

Overdose of Atypical Antipsychotics

Clinical Presentation, Mechanisms of Toxicity and Management

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Abstract

Historically, treatment for schizophrenia focused on sedation. The advent of the typical antipsychotics resulted in treatment aimed specifically at the underlying disease, but these agents were associated with numerous adverse effects, and were not particularly effective at treatment of the negative symptoms of schizophrenia. As a result, numerous atypical agents have been developed over the past 2 decades, including several agents within the past 5 years.

Overdose of antipsychotics remains quite common in Western society. In 2010, poison control centres in the US received nearly 43 000 calls related to atypical antipsychotics alone. Due to underreporting, the true incidence of overdose with atypical antipsychotics is likely much greater. Following overdose of an atypical antipsychotic, the clinical effects observed, such as CNS depression, tachycardia and orthostasis are largely predictable based on the unique receptor binding profile of the agent. This article, which focuses on

the atypical antipsychotics commonly used in the treatment of schizophrenia, discusses the features commonly encountered in overdose. Specifically, agents that result in QT prolongation and the corresponding potential for torsades de pointes, as well as unique features encountered with the various medications are discussed. The diagnosis of this overdose is largely based on history. Routine use of drug screens is unlikely to be beneficial. The primary goal of management is aggressive supportive care. Patients with significant CNS depression with associated loss of airway reflexes and respiratory failure need advanced airway management. Hypotension should be treated first with intravenous fluids, with the use of direct acting vasopressors reserved for persistent hypotension. Benzodiazepines should be used for seizures, with barbiturates used for refractory seizures. Intravenous magnesium can be administered for patients with a corrected QT interval exceeding 500 milliseconds.

1. Background

Prior to the 1950s, pharmacological treatment for schizophrenia relied nearly exclusively on the administration of sedative-hypnotic agents, such as barbiturates. The advent of two agents, the phenothiazine chlorpromazine and the butyrophenone haloperidol, marked a paradigm shift in the management of schizophrenia. No longer was the primary medicinal focus to simply provide sedation during periods of agitation, but rather, specific therapy was directed at controlling positive signs (e.g. delusion, hallucinations) of disease. These first two classes of antipsychotic medications, the phenothiazines and butyrophenones, also known as neuroleptics, are now referred to as 'typical' antipsychotics.

While the typical antipsychotics were beneficial at controlling positive symptoms, they provided relatively poor control of negative symptoms (e.g. alogia, social withdrawal) associated with schizophrenia.^[1] Consequently, in the 1990s, the atypical antipsychotics were developed. Characteristics that distinguished this new group of agents included production of fewer extrapyramidal symptoms (EPS) at therapeutic doses, a low tendency to cause tardive dyskinesia with prolonged administration, and efficacy in treating both positive and negative symptoms associated with schizophrenia.^[1-4]

Traditional thinking regarding the mechanism of schizophrenia resides on the dopamine hypo-

thesis, which suggests that many of the symptoms of schizophrenia are related to dopamine receptor agonism. Support for this hypothesis is based on the observations that dopamine D₂ receptor antagonism improves psychotic symptoms, and that dopamine agonists, such as amphetamines, can induce psychosis.^[5] This theory has come under question in recent years, however, as newer, more comprehensive theories have been developed. Alternative theories include the 'serotonin/dopamine' hypothesis, which suggests that serotonin 5-HT_{2A} receptor antagonism results in disinhibition of dopamine neurons.^[6] The efficacy of atypical antipsychotics, which target the 5-HT_{2A} receptor, supports this theory. Another theory, the glutamate theory, suggests that dysfunction of the glutamatergic system may be associated with psychosis, including schizophrenia.^[6] More recent evidence suggests partial agonism of the 5-HT_{1A} receptor, along with antagonism of the 5-HT₆ receptor (e.g. iloperidone) or 5-HT₇ receptor (e.g. lurasidone) may also be important in the management of schizophrenia.^[7] The existence of multiple theories, each with some supporting evidence, reflects the complexity of schizophrenia, and the importance of multiple different neurotransmitters and receptors in this disease.

In recent years, numerous new atypical antipsychotics have been introduced to the market. This manuscript reviews the clinical experience with overdose of these agents, and presents the required diagnostic and treatment management strategies.

2. Receptor Affinity

An understanding of the receptor binding profile of the antipsychotic agents allows the clinician to accurately predict both adverse effects that may occur with therapeutic dosing and toxic effects observed following overdose. Toxic effects are largely an exaggeration of pharmacological effects.^[2] Table I lists the receptor binding profile of common atypical antipsychotic agents.

