ANTIDEPRESSANTS, OLD AND NEW A Review of Their Adverse Effects and Toxicity in Overdose

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PHARMACOLOGIC ADVANCES IN EMERGENCY MEDICINE

ANTIDEPRESSANTS, OLD AND NEW
A Review of Their Adverse Effects and Toxicity in Overdose

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Traditionally prescribed for depression, antidepressant drugs more recently have been found to have additional indications in the treatment of other psychiatric and medical disorders. New classes of antidepressants have been developed, with multiple mechanisms of action.[18] Although efficacious, they have widely varying therapeutic indices. Antidepressants are among the most common drugs taken in overdose.[76] Antidepressants are among the most common drugs taken in overdose.[76] [168] [173] The emergency physician must be familiar with the expected effects of overdose of the various drugs available. This article reviews the different antidepressants, their adverse effects, and toxic properties in overdose, with emphasis on developments since 1993.

ANTIDEPRESSANTS

The cyclic antidepressants (CA) and irreversible monoamine oxidase inhibitors (MAOI), the first classes of drugs developed for the treatment of depression, represent the older generation of agents. The newer antidepressants were developed and marketed in part based on a possible lower risk of toxicity in overdose than that seen with the cyclic antidepressants, and experience has shown this to be true. In addition, they lack several of the side effects of earlier classes. They have several mechanisms of action and are classified here according to their major activities.

Selective Serotonin Reuptake Inhibitors

The selective serotonin reuptake inhibitors (SSRI) are the prototype of the newer antidepressant drugs. They were designed to act on serotonin receptors, with few or no effects on H1-muscarinic, and alpha1-adrenergic receptors, and little inhibition of fast sodium channels. As a result, they are as efficacious as the CA in the treatment of depression with few serious side effects, especially those that are cardiovascular in nature. They act in a complicated manner at both the presynaptic
neuron and at the postsynaptic neuron. They inhibit reuptake of serotonin, but the net effect of all their actions is the release of more serotonin from the axon terminal.

Fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), and citalopram (Celexa) are the SSRIs in use today. Although generally more tolerable than older generation antidepressants, they do have adverse side effects that can limit their use. Nausea, vomiting, and diarrhea are seen frequently, with nausea being the most common side effect. A meta-analysis of controlled clinical trials found that nausea, diarrhea, anxiety, insomnia, agitation, nervousness, and anorexia occurred significantly more frequently with the SSRIs than with CAs. Constipation, dizziness, dry mouth, blurred vision, and sweating developed significantly less often. Fluoxetine can produce insomnia, nervousness, restlessness, and anxiety. Sexual dysfunction is also seen with the SSRIs ranging from decreased libido to impotence and failure to ejaculate. Although tolerability is better with SSRIs than with CAs, the frequency of discontinuation of the drugs because of adverse effects might not be lower.

Serotonin reuptake inhibitors are metabolized by the cytochrome P450 system. The half-lives of these agents range from 17 to 33 hours, with the exception of fluoxetine, the half-life of which is 1 to 4 days. The major metabolite of fluoxetine, norfluoxetine, has a half-life of 7 to 15 days and is the only metabolite of an SSRI to have a clinically meaningful effect on serotonin reuptake.

Interactions with other drugs metabolized by this system can be expected to occur, but the clinical significance of this varies and depends on the specific drugs involved. Interactions with warfarin have been studied. Several case reports have identified patients whose previously stable INR increased after fluoxetine was begun. Both sertraline and citalopram can cause small but clinically insignificant increases in prothrombin time (PT). Paroxetine can lead to clinically significant bleeding.

Fluoxetine has also been found to interact with lithium and phenytoin, leading to serious toxicity. Fluvoxamine was noted to increase the plasma level of carbamazepine, with resulting evidence of clinical toxicity.

Because of the theoretical risk of inducing a hypertensive emergency or serotonin syndrome, the use of sumatriptan and intravenous dihydroergotamine in patients taking SSRI is contraindicated.

