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Adverse Effects and Toxicity of the Atypical Antipsychotics: What is Important for the Pediatric Emergency Medicine Practitioner

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Abstract

Medications are being used with greater frequency to address pediatric mental health problems, and in recent years atypical antipsychotic (AAP) prescriptions have increased more than any other class. Acute care practitioners must be aware of the pharmacology of AAPs and the conditions, on- and off-label, for which they are prescribed. This involves identifying and managing side effects that manifest both mentally and physically. Although “atypicality” confers a lower risk of movement side effects compared to conventional agents, children are more sensitive than adults to extrapyramidal reactions. Like adults, they also may present with toxic sedation, confusion, cardiovascular dysfunction, and metabolic derangements. Evaluation and management of these toxicities requires an index of suspicion, a careful symptom and medication history, physical examination, and targeted interventions. This review is designed to orient the emergency practitioner to the challenging task of recognizing and treating adverse effects related to acute and chronic atypical antipsychotic exposure in children.

Keywords

Atypical antipsychotics; extrapyramidal syndromes (EPS); neuroleptic malignant syndrome; QTc prolongation; Torsades de pointes

The past two decades have seen a greater emphasis on the use of pharmacotherapy in children with mental and behavioral disorders. Coincident with the growing armamentarium of psychotropic medications has been an increase in surveillance for and diagnosis of major mental illnesses such as bipolar disorder and schizophrenia in younger children. Although there remains debate about the phenomenology and prevalence of these disorders, especially in pre-pubescent children, these diagnostic labels call for treatment with antipsychotics in adults, so children are receiving medication trials of the same. And with an increase in the availability of different medications labeled as atypical antipsychotics (AAPs) has followed

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a corresponding increase in their prescription to patients across the lifespan, including children and adolescents, for symptoms of other illnesses as well.

Emergency departments (EDs) are facing dramatic increases in the volume of pediatric patients, presenting for evaluation and treatment of mental disorders, especially uninsured children. The reasons for these increases are multifactorial, but primarily related to the unavailability of or limited access to mental health services. In the last 10 years, there has been an exponential increase in the number of children – both young children and adolescents-being prescribed AAPs for mood and behavioral disorders. There are numerous adverse effects of these drugs seen with therapeutic use as well as emerging evidence on effects seen with chronic/longer duration of use. Given these facts, it is imperative that healthcare workers evaluating children and adolescents in the emergency setting are familiar with these medications. The purpose of this manuscript is to review the classification and pharmacology of atypical antipsychotic drugs, acute and chronic adverse effects with therapeutic use, and toxicity in overdose. In addition, treatment of specific adverse effects (e.g. dystonia, neuroleptic malignant syndromes) will be discussed. The pediatric emergency medicine practitioner is likely to encounter various medical scenarios requiring treatment decisions where knowledge of this information will be important.

EPIDEMIOLOGY OF ATYPICAL ANTIPSYCHOTIC USE

Three conventional antipsychotics are approved for use in children (haloperidol, thioridazine, pimozide) and others have been used off-label. In recent decades, a number of atypical dibenzepine compounds have been formulated, and their use quickly exceeded that of the old phenothiazines, thioxanthines, and butyrophenones. One study indicated that between 1996 and 2001 the percentage of new prescriptions for antipsychotics in children accounted for by AAPs increased from 6.8 % to 95.9%. (1) The greatest increases in use were seen in white male patients in their teens, but prescriptions in latency aged children nearly doubled, and use among preschool children increased 61%, as well.

Marketing forces for new medications and the movement away from talk therapies in child psychiatric practice, both financially driven trends, correlate with this rising use of antipsychotic medications in younger patients. The large increase in pediatric diagnosis of bipolar disorder is mostly due to the assignment of different kinds of behavioral dyscontrol and functional impairment seen in children of different ages as analogs of adult hypomania and mania. Antipsychotics are considered one component of pharmacotherapy for bipolar disorder along with mood stabilizers. Pediatric patients with the diagnosis of bipolar disorder account for a major proportion of the increased exposure of young people to antipsychotic medications; the agents are intended to address irritability, aggression, emotional instability, and disrupted sleep cycles. Some experts argue, however, that without diagnostic consistency over the lifespan and other reliable data, this practice change in favor of more bipolar diagnoses is misguided. (2)

Attention deficit hyperactivity disorder (ADHD) is a key differential diagnostic consideration in such children, for whom psychostimulants have become the cornerstone of standard treatment. Patients who are particularly hyperactive and/or have comorbid behavioral problems may have their care plans augmented with antipsychotics in an attempt to quell intolerable acting out. Other disruptive behavior disorders, oppositional defiant disorder and conduct disorder, prompt intervention with antipsychotics even more frequently, because of the severity of behavioral symptoms and the demands of parents, schools, and other societal institutions for more calm than such afflicted children can maintain on their own. Autism (used as a general term for the entire spectrum of pervasive developmental disorders) is another childhood mental health condition associated with types

of behavior that are sufficiently abnormal for which antipsychotic medications are frequently used when other therapies are not available or sufficient. The US Food and Drug Administration (FDA) has approved two AAPs, risperidone and aripiprazole, for the symptomatic treatment of irritability in autistic children and adolescents.

