

SSRI Safety in Overdose

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Background: The morbidity and mortality caused by tricyclic antidepressant (TCA) overdose are well recognized. Among newer antidepressants, the selective serotonin reuptake inhibitors (SSRIs) are thought to be safer in overdose. This study was designed to describe the signs, symptoms, and mortality associated with SSRI overdose. **Method:** English-language articles identified through MEDLINE (1985 through 1997), and case reports from the American Association of Poison Control Centers (AAPCC) (1987 through 1996) and United States Food and Drug Administration (FDA) adverse event database (through 1997) that describe findings of fatal and nonfatal overdoses involving SSRIs alone or in combination with other ingestants were reviewed. **Results:** SSRI antidepressants are rarely fatal in overdose when taken alone. During the 10 years that SSRI antidepressants have been marketed, there have been remarkably few fatal overdoses reported in the literature or to the AAPCC or FDA involving ingestion only of an SSRI. Moderate overdoses (up to 30 times the common daily dose) are associated with minor or no symptoms, while ingestions of greater amounts typically result in drowsiness, tremor, nausea, and vomiting. At very high doses (> 75 times the common daily dose), more serious adverse events, including seizures, electrocardiogram (ECG) changes, and decreased consciousness may occur. SSRI overdoses in combination with alcohol or other drugs are associated with increased toxicity, and almost all fatalities involving SSRIs have involved coingestion of other substances. **Conclusion:** The SSRI antidepressants are far safer than the TCAs in overdose. There is no apparent difference among SSRIs with respect to overdose safety.

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The lethality of tricyclic antidepressant (TCA) overdose is well established. In fact, clinicians and researchers first became aware of the deleterious cardiovascular effects of tricyclics because patients who took overdoses of TCAs died a cardiac death, from either heart block or arrhythmias. Not only is TCA overdose associated with significant morbidity and mortality, but also there is a relatively narrow range between therapeutic and toxic levels of drugs. Significant symptoms can result from ingestion of as little as 3 to 4 times the therapeutic daily dose. Not surprisingly, there was a time when tricyclic overdose resulted in thousands of deaths per year.

Despite the robust efficacy of tricyclic antidepressants, overdose fatality, along with anticholinergic side effects,

weight gain, orthostatic hypotension, and adverse impact on preexisting cardiovascular disease, have limited the clinical utility of the TCAs.

The selective serotonin reuptake inhibitors (SSRIs) have documented efficacy, in most circumstances, comparable to the tricyclics.¹⁻⁵ However, collectively the SSRIs are generally better tolerated than the tricyclics, and although the SSRIs are not without problematic side effects (e.g., anorgasmia), they do not have anticholinergic effects nor do they induce weight gain. Perhaps most importantly, the SSRIs do not have adverse cardiovascular effects and appear vastly safer than the tricyclics when taken in overdose.

The purpose of this article is to review the data available on SSRI overdose. There are significant problems inherent in reviewing overdose data:

1. Most overdoses are not of a single drug, but rather multiple substances, most often antidepressants in combination with benzodiazepines and/or alcohol. Thus, the attribution of symptoms or mortality to a single agent is not possible.
2. For many reasons, the reporting of overdoses is sporadic, and so it is impossible to establish true numerators and denominators with respect to rates of symptoms, severe adverse events, or mortality.
3. Reports of overdose often combine accidental ingestion by infants or young children with intentional overdose by adults.

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- Most often, it is only possible to estimate the amount of medication ingested in an overdose.
- The data recorded in an overdose situation are not standardized, so there rarely are complete data on the consequences of the overdose.

Thus, there are obstacles to the definitive characterization of the symptom and mortality profile of a medication when taken in overdose, and it is especially difficult to make comparisons between medications. Nonetheless, there are sufficient data available to describe the impact of an SSRI overdose.

METHOD

A MEDLINE search was conducted for the period 1985 through 1997 for all English-language reports (using keywords including *overdose*, *poisoning*, *toxicity*, and *suicide*) of overdose experience with any of 5 SSRIs—fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram. Published articles describing the safety experience during premarketing development and FDA-approved labeling for each of these drugs also were reviewed.