On the basis of in vivo and in vitro studies, it is possible to rank the SSRI in terms of their probability of causing significant drug-drug interactions (Table 1) (Table Not Available). Sertraline is the SSRI least expected to cause significant interactions.

**TABLE 1 -- LIKELIHOOD THAT NEWER ANTIDEPRESSANTS WILL CAUSE CLINICALLY SIGNIFICANT INTERACTIONS WITH DRUGS METABOLIZED BY THE CYTOCHROME P450 SYSTEM**

(Not Available)


The abrupt cessation of an SSRI has been associated with a constellation of symptoms termed the "SSRI discontinuation syndrome" (Table 2). It can start as early as a day after the drug is stopped and gradually resolves over a period of up to 3 weeks. The syndrome occurs more frequently among agents with a shorter half-life than it does with drugs having a longer half-life (e.g., fluoxetine). Resuming the drug or another SSRI leads to immediate resolution of symptoms, but treatment with benzodiazepines probably does not work.

**TABLE 2 -- SYMPTOMS REPORTED WITH THE SSRI DISCONTINUATION SYNDROME**

<table>
<thead>
<tr>
<th>Dizziness</th>
<th>Paresthesias</th>
<th>Impaired short-term memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertigo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lightheadedness | Gait instability
---|---
Anxiety | Insomnia
Agitation | Nausea
Irritability | Fatigue
Lethargy | Shortness of breath
Headache | Aches
Vivid or increased dreaming | Chills

**Overdose**

One reason for the success of the SSRIs is their perceived safety in the overdose situation, especially when compared with the CAs. Experience has shown this to be true. The fatal toxicity index (FTI), which represents the number of deaths per million prescriptions, and is considered a rough indicator of toxicity, was calculated to be 2.7 to 13.4 for the individual SSRI and 19.1-231.8 for the CA in one study;[23] and 2.02 for the class of SSRIs versus 34.14 for CAs in another.[77] These overdoses were due to ingestion of one antidepressant, with or without alcohol. Selective serotonin reuptake inhibitors produce less cardiovascular and neurologic toxicity.[126] The mean hospital stay is shorter and the cost of hospitalization significantly less for overdoses with SSRIs.[36]

Many patients who overdose on SSRI are asymptomatic. This is frequently the case with isolated ingestions of fluoxetine, sertraline, and possibly paroxetine.[15] [17] [64] [91] [110] Symptoms, when they do occur, are usually self-limited and consist of tachycardia, drowsiness, tremor, nausea, and vomiting.[15] [22] [59] [61] [91] [96] [110] [117] [123] [124] Higher doses are more likely to produce seizures and cardiotoxicity (widened QRS and QTc intervals that respond to sodium bicarbonate infusion).[15] [18] [59] [65] [68] [69] [123] [124] Fluvoxamine can cause sinus bradycardia at either high or low doses.[2] [59] [95]

When taken as part of a multi-drug ingestion toxicity is again more severe.[15] [22] [61] [91] [96] [110] [117] Most patients develop symptoms; when alcohol is consumed with the SSRI, decreased level of consciousness is most likely to result.[15] Ingestions with other drugs have led to dysrhythmias, multiple seizures, and death.[49] [59] [102] [109] [123] [124]

Deaths have been reported with the SSRIs, most often in conjunction with the ingestion of multiple drugs.[59] [102] [109] [115] The serotonin syndrome is possible when SSRIs are ingested with other drugs affecting serotonin metabolism. CAs[102] and MAOs,[75] [112] [124] [131] [154] are the most likely agents to cause this, but it is possible in patients taking no other drugs.[117]

