic drugs, including TCAs. Although the exact mechanism of ILE is not known, it probably involves redistribution of a lipophilic drug from the tissue receptors back into the vascular compartment in the context of a large bolus of concentrated lipid solution, the so-called lipid sink phenomenon.<sup>19,20</sup> Other mechanisms also are possible. Because of the potential for iatrogenic harm, its use is currently reserved for life-threatening toxicity that remains refractory to sodium bicarbonate. There are several different dosing strategies. One approach is to give 1.5 mL/kg of a 20% lipid solution during 2 to 3 minutes. This bolus can be repeated once in 5 minutes if there is no clinical improvement. If clinical improvement does occur, the bolus should be followed by an infusion of 0.25 mL/kg/min for 15 to 30 minutes.<sup>21</sup>

## Disposition

If no sinus tachycardia, decreased level of consciousness, or seizures have developed within 6 hours of an overdose, it is unlikely that toxicity will occur,<sup>22</sup> and the patient can be medically cleared from the emergency department for psychiatric disposition, if needed. Patients with signs of cyclic antidepressant toxicity should be admitted to an intensive care unit.



**Figure 151-1.** Top, Initial 12-lead electrocardiogram demonstrating substantial intraventricular conduction delay (QRS 146 milliseconds). Bottom, Repeated electrocardiogram after bicarbonate therapy.

## SELECTIVE SEROTONIN REUPTAKE INHIBITORS

### Principles of Disease

In recent years, the selective serotonin reuptake inhibitors (SSRIs) have become the mainstay for treatment of depression. As implied by their name, these drugs prevent the presynaptic reuptake of serotonin without affecting the synaptic concentration of other monoamines. Some of the more commonly used SSRIs available today include escitalopram and its enantiomer citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. Some SSRIs are coformulated with other agents in a single pill, like the combination of fluoxetine and olanzapine.

SSRIs have a wide therapeutic index.<sup>23</sup> Although they are safer in overdose than MAOIs and TCAs, they do have therapeutic limitations, such as the long delay until onset of antidepressant effect.<sup>24</sup> The SSRIs undergo hepatic metabolism. There is considerable variability in their half-life; however, paroxetine has one of the shortest half-lives (17 hours) compared with fluoxetine, which has one of the longest half-lives (53 hours for parent drug, 240 hours for active metabolite).<sup>25</sup>

### Clinical Features

Overdose of SSRIs is usually well tolerated and rarely fatal, with ingestions of up to 30 times the daily dose associated with few or no symptoms. Gastrointestinal upset and mild CNS depression can occur with large overdoses. Coma and seizures are rare, with incidences of approximately 2.4 and 1.9%, respectively.<sup>23</sup> The incidence of serotonin syndrome after SSRI overdose is variable, up to 14%,<sup>23</sup> but most other series report a much lower incidence.

Citalopram overdose deserves special mention because of a higher rate of QTc prolongation and seizures compared with other SSRIs.<sup>26-28</sup> Furthermore, onset of QTc prolongation may be delayed

for up to 13 hours.<sup>29</sup> Despite being the active enantiomer of citalopram, escitalopram appears to be less toxic than citalopram, with a lower incidence of seizure and QTc prolongation.<sup>26</sup>

Therapeutic administration of SSRIs may be associated with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).<sup>30,31</sup> Most cases of hyponatremia develop within 1 month and frequently within the first 2 weeks.<sup>31</sup> The overall incidence is not clear; however, in one small study, 12.5% of elderly patients taking an SSRI had SIADH, with an additional 12.5% of patients having mild asymptomatic hyponatremia.

### Diagnostic Strategies

Diagnosis of SSRI toxicity is often dependent on obtaining a history of overdose. Clinical features of toxicity are similar to those seen after overdose of many other toxicants, and urine drug of abuse screens do not detect SSRIs. An electrocardiogram can assess for conduction disturbances, especially QT prolongation. See Chapter 147 for other general management strategy. Specific SSRI levels are not performed by most hospital laboratories and do not influence management. They may help confirm overdose retrospectively.

### Management

Treatment of an SSRI overdose is largely supportive. Only rarely will patients require tracheal intubation because of loss of airway reflexes. Magnesium sulfate can be administered when the QT interval is prolonged. Intravenous administration of benzodiazepines should be used to treat seizures.

