

THE CARLAT REPORT

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Noah Capurso, MD, MHS

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Learning Objectives

After reading these articles, you should be able to:

1. Evaluate and treat patients who use inhalants.
2. Identify and manage over-the-counter medication misuse.
3. Assess the impact of designer drugs.

Inhalants: An Invisible Danger

Michael Weaver, MD, FASAM, professor and medical director at the Center for Neurobehavioral Research on Addictions at the University of Texas Medical School.

Dr. Weaver has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Inhalants are a diverse group of chemical compounds that are inhaled to obtain a brief high that is a little like an alcohol buzz. Many common household items can be used as inhalants. They include air dusters, epoxies such as model airplane glue, and a variety of hydrocarbons such as butane lighter fluid, gasoline, paint thinner, and other cleaning solvents (Weaver MF. *Hallucinogens and Other Drugs*. In *Addiction Treatment*. Newburyport, MA: Carlat Publishing; 2017). Even medical gases can be used recreationally, including nitrous oxide (“laughing gas”), ether, and amyl nitrite

Highlights From This Issue

Inhalants are easily obtainable chemicals not intended for human consumption that can cause severe end-organ damage when misused.

Designer drugs mimic the mechanisms of known substances, but often have much higher potencies, resulting in greater morbidities.

Dextromethorphan, antihistamines, and decongestants are the most commonly misused over-the-counter medications, each with their own particular adverse effects and risks.

(an anti-anginal vasodilator). See the table on page 3 for categories, names, and effects of some of the more common inhalants.

While many addictive drugs such as opioids or alcohol are used on a daily

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The Continuing Challenge of Designer Drugs

Marilyn A. Huestis, PhD

Senior fellow at the Institute on Emerging Health Professions, Thomas Jefferson University. Former Chief of the Chemistry and Drug Metabolism Section, IRP, National Institute on Drug Abuse (NIA).

Dr. Huestis has disclosed that she has received payment as a consultant for Dynacare Laboratories, which provides lab testing. Dr. Capurso has reviewed this article and found no evidence of bias in this educational activity.



CATR: Please tell us about your background.

Dr. Huestis: I've worn lots of hats over my career as a clinical chemist, toxicologist, and forensic toxicologist. I was at the National Institutes of Health for more than 23 years, where I had the pleasure of leading the Chemistry and Drug Metabolism Section, and for the last five years I've been running my own consulting company.

CATR: Let's start out by having you define the term designer drug.

Dr. Huestis: Designer drugs, also known as novel psychoactive substances, are synthesized to give effects that are qualitatively similar to commonly misused drugs, meaning they bind to the same receptors in the



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Inhalants: An Invisible Danger

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basis, inhalants are more commonly used sporadically and in specific social situations, such as at a party or rave. Inhalants are popular with younger people because they are easy to obtain and produce a brief high. In addition, there are very few legal penalties for possessing inhalants since they typically have other legal uses, in contrast to other illegal drugs. Certain inhalants, especially nitrites, are popular among men who have sex with men (MSM) as enhancements to sexual activity. When used infrequently and in moderation, inhalants rarely cause problems, and because they don't produce prominent physical dependence, you will be unlikely to see people who are exclusively addicted to specific inhalants. However, some people use these drugs frequently, mixing and matching them with a variety of other drugs.

How are inhalants used?

There are several methods of recreational use for these chemicals. "Huffing" or "bagging" involves inhaling fumes from a solvent-soaked rag, often inside a plastic or paper bag. Some inhalants, especially nitrites, are commercially available at head shops (stores specializing in the sale of drug paraphernalia) or gas station convenience stores packaged in plastic containers called "poppers." Some people inhale aerosol propellants for paint, hair spray, whipped cream, and other products directly from the spray can. Regardless of the method of use, all of these compounds have a very short duration of action, which tends to encourage frequent redosing.