The mainstay of treatment is gut decontamination.[15] [22] [49] [61] [69] [91] [96] [110] [117] Seizures are usually brief and self-limited, and respond to benzodiazepines.[69] Cardiac dysrhythmias also are usually self-limited, resolving within 24 hours.[123] [124] If treatment is necessary, they respond to standard treatment.[123] [124] [142] Emergency department (ED) treatment should consist of activated charcoal, with or without gastric lavage. If QRS prolongation is noted, sodium bicarbonate or hypertonic saline is useful.[65] [124]

**Serotonin, Norepinephrine, and Dopamine Reuptake Inhibitors**

Venlafaxine (Effexor) has been in use in the United States for several years. Its pharmacology is dose dependent. At low doses it acts similarly to the SSRI. At medium to high doses it inhibits norepinephrine reuptake and at high doses it weakly inhibits dopamine reuptake.[53] [158]

At therapeutic doses venlafaxine has an adverse event profile similar to the SSRIs.[108] [147] Nausea, insomnia, dizziness, somnolence, constipation, sweating, and dry mouth occur more frequently than with placebo. Tolerance to nausea develops with continued use. Like the SSRIs, it has low affinity for H1-histamine, and antimuscarinic and alpha1-adrenergic receptors, so that it is almost devoid of these side effects.[53]

One adverse effect associated with venlafaxine use is a mild elevation of diastolic blood pressure. This occurs in up to 13% of
patients, a rate similar to that seen with CA, and appears to be dose related, most commonly with doses greater than 200 to 300 mg/day. Patients already on antihypertensive medications do not experience a further rise in their blood pressures.

Sexual dysfunction similar to that seen with SSRI has been noted. A discontinuation syndrome similar to that seen with the SSRI has also been noted (see Table 2). As many as 78% of patients are affected, and as a result, a gradual tapering of the drug is recommended.

Not much is known about the metabolism of venlafaxine. It appears to be a weak inhibitor of CYP2D6, but toxicities from interactions with drugs metabolized by the cytochrome P450 system have not yet been reported. Use of the antidepressant with MAOIs has resulted in the serotonin syndrome.

Overdose

Experience in the overdose situation is beginning to accumulate. The most commonly reported symptoms are sinus tachycardia and decreased level of consciousness. Symptoms, when they occur, develop before or during ED evaluation. Brief and self-limited seizures are seen and can be treated with benzodiazepines. Hypotension requiring intravenous fluids and vasopressors has been reported. Most patients survive the overdose, but death has occurred after presumed massive ingestions. A mixed overdose with lamotrigine led to the development of ventricular tachycardia responsive to lidocaine (121), and the serotonin syndrome has been reported after isolated overdose. Although most people survive, significant toxicity is possible. Death is expected to be the exception, but larger studies are needed to assess its safety fully.

Norepinephrine and Dopamine Reuptake Inhibitor

Bupropion (Wellbutrin) is currently the only antidepressant in this class. It does not affect the serotonin system; beyond that, its mechanism of action is poorly understood.

The seizure potential of bupropion at therapeutic doses appears to be equal to that of CA, and the risk increases in patients given doses greater than the recommended 450 mg/day maximum, single doses of greater than 450 mg, those with bulimia, and those predisposed to seizures.

Side effects are similar to those for the SSRI with the exception of the absence of substantial sexual dysfunction. In fact, it can be useful in the treatment of SSRI-induced sexual dysfunction. It appears to be safe in patients with heart disease.

Interactions of bupropion with other drugs are not well described. Carbamazepine appears to enhance its metabolism, whereas valproic acid can decrease clearance of metabolites. Information on interaction with warfarin is not available.

Overdose

A study of 58 bupropion-only overdoses found that most patients develop symptoms, but these symptoms resolved with minimal specific treatment. Lethargy, tremors, and seizures were observed in 41%, 24%, and 21% of patients, respectively. Seizures began a mean of 3.7 hours after ingestion, and responded to either benzodiazepines or phenytoin. Cardiotoxicity was limited to sinus tachycardia. In only one report were more serious ECG abnormalities noted: QRS and QTC intervals were prolonged in one patient, and they normalized in under 48 hours without treatment. Although deaths have been associated with bupropion overdose, supportive care usually is all that is needed. Bupropion appears to be relatively safe in overdose.

