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Postmortem Forensic Toxicology of Selective Serotonin Reuptake Inhibitors: A Review of Pharmacology and Report of 168 Cases

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ABSTRACT: This paper reviews the complex pharmacology of the new class of antidepressant medications exhibiting selective inhibition of serotonin reuptake. The four selective serotonin reuptake inhibitors (SSRIs) considered—fluoxetine, fluvoxamine, sertraline and paroxetine—can result in toxicity and death through contributing to serotonergic excess resulting in serotonin syndrome, inhibiting the metabolism of other centrally acting drugs, leading to accumulation of toxic concentrations, and exerting complex vasoactive effects on the vascular smooth muscle. This latter feature is of particular concern in patients with preexisting heart disease.

An analytical method involving isolation of the drugs by liquid/liquid extraction at alkaline pH into *n*-butyl chloride, and analysis by gas chromatography/mass spectrometry (GC/MS) is described, together with some of its limitations. Toxicologic and cause and manner of death data were examined in 60 deaths involving fluoxetine, 5 involving fluvoxamine, 75 involving sertraline, and 28 involving paroxetine. Deaths involving drug toxicity were generally a result of ingestion of multiple drugs, and in only a small number of the cases was death attributed principally to the SSRI involved. The potential for drug interactions between members of this class of drugs is discussed as well as their metabolites and a variety of other therapeutic and abused drugs which can contribute to their toxicity.

In the absence of other risk factors, the lowest concentrations determined to have resulted in death were 0.63 mg/L for fluoxetine, 0.4 mg/L for paroxetine, and 1.5 mg/L for sertraline. We had insufficient data to make even this crude assessment for fluvoxamine. Drug-induced elevation of serotonin concentrations may be a significant risk factor for patients with atherosclerotic cardiovascular disease (ASCVD). Other factors including preexisting disease and the presence of other drugs and their pharmacology need to be carefully considered before determining the appropriate cause and manner of death in these cases.

KEYWORDS: forensic science, forensic toxicology, selective serotonin reuptake inhibitors, gas chromatography/mass spectrometry, serotonin syndrome

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Serotonin plays diverse roles in human physiology. Centrally, as a neurotransmitter, it affects mood, cognition, sleep, motor systems, appetite, sexual behavior, temperature regulation, and hormone secretion. Peripherally, it is a modulator of smooth muscle function in the cardiovascular and gastrointestinal systems. Serotonin also affects platelet aggregation. It is synthesized in vivo from L-tryptophan and degraded via metabolism by monoamine oxidase-A (MAO-A) to 5-hydroxyindole-3-acetic acid (5HIAA) and 5-hydroxytryptophol, with the former being by far the major metabolite (1). Drugs altering serotonin activity have been developed with particular emphasis on mood disorders indications. Selective inhibitors of serotonin reuptake (SSRIs) have recently become more popular than the classical tricyclic antidepressants (TCAs) in the treatment of a variety of affective disorders due to their specificity of action. This specificity allows physicians to titrate a drug against a particular disorder, simultaneously increasing the possibility of effective treatment, and decreasing the risk of unwanted side effects.

TCAs are classical antidepressants with poor selectivity in monoamine transporter inhibition, unwelcome side effects, and significant toxicity. They generally inhibit reuptake of serotonin, norepinephrine and dopamine in presynaptic neurons. This results in an across-the-board increase in available neurotransmitters, followed by plastic changes in pre- and postsynaptic receptors. The therapeutic use of TCAs has been limited by their affinity as antagonists of histamine H_1 receptors, associated with sedation; of adrenergic α_1 receptors, resulting in vasodilation with orthostatic hypotension and reflex tachyarrhythmias; and of cholinergic muscarinic M_1 receptors, causing classical "anticholinergic" side effects of dry mouth, blurred vision, urinary retention and constipation, recent memory impairment and further cardiac arrhythmias. Furthermore, tertiary amine TCAs are demethylated to active metabolites which are generally potent inhibitors of norepinephrine uptake, thereby adding to the cardiovascular and CNS toxicity of the parent drug. However, in spite of their larger side effect profile, a significant lack of response in up to 20 to 30% of patients (a trait they share with the SSRIs), and narrow therapeutic ranges, classical TCAs still have a significant role in the treatment of refractory and severe depressive illness (2,3).

A new generation of antidepressants that differ dramatically from the TCAs, in their affinity for specific receptors or transport systems, has been available for about eight years. Drugs classified as selective SSRIs are preferentially prescribed to patients diagnosed with obsessive compulsive disorder, depression, anxiety, bulimia nervosa, and migraines (4). Currently available in the U.S.

are fluvoxamine (Luvox®, Solvay), fluoxetine (Prozac®, Lilly), paroxetine (Paxil®, SmithKline Beecham) and sertraline (Zoloft®, Pfizer) (see Table 1). Other SSRIs are currently pending FDA approval. Other nonselective serotonin reuptake inhibitors such as venlafaxine and clomipramine are also seeing increased popularity.

SSRIs inhibit serotonin (5-hydroxytryptamine, or 5HT) reuptake at the presynaptic neuron (5). Acutely, an SSRI will increase serotonin at the level of the cell body of raphe neurons. This rise in somatodendritic serotonin desensitizes $5HT_{1A}$ autoreceptors, resulting in removal of the presynaptic inhibitory control they exert on synthesis and release of serotonin at the terminal. Consequently, postsynaptic receptors, in particular $5HT_{2A}$, downregulate, generating the delayed antidepressant activity typical of the SSRIs. Optimum efficacy of SSRIs is typically achieved over a period of 4 to 6 weeks. Characteristic side effects of SSRIs stem mainly, therefore, from excessive stimulation of postsynaptic serotonin receptors, such as $5HT_{2A}$, causing agitation, akathisia and sexual dysfunction, or of $5HT_3$ receptors, causing nausea and vomiting.

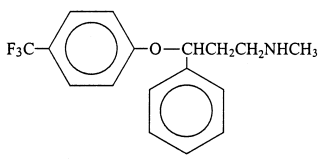
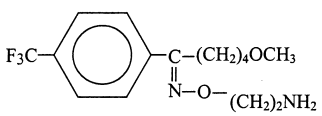
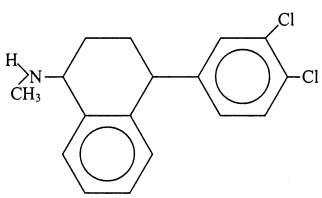
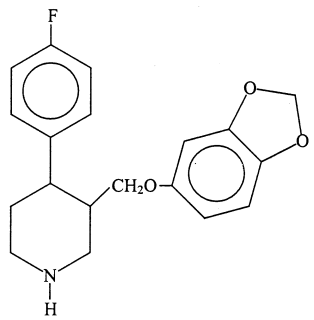
With the exception of paroxetine, the SSRIs all have active metabolites. The half-lives of these drugs and their metabolites range from a few hours to several days (Table 1). The longer half-lives are potentiated by the fact that most SSRIs and some of their active metabolites exhibit autoinhibition (often referred to as suicide inhibition), that is, inhibition of a drug's own metabolism by itself (6). This gives rise to a nonlinear kinetic relationship between dose and concentration and an increased half-life with increased dose. Fluoxetine, norfluoxetine, fluvoxamine, sertraline, and paroxetine are all known to exhibit autoinhibition.

Adverse drug reactions can occur due to pharmacodynamic or pharmacokinetic interactions. All are possible with atypical antidepressants, and we review here three main drug-induced complications: the serotonin syndrome, bleeding and cardiovascular effects, and inhibition of cytochrome P450 metabolism.

Whereas serotonin imbalance has been implicated in several major psychiatric disorders and raising serotonin neurotransmission can be beneficial, an excessive stimulation of serotonergic pathways can result in the potentially lethal serotonin syndrome. Excessive serotonin levels can arise from a simple overdose of a drug which prevents the reuptake of this neurotransmitter, but also in the presence of therapeutic amounts of multiple drugs with similar serotonergic properties. Compounding factors can include the presence of drugs that slow the rate of metabolism of serotonin such as the monoamine oxidase inhibitors phenelzine, moclobemide, or tranylcypromine. Also, contributions from usually benign drugs such as dextromethorphan, with significant serotonin reuptake inhibiting properties may be of great significance in the presence of these SSRI drugs (7,8).