Unlike the typical antipsychotics whose efficacy is derived from their affinity for the D₂ receptors, many of the newer, or atypical, antipsychotics derive their therapeutic efficacy from their affinity for various serotonin receptors. Of the many serotonin receptors, the 5-HT_{2A} receptor is the most often targeted of the atypical antipsychotics.

The beneficial and therapeutic effects of the typical antipsychotics are believed to occur as a result of D₂ receptor antagonism involving the mesolimbic and mesocortical system. The antiemetic property is believed to be the result of D₂ receptor antagonism in the area postrema (chemoreceptor trigger zone) of the medulla oblongata. Antagonism of the D₂ receptors in other regions of the brain, however, is believed to be responsible for many of the adverse effects of these agents. Antagonism in the tuberoinfundibular region is associated with hyperprolactinaemia, while blockade in the nigrostriatal region is as-

sociated with EPS. Blockade of D₂ receptors in the anterior hypothalamic region is associated with alterations in temperature set-point, and may be involved with the hyperthermia associated with neuroleptic malignant syndrome (NMS).^[13,14] While as a class the atypical antipsychotics have less affinity for D₂ receptors than the typical antipsychotics, many do have some D₂ receptor antagonism and, as a result, these same adverse effects, including EPS, can occur with the atypical antipsychotics. EPS occur in 50–75% of patients treated with typical antipsychotics. While the incidence of EPS is believed to be lower with the atypical antipsychotics, the exact incidence is not known.^[15]

Each atypical antipsychotic has a somewhat unique receptor binding profile. As a result, various agents within the classification of atypical antipsychotics have the ability to antagonise multiple different neurotransmitter receptors, including the α -adrenergic, histamine, muscarinic, dopamine and serotonin receptors. Atypical antipsychotics often antagonise the α -receptors, especially the α_1 -receptors on blood vessels, which may lead to peripheral vasodilation and subsequent orthostasis.^[16] Antagonism of the histamine H₁ receptors can cause sedation, while antagonism of the muscarinic M₁ receptors results in the classic anticholinergic toxicity, including mydriasis, tachycardia, hyperthermia, urinary retention and altered mental status.^[2,16,17] Virtually all antipsychotics

Table I. Receptor affinity (antagonism) based on drug^[2,8-12]

Drug	Dopamine D ₂	Serotonin 5-HT _{2A}	Muscarinic M ₁	Histamine H ₁	α -Adrenergic α_1
Amisulpride	2+	0	0	0	0
Aripiprazole	3+	3+	0	2+	2+
Asenapine	3+	3+	0	3+	3+
Clozapine	2+	3+	3+	3+	3+
Iloperidone	3+	3+	0	2+	0
Lurasidone	3+	3+	0	0	2+
Olanzapine	2+	3+	3+	2+	2+
Paliperidone	3+	3+	0	2+	3+
Quetiapine	1+	1+	3+	3+	3+
Remoxipride	1+	0	0	1+	0
Risperidone	3+	3+	0	0	2+
Sertindole	3+	3+	0	0	1+
Ziprasidone	3+	3+	0	0	3+

antagonise presynaptic and postsynaptic D₂ receptors in the CNS. When treatment is first initiated, antagonism of the D₂ receptor results in increased production and release of dopamine from the presynaptic cell. With on-going use, however, depolarization inactivation occurs, with a resultant decreased production and release of dopamine, along with continued postsynaptic receptor blockade.^[18] This concept of delayed inactivation of the dopamine receptors is commonly referred to as depolarization block.^[18] Antagonism of the serotonin receptors is believed to be responsible for the reduced rates of EPS associated with the atypical antipsychotics.^[7,19]

3. Pharmacokinetics/Toxicokinetics

While most of the atypical antipsychotics have relatively similar pharmacokinetic profiles, significant interindividual variation does occur. At therapeutic dosing, most drugs achieve the time to maximal concentration (t_{\max}) in less than 4 hours.^[2,20-27] Sertindole, olanzapine, ziprasidone and paliperidone, however, are notable exceptions.^[2,28-30] Olanzapine, ziprasidone and sertindole do not achieve a t_{\max} until 6, 7 and 10 hours, respectively.^[2,28] Due to a unique drug-delivery matrix, the t_{\max} of paliperidone is 25 hours.^[2,31-33] It should be noted that in overdose, however, the t_{\max} of a drug may be delayed, especially if the atypical agent possesses antimuscarinic activity, which can delay gastric emptying and slow gastrointestinal motility. Most atypical antipsychotics have a large volume of distribution, with risperidone, ziprasidone, sulpiride and remoxipride being exceptions.^[2,30,34,35] Virtually all, with the exception of amisulpride, are extensively protein bound.^[36,37]