Dangers of inhalant use

Because many inhalants are industrial solvents and other compounds not intended for human consumption, they can be quite dangerous. When directly inhaled, inhalant gas will replace lung volume normally occupied by air, potentially leading to hypoxia and end-organ hypoxic injury.

In addition to hypoxic effects, inhalants can have direct toxicity on many organ systems. Those who huff chronically are vulnerable to liver damage, kidney failure, peripheral neuropathy, and early dementia. Arrhythmias and neurotoxicity are particularly problematic and can eventually lead to death.

A particular concern is "sudden sniffing death syndrome," a rare but alarming condition in which a young and otherwise healthy person can die from a single heavy inhalant exposure. Most common with chlorofluorocarbon-based propellants and refrigerants, rapid death results from sensitization of myocardial cells to catecholamines, causing sudden arrhythmias, including fatal ones such as ventricular fibrillation (Shepherd RT, *Hum Toxicol* 1989;8(4):287-291).

Heavy use in an area that is not well ventilated can cause hypoxia as well as significant "secondhand" inhalant exposure. Many inhalants are highly flammable and can easily lead to injury from burns.

How to recognize inhalant use

Due to their typically sporadic use and brief high, inhalant intoxication is rare in the outpatient setting. It may occasionally be seen in the emergency department, especially in the context of other injuries related to huffing. But there are some signs and symptoms to watch for that may indicate your patient is using inhalants.

Some of the most obvious physical signs of inhalant misuse are dermatological. Hyperpigmentation from chronic inflammation, sores, and crusty lesions around the nose and mouth (called "glue sniffer's eczema") may be seen. Rhinorrhea, nose bleeds, pharyngeal erythema, and anosmia can result from direct contact with chemicals. Liver damage can cause an enlarged liver and scleral icterus. Neurological toxicity can result in nystagmus, peripheral neuropathy, and short-term memory loss. On labs, you might see anemia, elevated creatinine, elevated liver transaminases, or the presence of methemoglobin.

Addressing inhalant use

When asking about inhalants, I'll use the typical normalization method: "Many people have tried things like whippits or poppers (nitrous oxide or nitrites). Have you tried them or anything like them?" If the patient says no, I'll give other examples of "stuff you huff," like spray paint or gasoline fumes. Another important question is

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Inhalants: An Invisible Danger

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the frequency of use: Is it regular or just experimental? Opportunistic (sporadic) users will often mature out of the use of these drugs, but up to 20% of those who try inhalants will go on to develop a use disorder (Nguyen J et al, *Int J Drug Policy* 2016;31:15–24).

In more frequent users, I look for untreated depression and maladaptive coping skills. For MSM, it is worthwhile to ask about risk factors for sexually transmitted infections. For some, inhalants can act as a “gateway” drug, so always ask about use of other substances as well.

Treatment for inhalant use is behaviorally focused, primarily CBT, as there is no pharmacotherapy available for inhalant use disorder. Adolescent-focused intensive outpatient addiction treatment programs can be helpful, though they can be difficult to find. General outpatient treatment is generally easier to access. Therapy tends to focus on teaching adaptive ways of dealing with stressors rather than turning to substance use.

CATR VERDICT: Inhalant use is often overlooked and underdiagnosed but can have serious consequences. Looking for telltale signs, especially in adolescents and MSM, can help you intervene early and offer behavioral-based treatment.