Literature indicates that activation of the brain stem and spinal

TABLE 1—*Structure, half-life (t1/2), volume of distribution (V_d), and metabolites of drugs studied.*

Drug	Structure	$t_{1/2}$ (hr)	V_d (L/kg)	Metabolite
fluoxetine		24-72	26	norfluoxetine
fluvoxamine		16-26	25	fluvoxamine acid
sertraline		24-26	N/A	N-desmethylsertraline
paroxetine		7-37	3-28	methylene bridge is lost, resulting in catechol intermediate which is extensively sulphated and glucuronidated.

cord $5HT_{1A}$ receptor resulting from administration of SSRIs has been implicated in the development of "serotonin syndrome" (9). Interaction with dopamine and $5HT_2$ receptors may also be involved, and it has been hypothesized that serotonin syndrome may involve presynaptic inhibition of dopamine release or synthesis, in a manner similar to neuroleptic malignant syndrome (NMS) (10). Serotonin syndrome has been characterized by the presence of altered mental status, autonomic dysfunction, and neuromuscular hyperactivity (11). Sternbach (9) has proposed that for a diagnosis of serotonin syndrome, at least three of the following be present proximate to ingestion of a known serotonergic agent: agitation, mental status change, diaphoresis, myoclonus, diarrhea, fever, hyperreflexia, tremor, or incoordination.

The accepted treatment for serotonin syndrome is removal of the offending drug, supportive therapy, including cooling blanket, ice pack, or an ice water enema, and administration of dantrolene and cyproheptadine (11,12). Dantrolene eliminates excess Ca^{2+} released from the sarcoplasmic reticulum of skeletal muscle which is responsible for the catatonia/rigidity and secondarily the hyperthermia. Sometimes amantadine is added, which delays the reuptake of dopamine and facilitates its release. Cyproheptadine is an antihistaminic drug with nonselective serotonin receptor antagonist properties which has helped to resolve most of the symptoms of serotonergic excess. The appearance of hyperthermia [temperature $>$40.5°C (105°F)] in patients who have developed other symptoms of serotonin syndrome is indicative of a severe, potentially fatal disease process (10). Deaths due to serotonin syndrome may also occur due to the presence of predisposing factors, such as peripheral vascular disease, environmental hyperthermia, or seizure disorder (2,8,10,13).

Another potentially fatal side effect associated with many of the atypical antidepressants including SSRIs, occurs in subjects with heart disease. Increased serum serotonin levels due to the presence of drugs which inhibit 5HT reuptake, may play an important role in fatalities involving these drugs. The use of an SSRI leads to an initial increase in serum serotonin levels (14), which has complex effects on smooth muscle tone of the vasculature, since certain vasculatures are constricted by exposure to serotonin, while others are dilated. This depends mainly on the presence and relative densities of various subtypes of serotonin receptors. Because of this effect on vascular smooth muscle, there are good reasons to believe that β-blockers, such as propranolol and pindolol, will interact with SSRIs. It has been established that these heart and blood pressure medications also block $5HT_{1A}$ receptors, which has led to their occasional use in treatment of serotonin syndrome (12,15).

In addition to serotonergic activity, inhibition of cytochrome P450 isoenzyme metabolism can play an important role in toxicity resulting from these drugs, and should be considered when interpreting blood concentrations. Many serotonergic drugs are substrates for either CYP2D6 or 3A4, or both, and are often found in combination with each other and with other substrates for these isozymes such as beta blockers and TCAs. As a result, enzyme saturation due to competitive inhibition of 2D6 can lead to increased blood drug concentrations which can, in turn, lead to toxic side effects.

A number of drug overdose fatalities attributed to sertraline, fluoxetine, paroxetine, or fluvoxamine have been reported in the literature over the past few years (9,10,13,16–36). In this study we report the application of a common extraction method for the isolation of a range of SSRIs and their active metabolites, followed by analysis using gas chromatography/mass spectrometry (GC/MS). A series of cases analyzed according to these methods that disclosed the presence of SSRIs is presented and discussed. These include fatalities due to natural disease and trauma, in addition to deaths attributed in whole or in part to toxicity from these drugs.

Materials and Methods

The methods described below were used to analyze samples containing sertraline, N-desmethylsertraline, paroxetine, fluvoxamine, fluoxetine, and norfluoxetine. Sertraline (Zoloft®) and N-desmethyl sertraline were gifts from Pfizer Inc., paroxetine (Paxil®) was a gift from SmithKline Beecham, fluvoxamine (Luvox®) and fluvoxamine acid were gifts from Solvay, and fluoxetine (Prozac®) and norfluoxetine were obtained from Eli Lilly & Co. All other reagents were analytical grade or better and were obtained from Fisher.

Blood samples collected at autopsy during the investigation of a series of unrelated fatalities occurring in Washington State between 1995 and 1998, were each placed in separate 10 mL vials containing sodium fluoride and potassium oxalate (Vacutainer; Becton Dickinson, NJ). The samples were refrigerated until analysis was performed. Postmortem peripheral and central blood levels can vary a great deal, especially for drugs with a volume of distribution (V_d) greater than 3 L/kg. In a study of heart and femoral blood concentrations of a variety of drugs (37), Prouty and Anderson found that in heart blood, the concentration of several drugs increased as the postmortem interval increased, but that femoral blood concentrations more closely approximated concentrations in field blood taken via cardiac puncture by a medical examiner during the course of a death investigation. Although most samples in this review were from known peripheral or central origin, many were not labeled.

Liquid-liquid extractions were performed using a procedure based on that described by Foerster and co-workers (38,39) which has been modified for general use in this laboratory for screening basic drugs. Blood (1 mL), internal standards (diphenylamine and metycaine, 100 μL of 1 mg/L and 0.5 mg/L solutions, respectively), and pH 9 saturated potassium borate buffer (1 mL) were mixed and extracted with *n*-butyl chloride (3 mL). The organic fraction was back extracted into 3 M hydrochloric acid (1 mL), which was then basified with concentrated ammonium hydroxide and re-extracted into chloroform (100 μL). A 2 μL aliquot of the chloroform fraction was then injected for analysis by gas chromatography/mass spectrometry (GC/MS) on a 5890/5970 GC/MS (Hewlett Packard, Palo Alto, CA). Chromatographic separation was achieved using a 5% phenylmethylsilicone column (30 m × 0.32 μm i.d., Econocap; Alltech). The injection port temperature was 260°C. To maximize resolution, a temperature program from 120 to 200°C at 10°C/min, 200 to 220°C at 4°C/min, and 220 to 295°C at 8°C/min, held at the final temperature for 10 min was used. To increase sensitivity, analyses were performed using selected ion monitoring (SIM) mode. Characteristic fragment ions for these compounds are listed in Table 2, and the ions monitored in SIM analysis are as indicated. The method was specific and free from interference from other drugs including the commonly co-administered drugs, bupropion (Wellbutrin®) and its threoamino alcohol and morpholinol metabolites, trazodone (Desyrel®), venlafaxine (Effexor®), and its active metabolite O-desmethylvenlafaxine.

Results

Figure 1 is a standard mass chromatogram showing the chromatographic separation of bupropion, fluoxetine, fluvoxamine,

TABLE 2—*Principal ions in the mass spectra of serotonergic drugs and metabolites.* m/z *for selected ion monitoring are boldface.*

Compound	Principal Ions (*m/z*)
Bupropion	**100,** 57, 111, 75, **224,** 139, 166, 226
Threoamino alcohol	**100,** 77, 57, **208,** 115, 139, 226, 166
Bupropion morpholinol metabolite	44, **116,** 139, 111, 84, **224,** 226, 166
Norfluoxetine	134, **104,** 191, 77, 162, 51, 132, 251
Fluoxetine	**309,** 59, **104,** 78, 148, 115, 183, 164
Fluvoxamine artifact 1	**187,** 71, **276,** 45, 172, 200, 145, 299
Fluvoxamine artifact 2	72, 187, 258, 226, 172, 145, 198, 200
Fluvoxamine artifact 3	276, 71, 187, 145, 172, 200, 226, 299
Fluvoxamine artifact 4	71, 258, 226, 145, 242, 311, 329, 198
N-desmethyl sertraline	**119, 274,** 246, 292, 104, 193, 228, 159
Sertraline	**274, 159,** 262, 132, 103, 239, 304, 202
Trazodone	**205,** 70, 176, 56, 138, 231, 278, **371**
O-desmethyl venlafaxine	**58, 120,** 165, 91, 77, 149, 188, 213
Venlafaxine	**58, 134,** 179, 91, 121, 81, 180, 203
Paroxetine	**329, 192,** 70, 138, 177, 109, 53, 123

sertraline, venlafaxine, paroxetine, and trazodone from their metabolites and both internal standards, metycaine and diphenylamine. Bupropion's morpholinol metabolite and norfluoxetine were not completely resolved using this method, but we encountered no cases where both bupropion and fluoxetine were present. A modified temperature program (120 to 180°C at 15°C/min, then 180 to 295°C at 8°C/min, holding the final temperature for 8 min) was later developed which does resolve these two compounds (data not shown).

