Clinical Reviews

TOXICOLOGY AND OVERDOSE OF ATYPICAL ANTI PSYCHOTICS

Alicia B. Minns, MD and Richard F. Clark, MD

Department of Emergency Medicine, Division of Medical Toxicology, University of California, San Diego, San Diego, California

Reprint Address: Alicia B. Minns, MD, Department of Emergency Medicine, Division of Medical Toxicology, University of California, San Diego, 200 West Arbor Drive, MC 8925, San Diego, CA 92103

Abstract—Background: Second-generation antipsychotic medications, or “atypical antipsychotics,” are now first-line therapy in the treatment of schizophrenia and other psychotic disorders, and are additionally being used in a wide array of other psychiatric and non-psychiatric conditions in both adults and children. Overdose is frequently reported to poison control centers. Objectives: We review the toxicology and general management of poisonings involving the atypical antipsychotic medications. Discussion: The most serious toxicity involves the cardiovascular system and the central nervous system. All typical and atypical antipsychotics cause sedation, which is pronounced in overdose. The most common cardiovascular effects that occur after atypical antipsychotic overdose are tachycardia, mild hypotension, and prolongation of the QTc interval. Other clinical syndromes in overdose include neuroleptic malignant syndrome (NMS) and antimuscarinic delirium. Seizures may be observed. No antidotes exist for these poisonings, but they most often do well with supportive care. Conclusion: Antipsychotic overdose produces a gamut of manifestations that affect multiple organ systems. Treatment is primarily supportive. Specific therapies for NMS, hypotension, and seizures are discussed. © 2012 Elsevier Inc.

Keywords—atypical antipsychotic; overdose; ingestion; poisoning

INTRODUCTION

In 1952, a French surgeon who was exploring strategies to reduce surgical shock noticed that an antihistamine he was using, chlorpromazine, had a powerful calming effect on mentation (1). A psychiatrist, Pierre Denker, heard about these results and decided to try chlorpromazine in some of his most difficult-to-manage patients. The results were remarkable, and chlorpromazine was approved by the U.S. Food and Drug Administration (FDA) in 1954 (1). By the mid 1960s, approximately 50 million people around the world had been treated with this medication, and several other phenothiazines were introduced, including fluphenazine and thioridazine (1). Before that time, patients suffering from most psychiatric disorders requiring medical therapy were treated with sedatives such as barbiturates. Those with severe psychiatric disease were housed in institutions for indefinite periods of time, and treatment was often unsuccessful. In the last half-century, multiple antipsychotic drugs have been marketed and have improved morbidity in many individuals. Second-generation antipsychotics, or “atypical antipsychotics,” were introduced in 1989 and were anticipated to be equally effective for treatment of psychosis. They also had the advertised advantage of fewer extrapyramidal side effects such as dystonias, akathisia, parkinsonism, and tardive dyskinesia, at therapeutic dosing. These medications are now first-line therapy in the treatment of schizophrenia and are additionally being used in a wide array of conditions in both adults and children, including bipolar disorder, tic disorders, eating disorders, obsessive-compulsive disorder, and developmental disorders such as autism (2–4). We review the toxicology of the atypical antipsychotic medications.
DISCUSSION

Epidemiology

Overdose of antipsychotic medications is common. In 2009, there were over 43,000 calls to U.S. Poison Centers regarding atypical antipsychotics (5). In 2010, there were over 4000 calls to the California Poison Control System (CPCS) regarding both pediatric and adult antipsychotic exposures; two-thirds of these calls were regarding intentional ingestions. Ninety percent of 2010 CPCS exposures were to atypical antipsychotics; the remainder was to phenothiazine derivatives. Over 80% of these exposures were managed at a health care facility. There were 8 deaths reported (unpublished data).

Pharmacology

Antipsychotics are most commonly classified as “typical” or “atypical.” They can also be classified by their chemical structure. The “typical” antipsychotics, also called first-generation, include the commonly used butyrophenones (droperidol, haloperidol) and phenothiazines (chlorpromazine, promethazine, prochlorperazine, fluphenazine, thioridazine). These first-generation agents were also categorized based on their affinity for the dopamine D2 receptor as low potency, such as chlorpromazine, or high potency, such as haloperidol. The “atypical,” or second-generation agents, are defined clinically as having minimal or no extrapyramidal symptoms at clinically appropriate doses (6). There are now more than a dozen atypical antipsychotics in clinical use with a variety of differing chemical structures.

