An Update on Antidepressant Toxicity: An Evolution of Unique Toxicities to Master

Erica L. Liebelt, MD, FACMT

Antidepressant drugs have unique toxicities that are based on their pharmacology and determine their specific treatment. There are currently 4 classes of antidepressant drugs: monoamine oxidase inhibitors, cyclic antidepressants, selective serotonin reuptake inhibitors, and the atypical antidepressants which include a variety of other drugs. The selective serotonin reuptake inhibitors and atypical antidepressants are prescribed with the greatest frequency for depression in the United States, although the cyclic antidepressants are still being used for other clinical disease entities. The purpose of this manuscript was to review the different classes of antidepressant drugs including the differences in their pharmacology, unique toxicities, and treatment for their toxicities. Toxicities resulting from sodium channel blockade, excessive serotonergic activity, and food-drug and drug-drug interactions are discussed as they pertain to the specific antidepressants. Specific treatment modalities for each antidepressant class based on the pathophysiologic mechanisms are discussed.

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Some experts predict that depression will be the second largest killer of Americans after heart disease by 2020. Depression knows no age boundaries. Only in the last 2 decades has depression in children been taken very seriously. At any point in time, 10% to 15% of children and adolescents have some symptoms of depression [1]. According to the National Mental Health Association, one in 3 American children experiences depression and the rate of growth among children is increasing at an alarming rate of 23% per year. Major depression strikes about 1 in 12 adolescents. Among those adolescents who develop major depression, 1 in 14 will commit suicide as a young adult [2].

Studies have demonstrated that a comprehensive, multidisciplinary treatment plan consisting of pharmacologic antidepressant therapy in combination with other treatment strategies such as cognitive-behavioral therapy, family intervention, family education, and various prevention strategies is most successful in treating depression and preventing its persistence or reoccurrence into adulthood. Unfortunately, only 30% of children receive any sort of intervention or treatment for depression. Although the safety of antidepressant medications has come under intense scrutiny in the last 3 years, one has to weigh this risk against the benefit of these medications in alleviating major depressive symptoms in children. As with any drug, physicians and other health care providers must be aware of the toxicities of these medications—both their adverse effects and when taken in overdose. These classes of drugs have gone through a pharmacologic evolution that has resulted in a safer toxicity profile; yet, many of the “older” antidepressants are still being used for “drug-resistant” depression as well as for other diseases. The purpose of this manuscript is to review the different classes of antidepressant drugs including the differences in their pharmacology, unique toxicities, and treatment for their toxicities.

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Epidemiology of Antidepressant Drugs

In a study published in 2004, antidepressant use in children increased from 1.6% in 1998 to 2.4% in 2002, a 49% increase [3]. Over the course of the study, the growth in use was greater among girls (68%) than among boys (34%) and, for each sex respectively, growth was higher among younger boys and older girls. This study examined antidepressant use among approximately 2 million commercially insured pediatric beneficiaries 18 years and younger from 1998 to 2002. The fastest growing segment of users was found to be preschoolers aged 0 to 5 years, with use among girls doubling and use among boys growing by 64%. Throughout the 5-year period of the study, selective serotonin reuptake inhibitors (SSRIs) were the most commonly dispensed antidepressants, whereas tetracyclines were the least.

In 2005, of the greater than 2 million reported exposures, there were almost 32,000 exposures to antidepressants in children less than 19 years of age reported to the American Association of Poison Control's Toxic Exposure Surveillance Systems [4]. These included 27,524 exposures to SSRIs and 2600 exposures to cyclic antidepressants (CAs). The number of fatalities due to CAs has remained the same over the last 10 years. When looking at drug toxicity, it is important to distinguish between unintentional ingestions in young children where sequelae are usually mild or none at all vs ingestions in adolescents where the gesture is usually intentional and may result in more significant sequelae. However, unlike the SSRIs and other atypical serotonergic antidepressant drugs, ingestion of relatively small overdoses of CAs or monoamine oxidase inhibitors (MAOIs) can be associated with significant morbidity in young children.

Antidepressant Drugs and the Food and Drug Administration Black Box Warning

In October 2004, the Food and Drug Administration issued a Public Health Advisory announcing a multipronged strategy to warn the public about the increased risk of suicidal thoughts and behavior in children and adolescents being treated with antidepressant medications. The agency directed manufacturers to add a “black box” warning to the health professional labeling of all antidepressant medications to describe this risk and emphasize the need for close monitoring of patients started on these medications. (Fluoxetine or Prozac [Eli Lilly, Indianapolis, IN] is the only antidepressant approved to treat depression in children and adolescents.) The new warning does not prohibit the use of antidepressants in children and adolescents. However, it warns of the risk of suicide and encourages prescribers to balance this risk with clinical need. Much discussion and controversy ensued whether this black warning was justified based on the clinical evidence.