4. Overdose: Overview

In 2010, nearly 43 000 cases involving atypical antipsychotics were reported to US Poison Control Centers, with more than 13 200 of these cases representing patients treated in a healthcare facility. Despite the common occurrence of such ingestions, fatalities remain quite uncommon, with a case fatality rate of approximately 0.02%.^[38]

Due to their small size and lack of tolerance, paediatric patients may be at increased risk of developing symptoms following single pill ingestion of atypical antipsychotics.^[39]

The primary toxicities associated with overdose of atypical antipsychotic agents involve the neurological and cardiovascular systems.

Sedation is commonly encountered following overdose.^[16] The risk of CNS depression is dose-dependent, and large overdoses may produce coma. Profound CNS depression may lead to respiratory depression and loss of airway reflexes.^[40,41] As with the typical antipsychotics, all atypical antipsychotics have the ability to lower seizure threshold.^[16] The risk of seizures following overdose appears to be greatest with clozapine.^[33]

Clozapine, olanzapine and quetiapine each produce significant antagonism of the M₁ receptor.^[8] As a result, overdose of these agents can produce an agitated delirium characteristic of anticholinergic toxicity. Many antipsychotic agents also produce substantial α -adrenergic receptor blockade, which can result in miosis.^[2,42,43] Affinity of the atypical antipsychotic agents for α -receptors in the eye is greater than affinity for muscarinic receptors; therefore, miosis may occur despite presence of anticholinergic toxicity.

Extrapyramidal syndromes can occur with either typical or atypical antipsychotics. These syndromes can be divided into reversible and non-reversible symptoms. Reversible extrapyramidal syndromes include NMS, acute dystonia, and acute akathisia; all of which may occur as the result of an acute overdose. The non-reversible symptoms (e.g. tardive dyskinesia) are not likely to occur as a result of an acute overdose. Similarly, some of the EPS that occur over weeks (e.g. Parkinsonism) are unlikely to occur as a result of an acute overdose.^[44-48]

Cardiovascular manifestations characteristic of overdose of most atypical antipsychotics include hypotension, tachycardia and QT prolongation. Peripheral vasodilatation with reflex tachycardia and resultant orthostatic hypotension is commonly encountered due to significant α_1 -receptor antagonism. Muscarinic receptor antagonism may also contribute to the tachycardia. Antagonism of the delayed rectifier potassium channel (K_{IR})

may also occur, leading to prolongation of the corrected QT interval (QTc) on an ECG. The risk of QT prolongation and resultant torsades de pointes is dose dependent.^[16] As such, the risk of torsades de pointes is slightly increased in overdose.^[49] However, it should be realized that Bazett's formula tends to overestimate the QTc in tachycardic states. Thus, because many of these agents cause a co-existing tachycardia, the risk of torsades de pointes is probably less at a given QTc from overdoses on these agents, than a corresponding QTc at a lower heart rate. Furthermore, despite QT prolongation, the development of torsades de points remains relatively uncommon with use of antipsychotic drugs in the absence of a predisposing state, such as hypokalaemia, multiple drug ingestion and possibly certain genetic channelopathies.^[50] Monomorphic ventricular dysrhythmias are rarely described following an isolated atypical antipsychotic overdose.^[51]

5. Overdose (Specific Agents)

5.1 Amisulpride

Amisulpride is a substituted benzamide derivative, with a unique binding profile at the dopamine receptors.^[52,53] At low doses, amisulpride preferentially blocks presynaptic dopamine receptors responsible for dopamine synthesis and release, while at higher doses, it preferentially blocks postsynaptic dopamine receptors.^[53] Therapeutically, amisulpride is also associated with a biphasic absorption, in which one peak occurs 1 hour post-ingestion, while a second peak occurs after 3–4 hours.^[53] It is unclear if this biphasic response occurs with large overdose.