All antipsychotics have garnered their initial indications for the treatment of schizophrenia. Since this disease, like autism, is chronic, medications are often prescribed for indefinite periods of time. So, having medications that may offer relief from intrusive delusions and hallucinations without the burden of side effects recognized with long-term use of conventional agents is central to the attractiveness of the AAPs. Individuals under the age of 18 rarely qualify for this diagnosis, but true psychotic symptoms of a chronic nature do accompany other disorders that are first recognized in childhood. Autism is one, and mental retardation (or intellectual and developmental disability) is another. Atypical antipsychotic medications have therefore found widespread use in this latter group, prescribed for a variety of behavioral manifestations of apparent distress that cannot be ascertained by conventional means of psychiatric interviewing that provide guidance in managing more verbally capable patients.

The dramatic increase in prescriptions and utilization of the AAPs in the last 10 years has resulted in a significant increase in the number of reported exposures to these drugs, both in the therapeutic and overdose setting. In 2010, the National Poison Data System (NPDS) reported that the substance category which includes all antipsychotics (e.g. sedatives/hypnotics/antipsychotics) had the greatest rate of exposure increase in that year next to the analgesics with > 160,000 cases. (3) In fact it was the category associated with the largest number of fatalities; specifically 445, of which 29 were due to a single antipsychotic agent. It was also the category most frequently involved in pediatric (< 5 years of age) deaths with 6 occurring, 3 due to a single first generation antipsychotic. Most deaths involved quetiapine, olanzapine, or ziprasidone and were probably attributable in part to complications from co-ingestants.

CLASSIFICATION, PHARMACOLOGY, AND DISTINCTIVE FEATURES

Antipsychotic medications can be classified according to their chemical structure or by their receptor binding profiles, the latter lending to the terminology of “typical” or “atypical.” Typical or first generation antipsychotics include the phenothiazines (chlorpromazine, promethazine, prochlorperazine, fluphenazine, thioridazine) and the butyrophenones (haloperidol and droperidol). These traditional agents are also categorized based on their relative affinities for the dopamine D2 receptor as low potency (eg. thioridazine and chlorpromazine) or high potency, exemplified by haloperidol. They were/are used to treat primarily the “positive symptoms” of schizophrenia such as hallucinations, delusions, paranoia, and disorganization of thought. Antagonism of D2 receptors in the mesolimbic tract correlates with this therapeutic response, where roughly 70% receptor occupancy correlates with maximal benefit. However, the agents do not show regional specificity. Therefore blockade in other dopaminergic tracts—nigrostriatal, tuberoinfundibular, and mesocortical—produce adverse effects related to movement, sexual function, and blunted affect and behavior. The anticholinergic activity of low potency agents offers some protection against extrapyramidal side effects (EPS), but patients suffer an increased burden of antimuscarinic side effects including sicca, elimination problems, and cognitive impairment. Such problems prompted a search for agents that would be effective for psychosis, but spare movement side effects.

The AAPs include the second generation (SGA) and third generation antipsychotics (TGA), and are so-named because they do not cause neuroleptic the way that antipsychotic drugs

“typically” had. (Table 1) Serotonin (5-HT) receptor antagonism is the core feature of this atypicality which preserves the antipsychotic effects. Atypicals block D2 receptors, but they also block 5-HT receptors in corticolimbic pathways at therapeutic doses. In standard dose ranges, they therefore show lower overall D2 receptor occupancy, resulting in a lower risk of EPS. Some also appear to have faster binding off-rates that spare movement side effects due to less time occupying D2 receptors. (4) The TGAs aripiprazole and asenapine are distinguished by their partial agonist properties. Because the drugs (especially aripiprazole) have high binding affinities for monoaminergic receptors and extended central nervous system (CNS) half-lives, side effects can be long-lasting, and management of toxicity challenging.

The atypical drugs have some muscarinic and histaminic activity; and adrenergic receptor modulation. As a class, they may have more impact on myocardial ion currents through potassium rectifier channel antagonism than do the older agents. This effect appears to be less pronounced in children than in adults. (5)

All antipsychotic medications undergo extensive hepatic metabolism, and most are substrates for the cytochrome P450 system. Therefore, patients taking multiple medications risk both inefficacy and toxicity from antipsychotics due to complex interactions between and among substrates, inhibitors, and inducers. CYP2D6, CYP1A2, and CYP3A4 are the most important enzymes for catabolism of antipsychotics. Polymorphisms in genes encoding for these proteins and regulating their transcription have been recognized to have clinical implications for patients taking atypicals like aripiprazole and olanzapine. Such factors further complicate the assessment of cases of toxicity.

