


The Clinical Assessment and Treatment of Inhalant Abuse

Sina Radparvar, MD

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 SR, 0000-0001-5309-3923

Abstract

Although inhalant abuse is common, it is one of the most neglected and overlooked forms of substance abuse. Inhalants refer to a wide variety of substances including volatile solvents, aerosols, gases, and nitrites. The mechanism of action of inhalants has not been fully defined. Several molecular targets contribute to the pharmacology, including ion-channel proteins that control neuronal excitability. These agents interact with various receptors and can cause changes in cell-membrane fluidity and nerve-membrane ion channels. Three main pharmacologic categories of inhalants, namely, volatile solvents and anesthetic gases, nitrous oxide, and volatile alkyl nitrites, have distinct pharmacologies, mechanisms of action, and toxicities. Inhalants are linked to multisystem damage affecting the pulmonary, cardiac, dermatologic, renal, hematologic, gastrointestinal, hepatic, and neurologic systems. Chronic inhalant abuse can also cause psychiatric, cognitive, behavioral, and anatomical deficits in humans, leading to reduced productivity and quality of life. Inhalant abuse during pregnancy is associated with fetal abnormalities. Clinical assessment for inhalant abuse should be done systematically. After decontamination and stabilization of the patient, further history and physical examination is necessary to establish an appropriate diagnosis based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Laboratory testing for inhalant abuse is very limited, and imaging studies may be helpful in certain situations. The treatment of inhalant use disorder is similar to that of other substance abuse disorders and includes supportive care, pharmacotherapy, and behavioral therapy. Preventive measures are essential.

Corresponding Author

Sina Radparvar, MD
sina.x.radparvar@kp.org

Author Affiliations

Department of Addiction Medicine,
Southern California Permanente
Medical Group, Sylmar, CA, USA

Author Contributions

Sina Radparvar, MD, was the sole author responsible for all aspects of the article.

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Introduction

Inhalants are dangerous volatile agents. Except for anesthetic gases that are used in surgical settings, these agents were never designed for human consumption. Inhalant abuse involves the deliberate inhalation of substances to reach euphoria and an altered mental

state. Inhalants refer to a wide variety of substances including volatile solvents, gases, aerosols, and nitrites. Inhalant abuse is quite prevalent and is a problem seen around the world, especially in impoverished or marginalized cultural groups.¹ However, it is often not recognized and is an overlooked form of substance abuse. Health care practitioners are often unfamiliar

with the signs and symptoms of inhalant abuse and not well-equipped to assess these patients. In addition, the noninvasive route of administration and available legal status of these substances have fostered a low-risk perception. There has also been limited interest in and funding for investigation and research into this area. Adolescents and young adults who inhale the chemical vapors from substances such as industrial agents or household products for euphoria-inducing purposes do not suspect the severity of such risks as multi-organ damage and sudden death. Such substances are used in this age group because of their low cost, easy accessibility, wide availability, deregulated legal status, and rapid euphoria and as a replacement for other substances that may be difficult to obtain. Adult abusers of inhalants often use volatile alkyl nitrites in order to enhance sexual experiences. Inhalants comprise a diverse group with variable mechanisms of action and often unclear pharmacology, making classification difficult. Most commonly, they are grouped based on their common administration route rather than on distinctive pharmacologic effects, causing confusion and oversimplification for users and practitioners. The author proposes classification based on pharmacologic properties, as this method provides a more relevant and valuable grouping scheme similar to that used for other drugs of abuse. It also provides the treatment and research communities with more relevant information on mechanisms of action and toxicities within each group. In this suggested scheme, commonly abused inhalants are categorized into 3 main groups based on similarities in their pharmacologic properties: 1) volatile solvents and volatile anesthetic gases; 2) inorganic anesthetic gases (nitrous oxide); and 3) volatile alkyl nitrites, with a distinct mechanism of action as vasodilators. Such a classification scheme for the 3 main categories of abused inhalants and common products is listed in Table 1.

