Acting strange after trying to 'get numb'

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How would you handle this case?

Answer the challenge questions throughout this article Mr. L, age 17, is agitated and talking to the walls of his house. He took 24 diphenhydramine tablets in a possible suicide attempt after he broke up with his girlfriend. How would you treat him?

CASE Numb and confused

Mr. L, age 17, is admitted to the hospital after ingesting 24 diphenhydramine 25-mg tablets in 3 hours as a possible suicide attempt. His parents witnessed him behaving strangely and brought him to the hospital. They state that their son was visibly agitated and acting inappropriately. He was seen talking to birds, trees, and the walls of the house.

Mr. L says he is upset because he broke up with his girlfriend a week earlier after she asked if they could "take a break." He says that he took the diphenhydramine because he wanted to "get numb" to deal with the emotional stress caused by the break-up.

After the break-up, Mr. L experienced middle-to-late insomnia and was unable to get more than 3 or 4 hours of sleep a night. He reports significant fatigue, depressed mood, anhedonia, impaired concentration, and psychomotor retardation. He denies homicidal ideation or auditory and visual hallucinations.

As an aside, Mr. L reports that, for the past year, he had difficulties with gender identity, sometimes thinking that he might be better off if he had been born a girl and that he felt uncomfortable in a male body.

Which treatment option would you choose for Mr. L's substance abuse?

a) refer him to a 12-step program b) begin supportive measures c) administer activated charcoald) prescribe a benzodiazepine to control agitation

The authors' observations

As youths gain increasing access to medical and pharmaceutical knowledge through the Internet and other sources, it appears that adolescent drug abuse has, in part, shifted toward more easily attainable over-the-counter (OTC) medications. Diphenhydramine, a first-generation antihistamine, can be abused for its effects on the CNS, such as disturbed coordination, irritability, paresthesia, blurred vision, and depression. Effects of diphenhydramine are increased by the presence of alcohol, monoamine oxidase inhibitors, diazepam, hypnotics, sedatives, tranquilizers, and other CNS depressants. In 2011, diphenhydramine abuse was involved in 19,012 emergency room visits, of which 9,301 were for drug-related suicide attempts.1

Diphenhydramine is an inverse agonist of the histamine H1 receptor.² It is a mem-

Disclosures

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ber of the ethanolamine subclass of antihistaminergic agents.³ By reversing the effects of histamine on capillaries, diphenhydramine can reduce the intensity of allergic symptoms. Diphenhydramine also crosses the blood–brain barrier and antagonizes H1 receptors centrally.

Used as a common sleep aid and allergy medication, the drug works primarily as an H1 receptor partial agonist, but also is a strong competitive antagonist at muscarinic acetylcholine receptors.⁴ It is abused for its sedative effects and its capacity to cause delirium and hallucinations.5 Diphenhydramine can have a stimulatory effect in children and young adults, instead of the sedating properties seen in adults.6 Such misuse is concerning because diphenhydramine overdose can lead to delirium, confusion, and hallucinations, tachycardia, seizures, mydriasis, xerostomia, urinary retention, ileus, anhidrosis, and hyperthermia. In severe cases it has been associated with cardiac arrhythmias, rhabdomyolysis, status epilepticus, and death.^{4,6} Neurologic symptoms of diphenhydramine overdose are listed in Table 1.

HISTORY Polysubstance abuse

Mr. L has a 2-year history of major depressive disorder and a history of *Cannabis* abuse with physiological dependence; Robitussin (base active ingredient, guaifenesin) and hydrocodone abuse with physiological dependence; 3,4-methylenedioxymethamphetamine (MDMA) abuse; and diphenhydramine abuse. He also has a history of gender dysphoria, although he reports that these feelings have become less severe over the past year.

Mr. L attends bi-weekly appointments with an outpatient psychiatrist and reportedly adheres to his medication regimen: fluoxetine, 40 mg/d, and risperidone, 1 mg at bedtime. He denies previous suicidal ideation, suicide attempts, homicidal ideation, or homicidal attempts. He reports no history of

Table 1

Neurologic effects of diphenhydramine

Agitation
Confusion
Convulsions (seizures)
Delirium
Depression
Drowsiness
Hallucinations
Increased sleepiness
Nervousness
Seizures
Tremor
Unsteadiness

physical, sexual, or emotional abuse. He gets good grades in school and has no outstanding academic problems.

Mr. L began using *Cannabis* at age 14; his last use was 3 weeks before admission. He is guarded about his use of Robitussin, hydrocodone, and MDMA. However, Mr. L reports that he has researched diphenhydramine on the internet and believes that he can safely take up to 1,200 mg without overdosing. He reports normally taking 450 mg of diphenhydramine daily. Mr. L reports difficulty urinating after using diphenhydramine but no other physical complaints.

