Current Psychiatry

Psychosis: 6 steps rule out medical causes in kids

Time-saving algorithm combines efficiency with a thorough evaluation

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John, age 16, is admitted to our inpatient psychiatric unit, complaining of "a 2-week constant headache" caused by "voices arguing in my head." He has lived in Mexico with an uncle for 6 months but returned home last week for medical evaluation of his headaches.

His parents report that John developed normally until 3 years ago, when he gradually lost interest in his favorite activities and became socially withdrawn. He has not attended school in 2 years. He has no history of illicit drug use and is not taking prescription or over-the-counter medications.

Complete physical examination, neurologic exam, and routine screening lab test results are normal. Thinking that a high lead content of cookware used in Mexico might be causing John's symptoms, we order a lead level: result -0.2 mg/dL (<10 mg/dL

is normal for adolescents). We do no additional diagnostic tests—such as an EEG, CT, or MRI—because John's clinical presentation does not suggest a specific medical condition that could be causing or exacerbating his psychotic symptoms.

We diagnose schizophreniform disorder, but John's parents refuse to accept this diagnosis. They repeatedly ask if we can do more to identify a medical cause of their son's psychiatric symptoms.

As in John's case, young patients or their parents may resist the diagnosis of a chronic mental illness such as schizophrenia. Understandably, they may be invested in trying to identify "medically treatable" causes. You can address their anxieties by showing them that you have systematically evaluated medical causes of psychosis.

> Don't stop if you find one possible cause, as psychotic symptoms are often multifactorial

We offer such a tool: an algorithm (*page 37*) and tables to help you identify common and rare medical conditions that may cause or exacerbate psychotic symptoms in patients ages 3 to 18.

AN EVIDENCE-BASED ALGORITHM

Multiple factors—developmental, psychological, family, environmental, or medical—typically cause psychotic symptoms in a child or adolescent. Evaluating all possibilities is essential, but guidelines tend to minimize medical causes. American Academy of Child and Adolescent Psychiatry guidelines, for example, recommend that "all medical disorders (including general medical conditions and substance-induced disorders) are ruled out,"[1] but they do not specify which medical conditions to consider.

To supplement existing guidelines, we searched the literature and developed an evidence-based algorithm to help you systematically consider medical causes of pediatric psychotic symptoms. We excluded children age <3 because determining conclusively that a 2-year-old is experiencing "psychotic symptoms" is very difficult.[2]

How to use it. The algorithm walks you through a medical systems review. You begin with a complete history, then address six causes of psychotic symptoms: substance abuse, medication reactions, general medical conditions, unexplained somatic symptoms (such as from toxic environmental exposures), developmental and learning disabilities, and atypical presentations.

Don't stop if you find one possible cause of psychotic symptoms; continue to the end of the algorithm. The more factors you identify, the greater your chance of finding a treatable cause that may ameliorate your patient's symptoms.

To make the algorithm clinically useful, we listed conditions in order of decreasing probability of causing psychotic symptoms. For example, the first cause listed is substance-induced disorders,[3] which are most common among adolescent patients. We also "triaged" medical conditions from common to rare (based on estimated prevalence of association with psychotic symptoms), listing rare causes only in cases of atypical presentation or treatment resistance.

