

A review of olanzapine-associated toxicity and fatality in overdose

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Objective: Given the increasing use of atypical antipsychotics in psychiatric populations and the very limited data concerning the safety of such drugs, we examined the available data on olanzapine in untreated overdose situations. **Methods:** Available toxicity data concerning olanzapine were obtained from the Offices of the Medical Examiners of Canada, the Canadian Adverse Drug Reaction Monitoring Program and a review of the literature. **Results:** Despite the complexities and limitations of postmortem data analysis, 29 deaths were identified where an overdose of olanzapine was either the principal cause of toxicity or a significant contributor in combined toxicity. **Conclusions:** Olanzapine is associated with toxicity in certain overdose situations, but evidence of any relation is limited and likely influenced by the higher rates of cardiovascular disease and sudden death in subjects with schizophrenia. **Recommendations:** Similar toxicity data reviews should be conducted for all commonly prescribed psychotropics. Early signal detection and effective notification processes are crucial in the event that serious adverse effects do occur.

Objectif : Compte tenu de l'utilisation accrue des neuroleptiques atypiques chez les patients en psychiatrie et de la somme très limitée de données au sujet de l'innocuité de ces médicaments, nous avons examiné les données disponibles sur l'olanzapine dans des cas de surdose non traitée. **Méthodes :** Les données disponibles sur la toxicité de l'olanzapine ont été recueillies auprès de cabinets d'examineurs médicaux au Canada et du Programme canadien de surveillance des effets indésirables des médicaments, ainsi qu'au moyen d'un examen de la littérature scientifique. **Résultats :** Malgré la complexité et les limites de l'analyse des données après le décès, on est parvenu à établir que dans 29 décès, une surdose d'olanzapine était soit la principale cause de toxicité, soit un facteur contribuant considérablement à une toxicité mixte. **Conclusions :** Dans certains cas de surdose, l'olanzapine est associée à la toxicité, mais on ne peut établir avec certitude cette association, car les taux plus élevés de maladie cardiovasculaire et de mort subite chez les sujets atteints de schizophrénie influent probablement sur les données. **Recommandations :** Il faudrait effectuer d'autres examens semblables s'attachant aux données sur la toxicité de tous les psychotropes fréquemment prescrits. Lorsque des effets indésirables graves se produisent, il est essentiel de détecter rapidement les signaux et de prendre des mesures efficaces de notification.

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Introduction

Olanzapine is an atypical antipsychotic of the thienobenzodiazepine class. Although structurally and functionally related to clozapine, it possesses a more favourable side-effect profile.^{1,2} The symptoms in overdose are generally a reflection of olanzapine's known pharmacological actions and encompass somnolence, mydriasis, blurred vision, respiratory depression, hypotension and extrapyramidal and anticholinergic effects.³⁻⁶

Treated overdoses of up to 800 mg of olanzapine have been associated with blood (serum) concentrations of up to 991 ng/mL and have included symptoms such as central nervous system depression, tachycardia, hyperpyrexia, leukocytosis, elevated creatine phosphokinase levels and paradoxical miosis mimicking opioid or α_2 -agonist intoxication.⁶⁻¹¹

Olanzapine overdoses in children are generally associated with more significant adverse effects.^{3,8,12-17} Children therefore require more active intervention than adults. Olanzapine blood concentrations have been reported to be as high as 472 ng/mL (observed in an infant who survived after ingesting 10 tablets).¹⁸

Although the usual dose range for olanzapine is 5–15 mg/d, there are no standard reference values with respect to the expected concentrations of olanzapine after therapeutic administration. In clinical studies, steady state blood (plasma) concentrations of olanzapine are rarely over 150 ng/mL,¹⁹ but the potential for toxicity has been suggested at concentrations as low as 100 ng/mL.²⁰ However, it should be noted that toxicologic analysis of olanzapine is complicated by tissue redistribution after death, which leads to higher concentrations in postmortem blood samples; but conversely, olanzapine's instability in blood leads to lower concentrations in postmortem blood samples subjected to storage.¹⁸

A presentation at the 47th Annual Meeting of the Society of Forensic Scientists in Ottawa, Nov. 3–5, 2000, on the frequency of detection of olanzapine in deaths investigated by the medical examiner of Alberta stimulated authors to further analyze the available toxicity data concerning olanzapine.

