Neuroleptic Malignant Syndrome Associated With Atypical Antipsychotics in Pediatric Patients: A Review of Published Cases

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Objective: To retrospectively examine published cases of neuroleptic malignant syndrome (NMS) in patients aged 18 and below who had been treated with atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole).

Data Sources: Information was collected via MEDLINE searches in February 2006 and May 2007. The term *neuroleptic malignant syndrome* was used and cross-referenced with individual atypical antipsychotics. The authors also contacted (by telephone and in writing) pharmaceutical companies that produce and market atypical antipsychotics for any data on NMS.

Study Selection: Twenty case reports (written in English only and published from 1991–2007) were identified and reviewed. These publications all described symptoms of NMS in patients aged 18 or younger who had been treated with atypical antipsychotics.

Data Extraction: Data were reviewed and compared with 3 diagnostic criteria (DSM-IV-TR, Levenson's, and Caroff and Mann's) for NMS. Interventions and outcomes were also reviewed.

Data Synthesis: Twenty case reports were identified and presented with a descriptive approach. Sixteen cases met criteria for NMS, with at least 1 of the diagnostic sets utilized. The majority of cases involved male subjects. All patients recovered.

Conclusions: Young patients can develop NMS during treatment with atypical antipsychotics. Symptoms of this disorder are consistent with those described in adults. Although NMS is rare in this population, clinicians should maintain a high index of suspicion. Appropriate caution in treating children and adolescents with any antipsychotic is warranted.

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Experts relate that the use of atypical antipsychotics in pediatric populations has increased dramatically since their inception near the end of the twentieth century.[1] Due to comparable efficacy and improved tolerability over traditional neuroleptics in adult populations, clinicians have utilized these agents frequently in children and adolescents with psychosis. Research studies and practice guidelines support the use of atypical antipsychotics for children and adolescents with bipolar disorder.[2,3] Presently, atypical antipsychotics are also utilized to target behavioral and emotional symptoms of multiple other psychiatric illnesses in pediatric populations including pervasive developmental disorders, disruptive behavior disorders, tic disorders, and eating disorders.[4,5] Furthermore, risperidone has recently received U.S. Food and Drug Administration (FDA) approval for the treatment of irritability in autistic children aged 5 to 16, schizophrenia in patients aged 13 to 17, and as monotherapy for bipolar I manic and mixed episodes in patients aged 10 to 17. Aripiprazole is also now FDA approved for the treatment of schizophrenia in patients aged 13 to 17 and for the acute treatment of manic and mixed episodes of bipolar disorder I in patients aged 10 to 17. Recent studies indicate that the 1-year prevalence of use of atypical antipsychotics may be highest in male patients 10 to 14 years of age at 594.3 per 100,000.[6] With the increased use of these medications in the pediatric population, there

Table 1. Summary of Neuroleptic Malignant Syndrome Criteria (symptoms must be associated with antipsychotic administration)

Symptom	DSM-IV-TR[a]	Levenson[b]	Caroff and Mann[c]
Core	Fever	Fever	Fever
	Rigidity	Rigidity	Rigidity
		Elevated CK level	
Additional	Diaphoresis	Tachycardia	Altered mental status
	Dysphagia	Abnormal blood pressure	Tachycardia
	Tremor	Tachypnea	Labile blood pressure
	Incontinence	Altered mental status	Respiratory distress
	Altered mental status	Leukocytosis	Diaphoresis or sialorrhea
	Mutism	Diaphoresis	Tremor
	Tachycardia		Elevated CK level or myoglobinuria
	Labile blood pressure		Leukocytosis
	Leukocytosis		Acidosis
	Evidence of muscle damage (eg, elevated CK level)		Incontinence

[a]DSM-IV-TR[21] criteria: both core symptoms plus 2 or more additional symptoms required.
[b]Levenson[10] criteria: all 3 core symptoms, or 2 core and 4 additional symptoms, required. No additional symptoms required if all 3 core symptoms are present.
[c]Caroff and Mann[14] criteria: core symptoms present within 7 days of antipsychotic use plus 5 additional symptoms required.
Abbreviations: CK = creatine phosphokinase; DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision.

is a clear and warranted concern about their safety. Consensus guidelines address the safety and utilization of these medications in children and adolescents.[7,8] However, there are relatively few controlled trials or safety studies. Although common side effects are generally fairly mild, more serious consequences are a concern.[9]

Neuroleptic malignant syndrome (NMS) is a rare and poorly understood reaction to treatment with antipsychotics. Diagnostic criteria are controversial; however, clinical signs can include rigidity, fever, increased serum creatine phosphokinase (CK) levels, leukocytosis, autonomic instability, tachypnea, delirium, and diaphoresis.[10] This syndrome was first described nearly fifty years ago and has often been attributed to D_2 (dopamine) receptor blockade.[11] Estimates of the incidence of NMS in adult populations treated with typical neuroleptics vary. In the past, estimates of this rate were as high as 3%.[12] Contemporary studies indicate an incidence of 0.01% to 0.02%.[12–14] Studies of the frequency of NMS in populations treated with atypical antipsychotics are limited. However, this iatrogenic condition has been reported and studied in adult populations treated with second-generation antipsychotics.[15,16]

