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Postmortem Forensic Toxicology of Trazodone

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ABSTRACT: Trazodone is a popular antidepressant medication that has been available for approximately 30 years. It has a reputation as a safe drug with relatively few reported fatalities attributed solely to it. We review the pharmacology and forensic toxicology of trazodone and report toxicology and cause and manner of death in a series of 37 deaths in which trazodone was detected.

Although the normal upper therapeutic blood concentration for trazodone is about 2 mg/L, fatalities are rarely attributed solely to it at blood concentrations below 9 mg/L. Considering the pharmacology of the drug, potential interactions between other drugs with serotonin reuptake properties need to be considered, as does the increased susceptibility to the toxic effects in patients with pre-existing heart disease.

In the cases reviewed, none were attributed solely to trazodone, although trazodone was frequently present together with other serotonergic drugs, such as the selective serotonin reuptake inhibitors like fluoxetine and sertraline. Ten cases had blood trazodone concentrations above 2 mg/L. Of these cases, trazodone played a primary role in the death of three subjects, with blood concentrations all greater than 9 mg/L.

We confirm the conclusions of others that trazodone is a relatively safe drug except in massive overdose, although its toxicity may be influenced by the presence of other drugs and underlying pathophysiology.

KEYWORDS: forensic science, trazodone, forensic toxicology, serotonin syndrome

Trazodone (Desyrel®) is an atypical tetracyclic antidepressant, since it possesses antidepressant and also anxiolytic and hypnotic activities. It combines a powerful antagonism of $5HT_{2A}$ receptors and some serotonin reuptake blockade, and is often referred to as a serotonin antagonist reuptake inhibitor (SARIs). Also belonging in this class is nefazodone, a congener with similar indications, but with combined serotonin and norepinephrine reuptake blockade. This antagonism of $5HT_{2A}$ receptors distinguishes trazodone from pure selective serotonin reuptake inhibitors (SSRIs) such as sertraline, paroxetine, fluvoxamine and fluoxetine, and results in fewer unwanted side effects, such as agitation, anxiety, akathisia, and sexual dysfunction. Since its release in the early 1970s, trazodone has been widely prescribed, accounting for approximately one-third of the market for antidepressants in the United States. Its combination of sedation without anticholinergic effects has made it especially attractive in older patients who may be medically compromised or otherwise sensitive to the anticholinergic effects of the traditional tricyclic antidepressants (TCAs).

Trazodone has a reputation as a safe drug, with relatively low toxicity (1). In particular, trazodone has been successfully used in depressed patients with pre-existing cardiovascular disease. To examine this, we conducted a review of literature concerning trazodone-related deaths, and studied a series of deaths in which trazodone was detected in blood drawn at autopsy. The results of this review are discussed with respect to the mechanisms of toxicity that may be associated with death resulting from trazodone overdose, and the potential for drug interactions.

Methods and Materials

Trazodone (Desyrel®) was obtained from Sigma. 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 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. Most samples were peripheral blood, but some were central blood, and some were not labeled as to collection site.

These samples were extracted and subsequently analyzed via gas chromatography/mass spectrometry (GC/MS) using a method described previously (2). Briefly, 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). To increase sensitivity, analyses were performed using selected ion monitoring (SIM) mode. Characteristic fragment ions for trazodone were m/z 371 and m/z 205.

In addition to trazodone, this method was used to analyze the following drugs and metabolites: bupropion (Wellbutrin®) and its threoamino alcohol and morpholinol metabolites, venlafaxine (Effexor®), O-desmethyl venlafaxine, sertraline (Zoloft®), N-desmethyl sertraline, paroxetine (Paxil®), fluvoxamine (Luvox®), fluvoxamine acid, fluoxetine (Prozac®), and norfluoxetine, several of which are often found in combination with trazodone.

Results and Discussion

The above methods were applied to a series of death investigation cases submitted to our laboratory, and concentrations of all drugs found, including trazodone, along with demographic infor-

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mation and circumstances and cause and manner of death, are listed in Table 1. Twelve were accidents, 10 were natural deaths, 11 were suicides, 3 were undetermined, and one was a homicide. Therapeutic and toxic ranges for other drugs present in the blood samples, and their reuptake inhibition properties and the CYP450 isozyme(s) (if known) for which they are substrates were reviewed in preparation for interpretation (3–8). An excellent compilation and discussion of inducers, inhibitors, and substrates of cytochrome P450 isozymes is given by Rudy (3). Table 2 lists drug distribution data for five cases in which multiple tissues were tested.