Noradrenergic and Specific Serotonergic Antidepressants

Mirtazapine (Remeron) and milnacipran are the antidepressants in this class. Mirtazapine acts by inhibiting presynaptic alpha₂-receptors. alpha₂-Receptor antagonism disinhibits both serotonin and norepinephrine transmission. In addition, it blocks the serotonin-2 and serotonin-3 receptors, responsible for the anxiety-stimulating and gastrointestinal side effects seen with the SSRIs. Milnacipran prevents the reuptake of norepinephrine and serotonin and has no effects on the postsynaptic receptors.
Milnacipran is associated with a lower incidence of nausea and anxiety than the SSRI, but a higher incidence of dysuria, headache, and dry mouth.\(^{[101]}\)\(^{[107]}\)\(^{[125]}\)\(^{[169]}\) Mirtazapine's side effect profile is similar to the SSRIs, with dry mouth, fatigue, and drowsiness being the most common symptoms.\(^{[106]}\) It is, however, associated with a greater incidence of weight gain.\(^{[169]}\) Anticholinergic and sedative effects are seen less often than with CAs.\(^{[66]}\)\(^{[88]}\)\(^{[157]}\)

Little is known about their metabolism or potential for interaction with other drugs, except that these drugs appear to be weak inhibitors of the cytochrome P450 system.\(^{[116]}\) The serotonin syndrome was reported in a patient who was switched from fluoxetine to mirtazapine.\(^{[12]}\) More studies with this class of antidepressant are necessary to elucidate its drug-drug interaction profile.

**Overdose**

Given that few overdoses have been reported, both mirtazapine and milnacipran appear to be safe.\(^{[20]}\)\(^{[60]}\)\(^{[80]}\)\(^{[107]}\)\(^{[139]}\) With ingestions of up to 30 times the maximal recommended dose, sedation and drowsiness have occurred, requiring intubation in some cases. Cardiac conduction effects and seizures have not been reported. More experience with overdose is necessary before the full toxic potential becomes known.

**Serotonin 2 Receptor Antagonism With or Without Serotonin Reuptake Inhibition**

Like the SSRIs, nefazodone (Serzone) blocks the reuptake of serotonin, but it differs in that it inhibits the serotonin-2 receptor, whereas the SSRIs stimulate it. It also has some norepinephrine reuptake blockade capabilities and minimal alpha\(^{1}\) -adrenergic receptor antagonism.\(^{[16]}\) The mechanism of action of trazodone (Desyrel) is complex and not fully elucidated. Like nefazodone, it is a potent inhibitor of the serotonin 2 receptor, but it appears to have little effect on serotonin or norepinephrine reuptake.\(^{[5]}\) It also has high affinity for the alpha\(^{1}\) -receptor, which is probably responsible for some its side effects.\(^{[53]}\)

Consistent with the SSRI, nefazodone has a good side effect profile. Nausea and somnolence, followed by dry mouth, dizziness, constipation, asthenia, light headedness, and blurred vision are the most common symptoms seen.\(^{[50]}\)\(^{[143]}\) Only nausea and light headedness occur more often than with imipramine. Tolerance develops to these side effects with continued use. Discontinuation because of side effects is similar to fluoxetine and less than with CAs.\(^{[50]}\)\(^{[143]}\) Sexual dysfunction appears to be less common than with other antidepressants.\(^{[133]}\)\(^{[143]}\)

