



# Evaluation and Management of Children With Acute Mental Health or Behavioral Problems. Part II: Recognition of Clinically Challenging Mental Health Related Conditions Presenting With Medical or Uncertain Symptoms

Thomas H. Chun, MD, MPH, FAAP, Sharon E. Mace, MD, FAAP, FACEP, Emily R. Katz, MD, FAAP,  
AMERICAN ACADEMY OF PEDIATRICS Committee on Pediatric Emergency Medicine, AMERICAN  
COLLEGE OF EMERGENCY PHYSICIANS Pediatric Emergency Medicine Committee

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## INTRODUCTION

Part I of this clinical report (<http://www.pediatrics.org/cgi/doi/10.1542/peds.2016-1570>) discusses the common clinical issues that may be encountered in caring for children and adolescents presenting to the emergency department (ED) or primary care setting with a mental health condition or emergency and includes the following:

- Medical clearance of pediatric psychiatric patients
- Suicidal ideation and suicide attempts
- Involuntary hospitalization
- Restraint of the agitated patient
  - Verbal restraint
  - Chemical restraint
  - Physical restraint
- Coordination with the medical home

Part II discusses the challenges a pediatric clinician may face when evaluating patients with a mental health condition, which may be contributing to or a complicating factor for a medical or indeterminate clinical presentation. Topics covered include the following:

- Somatic symptom and related disorders
- Adverse effects of psychiatric medications

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**TABLE 1** Common Symptoms of Somatic Symptom and Related Disorders<sup>14</sup>

Pseudoneurologic	Gastrointestinal symptoms
Amnesia	Abdominal pain
Difficulty with swallowing or voice	Nausea
Vision or hearing impairment	Vomiting
Syncope	Bloating
Seizure	Diarrhea
Paralysis or paresis	Multiple food intolerances
Pain symptoms	Cardiopulmonary symptoms
Headache	Chest pain
Back pain	Dyspnea
Extremity pain	Palpitations
Dysuria	Dizziness

- Antipsychotic adverse effects
- Neuroleptic malignant syndrome
- Serotonin syndrome
- Children with special needs (autism spectrum disorders [ASDs] and developmental disorders [DDs])
- Mental health screening

The report is written primarily from the perspective of ED clinicians, but it is intended for all clinicians who care for children and adolescents with acute mental health and behavioral problems. An executive summary of this clinical report can be found at <http://www.pediatrics.org/cgi/doi/10.1542/peds.2016-1574>.

## SOMATIC SYMPTOM AND RELATED DISORDERS

### Overview

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* recognizes 7 distinct somatic symptom and related disorders, including somatic symptom disorder, illness anxiety disorder, conversion disorder (functional neurologic symptom disorder), psychological factors affecting other medical conditions, factitious disorder, other specified somatic symptom and related disorder, and unspecified somatic symptom and related disorder.<sup>1</sup> Each disorder has specific diagnostic criteria, which apply to both adults and children and which are not adjusted for children. All these disorders

refer to an individual's subjective experience of physical symptoms. These diagnoses can also be applied to situations in which the level of distress or disability is thought to be disproportionate to what is typically associated with the physical findings. For example, when a medical condition is present, if the physical problems do not fully explain the reported symptoms or severity, a somatic symptom and related disorder may apply.<sup>2</sup>

Additional criteria for somatic symptom disorders include the requirement that the complaints or fixations are not associated with material gain, nor are they intentionally produced.<sup>3</sup> Symptoms that are intentionally created are classified as factitious disorders; those that result in material gain are categorized as malingering. Lastly, the symptoms result in significant impairment in psychosocial functioning (eg, relationships with family or friends, academic or occupational difficulties).<sup>1</sup>

Epidemiologic studies have found that somatic symptom and related disorders are both common and a significant contributor to health care usage and costs. In adult primary care populations, between 10% and 15% of patients have a diagnosis of 1 of these disorders.<sup>4</sup> Among children and adolescents, recurrent abdominal pain and headaches account for 5% and between 20% and 55% of pediatric office visits, respectively; 10% of adolescents report frequent

headaches, chest pain, nausea, and fatigue.<sup>5</sup> Patients with somatic symptom and related disorders use all types of medical services (eg, primary, specialty, ED, and mental health care) more frequently,<sup>4,6-8</sup> are more likely to "doctor shop,"<sup>4</sup> and in 2005, were estimated to have incrementally added \$265 billion to the cost of health care in the United States.<sup>9</sup>

### Clinical Features and Studies of Pediatric Somatic Symptom and Related Disorders

The clinical presentations of somatic symptom and related disorders are myriad, most often involving neurologic, pain, autonomic, or gastrointestinal tract symptoms (Table 1). Children and adolescents often report such symptoms<sup>10,11</sup> and often have multiple visits for these symptoms in primary care and other settings.<sup>3,5,12,13</sup> Vague, poorly described complaints, recent or current stressful events, symptoms that fluctuate with activity or stress, and lack of physical findings and laboratory abnormalities are common.<sup>3</sup>

Symptoms of pediatric somatic symptom and related disorders often do not meet strict *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* diagnostic criteria and defy categorization. Other difficulties in caring for patients with these disorders in the ED are that few patients will have received a formal diagnosis, and ED clinicians rarely have access to sufficient clinical information to confirm the diagnosis.<sup>15-17</sup> In addition, the diagnosis of a "psychosomatic" illness can be stigmatizing to patients and families, resulting in them feeling unheard, disrespected, and defensive about their symptoms.<sup>5</sup> For these and other reasons, some prefer the term "medically unexplained symptoms".<sup>2,6,18,19</sup>

Several studies, including 1 performed jointly in the Pediatric

Research in Office Settings and Ambulatory Sentinel Practice Network collaboratives, have identified demographic and risk factors associated with pediatric somatic symptom and related disorders.<sup>2,8,20,21</sup> Patients who are adolescents, female, from minority ethnicities, from nonintact families, or from urban dwellings; who have past histories of psychological trauma; whose parents have lower education levels; and who have other family members with somatic symptom and related disorders are more likely to present with unexplained medical symptoms. Such patients are also at much higher risk of comorbid psychiatric problems.<sup>8</sup>

Other studies have approached this topic by investigating the prevalence of and relationships between psychiatric conditions in patients with unexplained medical symptoms. Emiroğlu et al<sup>22</sup> studied 31 patients referred to a pediatric neurology clinic for headache, vertigo, and syncope. When comprehensive testing did not reveal an identifiable medical cause for their symptoms, the patients were interviewed by a child psychiatrist. A large majority (93.5%) were found to have a diagnosable disorder according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria, the most common being mood and somatic symptom and related disorders. Other pediatric headache studies have found similar results.<sup>23,24</sup> Guidetti et al<sup>25</sup> followed patients for 8 years after referral to a pediatric neurology headache clinic. At follow-up, persistence or worsening of headaches was highly associated with the presence of comorbid psychiatric conditions, and resolution of headaches strongly correlated with the absence of mental health conditions. In this study, the most common mental health conditions were anxiety disorders and depression.

Other studies in other settings echo these findings. In a pediatric cardiology clinic study, Tunaoglu et al<sup>26</sup> reported a prevalence of 74% for psychiatric disorders, primarily depression, anxiety, and somatic symptom and related disorders, in patients referred for chest pain with normal medical workups. Campo et al<sup>27</sup> recruited patients from a pediatric primary care office. Using standardized psychiatric interviews, they found that patients with recurrent abdominal pain were significantly more likely to be diagnosed with anxiety (79%) and depressive disorders (43%) than controls. In a study from a pediatric rheumatology clinic, Kashikar-Zuck et al<sup>28</sup> also conducted standardized psychiatric interviews among patients with juvenile fibromyalgia. A high prevalence of current and lifetime anxiety and mood disorders was detected in this population.

### **Somatic Symptom and Related Disorders and the ED**

Somatic symptom and related disorders are a particularly vexing problem in the ED because of the potential harm to patients that may result from diagnostic uncertainty. It is understandable that a patient with 1 of these disorders might undergo extensive, invasive testing such as a lumbar puncture, be exposed to radiographic studies with ionizing radiation, or be given potent medications to treat their symptoms, which in turn could result in significant respiratory, cardiac, central nervous system (CNS), or hematologic adverse effects, potentially necessitating additional medications or procedures such as endotracheal intubation and mechanical ventilation to treat these adverse effects.