All dopamine receptors are coupled to G-proteins. Agonists binding to dopamine D1 receptors stimulate adenylyl cyclase and raise cAMP concentrations. D2 receptor agonists inhibit adenylyl cyclase and lower intracellular cAMP levels. Both first- and second-generation antipsychotics block dopamine D2 receptors. Many of the first-generation phenothiazine agents block both D1 and D2 receptors. The atypical antipsychotics bind less avidly to the D2 receptor, leading to fewer extrapyramidal effects (7). Atypical antipsychotics also antagonize serotonin receptors, mainly the 5HT2A receptor, mitigating the “negative” symptoms of schizophrenia (3). The so-called negative symptoms of schizophrenia include avolition, anhedonia, social withdrawal, and others.

As a class, the atypical antipsychotics have a decreased propensity to cause adverse motor side effects and prolactin elevations as compared to the first-generation antipsychotics. However, both the typical and atypical antipsychotics have side effects that exist along a spectrum and are related to the unique receptor-binding profiles of each agent. For example, some atypical antipsychotics have α1-adrenergic blockade (risperidone, olanzapine, quetiapine, and aripiprazole), which can cause orthostatic hypotension. Some antagonize central and peripheral muscarinic receptors (clozapine, olanzapine, quetiapine), which may result in sedation, sinus tachycardia, and urinary retention (4,8).

Clinical Effects

Antipsychotic overdose produces a gamut of manifestations that affect multiple organ systems (Table 1). The most serious toxicity involves the cardiovascular system and the central nervous system (CNS). All typical and atypical antipsychotics cause sedation due to CNS histamine H1 receptor blockade in therapeutic dosing and is pronounced in overdose. Sedation is most prominent with clozapine and quetiapine (4). The most common cardiovascular effects that occur after atypical antipsychotic overdose are tachycardia, mild hypotension, and prolongation of the QT interval (9). Below we discuss the more serious clinical syndromes that may be observed with antipsychotic overdose and therapeutic misadventure, as well as some unique features of the more commonly used atypical agents.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal idiosyncratic reaction to antipsychotic drug treatment with an incidence of 0.01–0.02%. Although the precise pathophysiological mechanisms of NMS are uncertain, antipsychotic-induced dopamine receptor-blockade is thought to play the pivotal triggering role in the condition (10). Patients with refractory delirium and certain medical conditions such as dehydration are at an increased risk of developing NMS (11). Haloperidol, either alone or in combination with other medications, has been implicated in the majority of reported cases (12). Whether this is related to an increased propensity for haloperidol to cause NMS or simply that this agent is most frequently used in managing refractory delirium in critically ill patients is unknown. The incidence of NMS occurring from atypical agents is unknown, although it has been sporadically reported with most of the commonly prescribed medications (11). Many of the atypical antipsychotic-linked cases of NMS have occurred with clozapine, which is intriguing given that extrapyramidal symptoms occur so rarely with this drug. Additionally, clozapine binds only loosely to the D2 receptor. Together, these characteristics suggest that low extrapyramidal inducing potential does not predict the occurrence of NMS, and D2 receptor affinity is unlikely to be the sole mechanism responsible for NMS (13).

NMS is characterized by hyperthermia, autonomic instability, neuromuscular rigidity, and altered mental status. It is often difficult to distinguish from more
common extrapyramidal side effects of antipsychotics and from other disorders with similar clinical presentations, such as serotonin syndrome. Hyperthermia is nearly universal in NMS, with average temperatures of 39.44°C (103°F) (12). The majority of patients are agitated, have some degree of muscular rigidity, and exhibit additional extrapyramidal effects such as tremor and bradykinesia. Several laboratory abnormalities are typically seen with NMS, although they are not specific for the diagnosis. For example, elevated serum creatinine kinase has been noted in 80% of cases reported in the literature; elevated white blood cell counts have been reported in 64% (12). There are several published diagnostic criteria, however, they all vary in what is considered core criteria.