Trazodone can be very sedating. In addition, postural hypotension, light headedness, and dizziness occur frequently. Gastric upset and lack of energy are also common, but anticholinergic effects are uncommon.\(^{[72]}\)\(^{[75]}\) Trazodone has been associated with nonsustained ventricular tachycardia and other dysrhythmias\(^{[75]}\)\(^{[164]}\) and should be used cautiously in patients with cardiovascular disease. Priapism has occurred in male patients of all ages taking trazodone.\(^{[167]}\) Its incidence is 1/1,000 to 1/10,000. The drug should be stopped by any patient who reports an increased frequency or duration of erections, or inappropriate erections.\(^{[167]}\) The serotonin syndrome has been reported in patients taking trazodone with other drugs known to precipitate it.\(^{[64]}\)\(^{[113]}\)\(^{[138]}\)

Nefazodone and trazodone are metabolized by the cytochrome P450 system. Nefazodone can inhibit the enzyme involved in the metabolism of astemizole, cisapride, and terfenadine and is contraindicated when these drugs are used.\(^{[143]}\) Nefazodone can increase the serum carbamazepine to toxic levels.\(^{[7]}\) Clinically insignificant increases in digoxin levels also have been reported with nefazodone,\(^{[37]}\) and in one patient, digoxin toxicity could have resulted from trazodone use.\(^{[136]}\) No change in levels of warfarin,\(^{[149]}\) cimetidine,\(^{[11]}\) phenytoin,\(^{[103]}\) or theophylline\(^{[38]}\) have been noted with nefazodone, but trazodone could have led to a subtherapeutic protime in a patient on warfarin.\(^{[7]}\)

**Overdose**

Experience with nefazodone in overdose is limited. In preclinical trials, seven reports of overdose were noted, with the maximal amount ingested 11.2 g.\(^{[143]}\) All patients recovered with supportive care. One seizure was reported in a patient who also ingested methocarbamol and ethanol. In another report,\(^{[57]}\) a patient who ingested 3 g was asymptomatic. Serotonin syndrome was noted in a patient taking nefazodone who overdosed on valproic acid.\(^{[19]}\) Further experience will delineate its toxic potential.
Trazodone is relatively safe in overdose. It has a FTI of 7.8 to 13.6;[23] [77] which is lower than the CAs. Reports of over 300 overdoses identified no deaths in trazodone-only ingestions.[58] [78] Drowsiness, ataxia, nausea, vomiting, and dry mouth were the most commonly seen symptoms. Supportive care is generally all that is required.

**Monoamine oxidase inhibitors**

Monoamine oxidase (MAO) is an enzyme involved in the metabolism of biogenic amines (e.g., norepinephrine, epinephrine, dopamine, serotonin) and xenobiotic amines (e.g., tyramine, ephedrine, phenylephrine).[56] Two subtypes exist: MAO-A and MAO-B, each with a different spectrum of activity. MAO-A has a higher affinity for norepinephrine, epinephrine, and dopamine, whereas MAO-B has a higher affinity for xenobiotic amines. Serotonin and tyramine are metabolized by both. The original MAOs were both nonspecific and irreversible in their inhibition. They have been in use for decades, with a well-known spectrum of adverse effects, drug-drug interactions, and toxicities in overdose. More recently, a new, reversible inhibitor of MAO-A has been marketed, moclobemide. It has little affinity for the MAO-B isozyme,[33] and these properties could give it several advantages over the older generation of MAOIs.

The focus of this review is on moclobemide. One of the major disadvantages of the older, irreversible MAOIs is the risk of a hypertensive crisis after eating foods rich in tyramine. Tyramine is a sympathomimetic amine that exerts its effect on blood pressure by displacing norepinephrine from the neuron.[56] As this effect is usually clinically important only in patients taking older MAOIs, these patients have had to follow strict dietary limitations. Research with moclobemide suggests this is not necessary when taking this drug. No tyramine-related hypertensive reaction was seen in 2300 patients taking moclobemide without dietary restrictions in one study.[163] The amount of tyramine necessary to increase systolic blood pressure by 30 mm Hg is much greater than that with phenelzine,[153] and tranylcypromine,[180] although slightly less than placebo.[178] This amount (150 mg) is unlikely to be consumed in a normal meal.[180] The effect wears off quickly, and by 3 days after the last dose of moclobemide, there is no response.[153]