While overdose experience is somewhat limited, there have been several cases described in which QT prolongation has occurred, as has torsades de pointes.^[49,54,55] Amisulpride may have some vagotonic effects, thereby causing bradycardia.^[56] Several cases involving amisulpride overdose describe relative or absolute bradycardia, with toxicity progressing over many hours. As a result, Isbister and colleagues have suggested that all amisulpride overdoses be observed for at least 16 hours post-ingestion.^[54] However,

in their case series, while cardiotoxicity progressed over hours, none of the four patients were asymptomatic and then developed late dysrhythmias. Consequently, while 6 hours of observation may be sufficient to medically clear an asymptomatic patient with a normal QT interval, a prolonged observation period may be indicated. A seizure has been described in a 30-year-old woman following an ingestion of amisulpride and dothiepin.^[57] However, given that tricyclic antidepressants are well known for inducing seizures, it is not clear what role the amisulpride had with regards to the seizure. CNS depression is frequently encountered.^[54] Because amisulpride has minimal, if any, α -effects at therapeutic dosing, orthostatic hypotension is unlikely to be encountered with overdose.

5.2 Asenapine

Asenapine, which was first introduced into the US market in 2009, is one of the newest atypical antipsychotic agents available.^[58] Unlike many other antipsychotics that are available in pill formulation, asenapine is only available as a sublingual tablet.^[59] Asenapine has a very low bioavailability (<2%),^[60] which might be beneficial in the case of an oral overdose. There are no published cases of asenapine overdoses, but CNS depression and QT prolongation may be expected. Because of significant affinity for the α -receptor, orthostatic hypotension would likely be encountered following overdose.

5.3 Aripiprazole

Aripiprazole is often considered a third-generation antipsychotic, because of its unique pharmacological profile. This drug is a mixed agonist-antagonist at the dopamine and serotonin receptors.^[61] Following overdose, CNS depression, tachycardia, gastrointestinal upset and sedation have been described.^[61,62] The CNS dysfunction can be prolonged.^[61,63,64] Furthermore, EPS have been described in a case of a 6-year-old who ingested a single 10 mg tablet of aripiprazole. In that case, the symptoms of drooling and flaccid facial muscles promptly resolved following the administration of diphenhydramine.^[61]

Unlike with many other atypical antipsychotics, significant QT prolongation is not a common feature of aripiprazole overdose.^[62] In fact, some data actually suggest that there may be some mild reduction in the QT interval.^[65] Due to the affinity of aripiprazole for the α -receptors, orthostatic hypotension can occur following overdose.

5.4 Clozapine

Clozapine was the first atypical antipsychotic introduced into the US market. Because of an unacceptably high rate of agranulocytosis, clozapine was initially withdrawn from the market, but re-emerged due to its superiority over other atypical antipsychotics for treatment of schizophrenia. Today, it is available only as part of a strict prescribing regimen for treatment-resistant schizophrenia.^[66]

Acute clozapine overdoses frequently result in CNS depression and tachycardia.^[67] Respiratory failure can occur. Despite its antimuscarinic properties, sialorrhoea is commonly encountered during therapy or following an acute overdose.^[68,69] Torsades de pointes has rarely been described following clozapine overdose, but these cases involved co-ingestants.^[70]

Agranulocytosis is occasionally encountered following chronic consumption of clozapine. Because it is an idiosyncratic reaction rather than dose-related, agranulocytosis is not expected following an overdose. In addition to agranulocytosis, chronic use of clozapine is associated with cardiotoxicity, including myocarditis and cardiomyopathy.^[71] While more common with chronic usage, myocarditis has been described following acute overdose of clozapine as well.^[72]

5.5 Iloperidone

Iloperidone, which is structurally related to risperidone, is the most recent atypical antipsychotic approved for use in the US.^[33] In pre-marketing studies, iloperidone was associated with significant increase in the QT interval.^[73] While human data on overdose are lacking, CNS depression, EPS, orthostasis and tachycardia would be expected. At therapeutic doses, iloperidone is not associated with any antimuscarinic proper-

ties,^[73,74] and as such, anticholinergic-induced delirium would not be expected in overdose. Because iloperidone does not have significant α -effects at therapeutic dosing, orthostatic hypotension would not be expected following acute overdose.

5.6 Lurasidone

Lurasidone joins asenapine and iloperidone as being one of the three new antipsychotics recently approved for use in the US for the management of schizophrenia.^[75,76] Lurasidone does not have high potency at the α_1 -receptor, and thus, orthostatic hypotension is relatively uncommon at therapeutic dosages.^[75,76] However, the incidence of orthostasis appears to be dose dependent^[75] and, thus, may be quite significant following overdose. During pre-marketing studies involving patients taking therapeutic dosages of lurasidone, significant QT prolongation was not observed.^[75] No human overdose data have been published. Nonetheless, CNS depression, orthostatic hypotension, tachycardia and possibly QT prolongation would be expected.