This GC/MS method was suitable for quantitation of sertraline, desmethylsertraline, paroxetine, venlafaxine and norvenlafaxine, and was linear over the range 0.01 to 10.00 mg/L. Typical regression coefficients were 0.997 or better. The limits of detection (LOD) and quantitation (LOQ) were determined according to a method described by Jones and Schuberth (40). Fluvoxamine is degraded at typical injection port temperatures (>250°C), and four peaks were frequently observed (artifacts 1–4). The largest of these (artifact 1) was used for quantitation in the cases described herein and correlation was poorer than for the other drugs. Major ion fragment masses from the mass spectra of the four artifacts are listed in Table 2. The limit of detection of 0.10 mg/L was also poorer for fluvoxamine using this method.

The method was applied to a series of 168 death investigation cases, and for those cases where the concentration of the SSRI exceeded the normal therapeutic ceiling referenced in the text, demographic information and circumstances, cause and manner of death, and concentrations of all drugs found, including SSRIs and their metabolites, are included in Tables 3-6. Cases with concentrations within the normal therapeutic range were considered and are discussed, but these data are not tabulated. Test of significance was a two-tailed Student *t*-test assuming unequal variance.

Discussion

With the exception of paroxetine, all of the SSRIs have active metabolites which are selective for serotonin reuptake inhibition, as well as inhibition of the enzymes systems responsible for their metabolism. This can result in elevated concentrations of the drugs or their metabolites, and greatly increased effects on serotonin mediated neurotransmission caused by these drugs, their active metabolites, and interaction with other serotonergic drugs which might be present. It is therefore important to consider metabolite concentrations and the potential for drug interactions when interpreting parent drug levels. The half-lives of most atypical antidepressants range from a few hours to several days (see Table 1).

An excellent summary of inducers, inhibitors, and substrates of cytochrome P450 isozymes is given by Rudy (41). Many serotonergic drugs are both substrates and inhibitors for CYP2D6 and 3A4, and as such are subject to metabolic autoinhibition, which may affect therapeutic response, and can increase concentrations above levels normally associated with therapeutic doses. For example, fluoxetine and paroxetine, are potent inhibitors of CYP2D6, responsible for the metabolism of most CNS and cardiovascular drugs. Fluvoxamine is a potent inhibitor of CYP3A4, which is the most abundant isozyme in human liver and is involved with metabolism of the majority of lipid soluble drugs.

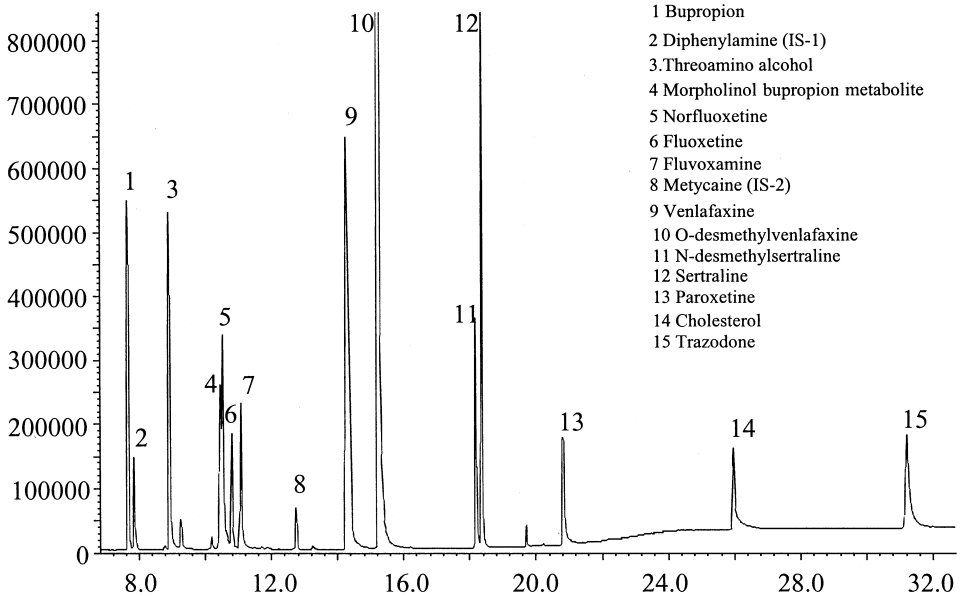


FIG. 1—*Mass chromatogram of analytes and other antidepressants isolated during extraction.*

TABLE 3—*Data on fatalities testing positive for Fluoxetine.*

Age	Sex	Central Periph	Fluoxetine/ Norfluoxetine (mg/L)	Alcohol (g/100 mL)	Other drugs	Conc. (mg/L)**	Circumstances	Cause	Manner
5 hrs	f	c	<0.05 <0.05	neg	Bupropion met.	<0.05	Maternal drug use	Platelet incompatibility	Natural
49	f	p	<0.05 0.11	neg	diazepam nordiazepam trazodone promethazine	0.22 0.21 0.26 0.15	Recent cancer diagnosis medications missing	Myocardial infarction/ASCVD	Natural
56	f	p	0.09 n.d.	neg	*	*	Hx Breast cancer	Dilated cardiomyopathy	Natural
37	m	p	<0.10 n.d.	neg	propoxyphene norproxyphene	0.47 0.55	Hx hypertension Hx sleep apnea	Intracerebral hemmorrhage due to hypertension	Natural
52	f	p	<0.10 0.18	neg	oxycodone amitriptyline nortriptyline	0.42 0.51 0.17	Suspect accidental overdose	Pulmonary thromboembolus	Natural
35	F	u	0.11 0.59	0.2	acetaminophen propoxyphene norpropoxyphene diphenhydramine	116.7 2.87 2.38 0.33	Found dead in bed	Acute intoxication alcohol and multiple drugs	Accident
47	m	p	0.14 0.24	neg	methamphetamine quinine trazodone morphine	0.21 3.7 1.3 0.02	Hx ethanol and drug abuse Sudden unexpected death	Acute methamphetamine and morphine abuse with chronic ethanolic liver disease	Undetermined
64	m	p	0.14 0.35	0.15	olanzapine	0.32	Hx of swallowing difficulties	Choked on food	Accident
50	m	p	0.15 0.5	0.06	butalbital acetaminophen	1.9 20.2	Hx depression	GSW	Suicide
44	f	p	0.15 0.32	0.04	diphenhydramine brompheniramine codeine lorazepam	4.8 <0.10 <0.05 0.12	Obese with chronic pain Recent Hx suicide attempts	Diphenhydramine/ ethanol intoxication	Suicide
39	m	p	0.18 n.d.	neg	methadone	0.39	Found dead Hx cocaine use	Bronchopneumonia	Natural
41	m	p	0.18 0.18	neg	diazepam nordiazepam	0.69 0.84	fell/jumped from cliff Hx IV drug and alcohol abuse	Broken neck	Undetermined
73	m	p	0.2 n.d.	neg	phenytoin lidocaine	5.8 pos	None	Subdural hemotoma	Natural
47	f	p	0.21 0.15	neg	dextromethorphan methadone doxepin	0.74 0.28 0.27	On methadone for Crohns disease	ASCVD	Natural
43	m	u	0.24 0.52	neg	alprazolam trazodone	<0.10 0.4	Hx depression	GSW	Suicide
54	f	p	0.25 0.9	neg	*	*	Hx diabetes Hx depression	Hypertension and ASCVD	Natural
38	f	p	0.25 0.3	neg	trazodone methadone	0.5 0.58	Found dead Hx of opiate abuse	Acute intoxication multiple drugs	Accident
41	f	p	0.27 0.56	neg	butalbital	4.91	Found dead in car note present	Undetermined	undetermined
45	m	p	0.27 0.46	neg	morphine amitriptyline nortriptyline codeine chlorpheniramine	0.4 0.08 <0.05 <0.05 0.15	Dead in hotel roon Drug paraphernalia present	Acute opiate intoxication	Accident
67	m	p	0.28 0.34	neg	acetaminophen phenytoin venlafaxine norvenlafaxine methocarbamol doxepin desmethyldoxepin propoxyphene	17.6 6.35 4.61 1.09 11.7 1.2 0.13 <0.05	Medication seeking multiple illnesses	Multiple drug intoxication	Accident
43	f	p	0.29 0.07	0.13	morphine	0.07	Found dead Hx alcohol abuse	Heroin overdose	Accident
48	f	p	0.36 1.18	neg	valproic acid	18	Found dead in bed	Hypertensive ASCVD	Natural
66	m	u	0.36 <0.10	neg	hydrocodone diltiazem	<0.10 0.46	Flipped over golf cart	Head/neck trauma	Accident