Classes of Antidepressants and Their Pharmacologic Differences

The pathophysiology of depression is complex and not completely understood. The evolution of pharmacotherapy for its treatment has been based on the scientific research at that particular time or discovered serendipitously through its use for another disease state. Proposed over 30 years ago, the monoamine hypothesis of depression suggests that the underlying biological or neuroanatomical basis for depression is a deficiency of central noradrenergic and/or serotonergic systems and that targeting this neuronal lesion with an antidepressant would tend to restore normal function in depressed patients. Considerable scientific evidence over the years, however, suggests that the acute effects of antidepressant treatments on brain norepinephrine (NE) and serotonin (5-HT) systems cannot account fully for their delayed therapeutic action. Modulation of receptor sensitivity to long-term antidepressant treatment may be a common mechanism for all of the classes of antidepressants, although the balance of which neurotransmitters and which receptors have safer profiles is an ongoing investigation.

There are 4 major classes of antidepressant drugs prescribed in the United States: MAOIs, CAs, SSRIs, and the atypical antidepressants (Table 1). Each class and drugs within the class have distinct pharmacologic activity.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors were initially used to treat tuberculosis and hypertension in the early 1950s; however, their mood-elevating properties were soon discovered and they were then prescribed for depression. Today, MAOIs are used only to treat depression which is resistant to the other classes of antidepressants because of their serious toxicity and severe drug-drug and drug-food interactions. Monoamine oxidase inhibitors irreversibly inactivate monoamine oxidase, which is an enzyme that degrades endogenous (NE, epinephrine, dopamine, serotonin) and exogenous (tyramine, amphetamines, ephedrine) biogenic amines before their reuptake into the presynaptic central nervous system (CNS) neurons. Monoamine oxidase inhibitors used to treat depression which are available in the United States include phenylzine, procarbazine, tranylcypromine, and isocarboxazid. They all irreversibly inhibit both the MAO isoenzymes A and B. Selelgeline (Eldepryl, Somerset Pharmaceuticals Inc, Tampa, FL), an antiparkinsonian drug, and pargyline (Eutonyl, Abbott Laboratories, Abbott Park, IL), an antihypertensive drug, are not generally associated with the same toxicity or drug interactions as the other MAOIs because they inhibit only the B isoenzyme. It
Table 1  Antidepressant classes, examples, pharmacologic mechanism, and clinical toxicity.

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monoamine oxidase inhibitors</strong></td>
<td></td>
<td>• Delayed onset of symptoms (6-24 h)</td>
</tr>
<tr>
<td>• Phenlzine (Nardil, Pfizer, New York, NY)</td>
<td>Irreversible inhibition of MAO A and B</td>
<td>• Anxiety, restlessness, headache, flushing, tremor, myoclonus, hyperreflexia, diaphoresis, tachycardia, moderate hypertension</td>
</tr>
<tr>
<td>• Tranylcypromine (Parnate, GlaxoSmithKline, Research Triangle Park, NC)</td>
<td></td>
<td>• Severe intoxication, delirium, agitation, seizures, ping-pong gaze, neuromuscular rigidity, severe hypertension fluctuating with hypotension and cardiovascular collapse, intracranial hemorrhage, hyperthermia</td>
</tr>
<tr>
<td>• Isocarboxazid (Marplan, Hoffmann-LaRoche, Nutley, NJ)</td>
<td></td>
<td>• Procarbazine (Matulane, Sigma - Tau Pharmaceuticals, Gaithersburg, MD)</td>
</tr>
</tbody>
</table>
is also important to note that St John's wort (Hypericum perforatum), an herbal medication used for its antidepressant properties, appears to act in part as an MAOI.

Cyclic Antidepressants

Cyclic antidepressants comprise a group of pharmacologically related agents used in the treatment of depression as well as neuralgic pain, migraines, enuresis, and attention-deficit hyperactivity disorder. They include the traditional tricyclic compounds imipramine, desipramine, amitriptyline, nortriptyline, doxepin, trimipramine, protriptyline, and clomipramine, as well as other cyclic compounds such as maprotiline and amoxapine.

Imipramine was the first tricyclic antidepressant (TCA) used for the treatment of depression in the late 1950s. Structurally related to the phenothiazines, imipramine originally was developed as a hypnotic agent for the sedation of agitated or psychotic patients and was serendipitously found to alleviate depression. From the 1960s until the late 1980s, the TCAs represented the major pharmacologic treatment for depression in the United States. However, by the early 1960s, cardiovascular and CNS toxicity were also recognized as major complications of TCA overdoses. The newer CAs were developed in the 1980s and 1990s to decrease some of the adverse effects seen with older TCAs, improve the therapeutic index, and reduce the incidence of serious toxicity. These included the tetracyclic drug maprotiline and the dibenzoxapine drug amoxapine.

