CHAPTER 146

Antidepressants

Michael D. Levine | Anne-Michelle Ruha

PRINCIPLES OF TOXICITY

Depression is one of the most common medical conditions in the United States, with a lifetime prevalence of nearly 20%.[1] 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 60-year-old monoamine hypothesis, which suggests that depressive symptoms are mediated through an imbalance of the dopaminergic, noradrenergic, and serotonergic systems.[1] 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 (MAO). Iproniazid, a derivative of isocarboxazid, subsequently became the first drug marketed specifically as an antidepressant.[2-3] 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. 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).

The morbidity of antidepressants in overdose varies greatly by specific class. Overall, however, there were nearly 110,000 overdoses on antidepressants reported to United States poison control centers in 2013. Despite representing only 4% of calls, they accounted for 9% of fatalities.[4]

MONOAMINE OXIDASE INHIBITORS

MAO is located on the outer mitochondrial membrane and is responsible for breakdown of cytoplasmic catecholamines. Monoamine oxidase type A (MAO-A) primarily deaminates serotonin and norepinephrine; monoamine oxidase type B (MAO-B) primarily deaminates phenylethylamine.[5-6] Tyramine and dopamine are metabolized equally by both isoenzymes.[5-6] 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.

Drugs targeting the MAO 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.

MAOIs have fallen out of favor for treatment of depression due to side effects from adverse drug and food interactions. However, their use in treatment of Parkinson's disease is increasing. Drugs that selectively inhibit MAO-B disproportionately increase dopamine concentrations in the striatum.[6] Selegiline is an irreversible MAO-B inhibitor used in the treatment of Parkinson's disease. Importantly, the selectivity for MAO-B is only present at low doses.[7] Rasagiline is also an irreversible inhibitor of MAO-B and has similar clinical efficacy with selegiline.[8] Furthermore, unlike selegiline, which is metabolized to L-methamphetamine, rasagiline is not metabolized to an amphetamine derivative.[9] Table 146.1 Summarizes the MAO-inhibitors currently available for use in the United States.

In addition to its antibiotic properties, linezolid, an oxazolidinone class antibiotic, is a reversible inhibitor of MAO, producing 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 scenario that leads to toxicity, the clinical presentation may differ. 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. Patients 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.

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 MAO, 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.[7] 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.[10] 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.

Differential Diagnoses

The differential diagnosis for MAOI toxicity includes sympathomimetic drugs of abuse such as cocaine and amphetamine derivatives, anticholinergic (or antimuscarinic) toxicity (eg,

TABLE 146.1

Summary of Monoamine Oxidase Inhibitor Agents Currently Available

GENERIC NAME	ROUTE	SELECTIVITY	FDA-APPROVED USES
Tranylcypromine	Oral	Nonselective	Depression
Phenelzine	Oral	Nonselective	Depression
Isocarboxazid	Oral	Nonselective	Depression
Selegiline	Oral or transdermal patch	MAO-B at lower doses; MAO-A at higher doses	Depression, Parkinson's disease

FDA, U.S. Food and Drug Administration; *MAO-A,* monoamine oxidase type A; *MAO-B,* monoamine oxidase type B.

diphenhydramine, cyclic antidepressants, anti-Parkinson drugs, and jimson weed), and methylxanthine toxicity (eg, theophylline and caffeine). Other toxicological considerations include acute withdrawal states (eg, ethanol and benzodiazepines), neuroleptic malignant syndrome (NMS) and the serotonin syndrome from other serotonergic drug combinations. Non-toxicologic causes to consider include environmental hyperthermia or heat stroke, febrile illness from infectious causes (eg, meningitis and encephalitis), pheochromocytoma, carcinoid syndrome, thyroid storm, and hypertensive emergency.

Diagnostic Testing

Laboratory abnormalities are nonspecific but can include hyperglycemia and leukocytosis, secondary to a hyperadrenergic state, and elevated creatine kinase due to rhabdomyolysis. 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 (ECG) to assess the QT and QRS intervals. Patients with chest pain should be evaluated for myocardial infarction. Measurement of serum glucose and electrolytes are indicated if the patient is obtunded. Because of the potential for intracranial hemorrhage in the setting of severe MAOI-induced hypertension, patients with a seizure or focal neurological deficit should undergo a non–contrast-enhanced head computed tomography (CT) scan.

Management

As with most intoxication, supportive care is paramount. Central nervous system (CNS) excitation should be treated with intravenous (IV) administration of benzodiazepines such as lorazepam and diazepam in usual titrated doses. Hyperthermia should be treated with external cooling using evaporative techniques and strategic ice packing. Hyperthermia that persists, despite administration of benzodiazepines and external cooling measures, may need intubation, ventilation, and chemical paralysis with a nondepolarizing neuromuscular blocker. Because typically only a single dose of a paralytic is required, the authors recommend rocuronium during rapid sequence intubation. The use of succinylcholine may incite hyperkalemia if rhabdomyolysis has occurred, and fasciculation from succinylcholine might further increase metabolic heat production. Furthermore, many of these patients are acutely hyperkalemic, which is a relative contraindication to succinylcholine. Mild hypertension should not be treated, but sustained severe hypertension (eg, systolic blood pressure exceeding 200 mm Hg or a diastolic exceeding 100 mm Hg) is best managed with a rapid, short-acting agent such as phentolamine (titrated slowly by repeated IV doses of 1 mg every 3 minutes) or nitroprusside (0.25 to 0.5 mcg/kg/min by IV infusion). Treatment should target a 25% reduction in the mean arterial pressure. Hypotension should first be managed by volume resuscitation with normal saline. 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.