ADVERSE EFFECTS WITH THERAPEUTIC USE

Although the SGA drugs were initially advertised as having fewer adverse effects due to their “atypicality,” recent evidence has not supported this claim. Thus, the emergency care provider must be prepared to recognize them in the non-overdose setting (Table 2). Most antipsychotics produce adverse effects by one of two mechanisms—dose-related and idiosyncratic. Idiosyncratic adverse reactions may occur in the context of routine therapeutic use and are related to individual susceptibility, which is usually pharmacogenetic and only partially correlated with dose. The antipsychotics, unlike many other classes of medications, have significant and even life-threatening idiosyncratic reactions associated with their use. Other common adverse effects are predictable, dose related, and proceed from their mechanisms of action on various neurotransmitter systems as outlined above, as well as other biologic processes.

Common adverse effects of the AAPs include sedation and somnolence. Obviously, this is problematic for school-age children who need prolonged and focused attentiveness during school hours as well as the vigor to participate in other social activities. Orthostatic hypotension, usually manifested as dizziness, is also potentially impairing. It is important that children keep well hydrated, especially in the summer months, to mitigate this effect. Dry mouth and urinary retention also occur commonly with the AAPs that have more potent antimuscarinic activity. Weight gain is a more chronic adverse effect that frequently results in treatment discontinuation—a complex issue for young people with mental illness that will receive more attention below.

Extrapyramidal Syndromes

The extrapyramidal syndromes (EPS) are a major group of adverse effects seen with therapeutic use of AAPs. Some comparative studies demonstrate that the risk of EPS is lower with the SGAs and their novel pharmacology. (6,7) However a recent systematic

review and meta-analysis of randomized controlled trials demonstrated a higher rate of extrapyramidal symptoms compared with placebo in children treated with risperidone (odds ratio [OR] 3.55;95% confidence interval [CI]: 2.04, 5.48) and aripiprazole (OR 3.7;95%CI: 2.37,5.77), indicating that the risk is not absent. Elevated rates of EPS were also shown with olanzapine. Neuromotor adverse effects appear to be uncommon in children treated with quetiapine and clozapine. There are not enough pediatric data on ziprasidone to reach satisfactory conclusions, though akathisia is not an uncommon clinical finding. (8) There is some evidence that EPS is more frequent and more severe in children and adolescents with mental disorders, especially in drug-naïve individuals. (7,9)

Acute dystonia typically develops within a few hours of starting treatment but may be delayed for several days or weeks. It is a movement disorder characterized by sustained involuntary muscle contractions of a single muscle or muscle group. It can affect the limbs, but more often involves the head and neck, including the extraocular muscles or the tongue. Oculogyric crisis, facial grimacing, protrusion of the tongue, and torticollis are common manifestations. Laryngeal dystonia is a rare, but potentially life-threatening variant that may be easily misdiagnosed, because it presents with throat pain, stridor, and dysphonia. Dystonia is sometimes mistaken for seizure activity and is more distressing and dramatic, but rarely life-threatening. Preservation of a clear sensorium is a helpful diagnostic clue. Left untreated, dystonia resolves slowly over several days after the drug is discontinued. Treatment with parenteral anticholinergic drugs usually produces a rapid resolution. Benztropine (2 mg intravenously or intramuscularly in adults; 0.05 mg/kg up to 2.0 mg in children) or diphenhydramine (50 mg IV or IM in adults; 1 mg/kg up to 50mg in children) may be used. Benzodiazepines should be considered if patients do not respond to anticholinergic drugs alone, but may also be used effectively as initial therapy. Patients can be discharged home once symptoms resolve, but should be treated for 48 to 72 hours with anticholinergic agents as recurrence in this early time after initial onset is high.

Akathisia is characterized by a sense of unease and a need to move around, usually in conjunction with a feeling of anxiety. It can therefore be difficult to diagnose and easily misinterpreted as a manifestation of an underlying psychiatric disorder, rather than as an adverse effect of therapy. Tapering or discontinuation of the offending agent is the primary treatment, and benzodiazepines can help to resolve symptoms more quickly. Parkinsonism is similar to idiopathic Parkinson's disease and characterized by rigidity, akinesia or bradykinesia, and postural instability. These symptoms usually emerge during the first few months of therapy. Parkinsonism is usually treated with dose reduction of the drug, anticholinergic augmentation, and/or dopamine agonists.