Trazodone has a half-life of between four and seven hours, and a volume of distribution of 0.9 to 1.5 L/kg. Pharmacologically, trazodone has mixed agonist/antagonist activity on serotonergic systems. It is metabolized by cytochrome P450 isozyme CYP2D6, to its active major metabolite, *m*-chlorophenylpiperazine (mCPP) (see Fig. 1), which is believed to contribute the potent serotonergic agonist properties of the drug (1), and beta-(3-oxo-s-triazolic(4-3α)pyridin-2-yl)propionic acid (OPTA). mCPP is also the active metabolite of nefazodone and the antipsychotics etoperidone and mepiprazole (9). It acts as a partial agonist of $5HT_{1A}$ and $5HT_{2C}$ receptors and blocks $5HT_{2A}$ receptors. In the presence of the full agonist serotonin, however, mCPP behaves as a blocker of 5HT1a and 5HT2c receptors, increasing the amount of serotonin present, which in turn indirectly facilitates noradrenergic transmission. mCPP has a longer half-life than either trazodone or nefazodone, and is hydroxylated by CYP2D6 (3). Since both trazodone and mCPP are metabolized by CYP2D6, responsible also for the metabolism of most CNS and cardiovascular drugs, inhibitors and inducers of CYP2D6 can alter their levels in biological fluids. For example, carbamazepine co-administration was shown to significantly decrease trazodone and mCPP plasma concentrations by induction of metabolism (10). Interestingly, CYP3A4 is also likely involved in trazodone metabolism to mCPP since the CYP3A4 inhibitor ketoconazole inhibited formation of mCPP from trazodone by human liver microsome (11). Therefore, drug interactions with substrates, inducers, and inhibitors of both families of cytochrome P450 2D6 and 3A4 might be expected. Other known pharmacokinetic drug interactions have involved the congestive heart failure drug digoxin (increased level), the antiepileptic phenytoin (increased), and the anticoagulant warfarin (one case of potentiation). Besides drug interactions through metabolism, there are a number of relevant pharmacodynamic drug interactions, in particular that of trazodone with all CNS depressants where the CNS depression will be the additive.

Trazodone possesses strong sedative (antihistaminic) and α_1-blocking properties, with side effects such as drowsiness, orthostatic hypotension, and priapism. The contribution of trazodone to psychomotor impairment, such as might impact driving, however, is less clear with contradictory findings reported (12,13). However, trazodone was found to produce similar dose-related increases in subject-ratings of drug effect and sedation as the benzodiazepine triazolam (14).

The recommended starting dose for trazodone is 150 mg/day, increasing by 50 mg/day at three- to four-day intervals, up to a maximum of 600 mg/day as needed and tolerated (7). In clinical studies involving four adult subjects, an average peak plasma concentration of 2.1 mg/L of trazodone and 0.01 mg/L of mCPP were measured within 2 to 4 h after being given a single 150 mg oral dose (15). Steady-state plasma levels of trazodone ranged from 0.49 to 1.21 mg/L in five patients treated for depression, while concentrations of mCPP ranged from 0.01 to 0.03 mg/L (16).

Despite the fact that trazodone has been widely used since its entry onto the market, questions continue to be raised regarding efficacy and toxicity related to its use. Shopsin et al. (17) cite several unpublished double-blind controlled studies conducted by different groups in which trazodone-treated patients had extremely low rates of response (10 to 20%). Consequently, a problem associated with trazodone therapy is the inability of some patients to tolerate doses sufficient to provide the antidepressant effects of the drug due to the onset of side effects such as oversedation, light-headedness, or confusion. Priapism and mania are two other common side effects associated with trazodone.

Another serious side effect of trazodone is orthostatic hypotension, a consequence of trazodone's potent inhibition of α-receptors. A series of case reports (18–20) has shown that trazodone can induce or aggravate atrial and ventricular arrhythmia, particularly in patients with pre-existing heart disease, but also in individuals with healthy cardiovascular function. However, trazodone appears to be safer in overdose than most other antidepressants, causing only mild central nervous system depression (although possibly serious hypotension) and few fatalities even in large overdoses of trazodone alone (21–27). There has been one case of serotonin syndrome reported in the literature involving trazodone and buspirone, a specific $5HT_{1A}$-agonist, in which only myoclonus appeared in the subject (28). Myoclonus alone, however, does not qualify for serotonin syndrome, and at least some autonomic and consciousness alterations are required to substantiate that diagnosis.