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 such as headache, flushing, or chest pain should be treated with phentolamine or nitroprusside. Patients with persistent severe headache and hypertension should have a head CT scan to assess for intracranial hemorrhage. Patients with chest pain should be evaluated for myocardial infarction (see Chapter 68).

Treatment of suspected serotonin syndrome is supportive (see later section) and consists primarily of the administration of benzodiazepines.

Disposition

Patients presenting with an MAOI overdose should be admitted to a monitored setting for 24 hours due to the risk of delayed, rapid deterioration and 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 over that period of time.

TRICYCLIC ANTIDEPRESSANTS

Principles of Toxicity

In the 1950s, imipramine became the first 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.[11] Whereas use of TCAs for treatment of depression has waned, use for other conditions, including treatment of migraines, various neuropathies, trigeminal neuralgia, and nocturnal enuresis has increased.

Clinical Features

Cyclic antidepressant toxicity can result from overdose of a TCA or 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 of these isoenzymes can decrease metabolism of these drugs, resulting in unexpectedly high serum concentrations and clinical toxicity. Conversely, inhibition of CYP2D6 and other P_{450} 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 interactions. Another drug interaction that

occurs with TCAs is the serotonin syndrome, which can result 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. Severely poisoned patients typically have symptoms within 6 hours of an overdose. Early cyclic antidepressant toxicity (within the first 2 hours) is primarily characterized by anticholinergic effects. These findings include dry mucosal membranes, urinary retention, and hot, dry skin. Despite having potent antimuscarinic properties, the pupils are often small due to *alpha* effects. Patients may be alert and confused, severely agitated, mute, hallucinating, or even deeply comatose. Speech is often rapid and mumbling in character. Seizures may occur and are likely to be multifactorial, resulting from increased synaptic monoamines, sodium channel inhibition, and 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 (2 to 6 hours post ingestion), myocardial depression resulting from severe sodium channel antagonism may also lead to hypotension and bradycardia.[12] Significant sodium channel blockade is associated with widening of the QRS interval. The degree of widening is prognostic. A QRS wider than 100 msec is associated with seizures, where as a QRS complex wider than 160 msec is associated with ventricular dysrhythmias. TCAs also block potassium efflux, which leads to a prolonged QT interval.[13] 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 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 corrected QT (QTc) interval are common. Chronic toxicity presents more gradually and should be considered in any confused patient taking therapeutic doses of a cyclic antidepressant.

Differential Diagnoses

Many agents with anticholinergic properties produce similar clinical features as TCAs. Diphenhydramine and carbamazepine, in particular, can also produce seizure and sodium-channel blockade. Agents that produce sympathomimetic toxicity (eg, cocaine) or serotonin syndrome (eg, SSRIs, MAOIs) should be included in the differential diagnosis. Other drugs with sodium channel blockade, and hence a wide QRS complex, includes the Vaughn-Williams class IA antidysrhythmics (eg, procainamide, disopyramide, quinidine) and class IC antidysrhythmics (eg, flecainide, encainide, and propafenone), along with amantadine, carbamazepine, cocaine, diphenhydramine, mesoridazine, and thioridazine. 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.

Diagnostic Testing

After overdose, the ECG 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 ECG is prognostic. Historically, it is felt that QRS duration longer than 100 milliseconds is predictive of seizures, whereas QRS duration longer than 160 milliseconds is predictive of ventricular dysrhythmias, but hard evidence does not exist for either of these assertions. Additional findings on the ECG include a rightward shift of the terminal 40 milliseconds of the QRS complex seen as an R wave in augmented vector right (aVR) longer than 3 milliseconds. Figure 146.1 demonstrates lead aVR following a tricyclic ingestion. QT prolongation is less important clinically than the QRS duration.

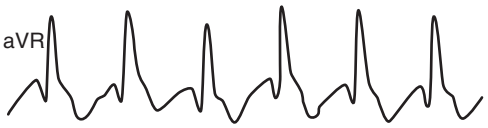

Fig. 146.1. Augmented vector right *(aVR)* demonstrating tall R wave.

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 (eg, antipsychotic medications, antimuscarinic agents, carbamazepine, or the muscle relaxant cyclobenzaprine). Quantitative serum tricyclic levels do not correlate with severity of illness.

Management

Ensuring stability of the airway, with adequate ventilation, and volume repletion are of primary importance. There are no randomized controlled trials demonstrating improved patient-oriented outcomes and decreased 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 an overdose and who is awake, alert, and cooperative and is not exhibiting any signs of toxicity (eg, no tachycardia or intraventricular conduction delay) can be given activated charcoal. However, due to risk of seizures with subsequent aspiration, activated charcoal is not routinely recommended, other than in the specific setting described. 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 in the clinical course. Early hypertension should not be treated. Hypotensive patients should first receive fluid resuscitation with an isotonic crystalloid. Patients who remain hypotensive should be treated with direct-acting vasopressors such as norepinephrine and epinephrine.