Psychogenic nonepileptic seizures (PNES, previously called “pseudoseizures”) in pediatric ED patients are an illustrative example of this conundrum. In their review

of identified PNES patients (the authors recognize that PNES is often unrecognized and underdiagnosed in the ED), Selbst and Clancy<sup>29</sup> found that all had multiple previous ED visits, 8 of 10 patients had been prescribed anticonvulsants in the past, 6 received anticonvulsants either in the ED or before arrival in the ED by prehospital personnel, all but 1 had invasive procedures and testing, and 8 were admitted to the hospital. Other studies have found similar rates of extensive medical testing in children with PNES.<sup>30</sup> Accurate diagnosis and appropriate referrals for these patients may be important, as Wyllie et al<sup>31</sup> found that on follow-up, 72% of patients’ PNES had resolved after psychiatric treatment. A particularly challenging problem when treating potential PNES in the ED is that some of these patients will have both a true seizure disorder and PNES, making airway management and the decision to give anticonvulsants for apparent seizure activity difficult and complex for ED physicians.

Several studies have investigated the impact of somatic symptom and related disorders on emergency department patients. Knockaert et al<sup>32</sup> prospectively enrolled 578 adult patients presenting to a Belgian ED with chest pain. Although the majority of these patients were found to have a cardiac or pulmonary disease as the etiology of their chest pain, the authors classified “somatization disorder” as the third leading cause (9.2%) of these ED visits. Another interesting finding from this study was that somatization disorder was more common among patients who were self-referred to the ED and those brought by ambulance. Although formal psychiatric evaluation was not performed on all patients, and classification as somatization disorder was based on the available clinical information and the final discharge diagnoses,

the authors believe that their methods underestimated the true prevalence. Other studies have found a higher prevalence of mental health disorders among adult ED patients with chest pain.<sup>17</sup>

Lipsitz et al<sup>33</sup> studied 32 pediatric ED patients who presented with chest pain and for whom no medical cause was found. Using a semistructured *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* interview to detect anxiety disorders, they found that 81% met diagnostic criteria for an anxiety disorder, with 28% meeting full criteria for panic disorder. Other pain symptoms such as headaches, abdominal pain, and back pain were common in these children, as were impaired quality of life and multiple domains of daily functioning. In a secondary analysis of a larger study on maternal and pediatric mental health problems, Dang et al<sup>34</sup> explored the relationship between mothers' somatic symptoms and subsequent pediatric ED use for their child. Maternal somatic symptoms were assessed with the Patient Health Questionnaire 15, a validated measure for inquiring about common somatic problems in outpatient settings. After covariates were adjusted for, mothers with high somatic symptom scores reported higher rates of depression symptoms, difficulty caring for themselves and their child, and a greater use of the ED for their child (odds ratio, 1.8; 95% confidence interval [CI], 0.99–3.38;  $P = .055$ ).

Although there are no known studies of interventions for pediatric ED patients, Abbass et al<sup>35</sup> performed an intriguing prospective study of adult ED patients with suspected somatic symptom and related disorders. If the treating ED physician made a provisional diagnosis of somatization after completing the medical evaluation of the patient, a referral was made for an outpatient mental health evaluation and intensive, short-term psychotherapy.

The mental health evaluation and treatment typically took place a few weeks after the ED visit, with patients receiving a mean of 3.8 psychotherapy sessions (range: 1–25 sessions). After the psychotherapy intervention, at 1-year follow-up, they found a mean reduction of 3.2 ED (69%) visits per patient (SD, 6.4; 95% CI, 1.3–5.0;  $P < .001$ ), compared with the year before the index ED visit. In addition, at follow-up patients reported significant improvement in their somatic symptoms and high satisfaction with the psychotherapeutic referral and intervention. Although this was not a randomized controlled trial, patients who were referred to psychotherapy but did not attend treatment did not show any changes in their ED use at 1 year follow-up.

### Treatment Strategies

Medically unexplained symptoms are extremely frustrating for patients, families, and medical providers. Parents and children often think that they are not being listened to and that physicians have misdiagnosed the problem, or potential causes of the symptoms have not been adequately evaluated.<sup>2,10</sup> These feelings can be intense and may be rooted in a fear that a medical illness is being missed, frustration over the lack of success in resolving the symptoms, the stigma of being labeled or perceived as “psychosomatic,” or difficulty in acknowledging that psychological and physical symptoms may be related.<sup>18</sup>

Prognosis often is unpredictable. In some cases, the episode can be brief and resolve. In other cases, the course is chronic and difficult to treat. The chronicity of the symptoms and previous response to treatment may be informative about the likely treatment course. Most experts agree that an empathetic, consistent, multidisciplinary, long-term treatment plan is helpful for chronic

cases.<sup>2,5,10,18</sup> This may include various psychotherapies (eg, cognitive-behavioral, rehabilitative, operant interventions, self-management strategies, and family or group therapy), consistent communication between all treating providers, and comprehensive treatment of comorbid psychiatric conditions.<sup>2</sup>

Although these treatment modalities are not practical or possible for the ED setting, there are some strategies that are applicable and may be helpful. Experts suggest the following<sup>2,5,18</sup>:

- **Provide reassurance:** First and foremost, it is important to convey to the patient and family that the patient's symptoms are being heard and taken seriously. Taking time to obtain a detailed history and comprehensive physical examination can help accomplish this goal. Some children and families may be reassured by the knowledge that their symptoms are not life or limb threatening. In addition, eliciting and addressing the child's and family's anxiety and fears about the patient's symptoms may be both clinically illuminating for the ED provider and comforting to the patient and family. It may also be important to reaffirm that their ED and outpatient providers are working and will continue to work with them to continue to evaluate and treat their symptoms.
- **Communicate:** Strategies to improve communication include emphasizing collaboration between the patient, family, and all caregivers; identifying common goals and outcomes; and introducing the idea of working on improving functioning in addition to working toward symptom resolution. In addition, educating the patient and family about the limitations of the ED setting, as well as the benefits of other settings for evaluation and treatment, may be helpful. Lastly, exploring the patient and family's

openness to the possibility that the symptoms may be psychologically related may be an important first step. Determining and using terms such as stress, temperament, anxiety, “nerves,” and other terms that are acceptable to the patient and family may assist in this goal.

- **Coordinate care:** Contacting and communicating with all involved care providers may be time consuming but is important in implementing a cohesive, comprehensive evaluation and treatment plan and may have the added benefit of providing reassurance to the patient and family as well as decreasing frustration and improving satisfaction.

## ADVERSE EFFECTS OF PSYCHIATRIC MEDICATIONS

The use of all psychotropic medications in pediatric populations over the last 2 decades has markedly increased.<sup>36,37</sup> Antipsychotic use, in particular, has shown large increases.<sup>38</sup> Especially notable is their burgeoning off-label use,<sup>39-41</sup> including in preschool-aged children.<sup>42-44</sup> Given the frequency and multiple medication regimens with which psychotropic agents are being prescribed,<sup>36</sup> ED clinicians are likely to encounter children and adolescents taking 1 or many of these medications. This section focuses on the clinical problems and diagnostic and treatment dilemmas one may encounter in the ED when caring for pediatric patients on antipsychotics and antidepressants.

An additional important consideration for ED clinicians is that many commonly used medications not typically thought of as psychotropic agents have dopaminergic and serotonergic properties similar to those of antipsychotics and antidepressants. For example, drugs used as antiemetics and for

**TABLE 2** Antipsychotic Adverse Symptoms

Neurotransmitter	Symptoms	Antipsychotics Commonly Associated With Symptom
Dopamine		
Nigrostriatal tract	Extrapyramidal symptoms (eg, dystonia, dyskinesia, akathisia, Parkinsonism)	High-potency “typical” antipsychotics (haloperidol)
Tuberoinfundibular tract	Hyperprolactinemia	All “typical” antipsychotics, risperidone
Preoptic tract	Hypothermia	Rare, possibly more common with atypical antipsychotics
Acetylcholine (muscarinic)	Sinus tachycardia, dry mucous membranes, mydriasis, urinary retention	Low-potency “typical” antipsychotics (chlorpromazine)
α-Adrenergic	Orthostatic hypotension, reflex tachycardia	Atypical antipsychotics
Histamine	Sedation	“Typical” antipsychotics
Mechanism unknown		
Potential etiology:	Wt gain, obesity, hyperlipidemia, metabolic syndrome, impaired glucose tolerance, hyperglycemia, type 2 diabetes	Atypical antipsychotics
Pancreatic versus CNS adrenergic		Highest risk: clozapine, olanzapine
α <sub>1</sub> , α <sub>2</sub> , dopamine D <sub>2</sub> , muscarinic, histamine H <sub>1</sub> , serotonin <sub>1</sub> , serotonin <sub>2</sub> , or serotonin <sub>6</sub>		Lower risk: quetiapine, risperidone
		Lowest risk: ziprasidone, aripiprazole

migraines (ie, prochlorperazine, metoclopramide, promethazine, and trimethobenzamide) are phenothiazines, the same type of medications as first-generation, “typical” antipsychotics. Droperidol, which has been used as an antiemetic and for agitation, is a butyrophenone, the same class as the antipsychotic haloperidol.<sup>45</sup> The number and scope of medications with serotonergic effects are surprising and are detailed in this section. Either alone or in combination with psychotropic serotonergic drugs, these medications can result in serotonin toxicity. Given how frequently these medications are used in clinical practice, familiarizing oneself with them and their potential adverse effects may be beneficial to ED clinicians.