Supporting tables. The following discussion sum-

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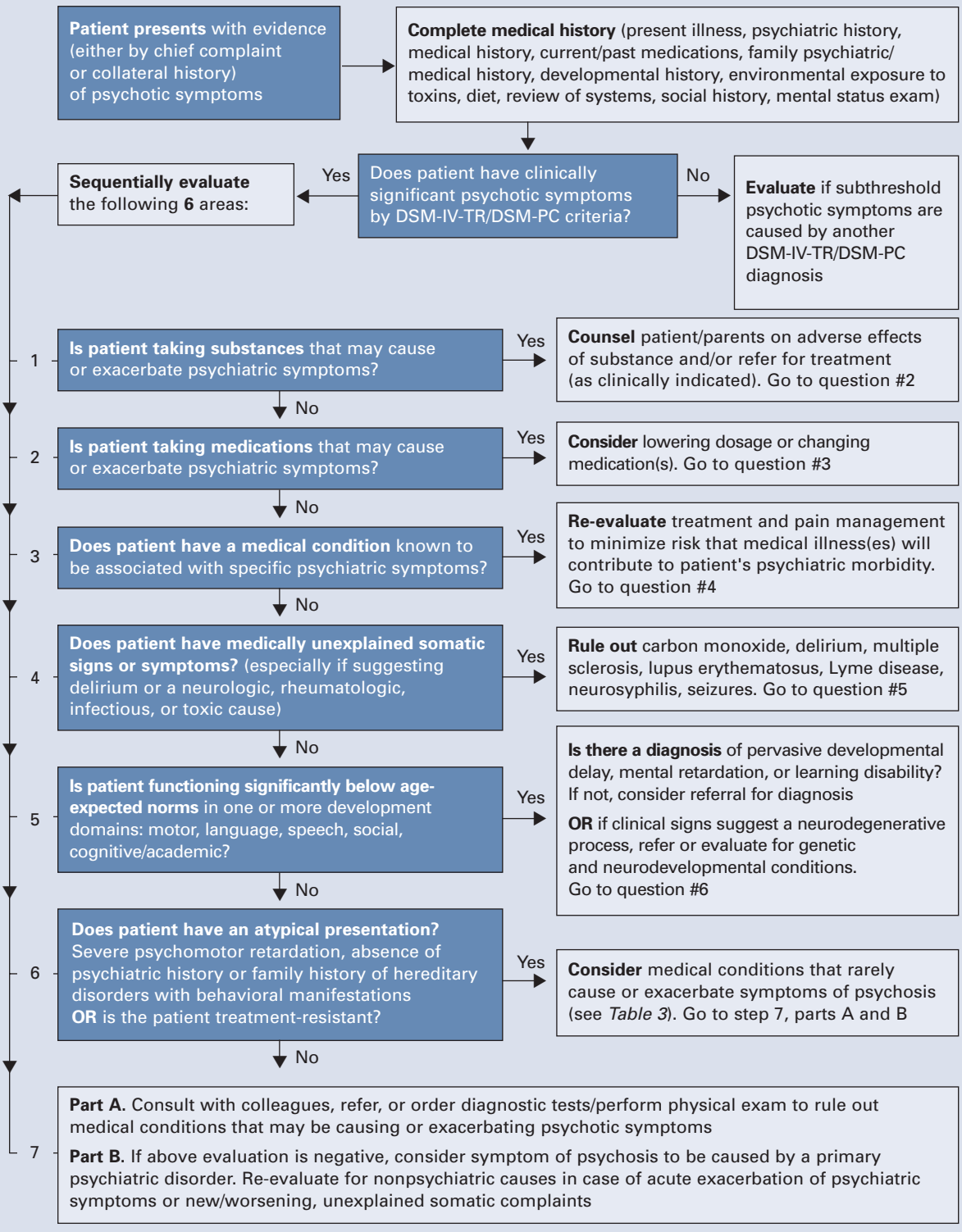
Algorithm

How to identify medical causes* of psychosis in patients ages 3 to 18



* Conditions that may cause or exacerbate clinical symptoms of psychosis.

Table 1

Drugs that may cause psychotic symptoms

Drug class	Psychotic symptoms: Bizarre behavior/ delusions	Psychotic symptoms: Auditory or visual hallucinations
Amphetamine-like drugs	X	X
Anabolic steroids	X	
Angiotensin-converting enzyme (ACE) inhibitors		X
Anticholinergics and atropine	X	X
Antidepressants, tricyclic		X
Antiepileptics	X	
Barbiturates	X	X
Benzodiazepines	X	X
Beta-adrenergic blockers	X	X
Calcium channel blockers	X	
Cephalosporins	X	X
Corticosteroids	X	
Dopamine receptor agonists	X	X
Fluoroquinolone antibiotics	X	X
Histamine H_1 receptor blockers		X
Histamine H_2 receptor blockers	X	
HMG-CoA reductase inhibitors	X	
Nonsteroidal anti-inflammatory drugs	X	
Opioids	X	X
Procaine derivatives (procainamide, procaine penicillin G)	X	X
Salicylates	X	X
Selective serotonin reuptake inhibitors		X
Sulfonamides		X