The most important aspect of treatment of NMS is withdrawal of the offending agent and supportive care, with particular attention to fluid and electrolyte balance and cooling. Pharmacologic interventions aim to reduce muscle rigidity using benzodiazepines and paralytic agents if needed, and controlling the agitation, which may be due to the underlying psychiatric disorder or a response to NMS. Oral dopamine agonists, such as bromocriptine and amantadine, may be utilized to reverse the dopamine blockade, but their use may be limited in critically ill patients (11,14). Dantrolene is a peripheral muscle relaxant and therapy for malignant hyperthermia that works by stabilizing the ryanodine receptor on sarcoplasmic reticulum, and has been recommended for the treatment of NMS. It has not been demonstrated to be particularly effective in the treatment of NMS, with evidence limited to case reports (10). The majority of people who survive an acute episode of NMS recover; however, a minority of individuals experience long-term sequelae such as cognitive deficits (11).

**Antimuscarinic Delirium**

Due to antagonism of central and peripheral muscarinic receptors, antimuscarinic delirium may be observed in overdose of many of the atypical agents. This occurs most often in toxicity with clozapine, olanzapine, and quetiapine, and to a lesser extent or not at all with risperidone, ziprasidone, and aripiprazole (4). Antimuscarinic findings suggesting poisoning include hyperthermia, tachycardia, blurred vision, flushed dry skin, absent bowel sounds, urinary retention, agitation, hallucinations, lethargy, mumbling speech, undressing behavior (generally due to hyperthermia), and repetitive picking behavior. Blurred vision and photophobia may be due to mydriasis. Antimuscarinic effects delay gastric emptying, potentially resulting in a prolonged duration of action or toxicity. Patients may be amnesic to the events.

Treatment of antimuscarinic effects is generally symptomatic. The most life-threatening issue with this toxicity is often the agitated behavior of the patient that can lead to wild, bizarre behavior. Although these individuals are not usually violent as are those exhibiting sympathomimetic toxicity, they can hallucinate and often require either physical or chemical restraint to avoid harm to the patient or the staff who might be involved in the restraint. “Soft” restraints are usually sufficient when needed, but modest sedation with benzodiazepines can be quite helpful. Physostigmine, a carbamate-type cholinesterase inhibitor can also be used in the management of antimuscarinic delirium. Small doses of 1–2 mg administered intravenously can usually reverse the delirium, and patients often will not be as agitated after the pharmacologic effects of physostigmine wear off in 30–60 min. Larger series examining the use of physostigmine have found it safe and effective, with a rare self-limited convulsion being associated with its use (15).

**Prolonged QTc/Dysrhythmias**

Electrocardiogram (ECG) abnormalities and cases of sudden death in patients prescribed antipsychotics have been noted for decades. The possibility of a causal link has been a continuing area of controversy, with concern about a relationship between QTc prolongation, torsades de pointes (TdP), and sudden death leading to the withdrawal or
restricted labeling of several psychiatric medications (16). TdP, from the French “twisting of the points” is an atypical ventricular tachycardia with complexes of changing amplitude that appear to twist around an isoelectric line. Although at times self-limited, TdP can degenerate to ventricular fibrillation, leading to sudden cardiac death.

The QT interval runs from the beginning of the QRS complex to the end of the T wave, representing the time between the onset of electrical depolarization of the ventricles and the end of repolarization. The QT interval shortens with increasing heart rate, and the QTc is the rate-corrected value. Although multiple formulas exist for making this correction, Bazett’s formula (QTc = QT/√RR) is the most widely used. QTc values >450 ms in men and 460 ms in women are generally considered prolonged. The clinical relevance of QT prolongation is unclear. There are not only multiple sources of variability in the measurement of the QTc interval, but there is marked intra-individual variability in the QT interval. For example, the QT differs between ECG leads, known as QT dispersion, and the QT interval is subject to other factors such as food consumption, sleep, and obesity (17). These factors make a strict divide between normal and abnormal QTc problematic.