Additionally, the annual report of the AAPCC Toxic Exposure Surveillance System was reviewed for the years 1987–1996,^{6–15} and individual case reports for each fatality involving ingestion of an SSRI alone were obtained from the AAPCC. Through the Freedom of Information Act, all reports contained in the FDA's database of spontaneously reported adverse events with fluoxetine, sertraline, paroxetine, and fluvoxamine were requested. This database was then searched for keywords including *overdose*, *poisoning*, *toxicity*, and *suicide*, and individual case reports were obtained.

Cases drawn from the AAPCC's annual compilation of fatal overdoses and the FDA's database of adverse drug reactions have been submitted voluntarily directly to the AAPCC, the FDA, or to a drug manufacturer, both by consumers and members of the health profession. Thus, the information has been spontaneously reported, and not verified, scientifically or otherwise, as to a cause and effect relationship.

Due to the spontaneous nature of the reporting systems, the cases reported to the AAPCC and the FDA are in many instances incomplete, making it difficult to rule out the involvement of other drugs or alcohol. In many cases, neither a specific cause of death (other than "drug overdose") nor pathology results are included in the reports.

Additionally, reported overdoses comprise both accidental ingestions (typically involving young children who may ingest only a small amount of drug) as well as overdoses with clear suicidal intent. It also is possible that some overlap in cases reported to each organization may have occurred. Finally, the absolute incidence of fatalities associated with overdoses of SSRIs alone cannot be cal-

Table 1. Fatal Overdoses Reported to AAPCC or FDA Involving Ingestion of an SSRI Alone*

Drug	Source	No. of Fatalities	Dose Ingested ^a (mg)	Plasma Drug Concentration ^a (ng/mL)
Fluoxetine	FDA	34	260–6000	Fluoxetine: 1300–7000 Norfluoxetine: 800–4152
Sertraline	AAPCC	2 ^b	Unknown	Unknown
	FDA	8	1100	Sertraline: 672–700 Desmethylsertraline: unknown
Paroxetine	AAPCC	1 ^b	Unknown	Unknown
	FDA	6	530–600	Paroxetine: 1000
Fluvoxamine	FDA	1	Unknown	Unknown

*Abbreviations: AAPCC = American Association of Poison Control Centers, FDA = U.S. Food and Drug Administration.

^aNot all case reports contained information on ingested dose or plasma concentrations. Ranges are given if more than one report contained such information.

^bOne case reported to the AAPCC involved an overdose with unknown amounts of both sertraline and paroxetine.

culated, as both the numerators and denominators are uncertain.

Because citalopram has only recently been approved for marketing in the United States, data on citalopram overdose situations come from non-FDA sources, such as the Swedish Poisons Information Centre.

Requests also were made to the manufacturers of each of the drugs for data on file regarding overdose experience, to which several (SmithKline Beecham Pharmaceuticals and H. Lundbeck A/S) responded in detail.

RESULTS

During the period 1985 through 1997, there were only 6 verified overdose deaths involving ingestion of an SSRI alone, 2 published in the literature^{16,17} and 4 confirmed by the drugs' manufacturers. An additional 51 cases of fatal overdoses with an SSRI in which no other substances were said to have been ingested have been reported to the AAPCC or FDA; these are summarized in Table 1. A detailed description of the experience with each drug follows.

FLUOXETINE

Clinical Trials

Two deaths were reported by the manufacturer among 38 reports of fluoxetine overdose with or without concomitant drugs or alcohol during clinical trials.¹⁸ One death involved 1800 mg of fluoxetine combined with an undetermined dose of maprotiline. Plasma concentrations of fluoxetine and maprotiline were 4570 ng/mL and 4180 ng/mL, respectively. The other fatality involved 3 drugs, resulting in plasma concentrations of 1930 ng/mL for fluoxetine, 1100 ng/mL for norfluoxetine, 1800 ng/mL for codeine, and 3800 ng/mL for temazepam.