Source: Adapted from reference 10.

marizes data that support the algorithm and its tables:

- medications reported to cause psychosis (*Table 1*)
- medical conditions most likely to cause psychosis (*Table 2, page 41*)
- medical conditions that rarely cause psychosis (*Table 3, page 43*).

SUBSTANCE ABUSE

Substance abuse is common among adolescents and adults with psychotic illnesses.[4] Drug-induced states can cause delusions, hallucinations, paranoia, and disorganized behavior,[5] which are reported most commonly during intoxication and withdrawal.[6] Diagnosis is often straightforward because of the temporal association between the substance abuse and onset of psychotic symptoms.

Little evidence supports a causal relationship between drug use and the development of chronic psychotic symptoms, however. Case reports link use of 3,4-methylenedioxymethamphetamine ("Ecstasy"), lysergic acid diethylamide (LSD), and marijuana to chronic schizophrenia-like symptoms.[7] The strongest evidence links long-term methamphetamine and cocaine use to chronic psychotic symptoms.[8,9]

MEDICATIONS

Side effects of at least 25 drug classes have been reported to mimic psychosis (*Table 1*),[10] but little is known about the incidence and prevalence of this problem. Case reports and chart

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Table 2

Common medical conditions that may cause pediatric psychosis symptoms*

Category	Conditions not to forget	Common symptoms/comments
Rheumatologic	Lupus erythematosus	Joint pain, fever, facial butterfly rash, prolonged fatigue
Infectious	Viral encephalitis	Fever, headache, mental status change; may occur in perinatal period
Neurologic	Multiple sclerosis	Varied neurologic deficits, especially ophthalmologic changes and weakness
	Neurosyphilis	Personality change, ataxia, stroke, ophthalmic symptoms
	Seizure (temporal lobe epilepsy, interictal psychosis)	Paroxysmal periods of sudden change in mood, behavior, or motor activity with or without loss of consciousness
Toxicologic	Carbon monoxide poisoning	Shortness of breath, mild nausea, headache, dizziness

* Clinically significant symptoms that meet DSM-IV-TR criteria for a primary psychiatric disorder.
Source: Citations supporting statements in this table are posted with this article at www.currentpsychiatry.com

reviews provide the only data that associate most medications with psychotic symptoms. These disagree on what defines a "psychotic symptom," and most fail to rule out delirium as a possible cause.

The relationship between glucocorticosteroids and psychotic symptoms has been studied extensively. A clear link has been found between corticosteroids at dosages >40 mg/d and a markedly elevated risk for transient psychotic symptoms.[11]

MEDICAL CONDITIONS

We identified 27 medical conditions that may cause or worsen clinical symptoms of psychosis (*Tables 2 and 3*) by searching PubMed, psychiatric journals, and neuropsychiatry and consult-liaison textbooks. We included only conditions:

- shown to cause significant morbidity in pediatric populations
- shown to have a statistically significant association with psychotic symptoms, or patients' symptoms consistently resolved when the condition was treated.

Neurologic conditions. Many neurologic conditions had been reported to cause psychotic symptoms,[12] but only four met at least one of our inclusion criteria. Psychotic symptoms are statistically associated with epilepsy,[13] Huntington's disease,[14] and Wilson's disease;[15] psychotic symptoms associated with multiple sclerosis resolve when the underlying medical condition is treated.[16]

Endocrine disorders. Behavioral disturbances (including psychosis) may be the earliest manifestation of an endocrine disorder.[17] Cushing's syndrome,[18] hyperthyroidism,[19] and hypothyroidism[20] —met our inclusion criteria.