We have described at length elsewhere the main drug-induced complications associated with the use of SSRIs: the serotonin syndrome, bleeding and cardiovascular effects, and inhibition of cytochrome P450 metabolism (2). In light of the serotonergic activity of trazodone, the possibility of developing one or more such complications in patients taking this drug can play an important role in toxicity, and must therefore be considered when interpreting blood levels, particularly when other drugs with serotonergic activity are present.

Several drug overdoses involving trazodone have been reported in the literature over the past few years, although few resulted in deaths (18–27,29–31). Reports of trazodone-related fatalities, however, are rare. Two such reports, both involving women in their 40s who were found dead at their residences, had blood trazodone levels of 15 and 23 mg/L, respectively (29,30). Root and Ohlson (26) reported two overdoses involving trazodone with blood concentrations significantly beyond the therapeutic range. One subject with a blood trazodone concentration of 25.5 mg/L survived with supportive therapy, while the second with a concentration of 9.69 mg/L died. There were several other drugs present in this latter case. Other reports of fatalities include a combined trazodone/dothiepin fatality with blood concentrations of 28.7 and 2.1 mg/L, respectively (31).

Martin and Pounder described the postmortem tissue distribution of trazodone (27) in two fatalities, one with a femoral blood trazodone concentration of 14.4 mg/L (also present were ethanol, 0.107 g/100 mL, and trimipramine, 5.5 mg/L), and the second with a femoral blood trazodone concentration of 15.5 mg/L (also present was ethanol, 0.034 g/100 mL). They concluded that unlike the tricyclic antidepressants, trazodone did not show any preferential concentration in solid organs or exhibit any postmortem redistribution. Our cases, however, showed that the central blood concentration was consistently higher than the peripheral, with an average ratio of 1.5. This is consistent with Anderson and Prouty (32) who reported a heart blood/femoral blood of 1.7 in a single case. This may, however, reflect *in vivo* differences in distribution, given the elevated liver levels, rather than postmortem redistribution (33). Furthermore, there are insufficient data points here to meaningfully

TABLE 1—*Demographic and analytical data on fatalities testing positive for trazodone.*

Age	Sex	Central/Periph.	Blood Trazodone mg/L	Alochol g/100 mL	Other Drugs	Conc., mg/L†	Circumstances	Cause	Manner
51	m	p	0.06	neg	cocaine met lidocaine	pos pos	Hx heart trouble; collapsed suddenly on floor	ASCVD	Natural
47	m	p	0.06	0.13	methadone cocaine cocaethylene benzoylecgonine paroxetine	0.69 0.28 <0.05 <0.25 0.17	Found dead Hx polydrug abuse	Combined drug overdose due to effects of methadone paroxetine, cocaine, and ethanol	Accident
42	m	u	0.11	neg	methadone valproic acid	0.18 16.00	Hx severe obesity Hx depression	Myocardial infarction/ASCVD	Natural
50	m	p	0.11	neg	morphine benzoylecgonine meperidine diltiazem	0.07 2.20 0.60 0.17	Hx opiate & cocaine abuse	Bacterial endocarditis w/sepsis due to parenteral drug abuse	Undetermined
38	m	u	0.13	neg	propoxyphene norpropoxyphene diazepam nordiazepam	8.80 8.20 0.20 0.42	Hx depression Hx Crohn's disease	Acute propoxyphene intoxication	Accident
49	m	p	0.14	neg	meperidine normeperidine hydromorphone paroxetine fluoxetine norfluoxetine	0.73 0.22 0.08 0.10 0.62 0.23	Physician dead in office Paraphernalia present	Multiple drug intoxication	Accident
19	f	p	0.15	neg	tranylcypromine fluoxetine norfluoxetine	1.94 1.38 0.71	Hx manic depression	Drug toxicity fluoxetine and tranylcypromine	Suicide
44	f	p	0.18	neg	cocaine sertraline N-desmethyl sertraline	3.60 0.12 0.17	Found unresponsive drug paraphernalia at scene	Acute intoxication multiple drugs	Accident
37	m	p	0.2	neg	tramadol fluoxetine norfluoxetine	2.40 1.00 0.84	Police stand off Shot self	GSW	Suicide
40	m	p	0.21	0.14	*	*	Strangulation marks and stab wound on neck	Right carotid perforation due to stab wound to neck	Homicide
44	f	p	0.25	neg	morphine, periph. morphine, central	0.20 0.27	Found dead at friend's residence	Acute intoxication due to combined effects of opiates and trazodone	Accident
55	f	p	0.25	neg	propoxyphene norpropoxyphene diphenhydramine metoclopramide fluoxetine norfluoxetine	3.23 0.80 1.26 0.22 0.49 0.29	Hx alcohol and propoxyphene abuse	Acute propoxyphene intoxication	Undetermined
22	f	p	0.26	neg	diazepam nordiazepam promethazine fluoxetine norfluoxetine	0.22 0.21 0.15 <0.05 0.11	Recent cancer diagnosis medications missing	Myocardial infarction/ASCVD	Natural
44	f	p	0.35	0.18	dextromethorphan promethazine antipyrine cocaine cocaethylene benzoylecgonine sertraline N-desmethyl sertraline	0.49 0.98 pos <0.05 <0.05 0.57 2.52 4.05	Hx alcoholism	Acute combined drug intoxication w/contributory cause of cirrhosis and prominent splenomegaly	Accident
61	f	p	0.37	neg	*	*	Hx of ASCVD; died at home	ASCVD	Natural