The aim of this review is to familiarize health care practitioners with inhalant abuse and to aid in the recognition, assessment, and treatment of patients presenting with this condition. The main grouping categories of inhalants and their pharmacologies, known mechanisms of action, and toxicities are presented. A clinical assessment for patients with inhalant abuse based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* is presented, including history, physical examination, laboratory testing, and imaging studies. Finally, a treatment approach for patients with inhalant

abuse is recommended including supportive care, pharmacotherapy and behavioral therapy.

Please see the Appendix for a complete list of definitions.

Volatile Solvents and Anesthetic Gases

PHARMACOLOGY

Inhalants in this group have high volatility and lipophilicity and are rapidly absorbed through the pulmonary system, bloodstream, and blood-brain barrier with immediate and brief effects. The peak in concentrations occurs within several minutes after inhalation.² These substances are rapidly metabolized in the liver, mainly through the cytochrome P450 system.¹ The pharmacologic effects of volatile solvents include rapid euphoric effects similar to alcohol or sedative intoxication and early stages of anesthesia. Although the volatile solvents are central nervous system (CNS) depressants, they may have initial excitatory effects through the release of epinephrine and activation of dopamine system. This initial excitation is followed by CNS depression mediated by the γ -aminobutyric acid (GABA) pathway.³ Through various molecular targets, chronic use of volatile solvents can cause changes in multiple brain circuits such as the reward-sensitive dopamine neurons of the ventral tegmental area. Volatile solvents can also impair the neurons in the medial prefrontal cortex, a brain region that is needed for behavioral flexibility during risk-/reward-based decision making.⁴ These reward-sensitive dopamine neurons can undergo plasticity as a result of the use of inhalant agents, thus affecting mesocorticolimbic circuitry that plays a substantial role in reward, motivation, cognition, and aversion.⁴ The exact molecular targets of volatile solvents and anesthetic gases have been difficult to locate, and a comprehensive theory as to the exact mechanism of action of these agents is yet to be formulated. Because of their simple molecular structure, the agents were initially thought to be nonpolar, exerting their action through the nonselective disruption of lipid membrane integrity.³ Later research showed that volatile solvents have significant molecular and brain-region selectivity, much like other drugs of abuse.³ However, no universal target has been identified to explain their mechanism of action. The most studied agent in this group is toluene, which belongs to the aromatic hydrocarbon family. Table 2 lists the receptor sites and

Pharmacologic class	Chemical (state)	Common sources
Volatile solvents and gases		
Aliphatic hydrocarbons	Butane, propane, methane (gas)	Lighter fluid, bottled fuel, aerosol propellants (hair spray, spray paint, deodorants, room fresheners, cooking oil sprays)
	<i>n</i> -Hexane (liquid)	Adhesive, gasoline, industrial solvents, rubber cement
	Isooctane (liquid)	Automotive fuel
	Kerosene (liquid)	Lighter fluid
	Naphtha (liquid)	Shoe polish, adhesive
	Turpentine (liquid)	Paint thinner, solvent
Aromatic hydrocarbons	Benzene (liquid)	Gasoline, rubber cement
	Toluene (liquid)	Adhesives, paint thinner, spray paint, rubber cement, nail polish remover
	Xylene (liquid)	Paint thinner, adhesive, degreaser
Esters	Ethyl acetate (liquid) Methyl acetate (liquid)	Adhesive, nail polish remover, paint activator Adhesive, nail polish remover, fragrance ingredient
	Dimethyl ether (liquid) Diethyl ether (liquid)	Fuel, aerosol propellant, refrigerant, "freeze" sprays, fuel
Halogenated hydrocarbons		
Chlorinated hydrocarbons	Carbon tetrachloride (liquid)	Cleaning solutions, aerosol propellants
	Chloroform (liquid) (trichloromethane)	Cleanser for plastic compounds, adhesive, spot remover
	Ethyl chloride (liquid) (chloroethane)	Topical anesthetic
	Methylene chloride (liquid) (dichloromethane)	Paint thinners, varnish removers, degreasing agent
	Tetrachlorethylene (liquid)	Dry cleaning agents, degreaser
	Trichloroethylene (liquid)	Dry cleaning agent, spot remover, degreaser
Fluorinated hydrocarbons	1,1,1-Trichloroethane (liquid)	Typewriter correction fluid
	Chlorofluorocarbons (gas) (freons: difluoroethane, dichlorofluoromethane, tetrafluoroethane, bromochlorodifluoromethane)	Refrigerants, various aerosol propellants (hair spray, spray paint, computer spray or duster, deodorants, room fresheners, fire extinguisher)
Ketones	Acetone (liquid) Methyl butyl ketone (liquid)	Nail polish remover, paint thinner solvent, adhesive, paint thinner
	Volatile anesthetic gases	
Alkane volatile anesthetics	Halothane (gas)	General anesthetic
Halogenated anesthetics ("flurane anesthetics")	Enflurane (gas), isoflurane (gas) sevoflurane (gas)	General anesthetic
Inorganic gaseous anesthetics		
Dinitrogen monoxide	Nitrous oxide (gas)	Canned whipped cream, balloon tanks
Volatile alkyl nitrites		
Nitrites	Amyl nitrite (liquid) Butyl nitrite (liquid) Isopropyl nitrite (liquid)	Angina medications (vasodilators), "poppers," "snappers," room deodorizers