Categories and Effects of Inhalants			
Chemical Name	Slang Name(s)	Source/Examples	Adverse Effects
Anesthetics			
Diethyl ether	Ether	Anesthetic, solvent	Dizziness, hallucinations
Nitrous oxide	Laughing gas, nox, whippits	Anesthetic, whipped cream propellant	Anemia, Guillain-Barré syndrome, neuropathy
Nitrites			
Amyl nitrite	Poppers, locker room	Anti-anginal medication	Dyspnea, anoxia
Butyl nitrite	Liquid gold, highball	Room deodorizer	Crusty skin lesions, methemoglobinemia
Cyclohexyl nitrite	Rush	Room deodorizer	
Isobutyl nitrite	Aroma of men	Popper	Syncope
Solvents/Fuels			
Carbon tetrachloride	Tet	Dry-cleaning agent	Liver damage
Chlorofluorocarbon	Freebies (freon)	Aerosol propellant, refrigerant	Sudden sniffing death syndrome
Butane	Fire dragon, gas huffer	Cigarette lighter fluid, spray paint	Sudden sniffing death syndrome
Epoxies	Glue	Model airplane glue	Goodpasture syndrome, heart failure
Gasoline		Vehicle fuel	White matter changes
Hexane		Paint remover, adhesive	Neuropathy
Methylene chloride		Paint remover, rust remover	Emphysema
Methyl-n-butyl ketone (MBK)		Solvent, adhesive	Neuropathy
Propane		Gas grill fuel, spray paint	Anoxia, heart failure
Toluene	TNT	Solvent, paint thinner, shoe polish	Brain atrophy, liver toxicity, renal tubular acidosis



Expert Interview

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brain and body. However, they are usually quantitatively much more potent than the drugs we’re used to seeing.

CATR: How did these come about? It feels like we’ve been talking more about designer drugs in the past few years.

Dr. Huestis: There certainly has been an explosion in their diversity and availability. The first class of designer drugs, the synthetic cannabinoids, appeared nearly 20 years ago. Scientists developed the first synthetic cannabinoids as pharmacological tools to study the endogenous cannabinoid system and published their synthetic methods in journals. Illicit manufacturers simply followed these methods to produce these products for recreational use. Of course, now, many new compounds are produced with molecule changes that can alter their pharmacological effects.

CATR: If designer drugs are simply analogs of existing compounds, why are they such a big problem? How exactly are they worse than the usual drugs we see on the streets?

Dr. Huestis: Designer drugs can be horrendously problematic in many ways. First is the sheer number of them. We used to worry about amphetamines, cannabis, cocaine, opiates, benzodiazepines, and PCP—along with a few others. But since 2004, according to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), we have over 750 new designer drugs, each with their own pharmacologic profile. Second, we lack safety studies. These compounds aren’t even tested on animals, let alone humans; the first people who experience the drugs’ effects are the people who buy them. And third is the absence of quality control. For instance, early versions of synthetic cannabinoids were sprayed onto dried plant material and sold. It was all done by hand, so there were “hot spots”—two people might take the same drug and one might die while the other one ends up OK because the concentration in different places varies wildly. In addition,

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drugs often contain chemical contaminants or are combined with other dangerous compounds. Finally, these drugs find their way into unexpected places. For example, highly potent designer opioids, which kill many people, are not only used to fortify heroin, but can be found in cocaine, benzodiazepines, counterfeit opioid pills, and even cannabis.

CATR: The danger of fentanyl derivatives has been widely reported. What other classes of designer drugs are there?

Dr. Huestis: Yes, there are many fentanyl derivatives, with the most worrying being carfentanil, which is hundreds of times more potent than fentanyl itself. Among the other classes, synthetic cannabinoids are the most common. There is also the class of designer stimulants as well. We are all familiar with the effects of stimulants like amphetamines and methamphetamine. These designer drug analogs are a class called synthetic cathinones, commonly referred to as “bath salts,” which are structurally based off the natural drug khat. They are stimulants, just like amphetamines, and have similar physiologic effects. Designer benzodiazepines are a popular new type of designer drug, as are hallucinogens that mimic LSD, PCP, and others.

CATR: How does the legal system deal with these drugs?

Dr. Huestis: It depends what part of the world you’re in. In many European countries, a drug is prohibited only if it is specifically listed by the government or their Drug Enforcement Administration (DEA) equivalent. In the US, the DEA also maintains a list of prohibited compounds. The difference is that the US has the Federal Analogue Act, which says compounds with a similar molecular structure or pharmacologic effect to a prohibited compound are also prohibited (www.law.cornell.edu/uscode/text/21/813).