Cyclic antidepressants inhibit the reuptake of NE and/or serotonin and thus functionally increase the amount of these neurotransmitters at CNS receptors. All of the CAs are competitive antagonists of the muscarinic acetylcholine receptors although with different affinities. The acetylcholine blockade is responsible for the central and peripheral anticholinergic adverse effects, such as dry mouth, urinary retention, blurred vision, and sedation. The CAs also antagonize peripheral α1-adrenergic receptors, producing vasorelaxation and orthostatic hypotension. The membrane-stabilizing effect of CAs is responsible for cardiac conduction abnormalities that occur even in therapeutic doses and, after overdose, is the primary mechanism of life-threatening cardiac toxicity. Finally, animal research demonstrates interactions of CAs on the γ-aminobutyric acid (GABA) receptor chloride-ionophore complex in the brain.

Amoxapine is a dibenzoxapine CA derived from the active antipsychotic loxapine. Although it has a 3-ringed structure, this drug has little similarity to the other tricyclics. It is a potent NE reuptake inhibitor, has no effect on serotonin reuptake, and blocks dopamine receptors. Maprotiline is a tetracyclic antidepressant that predominantly blocks the reuptake of NE. Both of these CAs have a slightly different toxic profile than the traditional TCAs.

Table 1 (continued)

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine (Cymbalta, Eli Lilly Indianapolis, IN)</td>
<td>• NE reuptake inhibitor&lt;br&gt;• Serotonin reuptake inhibitor</td>
<td>• Limited information, expected to be the same as venlafaxine</td>
</tr>
<tr>
<td>Nefazodone (Serzone, Bristol-Myers Squib, Princeton, NJ)</td>
<td>• Serotonin reuptake inhibitor&lt;br&gt;• Serotonin antagonism</td>
<td>• Dizziness&lt;br&gt;• Dry mouth&lt;br&gt;• Mild sedation</td>
</tr>
<tr>
<td>Trazodone (Desyrel Apothecon, Princeton, NJ)</td>
<td>• Serotonin reuptake inhibitor&lt;br&gt;• Serotonin antagonism&lt;br&gt;• α1-adrenergic blockade</td>
<td>• CNS depression&lt;br&gt;• Orthostatic hypotension&lt;br&gt;• Priapism&lt;br&gt;• SIADH&lt;br&gt;• Seizures</td>
</tr>
<tr>
<td>Mirtazapine (Remeron, Organon, West Roseland, NJ)</td>
<td>• α2-adrenergic blockade&lt;br&gt;• Serotonin reuptake inhibitor</td>
<td>• Sedation, altered mental status&lt;br&gt;• QTc prolongation&lt;br&gt;• Agranulocytosis</td>
</tr>
<tr>
<td>Bupropion (Wellbutrin, Zyban, GlaxoSmithKline, Research Triangle Park, NC)</td>
<td>• Dopamine reuptake inhibitor&lt;br&gt;• NE and serotonin reuptake inhibitor</td>
<td>• Anticholinergic toxicity&lt;br&gt;• Wide-complex tachycardia&lt;br&gt;• QTc interval prolongation&lt;br&gt;• Seizures&lt;br&gt;• Symptoms may be delayed up to 12-18 h if extended release</td>
</tr>
</tbody>
</table>

SIADH indicates syndrome of inappropriate antidiuretic hormone.
CNS indicates monoamine oxidase.
NE indicates norepinephrine.
Selective Serotonin Reuptake Inhibitors

The development of the SSRIs as a treatment for depression was in response to the discovery of the importance of the neurotransmitter serotonin in the pathophysiology of depression as well as the search for a class of drugs with a much safer profile than the CAs and MAOIs. Current SSRIs available in the United States and their pharmacologic activity are listed in Table 1. All of the SSRI antidepressants raise synaptic serotonin by inhibiting reuptake into presynaptic nerve terminals after depolarization of the neuron. Selective serotonin reuptake inhibitors are also used to treat obsessive-compulsive disorders, panic disorder, alcoholism, obesity, migraine headache, and chronic pain syndromes. Unlike TCAs and other atypical antidepressants, SSRIs have little direct interaction with sodium channels, cholinergic receptors, GABA receptors, or adrenergic reuptake. The SSRIs and their active metabolites are substrates for, and potent inhibitors of, cytochrome P450 enzymes, specifically CYP2D6 and other CYP isoenzymes, resulting in altered metabolism and drug-drug interactions in the presence of other xenobiotics.

Atypical Antidepressants

Atypical antidepressants are a class of drugs that have serotonin reuptake inhibition but also include other neurotransmitter activity thought to be beneficial for patients with depression (Table 1). Venlafaxine (Effexor, Wyeth Pharmaceuticals, Madison, NJ) belongs to a class of drugs known as the serotonin noradrenergic reuptake inhibitors. It is a bicyclic antidepressant that inhibits the reuptake of serotonin and NE and less potently inhibits the reuptake of dopamine at high doses. Nefazodone and trazodone are 2 drugs classified as serotonin-2 antagonists and reuptake inhibitors because they antagonize the serotonin receptor in addition to their inhibitory effects on the presynaptic reuptake of serotonin and NE. Mirtazapine has been termed a noradrenergic and specific serotonin antidepressant because it is a potent antagonist of central α2-adrenergic autoreceptors and heteroreceptors, and is an antagonist of serotonin 5-HT2 and 5-HT3 receptors. Bupropion also inhibits the reuptake of dopamine.