The onset of tardive dyskinesia or "late dyskinesia" is usually months to years after beginning therapy, and characterized by many distinct syndromes including orobuccal/lingual/masticatory movements, chorea, dystonia, myoclonus, blepharospasms and tics. It is a potentially irreversible long-term neurologic effect that is socially stigmatizing and can be disabling. Unfortunately, it is rather resistant to pharmacologic interventions. Anticholinergic therapy may worsen symptoms, and discontinuation of the causative drug may not necessarily result in resolution of symptoms. Management strategies include dose adjustments, switching medications, and treatment with gamma aminobutyric acid (GABA)-nergic agents. Although studies demonstrate that the 1-year rates of tardive dyskinesia in children treated with AAPs are relatively low, there is still a potentially greater risk in children treated with higher total antipsychotic doses or for longer durations. (10)

Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal reaction and has been reported to occur with every antipsychotic medication. Its true incidence is unknown as less severe episodes may go undiagnosed or unreported. The vast majority of NMS cases

occur in the context of therapeutic use rather than overdose. The clinical manifestations are described as a tetrad of altered mental status, muscular rigidity or “lead pipe” rigidity, hyperthermia, and autonomic dysfunction (Table 3). NMS typically evolves over a period of several days with the majority occurring within 2–4 weeks of initiating treatment, often in the context of escalating doses. However, it may occur even after prolonged use of an antipsychotic, particularly after a recent dose increase, addition of another drug, or the development of an intercurrent medical condition such as a febrile illness and/or dehydration. Because NMS has variable clinical manifestations, emergency care providers should be aware of its many possible clinical and laboratory features for early recognition and timely interventions to prevent complications. It may be difficult to distinguish NMS from other toxin-induced hyperthermic syndromes, and the patient may actually have a combination of these syndromes depending on their specific medication exposures. Anticholinergic, sympathomimetic, and serotonin toxicity all share common features with NMS. The medication history along with the more gradual onset of symptoms with NMS and the nature of neuromuscular abnormalities help to differentiate among these toxic syndromes. Specifically, serotonin toxicity is characterized by myoclonus and hyperreflexia, which are rarely observed in patients with NMS.

Aggressive supportive care is the mainstay treatment of NMS. Hyperthermia should be treated with external/internal cooling measures and sedation with benzodiazepines. Hypotension should be treated initially with volume resuscitation. Treatment recommendations for NMS are based on general physiologic principles, case reports, and case series. There is little conclusive evidence regarding better outcomes with particular pharmacotherapies. Benzodiazepines should be considered to treat the agitation, motor symptoms, and hyperthermia. Theoretically, dantrolene should be useful in treating significant muscular rigidity and hyperthermia based on its mechanism of action and use with malignant hyperthermia. Although it is suggested by many medical resources as a reasonable therapeutic agent for NMS, there is inadequate conclusive evidence. Similarly bromocriptine, levodopa, and amantadine all have dopamine agonist properties, making them theoretically appropriate choices in a syndrome that appears to result from excessive dopamine blockade; however, there is no outcome evidence to support their routine use. In fact, their use may be associated with exacerbation of underlying psychiatric illness by precipitating psychosis without corresponding somatic benefit. Consultation with a medical toxicologist, psychiatrist, and/or intensivist is warranted to guide therapy.

Metabolic Effects

There is growing evidence that metabolic abnormalities are associated more frequently with atypical antipsychotic use in children. It is important for emergency healthcare providers to be aware of these issues, especially when assessing co-morbid conditions and dosing medications. Consistent evidence demonstrates that the use of clozapine and olanzapine in adults is associated with clinically significant weight gain, and an increased risk of diabetes mellitus and dyslipidemia. A prospective cohort study published in 2009 demonstrated that first-time second-generation antipsychotic medication use in children 4–19 years of age was associated with significant weight gain with each medication in the class. (11) Metabolic changes - insulin levels, glucose, and lipids - varied among the 4 antipsychotic medications studied (aripiprazole, olanzapine, quetiapine, risperidone), but all trended toward more abnormalities. Frank diabetes and the metabolic syndrome rarely developed, but the study was limited by its short duration of a few months. Metabolic syndrome is the name for a group of risk factors that raises risk for heart disease, diabetes, and stroke, and includes high fasting blood sugar, high blood pressure, large waist circumference, high triglycerides and low HDL (high density lipoprotein).

A more recent meta-analysis of SGA use in children demonstrated the mean weight gain compared with placebo was highest for olanzapine at 3.47 kg (95%CI: 2.94,3.99) followed by risperidone, quetiapine and aripiprazole at the lowest mean weight gain of 0.85kg (95%CI: 0.58,1.13). Olanzapine and clozapine treatment were associated with the highest rate of metabolic laboratory abnormalities in cholesterol and triglycerides. Prolactin elevation occurred with risperidone and olanzapine therapy. Data on the use of ziprasidone and metabolic effects in children are scarce and thus no conclusions can be made. (8) Information about the more recently marketed agents is even sparser. Certainly, with the growing epidemic of obesity in children, the consequences of obesity, dyslipidemias, and the development of the metabolic syndrome in large cohorts of children on these medications is extremely concerning.