There is a paucity of information regarding NMS in patients 18 years of age and younger. This condition was documented in children treated with haloperidol in the 1970s, and at that time, authors argued that children and adolescents may be a vulnerable population.[17,18] In the past, awareness and recognition of this condition in children was likely low. For example, some investigators contend that previously, children given phenothiazines for nausea who developed NMS may have been incorrectly diagnosed with Reye syndrome.[19] Neuroleptic malignant syndrome may also present and progress differently in younger patients. Conversely, one review and statistical analysis of seventy-seven cases in children and adolescents treated with first-generation antipsychotics found little difference in the clinical presentation and course of NMS compared to adult populations.[20] These authors suggested that fever, tachycardia, and rigidity were cardinal symptoms of NMS. Cases reviewed often involved treatment with multiple neuroleptics (over 60% of patients) and a high mortality rate.[20] There is even less information available for clinicians regarding NMS and atypical antipsychotics in pediatric populations. No methodical review of cases has been published to date. The objective of this review was to critically examine reported cases of NMS associated with atypical antipsychotics in patients aged 18 and younger.

METHOD

Potential cases of NMS involving children and adolescents treated with atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) were collected from MEDLINE searches in February 2006 and May 2007. Studies were written in English only and published from 1991 to 2007. The term *neuroleptic malignant syndrome* was used and cross-referenced with individual atypical antipsychotics. References of relevant articles were inspected for further cases. Pharmaceutical companies who produce and market atypical antipsychotics studied in this review were also contacted (in writing and by telephone) for unpublished cases or relevant data regarding NMS in children and adolescents. Available information was reviewed to determine if described episodes were consistent with NMS. Due to the variability in symptom descriptions of NMS in youth, 3 different criteria were used to evaluate each case. This involved applying DSM-IV-TR,[21] Levenson's,[10] and Caroff and Mann's[14] criteria. The Caroff and Mann criteria are the most specific (Table 1). Cases also were evaluated

Table 2. Demographics and Summary of Case Reports of Neuroleptic Malignant Syndrome (NMS) in Patients Aged ≤ 18 Years Treated With Atypical Antipsychotics

Treatment and Reference	Age, y	Gender	NMS Criteria[a]	Concomitant Medications
Clozapine				
Skarpathiotakis and Westreich[24]	16	Male	DSM-IV-TR, Levenson	Olanzapine
Sachdev et al[25]	14	Male	None[b]	None
Sachdev et al[25]	15	Male	None[b]	None
Risperidone				
Mane et al[30]	17	Male	DSM-IV-TR, Levenson	None
Zalsman et al[31]	16	Male	None[b]	None
Zalsman et al[31]	17	Male	DSM-IV-TR, Levenson, Caroff and Mann	None
Ty and Rothner[32]	16	Male	DSM-IV-TR, Levenson	Haloperidol, lithium, perphenazine, valproic acid
Robb et al[33]	17	Female	Levenson	Lithium
Sharma et al[34]	15	Male	DSM-IV-TR, Levenson, Caroff and Mann	Valproic acid
Olanzapine				
Abu-Kishk et al[39]	11	Male	DSM-IV-TR, Levenson, Caroff and Mann	None
Hanft et al[40]	17	Male	DSM-IV-TR, Levenson, Caroff and Mann	Divalproex sodium
Berry et al[38]	16	Male	DSM-IV-TR, Levenson	Lithium
Ghaziuddin et al[42]	17	Female	DSM-IV-TR, Levenson, Caroff and Mann	Haloperidol
Mendhekar and Duggal[43]	16	Male	DSM-IV-TR, Levenson, Caroff and Mann	None
Ziprasidone				
Leibold et al[52]	15	Male	DSM-IV-TR, Levenson, Caroff and Mann	Bupropion, valproic acid
Aripiprazole				
Hammerman et al[54]	14	Female	None[b]	None
Spalding et al[55]	17	Male	DSM-IV-TR, Levenson	None
Palakurthi et al[56]	12	Male	DSM-IV-TR, Levenson	Methylphenidate
Multiple atypicals				
Aboraya et al[57]	18	Male	DSM-IV-TR, Levenson, Caroff and Mann	Risperidone, olanzapine, quetiapine
Chungh et al[48]	12	Female	Levenson	Risperidone, olanzapine, quetiapine, lithium, valproic acid

[a]Threshold for diagnosis met in each case with following criteria: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR)[21]; Levenson[10]; and/or Caroff and Mann.[14]
[b]These 4 cases were described as NMS in the literature. However, based on symptomatology presented, they did not reach the threshold for diagnosis of NMS with any of the 3 criteria applied.

with respect to contributing factors (such as polypharmacy, recent medication changes, comorbid medical diagnoses, and prior episodes of extrapyramidal symptoms [EPS]), interventions, and outcome.

RESULTS

Twenty published cases of purported NMS in patients aged 18 and younger were reviewed. Pharmaceutical companies did not have additional data or unpublished cases of NMS associated with atypical neuroleptics in this population. Eighty percent (N = 16) of the patients afflicted were male. The mean age was 15.4 years (range, 11–18 years). Details regarding the race of patients were not available in most case reports. Nine patients had the diagnosis of schizophrenia (1 of these individuals also had mental retardation and another was also diagnosed with a pervasive developmental disorder). Four patients were diagnosed with psychotic disorder not otherwise specified. Five had bipolar disorder. Another patient had major depressive disorder with psychotic features, and the other had a primary diagnosis of pervasive developmental disorder not otherwise specified.