5.7 Olanzapine

Olanzapine overdose causes symptoms typical of other atypical antipsychotics; CNS depression, miosis, tachycardia and anti-muscarinic-induced delirium.^[77-79] Coma, respiratory failure and hypotension can occur following large overdoses.^[43,51,79] Furthermore, like most other atypical antipsychotics, QT prolongation can occur.^[51] Symptoms usually resolve within 48 hours, but in the setting of massive overdose can be prolonged.^[79] In one small case series of olanzapine overdose, several patients developed rhabdomyolysis.^[78] However, it is not known based on this case series if the rhabdomyolysis was the result of the olanzapine directly, or rather, the consequence of prolonged CNS depression.

5.8 Quetiapine

Quetiapine is an atypical antipsychotic with significant antagonism of α_1 -receptors. This is responsible for the orthostatic hypotension commonly

encountered following overdose.^[2] Overdose of quetiapine may produce more hypotension than observed with overdose of other atypical antipsychotics.^[80] Because of significant affinity for the M₁ receptors, antimuscarinic features, including delirium and tachycardia, are common.^[2,80] Prolongation of the QT interval can occur.^[81-83]

5.9 Risperidone/Paliperidone

Risperidone is a prodrug, which requires metabolism to the active metabolite (9-hydroxyrisperidone) via cytochrome P450 (CYP) 2D6.^[84] Paliperidone, 9-hydroxyrisperidone, is the active metabolite, and as such, does not need biotransformation to become pharmacologically active. The primary toxicity observed in overdose is tachycardia.^[44,45] EPS, including acute dystonia, have been described following overdose of risperidone.^[44] Paliperidone is only available as a tablet composed of a trilayer core with two drug layers and an osmotic layer designed to provide a steady release of drug over a 24-hour period. As such, delayed onset and prolonged toxicity can occur following ingestion of paliperidone.^[85] Neither risperidone nor paliperidone have significant α_2 -effects in therapeutic dosing. However, significant tachycardia beyond simple orthostasis has been described following paliperidone overdose, raising the possibility of some antimuscarinic effects following overdose.^[85]

5.10 Ziprasidone

Both accidental ingestions of ziprasidone, as might occur in a paediatric population, as well as intentional overdose of ziprasidone are generally well tolerated, with most patients exhibiting either no effects or minimal effects.^[86,87] Of those who develop symptoms, sedation and tachycardia are most commonly observed.^[86,87] Nonetheless, severe, life-threatening toxicity has been described, including profound CNS depression with loss of airway reflexes.^[41] Several cases of torsades de pointes have been described following ziprasidone overdose.^[88,89] Of note, most cases involve co-ingestion of other drugs that also prolong the QT interval.

6. Diagnosis

The diagnosis of an acute antipsychotic overdose is largely based on history and physical examination. While no single feature on the physical examination is pathognomonic for atypical antipsychotic overdose, the combination of CNS depression, tachycardia, prolonged QT and possibly orthostatic hypotension or antimuscarinic features should indicate the possibility of such an overdose.

As for any patient with altered mental status, a capillary glucose should be obtained to exclude hypoglycaemia as the cause of the altered mental status. Similarly, as with most intentional overdoses, a serum paracetamol (acetaminophen) and aspirin (acetylsalicylic acid) concentration, along with an ECG should be obtained. Patients who are found unresponsive should be examined for evidence of trauma.

A urine drug screen is of limited utility, as antipsychotics are not screened for on routine immunoassays. Serum levels can be obtained to confirm a specific ingestion. However, given that they are not routinely available, and are frequently only available in a reference laboratory, the test is unlikely to be useful in the evaluation or management of the patient.

7. Treatment

Many patients will present following ingestion of atypical antipsychotic agents without evidence of toxicity. If a patient is awake and alert, and presents less than 1 hour following the ingestion, a single dose of activated charcoal can be administered orally if the patient is willing to drink it. If it has been more than 1 hour since ingestion, or if the patient is exhibiting any evidence of encephalopathy, activated charcoal should not be administered. As with most overdoses, activated charcoal should not be 'forced' on a patient, as the risk of aspiration typically exceeds any potential benefit from the activated charcoal.^[17]

All patients should have an intravenous line placed and be observed on a monitor for a minimum of 4 hours from the time of the ingestion. An ECG should be obtained. Laboratory testing

is determined based on the clinical situation. Accidental ingestions in young children may not require any specific testing. Patients with intentional overdoses should have a paracetamol and aspirin level drawn, as these are common co-ingestants in overdose settings.