### Antipsychotic Adverse Effects

Antipsychotics are prescribed for various childhood disorders, including oppositional-defiant disorder, conduct disorder, attention-deficit/hyperactivity disorder, and ASDs.<sup>46-49</sup> These medications have

also been used as antiemetics and antipruritics and to treat headaches, hiccups, and various neurologic disorders such as Parkinson disease, hemiballismus, ballismus, Tourette syndrome, and Huntington chorea.<sup>50,51</sup>

The common adverse effects of antipsychotics can be conceptualized and organized around the CNS neurotransmitters on which they act.<sup>45,50-54</sup> Table 2 lists the common adverse effects of antipsychotics and the medications with which they are most commonly associated.

It is important to note that antipsychotics have other clinically significant effects, including “black box” warnings from the US Food and Drug Administration (FDA) for thioridazine and droperidol because of their potential to cause dysrhythmias. Almost all antipsychotics cause some degree of QT<sub>c</sub> prolongation because of a quinidinelike effect. For most of the medications, however, the degree of QT<sub>c</sub> prolongation is small, which has given rise to a debate about the actual risk of dysrhythmias and torsades de pointes with antipsychotics

administered in their usual doses and routes of administration.<sup>45,47,48,55-60</sup>

Of note, intravenous (IV) haloperidol has been studied<sup>61</sup> but carries an FDA non-black box warning because of deaths associated with high doses and IV administration.<sup>62</sup> Therefore, experts suggest that intramuscular dosing of antipsychotics in the ED is the parental preferred route of administration. Table 3 details the factors that are thought to increase the risk of QT<sub>c</sub> prolongation and sudden death.<sup>48,51,63,64</sup> Table 4 lists the degree of QT<sub>c</sub> prolongation for common antipsychotics.<sup>65</sup>

#### Cardiac: Black Box Warning

Both thioridazine and droperidol have been issued FDA black box warnings for a potential association with prolonged QT interval, torsades de pointes, and sudden death. Since then, several studies have disputed this risk with droperidol.<sup>55-60</sup>

A large retrospective review of 2468 patients given droperidol in the ED found that no cardiovascular event occurred that did not have an alternative explanation, and only 6 serious adverse events occurred, with 1 cardiac arrest in a patient with a normal QT interval out of 2468 patients (0.2% = 6/2468).<sup>56</sup>

A pediatric study also suggested the safety and efficacy of droperidol when used to treat agitation, nausea and vomiting, headache, and pain.<sup>66</sup> Thus, "although droperidol can be associated with prolongation of the QT interval, there is not convincing evidence that the drug causes severe cardiac events."<sup>60</sup> Despite these and other studies, since the black box warning was issued, use of droperidol has declined exponentially.<sup>67,68</sup>

#### Neurologic

Acute extrapyramidal syndromes associated with antipsychotic medications include acute dystonia, akathisia, and a Parkinsonian syndrome. Acute dystonia is characterized by involuntary motor

**TABLE 3** Risk Factors for QT<sub>c</sub> Prolongation or Dysrhythmias With Antipsychotic Use

Coadministration with other QT <sub>c</sub> -prolonging medications
IV administration or high doses
Medically ill patients
Electrolyte abnormalities
Hepatic, renal, or cardiac impairment
Congenital long QT syndromes

tics or spasms usually involving the face, the extraocular muscles (oculogyric crisis), and the neck, back, and limb muscles and tends to occur after the first few doses of medication or after an increase in dosage. Laryngeal dystonia is a rare, potentially life-threatening adverse event that presents as a choking sensation, difficulty breathing, or stridor.<sup>45,48</sup>

Akathisia is a subjective feeling of restlessness, which generally occurs within the first few days of antipsychotic medication administration. Akathisia is found in up to 25% of patients<sup>51</sup> and has also been reported in patients receiving a single, standard dose (10 mg) of prochlorperazine. Both acute dystonia and acute akathisia tend to occur early in the course of treatment (ie, days to weeks after beginning an antipsychotic) and are easily reversed. To minimize these adverse effects, some advocate coadministering 25 to 50 mg of diphenhydramine or 1 to 2 mg of benztropine when giving an antipsychotic.<sup>69</sup> Others prefer to treat with anticholinergic agents (ie, diphenhydramine or benztropine) only if acute symptoms occur, followed by 2 days of oral therapy, given the prolonged half-life of antipsychotics.

The delayed-onset neurologic syndromes are Parkinsonism and tardive dyskinesia. The hallmarks of Parkinsonism are shuffling gait, cogwheel muscle rigidity, mask facies, bradykinesia or akinesia, pill-rolling tremors, and cognitive impairment. These symptoms are found in up to 13% of patients and

**TABLE 4** QT<sub>c</sub> Prolongation Associated With Antipsychotics

Medication	Mean QT <sub>c</sub> Prolongation, ms
Thioridazine	25-30
Ziprasidone	5-22
Pimozide	13
Clozapine	8-10
Haloperidol	7
Quetiapine	6
Risperidone	0-5
Olanzapine	2
Aripiprazole	0

generally occur weeks to months after the patient starts antipsychotic therapy.<sup>51</sup> Drug-induced Parkinsonism syndrome is often treated by adding an anticholinergic agent, adding a dopaminergic agonist (eg, amantadine), or decreasing the dosage of a typical antipsychotic or switching to an atypical antipsychotic. Considering the diagnosis of drug-induced Parkinsonism may be important, because early diagnosis and rapid withdrawal of the antipsychotic drug may improve the possibility of complete recovery.<sup>50</sup> Tardive dyskinesia is characterized by rapid involuntary facial movements (eg, blinking, grimacing, chewing, or tongue movements) and extremity or truncal movements. Respiratory dyskinesia is often undiagnosed, can lead to recurrent aspiration pneumonia, and includes orofacial dyskinesia, dysphonia, dyspnea, and respiratory alkalosis.<sup>45</sup> Tardive dyskinesia occurs in 5% of young patients per year and is more common with older, "typical" antipsychotics.<sup>50</sup>

Although antipsychotic medications have been noted to lower the seizure threshold in a dose-dependent manner, antipsychotic medication-induced seizures are rare (usually <1%) when therapeutic doses are used, except for clozapine, which has a 5% incidence of seizures at high dosages.<sup>45,51</sup>

#### Metabolic

Adverse effects, such as weight gain, hyperglycemia, and

hyperlipidemia, are common, especially with second-generation, “atypical” antipsychotics.<sup>45,50,51,70</sup> Antipsychotics vary in their metabolic adverse effects, with the highest risk associated with clozapine and olanzapine, an intermediate risk with quetiapine, risperidone, and chlorpromazine, and the lowest risk with haloperidol, ziprasidone, and aripiprazole.<sup>53</sup>

#### Other

Agranulocytosis is a potential adverse effect of the atypical antipsychotic drug clozapine. Patients on clozapine regularly have complete blood cell counts performed, usually weekly or monthly, to monitor for this adverse effect. Other adverse effects of various atypical antipsychotics include somnolence, anxiety, agitation, oral hypoesthesia, headache, nausea, vomiting, insomnia, and tremor.<sup>51</sup>

#### Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a potentially lethal syndrome consisting of the tetrad of mental status changes, fever, hypertonicity or rigidity, and autonomic dysfunction. It is presumed to be attributable to a lack of dopaminergic activity in the CNS, although hyperactivity of the sympathetic nervous system may also be involved. The deficiency of central dopaminergic activity can be attributable to dopamine antagonists or dopamine receptor blockade, dysfunction of the dopamine receptors, or withdrawal of dopamine agonists.<sup>50,71,72</sup>

With the increasing use of antipsychotic medications in the pediatric population, clinicians caring for children and adolescents may encounter this syndrome.<sup>73</sup> Given that NMS can be difficult to recognize and attenuated or incomplete presentations are possible, NMS is challenging to diagnose.<sup>71,74</sup> The incidence of NMS has been difficult

to determine, with estimates ranging from 0.02% to 3%.<sup>45,71,75</sup> Fortunately, mortality from NMS has decreased from 76% in the 1960s to <10% to 15% more recently.<sup>72,76–78</sup> Experts suggest considering NMS in the differential diagnosis of patients presenting with fever and altered mental status who are taking or may have taken an antipsychotic.<sup>74</sup>