Cardiovascular – Prolonged QTc Interval and Torsades de Pointes

Electrocardiogram (ECG) abnormalities and cases of sudden death in patients on typical and AAPs have been reported. However, the evidence to support a causal pathway from QTc prolongation to Torsades de pointes and sudden death that would warrant discontinuation and restricted labeling is less conclusive. Prolongation of the QT interval results from blockade of the delayed rectifier potassium current (I_{Kr}) and has been observed with both typical and AAPs, although most significantly with ziprasidone and thioridazine. (12) The risk of Torsades, a potentially fatal ventricular dysrhythmia, increases with increasing length of the QTc interval (QT interval corrected for heart rate). QTc prolongation is partly dose-related, although there appears to be a genetic disposition contributing to antipsychotic-induced dysrhythmogenesis with perhaps up to 10% of individuals who develop Torsades possessing mutations associated with the congenital long-QT syndrome. (13,14) From 2004–2007, the FDA Adverse Event Reporting Systems cataloged 76 cases of Torsades associated with antipsychotic use, with 28 due to ziprasidone, 19 due to haloperidol, 17 due to risperidone, and 12 due to quetiapine.

Evidence linking atypical antipsychotic use in children with development of clinically significant QTc prolongation is equivocal. In one study, QTc prolongation with ziprasidone was found to be only 10 milliseconds longer than with risperidone, quetiapine, or olanzapine. (15) However, another prospective open-label trial of 20 children demonstrated that low-dose ziprasidone showed statistically significant changes from baseline to peak values of QTc interval. In three subjects, the peak QTc reached or exceeded 450 milliseconds; one subject experienced a 114-millisecond prolongation, suggesting that underlying susceptibility in individuals does indeed play a major role. (16) In a recent case-control study of youth hospitalized with psychiatric disorders, a prolonged QTc on admission was rare and correlated with the presence of obesity and hypokalemia, but not with current use of antipsychotic drugs. (17) One can hypothesize that the low prevalence of QTc prolongation observed in pediatric patients on AAPs in contrast to a much higher prevalence of QT interval disturbances in older age groups may be the result of ischemic heart disease.

Given the hundreds of drugs that can cause QTc prolongation, it is necessary for the emergency physician to understand the potential for drug-drug interactions and increased risk of Torsades, when prescribing medications for children who are chronically on atypical antipsychotic therapy. A comprehensive list of medications causing QTc prolongation can be found in multiple sources. These medications can be classified by their risk in causing Torsades either alone or when used in conjunction with other medications based on available evidence. (18) Many commonly used medications in the ED cause QT prolongation and have a risk or conditional risk of causing Torsades. These include antimicrobials (e.g. azithromycin, erythromycin, ciprofloxacin), anti-emetics (e.g. ondansetron), antihistamines (e.g. diphenhydramine), procainamide, methadone, antidepressants (e.g. trazodone,

citalopram, venlafaxine, and paroxetine) and obviously other antipsychotics. The utility and cost-effectiveness of performing routine “screening” ECGs in the ED when prescribing or using these medications in the emergency setting are unknown. Eliciting a history of cardiac disease, a history of prolonged QT interval, and/or sudden death in family members is important in making decisions about the use of these medications.

Adverse Effects on Other Organ Systems

All antipsychotics can lower the seizure threshold, but seizures rarely complicate therapeutic use in children without additional risk factors. Other idiosyncratic reactions reported include photosensitivity, skin pigmentation, and hepatitis. All antipsychotics can cause leucopenia, although it is usually mild and without clinical relevance. Clozapine, however, is associated with a greater risk of agranulocytosis, and monitoring of white blood cells is mandatory. Interestingly clozapine is largely free of EPS, due in part to its antimuscarinic activity, yet sialorrhea is commonly reported as well, perhaps due to adrenergic stimulation of salivary glands. (19) Additionally but rarely, myocarditis has been associated with its use, likely the result of a type I hypersensitivity reaction—with mortality estimates as high as 50%. (20) In 2011, the FDA released an alert warning of serious allergic reactions including anaphylaxis in patients being treated with asenapine, some reported to have occurred after just one dose.