Table 1: Pharmacologic classification of commonly abused inhalants

pharmacologic actions of toluene as a representative of the volatile solvents.

ACUTE TOXICITIES: SUDDEN DEATH

Acute toxicities that can occur upon even 1 session of use of volatile solvents include sudden sniffing death syndrome with multiple possible etiologies.

Catecholamine release appears to be the most common cause for sudden death upon inhalant abuse. It is mainly seen with hydrocarbons (especially halogenated hydrocarbons), such as gasoline, benzene, trichloroethylene, and toluene.¹⁶ In this case, toxicity is related to the release of catecholamine that occurs within minutes of inhalant

Agent	Receptors or sites of action	Mechanism	Physiologic process	Ref
Toluene	Glutamate receptors (NMDA)	Inhibition	Antinociception, learning difficulties, memory, and perception deficits	5
	GABA _A receptors	Enhancement	Anxiolysis, amnesia, sedation, relaxation, and anticonvulsant activity	6
	Glycine receptors	Enhancement	Decrease in startle responses and spinal reflexes	6
	Nicotinic acetylcholine receptors	Inhibition	Antinociception; decrease in memory, arousal, muscle tone, and autonomic functions	7
	Serotonin type 3 receptors	Enhancement	Increase in arousal and emesis	8
	Sodium channels	Inhibition of cardiac-voltage-sensitive channels	Cardiac arrhythmias ^a	9
	Calcium channels	Inhibition of cardiac-voltage-sensitive channels	Cardiac arrhythmias ^a	9
	Potassium channels	Inhibition of GirKs ^b	Increase in neuronal excitability, changes in pain perception, and changes in memory modulation	10
	P2X-family ATP-gated ion channels ^b	Enhancement of P2X ₂ , P2X ₄ , P2X _{2/3} , and P2X _{4/6} ; inhibition of P2X ₃	Neuronal signaling with unknown physiologic relevance	11
Nitrous oxide	Glutamate receptors (NMDA)	Inhibition	Anesthetic effects; decrease in nociception, memory, learning, and perception	12
	Nicotinic acetylcholine receptors	Inhibition	Antinociception; decrease in memory, arousal, muscle tone, and autonomic functions	13
	Release of endogenous opioid peptides and α-adrenergic receptor activation	Activation	Decrease in nociception; increase in analgesia	12
	Irreversible oxidation and inactivation of methylcobalamin (a metabolically active form of vitamin B ₁₂)	Decrease in myelin synthesis due to inhibition of methionine synthase (blocks methionine production from homocysteine)	Megaloblastic anemia, myeloneuropathy, and subacute combined degeneration of spinal cord	12
Volatile alkyl nitrites	Guanylyl cyclase enzyme activation	Formation of cGMP, activation of protein kinase G and phosphorylation of myosin light chains	Smooth muscle relaxation and platelet inhibition	14
	RBC hemoglobin oxidation	Methemoglobinemia (chronic use)	Tissue hypoxemia	15

Table 2: Receptor sites and mechanisms of action for selected abused inhalants

^a Voltage-gated channels in myocardial tissue may contribute to sudden cardiac events, eg, “sudden sniffing death syndrome.”