Table continued

TABLE 3—*Continued.*

Age	Sex	Central Periph	Fluoxetine/ Norfluoxetine (mg/L)	Alcohol (g/100 mL)	Other drugs	Conc. (mg/L)**	Circumstances	Cause	Manner
41	f	u	0.37 0.34	0.09	chlordiazepoxide nordiazepam	3.36 0.05	Found dead	GSW	Suicide
50	f	p	0.40 0.30	neg	acetaminophen phenytoin diphenhydramine amitriptyline nortriptyline chlorpheniramine pseudoephedrine	14.7 8.5 0.9 0.8 0.3 0.2 4.3	Hx pain medication abuse Herbal remedies at scene	ASCVD	Natural
42	m	p	0.44 0.60	0.02	clonazepam trichloroethanol	0.04 276	Hx mental illness	Acute intoxication from chloral hydrate, fluoxetine and ethanol	Suicide
39	f	p	0.46 0.58	0.11	nordiazepam norpropxyphene codeine hydroxyzine mets amitriptyline mets morphine	0.15 <0.10 <0.05 pos pos 0.05	Heavy drinking in evening found dead in bed paraphernalia at scene	Acute intoxication due to morphine fluoxetine and ethanol	Accident
38	f	p	0.47 0.31	0.04	amitriptyline nortriptyline	0.2 0.2	Hx alcohol abuse Prior suicide attempts	Fatty metamorphosis of liver	Natural
55	f	p	0.49 0.29	neg	propoxyphene norpropoxyphene diphenhydramine trazodone metoclopramide	3.23 0.8 1.26 0.25 0.22	Hx alcohol and propoxyphene abuse	Acute propoxyphene intoxication	Undetermined
46	f	p	0.50 0.50	neg	*	*	Hx depression Jumped off bridge	Multiple trauma	Suicide
41	m	p	0.51 0.14	0.07	phenobarbital	38	Hx Seizures	Seizure disorder of unknown etiology	Natural
49	m	p	0.62 0.23	neg	meperidine normeperidine hydromorphone trazodone paroxetine	0.73 0.22 0.08 0.14 0.1	Physician dead in office Paraphernalia present	Multiple drug intoxication	Accident
52	f	p	0.63 0.28	0.11	chlorpheniramine diazepam	0.04 0.05	Self inflicted GSW Hx suicide threats	GSW	Suicide
35	f	c	0.66 0.54	neg	methadone promethazine hydroxyzine trazodone	1.2 0.81 0.33 0.99	Multiple Rx	Pulmonary embolism incompetant mitral valve	Natural
75	m	u	0.67 0.29	0.12	amphetamine sertraline N-desmethyl sertraline	2.1 0.57 0.55	Dead at home	ASCVD	Natural
31	f	u	0.68 0.38	neg	amitriptyline nortriptyline cyclobenzaprine phenytoin morphine	0.1 0.4 0.2 2.5 0.04	Dead in bed Diabetic Multiple chronic illnesses	Diabetes mellitus	Natural
50	f	u	0.69 0.35	neg	acetaminophen propoxyphene norpropoxyphene morphine	22.2 0.33 0.95 0.06	Found dead	Acute combined drug intoxication	Accident
22	f	p	0.74 0.25	neg	*	*	Fell while hiking taking Prozac for eating disorder	Head trauma	Accident
41	f	u	0.80 1.20	neg	trazodone	1.10	Long Hx depression	ASCVD	Natural
33	f	u	0.82 0.13	neg	amitriptyline nortriptyline methadone	0.43 0.52 0.70	Found dead Hx drug abuse	Acute intoxication, multiple drugs	Accident
44	m	u	0.83 1.50	neg	morphine	0.10	Hx alcoholism	Acute Intoxication fluoxetine and morphine	Accident
37	f	p	0.97 0.80	neg	diphenhydramine doxylamine chlordiazepoxide	14.50 11.30 0.23	Found dead at home Hx psychiatric disorder	Antihistamine overdose	Suicide

Table continued

TABLE 3—*Continued.*

Age	Sex	Central Periph	Fluoxetine/ Norfluoxetine (mg/L)	Alcohol (g/100 mL)	Other drugs	Conc. (mg/L)**	Circumstances	Cause	Manner
37	m	p	1.00 0.84	neg	tramadol trazodone	2.40 0.20	Police standoff Shot self	GSW	Suicide
48	f	u	1.03 0.40	0.04	fentanyl amitriptyline nortriptyline	0.00 0.89 0.75	Hx mental illness Sudden death	Acute combined drug intoxication	Accident
43	m	u	1.08 0.60	neg	meprobamate methadone oxycodone amitriptyline nortriptyline	<5.0 0.31 0.21 1.06 3.66	Found dead in bed	Mixed drug overdose	Accident
38	m	p	1.10 1.50	neg	promethazine diphenhydramine doxylamine methadone diazepam nordiazepam alprazolam hydroxyzine	0.30 0.15 0.26 0.51 0.18 0.14 0.08 0.18	Hx polydrug abuse	Acute intoxication multiple drugs	Accident
40	f	u	1.13 0.65	neg	trazodone verapamil norverapamil hydromorphone lidocaine	3.60 0.83 0.41 0.01 pos	Recent abdominal surgery Hx suicide attempts	Low salt syndrome with myocardial fibrosis	Natural
44	m	u	1.18 1.42	0.17	diphenydramine methadone	0.26 0.43	Hx back pain Hx medication abuse	Acute intoxication multiple drugs	Accident
32	f	u	1.19 0.83	0.22	trazodone	32.91	Found dead in hotel	Acute combined intoxication alcohol and drugs	Accident
50	m	u	1.29 1.65	0.15	acetaminophen diphenhydramine propoxyphene norpropoxyphene verapamil norverapamil	9.30 2.78 0.29 0.95 0.75 0.37	Hx diabetes Hx alcohol abuse	Ventricular fibrillation	Natural
19	f	p	1.38 0.71	neg	tranylcypromine trazodone	1.94 0.15	Hx manic depression	Drug toxicity fluoxetine and tranylcypromine	Suicide
37	f	u	1.40 0.75	neg	isopropanol acetone	0.24g/dL 0.13g/dL	Hx depression Hx alcohol abuse	Isopropyl alcohol intoxication	Undetermined
38	f	p	1.48 2.28	0.23	diphenhydramine	0.19	Found dead with suicide notes	Combined toxicity alcohol and fluoxetine	Suicide
20	m	p	1.60 0.60	n.a.	meperidine norpmeperidine	0.10 0.30	Meningitis/cerebral edema	Meningitis	Natural
…	f	p	1.73 0.93	neg	*	*	Called 911 with breathing problems	Cardiac arrythmia Intramuscular bridging of coronary artery Acute fluoxetine intoxication	Accident
54	f	p	2.40 n.d.	neg	imipramine desipramine sertraline desmethylsertraline buspirone	0.10 21.90 0.72 1.03 0.11	Found dead with empty pill bottles	Acute intoxication multiple drugs	Suicide
42	m	u	3.67 0.38	0.03	*	*	Hx depression	Fluoxetine overdose	Suicide
39	f	p	4.60 4.50	0.08	morphine trazodone	0.11 1.40	Death after IV drug use	Acute intoxication from fluoxetine, opiates, ethanol, and trazodone	Accident
41	m	u	6.66 20.27	0.05	trazodone	2.65	Found dead advanced decomposition	ASCVD	Natural

* No other drugs detected.
** Unless otherwise indicated.

TABLE 4—*Fatalities testing positive for fluvoxamine.*

Age	Sex	Central/ Periph	Fluvoxamine (mg/L)	Alcohol (g/100 mL)	Other Drugs	Conc, (mg/L)**	Circumstances	Cause	Manner
46	m	u	0.19	neg	*	*	Close contact head wound	GSW	Suicide
61	m	p	0.38	0.07	diphenhydramine	0.47	Dead at home	ASCVD	Natural
					hydrocodone	<0.05	ASCVD		
62	f	u	0.82	neg	diazepam	0.19	Known alcoholic and prescription drug abuser	Combined drug overdose	Accident
					nordiazepam	0.19			
					oxycodone	0.35			
					trazodone	0.21			
					propoxyphene	0.44			
					norproxyphene	0.27			
63	f	u	2.23	neg	*	*	Driver of car that flipped over	Head trauma	Accident
35	f	u	5.8	neg	topiramate	94	Polypharmacy suicide	Multiple drug intoxication	Suicide
					olanzapine	4.4			
					amantadine	34.2			
					valproic acid	33			

* No other drugs detected.
** Unless otherwise indicated.

The specific role of serotonergic drugs in fatalities is often difficult to determine because of the number of mechanisms of toxicity associated with them. A consideration of the circumstances surrounding the case, the relevant pathology, and the toxicology results should provide future investigators with baseline information regarding blood concentrations associated with different types of fatalities, and the likelihood that a role for the drug can be invoked.