Nausea and vomiting were the most frequently reported symptoms associated with the remaining nonfatal fluoxetine overdoses that occurred during clinical trials conducted by the manufacturer.¹⁸ Other prominent symptoms reported in overdose situations were agitation, restlessness, hypomania, and other signs of CNS excitation. One patient who reportedly ingested 3000 mg of fluoxetine (150 times the common daily dose of 20 mg, almost 40 times the maximum recommended daily dose of 80 mg) experienced 2 grand mal seizures that remitted spontaneously without specific anticonvulsant treatment.¹⁸

Published Reports

Case series. During the 10 years that fluoxetine has been available for the treatment of depression, several prospective studies as well as a number of case reports have been published describing the effects of fluoxetine in acute overdose situations. For example, 4 studies reported findings on 106, 44, 234, and 16 fluoxetine overdoses in 1990, 1990, 1992, and 1997, respectively.¹⁹⁻²² These cases included 229 fluoxetine overdoses in which coingestants were reported, and 137 in which patients reported that fluoxetine was ingested alone. Of the cases in which fluoxetine was ingested alone, at least 48 patients experienced no symptoms. The largest ingestion of fluoxetine among asymptomatic patients was 1500 mg (75 times the common daily dose of 20 mg). The most frequent symptoms experienced by those who ingested fluoxetine alone were tachycardia, and lethargy or drowsiness. Additional symptoms included QT prolongation, tremor, nausea, and vomiting.

With the exception of gastric decontamination, treatment beyond general supportive care was not required for the majority of patients who ingested fluoxetine alone. Most were treated in the emergency department only, and many were subsequently transferred to a psychiatric unit, whereas others were admitted to a medical floor for further observation or treatment. Patients recovered without sequelae.

The potential for serious toxicity appears higher in cases involving coingestion of fluoxetine with alcohol or other drugs. In the prospective study of 234 overdoses,²¹ patients ingesting fluoxetine and alcohol or other drugs were more likely to be symptomatic than those ingesting fluoxetine alone; 5 of 147 patients ingesting other drugs in combination with fluoxetine developed cardiac arrhythmias, 3 developed seizures, 3 suffered respiratory arrest, and 3 experienced dystonic reactions.

Case reports. Feierabend²³ described a 4-year-old girl who was believed by her family to have ingested 700 mg (approximately 43 mg/kg) of her mother's fluoxetine, resulting in plasma levels of 3080 ng/mL and 459 ng/mL of fluoxetine and norfluoxetine, respectively. She experienced sinus tachycardia, some degree of psychomotor agitation and dyskinesia, and an episode of unconsciousness,

all of which were transient, and subsequently resolved without sequelae.

Braitberg and Curry²⁴ reported that a 15-year-old girl ingested 900 mg of fluoxetine and experienced a seizure 9 hours after ingestion that remitted spontaneously. She then recovered fully.

Another case report²⁵ describes a 13-year-old boy with Tourette's syndrome and obsessive-compulsive disorder who ingested approximately 1880 mg of fluoxetine and had a generalized tonic clonic seizure 3½ hours later that remitted spontaneously. Plasma samples taken 15 hours after ingestion revealed a fluoxetine level of 1142 ng/mL and a norfluoxetine level of 322 ng/mL.

Only one case of a pure fluoxetine overdose resulting in fatality has been reported in the literature.¹⁶ In this case, a 58-year-old woman with a history of suicide attempts was found dead at home. She had 6000 mg of fluoxetine available to her at the time of her death, as she reportedly had obtained several prescription refills in the few weeks before her death. Postmortem blood levels were 6000 ng/mL and 5000 ng/mL of fluoxetine and norfluoxetine, respectively.

Rohrig and Prouty²⁶ report that a 28-year-old woman died after ingesting an overdose of fluoxetine and ethanol. Heart blood levels of ethanol were measured at 48 mmol/L and fluoxetine and norfluoxetine blood levels were 800 ng/mL and 650 ng/mL, respectively.