Patients with CNS depression, agitated delirium, respiratory depression or hypotension should also receive a chest radiograph to look for evidence of aspiration, and have renal and liver function assessed, as well as measurement of electrolytes and a creatinine phosphokinase to rule out rhabdomyolysis.

Optimal management of symptomatic patients who have overdosed on atypical antipsychotic medications is dependent on providing good supportive care. CNS depression may lead to insufficient airway reflexes and respiratory failure, necessitating intubation and mechanical ventilation. Aspiration pneumonitis may also result and require advanced respiratory support.

Tachycardia following overdose of atypical antipsychotics does not usually require specific treatment. Hypotension may occur in addition to tachycardia, as the result of peripheral vasodilatation due to effects on α -receptors. First-line therapy for management of hypotension is infusion of isotonic crystalloids, such as normal saline or lactated ringers.^[33] In most cases, the hypotension is not profound and, when present, usually responds to isotonic crystalloids. If hypotension persists, a direct acting vasopressor, such as phenylephrine, norepinephrine or epinephrine, should be started.

Seizures are not common following overdose of atypical antipsychotic agents, but may occur. First-line therapy is intravenous administration of benzodiazepines.^[33] Intramuscular benzodiazepines can be administered if intravenous access is not readily available, but the intravenous route is preferred. A common strategy for management of drug-induced seizures in an adult would include 2 mg of intravenous lorazepam, or 5–10 mg of intravenous diazepam. The dose can be repeated if the initial dose is unsuccessful in terminating the seizure, or if additional seizures develop. Seizures that continue despite an adequate dose of an intravenous benzodiazepine, should be treated with barbiturates (e.g. pheno-

barbital [phenobarbitone]).^[33] Patients with persistent seizures requiring treatment with both benzodiazepines and barbiturates may need to be intubated and mechanically ventilated. As with seizures of any aetiology, a capillary glucose concentration should be obtained to rule out hypoglycaemia as a cause of the seizure. Toxin-induced seizures, including those from atypical antipsychotic overdoses, should not be treated with anticonvulsants (e.g. phenytoin).

Dystonic reactions can occur with therapeutic doses or overdose of atypical antipsychotics, and may be treated with diphenhydramine.^[33] For an average size adult, 25–50 mg of oral or intravenous diphenhydramine is an appropriate starting dose. Because dystonic reactions can recur after the effect of the diphenhydramine is terminated, patients should be given a 2- to 3-day supply of diphenhydramine, if being discharged home. If dystonia occurs following overdose, and the patient also exhibits anticholinergic symptoms, diphenhydramine should be avoided. Benzodiazepines may be used to treat dystonia in such cases and may also be used to treat reactions that do not resolve following diphenhydramine.

A patient with a QTc interval exceeding 500 msec should receive 2–4 g of intravenous magnesium sulfate.^[90–92] Patients with a prolonged QTc who have experienced a transient episode of torsades de pointes should also receive magnesium.^[90] Those patients with persistent torsades de pointes should be treated with immediate defibrillation.^[90]

Treatment of CNS depression following atypical antipsychotic overdose is purely supportive in most cases, including providing airway protection when needed. However, for patients who have overdosed on agents with antimuscarinic properties (e.g. olanzapine, quetiapine, clozapine), physostigmine can be used in an attempt to reverse antimuscarinic-induced delirium.^[93,94] If administered, physostigmine should be given slowly, over several minutes. Contraindications to physostigmine use include intraventricular conduction delay, atrio-ventricular blocks, or a history of seizures or bronchospasm. The typical intravenous dose for an adult is 1–2 mg, administered over 5 minutes.^[95]

8. Conclusion

Atypical antipsychotics are a growing class of medications with an improved safety profile over their predecessors in regard to therapeutic use and overdose. Nonetheless, these agents interact with a wide variety of receptors and, as a result, can produce a range of clinical effects that can in some situations be life-threatening. Clinician awareness of the adverse effects and dose-dependent toxicities associated with these agents, and the ability to provide timely supportive care should allow for a positive clinical outcome following even the most serious overdoses of these agents.

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