### Disposition

Patients who overdose with an SSRI who are asymptomatic after 6 hours of monitoring are unlikely to have toxicity. Some authors

advocate for 13 hours of observation<sup>29</sup> after the ingestion of more than 1000 mg of citalopram or escitalopram. Symptomatic patients should be admitted to a monitored care setting.

## SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

### Principles of Disease

Duloxetine, venlafaxine, desvenlafaxine, and milnacipran are collectively referred to as serotonin-norepinephrine reuptake inhibitors (SNRIs). Desvenlafaxine, venlafaxine, and duloxetine are marketed in the United States for treatment of depression. Milnacipran, although it is used as an antidepressant in Europe, is currently approved in the United States only for treatment of fibromyalgia. In addition to the treatment of depression, duloxetine is commonly used in the management of diabetic neuropathy, fibromyalgia, and urinary stress incontinence.<sup>32</sup> Venlafaxine and its active metabolite desvenlafaxine are both available medically. The SNRIs may also produce dose-dependent inhibition of sodium channels.<sup>33</sup>

### Clinical Features

Duloxetine overdose produces CNS depression.<sup>34</sup> Most fatal overdoses of duloxetine described thus far have involved coingestants.<sup>32</sup> Thus, ascribing causality to duloxetine in these fatal cases is difficult.<sup>32</sup>

Venlafaxine and desvenlafaxine overdoses can result in neurologic, muscular, and cardiovascular toxicity.<sup>35</sup> Common findings include CNS depression, seizures, and tachycardia. Ventricular arrhythmias and QRS prolongation on the electrocardiogram may also occur.<sup>33,36,37</sup> After venlafaxine overdose, rhabdomyolysis can develop independently or as a result of seizures.<sup>35,38</sup> Both serotonin syndrome and *takotsubo* cardiomyopathy occur with venlafaxine overdose.<sup>39</sup>

Experience with milnacipran overdose is limited. Expected toxic effects include CNS depression and tachycardia. Acute, reversible cardiomyopathy,<sup>40</sup> serotonin syndrome, and at least one fatal intoxication have been described after overdose.<sup>40-42</sup>

### Diagnostic Strategies

Diagnosis of SNRI ingestion depends on history before onset of symptoms. Specific drug levels are not rapidly available and do not aid management. An electrocardiogram can detect QRS or QT interval prolongation. SNRIs are not detected by urine drug of abuse screens, but venlafaxine is associated with a false-positive phencyclidine screen.<sup>43,44</sup>

### Differential Considerations

Differential diagnoses of seizure, decreased level of consciousness, and tachycardia include sympathomimetic toxicity, cyclic antidepressant toxicity, anticholinergic toxicity, and serotonin syndrome.

### Management

Care of the patient with an SNRI overdose is supportive, with focus on ensuring airway patency and oxygenation. Hypotension is treated with crystalloid fluid resuscitation; if hypotension persists, direct-acting vasopressors such as norepinephrine should be used. Intraventricular conduction delay should be treated with sodium bicarbonate. First-line treatment of seizures is the intravenous administration of lorazepam or diazepam.

### Disposition

Patients who are asymptomatic with a normal 12-lead electrocardiogram after an observation period of 6 hours can be cleared for discharge. Symptomatic patients should be admitted to a monitored care setting. Those patients with conduction delay and coma should be admitted to an intensive care unit.

## MISCELLANEOUS ANTIDEPRESSANTS

### Bupropion

Bupropion is a monocyclic antidepressant that is structurally related to amphetamine.<sup>45</sup> In addition to its use as an antidepressant, it is used to assist in smoking cessation.<sup>46,47</sup> Its primary mechanism of action is inhibition of dopamine and norepinephrine reuptake, but it also acts as a noncompetitive inhibitor of nicotinic acetylcholine receptors.<sup>47</sup>

Seizures are a dose-dependent phenomenon and can occur with therapeutic dosing or overdose of bupropion.<sup>48</sup> At doses of 300 to 450 mg/day, the incidence of seizures is approximately 0.4%. Doses of 450 to 600 mg/day, however, are associated with a tenfold increased incidence of seizures.<sup>48</sup> Among sustained-release preparations, doses less than 450 mg/day are associated with a seizure incidence of 0.1%.<sup>48</sup>

Sinus tachycardia, tonic-clonic seizures, and agitation are common after overdose.<sup>45,49,50</sup> Intraventricular conduction delay is rare.<sup>45</sup> Because of the risk of delayed seizures, patients with intentional overdoses of extended-release bupropion should be admitted for 24 hours of observation.<sup>51</sup>

Treatment is primarily supportive. Patients with large overdoses may require endotracheal intubation because of CNS depression. Lorazepam and diazepam should be used to treat seizures. If seizures persist, phenobarbital or other GABA agonists may be used.