^b GirKs are found throughout the brain and cardiac cells and are involved in controlling neuronal excitability.

^c P2X ATP ion channels comprise a family of nonselective trimeric ligand-gated channels that bind ATP and induce channel-opening ion flux.

ATP = adenosine triphosphate; cGMP = cyclic guanosine monophosphate; GABA = γ-aminobutyric acid; GirKs = G-protein-gated inwardly rectifying potassium channels; NMDA = N-methyl-D-aspartic acid; RBC = red blood cell.

use and can trigger supraventricular or ventricular tachyarrhythmias caused by sympathetic activation or myocardial sensitization to the surge of catecholamines.¹⁷ Another etiology for sudden death is a sudden cooling injury to airways by inhalants such as chlorofluorocarbons (freons) inhaled directly into the mouth/larynx. This causes an intense, fatal reflex vagal nerve inhibition and reflex bradycardia. Extreme bradycardia can then evolve into asystole or secondary ventricular arrhythmias.¹⁷ Acute hypoxemia is another major etiology for sudden death in patients with volatile solvent abuse. This can occur by several

mechanisms: 1) direct toxicity from the systemic absorption of volatile solvents after inhalation, causing CNS effects and a decrease in respiration; 2) suffocation from bagging, which can be caused by the blockage of air into the lungs during the inhalation of fumes from a plastic bag placed over the head; 3) asphyxiation caused by a high concentration of inhaled fumes that can displace oxygen in the lungs; and 4) aspiration and choking from the inhalation of vomitus after inhalant use, which can cause severe brain hypoxia and death.¹⁸ Other etiologies for sudden death include fatal injury from an accident and fall due to impaired

judgment caused by the offending inhalant. Accidental flash fires (common with butane and propane) can also cause orofacial and airway tract burns and angioedema that can be fatal.¹⁸

CHRONIC TOXICITIES

Chronic use of volatile solvents can cause multi-system toxicities. Common volatile solvent toxicities include chemical pneumonitis, white matter degeneration of the brain (solvent-induced volume loss), myelin sheath degeneration, polyneuropathy, hepatotoxicity, renal toxicity, bone marrow suppression, lymphoma, and leukemia, among others.^{18,19} Unique toxicities of selected agents are listed in Table 3.

WITHDRAWAL SYMPTOMS

Withdrawal symptoms can occur with volatile solvents and gases and are similar to those occurring upon withdrawal of alcohol or benzodiazepines. These include nausea, vomiting, sweating, tachycardia, tremor, sleep disturbance, diaphoresis, psychosis, insomnia and seizures.²²

PRENATAL AND TERATOGENIC EFFECTS

Because of their high lipophilicity, volatile inhalants cross the placenta; thus, inhalant use during pregnancy can cause spontaneous abortions and fetal solvent syndrome.¹⁶ Fetal solvent syndrome is similar to fetal alcohol syndrome, as infants usually present with low birth weight, microcephaly, micrognathia, facial dysmorphism, craniofacial dysmorphism, cerebellar dysfunction, hearing loss, cleft palate, growth retardation, decrease in muscle tone and developmental delay.¹⁶ Neonatal withdrawals are also seen with inhaled volatile abuse.

Inorganic Gaseous Anesthetics

This category includes nitrous oxide (dinitrogen monoxide), a colorless and innocuous compound commonly known as laughing gas. It is a dissociative anesthetic used as an adjunct anesthetic and anxiolytic agent. Typical users are divided into 2 groups: Adult users are usually in the educated middle class and may include health care professionals (dentists). The other group is teenagers. Nitrous oxide is readily available as a propellant gas in aerosol cans and is often used as a propellant for whipped cream. It is also used in the automotive sector to increase engine performance. It can be purchased in balloons or in vials called whippets, sold at drug paraphernalia stores. The gas can be inhaled directly from