CATR: That seems like a good idea.

Dr. Huestis: It is in theory. But there’s hesitancy to define what an analog is because then manufacturers can try to find ways around the law. And this ambiguity can create a legal mess.

CATR: Can you give an example?

Dr. Huestis: For example, the primary psychoactive compound in cannabis is delta-9 THC. Manufacturers have created delta-8 THC, which has similar psychoactive effects, and they claim it’s legal based on the 2018 Farm Bill, which legalizes all hemp products that contain a negligible amount of delta-9 THC (www.tinyurl.com/sth48z). The DEA says no, it’s an analog, so it’s illegal. This hasn’t been court tested, and the result is a patchwork of areas where delta-8 THC is and isn’t legal—which is confusing for users, providers, and law enforcement (Chan-Hosokawa A et al, *J Anal Toxicol* 2021:bkab029). Another issue is that when the DEA sees a drug is associated with high morbidity and mortality, they issue an Intent to Schedule, which means the drug can be restricted, but only after six months. The response is a huge boost in sales of that compound on illicit websites. Internet vendors reduce prices, and the substance can be sold out literally within a day, put out onto the streets, and then replaced with something new. It’s a never-ending cycle.

CATR: Are most designer drugs now primarily bought and sold through the internet?

Dr. Huestis: Initially they were available at head shops, gas stations, places like that. Some are still available that way depending on legality. But the most popular route by far is for drugs to be purchased over the internet and sent through the mail—they arrive in a few days at your doorstep in plain packaging. There are very few seizures by customs because drugs are often sent in very small, sealed vials containing concentrates. The vials can be small and difficult to detect because the drugs they contain are so potent.

CATR: What are some of the side effects that clinicians should be aware of?

Dr. Huestis: Remember, designer drugs have qualitatively similar but quantitatively more potent effects. For instance, people have increased heart rate when they smoke cannabis; however, synthetic cannabinoids can cause heart attacks and strokes. In fact, there was an instance of three 16-year-olds who all had heart attacks after using synthetic cannabinoids together (www.tinyurl.com/28b864ty). Cannabis can cause paranoia and psychosis, but when caused by synthetic cannabinoids, these effects can be prolonged, severe, and associated with violence. In fact, there are multiple instances of murder and attempted murder where synthetic cannabinoid use is implicated. Synthetic cathinones are similar; they can affect your cardiovascular and central nervous systems much more severely than amphetamines or methamphetamines. Designer benzodiazepines can cause somnolence and sedation resulting in death, even at small doses. And, of course, we’ve already talked about the dangers of designer opioids.

CATR: What can providers do to treat intoxicated patients who present with these extreme effects?

Dr. Huestis: The fact that we don’t have antidotes to many of these drugs is a big problem. For designer opioids, of course, we have naloxone. For designer benzodiazepines, we have flumazenil. But that’s about it. For the most part, all physicians can do is supportive therapy—keep the airway clear, regulate heart rate, and aggressively control

“Designer drugs are synthesized to give effects that are qualitatively similar to commonly misused drugs, meaning they bind to the same receptors in the brain. However, they are usually quantitatively much more potent than the drugs we’re used to seeing.”

Marilyn A. Huestis, PhD

Expert Interview

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body temperature. Many of the synthetic cathinones can cause dangerous hyperthermia (Zaami S et al, *Eur Rev Med Pharmacol Sci* 2018;22(1):268–274). Antipsychotics and benzodiazepines can be used to control behavioral agitation. As an aside, I've been a proponent of making available the CB1 cannabinoid receptor antagonist rimonabant (Huestis MA et al, *Psychopharmacology (Berl)* 2007;194(4):505–515). It was used for weight loss overseas but was pulled from the market because of associations with depression and suicidal ideation. But wouldn't it be wonderful if it was available for one-time use in emergency rooms for synthetic cannabinoid overdoses? It could be lifesaving.