TABLE 1—*Continued.*

Age	Sex	Central/Periph.	Blood Trazodone mg/L	Alochol g/100 mL	Other Drugs	Conc., mg/L†	Circumstances	Cause	Manner
43	m	u	0.4	neg	alprazolam	<0.10	Hx depression	GSW	Suicide
					fluoxetine	0.24			
					norfluoxetine	0.52			
43	m	p	0.42	neg	morphine	0.16	Dead at home paraphernalia present	Acue opiate intoxication	Accident
					codeine	0.08			
					paroxetine	0.28			
38	f	p	0.5	neg	methadone	0.58	Found dead Hx opiate abuse	Intoxication methadone and other drugs	Accident
					fluoxetine	0.25			
					norfluoxetine	0.30			
38	m	p	0.5	neg	diphenhydramine	1.20	Overdosed on drugs in jail, found w/ suicide note	Multiple drug intoxication	Suicide
					loxapine	1.40			
					sertraline	0.75			
					N-desmethyl sertraline	0.38			
38	f	u	0.58	neg	morphine	0.47	None	Pulmonary edema due to drug overdose	Accident
					acetaminophen	41.00			
					trazodone	0.58			
					oxycodone	0.82			
					diphenhydramine	0.13			
					sertraline	0.80			
					desmethylsertraline	0.52			
35	f	c	0.99	neg	methadone	1.2	Multiple Rx	Pulmonary embolism incompetant mitral valve	Natural
					promethazine	0.81			
					hydroxyzine	0.33			
					fluoxetine	0.66			
					norfluoxetine	0.54			
41	f	u	1.1	neg	fluoxetine	0.80	Long Hx depression	ASCVD	Natural
					norfluoxetine	1.20			
36	m	p	1.26	neg	doxepin	4.50	Diabetic, depressed found dead	Multiple drug intoxication	Undetermined
					desmethyldoxepin	0.55			
					imipramine	0.81			
					desipramine	0.25			
					acetaminophen	3.57			
					zolpidem	0.17			
47	m	p	1.3	neg	methamphetamine	0.21	Hx ethanol and drug abuse; sudden unexpected death	Acute methamphetamine and morphine abuse with chronic ethanolic liver disease	Undetermined
					quinine	3.70			
					morphine	0.02			
					fluoxetine	0.14			
					norfluoxetine	0.24			
39	f	p	1.4	0.08	morphine	0.11	Death after IV drug use	Acute intoxication from fluoxetine, opiates, ethanol, and trazodone	Accident
					fluoxetine	4.60			
					norfluoxetine	4.50			
39	f	c	1.41	0.19	propoxyphene	6.60	Found dead in car; ID'd as official missing person 2 days prior	Acute multiple drug intoxication	Suicide
					norpropoxyphene	0.87			
					codeine	7.00			
					acetaminophen	521.00			
					ibuprofen	37.00			
					hydrocodone	1.28			
					diphenhydramine	1.09			
					sertraline	1.76			
					N-desmethyl sertraline	0.15			
49	m	u	2.00‡	0.20	imipramine	4.86	Hx ethanol abuse and suicidal gestures	Acute intoxication ethanol, imipramine and trazodone	Suicide
					desipramine	0.34			
41	m	u	2.65‡	0.05	fluoxetine	6.66	Found dead at home; advanced decomposition	ASCVD	Natural
					norfluoxetine	20.27			
40	f	u	3.60‡	neg	verapamil	0.83	Recent abdominal surgery; Hx suicide attempts	Low salt syndrome with myocardial fibrosis	Natural
					norverapamil	0.41			
					hydromorphone	0.01			
					lidocaine	pos			
					fluoxetine	1.13			
					norfluoxetine	0.65			