Methods

A comprehensive literature search of databases including, but not limited to, MEDLINE, EMBASE and International Pharmaceutical Abstracts, was conducted

using the keywords *atypical antipsychotics*, *drug toxicity*, *olanzapine* and *overdose*. All cases involving positive toxicology for olanzapine (including deaths ascribed to other causes) investigated by the medical examiner of Alberta were reviewed. All of the Canadian medical examiners and the Health Product Safety Information Division of the Canadian Adverse Drug Reaction Monitoring Program were contacted for information concerning similar cases reported in Canada from September 1996 to June 2001.

In Canadian jurisdictions, toxicology screening depends on the type of death; it is usual in cases of suspected drug overdose or drug abuse. Time from death to discovery is variable and may be unknown. Autopsy or external examination takes place as soon after death as possible (generally same or next day) but may be delayed over weekends and in isolated instances. If examination is delayed, the body is refrigerated as soon as possible. Specimens taken at examination are also refrigerated immediately. Postmortem blood is generally not frozen because freezing breaks up cells, and this interferes with the analysis. Thus, blood is optimally refrigerated at 4°C. Whole blood is used; the blood is not centrifuged because postmortem blood is generally hemolysed and does not separate well into cells and serum. Screening usually takes place within 2 days and determination of positive cases within 1 or 2 weeks. Analysis takes place immediately after extraction. Olanzapine is unstable in blood specimens, and because drug levels in liver are generally much higher and less susceptible to postmortem change, they are more useful for interpretation.

The analysis methods used in the Toxicology Laboratory of the medical examiner of Alberta are as follows (similar principles are employed in other toxicology laboratories).

For the quantitative analysis, postmortem blood, liver homogenate or diluted gastric contents (1 mL) were first made basic with borate buffer (pH = 12, 2 mL, vortex). Internal standard was added (clozapine was used as internal standard for olanzapine quantification until replaced by analog LY170222). The basified specimen was then extracted with 1-chlorobutane (8 mL). The organic fraction was extracted with dilute sulphuric acid (3 mL, 0.1 N) and discarded. The aqueous acid layer was retained and neutralized with sodium hydroxide (0.5 mL, 2 N), and olanzapine and internal standard were re-extracted with 1-chlorobutane. The chlorobutane was separated, concentrated under nitro-

gen and injected onto the gas chromatograph (GC) with nitrogen-phosphorus detection (NPD). The same process was used for sheep blood-based calibrators and controls. All chemicals were reagent grade or better, and solvents were distilled in-glass.

The oven temperature was ramped from 180°C to 300°C at 20°C/min, with the injector and detector temperatures at 260°C and 300°C, respectively. The 5 or more point calibration curve was usually linear over the range 100–5000 ng/mL, with a typical correlation coefficient of $r^2 = 0.99$ and a y-intercept of less than 0.05. Specimens with concentrations exceeding this range were diluted appropriately and re-analyzed. Assays using clozapine as internal standard tended to give quadratic rather than linear calibration curves, but with acceptable correlations (typically 0.997 with a y-intercept of 0.1). Under these conditions, olanzapine eluted at approximately 5.3 min and LY170222 at 5.5 min. Olanzapine extracts are unstable if exposed to air overnight and were analyzed immediately after extraction.

For the qualitative analysis, postmortem blood and urine specimens (when available) were screened by a panel of immunoassays (ELISA, fluorescence polarization immunoassay and radioimmunoassay); they were screened for volatiles (including ethanol) by headspace

GC and for acidic, neutral and basic solvent extracts by GC with NPD, electron capture detection (ECD) and mass spectroscopic detection (MSD). Olanzapine was detected by GC/NPD and GC/ECD and its identity confirmed with GC/MSD by comparison with an authentic standard. Other drugs that were detected were quantified as necessary by GC/NPD, GC/MSD or liquid chromatography procedures.

Results

Of the 29 toxicology cases with recorded olanzapine levels, 11 were reported in the literature (Table 1), 15 by medical examiners (Table 2, Table 3) and 1 in the Canadian Adverse Drug Reaction Monitoring Programme (Table 3). In addition, 2 other cases from the literature were deemed relevant and are discussed, although no olanzapine levels were available.