Hypertonic sodium bicarbonate is given only to treat specific evidence of sodium channel blockade such as a wide QRS and ventricular dysrhythmias. Sodium bicarbonate should not be given strictly due to tachycardia. Recommendations regarding the specific administration of sodium bicarbonate vary. We recommend a conservative approach by administering a bolus of 1 to 2 mEq/kg hypertonic sodium bicarbonate intravenous push (IVP) if the QRS interval exceeds 100 milliseconds. This dose may be repeated in a few minutes if the QRS does not narrow. After IV bolus, a sodium bicarbonate infusion can be used to maintain a pH between 7.50 and 7.55. Such an infusion can be created by the addition of 150 mEq sodium bicarbonate, 40 mEq potassium, and 850 mL of dextrose 5% in water (D5W). The infusion should be created with a 5% dextrose solution, and not normal saline, due to the risk of hypernatremia with the latter. The infusion should be administered at twice the normal maintenance rate, titrating to QRS width and pH. Alternatively, infusions of 1 mEq sodium bicarbonate per milliliter of fluid may be used if volume overload is a concern. Additional IV boluses of sodium bicarbonate may be

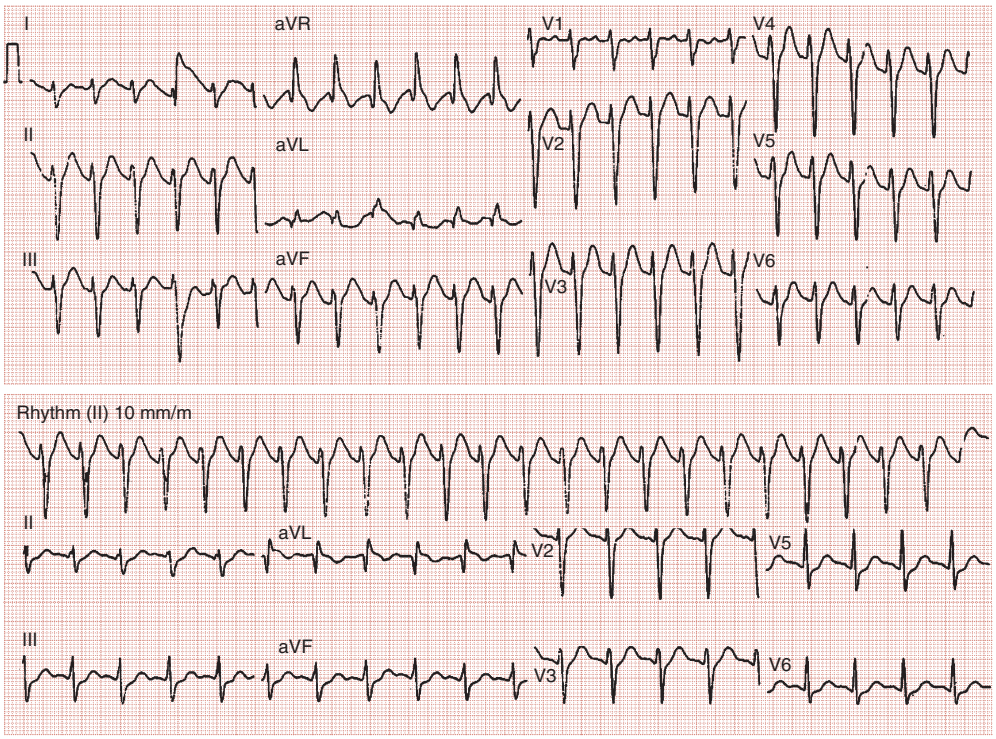

Fig. 146.2. *Top,* Initial 12-lead electrocardiogram (ECG) demonstrating substantial intraventricular conduction delay (QRS 146 milliseconds). *Bottom,* Repeated ECG after bicarbonate therapy. *aVF,* Augmented vector foot; *aVL,* augmented vector left; *aVR,* augmented vector right.

necessary if the QRS widens. Figure 146.2 demonstrates a 12-lead ECG 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. Class Ia or Ic antidysrhythmics should be avoided. Seizures are best treated with an IV benzodiazepine (lorazepam 1 to 2 mg IVP; diazepam 5 to 10 mg IVP) along with sodium bicarbonate. Refractory seizures can be treated with phenobarbital (15 to 18 mg/kg IV loading dose). Because seizure leads to acidosis and worsens the cardiac status, seizing patients who do not respond quickly to benzodiazepines or phenobarbital should be rapidly paralyzed and intubated if necessary to prevent increasing metabolic acidosis.

Physostigmine, the antidote of choice for pure anticholinergic toxicity (see Chapter 145) is considered by many experts to be contraindicated in the management of TCA overdose. Asystole has been reported after physostigmine use in TCA toxicity, particularly in patients with bradycardia and A-V block. It is not advised to administer this agent to patients with QRS or QTc prolongation following TCA overdose. However, we recommend it be considered in patients with delirium of unknown etiology who are therapeutically taking anticholinergic agents and in whom toxicity is suspected, but only if the PR, QRS, and QTc intervals are normal. Physostigmine (1 to 2 mg slow IV infusion over 5 minutes in adults) should be given with caution in a monitored setting, because it may exacerbate bradycardia, AV block, and seizures related to the overdose (see Chapter 145).

Intravenous lipid emulsion (ILE) therapy has gained interest recently for reversal of toxicity caused by lipophilic drugs, including TCAs.[14-15] Although the exact mechanism of ILE is not clearly defined, it likely 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.*[16] Other mechanisms such as enhanced cardiac metabolism are also possible explanations. Because not all studies reveal beneficial effects from ILE in the treatment of TCA toxicity and due to the potential for iatrogenic harm, its use is currently reserved for life-threatening toxicity that remains refractory to sodium bicarbonate administration.[17,18] ILE should be administered only on advice of a medical toxicologist or regional poison center. If ILE is to be administered, there are several different dosing strategies. We recommend 1.5 mL/kg of a 20% lipid solution over 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 may be followed by an infusion of 0.25 mL/kg/min for 15 to 30 minutes.[19]

Despite recent enthusiasm for ILE, its use is not without associated complications, including extreme lipemia resulting in interference with laboratory blood tests (complete blood counts, chemistries, and coagulation studies), as well as acute pancreatitis, and acute respiratory distress syndrome.