CATR: A treater must know what was ingested to provide a proper antidote if one is available. You've done a lot of work in identification of designer drugs through urinalysis.

Dr. Huestis: I have. Because many of these compounds are so potent, and we know so little about them, we often don't even know how to identify the agents a patient has used. Typical urine drug tests are done with immunoassays that are widely available for commonly misused substances. More accurate confirmation testing is done with mass spectrometry, which takes some time but is also generally available. However, we don't have immunoassays for most designer drugs, and mass spectrometry may not be useful because we don't know what metabolites to look for in the first place.

CATR: Does that mean it's not worth testing for designer drugs at all?

Dr. Huestis: I always encourage providers to send urine out for testing. Most small laboratories can't handle testing for all the known 700+ designer drugs; it's too expensive. But large hospital systems and reference labs with high-resolution mass spectrometry can screen for many compounds. The data might help not only your patient, but also public health. There are instances of highly potent drug batches causing mass overdose events with dozens or hundreds of people affected in a short time. Over 600 people became critically ill from a single batch of synthetic cannabinoids in Mississippi, for instance. In cases like these, urine toxicology information is very important for public health departments and medical examiners trying to respond to the situation in real time. There can also be third-party payment issues for send-out urine drug testing. Hospitals may be reluctant to identify specific drugs because it may compromise insurance company payment. Providers should figure out how to deal with this issue within their hospital system; think of the lives you may save!

CATR: Are there any other issues providers should be aware of in the management of acute intoxication?

Dr. Huestis: All patients presenting with intoxication by designer drugs should at the very least receive a psychiatry consult. It is important to determine whether the patient has developed a substance use disorder that needs further treatment. We also know there is a very high comorbidity of substance use and mental illness. So, it's not good enough to just support a patient through the intoxication and send them out the door.

CATR: And what about long-term treatment?

Dr. Huestis: We know that individuals can become both physiologically and psychologically dependent on designer drugs, except for hallucinogens, just like their more common counterparts. Unfortunately, we don't have data about how to treat designer drug addiction. The general practice has been to let the drug class guide the treatment (Klega AE and Keehbauch JT, *Am Fam Physician* 2018;98(2):85–92). The most common example is use of methadone or buprenorphine for patients using designer opioids. Designer opioids are now frequent contaminants in the illicit opioid supply. No one would recommend changing opioid use disorder treatment based upon whether a patient used designer opioids. Cognitive behavioral approaches, contingency management, and the limited pharmacologic options that we have for cannabis, stimulants, and benzos are probably similarly useful for the designer drugs with similar mechanisms of action, though we don't know for sure.

CATR: Given that the landscape of designer drugs is evolving so quickly, how can clinicians stay informed?

Dr. Huestis: I recommend starting with review articles accessible through PubMed. We published a thorough review in 2017 that is a good summary of the field, at least where things stood several years ago (Logan BK et al, *J Anal Toxicol* 2017;41(7):573–610). Our 2021 update is set to be published in the next few months. I contributed to a recent review of designer benzodiazepines that I would recommend as well (Brunetti P et al, *Pharmaceuticals (Basel)* 2021;14(6):560).

CATR: Any good internet sites that you'd recommend?

Dr. Huestis: Yes. The EMCDDA has a website with in-depth information that I highly recommend (www.emcdda.europa.eu/emcdda-home-page_en). It focuses on Europe, where the pattern of available drugs can be a bit different, but the information there is very useful. The Center for Forensic Science Research in Education (www.cfsre.org) is another good resource that provides up-to-date information for the US. In addition, the American College of Medical Toxicologists (www.acmt.net) is a good resource and they host informative webinars as well. Geographical differences make it especially difficult to stay current, so I also recommend getting comfortable working with the local poison control center and forensic laboratories, especially for clinicians who work in an emergency setting. These are the people who will be the first to know about the influx of new drugs.