NMS affects patients of all ages, with an apparent predominance in young adults and male patients (2:1).<sup>73,79–81</sup> It is unclear whether these are truly risk factors or reflect the patient population with the greatest use of antipsychotic medications.<sup>75</sup> Coadministration of psychotropic agents seems to be an especially high risk factor for precipitating NMS; in 1 study, more than half of people with reported NMS cases were taking concomitant psychotropic agents.<sup>77</sup> Other risk factors include dehydration, physical exhaustion, preexisting organic brain disease, and the use of long-acting depot antipsychotics. Neither duration of exposure to the drug nor toxic overdoses of antipsychotics appear to be associated with NMS. In addition, reintroducing the original precipitating drug may not lead to a reoccurrence of NMS, although patients with a history of NMS are at increased risk of recurrence.<sup>76,77</sup> The onset of NMS generally occurs within 7 days of starting or increasing antipsychotics and may last for 5 to 10 days even after the initiating agent is stopped. With depot forms of antipsychotics, however, onset of NMS symptoms may be more insidious and may last longer, up to 15 to 30 days.<sup>71,76,82</sup>

It was initially thought that newer atypical antipsychotics, which have both serotonin and dopamine-blocking properties, would not cause NMS because of their lower activity at dopamine receptors and their greater antiserotonergic activity. This has not turned out to

be the case. Both second-generation atypical antipsychotics and the third-generation aripiprazole, which has partial dopamine agonist activity, have all been implicated in causing NMS.<sup>76,79,83–87</sup>

Despite its name, NMS can also be triggered by the administration or withdrawal of other, nonantipsychotic medications. Administration of tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and lithium have been associated with NMS.<sup>75</sup> NMS also has been associated with the abrupt withdrawal of medications (eg, dopaminergic drugs used to treat Parkinson disease, such as levodopa, as well as baclofen, amantadine, some antipsychotics, and some antidepressants).<sup>74</sup> Lastly, the introduction to this section enumerates some of the medications commonly thought to be antiemetics or antimigraine therapies. They are, in fact, phenothiazines (ie, the same class of medications as first-generation, typical antipsychotics), but because of the clinical conditions for which they are used, they may not be suspected for being at risk for triggering NMS.

#### Pathophysiology

The cause of NMS is postulated to be a lack of dopaminergic activity in the CNS, principally affecting the D<sub>2</sub> receptors. Dopamine D<sub>2</sub> receptor antagonism leads to the manifestations of the NMS. Blockade of D<sub>2</sub> receptors in the hypothalamus produces an increased set point and loss of heat-dissipating mechanisms. Antagonism of the D<sub>2</sub> receptors in the nigrostriatal pathways and spinal cord via extrapyramidal pathways produces muscle rigidity and tremor. In the periphery, the increased release of calcium from the sarcoplasmic reticulum causes increased contractility, leading to muscle rigidity, increased heat production (with worsening of hyperthermia), and muscle cell

**TABLE 5** Differential Diagnosis of NMS<sup>72,89</sup>

Toxicologic	Psychiatric
Serotonin syndrome	Delirium
Anticholinergic poisoning	Lethal catatonia
Sympathomimetics	Factitious fever
Malignant hyperthermia	Munchausen syndrome
Monoamine oxidase inhibitor	CNS
Monoamine oxidase inhibitor interaction with drugs or foods	Intracranial tumors
Central anticholinergic syndrome	Vasculitis
Lithium	Stroke
Phencyclidine	Seizure
Infectious disease	Other
Encephalitis	Heatstroke
Meningitis	Rheumatologic (eg, systemic lupus erythematosus, lupus cerebritis)
Tetanus	Malignancies
Endocrine	HIV/AIDS
Pheochromocytoma	Porphyria
Thyroid disease	Familial Mediterranean fever
Adrenal disease	

breakdown with elevated creatine kinase and rhabdomyolysis. In addition, D<sub>2</sub> receptor antagonism by eliminating tonic inhibition of the sympathetic nervous system leads to sympathoadrenal hyperactivity and autonomic instability.<sup>72,75</sup>

#### Clinical Presentation

The hallmarks of NMS are hyperthermia, altered mental status, muscle rigidity, and autonomic instability. Manifestations of autonomic dysfunction, which may occur before other symptoms, include fever up to 41°C or higher, tachycardia, blood pressure instability, diaphoresis, pallor, cardiac dysrhythmia, diaphoresis, sialorrhea, and dysphagia.<sup>71,88</sup>

The most common neurologic finding is lead pipe rigidity, although akinesia, dyskinesia, or waxy flexibility may be present.<sup>45,77</sup> The alteration in mental status often takes the form of delirium but varies from alert mutism to agitation to stupor to coma.<sup>50,76</sup> Motor abnormalities may include rigidity, akinesia, intermittent tremors, and involuntary movements. Other less common neurologic or neuromuscular signs include a positive Babinski, chorea, seizures, opisthotonos, trismus, and oculogyric crisis.<sup>76,86</sup>

Complications include renal failure from rhabdomyolysis, thromboemboli, dysrhythmias, cardiovascular collapse, and respiratory failure from aspiration pneumonia or tachypneic hypoventilation caused by diminished chest wall compliance from muscle rigidity, which may result in endotracheal intubation and ventilatory support.<sup>50,71</sup>

#### Diagnosis

Because there are no pathognomonic clinical or laboratory criteria, NMS is a clinical diagnosis. The differential diagnosis for NMS is broad and is outlined in Table 5. An important component of the diagnosis is a history of antipsychotic use or withdrawal of a dopaminergic agent.<sup>45,86</sup> Numerous diagnostic criteria have been proposed, which have included the classic clinical symptoms and other supplemental criteria.<sup>1,79,81,88</sup> Additional proposed criteria include elevated creatine kinase,<sup>81</sup> leukocytosis, incontinence, dysphagia, mutism, and metabolic acidosis.<sup>1,79,81</sup>

Recently, a Delphi panel of international NMS experts convened to discuss NMS diagnostic criteria.<sup>90</sup> Although its purpose was not to create a new set of criteria, the

results reflect consensus on the relative importance of individual clinical and diagnostic features for making a diagnosis of NMS. On a 100-point scoring system (ie, the total number of points sum up to 100), each clinical feature of NMS was assigned a number of “priority points.” The point system is not meant to be used as a method for making the diagnosis of NMS; that is, there is no threshold number of points that indicate the presence or absence of NMS. Rather, it is meant to help clinicians determine which features of NMS are more important in making the diagnosis. The greater the number of points assigned, the greater the significance of the feature in making the diagnosis of NMS. The Delphi panel made the following assignments: exposure to dopamine antagonist or withdrawal of dopamine agonist within 3 days (20 points), hyperthermia (>100.4°F oral on ≥2 occasions [18 points]), rigidity (17 points), mental status alteration (13 points), creatine kinase elevation (≥4 times upper limit of normal [10 points]), sympathetic nervous system lability (10 points), hypermetabolism (5 points), and negative workup for infectious, toxic, metabolic, or neurologic causes (7 points). Sympathetic nervous system lability was defined as 2 or more of the following: elevated (systolic or diastolic ≥25% of baseline) or fluctuations (≥20 mm Hg diastolic or ≥25 mm Hg systolic change within 24 hours) in blood pressure, diaphoresis, or urinary incontinence. Hypermetabolism was defined as a heart rate increase ≥25% above baseline and respiratory rate ≥50% above baseline.

Leukocytosis, generally in the range of 15 000 to 30 000 cells per cubic millimeter, and electrolyte findings consistent with dehydration may be present. The etiology of elevated alkaline phosphatase, lactic dehydrogenase, and transaminases indicating impaired liver function



is unknown but may be secondary to acute fatty liver changes from the hyperpyrexia. An elevated serum aldolase and creatine kinase, often greater than 16 000 IU/L, may be attributable to severe, sustained muscle contractions. The elevated creatine kinase may lead to rhabdomyolysis, acute myoglobinuria, and renal failure. A nonspecific common finding is the presence of a low serum iron concentration in patients with NMS.<sup>77,86,91</sup> If a lumbar puncture is performed, the cerebrospinal fluid results may be normal or have nonspecific findings. Findings on an EEG, if obtained, are variable. The EEG results may be normal or demonstrate findings of a nonspecific encephalopathy, such as diffuse slowing.<sup>71,76</sup> There are no specific findings on postmortem histopathology of the brain.<sup>71</sup>

Differentiating NMS from serotonin syndrome and other toxidromes can be challenging. Clinical features that may help are detailed in Table 7 and the section on serotonin syndrome.