Graudins et al.²⁷ describe a case in which a patient ingested an overdose of fluoxetine and acetaminophen, resulting in plasma concentrations of 901 ng/mL fluoxetine, 451 ng/mL norfluoxetine, and 174 mg/L acetaminophen. The patient presented with lethargy and cardiac conduction delays (QRS complex of 110 milliseconds, QTc interval of 458 milliseconds) and experienced a seizure 16 hours after ingestion. After therapy with intravenous sodium bicarbonate therapy, the QRS complex narrowed to 90 milliseconds, and the patient subsequently recovered fully.

AAPCC Reports

There have been 7 fatalities resulting from overdose of fluoxetine with concomitant drugs or ethanol reported by the AAPCC since the release of fluoxetine in 1987.

FDA Reports

Since the release of fluoxetine in the United States in 1987, 34 fatal overdoses have been reported to the FDA in which fluoxetine was the only documented ingestant (see Table 1). Many of the reports are incomplete and lack information regarding exact cause of death, dose of fluoxetine ingested, and resulting plasma levels. However, 7 case reports listed plasma levels of fluoxetine and norfluoxetine ranging from 1300 to 7000 ng/mL and from 800 to 4152 ng/mL, respectively. None of these 7 case reports listed dosage ingested or exact cause of death.

Thirty-five nonfatal overdoses in which fluoxetine was the only reported ingestant resulted in serious adverse events. Of these, 30 cases involved patients who experienced convulsions (dose range, 100 mg–4000 mg). The remaining 5 case reports involved patients who experienced other serious adverse events such as cardiac arrest, torsades de pointes, QT prolongation, and ECG changes.

SERTRALINE

Clinical Trials

During premarketing clinical trials with sertraline, there were 79 reports of nonfatal overdoses, 28 of which were overdoses of sertraline alone.¹⁸ The reported overdoses ranged from 500 mg to 6000 mg (10 to 120 times the recommended starting dose of 50 mg/day, 2.5 to 30 times the maximum recommended daily dose of 200 mg), resulting in plasma sertraline concentrations ranging from < 5 ng/mL to 554 ng/mL. Resulting symptoms included drowsiness, nausea, vomiting, tachycardia, and ECG changes.

Ingestion of sertraline alone did not result in fatalities during clinical trials; there were 4 deaths involving overdoses of sertraline in combination with other drugs.¹⁸

Published Reports

In 1996, Klein-Schwartz and Anderson²⁸ performed a 2-year retrospective and a 6-month prospective study to characterize the toxicity of sertraline-only overdose. Of 52 patients who ingested up to 3500 mg of sertraline alone, 34 (11 children and 23 adults) experienced no symptoms (adult dose range, 250 mg–1800 mg). Those adults with symptoms (dose range, 250 mg–3500 mg) experienced lethargy, tachycardia or bradycardia, vomiting, and abdominal pain. Treatment consisted of supportive care including monitoring of vital signs and gastric decontamination.

Lau and Horowitz²⁹ prospectively studied sertraline overdoses reported to 5 western regional poison control centers. Of 40 nonfatal overdoses reported (dose range, 50 mg–8000 mg), 17 were sertraline-only overdoses. The most common symptoms reported in the sertraline-alone overdoses were tremor, lethargy, and nausea. There were 23 cases of sertraline overdose that involved ingestion of other medications; 4 of these patients were asymptomatic, whereas others reported lethargy, nausea, and vomiting. All patients recovered.

Caracci³⁰ described a 32-year-old woman who ingested an overdose of nearly 4000 mg of sertraline and experienced tremors, dizziness, and nausea for the following 2 days, insomnia for the following week, and then recovered fully.

AAPCC Reports

The AAPCC has reported 4 fatalities resulting from sertraline overdose in combination with other drugs, and 1

case in which it is not known whether concomitant ingestants were involved (see Table 1). In this case, the emergency medical services crew found an empty bottle of sertraline next to the patient and brought her into the emergency department in cardiac arrest. She was pronounced dead after 15 minutes. No other information about this case is available, thus it is not known whether concomitant drugs or alcohol may have contributed to the fatality.