Disposition

If the heart rate has not exceeded 100/minute for a period of at least 10 minutes, ECG intervals are normal, level of consciousness is normal, and no seizures have developed within 6 hours of a TCA overdose, it is unlikely that toxicity will occur.[20] The patient can be medically cleared from the emergency department for psychiatric evaluation and disposition if needed. Patients with signs of cyclic antidepressant cardiotoxicity, seizures, or coma should be admitted to an intensive care unit.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Principles of Toxicity

In recent years, the 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.

SSRIs have a wide therapeutic index. Most 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).

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% for each. The incidence of serotonin syndrome after SSRI overdose is variable, up to 15%, 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.[21-22] There has been some suggestion that the QT prolongation may be delayed with citalopram ingestion. However, there is not convincing data to support this delayed onset of toxicity. The QT prolongation does, however, appear to be dose dependent.[23] Despite being the active enantiomer of citalopram, escitalopram appears to be less toxic than citalopram, with a lower incidence of seizure and QTc prolongation.[21]

Therapeutic administration of SSRIs may be associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH).[24] Most cases of hyponatremia develop shortly after commencing care. The overall incidence is not well documented. 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.

Differential Diagnoses

The differential diagnosis for SSRI toxicity includes cyclic antidepressants, MAOIs, sedative hypnotics (eg, benzodiazepines, barbiturates), SNRIs, neuroleptic agents, and atypical antipsychotics.

Diagnostic Testing

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. An ECG can assess for conduction disturbances, especially QT prolongation. Specific SSRI levels are not performed by most hospital laboratories and do not influence management, although they may help confirm overdose retrospectively. A standard urine drug of abuse screen will not detect an SSRI.

Management

Treatment of an SSRI overdose is largely supportive. There is no role for activated charcoal or gastric lavage. Only rarely will patients require tracheal intubation because of loss of airway reflexes. For patients with a corrected QT interval greater than 500 msec, 2 grams of IV magnesium sulfate should be administered. IV administration of benzodiazepines (0.05 to 0.1 mg/kg of lorazepam via rapid IV bolus; or 0.1 to 0.2 mg/kg diazepam via rapid IV bolus) should be used to treat agitation and 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 12 hours of observation after the ingestion of more than 1000 mg of citalopram or escitalopram, although that recommendation is not universally accepted. If a patient with citalopram ingestion is to be cleared after 6 hours, a repeat ECG should be performed to assess the QT interval. Symptomatic patients should be admitted to a monitored care setting. Those patients with an intent of self-harm should be evaluated by a psychiatric service.

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS AND NOREPINEPHRINE REUPTAKE INHIBITORS

Principles of Toxicity

Duloxetine, venlafaxine, desvenlafaxine, milnacipran, and levomilnacipran are collectively referred to as *serotonin-norepinephrine reuptake inhibitors (SNRIs).* All of these agents, except milnacipran, are approved for use in the United States for treatment of major depression. Milnacipran, despite being used as an antidepressant in Europe, is only approved for treatment of fibromyalgia in the United States. Some of these agents are also approved for other disorders. For example, venlafaxine can be used to treat panic disorder, generalized anxiety disorder, or social phobia, whereas duloxetine is also used to treat chronic musculoskeletal pain, diabetic neuropathy, fibromyalgia, and generalized anxiety disorder. Venlafaxine and its active metabolite desvenlafaxine are both available medicinally. The SNRIs may also produce dose-dependent inhibition of sodium channels. Reboxetine is an isolated norepinephrine reuptake inhibitor. It is also used for the treatment of depression.

Clinical Features

Unlike the SSRIs, which are relatively benign in overdose, ingestion of any of the SNRIs can be dangerous. Fatal ingestions have been described with virtually all of the SNRIs. All of these agents may produce hyperadrenergic symptoms, including tachycardia and hypertension. Rarely, hypotension can be observed after massive overdose.[25-26] It is hypothesized that the hypotension may be the result of an acute cardiomyopathy.[27,28-30] Seizures can occur following ingestion of the SNRIs.[31-32] Unlike bupropion, however, which can have delayed onset of seizures, the onset of seizures following an SNRI ingestion would be expected to occur within the first several hours post ingestion.

Rhabdomyolysis has been reported independent of seizure activity following ingestions of venlafaxine.[33] Venlafaxine and desvenlafaxine overdoses can result in cardiovascular toxicity, manifesting as intraventricular conduction delay and ventricular dysrhythmias.[28] Venlafaxine has also been associated with QT prolongation.[34] Lastly, based on their mechanism of action, serotonin syndrome may develop after ingestion of these agents.

Differential Diagnoses

The differential diagnosis for SNRIs toxicity includes cyclic antidepressants, MAOIs, sedative hypnotics, serotonin reuptake inhibitors, neuroleptic agents, and atypical antipsychotic medications.

Diagnostic Testing

Specific drug levels are not rapidly available and do not aid management. An ECG 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.[35] In cases of a venlafaxine ingestion, a creatinine kinase and renal function tests should be obtained to assess for acute

rhabdomyolysis. As with any multidrug ingestion, serum acetaminophen and salicylate levels should be measured.