### Trazodone

Trazodone is an atypical antidepressant with a mechanism of action that includes antagonism of the 5-hydroxytryptamine type 2A (5-HT<sub>2A</sub>) receptor and alpha<sub>1</sub> receptor. Its use as an antidepressant has been somewhat limited by adverse effects, such as orthostatic hypotension, priapism, and sedation.<sup>52</sup>

Priapism is probably a result of trazodone's alpha-antagonism, with an incidence of 1/100 to 1/10,000. Whereas many drugs are associated with priapism, particularly those with alpha-antagonism or inhibition of type 5 phosphodiesterase, trazodone is responsible for a disproportionate number of reported cases.

After overdose, sedation and hypotension due to vasodilation are expected. Priapism is not typically associated with overdose of trazodone. Management is supportive, with airway protection, intravenous fluid resuscitation, and use of alpha-adrenergic agonists, such as norepinephrine, as needed for refractory hypotension.

### Nefazodone

Nefazodone, a phenylpiperazine antidepressant, is structurally similar to trazodone. It acts as an antagonist at the 5-HT<sub>2A</sub> receptor, and chronic administration is associated with receptor downregulation. Nefazodone is associated with weak inhibition of norepinephrine and serotonin reuptake. It is metabolized to several active metabolites. After overdose, most patients remain asymptomatic. Antagonism of the alpha<sub>1</sub> receptor is responsible for the orthostatic hypotension that can occur. Treatment is supportive.

**Table 151-1 Xenobiotics Commonly Implicated in Serotonin Syndrome**

Analgesics: tramadol, meperidine, pentazocine
Drugs of abuse: cocaine, amphetamine derivatives (e.g., methylenedioxymethamphetamine), lysergic acid diethylamide (LSD)
Monoamine oxidase inhibitors (e.g., isocarboxazid, linezolid, phenelzine, moclobemide, selegiline)
Miscellaneous: dextromethorphan, lithium, metoclopramide, St. John's wort
Selective serotonin reuptake inhibitors (e.g., milnacipran, venlafaxine)
Serotonin-norepinephrine reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)
Tricyclic antidepressants (e.g., amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline)

## SEROTONIN SYNDROME

### Principles of Disease

Serotonin syndrome is a potentially lethal condition resulting from excess serotonin accumulation in the synaptic cleft. This syndrome occurs after an isolated overdose of an SSRI, but it is more commonly a result of drug-drug interactions, especially with drug combinations that raise synaptic serotonin concentrations by different mechanisms.<sup>53</sup> Agonism of the 5-HT<sub>2A</sub> receptor appears to be largely responsible for this condition in humans.<sup>53-55</sup>

Whereas numerous xenobiotics have been implicated in causing serotonin syndrome, some of the most common are the SSRIs, SNRIs, TCAs, MAOIs, dextromethorphan, amphetamines, and designer amphetamines, including methylenedioxymethamphetamine (“ecstasy”), cocaine, meperidine, lithium, tramadol, buspirone, lysergic acid diethylamide (LSD), and linezolid<sup>53,56-60</sup> (Table 151-1). Serotonin syndrome is more likely to develop when drugs from different classes are combined, resulting in increased serotonin in the synaptic cleft from different mechanisms (e.g., increased release and impaired uptake).

### Clinical Features

Serotonin syndrome is described as a triad of mental status changes, autonomic instability, and increased neuromuscular activity, but the condition exists along a spectrum; some patients have only mild tremor and diarrhea, whereas others exhibit life-threatening manifestations.<sup>53</sup> Clinical features may include tremor, akathisia, gastrointestinal illness, clonus (inducible or spontaneous), rigidity, fever, seizures, and autonomic instability. The clonus is typically more pronounced in the lower extremities than in the upper extremities.

After an acute overdose of a serotonergic agent, symptom onset typically begins within several hours. With proper treatment, symptoms usually resolve within 24 hours but can persist for several days in severe cases.

### Diagnostic Strategies

There is no “gold standard” for the diagnosis of serotonin syndrome. Laboratory studies cannot be used to confirm or to exclude the diagnosis of serotonin syndrome. Rhabdomyolysis and hyperkalemia can occur as a result of increased neuromuscular activity, and these should be screened for as indicated on the basis of the clinical examination.