continues

TABLE 1—*Continued.*

Age	Sex	Central/Periph.	Blood Trazodone mg/L	Alochol g/100 mL	Other Drugs	Conc., mg/L†	Circumstances	Cause	Manner
42	f	u	3.61‡	0.18	oxycodone paroxetine	0.19 0.70	Suspected overdose	Combined drug overdose	Accident
27	m	p	4.3‡	neg	amitriptyline nortriptyline phenytoin fluoxetine norfluoxetine	6.50 2.70 15.80 0.14 0.28	Unresponsive at home; survived twelve hours	Combined drug overdose	Suicide
60	f	p	4.40‡	neg	temazepam	2.90	None	ASCVD with likely contribution from temazepam	Natural
50	m	u	4.95‡	neg	fluoxetine norfluoxetine ibuprofen nordiazepam	0.51 2.79 9.77 <0.10	Recently released from detox	ARDS Viral pneumonia	Natural
49	f	p	6.7‡	0.07	venlafaxine norvenlafaxine diazepam nordiazepam	0.33 0.16 <0.10 <0.10	Suicide by train; trazodone bottle on rails	Multiple trauma	Suicide
36	f	p	9.06‡	0.05	oxycodone acetaminophen	0.7 35.7	Hx alcohol abuse and depression; suicide note found at scene	Acute intoxication due to combined effects of trazodone, oxcodone, acetaminophen, and ethanol	Suicide
45	f	p	24.32‡	neg	diltiazepam temazepam sertraline N-desmethyl sertraline	3.35 7.75 1.76 0.57	Hx of depression	Acute intoxication due to combined effects of trazodone and benzodiazepines	Suicide
32	f	u	32.91‡	0.22	fluoxetine norfluoxetine	1.19 0.83	Found dead in motel room w/empty Rx drug bottles; no suicidal note	Acute alcohol and Rx drug overdose	Accident

* No other drugs detected.
† Unless otherwise indicated.
‡ Exceeds generally accepted therapeutic range.
Abbreviations:
ASCVD = Atherosclerotic cardiovascular disease.
GSW = Gunshot wound.
Hx = History.
IV = Intravenous.
Rx = Prescription.
ARDS = Adult Respiratory Distress Syndrome.

TABLE 2—*Postmortem tissue distribution of trazodone.*

Age	Sex	Blood		Bile	Urine	Vitreous	Liver*	Gastric*	c/p Ratio
		Central	Peripheral						
51	M	0.08	0.06	0.06	0.42	0.05	1.25	0.87	1.33
44	F	0.39	0.25	0.42	0.67	0.41	…	0.57	1.56
44	F	0.65	0.35	1.02	4.52	0.08	1.9	38.12	1.86
36	F	11.45	9.06	12.92	28.29	4.7	3.52	308.84	1.26
								mean	1.50
								s.d.	0.27

* All concentrations are mg/L except gastric and liver which are mg/kg.

interpret the statistical significance of these observations. The low volume of distribution (around 1 L/kg) for this drug is generally not associated with marked postmortem redistribution.

Because of the number of mechanisms of toxicity associated with trazodone, its specific role in fatalities is often difficult to determine. A consideration of circumstances, relevant pathology, and toxicology results of cases of trazodone-related death analyzed in this report should provide future investigators with baseline information regarding blood concentrations associated with different types of fatalities, and the likelihood that a role for trazodone can be invoked.

In the 37 cases reviewed here, we evaluated blood trazodone concentrations where the drug was detected during a routine postmortem toxicological examination. The concentration exceeded the normal upper therapeutic concentration of 1.5 mg/L in 11 cases, and was as high as 32.91 mg/L. Within the therapeutic range (<2.0 mg/L), trazodone at a concentration of 0.35 mg/L was probably inappropriately included as a contributory cause of death in a multiple drug overdose involving elevated sertraline, promethazine, and cocaine. There were no cases in which death was attributed to trazodone alone, supporting the reputation trazodone has as a safe drug. Several cases presented here with elevated blood trazodone concentrations, however, also had toxic concentrations of other drugs present, emphasizing the importance of considering the potential for interactions with other drugs or with preexisting disease.