Most instances of NMS involved treatment with a single atypical antipsychotic: clozapine (N = 2), risperidone (N = 5), olanzapine (N = 4), ziprasidone (N = 1), and aripiprazole (N = 3). Two of the articles described cases of NMS in patients treated with multiple atypical antipsychotics (N = 3). However, 11 individuals (55%) were taking at least 1 other psychotropic medication in addition to the atypical antipsychotic putatively inducing NMS. Sixteen (80%) of the patients had a dosage change in psychotropics within 1 week of the NMS episode. Finally, 10 patients (50%) had a prior episode of EPS. Results are summarized in Table 2. The mean maximum reported temperature was 38.4 (range, 37.0–39.5) degrees Celsius, and the mean maximum CK level was 4692 (range, 401–40,177) units/liter. There were no deaths reported, and, in general, patients recovered with identification, treatment, and supportive care.

Clozapine

Clozapine is a dibenzepine that was first developed in the 1960s. It is distinctive for its minimal D_2 dopamine receptor occupancy at effective doses. The mechanism of action of this antipsychotic is controversial due to its diverse pharmacologic characteristics.[22] Numerous cases of NMS in adult patients treated with clozapine have been reported.[23] Three cases of possible NMS in adolescents treated with clozapine were identified in this review.[24,25]

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One case involved a 16-year-old male patient with schizophrenia and a pervasive developmental disorder. This patient had a dystonic reaction with loxapine many months before treatment with clozapine.[24] He developed NMS within 8 hours of initiating a low dose (12.5 mg) of clozapine. Of note, he did receive a concurrent 5 mg dose of intramuscular olanzapine for agitation. His symptoms included somnolence, flushing, rigidity, fever, autonomic instability, and an elevated CK level. Symptomatology in this case met criteria for NMS with DSM-IV-TR and Levenson's criteria but not with Caroff and Mann's criteria due to a paucity of symptoms. This patient recovered with minimal interventions. The authors did concede that a dystonic reaction coupled with other medication side effects could be an alternate explanation.[24]

Sachdev and colleagues[25] described 2 other teenage cases of "clozapine-induced NMS." One involved a 14-year-old with schizophrenia treated with 375 mg of clozapine a day. Symptoms included leukocytosis, tachycardia, elevated CK levels, fever, and disorientation. This patient required discontinuation of clozapine, initiation of bromocriptine, and treatment with dantrolene. This patient was intermittently mute and had ongoing symptoms (fever, tachycardia, disorientation, elevated CK levels) for 7 weeks. His symptoms resolved subsequently with electroconvulsive therapy (ECT).

Another patient was a 15-year-old with schizophrenia and mild mental retardation who had symptoms of NMS while receiving chlorpromazine and lithium carbonate.[25] After the discontinuation of these agents, he was administered bromocriptine, dantrolene, and bilateral ECT. Symptoms of NMS resolved, but 8 weeks later he developed tachycardia and an elevated CK level after several weeks of treatment with clozapine at 300 mg daily. After cessation of clozapine, these symptoms resolved. This patient was subsequently rechallenged and treated with clozapine 150 mg daily successfully.[25] Based on available data, these latter 2 cases failed to meet criteria for the diagnosis of NMS when utilizing aforementioned criteria. Furthermore, these descriptions have been criticized by other researchers[26] who contend that clozapine has low D_2 affinity and a lack of extrapyramidal side effects in most cases and may be a useful medication for psychiatric patients with a history of NMS and that there are few data to support the idea that clozapine monotherapy induces NMS.[27]

Risperidone

Risperidone is a benzisoxazole derivative that was developed in 1988. It has potent D_2 and 5-HT_{2A} receptor antagonism.[28] In some cases, adults treated with risperidone have developed NMS.[11,29] Six cases describing NMS in adolescents treated with risperidone were reviewed.[30–34] These patients were aged 15 to 17. All recovered without significant sequelae.

One case involved a 17-year-old male patient with schizophrenia who developed symptoms hours after a dosage increase from 2 to 3 mg.[30] He had been taking risperidone 2 mg daily for at least 4 months prior to this. Symptoms in this case included fever, rigidity, elevated CK levels, and leukocytosis. He met criteria for NMS with DSM-IV-TR and Levenson's diagnostic categories. Initial treatment involved discontinuation of risperidone, oral bromocriptine, and intravenous diazepam. The patient's NMS symptoms resolved within 72 hours. Subsequently, this teenager was rechallenged with a low potency neuroleptic, which led to fever and elevated CK levels once again. Subsequently, this patient was treated successfully with clozapine and ECT. The authors stressed the utility of ECT as a treatment for NMS in youth populations.[30]

Another article described "atypical neuroleptic malignant syndrome" after treatment with risperidone in 2 adolescents.[31] The first case described a 16-year-old male patient with psychosis treated with risperidone for several weeks. Three days after an increase of 4 mg once daily to 5 mg once daily, he developed symptoms of NMS, which included a low grade fever, muscle stiffness, and elevated CK levels. The authors further noted that he appeared catatonic. His symptoms failed to meet full criteria with any of the diagnostic schemes utilized in this review. Risperidone was discontinued. He was given dantrolene and intravenous fluids. Subsequently, this patient was successfully rechallenged with clozapine.