Management

Care of the patient with an SNRI overdose is supportive, with focus on ensuring airway patency and adequate ventilation. There is no role for activated charcoal or gastric emptying. Hypotension (systolic blood pressure <90 mm Hg) should first be treated with a 20 cc/kg bolus of 0.9% normal saline. This bolus can be repeated if necessary. If hypotension still persists, a direct-acting vasopressor (such as epinephrine or norepinephrine) should be used. Intraventricular conduction delay with a widened QRS on ECG should be treated with sodium bicarbonate infusions (as described in the Tricyclic Antidepressants section earlier). First-line treatment of seizures is the IV administration of a benzodiazepine such as lorazepam or diazepam.

Disposition

Patients who are asymptomatic with a normal 12-lead ECG after an observation period of 6 hours can be cleared for discharge after appropriate psychiatric consultation. Patients with an intentional ingestion who develop manifestations of neurologic or cardiovascular toxicity (such as sedation, hypotension, tachycardia, and so on) should be observed in an in-patient monitored setting. Those with profound CNS depression or hemodynamic instability warrant intensive care unit admission. 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 unique class of antidepressant, which is also used for smoking cessation.[36] The primary mechanism of action is inhibition of dopamine and norepinephrine reuptake, but it can also act as a noncompetitive inhibitor of nicotinic acetylcholine receptors.[37]

Seizure activity is a dose-dependent phenomenon and can occur with therapeutic dosing or overdose of bupropion.[38] Seizures are relatively common after overdose and occur in approximately 30% of cases, the majority of which are initially tachycardic.[38-39]

Sinus tachycardia, tonic-clonic seizures, and agitation are common after overdose. Unlike many agents that produce seizures acutely following overdose, ingestion of extended release bupropion can produce delayed onset seizures. Both QRS and QT prolongation can occur with toxicity. Treatment is primarily supportive. Activated charcoal or gastric emptying are not indicated. Patients with large overdoses may require endotracheal intubation because of CNS and respiratory depression. Lorazepam or diazepam is effective for terminating seizures. If seizures persist, phenobarbital or other GABA agonists may be used. Sodium bicarbonate (150 mEq IV or 3 mEq/kg for pediatric patients) should be administered for any QRS prolongation. Additional bicarbonate should be given based on subsequent ECGs. Resuscitative ILE therapy has been described in anecdotal case reports with severely poisoned patients refractory to standard management measures. ILE should be undertaken only on the advice of a medical toxicologist or regional poison center.

Trazodone

Trazodone is an atypical antidepressant with a mechanism of action that includes antagonism of the 5-hydroxytryptamine type 2A (5-HT_{2A}) receptor and alpha_1 receptor. In addition, it is a serotonin receptor antagonist and reuptake inhibitor. Its use as an antidepressant has been historically somewhat limited by adverse effects (such as orthostatic hypotension, priapism, and sedation), although once-daily formulation has recently been released.[40]

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. Prolongation of the QT interval may occur. Management is supportive, with airway protection, IV fluid resuscitation, and use of alpha-adrenergic agonists such as norepinephrine as needed for refractory hypotension. Activated charcoal and gastric emptying are not indicated.

Nefazodone

Nefazodone, a phenylpiperazine antidepressant, is structurally similar to trazodone. It acts as an antagonist at the 5-HT_{2A} 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_1 receptor is responsible for the orthostatic hypotension that can occur. Treatment is primarily supportive.

SEROTONIN SYNDROME

Principles of Toxicity

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 interactions, especially with drug combinations that raise synaptic serotonin concentrations by different mechanisms. Agonism of the 5-HT_{2A} receptor appears to be largely responsible for this condition in humans.[41]

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 (Box 146.1). 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 (eg, 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. 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.

BOX 146.1

Xenobiotics Commonly Implicated in Serotonin Syndrome

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

BOX 146.2

The Hunter Criteria for Serotonin Syndrome

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 *and* agitation or diaphoresis
- Ocular clonus *and* agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonic with temperature >38° C *and* ocular clonus or inducible clonus

Differential Diagnoses

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

Diagnostic Testing

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 the 1990s and became the first widely used diagnostic algorithm. Additional criteria, including the Hunter criteria and the Boyer and Shannon criteria, have been developed. The Hunter criteria (Box 146.2) appear to be more sensitive than the Sternbach criteria, with fewer false positives.

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.

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 (eg, 5 to 10 mg of IV diazepam) for rigidity. More severe cases may require IV fluid resuscitation and large doses (eg, 10 to 20 mg of IV diazepam, with titration in 10 mg aliquots) of benzodiazepines or other sedative-hypnotic agents to gain control of symptoms. Cyproheptadine, a 5-HT_{2A} antagonist, is an adjunctive therapy for more severe cases, but there are no randomized controlled trials demonstrating improved benefit with cyproheptadine over supportive care and benzodiazepines alone. If cyproheptadine is available, the syndrome is severe or refractory to treatment, and the clinician is confident with the diagnosis, we recommend a single dose of 12 mg of cyproheptadine for patients with serotonin syndrome. If anticholinergic toxicity remains on the differential diagnosis, cyproheptadine should not be given, because it can worsen anticholinergic toxicity. Patients with hyperthermia that does not respond promptly to sedation with benzodiazepines should receive a nondepolarizing neuromuscular blocking agent (eg, rocuronium) during rapid sequence intubation. Typically only a single dose of a long-acting neuromuscular blocking agent is required.