ACUTE OVERDOSE

Toxicity and Presentation

Both intentional and unintentional overdoses of the AAPs produce dose-related toxicities, reflecting extensions of the pharmacologic effects of the drug. Clinical presentation depends on many factors in addition to dose, including the drug’s metabolism and corresponding genotypic make-up of the individual, co-morbid clinical conditions, co-ingestants, and also whether or not the child is naïve to the drug. Some of the idiosyncratic reactions detailed above, though not common, may also be seen in the overdose setting including QTc prolongation, Torsades, and NMS.

The toxicity seen with acute overdose of the newer antipsychotics primarily involves the CNS and cardiovascular systems. Specifically, impaired consciousness, ranging from drowsiness and somnolence to coma, is a common feature. Significant respiratory depression, however, is uncommon. As delineated above, anticholinergic toxicity may be seen more often with some of these drugs - clozapine, olanzapine, quetiapine - and in overdose, with asenapine. Central manifestations of this toxic syndrome include agitation, delirium, psychosis, hallucinations, and coma, some of which may be mistakenly attributed to the underlying psychiatric illness. Peripheral manifestations include tachycardia, mydriasis, flushed skin, decreased production of sweat and saliva, and urinary retention.

The most common cardiovascular effects reported after overdoses are tachycardia, mild hypotension, and prolongation of the QT interval. As discussed above, QT interval prolongation may occur in overdose, predisposing the patient to Torsades. However, a recent systematic literature review of cardiovascular effects following atypical antipsychotic medication overdose suggests that this occurrence is rare. (21) The review reported ingestions of aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. The review included 13 pediatric and 22 adolescent patients; no pediatric case involved a ventricular dysrhythmia or a cardiovascular death. There were 3 reports of children with QT interval prolongation: a 2.5 year old who ingested aripiprazole, a 17 month old who ingested ziprasidone, and a 14 year old who ingested quetiapine. Tachycardia was the most common cardiovascular effect. None of the pediatric cases reported QRS interval prolongation. Again, there may be risk factors (e.g. heart disease, electrolyte imbalances, genetic polymorphisms of cytochrome enzymes) and co-ingestants which increase the susceptibility

of some patients for this complication in overdose. QRS prolongation and wide-complex tachycardias are seen primarily with thioridazine and mesoridazine and usually not with any of the AAPs.

There are distinctive features of individual atypical antipsychotic overdoses based on isolated case reports and case series which are noted in Table 2. Overdoses of olanzapine have been characterized by profound and prolonged CNS depression as well as unpredictable fluctuation between sedation and agitation, this may be due to anticholinergic toxicity in conjunction with the drug's long half-life in overdose. In 1999, a case series of 4 patients reported olanzapine overdose mimicking opioid intoxication, severe CNS depression, miosis, and hypotension—with the exception of tachycardia instead of the expected bradycardia with opioid toxicity. (22) An unintentional ingestion of one ziprasidone tablet in a 30 month old resulted in coma requiring intubation, tachycardia, hypotonia, and miosis. (23) The miosis observed with many atypical antipsychotic overdose patients likely results from unopposed parasympathetic stimulation of the pupil by those drugs with significant alpha-1 adrenergic receptor blockade properties. Thus, AAPs should be added to opioids and alpha 2-adrenergic agonists (eg. clonidine, imidazolines) in the toxicologic differential diagnosis of the patient with CNS depression and miosis.

Case reports and series of patients with aripiprazole overdose report primarily sedation, vomiting, delayed onset of symptoms, and prolonged duration of symptoms. In one report, a 2.5 year old had persistent lethargy for over a week. (24) In another case series of pediatric exposures, a 6 year old who received two therapeutic doses of aripiprazole experienced lethargy, drooling, and flaccid facial muscles which improved with diphenhydramine. Three adolescent patients had either no symptoms or only transient lethargy. None of the patients had seizures, conduction abnormalities, or dysrhythmias. It is postulated that, in addition to the drug's extended CNS half-life, (25) the prolonged symptom duration is due to CYP2D6 "poor metabolism," thereby increasing the elimination half-life of the parent compound and the active metabolite. (26)

Prolonged anticholinergic delirium has been reported in an adolescent who overdosed on quetiapine, which is consistent with its strong antimuscarinic properties. (27) Paliperidone, one of the newer atypical antipsychotic, is the major active metabolic of risperidone. Limited experience in overdose suggests that, in addition to sedation, tachycardia is a common adverse effect. Due to the extended release delivery system of this drug, delayed and sustained toxicity may occur. (28) There are, as yet, no published data on iloperidone, lurasidone, or asenapine overdoses; the latter sublingual agent being particularly difficult to "overingest" because its bioavailability is minimal when swallowed.

Evaluation and Management

Since both the majority of antipsychotic medication toxicities and the conditions for which they are prescribed manifest neurobehaviorally, careful history taking and evaluation is essential, even in the ED. Then, if an antipsychotic medication is causing adverse effects and must be discontinued, the emergency physician can use a symptom-targeted strategy in crafting initial alternative treatments for the pediatric mental health patient.