Clinical Toxicity

Monoamine Oxidase Inhibitors

The clinical toxicity of MAOIs falls into 3 clinical syndromes: acute toxicity from overdose, serotonin syndrome, and hypertensive crisis resulting from food-drug and drug-drug interactions.
interactions. From a pathophysiologic standpoint, this toxicity results from release of excessive neuronal stores of vasoactive biogenic amines, inhibition of the metabolism of catecholamines or interacting drugs, or absorption of large amounts of dietary tyramine, which, in turn, releases catecholamines from neurons. Significant morbidity and a high mortality are associated with overdoses of the MAOIs used for depression.

Symptoms may be delayed 6 to 24 hours after an acute overdose. Because of the irreversible inactivation of MAO, toxic effects (and the potential for drug or food interactions) may persist for several days. Overdose is characterized by an initial period of sympathetic hyperactivity which is followed by cardiovascular collapse in severe cases. In the early phase of an overdose, patients may typically have irritability, anxiety, flushing, diaphoresis, tachycardia, and headache. Severe overdose is characterized by hyperthermia, seizures, and hypertension. Blood pressure fluctuations—severe hypertension followed by hypotension—and cardiovascular collapse are commonly seen in severe overdoses. Other symptoms may include nystagmus, mydriasis, opcosclonus (alternating “ping-pong” gaze), hallucinations, trismus, and delirium [3].

Secondary problems from CNS and autonomic hyperactivity and hyperthermia include rhabdomyolysis, renal failure, dehydration, intracranial hemorrhage, and myocardial infarction.

The serotonin syndrome or sometimes called “serotonin toxicity” is a potentially life-threatening complication of antidepressant drug therapy (Table 2). The clinical findings include altered mental status, increased neuromuscular tone, and autonomic excitation [6,7]. The syndrome most often occurs in the setting of the use of 2 or more drugs that increase CNS serotonin activity. Reports of serotonin syndrome after the combination of an MAOI with a number of commonly available prescription (SSRIs, meperidine, CAs) or nonprescription (dextromethorphan) medications are widespread. The long duration of effect of the MAOIs provides the explanation for the prolonged duration of risk for the development of the syndrome after the discontinuation of the drug. Thus, a “washout” period of at least 2 weeks is recommended before SSRI therapy is initiated after discontinuing an MAOI.

Hypertensive crises can result when pharmacologically active dietary amines (eg, tyramine) are ingested by patients taking most MAOIs (Table 3) [8]. Foods with high tyramine content include aged, mature cheeses; smoked pickled aged meats or fish; yeasts and meat extracts; red wines and broad beans. Sometimes this reaction is referred to as a cheese reaction because of its association with certain aged cheeses. Because it may also be caused by other indirectly acting sympathomimetic agents (eg, cocaine, amphetamine, methylphenidate, methamphetamine), this reaction probably should be referred to as an MAOI hypertensive reaction. It is characterized by hypertension and tachycardia. Headache, altered mental status, intracranial hemorrhage, myocardial ischemia/infarction, and seizures are usually secondary to the uncontrolled hypertension. Tyramine reactions have also been reported with people taking St John’s wort for depression [9]. Hypertensive crises usually last only several hours compared to MAOI overdoses in which symptoms can last several days.

Cyclic Antidepressants

Acute cardiovascular toxicity is primarily responsible for the morbidity and mortality attributed to CAs. Conduction delays include prolongation of the QRS interval and rightward shift of the terminal 40-millisecond QRS axis (T40-ms). PR, QRS, and QT interval prolongation can occur both in the setting of therapeutic and toxic doses of CAs. Sinus tachycardia (rate 120–160 beats per minute in an adult) is the most common dysrhythmia associated with CA toxicity and usually does not cause hemodynamic compromise. It is present in most patients with clinically significant CA poisoning. Ventricular tachycardia is the most common lethal ventricular dysrhythmia, although it may be difficult to distinguish this abnormal rhythm from sinus tachycardia with aberrant conduction. Sustained monomorphic ventricular tachycardia has been reported with nonfatal CA toxicity, although this is probably secondary to a supraventricular mechanism based on the electrophysiology analysis and alleviation with overdrive pacing [10]. This is a rare complication. Ventricular tachycardia occurs most often in patients with prolonged QRS interval and/or hypotension. Acutely poisoned patients with QRS widening usually have altered mental status. However, true fatal dysrhythmias are probably rare, as ventricular tachycardia and fibrillation occur in only about 4% of all cases. Torsades de pointes is not common with acute CA overdoses; it is more often found in people on therapeutic doses of CAs.