Studies of tolerability have found moclobemide to be very well tolerated. Dizziness, nausea, and insomnia occur more frequently than with placebo,[79] and insomnia and headaches are seen more often than with CAs. Nausea occurs one third as often as with the SSRIs,[3] but the combined use of moclobemide with an SSRI was associated with a large number of adverse effects.[74]

Hypertensive crisis and the serotonin syndrome are known to occur when the irreversible, nonspecific MAOIs are taken along with other drugs, and as a result, many medications are contraindicated in patients taking these (Table 3) (Table Not Available) . Studies with moclobemide are generally favorable. No interactions were found between moclobemide and norepinephrine or isoproterenol, and only negligible interactions with phenylephrine.[179] Moclobemide with antihypertensives did not cause postural hypotension, and no interaction was noted with digoxin or benzodiazepines. Cimetidine, however, increased moclobemide levels to twice that of controls.[179] It is probably wiser to use a different H2-blocker in these patients. A possible interaction with warfarin exists, but no formal study has been published.[41] When one is treating patients taking moclobemide it is probably safer to avoid the use of the drugs that are contraindicated with the older MAOIs that have not yet been studied.

**TABLE 3 -- DRUGS CONTRAINDICATED WITH MONOAMINE OXIDASE INHIBITORS**

(Not Available)


**Overdose**

Moclobemide seems to have a wide therapeutic index and appears safe in overdose, although fewer than 50 cases have been reported. Only one death possibly caused by moclobemide alone has been reported (trifluoperazine and diazepam were also present at subtherapeutic levels).[26] Nausea, vomiting, somnolence, fatigue, agitation, and tachycardia have been noted in other cases.[83] [111] Conservative treatment using activated charcoal with or without gastric lavage has been given, and patients generally recover within 24 hours. When other substances are coingested, however, toxicity is increased. Fatality is much more likely, and reported deaths appear to be due to the serotonin syndrome.[52] [75] [131] [154] Thus, patients with moclobemide-only ingestions are expected to do well with only supportive care, whereas patients with coingestions are at higher risk for an adverse outcome.
**Cyclic Antidepressants**

Cyclic antidepressants have been marketed for several decades:

- Tricyclics
- Secondary amines
  - Desipramine
  - Nortriptyline
  - Protriptyline
- Tertiary amines
  - Amitriptyline
  - Clomipramine
  - Doxepin
  - Imipramine
  - Trimipramine
- Dibenzoxazepine derivative
- Amoxapine
- Tetracyclics
- Maprotiline

They are the standard to which newer antidepressants are compared, and they have a well-known side effect profile. Their potential for serious toxicity in overdose was one of the factors that led to the development of the newer antidepressants, such as the SSRIs. Two of the newer antidepressants, introduced in the 1980s, amoxapine and maprotiline, are similar to the earlier CAs in terms of their structures and toxicities,[75] and are considered in this section.

Cyclic antidepressants have varying abilities to block the reuptake of norepinephrine and serotonin.[53] They also block muscarinic cholinergic receptors, H1-histamine, and alpha1-adrenergic receptors to varying degrees.[53] This leads to their multiple side effects (Table 4). Because of their effects on the cardiovascular system, they are not the preferred drugs for patients with preexisting heart disease.[24]

### TABLE 4 -- SIDE EFFECTS OF CYCLIC ANTIDEPRESSANTS AT THERAPEUTIC DOSES

<table>
<thead>
<tr>
<th>Muscarinic/anticholinergic</th>
<th>Receptor Blockade</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>H1-histamine</td>
<td>alpha1-adrenergic</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>Sedation</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td></td>
<td>Drowsiness</td>
<td>Sedation</td>
</tr>
</tbody>
</table>
Constipation
Urinary retention
Sinus tachycardia
Short-term memory impairment

**Multiple Receptors or Receptor Unknown**
Cardiac conduction abnormalities
Seizures
Induction of mania or hypomania in bipolar patients or patients with family history

Although CA are metabolized by the cytochrome P450 system, they are not potent inhibitors of it, and clinically important interactions are not generally observed. Although the serotonin syndrome has occurred in patients using both CA and newer antidepressants (see sections on Newer Antidepressants), their combined use is becoming clinically accepted. A 2-week washout period is needed to prevent serious interactions when switching a patient from a MAOI to a CA.