### *Treatment*

Management of NMS involves primarily supportive care and removal of the initiating agent. If NMS is triggered by the abrupt withdrawal of an anti-Parkinsonism drug, reintroduction of the drug may be considered.<sup>72</sup> Cardiorespiratory compromise may be managed with standard, supportive measures. Dehydration or elevated creatine kinase and rhabdomyolysis may be treated with IV fluids. If renal failure occurs, hemodialysis may be necessary (however, dialysis does not remove antipsychotics that are protein bound). For agitation, experts suggest benzodiazepines as the first-line agent. Fever can be treated with external cooling measures, such as cooling blankets.<sup>72,75</sup>

Suggestions for NMS treatment are based on case reports and clinical experience, not rigorous clinical

trials, limiting the strength of the evidence base. The most frequently administered drugs have been dantrolene, bromocriptine, and amantadine. Dantrolene decreases muscle rigidity, and thermogenesis caused by the tonic contraction of muscles. It blocks the release of calcium from smooth muscle cells' sarcoplasmic reticulum, uncoupling actin and myosin chains, resulting in muscle relaxation. Commonly used dosages in NMS are 1 mg/kg by IV push followed by 0.25 to 0.75 mg/kg every 6 hours. The drug may be continued until symptoms resolve or a maximum of 10 mg/kg is reached.<sup>72,77</sup>

The utility of CNS dopaminergic agents is unclear and controversial. Therefore, consultation with a toxicologist or poison control center may be helpful. Bromocriptine is a centrally acting dopamine agonist. Experts suggest an initial dosage of 1.25 to 2.5 mg twice a day, which may be increased to 10 mg 3 times a day. Muscle rigidity usually responds quickly to bromocriptine, but fever, blood pressure, and creatine kinase levels may take several days to normalize. Amantadine has dopaminergic and anticholinergic effects. A common starting dosage is 100 mg orally, with a maximum dosage of 200 mg twice a day.<sup>72,77,86</sup> Benzodiazepines are often used for agitation and rigidity. Electroconvulsive therapy has been used in some pharmacotherapy-resistant cases.<sup>72,77</sup>

ED clinicians may not have seen or treated many cases of NMS. Potential resources for caring for these patients include toxicologists, a poison control center, and the NMS Information Service, which can be accessed through its Web site (<http://www.nmsis.org/index.asp>). Staffed by NMS experts, the NMS Information Service provides information, education, and phone consultation regarding the diagnosis and treatment of NMS.

## **Serotonin Syndrome**

Serotonin syndrome occurs in all ages, from infants and children to older adults. It has even been reported in newborn infants as a result of in utero exposure.<sup>92</sup> The incidence of and mortality from serotonin syndrome have been increasing and may escalate in the future<sup>93,94</sup> because of the growing number and use of proserotonergic medications, such as SSRIs, other classes of psychiatric medications (eg, other antidepressants and anxiolytics), antibiotics, opiate analgesics, antiemetics, anticonvulsants, antimigraine drugs, anti-Parkinsonism drugs, muscle relaxants, and weight-reduction or bariatric medications (Table 6). In addition to prescription medications, a wide variety of over-the-counter medications, herbal and dietary supplements, and drugs of abuse have all been associated with serotonin syndrome.<sup>95</sup>

Serotonin syndrome occurs in approximately 16% to 18% of patients who overdose with an SSRI.<sup>93</sup> The true incidence of serotonin syndrome is difficult to estimate, given that many instances are probably undiagnosed or misdiagnosed.<sup>96,97</sup> Variable clinical manifestations (eg, lack of the classic triad of symptoms), wide spectrum of disease from mild to life-threatening, symptoms that are easily misattributed to the patient's underlying mental condition (eg, anxiety and akathisia), lack of awareness of the disorder, and the vast number of medications, other agents, and combinations of medicines or agents that can cause serotonin syndrome all may contribute to missed diagnoses.<sup>93,97,98</sup>

### *Pathophysiology*

In the CNS, serotonin (5-hydroxytryptamine) regulates temperature, attention, and behavior. Peripherally, serotonin

**TABLE 6** Medications and Other Agents Associated With Serotonin Syndrome

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Psychiatric drugs
Antianxiety drugs: direct serotonin antagonists
Buspirone
Antimanic drugs: increased postsynaptic receptor sensitivity
Lithium
Antidepressants
Antidepressants: tricyclic antidepressants
Amitriptyline
Clomipramine
Nortriptyline
Antidepressants: monoamine oxidase inhibitors
Phenelzine
Antidepressants: SSRIs
Citalopram
Fluoxetine
Paroxetine
Sertraline
Antidepressants: 5HT <sub>2A</sub> receptor blockers
Nefazodone
Trazodone
Antidepressants: serotonin-norepinephrine reuptake inhibitors
Venlafaxine
Duloxetine
Nonpsychiatric drugs
Skeletal muscle relaxants
Cyclobenzaprine
Opioid analgesics
Fentanyl
Meperidine
Oxycodone
Pentazocine
Tramadol
Hydrocodone
Antibiotics
Linezolid
Antiretroviral (protease inhibitor)
Ritonavir
Anticonvulsants
Carbamazepine
Valproic acid
Antiemetics
Metoclopramide (Reglan)
5HT <sub>3</sub> receptor antagonists
Ondansetron
Antimigraine drugs
Ergot alkaloids: ergotamines
Triptans (5 HT <sub>1B</sub> and 5HT <sub>1B</sub> receptor agonists; eg, sumatriptan)
Antiparkinsonian drugs
Carbidopa/levodopa
Bariatric medications (weight reduction)
Sibutramine
Over-the-counter medications
Dextromethorphan (cough suppressants and cold remedies)
Drugs of abuse
3,4-Methylenedioxymethamphetamine (Ecstasy)
Cocaine
Lysergic acid diethylamide
Methamphetamine
Herbals
<i>Hypericum perforatum</i> (St John's wort)
Dietary supplements
<i>Panax ginseng</i> (ginseng)
L-tryptophan
5-hydroxytryptophan

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This is not an all-inclusive list but gives an overview of the wide range of agents that can trigger the serotonin syndrome. Drugs are listed by their therapeutic category. This list is not intended to endorse any given drug or product.

modulates gastrointestinal tract motility, vasoconstriction, bronchoconstriction, and platelet aggregation. Seven families of serotonin receptors have been identified, with serotonin syndrome resulting from excess CNS serotonin,<sup>98,99</sup> primarily caused by overstimulation of serotonin<sub>2A</sub> receptors.<sup>100,101</sup>

Excessive serotonin activity may result from myriad mechanisms, including increased release of serotonin (eg, cocaine, amphetamines), increased production of serotonin (eg, L-tryptophan in stimulant products), inhibiting reuptake of synaptic serotonin (eg, tricyclic antidepressants, SSRIs), decreased neuronal metabolism of serotonin via inhibition of monoamine oxidase inhibitors, direct stimulation of serotonin receptors (eg, lysergic acid diethylamide, migraine drugs such as sumatriptan, buspirone), and increased postsynaptic receptor responsivity (eg, lithium).<sup>93,95</sup>

A single dose of a single proserotonergic agent may precipitate serotonin syndrome. However, many cases occur after exposure to 2 or more drugs that increase the serotonin activity. Examples of combinations of proserotonergic medications causing serotonin syndrome include reports of SSRIs and fentanyl (given during procedural sedation),<sup>102</sup> erythromycin,<sup>96</sup> and St John's wort (an over-the-counter herbal supplement).<sup>95</sup> In addition, serotonin syndrome has also been reported in a patient withdrawing from a serotonergic agent.<sup>100</sup>

### *Clinical Presentation*

The clinical triad of the serotonin syndrome consists of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities. One of the greatest challenges of this diagnosis is its extremely

variable presentation. Many patients do not exhibit all these clinical characteristics.<sup>103</sup> Some patients will have severe symptoms, such as high fever (up to 41.1°C), severe hypertension, and tachycardia that may deteriorate into hypotension, shock, agitated delirium, muscular rigidity, and hypertonicity. Mild cases may range from tremor and diarrhea to tachycardia and hypertension but no fever. Symptom onset is generally rapid, often within minutes of exposure to the precipitating agent, with most patients presenting within 6 to 24 hours.<sup>100</sup>

Agitated delirium is the most common form of mental status change, although this too has a wide spectrum of severity, including mild agitation, hypervigilance, slightly pressured speech, and easy startle. Diaphoresis, shivering, mydriasis, increased bowel sounds, and diarrhea are common signs of autonomic dysfunction.<sup>95,100</sup> Myoclonus is the most common neuromuscular finding,<sup>98</sup> but other abnormalities are possible, including muscular rigidity, hypertonicity (which may in turn contribute to hyperthermia), hyperreflexia and clonus (which are more pronounced in the lower than the upper extremities), horizontal ocular clonus, tremor, and akathisia. In some cases, muscle hypertonicity may be so severe that it overpowers and obscures tremor and hyperreflexia.