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 who can have serious, potentially life-threatening withdrawal.[42] Antidepressant discontinuation syndrome does not always develop, but when it does, it typically starts within the first 3 days after therapy is stopped. This syndrome is difficult to distinguish from recurrence of the underlying depression, which has overlap of some symptoms.

Antidepressant discontinuation syndrome occurs with all major classes of antidepressants. 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 (eg, dizziness, ataxia), sleep disturbances, gastrointestinal symptoms, affective symptoms (eg, irritability, anxiety), sensory symptoms (eg, electric shock–like sensation, paresthesias), and general somatic symptoms (eg, headache, tremor, anorexia, diaphoresis). The syndrome is more common after discontinuation of drugs with shorter half-lives (eg, paroxetine) than of drugs with longer half-lives (eg, 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 tapering dose.

KEY CONCEPTS

- Although rarely used for depression, MAOIs are used in the treatment of Parkinson's disease.
- Because serious symptoms can occur after a lengthy latent period, patients with reported MAOI overdose should be admitted for 24 hours, regardless of symptoms. Symptoms are characterized by tachycardia, hypertension, and CNS changes, and later cardiovascular collapse.
- The primary manifestations of TCA toxicity are seizures, tachycardia, and intraventricular conduction delay. IV sodium bicarbonate should be administered for QRS prolongation.
- SSRIs are relatively benign in overdose.
- SNRI ingestions can result in seizures, tachycardia, and occasionally intraventricular conduction delay.
- The hallmark feature of serotonin syndrome is lower extremity rigidity with spontaneous or inducible clonus, especially at the ankles.
- Serotonin syndrome is primarily treated with supportive care, including discontinuation of the offending agent, and benzodiazepines.