Refractory hypotension is probably the most common cause of death from CA overdose. The etiology of CA-induced hypotension is multifactorial. Direct myocardial depression is secondary to sodium channel blockade which disrupts the subsequent coupling of calcium entry into the cells, thereby impairing myocardial contractility and α-adrenergic blockade. Prolonged cardiac massage may be necessary in cases of asystole due to CAs. Successful recovery has occurred in both children and adults receiving cardiopulmonary resuscitation despite periods of asystole exceeding 90 minutes [11,12].

Seizures and altered mental status are the primary manifestations of CNS toxicity. Delirium, disorientation, agitation, and/or psychotic behavior with hallucinations may be present. These alterations in consciousness are then usually followed by lethargy, rapidly progressing to obtundation and coma. CA–induced seizures are usually generalized and brief and most often occur within 1 to 2 hours of ingestion.
Anticholinergic effects can occur early or late in the course of CA toxicity. Pupils may be dilated and poorly reactive to light. Other anticholinergic effects include dry mouth, dry flushed skin, hyperthermia, urinary retention, and ileus. Reported pulmonary complications include acute lung injury, aspiration pneumonitis, and the adult respiratory distress syndrome. Acute lung injury may also be the result of coma, hypotension, pulmonary infection, and excessive fluid administration along with the primary toxic effects of CAs [13].

Several reports describe sudden death in children taking therapeutic doses of CAs [14,15]. QT prolongation with resultant torsades de pointes, advanced atrioventricular conduction delays, blood pressure fluctuations, and ventricular tachycardia are postulated mechanisms, although whether any of these effects contributed to the reported deaths is unknown. Prospective studies in children on therapeutic doses of CAs have failed to find any significant cardiac abnormalities as compared to children not on CAs [16,17].

**Unique Toxicity From Atypical CAs**

Although the incidence of serious cardiovascular toxicity is lower with amoxapine overdoses, the incidence of seizures is significantly greater than for the traditional CAs, and status epilepticus may develop that is refractory to standard anticonvulsant therapy. Similarly, the incidence of seizures, cardiac dysrhythmias, and duration of coma is greater with maprotiline toxicity as compared to the older CAs.

**Selective Serotonin Reuptake Inhibitors**

Because of the wide therapeutic index of the SSRIs, most patients with an acute overdose will have mild or no symptoms after an overdose. The majority of symptoms that occur are direct extensions of the pharmacologic activity in therapeutic doses. Acute signs and symptoms include nausea, vomiting, dizziness, blurred vision, tachycardia, and CNS depression. Unique toxicities from particular SSRIs include seizures, QTc prolongation, and QRS widening with citalopram and its enantiomer escitalopram [18,19]. Seizures have been rarely reported with some of the other SSRIs (Table 1). It is uncommon to see serotonin syndrome after an acute overdose of SSRIs.

**Serotonin Syndrome**

The diagnosis of the serotonin syndrome or “serotonin toxicity” with severe symptoms is based on a variety of autonomic, neuromuscular, and CNS signs and symptoms (Table 2). Clinical manifestations may range from mild confusion, tachycardia, and tremor to coma, hyperthermia, and muscular rigidity. It usually begins a short time after the addition of a second serotonergic agent or an increase in dosage of an agent and rarely occurs after a single overdose. Almost any combination of serotonergic agents can produce a serotonin syndrome and it is important to be familiar with these agents whether they be prescription drugs, herbal medications, or over-the-counter medications. There are currently no diagnostic tests available that can determine whether a patient is experiencing serotonin syndrome. Diagnosis is based upon the presence of a set of signs and symptoms (Table 2) [6]. Extreme cases are easy to recognize; however, mild cases are more difficult to distinguish from other causes because symptoms are nonspecific.

**Atypical Antidepressants**

The atypical antidepressants each present unique toxicities in overdose. Patients with acute venlafaxine overdose may present with tachycardia, CNS depression, hypotension, hyperthermia, seizures, QRS and QTc prolongation, and ventricular tachycardia [20-22]. Information on duloxetine overdose is limited but is expected to have similar effects. Effects seen after acute bupropion overdose include tachycardia, hypertension, and seizures. Conduction delays (QRS and QTc prolongation) as well as wide-complex tachycardia similar to the TCAs have also been reported [23,24]. Seizures and other clinical effects may be delayed up to 18 hours, especially after ingestion of sustained-release preparations [25]. Symptoms are reported to continue for up to 48 hours.

Trazadone most commonly causes CNS depression and orthostatic hypotension. It is rarely reported to cause
seizures and the syndrome of inappropriate antidiuretic hormone secretion [26]. Acute overdose of mirtazapine primarily causes altered mental status, tachycardia, hypotension, QTc prolongation, and sometimes respiratory depression.