Cushing's syndrome—caused by long-term

systemic glucocorticoids and thyroid disorders—is not uncommon in children and adolescents but rarely presents with psychotic behaviors. For each endocrine disorder we included, however, at least one case report described delayed diagnosis because of prominent psychosis. Treating the endocrinopathies resolved the psychotic symptoms.

Genetic disorders. Genetically determined neurodevelopmental disorders usually present in very young children, but some may appear later. Genetic conditions that co-occur with psychotic symptoms at rates significantly greater than the population prevalence include Prader-Willi syndrome,[21] metachromatic leukodystrophy,[22] Turner's syndrome,[21] velocardiofacial syndrome,[23] and Wilson's disease.[15]

Carbon monoxide, lead, or mercury poisoning can present with psychotic symptoms

Acute intermittent porphyria, GM_2 gangliosidosis (Tay-Sachs disease), and homocystinuria are rare conditions with unknown prevalence in patients with psychotic disorders. Still, they are important to consider when evaluating youths with psychosis because case reports link their treatment with psychotic symptom resolution.[24-26]

Infectious disease. An infectious CNS disease does not usually present with psychotic symptoms only. When this does happen, making the correct diagnosis as soon as possible is critical because early treatment is associated with better outcomes.[27] Misdiagnosis as a primary psychotic disorder may expose a patient to psychotropics that may adversely affect clinical outcome.

Viruses that affect the CNS (viral encephalopathies) are the infections most likely to cause psychotic symptoms. By decreasing frequency, they are human simian virus, HIV, influenza, measles, Epstein-Barr virus, mumps, and rabies.[27,28] Bacterial infections that cause psychosis include mycoplasma pneumonia,[29] syphilis,[30] typhoid fever,[31] and Lyme disease.[32]

Brain tumor. Childhood brain tumors often present with behavioral symptoms associated with headache, vomiting, visual changes, and motor and cognitive symptoms. A CNS tumor rarely presents with isolated neuropsychiatric symptoms.[33] A few case reports describe intracranial tumors initially misdiagnosed as primary psychotic illness because of prominent psychotic symptoms.[34,35] In each case, these symptoms resolved with tumor resection.

A temporal relationship does not necessarily equate to a "causal" relationship, however. Tatter et al[36] describe a case of "reoccurrence" of manic symptoms initially thought to be caused by an arteriovenous malformation (AVM) 10 years after the AVM was successfully removed. The important point is that, although rarely, pediatric brain tumor can present with prominent psychotic symptoms.

Environmental toxin exposure may cause well-defined psychiatric syndromes,[37] although frank psychosis is uncommon at presentation. Most often, environmental toxins produce an encephalopathic process of which psychosis may be one symptom. A few toxic exposures—such as lead,[38] carbon monoxide,[39] and elemental mercury[40]—have presented with prominent psychotic symptoms without other encephalopathic symptoms.

Collagen vascular disease is associated with significantly elevated rates of psychiatric illness, especially depression, but only systemic lupus erythematosus (SLE) is known to be associated with prominent psychosis. Case series report delayed SLE diagnosis in patients with this presentation.[41]

High-dose pulse corticosteroids have been reported to effectively treat SLE-related psychotic symptoms,[42] although high-dose corticosteroids can also cause psychotic symptoms. The timing and character of the symptoms can help you