**Overdose**

Cyclic antidepressants are extremely dangerous in overdose. They have a FTI of 34.1 deaths per million prescriptions (compared to a FTI of 13.5 for MAOI and 2.0 to 6.2 for SSRIs and "atypical" antidepressants). Toxicity is believed to be due to their effects on the cardiovascular and neurologic systems. Patients become symptomatic very quickly after an overdose, and the mean time from arrival at the hospital to death can be as little as 5.4 hours. Many or few symptoms can develop during the course of the overdose.

Much research has gone into attempting to predict the severity of the overdose and the risk of complications. This discussion focuses on recent advances.

The usefulness of serum CA levels has been debated. For practical purposes, they are usually not available for the emergency physician’s use, but in centers where they are, they can be helpful in assessing a patient’s risk or in managing the patient's further hospital care.

Much of the effort toward assessing severity has been directed at the ECG. Traditionally, a QRS duration greater than 100 msec and a terminal 40-msec frontal plane axis greater than 120° have been considered the most reliable indicators of serious toxicity. Recent data tend to support this in adults. The terminal 40-msec axis has poor sensitivity in predicting complications in children. Although the QTc interval, terminal 40-msec axis, QRS duration, terminal R wave height in lead AVR, and the ratio of the heights of the R to S waves in AVR are all associated with an increased risk for major complications, the ECG is not sensitive nor specific enough to be used alone. Decreased variation in the R-R interval was noted in patients taking CAs, and this can be useful in assessing the overdose patient, provided that more studies support this and heart rate analysis becomes more easily obtainable.

Currently accepted care of the CA overdose patient is to discharge from the ED a patient who has been observed for 6 hours; has no cardiovascular, neurologic, or respiratory signs or symptoms of poisoning; and has bowel sounds. A prospective study of these criteria (without including bowel sounds) found that all of the patients without any of these criteria were free of complications during their hospital stay. Positive predictive value for these criteria was 34%.

Classic treatment of severe CA overdose has involved reducing and reversing toxicity. Recent research has focused on a continuing evaluation of current modalities, and a search for new methods of treatment.

Outcome does not appear to be altered by the use of gastric lavage, and simply giving the patient activated charcoal can be adequate. Conversely, the use of hypertonic sodium bicarbonate was associated with a shorter ICU and hospital stay.

Glucagon (10 mg IV, then 10 mg IV over 6 hours) was reported to increase blood pressure and decrease QRS intervals in a patient who was not responding to sodium bicarbonate. The use of extracorporeal circulation has been reported in two
patients. One, an 18-month-old child, survived; the other, a 37-year-old woman, died 4 weeks later of complications. CA-specific antibodies are in development and have been shown to be helpful in CA overdoses in rats.

SUMMARY

The newer antidepressants are as efficacious as the older agents in the treatment of depression. They have a side effect profile that is different from the older drugs and are generally better tolerated. Drug-drug interactions do exist with some of these agents and can usually be predicted from knowledge of their metabolism. When taken in overdose as the sole agents they are rarely fatal; seizures, nausea, vomiting, decreased level of consciousness, and tachycardia are common. In combination with other drugs, toxicity can be more severe. The serotonin syndrome can occur with many of these drugs, and the emergency physician must be vigilant in the evaluation of the overdose patient. CAs and older MAOIs are still in use and remain dangerous when taken in overdose. Patients asymptomatic after a period of observation in the ED usually can be discharged after psychiatric evaluation, when it is required.

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