Fluoxetine

Fluoxetine (Prozac®) was the first of the selective serotonin reuptake inhibiting drugs approved for use in the United States. A starting dose of 20 mg/day is recommended going up to 80 mg/day to treat more refractory conditions. A single, oral 40 mg dose in adults has been shown to produce peak plasma fluoxetine levels of 0.02 to 0.06 mg/L within 6 to 8 h (42). In multiple-dose clinical trials, 24 patients receiving 20 to 60 mg of the drug daily developed steady-state plasma levels of 0.03 to 0.47 mg/L for fluoxetine and 0.02 to 0.47 mg/L for norfluoxetine (43). Norfluoxetine, fluoxetine's active metabolite, is also specific for 5HT reuptake inhibition, and both compounds exhibit autoinhibition, causing a nonlinear relationship between dose and concentration.

The most common severe side effects associated with fluoxetine therapy are syndrome of inappropriate secretion of antidiuretic hormone (SIADH), manifested by impaired water excretion and associated hyponatremia, hypoosmolality, resulting in lethargy, anorexia, nausea, vomiting, muscle cramps, coma, convulsions and death (1) and serotonin syndrome (6,44). Patients with heart disease may also experience vasoconstriction stemming from the presence of excess platelet 5HT (45).

The appearance of serotonin syndrome is, however, the most common life-threatening side effect of a pure fluoxetine overdose. Isoenzyme inhibition of CYP2D6, 2C9, 2C19, and 3A4, by fluoxetine and norfluoxetine can contribute to toxicity from other substrates for these isozymes, by altering their pharmacokinetics, increasing steady state levels, and slowing their elimination. Furthermore, the very long elimination half-life of norfluoxetine (7 to 14 days), presents the possibility for continued interactions with other drugs for some days after a significant overdose (46).

Drugs for whose metabolism fluoxetine and norfluoxetine have been specifically identified as inhibitors in humans include theophylline, alprazolam, propranolol, desipramine, and carbamazepine. This inhibition can be marked, as fluoxetine and norfluoxetine appear to have an apparent dissociation constant of the antagonist in the twofold to fourfold range (46).

Several reports of serotonin syndrome involving fluoxetine, only some of which had fatal outcomes, have been reported in the literature (8,45–49). While it can result from administration of this drug alone, the condition is more likely to occur when fluoxetine is administered in conjunction with monoamine oxidase inhibitors (MAOIs) or L-Tryptophan. Six fatalities are reported in the literature involving adults who ingested from 1 to 2 g of fluoxetine and, in four of the cases, at least one other drug. Patients had blood fluoxetine and norfluoxetine concentrations ranging from 1.3 to 6.8 and 0.9 to 5.0 mg/L, respectively (23–25).

During the course of this review we examined 60 fatalities in which fluoxetine was detected, of these 20 were ruled natural deaths, 13 suicides, 21 accidents, and 6 undetermined. Concentrations of fluoxetine and norfluoxetine ranged from below the limit of quantitation (0.05 mg/L for both) to 6.66 and 20.27 mg/L, respectively. Thirty of the cases had concentrations above the normal therapeutic range of up to 0.50 mg/L. None of the deaths with lower concentrations were attributed in any significant part to the fluoxetine, however, the fluoxetine cannot be ruled out as having contributed to the elevated levels of other drugs present in toxic concentrations in these cases, including, propoxyphene, amitriptyline, nortriptyline, venlafaxine and trazodone. Table 3 presents demographic, circumstantial, toxicological and pathological information on cases with fluoxetine. Many of these deaths were certified as being due to other pathological or toxicological causes. Nine of these cases were ruled as natural deaths. Fluoxetine was invoked as a contributory factor in drug toxicity deaths in 15 cases, and was the primary contributory factor in at least four others, where blood concentrations were typically greater than 1 mg/L. Only one case was certified as exclusively a fluoxetine overdose, in which the concentrations of fluoxetine and norfluoxetine were 3.67 and 0.38 mg/L, respectively. The cause of death in the case with the highest concentration, 6.6 mg/L, was most likely incorrectly ascribed to atherosclerotic cardiovascular disease (ASCVD); however, as noted elsewhere in this report, patients with significant heart disease may be predisposed to the cardiac effects of these SSRI drugs.

It was found that for cases in which the fluoxetine concentration was within the normal therapeutic range, i.e., less than 0.50

TABLE 5—*Fatalities testing positive for sertraline above therapeutic threshold of 0.21 mg/L.*

Age	Sex	Central/ Periph	Sertraline/ Norsertraline (mg/L)	Alcohol (g/100 mL)	Other Drugs	Conc. (mg/L)**	Circumstances	Cause	Manner
46	f	u	0.21 0.24	neg	amitriptyline nortriptyline	0.84 0.47	Hx marital dispute	Acute combined prescription drug intoxication	Suicide
54	f	u	0.22 0.05	0.02	amitriptyline nortriptyline cyclobenzaprine	1.26 0.73 0.17	Found dead at home with suicide note	Acute intoxication multiple drugs	Suicide
35	m	p	0.22 0.34	neg	benzoylecgonine diazepam nordiazepam	0.32 0.13 <0.05	Dead at residence Recent needle punctures	Acute intoxication multiple drugs	Accident
45	f	u	0.22 1.24	neg	lidocaine carbamazepine	pos 3.10	Insulin-dependent diabetic	ASCVD with contributory diabetes	Natural
43	f	u	0.23 0.05	0.465	*	*	Insulin-dependent diabetic Found dead at home	Diabetes mellitus	Natural
54	f	p	0.24 n.d.	neg	*	*	Jumped in front of semi truck	Multiple trauma	Suicide
37	m	u	0.26 0.08	neg	oxycodone	1.00	Found dead Took spouses medication	Acute intoxication due to prescription drugs	Accident
40	m	p	0.27 0.43	neg	methadone amitriptyline nortriptyline	0.14 0.08 0.14	Found dead after apparently getting high Hx suicide ideation	Acute multiple drug intoxication	Accident
86	f	p	0.27 1.30	neg	*	*	Choked on food	ASCVD	Natural
25	f	p	0.29 1.19	neg	thioridazine valproic acid	1.68	Hx suicide attempts Multiple meds at home	Acute intoxication sertraline and thioridazine	Accident
47	f	u	0.29 1.46	neg	morphine diphenhydramine methadone	0.51 0.25 0.15	Hx drug overdoses	Acute multiple drug intoxication	Undetermined
46	m	p	0.30 n.d.	0.09	methadone doxepin diazepam nordiazepam morphine	0.27 0.10 0.05 0.28 <0.01	Found dead at home	ASCVD	Natural
45	f	p	0.32 0.38	neg	morphine cocaine cocaethylene	0.05 0.05 0.05	Found unresponsive drug paraphernalia at scene	Cirrhosis of liver and acute multiple drug intoxication	Accident
56	m	p	0.32 0.84	neg	diazepam nordiazepam	0.09 0.06	Hanging	Hanging	Suicide
43	m	p	0.36 1.17	neg	diazepam nordiazepam	0.35 0.95	GSW to head	GSW	Suicide
36	m	p	0.37 0.53	0.06	methadone acetaminophen	0.09 10.00	Contact shotgun wound of head	GSW	Suicide
52	f	u	0.38 0.25	0.24	morphine	0.16	Hx IV drug/alcohol abuse	Acute intoxication due to alcohol and opiates	Accident
52	m	u	0.39 1.06	neg	diphenhydramine verapamil	1.69 4.10	Found dead at home	Acute verapamil intoxication with contributory ASCVD	Suicide
87	f	p	0.50 0.50	neg	diazepam	<0.05	Died in hospital	COPD congestive heart failure	Natural
47	m	p	0.53 1.57	0.08	morphine cocaine cocaethylene ecgonine methyl ester ecgonine ethyl ester benzoylecgonine	0.11 0.13 0.09 pos pos 1.30	Found in motel room Paraphernalia at scene	Acute intoxication multiple drugs and alcohol	Undetermined