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Table 3

Medical conditions that rarely cause pediatric psychosis symptoms*

Category/condition	Symptoms/comments
Endocrine	
Hyperthyroidism	Tachycardia, weight loss, excessive sweating, tiredness, inability to sleep, diarrhea, shakiness, muscle weakness
Thymoma/myasthenia gravis	Shortness of breath, swelling of face, muscle weakness (especially around eyes)
Hematologic	
Porphyria (acute intermittent porphyria, porphyria variegate)	Intermittent abdominal pain (severe) accompanied by dark urine
Genetic	
Fabry's disease	Burning sensations in hands and feet that worsen with exercise and hot weather
Niemann-Pick disease, type C	Vertical gaze palsy, hepatosplenomegaly, jaundice, ataxia
Prader-Willi syndrome	Obesity, hyperphagia, mild to moderate mental retardation, hypogonadism, tantrums, obsessive-compulsive disorder
Infectious	
Epstein-Barr virus	Fever, sore throat, adenopathy, fatigue, poor concentration
Lyme disease	Target lesion, fever; high-risk geographic area
Malaria/typhoid fever	Fever, mental status change; endemic area
Mycoplasma pneumonia	Fever, mental status change; may occur in absence of pneumonia
Rabies	History of exposure
Metabolic	
Citrullinemia	Mental status change, high plasma citrulline and ammonia
Tay-Sachs disease	Unsteadiness of gait and progressive neurologic deterioration
Homocystinuria	Dislocated lenses, blood clots, tall stature, some mental retardation
Juvenile metachromatic leukodystrophy	Cognitive decline, ataxia, pyramidal signs, peripheral neuropathy, dystonia; 60% of cases present before age 3
Neurologic	
Central pontine myelinolysis	Suspect in patient with pathogenic polydipsia
Huntington's disease	Chorea, myoclonic seizures, poor coordination, emotional lability
Moyamoya disease	Paresis, syncopal episodes
Narcolepsy	Excessive daytime sleepiness, cataplexy
Subacute sclerosing panencephalitis	Visual hallucinations, loss of developmental milestones
Traumatic brain injury	Occurring 4 to 5 years after a loss of consciousness >30 minutes
Wilson's disease	Tremors, muscle spasticity, possible liver inflammation
Nutritional	
Pellagra (vitamin B_6 deficiency)	Redness, swelling of mouth and tongue, diarrhea, rash, abnormal mental functioning; seen with isoniazid treatment for tuberculosis
Oncologic	
Cancers (pancreatic, CNS papilloma, germinoma)	Postural headache, neurologic signs, increased intracranial pressure, early morning nausea, vomiting
Toxicologic	
Lead intoxication	Headache, fatigue, mental status change
Mercury poisoning	Abdominal pain, bleeding gums, metallic taste; history of exposure

* Clinically significant symptoms that meet DSM-IV-TR criteria for a primary psychiatric disorder.

Source: Citations supporting statements in this table are posted with this article at www.currentpsychiatry.com

Related resources

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determine whether using corticosteroids is helping or making the patient worse.

USING THE ALGORITHM

John's mother and father fear that the inpatient team's diagnosis of a primary psychotic disorder means that a medical cause has been permanently "ruled out." To reassure them, we use the algorithm to explain in concrete terms the thought process that led us to John's psychiatric diagnosis. We walk them through the algorithm and its tables, explaining how we used evidence to rationally rule out all known medical causes of psychotic symptoms in pediatric patients.

John's parents are relieved to know that the case is not closed, even though we found no medical cause for their son's condition. If more clinical data become available, we remain open to considering the possibility that medical conditions could be causing or worsening their son's symptoms.

Bottom Line

Children and adolescents with psychotic symptoms present a clinical challenge because of the broad differential diagnosis. The evidence-based algorithm and tables in this article can help you identify substance-induced, pharmacologic, and general medical conditions that may cause or exacerbate psychotic symptoms.

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Continued brief summary of prescribing information from previous page.

Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules

Adverse Events in Clinical Studies with Focalin™ XR – Adults

Adverse Events Associated with Discontinuation of Treatment: In the adult placebo-controlled study, 10.7% of the Focalin XR-treated patients and 7.5% of the placebo-treated patients discontinued for adverse events. Among Focalin XR-treated patients, insomnia (1.8%, n=3), feeling jittery (1.8%, n=3), anorexia (1.2%, n=2), and anxiety (1.2%, n=2) were the reasons for discontinuation reported by more than 1 patient.