**Diagnostic Testing**

There are no specific diagnostic tests with the exception of the electrocardiogram (ECG) that will help the health care provider acutely in the diagnosis and management of a patient with an antidepressant overdose. However, investigations may be required for other conditions in the differential diagnosis. Quantitative antidepressant serum concentrations are not available immediately in most hospital settings and will not help guide the acute management.

Cyclic antidepressant toxicity results in distinctive and diagnostic ECG changes that may allow early diagnosis and targeted therapy when the clinical history and physical examination may be unreliable. The maximal limb lead QRS interval duration is an easily measured ECG parameter that is a sensitive indicator of toxicity. A QRS interval duration of 120 ms or more is considered abnormal.

### Table 4: Treatments for antidepressant toxicity.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seizures</strong></td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td></td>
<td>Lorazepam: 0.05-0.1 mg/kg per dose</td>
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<tr>
<td></td>
<td>Diazepam: 0.25 mg/kg per dose</td>
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<tr>
<td></td>
<td>Phenobarbital: 20 mg/kg per dose load</td>
</tr>
<tr>
<td><strong>Hypertension associated with MAOI toxicity</strong></td>
<td>Nitroprusside continuous infusion: 0.5 mcg/kg/min; titrate to effect</td>
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<tr>
<td></td>
<td>Phentolamine mesylate: 2-5 mg aliquots every 10 min (0.1 mg/kg per dose)</td>
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<tr>
<td></td>
<td>Contraindicated: β-adrenergic antagonents, α-methyldopa, clonidine</td>
</tr>
<tr>
<td><strong>Hyperthermia</strong></td>
<td>External cooling methods (water mist/fans, ice, cooling blanket)</td>
</tr>
<tr>
<td></td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td></td>
<td>Paralytic (nondepolarizing agent)/intubation</td>
</tr>
<tr>
<td></td>
<td>Cyproheptadine (serotonin-mediated hyperthermia unresponsive to initial cooling modalities)</td>
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<tr>
<td></td>
<td>4-8 mg q 1-4 h up to max 32 mg/d (0.25 mg/kg per day)</td>
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<tr>
<td></td>
<td>Dantrolene not recommended</td>
</tr>
<tr>
<td><strong>Conduction delays</strong></td>
<td>QRS ≥ 120 ms, T40-ms rotation ≥ 130°, R wave aVR 3mm on ECG</td>
</tr>
<tr>
<td></td>
<td>NaHCO₃ boluses: 1-2 mEq/kg IV boluses every 3-5 min to reverse the abnormality</td>
</tr>
<tr>
<td><strong>Wide-complex dysrhythmias</strong></td>
<td>NaHCO₃ boluses: 1-2 mEq/kg IV boluses every 3-5 min to reverse the dysrhythmia</td>
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<tr>
<td></td>
<td>Hypertonic saline: 10 ml/kg 3% saline (5 mEq/kg NaCl) if dysrhythmia is accompanied by hypotension</td>
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<tr>
<td></td>
<td>Lidocaine: 1 mg/kg slow IV bolus followed by infusion of 20-50 mcg/kg/min</td>
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<tr>
<td></td>
<td>Magnesium sulfate: 1-2 g IV bolus; 3 mg/min</td>
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<tr>
<td></td>
<td>Torsades de pointes unresponsive to sodium bicarbonate should be treated with magnesium, isoproterenol, and overdrive pacing</td>
</tr>
<tr>
<td></td>
<td>Consider overdrive pacing for sustained polymorphous ventricular tachycardia unresponsive to sodium bicarbonate</td>
</tr>
<tr>
<td><strong>Hypotension</strong></td>
<td>Volume with normal saline: 20 ml/kg per bolus</td>
</tr>
<tr>
<td><strong>MAOI toxicity</strong></td>
<td>Norepinephrine: 0.1-1 mcg/kg/min titrate to effect</td>
</tr>
<tr>
<td><strong>Cyclic antidepressants</strong></td>
<td>NaHCO₃ boluses: 1-2 mEq/kg boluses every 3-5 min intervals; repeat until hypotension improves and/or arterial pH 7.5</td>
</tr>
<tr>
<td></td>
<td>Hypertonic saline: 10 ml/kg 3% saline (5 mEq/kg NaCl)</td>
</tr>
<tr>
<td></td>
<td>Norepinephrine continuous infusion: 0.1-1 mcg/kg/min</td>
</tr>
<tr>
<td></td>
<td>Cardiac bypass/aortic balloon pump, ECMO for refractory hypotension</td>
</tr>
<tr>
<td><strong>Neuromuscular rigidity (MAOI toxicity, serotonin syndrome)</strong></td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td></td>
<td>Lorazepam: 1-2 mg IV q 15-20 min (0.05-0.1 mg/kg per dose)</td>
</tr>
<tr>
<td></td>
<td>Diazepam: 5-10 mg IV q 10 min (0.25 mg/kg per dose)</td>
</tr>
<tr>
<td></td>
<td>Cyproheptadine 4-8 mg PO q 1-4 h (max, 32 mg) or 0.25 mg/kg per day divided q 1-4 h</td>
</tr>
</tbody>
</table>