CATR: Thank you for your time, Dr. Huestis.



Misuse of Over-the-Counter Medications

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Dr. Ton and Dr. Anbarasan have disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Misuse of over-the-counter (OTC) medications is more common than you might think, especially among younger patients. In 2020, 3.2%–4.6% of high schoolers intentionally misused an OTC medication at least once in the past year (www.tinyurl.com/u7rxzvvp).

The top three most frequently misused OTC medications are the cold medication dextromethorphan (DXM), antihistamines, and decongestants with stimulant-like properties (see table at right). We'll review what you should know about each of these medications and what to do about patient misuse.

Dextromethorphan

DXM, a cough suppressant primarily found in cold medications, is the most commonly misused OTC drug (Schifano F et al, *Front Psychiatry* 2021;12:657397). Although it is an analog of codeine, DXM has no effect on opioid receptors and is not an analgesic. You've probably heard about it as the active ingredient of Nuedexta, a treatment for pseudobulbar affect. Nuedexta is DXM packaged with quinidine, the latter being present only to inhibit 2D6 metabolism of DXM, thereby raising its level.

DXM's active metabolite is dextrorphan, an N-methyl-D-aspartate (NMDA) antagonist that inhibits the excitatory neurotransmitter glutamate, causing sedative, dissociative, and hallucinogenic states. These effects typically start 30–60 minutes after a dose and can last up to six hours. Slang terms you might hear include “robotripping,” which refers to intentionally taking large doses, and “triple C's,” which stands for Coricidin Cough & Cold, a common medication brand that contains DXM.

DXM's psychoactive effect is dose dependent. A small dose of intentionally misused DXM is usually 100–200 mg (which is already higher than the usual cough suppressant dose of 30 mg every 6–8 hours). At this level, patients will

experience mild stimulation, some restlessness, and euphoria. Large doses, as much as 1500 mg, can cause intense hallucinations, dissociation, paranoia, delusions, out-of-body experiences, and a loss of motor coordination (Dept of Justice/DEA Drug Fact Sheet, 2020; www.tinyurl.com/d4ts3a6e).

DXM misuse is associated with many potentially dangerous effects. While acutely intoxicated, people can experience autonomic instability (fluctuations in blood pressure and heart rate), gastrointestinal distress (diarrhea or constipation), and a host of neurological problems such as amnesia, ataxia, dystonia, hallucinations, and seizures. Chronic DXM misuse can be detrimental to the nervous system, causing psychosis, cognitive impairment, and peripheral neuropathy.

Other side effects are not due to DXM itself, but to other components in its formulation. For example, DXM is often sold as dextromethorphan hydrobromide, which can cause the rare syndrome of bromide toxicity, called bromism. This is characterized by a wide array of psychiatric symptoms, including psychosis, seizures, and delirium, along with a characteristic pustular rash. DXM may be coformulated with agents that have their own toxicities, most notably acetaminophen, chlorpheniramine, and pseudoephedrine. Finally, combining DXM with serotonergic agents risks serotonin syndrome, so be cautious when prescribing antidepressants to patients who are known to misuse DXM.

Because of the potential for misuse, some states have begun to restrict OTC DXM sales as well as enforce a minimum age, typically 18, for DXM purchase. A few states have

imposed a maximum amount that a person can purchase or possess, and still others have begun to require a prescription.

Antihistamines

Antihistamine misuse had a moment in the spotlight in 2020. In a sweeping TikTok trend called the “Benadryl Challenge,” people were encouraged to take supratherapeutic doses of diphenhydramine and film the effects. The trend was widespread enough that the FDA posted a warning about its dangers (www.tinyurl.com/ksas4rap).