Mr. L lives with his father and stepmother and has a history of one psychiatric hospitalization at a different facility 2 months ago, followed by outpatient therapy. He obtained his Graduate Equivalency Diploma (GED) and plans to attend college.

At age 5, Mr. L emigrated from Turkey to the United States with his parents. His mother returned to Turkey when he was age 6 and has had no contact with her son since. Whenever Mr. L visits Turkey with his father, the patient refuses to see her, as per collaterals. He gets along well with his stepmother, who is his maternal aunt. Mr. L has been bullied at school and reportedly has few friends.

Clinical Point

Diphenhydramine is abused for its sedative effects and its capacity to cause delirium and hallucinations



Table 2

Abused over-the-counter medications

Class	Medication	Medical (legal) use	Nonmedical use
Dietary supplements	Supplement with piperazine	Anorexia	Hallucinations
Dissociative	Dextromethorphan	Cough suppressant	Dissociative effect
substances	Coricidin	Decongestant	Euphoria
	Chlorpheniramine	Decongestant	Euphoria
	Dimenhydrinate	Antiemetic	Euphoria, hallucinations
	Diphenhydramine	Sedation	Euphoria "high"
Stomach preparations	Calcium-bromide combinations	Antacid stomach medication	Euphoria, hallucinations
Stimulants	Nicotine gum	Smoking cessation	"High"
	Phenylpropanolamine	Decongestant	"High," physical performance enhancement
	Ephedrine	Anti-asthma	Prolonged erection and sexual performance
	Pseudoephedrine	Decongestant	Prolonged erection and sexual performance
	Methylephedrine	Decongestant	Prolonged erection and sexual performance
	Caffeine	Awareness	Performance enhancement
	Ephedra	Stimulant	"High"
	Cyclizine	Antihistamine	Euphoria
	Epinephrine	Bronchodilator	Euphoria
Laxatives	Oral and rectal laxatives	Anti-constipation	Psychological dependence
Sedatives	Diphenhydramine	Sedation	Sedation
Steroids	Androstenedione (herbal sources)	Hormone replacement	Exercise enhancement
Herbal	Antidepressant	Antidepressant	Adverse psychiatric reactions
	Detox cocktail	Detox from drugs	Serotonin syndrome

Source: Lessenger JE, Feinberg SD. Abuse of prescription and over-the-counter medications. J Am Board Fam Med. 2008;21(1):45-54. Reproduced by permission of the American Board of Family Medicine

On mental status examination, Mr. L has an appropriate appearance and appears to be his stated age. He shows good eye contact and is cooperative. Muscle tone and gait are within normal limits. He has no abnormal movements. Speech, thought processes, and associations are normal. He denies auditory hallucinations, visual hallucinations, suicidal ideation (although he presented with a probable suicide attempt), or homicidal ideation. No delusions are elicited.

Mr. L shows poor judgment about his drug use and situation. He demonstrates limited insight, because he says his only goal is to get out of the hospital. He is alert, awake, and oriented to person, place, and time. He shows no memory or knowledge impairment. He appears euthymic with an inappropriate and constricted affect. On neurologic exam, he had mild tremors in his hands.

The authors' observations

Treatment for diphenhydramine overdose should begin quickly to prevent lifethreatening effects and reduce the risk for mortality. The toxin can be removed from the patient's GI tract with activated charcoal or gastric lavage if the patient presents within 1 hour of ingesting the substance. Administering IV fluids will prevent dehydration. Cardiac functioning is monitored and benzodiazepines could be administered to manage seizures.

Key elements of a toxicologic physical examination include:

Clinical Point

Diphenhydramine can have a stimulatory effect in children and young adults, instead of sedating properties seen in adults

Physical findings of nonmedical use

Acute psychosis
Neuropsychiatric symptoms
Euphoria psychosis
Euphoria psychosis
Extreme euphoria, hallucinations
Tachycardia, euphoria, hallucinations, psychosis
Neuropsychiatric symptoms
Agitation
Agitation, rapid heartbeat
Priapism
Priapism
Priapism
Agitation, rapid heartbeat
Agitation, tachycardia, flushing
Euphoria
Headache, nausea, chest pains
GI disturbances
Somnolence, coma
Acne, glandular failure, hyperaggressive behavior
Psychosis
Psychosis

• eyes: pupillary size, symmetry, and response to light (vertical or horizontal nystagmus)

• oropharynx: moist or dry mucous membranes, presence or absence of the gag reflex, distinctive odors

• abdomen: presence or absence and quality of bowel sounds

Related Resources

• Carr BC. Efficacy, abuse, and toxicity of over-the-counter cough and cold medicines in the pediatric population. Curr Opin Pediatr. 2006;18(2):184-188.

-Thomas A, Nallur DG, Jones N, et al. Diphenhydramine abuse and detoxification: a brief review and case report. J Psychopharmacol. 2009;23(1):101-105.