An update on antidepressant toxicity
duration longer than 100 milliseconds is associated with an increased incidence of serious toxicity including coma, need for intubation, hypotension, seizures, and dysrhythmias, making this ECG parameter a useful indicator of toxicity [27]. A T40-ms between 120° and 270° is also associated with CA toxicity, and in one study, it was found to be a more sensitive indicator of general toxicity than the QRS interval alone [28,29]. An abnormal rightward axis can be estimated by observing a negative deflection (terminal S wave) in lead I and a positive deflection (terminal R wave) in lead aVR (Figure 1).

Easily quantifiable measurements in lead aVR on a routine ECG can also predict toxicity. In a prospective study of 79 patients with an acute CA overdose, Liebelt et al [30] demonstrated that the amplitude of the terminal R wave and R wave/S wave ratio in lead aVR (RaVR, Rs/aVR) was significantly greater in those patients who developed seizures and ventricular dysrhythmias. The sensitivity of RaVR = 3 mm and Rs/aVR = 0.7 in predicting seizures and dysrhythmias was comparable to the sensitivity of a QRS > 100 milliseconds. In this study, an RaVR of 3 mm or more was the only ECG variable that significantly predicted these complications.

Documenting the absence of these abnormalities on sequential ECGs, however, provides further evidence that cardiac toxicity is not developing. Serial ECGs should be obtained to monitor for worsening of these parameters, which might signal the need for further interventions. Based on published data demonstrating ongoing changes of the QRS and T40-ms axis despite therapeutic interventions [31], ECG parameters alone are not ideal and should be used in conjunction with the patient’s clinical presentation, history, and course during the first several hours in decision making with regard to disposition and interventions.

**Specific Treatment for Antidepressant Toxicity**

Airway, ventilation, and circulation should be assessed and managed according to pediatric advanced life support recommendations. Orogastric lavage has not been shown to be of value in changing clinical outcome especially greater than 1 hour after ingestion [32]. Activated charcoal should only be administered to patients within 1 to 2 hours of ingestion of a potentially toxic dose who can protect their airway. The utility of decontamination in unintentional ingestions of 1 or 2 pills in children is limited and should be weighed strongly against the risks and complications associated with their use.

**Monoamine Oxidase Inhibitors Toxicity**

All patients with presumed MAOI overdose should be monitored and observed in a setting with appropriate cardiopulmonary monitoring for at least 24 hours regardless of the clinical findings because of the potential for delayed toxicity. Because fluctuating blood pressure is characteristic of serious MAOI intoxication, titratable drugs such as sodium nitroprusside with rapid onset and termination of action should be chosen to treat the hypertension (Table 4). Phentolamine, an α-adrenergic antagonist, can also be used to control hypertension. Because MAOI toxic patients demonstrate increased sensitivity to all vaspressors, initial doses should be significantly reduced and then titrated to effect. The use of β-adrenergic antagonists is contra-indicated for hypertension control because of the potential for unopposed α-adrenergic vasoconstriction which could escalate hypertension.

Dopamine is not an effective choice for the hypotension because its pressor effects are indirect and rely on catecholamine release from sympathetic neurons. Norepinephrine (Levophed) is a more optimal choice because it is a direct-acting agent.

Hyperthermia must be treated aggressively with external cooling measures (ice baths, ice water mist/fans, cooling blankets). Benzodiazepines should be used initially to control seizures, muscular rigidity, and agitation contributing to the hyperthermia.

**Serotonin Syndrome**

Benzodiazepines are first line therapy in serotonin syndrome for control of autonomic manifestations, neuromuscular manifestations, anxiety, and agitation. External cooling should be used in conjunction with aggressive high-dose benzodiazepines for hyperthermia and progression muscular rigidity. Paralysis and intubation may be necessary for severe cases. Several reports have demonstrated success with cyproheptadine (Periactin, Marck and Co, Whitehouse Station, NJ), a serotonin antagonist, for symptoms of serotonin toxicity [33,34]. Consultation with a medical toxicologist before initiating this therapy is suggested.

**MAOI-Food/MAOI-Drug Hypertensive Crisis**

Treatment of symptoms in patients with MAOI-food or MAOI-drug interactions is similar to the symptomatic and supportive care described for acute MAOI overdose. However, as mentioned previously, these symptoms may only last 4 to 8 hours and thus the patient may be observed in the emergency department or observation unit until resolution is complete.