Table continued

TABLE 5—*Continued.*

Age	Sex	Central/ Periph	Sertraline/ Norsertraline (mg/L)	Alcohol (g/100 mL)	Other Drugs	Conc. (mg/L)**	Circumstances	Cause	Manner
75	m	u	0.57 0.55	0.12	amphetamine fluoxetine norfluoxetine	2.10 0.67 0.29	Found dead moderately decomposed	ASCVD	Natural
75	m	u	0.59 2.27	neg	*	*	Hx depression	ASCVD	Natural
45	m	u	0.58 1.05	neg	*	*	Hx Parkinson's disease, paranoid schizophrenic Found in bathtub	Drowning due to Parkinson's disease	Accident
67	f	u	0.66 0.27	neg	methadone	1.00	Hx alcoholism, drug abuse	Acute opiate intoxication	Accident
37	m	p	0.72 1.60	neg	methadone amitriptyline nortriptyline trimethoprim fluconazole	0.30 0.13 0.11 pos pos	HIV+ found dead Hx methamphetamine use	Acute intoxication due to sertraline methadone, amitriptyline and nortriptyline	Accident
49	m	u	0.75 0.82	neg	verapamil norverapamil	0.07 0.16	Found dead in pickup after shooting two other people	GSW	Suicide
38	m	p	0.75 0.38	neg	diphenhydramine loxapine trazodone	1.20 1.40 0.50	Died following fight in county jail Wrote note with suicidal intent	Multiple drug intoxication	Suicide
38	f	u	0.80 0.52	neg	morphine acetaminophen trazodone oxycodone diphenhydramine	0.47 41.00 0.58 0.82 0.13	None	Pulmonary edema due to drug overdose	Accident
50	m	u	0.80 n.d.	neg	amitriptyline nortriptyline propoxyphene norpropxyphene	1.34 1.26 1.57 0.87	Disabled Vietnam veteran Found dead	Prescription drug overdose	Accident
47	m	u	0.85 0.21	0.07	diazepam nordiazepam	0.61 <0.1	Paraplegic found dead Hx suicide attempts Empty pill bottles in hand	Intoxication ethanol and multiple drugs	Suicide
50	m	p	0.89 3.67	neg	*	*	Hx depression Found dead with GSW	GSW to head	Suicide
37	f	u	0.90 6.20	neg	diphenhydramine	0.30	Dead in pool Hx mental illness Hx suicide attempts	Asphyxia due to drowning	Accident
49	m	u	1.17 3.01	neg	trimethoprim	2.02	Hx alcohol and drug abuse Found unresponsive	Acute sertraline intoxication with chronic ethanolic liver disease and hepatic failure	Undetermined
51	m	u	1.25 1.16	neg	cocaine benzoylecgonine nordiazepam	1.40 3.70 <0.10	Fell in trailer, hitting head	Acute cardiopulmonary arrest due to fractured 3rd vertebrae	Accident
39	f	u	1.76 0.15	0.19	propoxyphene norpropoxyphene codeine acetaminophen ibuprofen hydrocodone diphenydramine trazodone	6.60 0.87 7.00 521.00 37.00 1.28 1.09 1.41	Found dead in car	Acute combined drug intoxication	Suicide
45	f	p	1.76 0.57	neg	diltiazem temazepam trazodone	3.35 7.75 24.32	Hx of depression	Acute combined drug intoxication	Suicide

Table continued

TABLE 5—*Continued.*

Age	Sex	Central/ Periph	Sertraline/ Norsertraline (mg/L)	Alcohol (g/100 mL)	Other Drugs	Conc. (mg/L)**	Circumstances	Cause	Manner
44	f	p	2.52 4.05	0.18	dextromethorphan promethazine antipyrine cocaine cocaethylene benzoylecgonine trazodone	0.49 0.98 pos <0.05 <0.05 0.57 0.35	Hx alcohol abuse	Acute combined drug intoxication Advanced micronodular cirrhosis	Accident
59	m	p	3.03 0.43	neg	desipramine diazepam nordiazepam	0.75 <0.05 <0.05	Hx depression Hx suicide attempts	Drug overdose	Undetermined
32	f	p	4.20 15.30	neg	morphine nordiazepam	0.10 1.10	Found dead spoons with heroin residue present	Acute intoxication multiple drugs	Accident

* No drugs detected.
** Except where otherwise indicated.

mg/L (data not shown), the concentration of the parent drug was generally less than that of the metabolite, while at higher concentrations the reverse was true. The mean fluoxetine/norfluoxetine ratios were significantly different ($p < 0.05$) at 0.88 and 4.17 for the therapeutic ($n = 25$) and supra-therapeutic ($n = 29$) groups, respectively. While this is consistent with death shortly following a large overdose, powerful suicide inhibition of metabolism by high fluoxetine concentrations and saturation of metabolic capacity may both contribute to these elevated ratios in overdose.

In terms of potential for interactions with other drugs, trazodone, a weak inhibitor of serotonin reuptake was present in 14 cases including the two highest fluoxetine cases. In these latter cases, the co-inhibition of fluoxetine metabolism by trazodone and vice versa, likely contributed to the elevated levels of both. Tricyclic antidepressants were present in eight cases, and other SSRIs were present in only two, specifically sertraline and paroxetine. In one case, with an elevated fluoxetine concentration (1.38 mg/L), the monoamine oxidase inhibitor tranylcypromine was present in overdose. This combination is specifically contraindicated, because of its potential to cause elevated serotonin concentrations resulting in serotonin syndrome, and is a likely mechanism for this death. Generally in the cases reviewed, the potential for the combined toxicity of the drugs was recognized by the pathologist by attributing the death to multiple drug intoxication even when the concentrations of one or more of the drugs were within the normal, or slightly elevated range. In the light of the information now available on these other cases, the two certified natural deaths, with fluoxetine concentrations of 1.60 and 6.66 mg/L would bear some re-evaluation.

Fluvoxamine

The recommended starting dose of fluvoxamine for adults is 50 mg, with the final dose in the range of 100 to 300 mg, titrated for efficacy. Approximately one week of multiple oral fluvoxamine (Luvox®) dosing of 100 to 300 mg/day in 30 normal volunteers yielded steady-state plasma levels ranging from 0.09 to 0.55 mg/L (50). In elderly patients, aged 66 to 73 years, mean plasma fluvoxamine concentrations were 40% higher than in younger subjects, aged 19 to 35 years, likely the results of metabolic function changes, renal function decrease, V_d alterations, or a combination of all three. Concentrations of its active metabolite, fluvoxamine acid, were not reported in either of these studies. As with the other SSRIs previously discussed, fluvoxamine acid is selective for serotonin reuptake inhibition, although it is 1 to 2 orders of magnitude less potent than the parent compound (43).

Like fluoxetine, fluvoxamine exhibits autoinhibition, and may be involved in metabolic interactions involving CYP1A2, 2C19, and 3A4 when other substrates for these isozymes are present, as fluvoxamine is a potent inhibitor of all three. There have been specific reports of interactions between fluvoxamine and theophylline, imipramine, desipramine, carbamazepine, and clozapine (47). The nature of these interactions is generally of an increase in concentration, and extended half-life; however, compared to the influence of fluoxetine, the interaction by virtue of a lower K_i, is lower by an order of magnitude (47).

There has been one report of of bleeding disorders in several patients taking fluvoxamine (6). In addition, fluvoxamine may be involved in cases of serotonin syndrome, and should be evaluated carefully when present together with other serotonergic agents. The authors of a comparative study of the incidence of hyponatremia in patients taking SSRIs found that 11 out of 736 cases of hyponatremia and SIADH involved fluvoxamine, compared to 554 involving fluoxetine (44). There have been 354 cases of deliberate or accidental overdose involving fluvoxamine reported, 19 of which had fatal outcomes (43).

There appear to be no reports in the literature of fatalities due exclusively to fluvoxamine. Wu Chen (51) reports an asphyxial suicide in which fluvoxamine was present at a concentration of 3.11 mg/L. Isacsson et al. (36) quote a toxic concentration for fluvoxamine of 3 mg/L, although the basis for this is unclear. They also conclude that there is a greater risk for suicidal acts in patients taking fluvoxamine, among other drugs, than in patients in therapy with classical tricyclic antidepressants. These authors reported toxic concentrations were present in 9 of 35 fatalities in which fluvoxamine was found.