The second patient was a 17-year-old male subject treated for psychotic and manic symptoms.[31] He received valproic acid and perphenazine (which was discontinued due to side effects) prior to treatment with risperidone. After 1 dose of 1 mg of risperidone, he developed a fever, elevated blood pressure, diaphoresis, disorientation, elevated CK levels, rigidity, leukocytosis, and a papular rash (which is atypical for NMS). His presentation was consistent with the diagnosis of NMS in all 3 criteria. All medications were discontinued. He was given intravenous fluids, admitted to a medical unit, and monitored closely. He required medications for agitation and aggression subsequently. This initially involved lorazepam and diazepam. These agents were not effective. Perphenazine was reinitiated, and after 4 days all symptoms of NMS resolved.[31]

Ty and Rothner[32] reported a case involving a 16-year-old male patient with schizoaffective disorder. He developed hyperthermia, rigidity, and confusion 4 days after the initiation of an unspecified dose of risperidone. In the preceding weeks, he had been given haloperidol, risperidone, lithium, perphenazine and valproic acid. This patient was transferred to a medical unit, hydrated aggressively, monitored closely, and given medications (dantrolene and lorazepam). His symptoms resolved in less than 2 weeks with treatment for NMS.[32] Based on DSM-IV-TR

and Levenson's criteria, he suffered from NMS. However, attributing this to risperidone is problematic due to a treatment course involving multiple medications.

Robb and colleagues[33] described a 17-year-old female patient with mania who was treated with lithium and risperidone. Within 2 days of initiating risperidone (0.5 mg daily on day 1 and then 0.5 mg twice daily on day 2), she developed rigidity, myalgia, elevated CK levels, and a fever. Her presentation met criteria for NMS with Levenson's criteria. Risperidone was discontinued and dantrolene was initiated. Treatment also involved medical monitoring, intravenous fluids, and acetaminophen. This patient completely recovered.[33]

Another case published involved a 15-year-old male patient with mania.[34] He had EPS and a poor response with haloperidol and lithium carbonate. Subsequently, these medications were discontinued and he was treated with valproic acid. He was also given amantadine. Risperidone was initiated and increased to a dose of 4 mg daily over 4 days. This patient developed EPS once again. Risperidone was discontinued at this point and he received only valproic acid for 8 days. He was administered risperidone 1 mg daily for ongoing psychotic symptoms. Within 1 day of this, he developed symptoms of NMS, including fever, tachycardia, tachypnea, fluctuating blood pressure, diaphoresis, incontinence, rigidity, disorientation, leukocytosis, and elevated CK levels. These symptoms met the diagnosis for NMS with all 3 criteria. Psychotropic medications were discontinued and he improved with medical attention (bromocriptine, amantadine, supportive care in the intensive care unit).[34]

Olanzapine

Olanzapine was developed, tested, and FDA approved from 1990 to 1997. It is a thienobenzodiazepine derivative and has a chemical structure similar to clozapine. Olanzapine has activity at multiple dopamine, muscarinic, and serotonin receptor sites.[35] This drug has also induced NMS in adult patients.[36–38] Five cases of olanzapine induced or associated NMS in patients ages 11 to 17 were obtained for review.

Abu-Kishk and colleagues[39] documented the course of an 11-year-old boy with acute psychosis who developed symptoms of NMS (fever, elevated blood pressure, tachycardia, tachypnea, rigidity, elevated CK levels, and disorientation) following 1 intramuscular dose of clotiapine. He had an extensive medical evaluation and monitoring on a medical unit over 2 weeks. The patient's vital signs, symptoms, and CK levels all stabilized. Subsequently, he was treated with olanzapine at an unspecified dose due to ongoing psychotic symptoms. Within hours, NMS symptoms (fever, elevated blood pressure, tachycardia, respiratory distress, sialorrhea, disorientation, and rigidity) returned. This patient met the diagnosis for NMS with the 3 criteria utilized. He was treated in the intensive care unit (ICU) with intubation, supportive care, bromocriptine, and dantrolene. Ultimately, this boy's condition improved; he was extubated and discharged within a week with no ongoing psychotropics.[39]

A 17-year-old treated for symptoms of mania and psychosis developed NMS after brief exposure to olanzapine (at a dose of 2.5 mg twice a day and 5 mg at bedtime) and divalproex sodium.[40] Within 2 days he developed diaphoresis, tachycardia, elevated blood pressure, fever, mutism, disorientation, and elevated CK levels. These symptoms fulfilled the diagnosis of NMS with all 3 criteria. This patient was transferred to a medical center and required mechanical ventilation, intravenous fluids, and dantrolene. This teenager recovered after 2 weeks of treatment and monitoring. Subsequently, he was treated with clozapine successfully. The authors also described symptoms suggestive of lethal or malignant catatonia.[40] This illustrates contemporary theories regarding NMS and malignant catatonia. Currently, many researchers conceptualize NMS as a drug-induced variant of malignant (or lethal) catatonia.[41]

An additional case involved a 16-year-old male patient who initially developed severe EPS while taking risperidone for bipolar disorder.[38] Nearly 4 months later he developed NMS after taking olanzapine (20 mg per day) and lithium for 2 weeks. Symptoms in this case included a fever, tachycardia, rigidity, myalgia, urinary retention, leukocytosis, and an elevated CK level. The information provided did not meet Caroff and Mann's criteria for NMS but reached threshold for diagnosis with Levenson's and DSM-IV-TR criteria. This patient's medications were discontinued and his fever remitted in 3 days. His rigidity improved in 1 week, and laboratory values normalized in approximately 1 week. Two weeks after recovering, this patient was rechallenged and treated successfully with risperidone.[38]