**Cyclic Antidepressant Toxicity**

The primary therapy for treating wide-complex dysrhythmias, as well as for reversing conduction delays and hypotension, is the combination of plasma alkalization and sodium loading. This therapy can also be used for the wide-complex tachycardia observed with the SSRIs and atypical antidepressants as the pathophysiology is presumed to be similar. Controlled in vitro and in vivo studies in various animal models demonstrate that hypertonic
NaHCO₃ is effective in reducing QRS prolongation, increasing blood pressure, and reversing or suppressing ventricular dysrhythmias caused by CA toxicity [35]. The primary mechanism by which this reverses the toxicity is by increasing the extracellular concentration of sodium which overcomes the blockade of the sodium channels through gradient effects, although there are mechanisms that play a less important role. A recent systematic review of all animal and human studies published until 2001 revealed that alkalinization therapy was beneficial for compromising dysrhythmias and shock [36].

The optimal dosing and mode of administration of hypertonic NaHCO₃, as well as indications for initiating and terminating this treatment, are not supported by controlled clinical studies. Instead, this information is extrapolated from animal studies, clinical experience, and an understanding of the pathophysiologic mechanisms of CA toxicity. A bolus or rapid infusion over several minutes of hypertonic NaHCO₃ (1-2 mEq/kg) should be administered initially [37,38]. Higher doses have been used successfully to treat patients, but experience is limited. Continuous ECG monitoring should be in place to follow the progression of the ECG abnormalities. Additional boluses every 3 to 5 minutes may be administered until the QRS interval narrows and the hypotension improves. Blood pH should be monitored after several bicarbonate boluses, aiming for a target pH of no greater than 7.50 to 7.55. Because there may be redistribution of the CA from the tissues into the blood over several hours, it may be reasonable to begin a continuous sodium bicarbonate infusion to maintain the pH in this range. Differences in outcomes between repetitive boluses alone and boluses with further bicarbonate infusions are not well studied. Although diluting NaHCO₃ in dextrose water or saline renders it less hypertonic, reducing the sodium gradient effect, the beneficial effects of pH elevation may still be warranted. There is no evidence to support prophylactic alkalinization in the absence of severe cardiovascular toxicity.

Hypertonic sodium chloride solution (15 mEq Na/kg) is highly efficacious in reversing QRS prolongation and hypotension, although an adequate direct comparison with NaHCO₃ is not available [37,39]. The use of hypertonic saline solutions (3% NaCl) or combined NaHCO₃ and normal (0.9%) saline solutions for rapid infusion theoretically should be efficacious, although these modalities have not been adequately studied in humans. A recent case report describes the successful use of 7.5% NaCl to treat hypotension and QRS widening with ventricular ectopy in a patient with a nortriptyline overdose that was unresponsive to sodium bicarbonate and normal saline boluses [39]. The role of hypertonic saline remains undefined. However, it could be considered in situations of refractory hypotension, wide-complex tachycardia, and/or dysrhythmias. Potential risks of this treatment include fluid and sodium overload.

Other treatment modalities are shown in Table 4. Benzodiazepines should be used for seizures. Norepinephrine is the vasopressor of choice if sodium bicarbonate therapy and hypertonic saline fail, although epinephrine has been used successfully in animal models [40]. Wide-complex dysrhythmias which do not resolve with sodium bicarbonate or hypertonic saline therapy should be treated with lidocaine and/or magnesium sulfate [41,42]. Torsade de pointes, unresponsive to sodium bicarbonate therapy, should be treated with magnesium, isoproterenol, and/or overdrive pacing. Overdrive pacing may be considered for sustained wide-complex tachycardia which is unresponsive to alkalinization and sodium loading. Ventricular bradyarrhythmias (which are usually a terminal sign) may be treated with isoproterenol and a temporary pacemaker.

If pharmacologic measures fail to correct hypotension, extracorporeal life support measures should be considered. Extracorporeal membrane oxygenation, extracorporeal circulation, and cardiopulmonary bypass are successful adjuncts for refractory hypotension and life support when maximum therapeutic interventions fail [43,44]. Flumazenil and physostigmine should not be used in the setting of CA toxicity because of the risk of precipitating seizures and cardiac arrest. Class IA and class IC antidysrhythmics should not be used because they are also sodium channel blockade drugs and may precipitate or exacerbate the wide-complex dysrhythmias.

### Atypical Antidepressant Treatment

The seizures seen with the atypical antidepressants should be treated with benzodiazepines. Wide-complex dysrhythmias should be managed similarly to those that occur with the CAs with sodium bicarbonate and hypertonic saline.

### Summary

Antidepressant drugs fall primarily into 4 classes, each possessing its own unique adverse effects and toxicities when taken in overdose. The SSRIs and atypical antidepressants are prescribed with the greatest frequency for depression in the United States and tend to have a safer toxicity profile than the CAs and MAOIs, although the latter 2 categories are still being used for other clinical disease entities. Recognition and specific treatment for excessive serotonergic activity, sodium channel blockage, food-drug and drug-drug interactions, and other unique toxicities are important for the emergency health care provider. Most importantly, initiating basic supportive care and recognizing the special toxicities of these drugs will direct the appropriate evaluation and treatment.

### References