Drug Brand Names

Diazepam • Valium Hydrocodone • Vicodin Diphenhydramine • Benadryl Risperidone • Risperdal Fluoxetine • Prozac

• skin: warm and dry, warm and sweaty, or cool

• neurologic: level of consciousness and mental status, presence of tremors, seizures, or other movement disorders, presence or absence and quality of deep tendon reflexes.⁷

If a child or adolescent patient cannot communicate how much of a drug he (she) has ingested, questions to ask parents or other informants include:

• Was the medication purchased recently, and if so was the bottle or box full before the patient took the pills?

• If the medication was not new, how many pills were in the bottle before the patient got to it?

 If the medication was prescribed, how many pills were originally prescribed, when was the medication prescribed, and how many pills were already taken prior to the patient getting to the bottle?

• How many pills were left in the bottle?

• How many pills were seen around the area where the patient was found?

• How many pills were found in the patient's mouth?⁷

continued

Bottom Line

Abuse of over-the-counter (OTC) drugs, such as diphenhydramine, among youths is a growing problem. Remember to question adolescents who appear intoxicated or to have overdosed not only about abuse of alcohol and illicit substances but also of common—and easily and legally accessible—OTC drugs.

Clinical Point

Treatment of diphenhydramine overdose should begin quickly to reduce the risk for mortality

Recommendations

It is well known that OTC medication abuse is a growing medical problem (*Table 2, page 52*). Antihistamines, including diphenhydramine, are readily available to minors and adults. Because of the powerful sedating effects of antihistamines, many adolescent health practitioners give them to patients who have insomnia as a sleep aid.⁸ As in our case, antihistamines are used recreationally for their hallucinogenic effects, at dosages of 300 to 700 mg.⁹ Severe symptoms of toxicity, such as delirium and psychosis, seizures, and coma, occur at dosages \geq 1,000 mg.⁹

With growing abuse of these medications, we aim to encourage detailed history taking about abuse of OTC drugs, especially diphenhydramine in adolescent patients.

OUTCOME Improvement, discharge

Mr. L is given a dual diagnosis of diphenhydramine-induced psychotic disorder with hallucinations and diphenhydramine-induced depressive disorder, both with onset during intoxication. He also is given a provisional diagnosis of psychotic disorder not otherwise specified and major depressive disorder. Last, he is given a diagnosis of *Cannabis* dependence with physiological dependence, MDMA abuse, hydrocodone abuse, and Robitussin abuse.

Mr. L is maintained on fluoxetine, 40 mg/d, and risperidone, 1 mg at bedtime and 0.5 mg in the morning. He receives milieu, individual, group, recreational, and medical therapy while in the hospital. Symptoms abate and he is discharged with a plan to follow up with outpatient providers.

References

- U.S. Department of Health and Human Services. Drug Abuse Warning Network, 2011: National estimates of drugrelated emergency department visits. http://www.samhsa. gov/data/2k13/DAWN2k11ED/DAWN2k11ED/htm. Published May 2013. Accessed on September 29, 2014.
- Yamashiro K, Kiryu J, Tsujikawa A, et al. Suppressive effects of histamine H1 receptor antagonist diphenhydramine on the leukocyte infiltration during endotoxin-induced uveitis. Exp Eye Res. 2001;73(1):69-80.
- Skidgel RA, Kaplan AP, Erdos EG. Histamine, bradykinin, and their antagonists. In: Brunton L, Chabner B, Knollman B, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York, NY: McGraw Hill; 2011: 911-935.
- Vearrier D, Curtis JA. Case files of the medical toxicology fellowship at Drexel University. Rhabdomyolysis and compartment syndrome following acute diphenhydramine overdose. J Med Toxicol. 2011;7(3):213-219.
- Ho M, Tsai K, Liu C. Diphenhydramine overdose related delirium: a case report. Journal of Emergency and Critical Care Medicine. 2006;17(2):77-79.
- Krenzelok EP, Anderson GM, Mirick M. Massive diphenhydramine overdose resulting in death. Ann Emerg Med. 1982;11(4):212-213.
- Inaba AS. Toxicologic teasers: Testing your knowledge of clinical toxicology. Hawaii Med J. 1998;57(4):471-473.
- Kaplan SL. Busner J. The use of prn and stat medication in three child psychiatric inpatient settings. Psychopharmacol Bull. 1997;33(1):161-164.
- Radovanovic D, Meier PJ, Guirguis M, et al. Dosedependent toxicity of diphenhydramine overdose. Hum Exp Toxicol. 2000;19(9):489-495.

Clinical Point

Antihistamines are used for their hallucinogenic effects at dosages of 300 to 700 mg; severe symptoms of toxicity emerge at ≥1,000 mg