Ghaziuddin and colleagues[42] described the course of a 17-year-old female patient with psychotic and catatonic symptoms. She developed symptoms of NMS after 4 days of treatment with haloperidol and olanzapine (5 mg in the morning and 10 mg in the afternoon).[42] Symptoms included mutism, fever, tachycardia, elevated blood pressure, urinary incontinence, rigidity, tremors, catalepsy, and elevated CK levels. Olanzapine's role in this symptomatology is equivocal, and this patient likely had malignant catatonia prior to antipsychotic exposure. However, her symptoms reached the threshold for diagnosis of NMS with all 3 diagnostic sets. After 6 weeks and multiple hospitalizations, this patient was treated with ECT successfully. The authors stressed the importance of early identification of NMS (or catatonia) and timely use of ECT.[42]

Mendhekar and Duggal[43] described a case of NMS in a 16-year-old male adolescent with schizophreniform disorder. This teenager developed EPS after treatment with

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haloperidol 10 mg daily. Haloperidol was discontinued and he did not take medications for 2 weeks. After treatment with olanzapine 7.5 mg daily, EPS developed once again. Over the next week, he displayed symptoms of NMS (fever, rigidity, disorientation, urinary incontinence, autonomic instability, diaphoresis, leukocytosis, and elevated CK levels) that reached threshold for diagnosis based on all 3 criteria. This teenager was treated with bromocriptine for 4 weeks, and symptoms of NMS resolved over 10 days. Of note, this patient developed a persistent amnesia and severe cognitive impairment. Overall, his cognition slowly improved, but 2 months later he had ongoing memory deficits that included retrograde amnesia and anterograde amnesia.

Quetiapine

Quetiapine is a dibenzothiazepine derivative that was FDA approved in 1997 for schizophrenia in adults. It is an antagonist at a myriad of neurotransmitter receptors, including adrenergic, dopaminergic, histaminergic, and serotonergic receptors.[44,45] There are case reports of NMS associated with quetiapine in adult populations.[46,47]

One case, described in detail later in this review, involved a 12-year-old girl with bipolar disorder not otherwise specified and mild mental retardation.[48] She received risperidone initially and developed symptoms of NMS. Subsequently, this patient was treated with olanzapine and quetiapine. Each medication exacerbated her NMS symptoms and she was ultimately treated with ECT.[48] It is difficult to attribute NMS to quetiapine in this case, as multiple medications were administered over several weeks.[48] Other than this case, the youngest case of quetiapine-associated NMS described in the literature involved a 20-year-old male patient with schizophrenia.[49]

Ziprasidone

Ziprasidone was first FDA approved and marketed in 2001 for the treatment of schizophrenia in adults. It is now also FDA approved for the treatment of manic and mixed episodes associated with bipolar disorder in adults. Ziprasidone is a serotonin ($5\text{-}HT_{2A}$) and dopamine (D_2) antagonist.[50] Ziprasidone-associated NMS has been reported in adult patients.[51] One case has been published involving NMS associated with ziprasidone use in a 15-year-old male patient with schizoaffective disorder.[52] He was treated with ziprasidone (80 mg a day) for 8 weeks prior to the event. This patient was also taking bupropion and valproic acid. Based on available information, his symptomatology (fever, tachycardia, rigidity, diaphoresis, tremors, disorientation, urinary incontinence, leukocytosis, and elevated CK levels) exceeded threshold for NMS with all criteria. The patient was admitted to the pediatric ICU and given intravenous dantrolene. His treatment also included aggressive intravenous hydration and sodium bicarbonate to alkalinize his urine. After 9 days, symptoms of NMS remitted. Two months later, he had a normal physical and neurologic exam. His psychiatric symptoms were successfully addressed with olanzapine.[52]

Aripiprazole

Aripiprazole is a dihydroquinolinone with novel pharmacologic actions. The FDA first approved this medication in 2002. It is a partial agonist at dopamine (D_2 and D_3) and serotonin ($5\text{-}HT_{1A}$) receptors. Conversely, it acts as an antagonist at different serotonin ($5\text{-}HT_{2A}$) receptors.[53] Three cases of patients with symptoms of NMS or "atypical neuroleptic malignant syndrome" associated with aripiprazole were reviewed.[54–56]

Hammerman et al.[54] recently described a case involving a 14-year-old girl with psychotic depression and mental retardation. Within 48 hours of initiating aripiprazole (5 mg daily), she developed symptoms of NMS, which included tremors, sialorrhea, rigidity, gait abnormalities, urinary incontinence, and an elevated CK level. However, she did not have a fever or autonomic instability. Hence, this presentation did not meet criteria for NMS with the 3 diagnostic sets utilized. This patient was admitted to a medical unit, aripiprazole was discontinued, her urine was alkalinized, and she was given lorazepam for 2 days. At this point, she returned to her baseline state. The authors stressed the importance of early recognition of even partial symptoms of NMS in patients receiving atypical antipsychotics.[54]

A second case involved a 17-year-old male patient with paranoid schizophrenia.[55] After 3 days of treatment with aripiprazole (15 mg daily), he developed symptoms of NMS including a tremor, a low-grade temperature elevation, rigidity, sialorrhea, hypertension, and elevated CK levels. His symptoms met diagnosis for NMS with DSM-IV-TR and Levenson's criteria. This patient was ultimately treated with ECT and recovered.[55]