Children with autism commonly present to the ED when caregivers and families are concerned about behavioral problems that appear to be either alleviated by or caused by psychotropic medications such as the atypicals. Differentiating them in a way that suggests a proper course of treatment can be particularly challenging. Similar challenges accompany the evaluation and treatment of pre-school aged children taking antipsychotic medications, in whom the most common diagnoses are (in addition to autism) mental retardation, ADHD, and other disruptive behavior disorders. (29)

Evaluation and subsequent diagnosis of toxicity are based on history coupled with predictable symptoms and physical findings; specifically, CNS depression, tachycardia, hypotension and miosis are commonly seen with pure atypical antipsychotic intoxication. Co-ingestants and unique toxicities of individual agents may produce variations to this toxic syndrome. Plasma concentrations of specific agents are not widely available and, although helpful in forensic settings, are not useful in the acute management of an overdose patient. Routine urine drug-of-abuse screens do not detect the AAPs and are therefore not helpful in acute management, except for the false-positive cross reactivity with TCA immunoassays that can sometimes be seen with quetiapine and olanzapine.

Activated charcoal may be considered if administered within 1–2 hours of toxic ingestion, as long as no contraindications exist, such as the presence of sedation or vomiting. Because of paliperidone's sustained release formulation and prolonged absorption, later use of charcoal or even whole bowel irrigation with an iso-osmotic polyethylene glycol solution may be considered. Otherwise, management consists primarily of symptomatic and supportive care.

There is no specific antidote for atypical antipsychotic toxicity with the exception of dystonia and the use of anticholinergic agents as discussed above. An ECG and cardiac monitoring should be initiated with any suspected overdose. Serum electrolytes should be checked and abnormalities corrected, especially hypokalemia and hypomagnesemia, because their presence may portend QT-related dysrhythmias. The efficacy of prophylactic administration of magnesium for QT interval prolongation in the presence of normal serum magnesium concentrations for the prevention of further interval prolongation and Torsades is unknown. Cardiac monitoring should continue until the patient is asymptomatic and the interval is normal. Standard therapy for emergent Torsades including magnesium, overdrive pacing, and isoproterenol should be considered; however, there is no conclusive evidence regarding the efficacy of these treatments in the setting of antipsychotic toxicity.

Because most of the atypical antipsychotic medications have a high degree of lipid distribution within the body, the use of intravenous lipid emulsion may be considered in select cases of significant toxicity. Its use in overdose of AAPs is limited but reported with some success. (30) In general, standard intensive care and monitoring is sufficient; however, providers should be prepared for potentially variable and prolonged courses of recovery based upon the complex pharmacology of these agents.

SUMMARY

As with other classes of psychotropic medication, the AAPs are sometimes ingested purposefully by young people with mental illness, so acute overdose toxicity will be encountered in the ED setting. Supportive care, cardiac monitoring, and attention to physiologic and symptomatic needs will yield good outcomes, even if the hospital course is protracted due to CNS effects. The much greater challenge for the emergency physician is the regularity with which children taking these agents display variable neurophysical symptoms and complex comorbidity. It is important to be aware of the pharmacologic properties of AAPs and the psychiatric conditions of the patients for whom they are prescribed. Acute, sub-acute, and even chronic effects on movement regulation are possible, and demand targeted intervention. In addition, the idiopathic and long-term effects of the AAPs have health consequences of their own, thus complicating the presentation of other diseases related to obesity and metabolic derangements that are affecting youth at an alarming rate. All of these challenges confront the emergency physician in a climate of unmet mental health needs with growing iatrogeny from psychopharmacologic prescribing.

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Table 1

Pharmacology of FDA approved atypical antipsychotics.