The repolarization phase of the cardiac action potential is generated by the movement of various ion currents in cardiac cells. The repolarization phase is primarily the result of outward movement of potassium ions through the delayed rectifier potassium channel (IK). Virtually all drugs known to cause TdP have been shown to block this channel. The risk of TdP increases with increasing length of the QTc interval, however, this relationship is not linear. An individual change in the QTc of >60 ms compared to baseline or an absolute QTc >500 ms should raise concern about the risk of drug-induced dysrhythmia (17). There also seems to be a genetic disposition contributing to antipsychotic-induced dysrhythmogenesis, with perhaps up to 10% of individuals who develop TdP possessing mutations associated with congenital long-QT syndrome (16,18).

QTc prolongation with antipsychotic drugs is dose related (19). There are also marked differences between specific agents and their potential for this effect, with ziprasidone and thioridazine causing the most marked QTc prolongation in therapeutic use (17). The majority of studies assessing QTc prolongation have been in chronic therapeutic use, although conclusions have been generalized to overdose patients. Although QTc prolongation has been well reported after atypical antipsychotic overdose, there is a paucity of reported cases of TdP in this situation. Deaths occurring from antipsychotic overdose often involved co-ingestants, and many were due to a non-pharmacologic cause such as aspiration pneumonia (9). QRS prolongation alone, resulting from sodium channel blockade, rarely occurs with these agents, but is most frequently associated with quetiapine.

Metabolic Syndrome

A serious concern for patients on atypical antipsychotics is the development of metabolic syndrome, which encompasses obesity, hypertension, dyslipidemia, and impaired glucose tolerance. This collection of risk factors is associated with increased morbidity and mortality due to type 2 diabetes mellitus and cardiovascular disease. Although the etiology of metabolic syndrome in psychiatric patients is unknown, it is generally believed that the disease itself with the associated lifestyle and dietary habits are contributing factors. Insulin resistance and weight gain also seem to play crucial roles. Patients treated with olanzapine and clozapine have the highest propensity to develop metabolic syndrome (20–22).

INDIVIDUAL AGENTS

Clozapine

Clozapine was the first of the atypical antipsychotics to be developed. It was introduced in the early 1970s with enthusiasm due to its demonstrated low incidence of negative and extrapyramidal effects, but this was followed by voluntary withdrawal from the market in 1974 due to its association with agranulocytosis (23). However, in 1989, as a result of studies demonstrating it to be superior to other antipsychotic drugs in the treatment of refractory schizophrenia, the FDA re-approved the use of clozapine. Clozapine remains a unique agent in both its therapeutic benefit and adverse effects. It is largely free of extrapyramidal effects such as tardive dyskinesia, and is particularly effective at treating the “negative” symptoms of schizophrenia, such as anhedonia, avolition, blunted affect, and lack of emotion (24). Nevertheless, clozapine has several unwanted clinical effects that have lead to discontinuation in about 8% of patients (23). The most common adverse effects include orthostatic hypotension, gastrointestinal symptoms, and sedation. Sialorrhea is a common effect, which is puzzling considering the antimuscarinic effects of this drug (24). Grand mal seizures may be observed in higher therapeutic doses and in overdose. The 1% risk of agranulocytosis with this drug necessitates weekly blood monitoring upon its initiation (1,23). Additionally, clozapine has been rarely associated with myocarditis, an uncommon type I hypersensitivity reaction with mortality estimates as high as 50% (25,26).

Risperidone

Overdoses of risperidone seem to cause minimal effects and are characterized by tachycardia and dystonic reactions. Orthostasis has also been reported and generally responds to intravenous fluids. Dystonic reactions seem to
be the most distinctive feature, occurring in 11% of risperidone overdoses in one series. All cases were treated with benztropine, and in all but one case, symptoms resolved soon after treatment (27). Delayed respiratory depression has been reported but is not a prominent feature in overdose (28).