Palakurthi et al.[56] described a case involving a 12-year-old boy with a pervasive developmental disorder who developed NMS after 2 days of treatment with aripiprazole 10 mg daily. This was his only exposure to antipsychotic medications, but he was also taking 36 mg of methylphenidate daily prior to the initiation of aripiprazole. Symptoms of NMS in this case included fever, rigidity, disorientation, autonomic instability, respiratory distress, urinary incontinence, leukocytosis, and elevated CK levels. These symptoms reached DSM-IV-TR and Levenson's criteria for diagnosis. With supportive care, dantrolene, and bromocriptine, he recovered within 1 week.[56]

Multiple Atypical Antipsychotics

Two cases of NMS available for review involved treatment with multiple atypical antipsychotics within a narrow time frame.[48,57] One involved an 18-year-old male patient treated for schizophrenia.[57] He received risperidone

(6 mg daily) for 8 days and developed EPS. Risperidone was discontinued and olanzapine (10 mg daily) was initiated. After 4 days, this boy developed rigidity, fever, tachycardia, respiratory distress, elevated blood pressure, and an elevated CK level. These symptoms met the criteria for the diagnosis of NMS with all 3 diagnostic sets. Treatment involved discontinuation of neuroleptics, transfer to a medical unit, and intravenous fluids. His symptoms resolved over 2 weeks and quetiapine was initiated. Over the next 2 months, the dose was escalated to 800 mg daily. He responded to this and had no further symptoms of NMS 15 weeks later.[57]

Another case report of NMS was in a 12-year-old female patient with bipolar disorder and mental retardation exposed to quetiapine and other atypical antipsychotics.[48] After twenty-five days of treatment with risperidone, she developed a fever, myalgia, disorientation, lethargy, tachycardia, respiratory distress, and elevated CK levels. After discontinuing risperidone, her symptoms resolved in 1 week. At this point, olanzapine and valproic acid were initiated and symptoms of NMS returned (fever and elevated CK level) after 2 days. Olanzapine was withdrawn and her temperature and CK levels normalized. Valproic acid was not sufficient in controlling her aggression, and quetiapine was added to her medication regimen. After 3 days of quetiapine (75 mg daily), she developed a high fever and elevated CK levels once again. Subsequently, quetiapine was discontinued and she was given lithium and valproic acid for sixty-nine days. Ultimately, these agents did not control her mania, and she was rechallenged with olanzapine. Symptoms of NMS emerged after 4 days of treatment with olanzapine. Olanzapine was discontinued once again. This patient recovered but had ongoing symptoms of mania, which resolved with a course of ECT. She was then maintained on valproic acid successfully as an outpatient. The symptoms described in this case met Levenson's criteria for the diagnosis of NMS. These cases are complex, as it is difficult to determine the relative contribution of each agent involved.

DISCUSSION

Atypical antipsychotics generally have favorable side effect profiles and comparable efficacies to traditional neuroleptics.[2–4] As with adults,[11,29] NMS can develop in children and adolescents treated with atypical antipsychotics. Based on available literature, this may involve classic symptoms of NMS (fever, rigidity, autonomic instability, and laboratory abnormalities). Although presentations of NMS in all ages can be heterogeneous, the existence of an "atypical" form (e.g., presentations lacking hyperthermia or rigidity) of this condition remains controversial.[15,16] Most published cases of NMS associated with atypicals in pediatric patients involved male patients (N = 16 or 80%). However, adult studies of NMS suggest that sex is not a risk factor.[58] Based on this review, polypharmacy, recent medication changes, and prior episodes of EPS are possible risk factors for NMS in children and adolescents treated with atypical antipsychotics. In fact, of the twenty cases reviewed, 10 patients (50%) were taking more than 1 psychotropic medication when NMS developed. Sixteen (80%) of the patients had a medication change in the preceding week. Ten individuals (50%) had an episode of EPS prior to NMS. Although it is difficult to make definitive conclusions regarding diagnoses, mental retardation, schizophrenia, and mood disorders could confer a higher risk for NMS in children and adolescents.

The 3 most commonly used criteria for NMS are DSM-IV-TR, Levenson's, and Caroff and Mann's, with Caroff and Mann's being the most stringent. In this review involving children and adolescents treated with second-generation antipsychotics, 16 case reports met the diagnosis for NMS based on at least 1 of these definitions, and 8 cases met criteria for the diagnosis of NMS based on all 3 definitions. Clearly, more work is needed to identify a consistent and clear-cut description of NMS in the pediatric age group. Based on available information, it is not known if there are developmental differences in the phenomenology, pathophysiology, or course of NMS.

No deaths or serious long-term effects were reported in cases reviewed, with the exception of ongoing cognitive deficits in 1 patient.[43] This lack of long-term effects could be attributed to early identification and treatment of NMS. Other possibilities include a milder course of NMS involving atypical antipsychotics, greater resiliency of children and adolescents to the serious sequelae of NMS, or the small number of actual cases. Nine of these patients (45%) were ultimately rechallenged and treated successfully with antipsychotics. In 8 cases, this involved an atypical antipsychotic (4 with clozapine, 1 with risperidone, 1 with olanzapine, and 2 with quetiapine). The other patient was given perphenazine after an episode of NMS. Electroconvulsive therapy proved to be an effective intervention for NMS and underlying psychiatric illnesses in 5 (25%) of the cases reviewed. This may be an underutilized treatment modality for NMS.