Adverse Events Occurring at an Incidence of 5% or More Among Focalin™ XR-Treated Patients: Table 2 enumerates treatment-emergent adverse events for the placebo-controlled, parallel-group study in adults with ADHD at fixed Focalin XR doses of 20, 30, and 40 mg/day. The table includes only those events that occurred in 5% or more of patients in a Focalin XR dose group and for which the incidences in patients treated with Focalin XR appeared to increase with dose. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 2
Treatment-Emergent Adverse Events[1] Occurring During Double-Blind Treatment – Adults

	Focalin™ XR 20 mg N=57	Focalin™ XR 30 mg N=54	Focalin™ XR 40 mg N=54	Placebo N=53
No. of Patients with AEs				
Total	84%	94%	85%	68%
Primary System Organ Class/ Adverse Event Preferred Term				
Gastrointestinal Disorders	28%	32%	44%	19%
Dry Mouth	7%	20%	20%	4%
Dyspepsia	5%	9%	9%	2%
Nervous System Disorders	37%	39%	50%	28%
Headache	26%	30%	39%	19%
Psychiatric Disorders	40%	43%	46%	30%
Anxiety	5%	11%	11%	2%
Respiratory, Thoracic and Mediastinal Disorders	16%	9%	15%	8%
Pharyngolaryngeal Pain	4%	4%	7%	2%

[1]Events, regardless of causality, for which the incidence was at least 5% in a Focalin XR group and which appeared to increase with randomized dose. Incidence has been rounded to the nearest whole number.

Two other adverse reactions occurring in clinical trials with Focalin XR at a frequency greater than placebo, but which were not dose related were: Feeling jittery (12% and 2%, respectively) and Dizziness (6% and 2%, respectively).

Table 3 summarizes changes in vital signs and weight that were recorded in the adult study (N=218) of Focalin XR in the treatment of ADHD.

Table 3
Changes (Mean ± SD) in Vital Signs and Weight by Randomized Dose During Double-Blind Treatment – Adults

	Focalin™ XR 20 mg N=57	Focalin™ XR 30 mg N=54	Focalin™ XR 40 mg N=54	Placebo N=53
Pulse (bpm)	3.1 ± 11.1	4.3 ± 11.7	6.0 ± 10.1	-1.4 ± 9.3
Diastolic BP (mmHg)	-0.2 ± 8.2	1.2 ± 8.9	2.1 ± 8.0	0.3 ± 7.8
Weight (kg)	-1.4 ± 2.0	-1.2 ± 1.9	-1.7 ± 2.3	-0.1 ± 3.9

Adverse Events with Other Methylphenidate HCl Dosage Forms

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed below may also occur.

Other reactions include: ***Cardiac:*** angina, arrhythmia, palpitations, pulse increased or decreased, tachycardia; ***Gastrointestinal:*** abdominal pain, nausea; ***Immune:*** hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura; ***Metabolism/Nutrition:*** anorexia, weight loss during prolonged therapy; ***Nervous System:*** dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis; ***Vascular:*** blood pressure increased or decreased, cerebral arteritis and/or occlusion

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate: ***Blood/Lymphatic:*** leukopenia and/or anemia; ***Hepatobiliary:*** abnormal liver function, ranging from transaminase elevation to hepatic coma; ***Psychiatric:*** transient depressed mood, aggressive behavior; ***Skin/Subcutaneous:*** scalp hair loss

Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules, like other methylphenidate products, is classified as a Schedule II controlled substance by Federal regulation.

Abuse, Dependence, and Tolerance

See WARNINGS for boxed warning containing drug abuse and dependence information.

OVERDOSAGE

Signs and Symptoms

Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Poison Control Center

The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

Recommended Treatment

As with the management of all overdosage, the possibility of multiple drug ingestion should be considered.

When treating overdose, practitioners should bear in mind that there is a prolonged release of dexmethylphenidate from Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules.

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis for Focalin overdosage has not been established.

Store at 25°C (77°F), excursions permitted 15°-30°C (59°-86°F). [See USP Controlled Room Temperature.]

Dispense in tight container (USP).

Focalin™ XR is a trademark of Novartis AG
SODAS® is a trademark of Elan Corporation, plc.

This product is covered by US patents including 5,837,284, 5,908,850, 6,228,398, 6,355,656, and 6,635,284.

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