**Olanzapine**

Olanzapine resembles clozapine both chemically and pharmacologically, although monitoring for agranulocytosis is not required with olanzapine because this effect is much less common (29,30). Overdoses have been characterized by CNS depression and unpredictable fluctuation between sedation and agitation (29,31). Olanzapine ingestions have been associated with increased creatine kinase, although the mechanism by which this occurs remains unclear (32).

**Quetiapine**

CNS depression is the most common adverse effect after quetiapine overdose. Tachycardia and hypotension are also common clinical manifestations in these cases. Quetiapine has a high affinity for histamine and adrenergic α-1 receptors, accounting for the clinical effects. Tachycardia has been reported to occur in about half of overdose patients and is likely from quetiapine’s antimuscarinic effects, as well as a reflex response to α-1-induced vasodilatation (6).

**Ziprasidone**

Ziprasidone has a low affinity for dopamine D2 receptors and a much higher affinity for serotonin (5HT2) receptors; the serotonin/dopamine ratio is one of the highest among the atypicals (33). Ziprasidone is more likely to cause QT prolongation compared to other agents, with a mean prolongation of 15–20 ms over baseline QT durations at peak plasma concentrations in therapeutic use (3,4,34). Although combined poisonings with ziprasidone and other agents have been linked to TdP, uncomplicated ziprasidone overdose has not yet been described to cause this dysrhythmia (35–37). Drowsiness is the most common symptom reported in overdose (38).

**Aripiprazole**

In contrast to the other agents, aripiprazole acts as a partial agonist at D2 and serotonin 5-HT1a receptors, and as an antagonist at 5-HT2a receptors (39). Due to this unique pharmacologic profile, it has been labeled a “third-generation” antipsychotic and dopamine-serotonin stabilizer (40). Reports of overdose suggest that aripiprazole mainly causes sedation, which can be delayed. One report describes the onset of sedation in a patient occurring at 9 h after an intentional overdose (39). However, aripiprazole lacks clinically significant effects on cardiac conduction and is well tolerated in reported series thus far (40–42).

**Amisulpride**

Amisulpride is a new antipsychotic with high affinity for D2 and D3 dopamine receptors, with lower affinity for serotonergic, adrenergic, and cholinergic receptors (43). Amisulpride overdose has been characterized by cardiac effects, with CNS effects being less common. This contrasts with most newer antipsychotics that predominantly cause CNS depression. In a recent prospective cohort, TdP occurred in 7% of overdoses, and more than two-thirds of patients developed prolonged QT interval (44).

**Paliperidone**

Paliperidone (9-hydroxy risperidone) is the newest atypical antipsychotic to be approved by the FDA and is the major active metabolite of risperidone. Risperidone requires metabolism by hepatic CYP2D6 to the active metabolite for effectiveness. Paliperidone is only heptically metabolized to a small extent, therefore, is effective in patients who have hepatic dysfunction or impaired CYP2D6 metabolism. Paliperidone is available as an extended-release formulation with a unique three-layer delivery system, allowing for steady release of the drug over 24 h, with maximal serum concentrations at 24 h (45). Limited experience in overdose suggests that tachycardia is a common adverse event. Due to the unique design of this drug, delayed and sustained toxicity may occur (46,47).

**MANAGEMENT OF ATYPICAL ANTIPSYCHOTIC OVERDOSE**

Diagnosis of antipsychotic overdose is based on a history of ingestion coupled with predictable symptoms and physical findings. Plasma concentrations of specific atypical antipsychotic agents are not widely available, and although helpful in forensic settings, are not useful in the acute management of an overdose patient. Co-ingestion is common, and obtaining a serum acetaminophen concentration should be considered in all cases. There are numerous other common co-ingestants with routinely available serum levels such as ethanol, salicylate, lithium, and valproic acid often found in overdose patients with access to psychiatric medications; screening for these specific agents should be based on the history and physical examination. Routine urine drug-of-abuse screens do not detect antipsychotics and are not helpful in the acute management of an adult overdose patient.
Gastric emptying procedures are rarely if ever necessary with any antipsychotic medications. Activated charcoal will bind virtually all psychiatric medications (with the exception of lithium) and may be considered if administered within an hour of ingestion, as long as no contraindications exist, such as the presence of sedation or vomiting. Paliperidone is so far the only sustained-release atypical antipsychotic preparation, and with its potentially prolonged absorption, whole bowel irrigation with an isoelectric polyethylene glycol solution may be considered.