A sixth fatality involved a mixed overdose of sertraline and paroxetine (see Table 1). In this case, a 36-year-old woman was unresponsive upon arrival to the emergency department after ingesting unknown amounts of the 2 SSRIs. She remained unresponsive after being placed on a ventilator and administered naloxone. The patient remained comatose with fixed and dilated pupils, and expired within 24 hours. No other information was reported and no postmortem examination was performed. Thus, it is unclear whether this fatality involved coingestion of substances other than the 2 SSRIs.

FDA Reports

Since 1992, 8 fatal overdoses have been reported to the FDA in which sertraline was the only drug believed to have been involved (see Table 1). Although the data reported are incomplete, in 2 cases the blood concentrations of sertraline were recorded at 700 ng/mL and 672 ng/mL. The patient whose blood levels were measured at 700 ng/mL presented to the emergency room in cardiac arrest and died later that day. None of the other reports documented the exact cause of death, with the exception of 1 case in which the patient ingested 22 sertraline tablets and experienced ECG changes prior to death.

Three additional cases were reported in which possible pure sertraline overdose resulted in ECG abnormalities. In 1 such case, a 13-year-old female ingested 650 mg of sertraline, and in another, a 22-year-old woman ingested 500 mg of sertraline. In the final case, a 23-year-old man had a seizure and QT prolongation after ingesting an unknown amount of sertraline. In all 3 cases, the patients recovered fully.

Finally, 4 cases were reported in which patients ingested overdoses of sertraline and experienced seizures (dose range, 500 mg–1000 mg).

PAROXETINE

Clinical Trials

In cases of reported overdoses on paroxetine alone or in combination with other drugs during premarketing trials, patients experienced nausea, vomiting, drowsiness, dizziness, sinus tachycardia, sweating, and dilated pupils.¹⁸ In cases where hospitalization was required, medical treatment included gastric lavage or administration of activated charcoal or syrup of ipecac. No ECG abnormalities,

coma, or convulsions were reported following pure paroxetine overdose. All patients recovered fully, including those who ingested up to 2000 mg of paroxetine (100 times the common daily dose of 20 mg, 40 times the maximum recommended daily dose of 50 mg).¹⁸

Postmarketing reports to SmithKline Beecham through 1995 include 188 (135 validated) overdoses which occurred while a patient was treated with paroxetine, 19 of which were fatalities (S. Wiejowski, Pharm.D., written communication, December 1997). Of these, 17 involved ingestion of substances in addition to paroxetine or other factors. Of 2 fatalities in which only paroxetine was ingested, 1 patient (who ingested 800 mg) was found dead in an automobile with the cause of death attributed to hypothermia. Little information is available about the other fatality; however, autopsy reports suggested elevated plasma levels of paroxetine. In the remaining reports of overdose, the patients recovered without sequelae.

Published Reports

Myers et al.³¹ reviewed paroxetine overdoses reported to the Pittsburgh Poison Control Center over a 12-month period. Among 35 people (26 adults) who ingested from 10 mg to 1000 mg of paroxetine, 8 experienced no symptoms, while others experienced symptoms such as vomiting, drowsiness, and tremors. The 16 overdoses involving coingestants had symptoms consistent with the coingestant.

Myers and Krenzelok³² further reviewed 28 ingestions by children (10 months to 17 years of age) of paroxetine alone reported to the Pittsburgh Poison Control Center over a 24-month period. Ingested amount ranged from 10 mg to 800 mg. Twenty-two of the children were asymptomatic, and the remaining 6 suffered symptoms such as drowsiness, vomiting, orthostatic hypotension, and tachycardia. All patients recovered fully without sequelae.

Gorman et al.³³ reported a case in which a patient took 400 mg of paroxetine alone and experienced no symptoms.

AAPCC Reports

The AAPCC has reported 3 fatalities in which paroxetine was ingested concomitantly with other drugs (including the sertraline/paroxetine ingestion previously described). To date, no cases of fatalities resulting from paroxetine-only overdose have been reported to the AAPCC.