Agent	Toxicity
Benzene	Chemical pneumonitis, hepatorenal toxicity, malignancy, leukemia, aplastic anemia
Butane, propane	Chemical burn injuries
Chlorinated hydrocarbons	Chemical pneumonitis, hepatorenal toxicity
Chlorofluorocarbons (freons)	Upper-airway cold injury and edema, cardiac toxicity through vagal nerve stimulation, pulmonary edema
Carbon tetrachloride	Hepatic toxicity
Dimethyl ether	Upper-airway cold injury and edema, cardiac toxicity through vagal nerve stimulation
Gasoline	Organic lead encephalopathy, chemical pneumonitis
Halothane	Hepatorenal toxicity
<i>n</i> -Hexane	"Hexane neuropathy" ^a
Methyl butyl ketone	Polyneuropathy (distal axonopathy)
Methylene chloride	Carbon monoxide production, "delayed carboxyhemoglobinemia" ^b
Nitrites (amyl nitrite, butyl nitrite, isopropyl nitrite)	"Nitrite rush," ^c bronchial spasms, acquired methemoglobinemia, hypotension (coronary vasodilation)
Nitrous oxide	"Dissociated experience," ^d hypoxia, hypotension, heart block, frostbite, pneumothorax, memory loss, psychosis, megaloblastic anemia, myeloneuropathy, bone marrow suppression
Trichlorethylene	Trigeminal neuralgia, hepatocellular injury
Toluene	Leukoencephalopathy, degeneration of myeline sheath, hepatotoxicity, renal tubular acidosis, hypokalemia, hematuria, albuminuria, pyuria
Xylene	Encephalopathy, hepatorenal toxicity, chemical pneumonitis

Table 3: Unique toxicities of selected inhalants

^a *n*-Hexane neuropathy refers to gradual sensorimotor neuropathy with demyelinating features, paresthesia, and paralysis.²⁰

^b Methylene chloride is metabolized into carbon monoxide in the liver, resulting in elevated carboxyhemoglobin; however, the production of carboxyhemoglobin is delayed by several hours.²⁰

^c Nitrite rush refers to peripheral vasodilation and an increase in intracranial pressure, causing feelings of warmth, headache, dizziness, skin sensitivity, tachycardia, and general feelings of excitement.²¹

^d Dissociated experience refers to symptoms of dizziness, stiffness, warmth, tingling, numbness, and auditory hallucinations.¹⁹

the nitrous gas cartridges (bulbs or whippets) into the mouth, or it can be transferred by discharging the cartridges into another object such as a balloon for the purpose of inhalation.

PHARMACOLOGY

Nitrous oxide appears to have anesthetic and opioid analgesic effects. It is rapidly absorbed by diffusion across the alveolar basement membranes and then eliminated also through the lungs.²³ Absorption and

elimination are very fast, both taking place in under 5 minutes.²⁴ Inhalation of nitrous oxide creates a dissociative experience with symptoms of numbness, warmth, and disorganized thinking.¹⁹ Nitrous oxide depresses all sensations including auditory, pain, temperature, touch, and proprioception.¹⁹ Drowsiness and mood alteration are common, and mentation may be impaired. Dysphoria, inappropriate behaviors, giddiness, laughing, and crying may be seen. Nitrous oxide increases renal and hepatic vascular resistance.²³ Thus, it causes a decrease in renal blood flow, hepatic blood flow, and the glomerular filtration rate. It also activates the chemoreceptor trigger zone and the vomiting center in the medulla, which can cause induction of the vomiting reflex.²⁵ The mechanism of action and receptor sites are listed in Table 2

TOXICITY

Common toxicities are listed in Table 3.

Volatile Alkyl Nitrites

Inhaled volatile alkyl nitrites comprise a group of chemicals (amyl nitrite, butyl nitrite, and cyclohexyl nitrite) that were originally used to dilate coronary arteries in the treatment of angina pectoris. They were later discontinued for this use in favor of longer-acting agents. Originally, butyl nitrite and amyl nitrite were packaged in glass vials that had to be broken to be opened. This gave rise to the terminology poppers. Today, these agents can be purchased online or at adult novelty stores and are often packaged in small bottles similar to energy shots in various sizes.²⁶ Brand names include Jungle Juice, Sub-Zero, Iron Horse, Quick Silver, Super Rush, and Extreme Formula, among others.²⁶