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

REFERENCES

1. Bostwick JM: A generalist's guide to treating patients with depression with an emphasis on using side effects to tailor antidepressant therapy. Mayo Clin Proc 85:538–550, 2010.
2. Shulman KI, Herrmann N, Walker SE: Current place of monoamine oxidase inhibitors in the treatment of depression. CNS Drugs 27:789–797, 2013.
3. Juli A, Juli L: New antidepressant drugs for new depressions. Psychiatr Danub 26(Suppl 1):115–116, 2014.
4. Mowry JD, Spyker DA, Cantilena LR: 2013 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st Annual report. Clin Toxicol 52:1032–1283, 2014.
5. Chajkowski-Scarry S, Rimoldi JM: Monoamine oxidase A and B substrates: probing the pathway for drug development. Future Med Chem 6:697–717, 2014.
6. Finberg JP: Update on the pharmacology of selective inhibitors of MAO-A and MAO-B: focus on modulation of CNS monoamine neurotransmitter release. Pharmacol Ther 143:133–152, 2014.
7. Shulman KI, Herrmann N, Walker SE: Current place of monoamine oxidase inhibitors in the treatment of depression. CNS Drugs 27:789–797, 2013.
8. Marconi S, Zwingers T: Comparative efficacy of selegiline versus rasagiline in the treatment of early Parkinson's disease. Eur Rev Med Pharmacol Sci 18:1879–1882, 2014.
9. Muller T, Hoffman JA, Dimpfel W, et al: Switch from selegiline to rasagiline is beneficial in patients with Parkinson's disease. J Neural Transm 120:761–765, 2013.
10. Finberg JP, Gillman K: Selective inhibitors of monoamine oxidase type B and the "cheese effect." Int Rev Neurobiol 100:169–190, 2011.
11. Preskorn SH: CNS drug development. Part I: The early period of CNS drugs. J Psychiatr Pract 16:344–349, 2010.
12. Foianini A, Joseph Wiegand T, Benowitz N: What is the role of lidocaine or phenytoin in tricyclic antidepressant-induced cardiotoxicity? Clin Toxicol 46:325–330, 2010.
13. Alvarez PA, Pahissa J: QT alterations in psychopharmacology: proven candidates and suspects. Curr Drug Saf 5:97–104, 2010.
14. Blaber MS, Khan JN, Brebner JA, et al: "Lipid rescue" for tricyclic antidepressant cardiotoxicity. J Emerg Med 43:465–467, 2012.
15. Levine M, Hoffman RS, Lavergne V, et al: Systematic review of the effects of intravenous lipid emulsion therapy for non-local anesthetics toxicity. Clin Toxicol 54(3):194–221, 2016.
16. Heinonen JA, Litonius E, Backman JT, et al: Intravenous lipid emulsion entraps amitriptyline into plasma and can lower its brain concentration: an experimental intoxication study in pigs. Basic Clin Pharmacol Toxicol 113:193–200, 2013.
17. Varney SM, Bebarta VS, Vargas TE, et al: Intravenous lipid emulsion therapy does not improve hypotension compared to sodium bicarbonate for tricyclic antidepressant toxicity: a randomized, controlled pilot study in a swine model. Acad Emerg Med 21:1212–1219, 2014.
18. Levine M, Skolnik AB, Ruha AM, et al: Complications following antidotal use of intravenous lipid emulsion therapy. J Med Toxicol 10:10–14, 2014.
19. American College of Medical Toxicology: Interim guidance for the use of lipid resuscitation therapy. Available at: <www.acmt.net/_Library/Membership_Documents/Lipid_resuscitation_G_4F9E49_-_for_member_comment.pdf>.
20. Woolf AD, et al: Tricyclic antidepressant poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 45:203–233, 2007.
21. Hayes BD, Klein-Schwartz W, Clark RF, et al: Comparison of toxicity of acute overdoses with citalopram and escitalopram. J Emerg Med 39:44–48, 2010.
22. Fitzgerald KT, Bronstein AC: Selective serotonin reuptake inhibitor exposure. Top Companion Anim Med 28:13–17, 2013.
23. Waring WS: Clinical use of antidepressant therapy and associated cardiovascular risk. Drug Healthc Patient Saf 4:93–101, 2012.
24. Mannesse CK, Jansen PA, Van Marum RJ, et al: Characteristics, prevalence, risk factors, and underlying mechanisms of hyponatremia in elderly patients treated with antidepressants: a cross-sectional study. Maturitas 76:357–363, 2013.
25. Levine M, Truitt CA, O'Connor AD: Cardiotoxicity and serotonin syndrome complicating a milnacipran overdose. J Med Toxicol 7:312–316, 2011.
26. Ware TL, McCloskey K, Ryan MM, et al: Venlafaxine ingestion in a 4-year-old girl. J Paediatr Child Health 48:1047–1048, 2012.
27. Chan AN, Gunja N, Ryan CJ: A comparison of venlafaxine and SSRIs in deliberate self-poisoning. J Med Toxicol 6:116–121, 2010.
28. Batista M, Dugernier T, Simon M, et al: The spectrum of acute heart failure after venlafaxine overdose. Clin Toxicol 51:92–95, 2013.
29. Christoph M, Ebner B, Stolte D, et al: Broken heart syndrome: Tako Tsubo cardiomyopathy associated with an overdose of the serotonin-norepinephrine reuptake inhibitor venlafaxine. Eur Neuropsychopharmacol 20:594–597, 2010.
30. Neil CJ, Chong CR, Nguyen TH, et al: Occurrence of Tako-Tsubo cardiomyopathy in association with ingestion of serotonin/noradrenaline reuptake inhibitors. Heart Lung Circ 21:203–205, 2012.
31. Reichert C, Reichert P, Monnet-Tschudi F, et al: Seizures after single-agent overdose with pharmaceutical drugs: analysis of cases reported to a poison center. Clin Toxicol 52:629–634, 2014.
32. Pellicciari A, Balzarro B, Scaramelli A, et al: Generalized tonic-clonic seizure secondary to duloxetine poisoning: a short report with favorable outcome. Neurotoxicology 33:189–190, 2012.
33. Huang SS, Yang HY, Lin YC, et al: Low-dose venlafaxine induced severe rhabdomyolysis: a case report. Gen Hosp Psychiatry 34:436, E5-7, 2012.
34. Jasiak NM, Bostwick JR: Risk of QT/QTc prolongation among newer non-SSRI antidepressants. Ann Pharmacother 48:1620–1628, 2014.
35. Brahm NC, Yeager LL, Fox MD, et al: Commonly prescribed medications and potential false-positive urine drug screens. Am J Health Syst Pharm 15:1344–1350, 2010.
36. Hughes JR, Stead LF, Hartmann-Boyce J, et al: Antidepressants for smoking cessation. Cochrane Database Syst Rev (1):CD000031, 2014.
37. Carroll FL, Blough BE, Bascarella SW, et al: Bupropion and bupropion analogs as treatments for CNS disorders. Adv Pharmacol 69:177–216, 2014.
38. Lewis JC, Sutter ME, Albertson TE, et al: An 11-year review of bupropion insufflation exposures in adults reported to the California Poison Control System. Clin Toxicol 52:969–972, 2014.
39. Reichert C, Reichert P, Monnet-Tschudi F, et al: Seizures after single-agent overdose with pharmaceutical drugs: analysis of cases reported to a poison center. Clin Toxicol 52:629–634, 2014.
40. Fagiolini A, Comandiani A, Catena Dell'Osso M, et al: Rediscovering trazodone for the treatment of major depressive disorder. CNS Drugs 26:1033–1049, 2012.
41. Volpi-Adabie J, Kaye AM, Kaye AD: Serotonin syndrome. Ochsner J 13:533–540, 2013.
42. Ogle NR, Akkerman SR: Guidance for the discontinuation or switching of antidepressant therapies in adults. J Pharm Pract 26:389–396, 2013.

CHAPTER 146: QUESTIONS & ANSWERS

146.1. A 42-year-old woman presents after ingesting an unknown number of pills in a suicide attempt. She does not know the name of the medication she ingested but knows it is an antidepressant. She denies taking any co-ingestants. Currently, she has no complaints; her vital signs, physical examination findings, and electrocardiogram (ECG) are normal. To receive a psychiatric evaluation, she must be transferred off-site. How long should she be observed in the emergency department before transfer to a psychiatric facility?

A. 1 hour
B. 2 hours
C. 6 hours
D. 12 hours

Answer: C. The most dangerous class of antidepressants is the cyclic antidepressants. Typically, peak plasma concentrations and therefore peak effect occur in 2 to 4 hours. However, in overdose, the anticholinergic effects of these agents may result in delayed gastric emptying and delay peak absorption to 6 hours. Most serious signs and symptoms occur within 30 to 60 minutes of ingestion. If the patient has tachycardia or seizure or decreased level of consciousness at 6 hours, she should be admitted for medical observation. If any of these pills were a monoamine oxidase inhibitor (MAOI), however, the patient should be admitted to the hospital for 24 hours.

146.2. After sinus tachycardia, what is the most common electrocardiographic abnormality seen in cyclic antidepressant overdose?