Elian²¹ and Stevens et al²² reported a case each (1, 2) involving the suicidal ingestion of 600 mg of olanzapine. Anderson and Kuwahara¹⁸ identified olanzapine in 35 cases where the cause of death was not immediately apparent or a toxicology screen had been specifically requested. In most cases, the cause of death was attributed to other drugs (including multiple drug intoxication),

Table 1: Olanzapine toxicity cases from the literature

Study	Case no.	Patient information*		Clinical findings			
		Age, yr	Sex	Olanzapine levels†	Other drugs detected	Cause of death, postmortem findings	Manner of death
Elian ²¹	1	59	F	Blood 4900 Gastric 4100	None	Olanzapine toxicity	Suicide
Stevens et al ²²	2	—	—	Blood 1238	None	Olanzapine toxicity	Suicide
Anderson and Kuwahara ¹⁸	3	23	F	Ht blood 1300 F blood 1200	Paroxetine	Combined effects of olanzapine and paroxetine	Unclassified
Anderson and Kuwahara ¹⁸	4	39	M	Ht blood 4800 F blood 1600	None	Olanzapine toxicity	Accidental Suicide
Gerber and Cawthon ²³	5	63	M	Blood 237 Gastric 17400	None	Olanzapine toxicity	Suicide
Gerber and Cawthon ²³	6	38	M	Blood 675 Gastric 197	Risperidone (negligible)	Olanzapine toxicity and coronary artery disease	Accidental
Robertson and McMullin ²⁰	7	43	M	Blood 160	Lithium	Olanzapine toxicity and seizure disorder	Unclassified
Robertson and McMullin ²⁰	8	20	M	Blood 330	7-amino clonazepam	Olanzapine toxicity	Unclassified
Levine et al ²⁴	9	—	—	Blood 160 Urine 1300	None	Combined methadone and olanzapine toxicity	Unclassified
Levine et al ²⁴	10	—	—	Blood 980 Urine 2800	None	Olanzapine toxicity	Unclassified
Litovitz et al ²⁵	11	21	—	Blood 1700	None	Olanzapine toxicity	Unclassified

Note: F = female; M = male; Ht = heart; F blood = femoral blood.

*Blanks indicate data not recorded.

†Blood levels in ng/mL; gastric total contents in ng/mL; urine in ng/mL.

the decedent's actions or the circumstances involved. Heart and femoral blood olanzapine concentrations ranged from 25 ng/mL to 4800 ng/mL and 25 ng/mL to 1600 ng/mL, respectively. Although these levels were equal to or greater than accepted therapeutic levels, 2 cases (3, 4) specifically indicated olanzapine toxicity.

Of 11 deaths ascribed to natural causes, significant cardiovascular disease was noted in 8 (age range 22–32 yr). Gerber and Cawthon²³ attributed 2 deaths to olanzapine in a 5-month period from December 1997 — 1 was a suicide (5) and the other believed to be due to direct toxicity in a 38-year-old man (6) who had been taking 30 mg olanzapine daily for 8 months before he died (autopsy findings included coronary artery disease and a non-significant blood concentration of risperidone). Robertson and McMullin²⁰ analyzed 58 postmortem whole blood specimens (for most, the cause and manner of death were unknown); olanzapine concentrations ranged from 10 ng/mL to 5200 ng/mL (mean 358 ng/mL, median 130 ng/mL). Two deaths were attributed to olanzapine toxicity — 1 was a 43-year-old man with a history of seizure disorder (7) and the other (believed to be direct toxicity) was a 20-year-old man purportedly taking 70 mg of olanzapine daily (8). Of 7 cases investigated in a 5-month period, Levine et al²⁴

attributed 2 deaths to olanzapine toxicity (9, 10); olanzapine blood concentrations in the other 5 cases were between 40 ng/mL and 270 ng/mL, and urine concentrations were between 190 ng/mL and 500 ng/mL.