FDA Reports

Six fatalities have been reported to the FDA in which paroxetine was the only known ingestant (Table 1). One patient had blood paroxetine levels that were 10 times above normal. In another report, the heart blood level was measured at 170 ng/mL. An additional case reported that a 42-year-old male ingested 26 to 28 tablets of paroxetine

and subsequently died of cardiac arrest after several seizures. The medical examiner reported that screens for alcohol and other drugs were negative. Finally, a patient ingested 600 mg of paroxetine, presented with a hypotensive episode, and then "appeared to go into cardiogenic shock."

One possible pure paroxetine overdose caused ECG abnormalities, followed by full recovery. Two others resulted in seizures.

FLUVOXAMINE

Clinical Trials

In contrast to other SSRIs, fluvoxamine is not approved in the United States for the treatment of depression, but is approved for the treatment of obsessive-compulsive disorder. A total of 354 cases of overdose involving fluvoxamine were reported during clinical trials and postmarketing surveillance in Europe, including 19 fatalities.¹⁸ Of the reported fatalities, 17 involved coingestion of fluvoxamine with other drugs, and 2 involved ingestion of fluvoxamine alone. No further information is available on these fatalities. At least 309 of the remaining 335 patients recovered completely after gastric lavage and symptomatic treatment. One patient ingested 10,000 mg of fluvoxamine (100 times the minimum effective daily dose, about 33 times the maximum recommended daily dose of 300 mg) and fully recovered with no sequelae. Common symptoms associated with pure fluvoxamine overdose included drowsiness, diarrhea, vomiting, and dizziness.¹⁸

Published Reports

Garnier et al.³⁴ reviewed 221 cases of intentional fluvoxamine overdose that were reported to the Paris Poison Centre, and 78 cases of fluvoxamine overdose collected by the International Drug Safety Department of Duphar BV (the Dutch subsidiary of Solvay S.A.). In 69 cases, fluvoxamine was ingested alone (dose range, 150 mg–9000 mg). Symptoms including drowsiness, tremor, nausea, vomiting, abdominal pain, moderate bradycardia, and/or anticholinergic effects, such as dry mouth, mydriasis, sinus tachycardia, and urinary retention, were observed when the fluvoxamine dose was less than 1000 mg. At higher doses, other symptoms (e.g., decreased consciousness) were reported.

Ingestion of fluvoxamine with concomitant drugs or alcohol resulted in more serious toxicity. For example, seizures occurred in 5 cases in which higher doses (>1500 mg) and concomitant drugs were ingested. Thirteen cases in which patients ingested large doses of fluvoxamine (range, 2500 mg–6100 mg) concomitantly with other substances resulted in fatalities.

AAPCC Reports

The AAPCC has not reported any fatalities involving fluvoxamine to date.

FDA Reports

The single report of a fatal overdose in which fluvoxamine was the only drug reported to have been ingested did not include the blood levels of fluvoxamine, pathology findings, or exact cause of death (see Table 1).

CITALOPRAM

Clinical Trials

Citalopram, an approved antidepressant in more than 60 countries worldwide, recently was approved for marketing by the United States Food and Drug Administration. During premarketing clinical trials involving 4422 citalopram-treated patients, 15 overdoses (up to 2000 mg) with citalopram, either alone or in combination with other ingestants, were reported (Forest Laboratories, Inc., data on file, 1998). There were no fatalities. Of the patients who ingested citalopram alone, 2 were asymptomatic, and in other cases symptoms such as nausea, somnolence, increased sweating, and tachycardia were reported. In several patients ingesting citalopram and other substances, including benzodiazepines and alcohol, more serious symptoms, including loss of consciousness, were observed.

During postmarketing surveillance outside the United States (1989 through mid-1998), there have been 2 reports to H. Lundbeck A/S of fatalities from overdose of citalopram alone, 1 of which also has been published in the literature¹⁷ (see below). In the other case, a 17-year-old female with a previous suicide attempt ingested 2800 mg of citalopram (140 times the common daily dose of 20 mg). The patient developed generalized seizures approximately 4 hours after ingestion and did not regain consciousness. Serum citalopram concentration was 2993 ng/mL 6 hours postingestion (Forest Laboratories, Inc., data on file, 1998).