OTC antihistamines come in two flavors: first generation, which readily cross the blood-brain barrier, and second

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Commonly Misused Over-the-Counter Medications		
Drug/Common Trade Names	Medical Use	Side Effects
Dextromethorphan		
<ul style="list-style-type: none"> Robitussin Pediacare Vicks 44 Cough Relief Delsym Coricidin (Be aware of coformulations) 	<ul style="list-style-type: none"> Cough suppressant 	<p><i>Acute:</i></p> <ul style="list-style-type: none"> Autonomic instability GI distress Neurologic dysfunction Psychosis <p><i>Chronic:</i></p> <ul style="list-style-type: none"> Cognitive impairment Chronic psychosis Peripheral neuropathy
Antihistamines		
<p>Chlorpheniramine</p> <ul style="list-style-type: none"> Aller-Chlor Chlorphen 	<ul style="list-style-type: none"> Rhinitis Cold relief 	<ul style="list-style-type: none"> Anticholinergic effects Delirium Physiologic dependence
<p>Cyclizine</p> <ul style="list-style-type: none"> Bonine (discontinued) Emoquil 	<ul style="list-style-type: none"> Motion sickness 	
<p>Dimenhydrinate</p> <ul style="list-style-type: none"> Dramamine 	<ul style="list-style-type: none"> Motion sickness 	
<p>Diphenhydramine</p> <ul style="list-style-type: none"> Benadryl 	<ul style="list-style-type: none"> Allergy Insomnia Pruritis 	
<p>Doxylamine</p> <ul style="list-style-type: none"> Unisom 	<ul style="list-style-type: none"> Allergy Cold relief Insomnia 	
Decongestants		
<p>Propylhexedrine</p> <ul style="list-style-type: none"> Benzedrex 	<ul style="list-style-type: none"> Nasal congestion 	<ul style="list-style-type: none"> Hallucinations Physiologic dependence
<p>Pseudoephedrine</p> <ul style="list-style-type: none"> Sudafed Dimetapp Coricidin 	<ul style="list-style-type: none"> Nasal congestion 	<ul style="list-style-type: none"> Racing thoughts Anorexia Insomnia Psychosis

Misuse of Over-the-Counter Medications

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generation, which do not. Given their CNS effects, commonly misused antihistamines are almost always first generation. These include diphenhydramine (Benadryl), doxylamine, dimenhydrinate, cyclizine, and chlorpheniramine. They antagonize central H1 receptors and peripheral acetylcholine receptors to relieve allergies and nausea.

At low doses (eg, 25–50 mg diphenhydramine), antihistamines cause sedation and anxiolysis, but at higher doses (eg, 300 mg up to > 1000 mg), their anticholinergic properties can cause delirium, hallucinations, and even transient psychosis, especially in individuals with mental illness or concomitantly using other substances. Though typically sedating, antihistamines can be activating and stimulant-like when combined with other drugs such as cannabis and stimulants (Schifano et al, 2021).

Clinicians may be surprised to learn that many antihistamines are also anticholinergic. In fact, most side effects of antihistamine misuse (tachycardia, dry mouth, blurred vision, constipation, urinary retention, and delirium) come from this activity. Chronic overuse can lead to

physiologic dependence, with patients experiencing cravings, insomnia, irritability, GI distress, and withdrawal symptoms. The only evidence-based approach to treating patients who are physiologically dependent is with a gradual taper as tolerated.

Decongestants

Pseudoephedrine and propylhexedrine are nasal decongestants that are increasingly being misused for their stimulant-like effects at high doses (Aschenbrenner DS, *Am J Nurs* 2021;121(7):24). These medications are sympathomimetic agents, increasing monoamine release and activity on alpha-, beta1-, and beta2-adrenergic receptors.