Second Generation Atypical	Year	Mechanism	Distinctive Pharmacology Characteristics
Clozapine (Clozaril®)	1989	Dopamine and serotonin antagonist Partial serotonin agonist	+++ Muscarinic antagonism +++ α_1 adrenergic antagonism + Delayed rectifier (I_{Kr}) current blockade
Risperidone (Risperdal®)	1993	Dopamine & serotonin antagonist	++ α_1 adrenergic antagonism
Olanzapine (Zyprexa®)	1996	Dopamine & serotonin antagonist	+++ Muscarinic antagonism ++ α_1 adrenergic antagonism
Quetiapine (Seroquel®)	1997	Dopamine & serotonin antagonist	+++ Muscarinic antagonism ++ α_1 adrenergic antagonism
Ziprasidone (Geodon®)	2001	Dopamine & serotonin antagonist Partial serotonin agonist Serotonin & NE reuptake inhibitor	++ α_1 adrenergic antagonism +++ Delayed rectifier (I_{Kr}) current blockade
Paliperidone (Invega®)	2006	Active metabolite of risperidone Dopamine and serotonin antagonist	+ α_1 and α_2 adrenergic antagonism
Iloperidone (Fanapt®)	2009	Dopamine and serotonin antagonist	+ α_1 adrenergic antagonism
Lurasidone (Latuda®)	2010	Dopamine & serotonin antagonist	++ α_2 and + α_1 adrenergic antagonism ? Delayed rectifier (I_{Kr}) current blockade
3rd Generation Atypical			
Aripiprazole (Abilify®)	2002	Partial dopamine D2 agonist Partial serotonin 5-HT1A agonist Serotonin 5-HT2 antagonism “Dopamine-Serotonin System Stabilizer”	++ α_1 adrenergic antagonism
Asenapine (Saphris®)	2009	D2 antagonist ? Partial D1 agonist Serotonin 5-HT2 antagonism Partial serotonin 5-HT1 agonist	+ Muscarinic antagonism + H2 receptor antagonism + α_1 and α_2 adrenergic antagonism

Dopamine antagonist: D2 receptors

Dopamine agonist: D1 receptors

Serotonin antagonist: 5-HT2A receptors

Serotonin agonist: 5-HT1A receptors

 α_1 -Adrenergic antagonism – Hypotension

Muscarinic antagonism – central and peripheral anticholinergic effects

Sodium channel blockade – QRS interval widening; myocardial depression

Delayed rectifier (I_{Kr}) current blockade – QT prolongation and Torsades de pointes

Table 2

Adverse effects/toxicities of atypical antipsychotics.

Organ System	Adverse Effects/Toxicities	Distinctive Adverse Effects/Toxicities
Central Nervous System	Somnolence, sedation Coma Respiratory depression Hyperthermia or hypothermia seizures Central anticholinergic syndrome	Clozapine: Agranulocytosis, sialorrhea, seizures, rarely myocarditis More weight gain More metabolic abnormalities Risperidone: Dystonic reactions more common Orthostasis Olanzapine Fluctuating sedation and agitation More weight gain More metabolic abnormalities Quetiapine Tachycardia, orthostasis common Sedation Delirium Ziprasidone Akathisia QTc prolongation more pronounced Paliperidone Similar to risperidone Delayed onset and prolonged symptoms Aripiprazole Prolonged sedation EPS more common Asenapine Severe allergic reactions, anaphylaxis Lurasidone Akathisia Sleep-wake disturbance
Central Nervous System: Extrapyramidal Syndromes	Acute dystonia Akathisia Parkinsonism Tardive dyskinesia Neuroleptic malignant syndrome (NMS)	
Cardiovascular	Tachycardia Hypotension (orthostatic or resting) Myocardial depression	
Cardiovascular: Electrocardiography	QT interval prolongation Torsades de pointes	
Endocrine	Amenorrhea, oligomenorrhea, or metorrhagia Galactorrhea Gynecomastia	
Metabolic	Weight gain Hyperglycemia Diabetes Hypertension Metabolic syndrome *	
Gastrointestinal	Nausea, vomiting Dry mouth Impaired peristalsis Hepatic toxicity-elevated transaminases and fatty liver	
Genitourinary	Urinary retention Ejaculatory dysfunction Priapism	
Ophthalmic	Miosis Visual blurring	
Dermatologic	Impaired sweat production Cutaneous vasodilation	
Hematologic	Leukopenia Agranulocytosis (Clozapine)	

* Metabolic syndrome is the name for a group of risk factors that raises risk for heart disease, diabetes, and stroke, and includes high fasting blood sugar, high blood pressure, large waist size, high triglycerides and low HDL (high density lipoprotein).

Table 3

Neuroleptic malignant syndrome: clinical features and treatment.

Clinical Features	
Altered mental status	Delirium, lethargy, confusion, stupor, catatonia, coma
Motor symptoms	Muscle rigidity, tremor, dysarthria, mutism, akinesia, cog wheeling, dysphagia, dysphonia, choreiform movements
Hyperthermia	Temperature > 100.4 °F (38°C)
Autonomic instability	Tachycardia, hypertension, hypotension, diaphoresis, Irregular respirations, dysrhythmias
Laboratory abnormalities	Increased muscle enzymes – CPK, LDH Leukocytosis Renal insufficiency Metabolic acidosis Aminotransferase elevation Myoglobinuria Hyponatremia Increased prothrombin time/partial thromboplastin time
TREATMENT	
Supportive care	External/internal cooling Intravenous hydration/urine alkalinization
Sedation	Benzodiazepines Paralysis with intubation
Dantrolene	Consider for significant muscle rigidity and/or hyperthermia
Bromocriptine, Amantadine, Levo-Dopa	No conclusive evidence to support routine use