Trazodone was considered by the pathologist to be a contributor to toxicity in five of the intoxication deaths. In one case with a blood trazodone concentration of 3.6 mg/L, the paroxetine concentration was considerably in excess of the normal therapeutic range. The presence of trazodone in this case, however, makes the likely toxicity greater. In one case with a concentration of 6.7 mg/L, the scene circumstances indicated a massive recent overdose, with numerous pills still undigested in the gastric contents. The actual cause of death, however, was suicide by train.

The literature reviewed above supports the potential for fatalities with blood concentrations of around 9 mg/L and greater, while noting the survival of patients with significantly higher concentrations. In our series, this threshold limit appears similar, with only the three latter cases being clearly attributable primarily to trazodone, and in each case the blood trazodone concentration exceeded 9 mg/L. In the final case the death was certified as an accident in the absence of a note, but given the very high concentration, accidental ingestion is unlikely.

While at highly elevated concentrations CNS depression is a likely mechanism of death, at lower concentrations other mechanisms need to be considered. In terms of potential for interaction, a drug with significant serotonin reuptake blocking properties (sertraline, paroxetine, venlafaxine, fluoxetine, amitriptyline, nortriptyline, imipramine, desipramine, tramadol) was also present in 28 (76%) of the cases we reviewed. This strongly suggests a pattern of prescribing trazodone with these other serotonin active compounds, creating the potential for development of elevated serotonin concentrations.

This could, in the extreme, result in a serotonergic crisis, or serotonin syndrome, although there was no clear evidence for this either from the scene, witnesses, or pathology in this series of cases. There are some reports of serotonin syndrome with trazodone, and generally drug interaction is the culprit. Nisijima et al. (34) described a typical serotonin syndrome in a patient receiving trazodone with amitriptyline and lithium. George and Godleski (35) also reported a potential serotonin syndrome with trazodone and fluoxetine co-administration. This latter combination was also responsible for speech dysfunction in patients having suffered traumatic brain injuries (36), and a similar combination, sertraline with trazodone, was associated with dystonia (37). In less extreme cases, however, elevated circulating serotonin may present a significant risk factor for patients with pre-existing heart disease. The cause of death in at least six of these decedents was listed as ASCVD. Trazodone-medicated vasospecific effects may be the factor that precipitated the cardiovascular crisis in these susceptible patients.

Drugs of abuse were frequently found in the decedents in our series also. Morphine was present in four cases, and cocaine and/or its metabolites in five. While trazodone is known to reduce cocaine-induced hypertension, it also results in elevated plasma norepinephrine concentrations when administered together with cocaine (38), providing another risk factor for ASCVD patients. A similar interaction may be expected for methamphetamine, present in one case in this series. Furthermore, the serotomimetic properties of the amphetamines (39) make its consideration as a contributor to serotonin excess important also.

Periodically, concerns are raised about the contribution of specific drugs such as trazodone to suicidal ideation; however, a study of rates of suicide among depressed patients taking ten different antidepressants showed none was associated with an increased rate of suicide (40). These findings justify the conclusions of a British study and advocating the use of antidepressant medications with lower toxicity such as trazodone (23). Prescribers, however, are cautioned that since trazodone may fail to suppress suicidal ideation, at least early in therapy, they should prescribe the minimum number of pills to prevent accidental or voluntary ingestion of massive doses by depressed patients.

Conclusions

Trazodone is a second-generation atypical antidepressant widely prescribed due to its combination of sedation without anticholinergic effects, especially in older, medically compromised patients or those who are otherwise sensitive to the anticholinergic actions of the standard tricyclic antidepressants. As with most of the SSRIs, trazodone's active metabolite, mCPP, also acts on the serotonin system, and it may be appropriate to consider testing for this in future cases, although it is not routinely done. It is clear that trazodone plays a role in a significant number of deaths; however, most of these are multiple-drug intoxications. Among the cases presented here, none were attributable to trazodone alone, although it was a primary causative factor in three cases with blood concentrations between 9.06 and 32.91 mg/L. In light of this fact, it is especially important to consider interaction of other drugs, especially SSRIs, TCAs, and MAOIs in combination with trazodone when assigning cause of death.

The complex vasoactive effects of trazodone on cardiac muscle may be more relevant than previously appreciated, and consideration of the presence of trazodone as an additional risk factor in these cases should not be overlooked.

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