Some patients misuse these drugs for their euphoric effects, but others use them to suppress appetite, boost athletic performance, or improve concentration. Pseudoephedrine, of course, is also used in the illicit manufacture of methamphetamine. Pseudoephedrine is usually sold as tablets or as a syrup, so people typically consume it orally. Propylhexedrine is also misused orally but is generally sold as a nasal spray—patients either mix the medication with water and drink the resulting solution

or swallow the medication-soaked cotton ball contained inside the inhaler.

Side effects of these medications are like those of methamphetamine. Acutely, and at lower doses (misuse starts at > 250 mg pseudoephedrine daily), patients experience euphoria, insomnia, anorexia, and accelerated thinking. Higher doses (up to 1500 mg pseudoephedrine daily) can cause florid psychosis with intense auditory and visual hallucinations, persecutory delusions, and disorganized thought patterns (www.tinyurl.com/d4ts3a6e). And like many commonly misused drugs, long-term decongestant misuse can result in physiologic dependence. There have been multiple reports of withdrawal symptoms, including dysphoria, restlessness, persistent abnormal perceptions, and depression (Alevizos B, *Eur Psychiatry* 2003;18(8):423–425).

Unlike antihistamines, OTC sale of pseudoephedrine is federally regulated, and the drug is kept “behind the counter” throughout the US.

Working with patients

Clinicians often don’t ask about OTC drug misuse, and patients typically don’t

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These questions are intended as a study guide. Please complete the test online at www.carlataddictiontreatment.com. Learning objectives are listed on page 1.

- What is the most effective first-line treatment for inhalant use disorder (LO #1)?
 - a. SSRIs
 - b. Psychodynamic therapy
 - c. CBT
 - d. SNRIs
- You want to learn about your adolescent patient’s over-the-counter (OTC) drug use history. What would be the most effective strategy (LO #2)?
 - a. Interview the patient and their family together, and ask about general substance use
 - b. Interview the patient and their family together, and explicitly ask about OTC drug use
 - c. Interview the patient and their family separately, and explicitly ask about OTC drug use
 - d. Interview the patient and their family separately, and ask about general substance use
- According to Dr. Huestis, what is the general treatment for long-term designer drug misuse (LO #3)?
 - a. Avoid using pharmacotherapy
 - b. Let the drug class guide the treatment
 - c. Treatment for designer drug misuse has not been studied
 - d. Opt for intensive inpatient treatment, which tends to outperform outpatient treatment for designer drug misuse
- According to a 2016 study, up to 20% of sporadic inhalant users develop a use disorder (LO #1).
 - a. True
 - b. False
- According to Dr. Huestis, which of the following characterizes the effects of designer drugs compared to their commonly used counterparts (LO #3)?
 - a. Qualitatively similar and less potent
 - b. Qualitatively different and equally potent
 - c. Qualitatively similar and more potent
 - d. Qualitatively different and more potent

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Misuse of Over-the-Counter Medications

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report it. Without any validated screening tools, OTC drug misuse can easily fly under the radar. Be sure to ask patients explicitly about OTC drugs and whether they take the drugs recreationally. For adolescents, practice guidelines suggest interviewing parents and patients separately, especially when it comes to asking about substance use (Gracious B et al, *J Child Adolesc Psychopharmacol* 2010;20(6):521–524).

Many patients believe that OTC medications are safer than prescription drugs, which of course is not always the case. Be sure your patients understand that OTC medication misuse can be just as risky and dangerous as misusing prescription medications or street drugs. Impress upon them that misused OTC drugs can and do cause serious side effects and fatalities.

There is little research on how to treat OTC medication misuse. The best treatment is prevention of use, which entails educating patients about the toxicity risks. The therapies employed in any substance use disorder can be helpful, such as cognitive behavioral therapy, contingency management, and motivational interviewing.

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VERDICT:

The three most commonly misused classes of OTC medication all have potential for serious medical and psychiatric side effects, which many clinicians and patients are unaware of. Ask patients explicitly about their use of these medications and use psychotherapy and behavioral techniques for treatment.

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