The Sternbach criteria were developed in 1991 and became the first widely used diagnostic algorithm.<sup>61</sup> Additional criteria, including the Hunter criteria<sup>62</sup> and the Boyer and Shannon criteria,<sup>53</sup> have been developed. The Hunter criteria (Table 151-2) appear to be more sensitive than the Sternbach criteria, with fewer false positives.<sup>62</sup>

**Table 151-2 The Hunter Criteria for Serotonin Syndrome<sup>62</sup>**

In the setting of exposure to a known serotonergic agent, serotonin syndrome can be diagnosed by the presence of any of the following:
Spontaneous clonus
Inducible clonus <i>and</i> agitation or diaphoresis
Ocular clonus <i>and</i> agitation or diaphoresis
Tremor and hyper-reflexia
Hypertonic with temperature > 38° C <i>and</i> ocular clonus or inducible clonus <b>Text</b>

In general, a history of overdose or of recently starting an additional serotonergic agent along with clinical findings consistent with this diagnosis should raise the concern for serotonin syndrome.

### Differential Considerations

The differential diagnosis of serotonin syndrome includes neuroleptic malignant syndrome, malignant hyperthermia, sympathomimetic toxicity, anticholinergic toxicity, strychnine toxicity, bupropion toxicity, and GABA withdrawal. Nontoxicologic considerations include thyroid storm, meningitis, idiopathic seizure, intracranial hemorrhage, and hypoglycemia.

### Management

Management is supportive, with removal of the offending agents being paramount. Mild cases may require only discontinuation of the offending agent and low-dose benzodiazepines for rigidity. More severe cases may require intravenous fluid resuscitation and large doses of benzodiazepines or other sedative-hypnotic agents to gain control of symptoms. A trial of cyproheptadine, a 5-HT<sub>2A</sub> antagonist, is an appropriate adjunctive therapy for more severe cases,<sup>53,63</sup> but there are no randomized controlled trials demonstrating improved benefit with cyproheptadine over supportive care and benzodiazepines alone.<sup>64</sup> Patients with hyperthermia that does not respond promptly to sedation with benzodiazepines should receive a nondepolarizing neuromuscular blocking agent after endotracheal intubation.

### Disposition

Patients with all but the mildest forms of serotonin syndrome should be admitted to a monitored care setting. Those with unresponsiveness and rigidity should be admitted to an intensive care unit.

## DISCONTINUATION SYNDROMES

After the abrupt discontinuation of certain antidepressants, patients can experience a withdrawal, or discontinuation, syndrome. Unlike potentially life-threatening GABA withdrawal from ethanol or benzodiazepines, the discontinuation syndrome from antidepressants is rarely life-threatening but can result in significant discomfort. One notable exception involves neonates born to mothers using TCAs<sup>65</sup> or SSRIs, who can have serious, potentially life-threatening withdrawal. Antidepressant discontinuation syndrome does not always develop, but when it does, it typically starts within the first 3 days after therapy is stopped.<sup>66</sup> This syndrome is difficult to distinguish from recurrence of the underlying depression, which has overlap of some symptoms.

Antidepressant discontinuation syndrome was first described in the 1950s with imipramine, but it has been described with all major classes of antidepressants.<sup>66</sup> Withdrawal from SSRIs involves both physical and psychological symptoms, most

commonly nausea, lethargy, headache, and dizziness. The symptoms can be divided into six general categories: dysequilibrium (e.g., dizziness, ataxia), sleep disturbances, gastrointestinal symptoms, affective symptoms (e.g., irritability, anxiety), sensory symptoms (e.g., electric shock–like sensation, paresthesias), and general somatic symptoms (e.g., headache, tremor, anorexia, diaphoresis).<sup>66</sup> The syndrome is more common after discontinuation of drugs with shorter half-lives (e.g., paroxetine) than of drugs with longer half-lives (e.g., fluoxetine). TCA withdrawal is similar to SSRI withdrawal, although sensory abnormalities and

equilibrium disturbances are rare with TCA discontinuation. Non–life-threatening arrhythmias are rare after discontinuation of the TCAs.

Patients with mild withdrawal symptoms do not require any specific therapy. For those patients with more severe symptoms, treatment involves restarting of the antidepressant, followed by a gradual taper.

*The references for this chapter can be found online by accessing the accompanying Expert Consult website.*

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