Published Reports

Recently, a Swedish poison control center published findings from 108 cases of citalopram-only overdoses reported since 1993.³⁵ In 94 cases, the dose taken ranged from 140 mg to 5200 mg (7 to 260 times the common daily dose of 20 mg, approximately 2.5 to 90 times the maximum recommended daily dose of 60 mg). In overdoses of less than 600 mg, symptoms such as nausea, dizziness, tachycardia, tremor, drowsiness, and somnolence were reported. Higher doses (30–100 times the common daily dose) were associated with convulsions and tachycardia. There were no instances of arrhythmia, and all patients, including 1 who ingested 5200 mg, the highest known overdose, recovered without sequelae.

Among 6 reported cases of fatal citalopram overdose, 5 involved other sedative drugs or ethanol, as well as large doses of citalopram (range, 840 mg–3920 mg).¹⁷ The single pure citalopram fatality resulted from an ingestion of nearly 4000 mg of citalopram—more than a 6-month supply of the drug at the common daily dose of 20 mg. In this

case, a 56-year-old male was found dead in his car in a parking lot. The concentrations of citalopram and demethylcitalopram in blood samples taken from the femoral vein were 16,000 ng/mL and 500 ng/mL, respectively, more than 75 times the therapeutic concentration.

Grundemar et al.³⁶ described in detail 5 cases of massive citalopram overdose in which all patients survived. At least 3 of the 5 cases involved coingestion of citalopram with ethanol or other drugs. Four of the 5 patients had seizures, and the fifth (in which the patient also ingested 375 mg of oxazepam) was amnesic. ECG changes, including prolongation of QT_c interval (to values > 440 milliseconds) were reported. All patients recovered without sequelae.

Since citalopram was only recently approved in the United States, neither the AAPCC nor the FDA has received any postmarketing case reports involving citalopram overdose.

DISCUSSION

Results of both prospective studies and individual case reports indicate that the potential for toxicity in overdose of SSRIs (including fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram) is very much less than that of TCAs. Whereas approximately 100 to 150 fatal overdoses with TCAs were reported to the AAPCC each year, only 16 fatal overdoses involving SSRIs (with or without concomitant coingestants) were reported to the same organization during the period 1987 through 1996.

In general, overdoses with SSRIs alone very rarely result in fatality, and most patients recover without sequelae. Moderate overdoses (up to 30 times the common daily dose) are associated with minor or no symptoms. Acute ingestion of SSRIs at doses up to 50–75 times the common daily doses typically result in symptoms including drowsiness, tremor, nausea, and vomiting. At higher doses, more serious adverse events, including seizures, ECG changes, and decreased consciousness may occur. With exceptionally large acute overdoses of these drugs (≥ 150 times the common daily therapeutic dose), fatalities have been reported. Not surprisingly, SSRI overdoses in combination with alcohol or other drugs appear to be associated with increased toxicity, and most fatalities involving SSRIs have involved coingestion of other substances.

The signs and symptoms of acute overdoses with fluoxetine and with citalopram are more thoroughly characterized than overdoses with other SSRIs, as both fluoxetine and citalopram have been marketed for approximately 10 years. During this time, both fluoxetine and citalopram have been ingested in hundreds of overdose situations, yet each has caused only 1 well-documented fatality in cases of SSRI-only overdose.^{16,17} As with all antidepressants, more fatalities are reported when there is coingestion with other substances.

Although much less is known about overdoses with other SSRIs, the very few instances of fatalities suggest that SSRIs generally share the favorable safety in overdose profile observed with fluoxetine and citalopram. The relatively benign profile of SSRI overdose represents a distinct advantage compared with the TCAs. However, coingestion is very common, especially with alcohol and benzodiazepines, and can greatly increase toxicity.

Drug names: citalopram (Celexa), fluoxetine (Prozac), fluvoxamine (Luvox), maprotiline (Ludiomil), naloxone (Narcan and others), oxazepam (Serax and others), paroxetine (Paxil), sertraline (Zoloft), temazepam (Restoril).

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