Despite the rare occurrence of NMS, psychiatrists and pediatricians should remain vigilant for its possible symptoms while treating pediatric populations with any antipsychotic medication. Parents and caregivers should also be aware of possible risks and presenting symptoms (unexplained fever for example) in children treated with these medications. Further research regarding NMS in children and adolescents is imperative. This could improve identification, minimize morbidity, elucidate appropriate treatment, and provide additional data for the informed consent process.

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Drug names: amantadine (Symmetrel and others), aripiprazole (Abilify), bromocriptine (Parlodel and others), bupropion (Wellbutrin and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, FazaClo, and others), dantrolene (Dantrium and others), diazepam (Diastat, Valium, and others), divalproex sodium (Depakote), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), loxapine (Loxitane and others), methylphenidate (Concerta, Ritalin, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), tetracycline (Bristacycline, Sumycin, and others), valproic acid (Depakene and others), ziprasidone (Geodon).

REFERENCES

1. Patel NC, Crismon ML, Hoagwood K, et al. Trends in the use of typical and atypical antipsychotics in children and adolescents. J Am Acad Child Adolesc Psychiatry 2005;44(6):548–556
2. Delbello MP, Kowatch RA, Adler CM, et al. A double-blind randomized pilot study comparing quetiapine and divalproex for adolescent mania. J Am Acad Child Adolesc Psychiatry 2006;45(3):305–313
3. McClellan J, Kowatch R, Findling RL, et al. Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2007;46(1):107–125
4. Findling RL, Steiner H, Weller EB. Use of antipsychotics in children and adolescents. J Clin Psychiatry 2005;66(suppl 7):29–40
5. DelBello M, Grcevich S. Phenomenology and epidemiology of childhood psychiatric disorders that may necessitate treatment with atypical antipsychotics. J Clin Psychiatry 2004;65(suppl 6):12–19
6. Curtis LH, Masselink LE, Ostbye T, et al. Prevalence of atypical antipsychotic drug use among commercially insured youths in the United States. Arch Pediatr Adolesc Med 2005;159(4):362–366
7. Schur SB, Sikich L, Findling RL, et al. Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth (TRAAY), pt 1: a review. J Am Acad Child Adolesc Psychiatry 2003;42(2):132–144
8. Pappadopulos E, Macintyre Ii JC, Crismon ML, et al. Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth (TRAAY), pt 2. J Am Acad Child Adolesc Psychiatry 2003;42(2): 145–161
9. Findling RL, Schulz C, Reed MD, et al. The antipsychotics: a pediatric perspective. Pediatr Clin North Am 1998;45(5):1205–1233
10. Levenson JL. Neuroleptic malignant syndrome. Am J Psychiatry 1985; 142(10):1137–1145
11. Caroff SN, Mann SC, Campbell EC. Atypical antipsychotics and neuroleptic malignant syndrome. Psychiatr Ann 2000;30:314–321
12. Strawn JR, Keck PE, Caroff SN. Neuroleptic malignant syndrome. Am J Psychiatry 2007;164(6):870–876
13. Guerrero RM, Shifrar KA. Diagnosis and treatment of neuroleptic malignant syndrome. Clin Pharm 1988;7(9):697–701
14. Caroff SN, Mann SC. Neuroleptic malignant syndrome. Med Clin North Am 1993;77:185–202
15. Hasan S, Buckley P. Novel antipsychotics and the neuroleptic malignant syndrome: a review and critique. Am J Psychiatry 1998;155(8): 1113–1116
16. Ananth J, Parameswaran S, Gunatilake S, et al. Neuroleptic malignant syndrome and atypical antipsychotic drugs. J Clin Psychiatry 2004; 65(4):464–470
17. Shields WD, Bray PF. A danger of haloperidol therapy in children. J Pediatr 1976;88(2):301–303
18. Geller B, Greydanus DE. Haloperidol-induced comatose state with hyperthermia and rigidity in adolescence: 2 case reports with a literature review. J Clin Psychiatry 1979;40(2):102–103
19. Casteels-Van Daele M, Van Geet C, Wouters C, et al. Reye syndrome revisited: a descriptive term covering a group of heterogeneous disorders. Eur J Pediatr 2000;159:641–648
20. Silva RR, Munoz DM, Alpert M, et al. Neuroleptic malignant syndrome in children and adolescents. J Am Acad Child Adolesc Psychiatry 1999; 38(2):187–194
21. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000:795–798
22. Meltzer HY. An overview of the mechanism of action of clozapine. J Clin Psychiatry 1994 Sep;55(suppl B):47–52
23. Anderson ES, Powers PS. Neuroleptic malignant syndrome associated with clozapine use. J Clin Psychiatry 1991;52(3):102–104
24. Skarpathiotakis M, Westreich N. NMS after clozapine initiation [letter]. J Am Acad Child Adolesc Psychiatry 2005;44(11):1101–1102
25. Sachdev P, Kruk J, Kneebone M, et al. Clozapine-induced neuroleptic malignant syndrome: review and report of new cases. J Clin Psychopharmacol 1995;15(5):365–371