Toxic Exposure Surveillance System (TESS) data are compiled by the American Association of Poison Control Centers in conjunction with most US poison control centres. In their 1998 annual report, 7 fatal exposures involving olanzapine were described (6 from acute intentional overdose);²⁵ 3 cases appeared to involve olanzapine alone, but blood levels were available in 1 case only (11). Of the other 2 cases, 1 was a 38-year-old man who died, despite active intervention, of cerebral hemorrhage with hypotension and hyperpyrexia; blood results included hyperglycemia, hypokalemia and elevated creatine phosphokinase. No details were available on the other case attributed to olanzapine toxicity (these 2 cases are included in the total).

Of the TESS cases involving coingestants, 1 was a 35-year-old man who was taking olanzapine 10 mg twice daily and developed hyperpyrexia, refractory hypotension and bleeding after taking a 20-mg paroxetine tablet; he died despite intervention. Wong et al²⁶ reported 5 cases in which cause of death was ascribed to pulmonary embolus, arteriosclerotic heart disease,

Table 2: Olanzapine toxicity cases from the medical examiner of Alberta

Case no.	Patient information		Clinical findings			
	Age, yr	Sex	Olanzapine levels*	Other drugs detected	Cause of death, postmortem findings	Manner of death
12	50	M	Ht blood 1170 Liver 13000 Gastric 460	Bupropion Fluoxetine Norfluoxetine	Acute multiple drug toxicity	Suicide
13	57	F	F blood 970 Liver 18000 Gastric 5500	Paroxetine Chlordiazepoxide Demoxepam Nordiazepam Flurazepam	Acute combined olanzapine and paroxetine toxicity	Suicide
14	51	F	IVC blood 660 Liver 24000 Gastric 600	Codeine Acetaminophen Carbamazepine	Acute combined drug toxicity	Suicide
15	42	F	Cent blood 1700 Liver 27000 Gastric 1000	Codeine Acetaminophen	Combined toxicity of olanzapine and codeine	Undetermined
16	36	F	Ht blood 4410 Liver 47000 Gastric 24000	No other drugs	Acute olanzapine toxicity	Suicide
17	28	M	Ht blood 2000 Liver 56000 Gastric 83000	No other drugs	Olanzapine overdose	Suicide

Note: M = male; F = female; Ht = heart; F blood = femoral blood; IVC = inferior vena cava; Cent = central.
*Blood levels in ng/mL; liver levels in ng/g; gastric total contents in ng/mL.

injuries due to suicide and undetermined sudden death (2 cases). All cases involved other coingestants, and olanzapine blood concentrations ranged from 190 ng/mL to 1240 ng/mL.

Thus, a total of 13 deaths in which olanzapine appeared to significantly contribute, either in combined toxicity or as the principal cause of toxicity, were identified from the literature.

Of the 27 cases from the Alberta medical examiner in which olanzapine was detected, 6 were attributed to olanzapine toxicity. In cases 12, 13 and 14, the high concentrations of concomitant drugs suggested acute combined toxicity, but in cases 15, 16 and 17, olanzapine was the primary intoxicant (olanzapine blood concentrations of 1170, 970, 660, 1700, 4410 and 2000 ng/mL [mean 1810 ng/mL] and liver concentrations of 13 000, 18 000, 24 000, 27 000, 47 000 and 5600 ng/g [mean 30 800 ng/g], respectively). In the other cases, drugs other than olanzapine predominated, except for 1 case

in which olanzapine was the only drug detected, but death was due to diabetic ketoacidosis, and another case in which death was due to atherosclerotic coronary artery disease. Five cases may also have involved excess or an overdose of olanzapine (olanzapine blood concentrations 170–1540 ng/mL, liver concentrations 2500–4900 ng/g), but the primary toxicity was ethanol plus other drugs. Blood concentrations of olanzapine in the remaining 16 cases ranged from 85 ng/mL to 490 ng/mL (mean 260 ng/mL). Five of those examined were found to have significant atherosclerosis, which was determined to be the cause of death. One case involved hypertension, and 2 of those who died had diabetes.