We report here data on five fatalities in which fluvoxamine was present (Table 4). In none of these cases was the drug specifically implicated in the death, although in two cases it did exceed the normal therapeutic range and in one case, the threshold for toxicity of 3 mg/L as defined by Isacsson. In the latter case however, the novel sulfamate-substituted monosaccharide anticonvulsant topiramate which

TABLE 6—*Data on fatalities testing positive for paroxetine.*

Age	Sex	Central/ Peripheral	Paroxetine (mg/L)	Alcohol (g/100 mL)	Other Drugs	Conc. (mg/L)*	Circumstances	Cause of Death	Manner
39	m	p	<0.05	neg	morphine	0.2	Found dead in bathroom paraphernalia present	Opiate toxicity	Accident
					codeine	<0.05			
					thioridazine	<0.05			
					monoacetylmorphine	<0.05			
69	f	p	0.08	neg	phenytoin	13.8	Unexpected death alleged poisoning	Carcinomatosis of abdomen	Natural
43	m	u	0.1	neg	methadone	0.39	Found dead at home	Methadone intoxication alcoholic cardiopathy	Accident
					venlafaxine	0.19			
					amitriptyline	<0.05			
					nortriptyline	0.26			
47	f	u	0.1	neg	amitriptyline	0.15	Neck and back pain stopped breathing while asleep severe cirrhosis	Hepatic renal failure due to liver cirrhosis	Natural
					nortriptyline	0.07			
					acetaminophen	10.5			
					ibuprofen	11.1			
					oxycodone	<0.10			
					hydrocodone	<0.10			
					dihydrocodeine	<0.10			
					promethazine	<0.10			
					lidocaine	pos			
49	m	p	0.1	neg	meperidine	0.73	Physician dead in office paraphernalia present	Multiple drug intoxication	Accident
					normeperidine	0.22			
					hydromorphone	0.08			
					trazodone	0.14			
					fluoxetine	0.62			
					norfluoxetine	0.23			
40	f	p	0.13	neg	morphine	0.02	Long-term care for nutritional support	Undetermined	Natural
					lidocaine	pos			
					trimethobenzamide	pos			
50	m	p	0.14	neg	morphine	0.11	Hx alcohol and drug abuse	ASCVD	Natural
					diphenydramine	<0.05			
					diazepam	0.11			
					nordiazepam	0.21			
39	m	p	0.14	neg	felbamate	9.1	Found dead Hx of seizures sleep apnea device	Blunt force injury to head seizure disorder	Accident
					ibuprofen	6.7			
60	f	u	0.16	neg	chlorpheniramine	0.07	Myocardial infract severe ASCVD	ASCVD	Natural
					dextromethorphan	0.08			
					amitriptyline	<0.05			
					nortriptyline	<0.05			
					codeine	<0.05			
61	m	p	0.16	neg	amantadine	0.61	Hit by car	Trauma	Accident
					verapamil	0.12			
					norverapamil	<0.10			
47	m	p	0.17	0.13	methadone	0.69	Found dead Hx polydrug abuse	Combined drug overdose due to effects of methadone paroxetine, cocaine and ethanol	Accident
					cocaine	0.28			
					cocaethylene	<0.05			
					benzoylecgonine	<0.25			
					trazodone	0.06			
39	m	p	0.2	neg	methamphetamine	0.85	Dead at residence Hx stimulant abuse	ASCVD	Natural
					amphetamine	0.1			
					nortriptyline	0.67			
					carbamazepine	6.2			
					nortriptyline metabolite	pos			
45	f	p	0.23	neg	dextromethorphan	<0.10	Collapse/ resuscitation Hx alcohol abuse	ASCVD	Natural
					imipramine	0.15			
					desipramine	1.1			
					diazepam	<0.10			
					morphine	0.07			
					phenytoin	11			
					acetaminophen	4.5			
					midazolam	0.1			
42	m	p	0.25	neg	*	*	Mental disorder	Chronic alcoholism/ fatty liver	Natural

Table continued

TABLE 6—*Continued.*

Age	Sex	Central/ Peripheral	Paroxetine (mg/L)	Alcohol (g/100 mL)	Other Drugs	Conc. (mg/L)*	Circumstances	Cause of Death	Manner
43	m	p	0.28	neg	morphine codeine trazodone	0.16 0.08 0.42	Death at home paraphernalia present	Acute opiate intoxication	Accident
42	f	p	0.3	0.02	clozapine diphenhydramine	0.48 0.07	Bipolar disorder prior OD attempts	Pulmonary emphysema cardiomegaly, morbid obesity	Natural
45	f	p	0.41	neg	amitriptyline nortriptyline oxycodone quinine dextromethorphan	0.8 0.42 0.27 0.35 <0.10	Chronic multiple illnesses	Alcoholic liver disease	Natural
40	f	p	0.41	neg	alprazolam	<0.05	Found dead following argument	Paroxetine overdose	Suicide
77	m	p	0.47	0.07	*	*	Homicide/ suicide	GSW	Suicide
Stillbirth	m	u	0.55	neg	lidocaine bupivacaine	pos pos	Stillbirth at 38 wks maternal Hx IV drug use	Stillbirth specific cause undetermined	Natural
26	f	p	0.6	neg	morphine	0.05	Hx of drug abuse paraphernalia at bedside	Acute intoxication morphine and paroxetine	Undetermined
42	f	u	0.7	0.18	trazodone oxycodone	3.61 0.19	Suspected overdose	Combined drug overdose	Accident
51	f	u	3.84	neg	dextromethorphan hydroxyzine trazodone	0.21 4.4 0.78	Hx of depression	MI/ASCVD	Undetermined

* No other drugs detected.
** Unless otherwise indicated.

potentiates GABA and olanzapine, (an atypical antipsychotic with $5HT_2$ and D_4 receptor blocking activity) were also present in great excess, and the death was attributed to multiple drug intoxication.

Sertraline

A starting dose of 50 mg/day is recommended, titrating up to 200 mg/day for refractory patients. Serum sertraline levels of 0.03 to 0.19 mg/L were measured in patients after 14-day oral dosages of 50 to 200 mg (52). Patients on chronic oral daily doses of 100 to 300 mg achieved steady-state plasma levels ranging from 0.02 to 0.21 mg/L of sertraline, with N-desmethylsertraline concentrations (the active metabolite) averaging 167% of the parent drug concentration (53). N-desmethylsertraline, like norfluoxetine, is selective for serotonin reuptake inhibition, although it possesses only 10 to 20% of the pharmacological activity of the parent drug (54).

Like fluoxetine, the most common severe adverse reactions associated with sertraline are serotonin syndrome, resulting from interaction with other serotonergic drugs, and combined drug overdose. The latter can result from isoenzyme inhibition, as sertraline is a substrate for CYP3A4 and inhibits both 3A4 and 2D6. In addition, one report of bleeding disorders associated with sertraline use has been reported in the literature (55). The study of incidence of hyponatremia and SIADH cited earlier (44) showed that 86 out of 736 cases involved sertraline. Cases of serotonin syndrome involving sertraline, although less common than those involving fluoxetine, have been reported in which a variety of other drugs, including MAOIs phenelzine, isocarboxazid, and tranylcypromine were present (56–59).

No sertraline-only overdoses have previously been reported in the literature. In a case analyzed by this laboratory, an adult male who committed suicide by drug overdose was found to have sertraline and N-desmethylsertraline blood levels of 0.61 and 1.60 mg/L, respectively, (diphenhydramine was also present at 0.58 mg/L) (60). In another suicidal overdose, a sertraline level of 1.56 mg/L was measured in the blood of a 51-year-old woman (26). The N-desmethyl sertraline concentration was not determined, however, due to the nonavailability of a standard. The benzodiazepine bromazepam and the antipsychotic levomepromazine were also present. A report of the distribution of sertraline in seven fatalities not caused by sertraline intoxication listed central blood concentrations ranging from 0.23 to 0.46 mg/L of sertraline and 0.08 to 0.99 mg/L of N-desmethylsertraline, and noted high liver concentrations of both compounds relative to those in other tissues (27). Finally, McIntyre et al. studied the postmortem tissue distribution of drugs in a sertraline-related death in which the selective MAO_A inhibitor moclobemide and the antipsychotic pimozide were also present (32). The sertraline concentration was 0.08 mg/L, and the death was ascribed to drug toxicity. However, others have noted that the pimozide concentration in that case may have been sufficient to cause death on its own (61).

During the course of this review, 75 fatalities occurred in which sertraline or its metabolite were detected. Of these deaths, 26 were accidents, 23 were suicides, 17 were natural, 8 were undetermined, and one was a homicide. Concentrations of sertraline and N-desmethylsertraline ranged from below the limit of quantitation (0.05 mg/L for both) to 3.03 and 6.20 mg/L, respectively. None of the deaths with concentrations in the therapeutic range were attributed in any significant part to the sertraline; however, as with fluoxetine, sertraline cannot be ruled out as having contributed to the elevated levels of other drugs present in toxic concentrations in these cases, including in this case, trazodone, amitriptyline, and diazepam. Thirty-seven of the cases had concentrations above the normal therapeutic range of up to 0.21 mg/L. Table 5 presents demographic, circumstantial, toxicological and pathological information on these cases. Of these, seven were certified as natural deaths. Sertraline was invoked as a contributory factor in drug toxicity deaths in 17 cases, and was a principle contributory factor in at least five cases. Other drugs were, however, present in all cases attributed to drug toxicity. Sertraline appeared to be the primary contributing factor when blood concentrations were greater than 1.5 mg/L. As with fluoxetine, there was a tendency for the sertraline concentration to be less than that of the metabolite in cases where the parent drug was within the therapeutic range, for reasons discussed above. The mean sertraline/N-desmethylsertraline ratios were significantly different ($p < 0.05$) at 0.74 and 2.00 for the therapeutic ($n = 25$) and supratherapeutic ($n = 36$) groups, respectively.