26. Weller M, Kornhuber J. Clozapine and neuroleptic malignant syndrome: a never-ending story. J Clin Psychopharmacol 1997;17(3):233–234
27. Weller M, Kornhuber J. Does clozapine cause neuroleptic malignant syndrome? [letter] J Clin Psychiatry 1993;54(2):70–71
28. Janssen PAJ, Niemegeers CJE, Awouters F, et al. Pharmacology of risperidone (R 64 766), a new antipsychotic with serotonin-S2 and dopamine-D2 antagonist properties. J Pharmacol Exp Ther 1988;244: 685–693
29. Farver DK. Neuroleptic malignant syndrome induced by atypical antipsychotics. Expert Opin Drug Saf 2003;2(1):21–35
30. Mane A, Baeza I, Morer A, et al. The neuroleptic malignant syndrome associated with risperidone in a male with early-onset schizophrenia. J Child Adolesc Psychopharmacol 2005;15(6):844–845
31. Zalsman G, Lewis R, Konas S, et al. Atypical neuroleptic malignant syndrome associated with risperidone treatment in two adolescents. Int J Adolesc Med Health 2004;16(2):179–182
32. Ty EB, Rothner AD. Neuroleptic malignant syndrome in children and adolescents. J Child Neurol 2001;16(3):157–163
33. Robb AS, Chang W, Lee HK, et al. Risperidone-induced neuroleptic malignant syndrome in an adolescent. J Child Adolesc Psychopharmacol 2000;10(4):327–330
34. Sharma R, Trappler B, Ng YK, et al. Risperidone-induced neuroleptic malignant syndrome. Ann Pharmacother 1996;30:775–778
35. Meltzer HY, Fibiger HC. Olanzapine: a new atypical antipsychotic drug. Neuropsychopharmacology 1996;14(2):83–85
36. Biswas PN, Wilton LV, Pearce GL, et al. The pharmacovigilance of olanzapine: results of a post-marketing surveillance study on 8858 patients in England. J Psychopharmacol 2001;15(4):265–271
37. Kogoj A, Velikonja I. Olanzapine induced neuroleptic malignant syndrome: a case review. Hum Psychopharmacol 2003;18(4):301–309
38 . Berry N, Pradhan S, Sagar R, et al. Neuroleptic malignant syndrome in an adolescent receiving olanzapine-lithium combination therapy. Pharmacotherapy 2003;23(2):255–259
39. Abu-Kishk I, Toledano M, Reis A, et al. Neuroleptic malignant syndrome in a child treated with an atypical antipsychotic. J Toxicol Clin Toxicol 2004;42(6):921–925
40. Hanft A, Eggleston CF, Bourgeois JA. Neuroleptic malignant syndrome in an adolescent after brief exposure to olanzapine. J Child Adolesc Psychopharmacol 2004;14(3):481–487
41. Taylor MA, Fink M. Catatonia in psychiatric classification: a home of its own. Am J Psychiatry 2003;160(7):1233–1241
42. Ghaziuddin N, Alkhouri I, Campine D, et al. ECT treatment of malignant catatonia/NMS in an adolescent: a useful lesson in delayed diagnosis and treatment. J ECT 2002;18(2):95–98
43. Mendhekar DN, Duggal HS. Persistent amnesia as a sequel of olanzapine-induced neuroleptic malignant syndrome. J Neuropsychiatry Clin Neurosci 2006;18(4):552–553
44. Casey DE. Seroquel: preclinical and clinical findings of a new atypical antipsychotic. Exp Opin Invest Drugs 1996;5:939–957
45. Saller CF, Salama AI. Seroquel: biochemical profile of a potential atypical antipsychotic. Psychopharmacology (Berl) 1993;112(2–3): 285–292
46. Solomons K. Quetiapine and neuroleptic malignant syndrome. Can J Psychiatry 2002;47(8):791–792
47. Sing KJ, Ramaekers G, Van Harten PN. Neuroleptic malignant syndrome and quetiapine. Am J Psychiatry 2002;159(1):149–150
48. Chungh DS, Kim BN, Cho SC. Neuroleptic malignant syndrome due to three atypical antipsychotics in a child. J Psychopharmacol 2005;19(4): 422–425
49. Stanley AK, Hunter J. Possible neuroleptic malignant syndrome with quetiapine [letter]. Br J Psychiatry 2000 May;176:497
50. Seeger TF, Seymour PA, Schmidt AW, et al. Ziprasidone (CP-88,059): a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. J Pharmacol Exp Ther 1995;275:101–113
51. Murty RG, Mistry SG, Chacko RC. Neuroleptic malignant syndrome with ziprasidone. J Clin Psychopharmacol 2002;22(6):624–626

52. Leibold J, Patel V, Hasan RA. Neuroleptic malignant syndrome associated with ziprasidone in an adolescent. Clin Ther 2004;26(7):1105–1108
53. Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry 2002;63(9):763–771
54. Hammerman S, Lam C, Caroff SN. Neuroleptic malignant syndrome and aripiprazole. J Am Acad Child Adolesc Psychiatry 2006;45(6):639–641
55. Spalding S, Alessi NE, Radwan K. Aripiprazole and atypical neuroleptic malignant syndrome [letter]. J Am Acad Child Adolesc Psychiatry 2004;43(12):1457–1458
56. Palakurthi HB, Parvin MM, Kaplan S. Neuroleptic malignant syndrome from aripiprazole in an agitated pediatric patient. Clin Neuropharmacol 2007;30:47–51
57. Aboraya A, Schumacher J, Abdalla E, et al. Neuroleptic malignant syndrome associated with risperidone and olanzapine in first-episode schizophrenia. W V Med J 2002;98(2):63–65
58. Keck PE Jr, Pope HG Jr, Cohen BM, et al. Risk factors for neuroleptic malignant syndrome. Arch Gen Psychiatry 1989;46:914–918

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