Of the 12 Canadian medical examiners contacted, 4 (Quebec, Manitoba, Yukon, British Columbia) provided 9 cases (18–26). Saskatchewan records drug overdose as cause of death but not the offending drug; Nova Scotia does not have a computerized database;

Table 3: Olanzapine toxicity cases from medical examiners in British Columbia, Manitoba, Quebec and Yukon and from the Canadian Adverse Drug Reaction Monitoring Program

Case no.	Patient information		Clinical findings			
	Age, yr	Sex	Olanzapine levels*	Other drugs detected	Cause of death, postmortem findings	Manner of death
18	43	M	Blood 456	Oxazepam	Combined drug toxicity	Suicide
19	61	F	Blood 206	Procyclidine	Cardiac arrhythmia, previous myocardial infarction, diabetes, cerebral arteriosclerosis and olanzapine toxicity	Unclassified
20	48	F	Blood 352	Codeine Venlafaxine N-desalkylflurazepam 2-OH-ethylflurazepam Metoclopramide Ethanol	Mixed drug overdose, breast carcinoma, asthma and obesity	Unclassified
21	34	M	Blood 55	Phenytoin (negligible) Codeine Oxycodone Alprazolam Citalopram	Cardiac arrhythmia	Unclassified
22	53	F	Blood 5700	Valproic acid	Olanzapine overdose	Unclassified
23	57	F	Liver 7200	Lorazepam Ethanol (decomposition)	Olanzapine overdose	Accidental
24	45	M	Ht blood 1160 Liver 163000 Gastric 940000	No other drugs	Olanzapine overdose and cardiorespiratory failure	Suicide
25	46	M	Liver 10000 Spleen 7400 Gastric 8100	Ethanol (decomposition)	Olanzapine toxicity	Suicide
26	37	M	Blood 1690	None	Olanzapine toxicity	Suicide
27	30	M	Blood 520	None	Olanzapine toxicity	Suicide

Note: M = male; F = female; Ht = heart.

*Blood levels in ng/mL; liver levels in ng/g; gastric total contents in ng/mL; spleen levels in ng/mL.

Newfoundland and Prince Edward Island had no cases on record. Six cases (18–23) involved concomitant drugs; in 3 cases, olanzapine (24–26) was the only drug. Cardiovascular disease and diabetes were reported in 1 case (19), and obesity, asthma and breast carcinoma were reported in 1 case (20).

The Canadian Adverse Drug Reaction Monitoring Program Newsletter of July 2000²⁷ advised that olanzapine was reported as a suspected drug in 22 deaths, including 8 involving suicide or overdose and 14 due to a variety of causes (e.g., neuroleptic malignant syndrome, arrhythmia, myocardial infarction, heart failure and pneumonia, sepsis, sudden death, mesenteric thrombosis, choking and unknown). Of the overdose cases, 1 was previously reported (25), 1 was attributed to primary olanzapine toxicity (27) (blood concentration 520 ng/mL) and 1 was due to combined bupropion and fluoxetine toxicity, also previously reported (12). Malignant hyperpyrexia was reported as the cause of death in an overdose of olanzapine (150 mg) and diphenhydramine (20 mg). The cause of death was not determined in 1 case in which olanzapine was added to an existing regimen of loxapine, nor in 1 case of a patient with hypertension, chronic obstructive pulmonary disease, adrenal insufficiency and irritable bowel syndrome (with a 34-kg weight gain in 2 years) who was taking multiple medications.

Of note, all information provided by the Health Product Safety Information Division is subject to the caveat that data are unpublished and received from a variety of sources; thus, cause and effect relations have not been established.

From medical examiners' reports and the Canadian Adverse Drug Reaction Monitoring Program, there were 16 cases in which olanzapine was identified as the principal cause of toxicity or contributory in combined toxicity.

Discussion

Given the limitations of autopsy material, a causal relation cannot be inferred from the data presented. Nonetheless, there are potentially 29 cases in which acute olanzapine toxicity appears to have contributed to death. These numbers are definitely small when compared with the number of prescriptions for olanzapine, but it is likely that data for many cases (not just involving olanzapine) are not readily accessible and therefore represent underestimates of the total num-

bers of possible drug-related toxicity cases.