A. Left bundle branch block
B. PR prolongation
C. QRS prolongation
D. QT prolongation
E. Right bundle branch block

Answer: C. After sinus tachycardia, QRS prolongation of more than 100 milliseconds is the most common specific finding and results from sodium channel–blocking effects of the cyclic antidepressant. Prolonged PR and QT intervals, as well as a right bundle branch block, can also occur but are less common.

146.3. Which of the following treatment options would be the most appropriate to consider in the awake, asymptomatic

patient who presents within 1 hour of a large overdose of a tricyclic antidepressant (TCA)?
A. Activated charcoal
B. Endotracheal intubation
C. Gastric lavage
D. Physostigmine
E. Sodium bicarbonate

Answer: A. Physostigmine should never be prophylactically administered and its use in TCA overdose is generally considered contraindicated, particularly in patients with bradycardia, A-V block, and seizures related to the overdose. Sodium bicarbonate should not be prophylactically administered either, but it should be administered as an intravenous (IV) bolus for patients with intraventricular conduction delay and QRS widening. Endotracheal intubation is indicated for patients with significant central nervous system (CNS) depression who are not able to protect their airway. Gastric lavage is not routinely indicated. Activated charcoal can be considered in an awake individual. It should not be "forced" on someone who will not voluntarily drink it (eg, by placement of a nasogastric tube for the purpose of administering charcoal) because of the increased risk of aspiration and subsequent charcoal pneumonitis.

146.4. A 23-year-old man presents after an ingestion of a cyclic antidepressant. His initial vital signs are normal. During your initial evaluation, the patient begins to seize. Which agent should be administered first?
A. Lorazepam
B. Phenobarbital
C. Phenytoin
D. Propofol
E. Valproic acid

Answer: A. Lorazepam or any other benzodiazepine is the first-line treatment of toxin-induced seizures. Intravenous phenytoin can increase the incidence of ventricular tachycardia and is not generally effective in controlling toxin-induced seizures. Phenobarbital and propofol are effective but take longer to give and typically are used after benzodiazepines. Valproic acid is not likely to be effective.

146.5. A 57-year-old woman presents with altered mental status. A friend states that the patient takes antidepressant medications and has recently been complaining of symptoms of an upper respiratory tract infection. The patient is noted to have a temperature of 39.2° C and a pulse of 135 beats/minute. Otherwise, her vital signs are within normal limits. On examination, she has a tremor, myoclonus, and diaphoresis. Which of the following is the most consistent with this presentation?
A. Anticholinergic syndrome
B. Cocaine intoxication
C. Cyclic antidepressant overdose
D. Neuroleptic malignant syndrome (NMS)
E. Serotonin syndrome

Answer: E. Symptoms of serotonin syndrome include altered mental status, agitation, ataxia, diaphoresis, diarrhea, hyperreflexia, hyperthermia, myoclonus, shivering, and tremor. Many of the symptoms are similar to symptoms caused by NMS and sympathomimetic overdoses; however, myoclonus is unique to the serotonin syndrome. Additional historical features consistent with the serotonin syndrome are the fact that the patient is taking an antidepressant, possibly a selective serotonin reuptake inhibitor (SSRI), and has likely added an over-the-counter "cold" medication. Many of these medications contain dextromethorphan, which also decreases serotonin reuptake and can precipitate the serotonin syndrome in patients taking SSRIs.

146.6. A 24-year-old man presents after taking an overdose of his antidepressant. He does not know the name of the drug. He has no complaints, and his vital signs and physical examination findings are normal. Soon after completing your evaluation, the patient experiences a tonic-clonic seizure. Which of the following antidepressants is most likely to produce seizures without other symptoms of severe toxicity?
A. Amitriptyline
B. Bupropion
C. Fluoxetine
D. Phenelzine
E. Trazodone

Answer: B. Bupropion can induce seizures even at therapeutic levels. Other adverse effects include tachycardia, tremulousness, hallucinations, and QRS prolongation. Cyclic antidepressants (amitriptyline), selective serotonin reuptake inhibitors (SSRIs; fluoxetine), and monoamine oxidase inhibitors (MAOIs; phenelzine) can also cause seizures but less frequently than bupropion and usually with other symptoms of serious intoxication such as central nervous system (CNS) depression or QRS prolongation.

146.7. A patient is prescribed a new medication that he takes each night. After 4 days, he is drowsy and noted to have orthostatic hypotension, nausea, vomiting, and priapism. What medication is most likely involved?
A. Amitriptyline
B. Bupropion
C. Fluoxetine
D. Phenelzine
E. Trazodone

Answer: E. Trazodone and nefazodone may cause orthostatic hypotension and lethargy. Priapism is a relatively unique complication of trazodone and is more common with therapeutic use rather than in acute overdose.

146.8. A patient presents after a substantial accidental overdose of her monoamine oxidase inhibitor (MAOI), which she confused with her megavitamin therapy. There is no need for psychiatric evaluation. She is asymptomatic and has normal vital signs and a normal physical examination. What is the appropriate disposition?
A. Admit to intensive care unit for a minimum of 24 hours of observation
B. Admit to ward for a minimum of 24 hours of observation
C. Discharge home
D. Observe for 6 hours, then discharge home
E. Observe for 12 hours, then discharge home

Answer: A. All patients who overdose on MAOIs should be admitted for at least 24 hours of observation because symptom onset is often delayed. In addition, the effects of overdose may be severe and require aggressive therapy.