Significant morbidity and mortality are associated with serotonin syndrome. Severe cases are characterized by rhabdomyolysis with an elevated creatine kinase, metabolic acidosis, elevated serum aminotransferase, renal failure with an elevated serum creatinine, seizures, and disseminated intravascular coagulopathy. Approximately one-quarter of patients are treated with intubation, mechanical ventilation, and admission to an ICU. The mortality rate is approximately 11%, with

the most common cause of death being inadequate management of hyperthermia.<sup>98</sup>

### Diagnosis

The differential diagnosis of serotonin syndrome includes other disorders precipitated by medications or drug toxicity reactions (eg, NMS and malignant hyperthermia, anticholinergic syndrome, and withdrawal syndromes including delirium tremens); CNS disorders spanning infection (meningitis, encephalitis), tumors, and seizures; and psychiatric disorders such as acute catatonia.

Differentiating between serotonin syndrome and other medication-induced syndromes can be challenging and may be important, given that treatment may differ depending on the underlying etiology. Table 7 details both the similar and differentiating features of these syndromes. The most common clinical finding of serotonin syndrome is myoclonus, which occurs in slightly more than half (57%) of cases.<sup>98</sup> Some experts believe that clonus and hyperreflexia are “highly diagnostic for the serotonin syndrome and their occurrence in the setting of serotonergic drug use establishes the diagnosis.”<sup>100</sup>

As with NMS, there are no pathognomonic laboratory or radiographic findings of serotonin syndrome. Testing may be obtained on the basis of clinical suspicion and may include a complete blood cell count, electrolytes, serum urea nitrogen, creatinine, arterial blood gas (checking respiratory status and for metabolic acidosis), hepatic transaminases, creatine kinase, urinalysis, toxicology screens, coagulation studies, electrocardiography, EEG, and brain imaging studies.

Clinical diagnostic criteria for serotonin syndrome have been proposed.<sup>104,105</sup> Hunter criteria<sup>104</sup>

have a higher sensitivity (84% vs 75%) and specificity (97% vs 96%) than Sternbach criteria.<sup>105</sup> In addition, the use of the Sternbach criteria may exclude mild, early, or subacute serotonin syndrome. Others prefer modified Dunkley criteria.<sup>100,104</sup> According to the modified Dunkley criteria, the diagnosis can be made if the patient has taken a serotonergic drug within the last 5 weeks and has any of the following: tremor and hyperreflexia; spontaneous clonus; muscle rigidity, temperature >38°C, and either ocular clonus or inducible clonus; ocular clonus and either agitation or diaphoresis; or inducible clonus and either agitation or diaphoresis.<sup>100</sup> Other variations of these diagnostic criteria have been proposed. They all include a serotonergic drug having been started or the dosage increased and other possible etiologies (eg, NMS, substance abuse, withdrawal, infection, other toxidromes) having been ruled out, plus the presence of specific signs and symptoms.<sup>95,106,107</sup>

### Treatment

Treatment often involves discontinuing the precipitating agent and providing supportive care. Supportive care may include treatment of agitation (eg, benzodiazepines), amelioration of hyperthermia, and management of the autonomic instability (eg, IV fluids and other agents to address abnormal vital signs). In addition, for those with severe serotonin syndrome (eg, temperature >41.1°C), emergency sedation, neuromuscular paralysis, and intubation may be considered. Physical restraints may be detrimental, because they may exacerbate isometric contractions, thereby worsening hyperthermia and lactic acidosis and increasing mortality.<sup>98</sup>

In severe cases, serotonin<sub>2A</sub> antagonists may be considered, with cyproheptadine being most commonly used. The adult dosage of

**TABLE 7** Differentiation of the Drug Toxicity Syndromes

	Serotonin Syndrome	NMS	Malignant Hyperthermia	Anticholinergic Poisoning
Etiology	Excessive serotonin	Decreased dopamine	Calcium release from sarcoplasmic reticulum	Inhibit acetylcholine binding to muscarinic receptors
Precipitant	Proserotonergic drugs	Dopamine antagonist or withdrawal of dopaminergic drug	Inhalational anesthetic with or without succinylcholine	Anticholinergic drugs or antimuscarinic drugs
History	Nonidiosyncratic, add new drug, ↑ dosage of drug, or add second drug	Idiosyncratic, exposure to dopamine antagonist drug or withdrawal from dopaminergic drug	Inherited (+ family history) or new genetic mutation	Anticholinergic drug exposure antihistamines, tricyclic antidepressants, sleep aids, cold preparations, diphenhydramine, atropine
Onset	Minutes to hours Usual: 6–24 h	Days Usual: 1–7 d	Hours Usual: <12 h	Minutes to hours Usual: 0.5–24 h
Vital signs				
Temperature	Elevated ( $\leq 41.1^{\circ}\text{C}$ )	Elevated ( $\leq 41.1^{\circ}\text{C}$ )	Elevated ( $\leq 46^{\circ}\text{C}$ )	Mild elevation ( $< 38.8^{\circ}\text{C}$ )
Heart rate	Tachycardia	Tachycardia	Tachycardia	Tachycardia
Respirations	Tachypnea	Tachypnea	Tachypnea	Tachypnea
Blood pressure	Hypertension (may deteriorate to hypotension)	Hypertension	Hypertension	Hypertension (mild)
Mental status	Agitated delirium	Variable: alert, mutism, stupor, coma	Agitation	Agitated delirium
Neuromuscular abnormalities				
Muscle tone	Increased, lower extremities greater than upper extremities	“Lead pipe” rigidity	Rigor mortis–like rigidity (masseters or generalized)	Normal
Muscle reflexes	Hyperreflexic, clonus; may be masked by hypertonicity	Slowed, bradyreflexic	Hyporeflexic	Normal
Physical examination				
Skin	Diaphoretic	Diaphoretic	Diaphoretic, mottled	Hot, dry, erythema <sup>a</sup>
Pupils	Mydriasis	Normal	Normal	Mydriasis
Mucous membranes	Sialorrhea	Sialorrhea	Normal	Dry <sup>a</sup>
Gastrointestinal motility	Hyperactive bowel sounds, may have diarrhea	Normal or hypoactive bowel sounds	Hypoactive bowel sounds	Hypoactive or absent bowel sounds
Treatment considerations				
General	Discontinue precipitant drug, supportive care, benzodiazepine for agitation			
Specific	If severe: serotonin <sub>2A</sub> antagonists (eg, cyproheptadine)	If severe: smooth muscle relaxant (eg, dantrolene), dopamine agonists (eg, bromocriptine, amantadine)	If severe: dantrolene	Sodium bicarbonate for prolonged QRS or dysrhythmias, treat hyperthermia, physostigmine

All of these drug toxicity syndromes can present with altered mental status, autonomic dysfunction, and neuromuscular abnormalities as manifested by abnormal vital signs including fever, hypertension, and tachycardia. Treatment in all 4 syndromes may include removing the precipitating agent and providing supportive care. Other specific therapy may differ depending on the disorder. Not all patients will have all the classic signs and symptoms. For example, a patient with mild serotonin syndrome may be afebrile but have tachycardia and hypertension. Typical findings are listed in this table.

<sup>a</sup> Anticholinergic syndrome described as “Red as a beet, dry as a bone, hot as a hare, blind as a bat, mad as a hatter, full as a flask.”

cyproheptadine is usually 12 to 24 mg over 24 hours, typically starting with 12 mg, followed by 2 mg every 2 hours for continuing symptoms, and a maintenance dose of 8 mg

every 6 hours, given orally. There is no parenteral form, but tablets have been crushed and administered via a nasogastric tube. The pediatric dosage is usually 0.25 mg/kg per day,

divided into 2 or 3 doses daily, up to a maximum of 12 mg. Chlorpromazine, an antagonist of serotonin<sub>2A</sub> receptors as well, is available in a parenteral form but has the disadvantage that

it can cause hypotension and may increase muscle rigidity, decrease the seizure threshold, and worsen NMS.<sup>98</sup> Both drugs may be effective,<sup>108</sup> but cyproheptadine is preferred by most experts.<sup>99,100</sup>

Low dosages of direct-acting sympathomimetic amines (eg, phenylephrine, norepinephrine, and epinephrine) or short-acting drugs such as esmolol or nitroprusside have been used to manage fluctuating blood pressure and heart rate. Use of indirect agents (eg, dopamine) may not be efficacious, because the mechanism of action of these drugs includes intracellular metabolism via catecholamine-O-methyl transferase to metabolize the dopamine to epinephrine and norepinephrine, which may result in overshooting the desired effect.