In acute overdose of an antipsychotic agent, an ECG should be obtained and cardiac monitoring initiated. If ECG abnormalities are noted, cardiac monitoring should be extended. Serum electrolytes should be checked and abnormalities corrected, especially hypokalemia and hypomagnesemia, because their presence may exacerbate QT-related dysrhythmias. Hypotension resulting from peripheral α1-blockade typically responds to intravenous fluids. If vasopressors are required, an agent with α-agonist activity, such as norepinephrine or phenylephrine, should be used. Seizures should be treated with benzodiazepines or barbiturates.

Antipsychotic overdose should always warrant monitoring of the QRS and QT durations of the patient’s ECG. QRS prolongation from sodium channel blockade, at times leading to ventricular dysrhythmias, was once more common after overdose of first-generation agents such as thioridazine, but has largely disappeared with the atypical agents (47). However, monitoring of QT duration in these atypical antipsychotic poisonings is important. There is no proven therapy to correct QT prolongation after antipsychotic poisoning, and all patients with prolonged QT or QTc intervals should be monitored until all symptoms resolve and durations have returned to normal. If ventricular dysrhythmias such as TdP occur, standard therapy with magnesium and overdrive pacing should be considered, but the efficacy of these treatments in this setting is unproven. QRS prolongation will be rare in overdose of the atypical agents unless co-ingestants are involved. If QRS prolongation (> 120 ms) is observed in overdose of these agents, sodium bicarbonate should be administered until serum pH is normalized, and toxicity from other psychiatric medications should be suspected.

Finally, most of the atypical antipsychotic agents have a high degree of lipid distribution within the body. Recent case studies and animal models have proposed the use of high doses of intravenous lipid emulsion as a means of decreasing toxicity after overdose of lipid-soluble agents such as bupivacaine (48). This idea has been used in overdose of atypical antipsychotics with mixed success (49). If considered, lipid emulsion therapy should be instituted with a bolus of 1.5 mL/kg of a 20% solution, followed by an infusion if indicated.

In patients undergoing psychiatric evaluation in the Emergency Department, it is recommended to obtain a baseline ECG if a new therapy is being instituted, especially for agents known to have the greatest effect on the QTc, such as ziprasidone (4). Similarly, Emergency Physicians need to consider a patient’s medication list when instituting a new medication that could additively prolong the QTc interval.

Most antipsychotic medications, including the atypicals, with the exception of paliperidone and possibly aripiprazole, are rapidly absorbed from the gastrointestinal tract, and symptoms should begin within 6 h of ingestion. Asymptomatic individuals at the end of a 6-h observation period (with the exception of the paliperadone and aripiprazole), can generally be medically cleared unless co-ingestants are involved or other medical conditions need to be considered.

**CONCLUSION**

Although the atypical antipsychotic medications may be judged as safer than the older typical antipsychotics, their potential effects on multiple organ systems need to be considered in overdose patients. Monitoring for neuroleptic malignant syndrome, antimuscarinic delirium, and cardiac effects are concerns, as well as the potential for seizures, extrapyramidal effects, and agranulocytosis (with clozapine).

**REFERENCES**


ARTICLE SUMMARY

1. Why is this topic important?
   Atypical antipsychotic medications are commonly prescribed, and overdose of these medications is frequently reported.

2. What does this review attempt to show?
   Antipsychotic overdose produces a gamut of manifestations that affect multiple organ systems.

3. What are the key findings?
   The most serious toxicity involves the cardiovascular system and the central nervous system. Possible effects include neuroleptic malignant syndrome, antimuscarinic delirium, and cardiac effects such as prolongation of the QTc interval, as well as hypotension and seizures.

4. How is patient care impacted?
   Although the atypical antipsychotic medications may be judged as safer than the older typical antipsychotics, their potential effects on multiple organ systems need to be considered in overdose patients. Monitoring of QT duration is important. Management of overdose is largely supportive.