In terms of potential for interactions with other drugs, TCAs were present in four cases, three of which were attributed to combined drug toxicity. Another SSRI, fluoxetine, was present in only one case, and trazodone was present in five. Of note is one case with a sertraline concentration of 1.25 mg/L, where the death was a result of accidental trauma. The case with a sertraline concentration of 2.52 mg/L most likely represents an intentional overdose, although it was certified as accidental. The drug was substantially transformed into its metabolite also, so that in this case at least, enzyme inhibition by dextromethorphan was apparently not a factor.

Paroxetine

Recommended daily dosing for paroxetine is based on a starting dose of 20 mg with 10 mg increments to 50 mg, until efficacy is achieved. In 29 healthy subjects given a single 20 mg oral dose of paroxetine, peak plasma levels of 0.01 to 0.03 mg/Lwere measured within 3 to 8 h (62). Steady-state plasma levels averaging 0.06 mg/L were measured in 15 healthy adult males who received a single 30 mg/day oral dose for 30 days (43). Paroxetine is extensively biotransformed to largely inactive metabolites via oxidation, methylation, and conjugation, so in contrast to other atypical antidepressants, metabolite concentrations may be regarded as irrelevant with respect to toxicity. One case of serotonin syndrome involving paroxetine has been reported in the literature (13). In this case, the subject, a 51-year-old man, developed symptoms of serotonin syndrome after self-medicating with Nyquil (containing dextromethorphan, known serotonin reuptake inhibitor) while also taking paroxetine; however, no blood drug concentrations were reported. These symptoms later dissipated and the subject fully recovered. This subject also had significant peripheral vascular disease, which may have played a role in his development of serotonergic crisis. Patients such as this one with cardiovascular disease are particularly vulnerable to toxic side effects of paroxetine and other SSRIs due to exaggerated vasoconstriction by excess platelet 5HT (9).

Like fluoxetine, norfluoxetine, and fluvoxamine, paroxetine exhibits autoinhibition of metabolism, which may potentiate both therapeutic and toxic effects of the drug (6). Hyponatremia and SIADH are common side effects associated with paroxetine. The authors of the study of incidence of hyponatremia and SIADH in patients taking SSRIs mentioned earlier (44) found that 91 out of 736 cases involved paroxetine, compared with 554 involving fluoxetine, 86 involving sertraline, and 11 involving fluvoxamine. Cytochrome P450 isoenzyme inhibition may also play a role in toxicity in cases involving other drugs which are CYP2D6 or 3A4 substrates, by extending the half-life, and leading to increased concentrations. Paroxetine is both a substrate and potent inhibitor of 2D6 and a weak inhibitor of 3A4.

A number of fatalities involving paroxetine have been reported in the literature, although often other drugs are present also. In a case of assisted suicide, a 72-year-old woman ingested a large quantity of paroxetine, phenobarbital, amitriptyline, and dimenhydrinate. Paroxetine concentrations in central and peripheral blood, liver, bile, and gastric contents were 5.6, 1.4, 37.0, 2.6, and 1.8 mg/L. Paroxetine could not be detected in vitreous fluid (Logan BK, unpublished data). In another case, a woman who intentionally overdosed on paroxetine was found to have blood and liver paroxetine concentrations of 0.24 mg/L and 3.5 mg/kg, respectively. Amitriptyline was also present, at concentrations of 0.43 mg/L and 6.8 mg/kg (28). Singer and Jones (34) describe a case of apparent serotonin syndrome resulting from a suicidal ingestion of paroxetine and moclobemide, a specific and reversible MAO_A inhibitor. In that case, subclavian blood paroxetine concentrations of 1.58 mg/L were reported, and the authors note that increased neuronal serotonin concentrations would likely precipitate the clenched jaw, incoherence, shivering, and seizures seen in this case that are characteristics of serotonin syndrome. Vermuelen (33) reported two cases of fatalities attributed to paroxetine alone with concentrations of 4.0 and 3.7 mg/L, and a third in which imipramine and desipramine were also implicated with a paroxetine concentration of 1.4 mg/L. A final fatal case involving toxicity from paroxetine alone (63) had a concentration of 0.99 mg/L.

In our series, we report paroxetine concentrations in 28 cases where the drug was detected during a routine postmortem toxicological examination (Table 6). The range of concentrations encountered for paroxetine was from below the limit of quantitation (0.05 mg/L) to 3.84 mg/L. Concentrations exceeded the peak steady state concentration of 0.06 mg/L reported from clinical trials (30 mg/day) in all but one case, which is partly a function of the limits of quantitation for this assay. The lowest concentration at which death was attributed to paroxetine alone was 0.41 mg/L. Several other cases with higher concentrations also had toxic concentrations of other drugs present, so the role of paroxetine was less clear, although again, any drug which is a substrate for P4502D6 could potentially accumulate at toxic concentrations even following appropriate use, due to the inhibition of its metabolism by paroxetine. Surprisingly, the case with the highest concentration of paroxetine (3.84 mg/L) was certified by the coroner as a myocardial infarction due to ASCVD. Given the effects of SSRIs on vascular smooth muscle, it is likely that such an elevated concentration would at least have played a contributory role in the death.

In summary, it appears that many patients achieve blood concentrations of paroxetine well in excess of those expected from clinical studies, without directly fatal consequences, their deaths occurring from a variety of other causes. These concentrations could result from the use of excessive dosing by clinicians, patient

noncompliance with medication, or interaction with drugs which inhibit the metabolism of this class of drugs, particularly other SSRIs, or individual clearance disturbances. Also, as noted earlier since paroxetine exhibits autoinhibition, at elevated concentrations the pharmacokinetics of the drug might approach zero-order elimination kinetics leading to increasing elimination half-lives and blood concentrations. Other factors to consider include the presence of other antidepressant drugs, which selectively or not, block the reuptake of serotonin.

Conclusions

Selective serotonin reuptake inhibitors are a new class of antidepressants preferentially prescribed for a variety of conditions due to the low incidence of untoward side effects associated with their use. The active metabolites of the SSRIs are selective for inhibition of serotonin reuptake like their parent drugs. In spite of their relative safety, SSRIs can still cause or contribute to drug toxicity deaths. The major mechanism is through serotonergic excess, resulting from overdosage, inhibition of the major cytochrome P450 isozymes responsible for their metabolism, or coingestion with other serotonin blocking drugs, or monoamine oxidase inhibitors. This may be manifested as serotonin syndrome, although postmortem diagnosis of this condition is difficult, unless documented clinically proximate to death and so is unlikely to appear on most death certificates even when these drugs are directly implicated. As noted below, acute intoxication in healthy individuals was uncommon; however, the second mechanism which can result in acute toxicity, namely the coronary vasoconstriction or dilation associated with elevated serum serotonin levels, is of considerable importance in the presence of a pre-existing cardiac pathology such as ASCVD, which was a feature of at least 20% of the cases in our series. The concentration of the drug required to produce these effects will vary from patient to patient, as a result of their individual pathology and other drugs ingested. When multiple drugs with serotonergic activity, including other SSRIs, TCAs and MAOIs, are present, even if all are in the therapeutic range, they may be sufficient to contribute to the death in the absence of other anatomic or toxicologic causes.

Drug interactions from illicit drug use, in particular amphetamines and cocaine, are also relevant. Whereas amphetamines and cocaine block reuptake of all major amine neurotransmitters (serotonin, norepinephrine and dopamine), amphetamines also facilitate release, inhibit MAO enzymes and act as partial agonists of monoamine receptors, thereby contributing to the excessive serotonergic or excitatory tone, both centrally and peripherally. These drugs might therefore precipitate serotonin syndrome and vascular accidents in patients prescribed SSRIs, as well as induce acute psychotic state and exaggerated behaviors. The significance of these other drugs should therefore be carefully considered in determining cause and manner of death, especially in cases with ASCVD.

Of the 168 cases reviewed here, fewer than 12 were due to an acute overdose of an SSRI on its own, and these were at consistently elevated concentrations, reflecting large intentional overdoses. In death resulting from overdoses of other drugs which are substrates for the metabolic systems for which the SSRIs or their metabolites are inhibitors, the possibility that even therapeutic concentrations of the SSRI played a contributory role cannot be ruled out.

The apparent safety of this class of drugs is nonetheless a highly positive feature given that the nature of the illness being treated makes this population at high risk for drug overdose as suicidal attempts or gestures. More frequently in our series the drug was taken in overdose with other psychoactive or abused drugs. Generally SSRI agents were not a principal causative or contributing factor in drug deaths at concentrations below 0.63 mg/L for fluoxetine, 0.4 mg/L for paroxetine, and 1.5 mg/L for sertraline. We had insufficient data to make even this crude assessment for fluvoxamine.

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