Management of hyperthermia often involves terminating the extreme muscle activity. In addition to treating agitation, benzodiazepines may be useful in controlling muscular activity in moderate cases. In severe cases, paralysis with nondepolarizing drugs (eg, vecuronium or rocuronium) and intubation may be considered. Some experts suggest that succinylcholine may be risky with these patients, secondary to hyperkalemia and rhabdomyolysis, which may be present and ultimately result in dysrhythmias. Because the fever of NMS is secondary to muscular hyperactivity and not effects on the hypothalamic thermoregulation set point, antipyretics typically are not efficacious.<sup>96,99,108</sup>

Patients with serotonin syndrome can deteriorate rapidly; therefore, close observation and preparation for rapid intervention may be considered. In milder cases, evaluation, observation, and discharge with close, additional outpatient management may be considered. As mentioned previously, discussing these patients' care with a toxicologist or poison control center may be helpful.

## CHILDREN WITH SPECIAL NEEDS

### Autism Spectrum and Developmental Disorders

In recent years, there has been a sharp increase in the incidence of ASDs and DDs,<sup>109</sup> with corresponding interest and growth in treatment strategies. Investigated therapeutic modalities include psychobehavioral therapies,<sup>110–115</sup> psychopharmacology,<sup>116–118</sup> occupational and language therapies,<sup>119–121</sup> and complementary and alternative medicines.<sup>122</sup>

Unfortunately, many studies have had methodologic limitations (eg, small sample sizes, variability in study populations, methods or interventions used, and outcomes measures) and are not applicable to the medical setting.<sup>123–125</sup> Three evidence-based reviews of this topic conclude that there is adequate evidence for only a limited number of therapies (eg, pharmacotherapy), although several other strategies show promise (eg, early and intensive behavioral therapy, social skills training, and visual communication systems).<sup>125–128</sup> Given these limitations, the strategies discussed below are based primarily on expert, consensus opinion.

#### *ASD-DD–Sensitive Care Resources*

A wide range of ED health professionals can champion, organize, design, and coordinate ASD-sensitive ED care, including physicians, nurses, nursing assistants, nurse practitioners and physician assistants, social workers, and child life specialists. Non-ED professionals who may be helpful include developmental-behavioral pediatricians, child psychologists and psychiatrists, special education teachers, speech-language therapists, and occupational therapists.

Often, the most important ASD-DD “experts” to consult are the child’s parents. Parents of children with ASDs or DDs know what strategies

work with their children (eg, which words, actions, or stimuli calm and help their child and which have the opposite effect). Parents can also be “interpreters” for ED clinicians, deciphering the significance of their child’s actions and behaviors and facilitating communication with their child. Spending some time asking parents about their child is likely to be a productive, efficient method for tailoring effective ED care for these patients.

#### *Strategies for ASD-DD–Sensitive ED Care*

Typical strategies for caring for children with ASD-DD are listed in Table 8.<sup>128</sup> Children with ASD-DD are often hypersensitive to environmental stimuli (eg, light, sound, and activity). Simple solutions include using a quiet office or counseling room (if available) instead of a loud, stimulating examination room. If this type of patient space is not available, an alternative solution may be to use a quiet examination room, away from the busy, noisy areas of the ED, with dimmed lighting (eg, turning off some lights or using a single lamp).

Studies have demonstrated that visual communication systems (VCSs) can improve communication with children with language disabilities.<sup>129–132</sup> VCS products are the most commonly used communication adjuncts and are widely available. There are numerous commercial or free and print and electronic products (eg, Web sites, “apps,” devices). A visual schedule (Fig 1) exemplifies how a VCS can be used to prepare a child with ASD-DD for an upcoming event or activity. Visual schedules help children organize themselves, understand what will happen next, highlight or introduce activities that are unfamiliar to them, and create smoother transitions, all of which may decrease children’s anxiety.

If a child has his or her own personal VCS, it may be advantageous to use

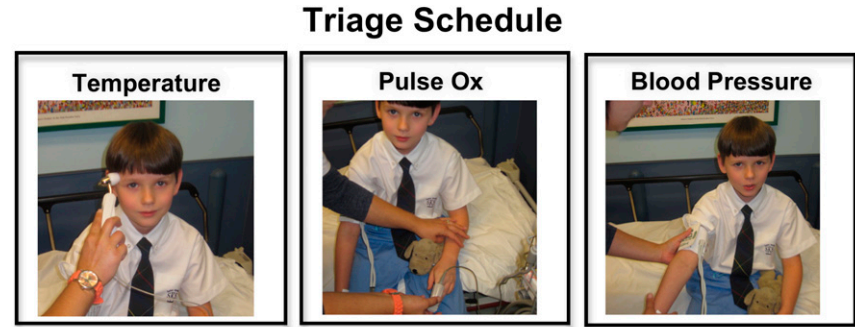
**TABLE 8** Nonpharmacologic Strategies for Caring for Children With ASD-DD

Environmental modification (light, noise, other stimuli)
Visual communication systems
Transition planning
Occupational or physical therapy techniques

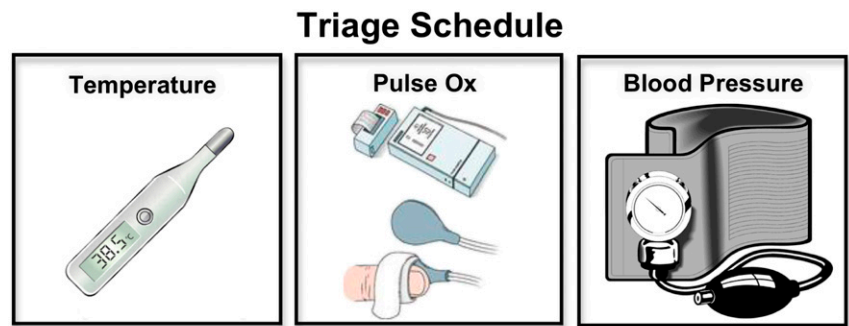
the VCS, because the child will be familiar with pictures. A potential disadvantage of a personal VCS is that the set of images may not have the necessary medical pictures. A simple and inexpensive solution to this problem is to create a custom set of images of the ED setting. This can easily be done with clip art or digital photography images, which are then printed and laminated. If digital photography is used, taking pictures of the ED staff, equipment, and commonly performed procedures is a simple method for creating a customized VCS for your setting (Fig 2).

Transitions are often problematic for children with ASD-DD, including changing from 1 activity to the next, moving from 1 setting to another (especially new settings), and breaks or deviations from their usual routines. For these reasons, a medical visit may be upsetting or unsettling to these children. Fortunately, many parents are familiar with anticipating and planning for these types of transitions. For example, these parents talk to their children before a new experience, describe what will happen and the sequence of events, and explain what might be upsetting to the children and how they will handle these stressful situations. Preparing children with ASD-DD for a medical visit ideally begins before or while en route to the visit and is an ongoing process once they arrive.

Anticipating and building breaks in a schedule may be helpful. Many children with ASD-DD are able to remain on task for only short periods of time. Regular, brief breaks in the schedule may be helpful to these children. As time consuming as it may be, in the total calculus of planning



**FIGURE 1** Digital photograph visual schedule. Photo credit: Thomas H. Chun, MD, MPH, FAAP.



**FIGURE 2** Clip art visual schedule.

the ED visit this may still be a time-neutral strategy relative to the time consumed by unsuccessful strategies. At the least, this strategy is likely to be more satisfactory to children, their parents, and ED clinicians.

Desensitization strategies that are used with all children (eg, gradually approaching and engaging with children, bending down to interact at children's level, allowing children to play with medical instruments or to use them on you or their parent first, distracting them with a toy or game, and having children held or comforted by parents while they are examined) also may help with children with ASD-DD. For some, however, the same strategies may benefit from significant augmentation, literally breaking each step down into several incremental, smaller steps. It may take several visits and interactions and multiple attempts before children will allow you to approach and examine them.

Other children with ASD-DD are very sensitive about their personal space. Starting at the periphery (ie, toes and fingers) and slowly moving centrally may help relax children and facilitate the examination. These types of desensitization strategies have been successfully used for phlebotomy attempts in children with ASD-DD.<sup>133</sup>

Many children with ASD-DD find value in occupational therapy (OT). OT techniques that are directly applicable to medical settings involve sensory integration and tasks that can be used as distraction techniques. Children with ASD-DD have variable responses to touch, with some finding it soothing and others becoming distressed by touch. Some find "deep pressure" (ie, the feeling of weight on their bodies) relaxing, but others respond to light touch. Devices such as weighted blankets or shawls for deep pressure and gentle massaging devices for light touch frequently are used. These products

can be purchased through OT supply vendors, but simple substitutes can be found easily in medical settings. For example, a radiology lead vest or apron is an easy facsimile of a weighted blanket. Gently stroking the child with gauze or cast underpadding provides an excellent light touch massage.