The findings have clinical relevance, but the significance, particularly for olanzapine, is unclear given the lack of comparative data at this point. The inherent difficulties in collecting these data include lack of computerized databases, toxicology findings not systematically recorded by drug, and cause of death not recorded as an overdose. Interpretation of postmortem concentrations of new drugs is particularly difficult because no postmortem database exists and perimortem details are usually unavailable. Postmortem concentrations are usually compared with therapeutic or pharmacokinetic data because this is the only information available and, consequently, high concentrations are interpreted as consistent with overdose. Furthermore, the number of cases detected is not only a function of the frequency of drug use in that particular jurisdiction but also of the analytical procedures used by the investigating laboratory. Thus, clozapine, olanzapine and quetiapine are readily detected by standard screening techniques (GC/MSD but not immunoassay) and can therefore be quantified where indicated. However, risperidone and pimozide are not detected by the screening procedures used in most postmortem toxicology laboratories, and their overdose occurrence is thus likely to be under-reported.

The relative safety of the atypical antipsychotics has been comprehensively reviewed elsewhere.²⁸ In a study of elderly patients, Nasrallah et al²⁹ found a lower mortality rate with atypical antipsychotic use (4.8%) than with haloperidol (21.4%) over a 2-year period. Also, a review of 574 inquiries to the UK National Poisons Information Service over 9 months revealed no fatalities after overdoses of atypical antipsychotics.³⁰ The authors concluded that olanzapine and risperidone had a more favourable overdose profile than clozapine or sulpiride, and that monitoring poisons centre inquiries was a useful way of comparing overdose toxicities. However, the outcome of treated overdoses in hospital settings likely differs from outcomes for individuals who do not receive active intervention, and, as the authors comment, patients who die outside of hospital are unlikely to be revealed by inquiries to a poison centre.³⁰

Early administration of activated charcoal may decrease the oral bioavailability of olanzapine by 50%–60%. Gardner et al³¹ reported rapid recovery with the use of activated charcoal in a 29-year-old woman from an overdose of 1110 mg of olanzapine that was associated with initial tachypnea, tachycardia, unstable

blood pressure and hypoxemia. The findings of this review suggest an adverse outcome for patients (often with pre-existing undetected physical pathology such as cardiovascular disease) who take overdoses of multiple medications and do not receive intervention.

Olanzapine has a high volume of distribution (i.e., 10–20 L/kg), and liver levels are significantly higher than blood levels. After death, significant redistribution from liver to central blood specimens occurs, and the higher range of olanzapine concentrations in post-mortem blood is consistently observed independent of any assay differences. Higher concentrations are also observed in central (heart) blood specimens than in peripheral (femoral) blood specimens.¹⁸ Tissue redistribution after death has been demonstrated for tricyclic antidepressants and antipsychotics;^{32,33} consequently, in many postmortem situations, liver concentrations are a more reliable indicator of overdose.

Postmortem olanzapine blood concentrations may not represent true antemortem or perimortem levels and should be interpreted cautiously. In only 1 case of our series (17) was an antemortem specimen available for comparison. The patient died approximately 2 hours after admission to hospital, and the postmortem olanzapine heart blood concentration was elevated 5-fold over the antemortem level. Although most olanzapine-related deaths involve multiple concomitant drug ingestion and other physical risk factors, death due primarily to olanzapine toxicity has been suggested at concentrations as low as 100 ng/mL.²⁰ The stability of olanzapine in postmortem blood during storage should be considered because blood concentrations have been found to decrease by 23%–84% from their original levels during storage.^{18,24} This suggests that dependent upon time of analysis, olanzapine levels may have been even higher at the time of death. Thus, because of olanzapine's instability in blood, sample concentrations should be measured as soon as possible after death. Compounds with a heterocyclic sulfur atom, such as chlorpromazine and perphenazine, are readily oxidized to sulfoxides and sulfones and are unstable in liver homogenates;³⁴ olanzapine may be similarly subject to *in vitro* degradation.

The significant variation in blood concentrations of olanzapine in clinical practice makes it difficult to interpret postmortem findings. The average peak blood (plasma) concentration was 11 ng/mL after a single oral dose of 12.2 mg,²⁴ and it was 10 ng/mL after repeated doses of 10 mg/d.²¹ A number of studies have

suggested a minimum effective therapeutic blood (plasma) concentration of 9–10 ng/mL^{35,36} and a therapeutic range of 9–23 ng/mL.³⁷ However, others report a significantly higher range of values in clinical practice. An analysis of 1653 clinical blood (serum) samples found olanzapine concentrations to range from 3 ng/mL to 390 ng/mL, with 86% of samples between 5 ng/mL and 75 ng/mL (mean 36 ng/mL, median 26 ng/mL).²⁰ Similarly, Xue et al³⁸ proposed a therapeutic range of 5–75 ng/mL on the basis of 231 patient blood (serum) samples in which 90% of values fell within this range (mean 33 ng/mL, median 28 ng/mL). An even wider range (< 5–103 ng/mL) was detected in 369 samples obtained from 173 inpatients taking 5–30 mg/d, and levels were found to be highly variable between individuals (dosing regimens and time of collection relative to time of ingestion were not recorded).³⁶

The rate of metabolism of olanzapine can vary up to 20-fold among individuals, and because of extensive first-pass metabolism (up to 40%), large overdoses result in nonlinear pharmacokinetics leading to significant increases in blood concentrations.⁷ Hiemke et al³⁶ found olanzapine blood (serum) concentrations were increased 3-fold and 2-fold with doses of 5 mg/d and 20 mg/d, respectively, when olanzapine was combined with fluvoxamine, suggesting a competitive inhibition effect. Olanzapine is extensively metabolized in the liver,³⁹ and an impairment of enzyme-mediated metabolism may lead to variable blood concentrations. However, the existence of multiple pathways for olanzapine metabolism suggests that an alteration of one route of metabolism may not necessarily result in significant change in the clearance of olanzapine *in vivo*. In many overdose situations, there is often limited information concerning concomitant medications that were recently prescribed but not necessarily taken at the time of overdose. Furthermore, in clinical practice, antipsychotics are frequently taken in conjunction with other drugs and at greater than recommended doses.

Although the specific pathophysiology remains undetermined at this time, it has been suggested that the most likely mechanism of death in an overdose of olanzapine involves cardiac toxicity at the cellular membrane level.²³ This would be consistent with the inferred nature and rapidity of the terminal event, but there are no data indicative of a direct cardiac toxicity with olanzapine. Sudden death is more common in patients with psychiatric problems, particularly those receiving antipsychotic drugs.^{40–44} A data mining study of the World

Health Organization database of adverse reactions detected a strong signal for an association between clozapine, cardiomyopathy and myocarditis⁴⁴ and for antipsychotics as a group; but in fact, there were fewer reports for olanzapine than for haloperidol or risperidone. An analysis of 85 fatal intoxications found that pimozone and olanzapine were less likely to be associated with death in overdose than prothipendyl and chlorprothixene,⁴⁵ which is surprising given pimozone's known cardiotoxicity.⁴⁶ Prolongation of the QT interval may play a role in fatal arrhythmias, but olanzapine appears to have the least direct effect compared with risperidone, quetiapine or thioridazine.⁴⁶ Cardiovascular disease is an important risk factor for ischemic and thrombotic vascular events as well as for QT prolongation, and the increased prevalence of coronary artery disease in patients with schizophrenia^{42,47} may be relevant in the context of elevated psychotropic drug concentrations after overdose. Similarly, diabetes mellitus and obesity (both additional risk factors for cardiovascular disease) are more prevalent in patients with schizophrenia, and an increased risk of these disorders has been reported in patients taking olanzapine.⁴⁸⁻⁵⁰ Finally, given the frequency of antipsychotic combination therapy and psychotropic polypharmacy in clinical practice, the possibility of increased risk of toxicity when olanzapine is combined with other psychotropics also requires further research.

In summary, although olanzapine has been associated with toxicity in certain overdose situations, evidence of any direct relation remains limited. The adverse consequences of overdose are compounded in psychiatric populations because of frequent, yet often undiagnosed or untreated physical illnesses, complex polypharmacy with high doses of psychotropic drugs and delayed or absent interventions. Infrequent, serious adverse effects can occur, and early signal detection and effective notification processes are crucial when they do occur. It is recommended that similar toxicology data reviews be conducted for commonly prescribed psychotropic drugs.

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