Distraction may be a useful adjunct in children with ASD-DD. Occupying a child's hands or body with "fidget toys" is a typical strategy. OT devices (eg, grip strengthening and manual dexterity devices, devices to improve balance) also may serve this function. With appropriate supervision, simple substitutes for these devices are also easily made (eg, a loosely wound roll of gauze or cast underpadding can be a substitute for a squeeze toy). Rocking in a rocking chair or nylon folding sports stadium seat also can calm children (Fig 3).

#### *Psychopharmacology and ASD-DD*

There are no rigorous evidence-based guidelines regarding psychotropic medications for children with ASD-DD. Although there is strong evidence for the use of psychotropic medications in ASD-DD,<sup>116,117,125</sup> there are no controlled trials of these medications for acute agitation or sedation. Currently, there are no known contraindications to using common sedating medications for children with ASD-DD, although some experts believe that atypical medication responses may be more common (eg, idiosyncratic, disinhibition, or paradoxical reactions). Inquiring about the previous reaction to medications often is helpful, as may be beginning with lower medication dosages to observe and determine the child's response to the medication.<sup>134</sup>

#### **MENTAL HEALTH SCREENING**

*For a discussion of mental health screening strategies in primary care settings, please refer to the American*

*Academy of Pediatrics clinical report on screening for behavioral and emotional problems.*<sup>135</sup>

#### **The Advantages of the ED Setting**

The ED may be an ideal setting for screening and identifying high-risk, difficult-to-reach pediatric populations with mental health problems. Many teenagers either do not have a primary care provider or face significant barriers to accessing such health care. For these adolescents, the ED often is their main or only source of medical care.<sup>136,137</sup> Other high-risk groups for mental health and substance use problems are homeless adolescents and school dropouts,<sup>138-143</sup> both of whom disproportionately seek medical care in the ED.

Finally, male adolescents may preferentially seek care in EDs because they are less likely to participate in primary or mental health care.<sup>144,145</sup>

#### **Feasibility and Acceptability of ED Mental Health Screening**

Several rapid, efficient, and accurate ED mental health screening tools have been developed and show promising results. As few as 2 screening questions have been found to be helpful in detecting depression in both adult and pediatric ED settings as well as problematic adolescent alcohol use.<sup>146-148</sup>

A 4-question adolescent suicide screen has been shown to have good sensitivity, specificity, and predictive value across a range of teenagers seeking care in the ED and can be accurately administered by non-mental health professionals.<sup>149-151</sup> Similarly, an 8-question screen was shown to have excellent predictive characteristics for detecting posttraumatic stress symptoms in children who sustained traffic-related injuries.<sup>152</sup>

Given the clinical and time pressures of the ED setting, it is important that mental health screening be



**FIGURE 3**

Example of rocking in a sports chair. Photo credit: Thomas H. Chun, MD, MPH, FAAP.

acceptable to adolescents, their parents, and ED clinicians. Numerous studies have shown the acceptability of such screening. Teenagers and parents both report favorable attitudes toward mental health screening during an ED visit.<sup>153,154</sup> In this study, suicide and drug and alcohol screening rated as more important than other mental health problems. Female adolescents and their parents, more than male adolescents, expressed positive views on screening. In another study, both teenagers and their caregivers perceived ED depression screening as a sign of caring and concern for the adolescent.<sup>155</sup> Suicide screening has been found to be acceptable to 60% to 66% of patients and parents, with 96% of participants agreeing that suicide screening is appropriate in the ED.<sup>149,150,156</sup>

What do ED clinicians think about mental health screening in the ED? Is such screening acceptable to them? Perceived and real barriers to such screening exist, including lack of training, time constraints, and increasing ED patients' length of stay. Williams et al<sup>154</sup> investigated this question and found that 99% of physicians and 97% of nurses stated that a brief, validated screening tool did not interfere with patient care. In addition, research staff endorsed "no difficulty" in administering the screen to 73% of participants. Lastly, a significant and important finding of the study by Horowitz et al<sup>149</sup> was

that real-time evaluation of positive suicide screens did not increase ED patients' length of stay.

### ED Mental Health Screens

Many mental health screening tools have been developed or tested in the ED setting. Although not validated in general ED populations, they have the potential to increase ED mental health screening. One example is an abbreviated version of the Home, Education/School, Activities, Drugs, Depression, Sexuality, Suicide, Safety (HEADDSSS) mnemonic for adolescent psychosocial assessment, which was adapted for and tested in an ED.<sup>157</sup> The Home, Education, Activities and Peers, Drugs and Alcohol, Suicidality, Emotions and Behaviors, Discharge Resources (HEADS-ED) was found to be reliable and accurate, with good concurrent and predictive validity for future psychiatric evaluation and hospitalization.<sup>158</sup>

Horowitz et al<sup>149,151,159</sup> have performed several studies on ED suicide screening, most recently by using multiple logistic regression modeling to determine which suicide screening questions best screen for and identify occult suicidal youth.<sup>150</sup> A 4-question model was found to optimize sensitivity (97%; 95% CI, 91%–99%), specificity (88%; 95% CI, 84%–91%), and negative predictive value (99%, 95% CI, 98%–99%) for ED patients presenting with both psychiatric and nonpsychiatric conditions. The 4 domains of suicidal ideation are current suicidal ideation, past suicide attempts, current wish to die, and current thoughts of being better off dead. Given the prevalence of suicidal ideation and attempts and the morbidity and mortality associated with attempts, screening patients with unclear or high risk of suicide (eg, those presenting with ingestions, acute intoxication, single-car motor vehicle crashes, and significant falls) also may be important.

Both depression and alcohol abuse may be screened for with 2 questions. Rutman et al<sup>147</sup> found that the 2 questions “During the past month, have you often been bothered by feeling down, depressed, or hopeless?” and “During the past month, have you often been bothered by little interest or pleasure in doing things?” were 78% sensitive (95% CI, 73%–84%) and 82% specific (95% CI, 77%–87%) for adolescent depression. These 2 questions have similar screening properties in adult ED patients as well.<sup>146</sup> Both Newton et al and the National Institute of Alcohol Abuse and Alcoholism (NIAAA) have developed 2-question screens for problematic teenage alcohol use.<sup>148,160</sup> Newton et al also believe that a single question may efficiently screen for marijuana use. They used the following questions: “In the past year, have you sometimes been under the influence of alcohol in situations where you could have caused an accident or gotten hurt?”, “Have there often been times when you have a lot more to drink than you intended to have?”, and “In the past year, how often have you used cannabis: 0 to 1 time, or greater than 2 times?” Teenagers who answer “yes” to 1 alcohol question or to the marijuana question have an eightfold and sevenfold increased risk of having a substance use disorder, respectively. The 2 NIAAA questions vary according to the patient's age and explore the patient's and their friends' experience with alcohol. The NIAAA currently is investigating the reliability as well as the concurrent, convergent, discriminant, and predictive validity of this screen.<sup>161</sup>

Computerized screening may add advantages and efficiency to ED mental health screening. They can be administered with little ED clinician time or effort and have been used successfully in both pediatric and general ED settings for general health and mental health screening, alcohol use,<sup>162–164</sup> interpersonal and intimate

partner violence,<sup>165,166</sup> weapons,<sup>167</sup> injury prevention,<sup>168</sup> and HIV risk behaviors.<sup>169</sup> Adolescents not only rated these screens as highly acceptable but also may prefer such health interventions.<sup>170–172</sup> Fein and Pailler<sup>140,173</sup> have developed and implemented an electronic tool for universal screening of ED adolescent physical and mental health risks. The screen was presented to patients by a nurse or medical technician. After the screen was scored, the adolescent's results were printed out and reviewed by the treating physicians. This method resulted in a 68% increase in identification of psychiatric illnesses and subsequently a 47% increase in mental health assessments.

### LEAD AUTHORS

Thomas H. Chun, MD, MPH, FAAP  
Sharon E. Mace, MD, FAAP, FACEP  
Emily R. Katz, MD, FAAP

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Brian R. Moore, MD, FAAP – *National Association of EMS Physicians*  
Katherine E. Remick, MD, FAAP – *National Association of Emergency Medical Technicians*  
Sally K. Snow, RN, BSN, CPEN, FAEN – *Emergency Nurses Association*  
David W. Tuggle, MD, FAAP – *American College of Surgeons*



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Stephanie Wauson

#### ABBREVIATIONS

ASD: autism spectrum disorder  
CI: confidence interval  
CNS: central nervous system  
DD: developmental disorder  
ED: emergency department  
FDA: US Food and Drug Administration  
IV: intravenous  
NIAAA: National Institute of Alcohol Abuse and Alcoholism  
NMS: neuroleptic malignant syndrome  
OT: occupational therapy  
PNES: psychogenic nonepileptic seizures  
SSRI: selective serotonin reuptake inhibitor  
VCS: visual communication system

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