PHARMACOLOGY

The effects of nitrites are immediate within 10 seconds and can last up to 5 minutes.¹⁹ The drug reaches the lungs quickly and diffuses through the pulmonary alveoli. After reaching the tissues of the body, the drug has vasodilation action on both cranial and peripheral vasculature, causing headache, light-headedness, euphoric effects, flushing of the skin, tachycardia, visual distortions, a slowed perception of time, syncopal feelings, a sensation of excitement, and euphoric effects.¹⁹ Nitrites are metabolized rapidly by hepatic glutathione-organic nitrite reductase hydrolytic denitration, with 60% excreted in the urine.²⁷ Unlike other inhalants, nitrites are usually not used to generate euphoric effects. They are usually used by adults to enhance

their sexual encounters and experiences, and they have long history of being abused in sexual interactions among homosexual and bisexual men. Nitrites enhance sexual perception and pleasure by generating the rush or feeling of excitement that is perceived by users as an augmentation of the intensity of sexual orgasm. They are also associated with sexually transmitted diseases and HIV/AIDS because they increase the blood flow to the anal cavity and cause relaxation of the anal sphincter.²¹ This can, in turn, facilitate forceful sexual activity and provide a more efficient acquisition of blood-borne infections due to traumatic nature of anal intercourse.²¹ mechanism of action of nitrites is listed in Table 2.

TOXICITY

Common toxicities of nitrites are listed in Table 3.

Management of Acute Inhalant Exposure and Acute Inhalation Injuries

For patients presenting with acute CNS symptoms, cardiopulmonary symptoms, trauma, or burns, emergency management may be indicated. The primary treatment for acute inhalation toxicity focuses on the elimination of offending toxins; the treatment of acute symptoms; and the stabilization of airway, breathing, and circulation. Decontamination of the patient may be needed. Remove contaminated clothing and perform external decontamination of the skin, hair, and eyes as needed. Gastric decontamination is contraindicated because of the high likelihood of aspiration, especially with highly volatile, low-viscosity hydrocarbons. Pulse oximetry should be performed to assess the degree of oxygenation and state of pulmonary function and effort. If chest x-ray indicates chemical pneumonitis, provide respiratory support, intravenous hydration, and oxygen. Adrenergic β 2 receptor bronchodilators (albuterol) can be useful. Instruct the patient to take nothing by mouth, and admit the patient to the hospital for observation and further treatment. Patients suspected to have acute volatile inhalant intoxication should have continuous electrocardiogram monitoring because many inhalants, especially the volatile solvents, can be pro-arrhythmic. Arterial blood gases should be measured to assess for acidosis, hypoxemia, and hypercarbia. Myocardial irritability can be a problem with inhalation exposure; thus, any use of catecholamines such as epinephrine should be undertaken with caution.²⁰ β -Blockers can be considered to protect the

catecholamine-sensitive myocardium.²⁰ Cardio-pulmonary monitoring is recommended because of the possibility of apnea and cardiac arrest after acute exposure. The skin and oral cavity should be examined carefully for sites of burns, especially if use of flammable solvents (butane, propane) is suspected. If a patient has had extended loss of consciousness and/or felt fatigue with the need to lie down for prolonged periods, rhabdomyolysis may be present and should be ruled out by means of a serum creatine phosphokinase or urine myoglobinuria test. Hypokalemia can also be a common cause of muscle weakness. Metabolic acidosis is common in hydrocarbon abuse and should be ruled out by electrolyte and arterial blood gas (ABG) testing or treated if present. Carboxyhemoglobin levels should be obtained, especially if the patient remains hypoxemic despite oxygen administration or is suspected to have had exposure to methylene chloride. Conventional two-wavelength pulse oximetry does not reliably indicate levels of methemoglobin concentration, so diagnosis should be confirmed by ABG testing to document the methemoglobin percentage. Carboxyhemoglobin elevation can be treated with oxygen. Cyanosis related to methemoglobinemia due to nitrite ingestion also necessitates confirmation by ABG testing. It does not respond to therapy with oxygen administration alone and requires the use of methylene blue. A computed tomography scan of the brain should be considered if occult trauma is suspected in patients with inhalant abuse. The imaging studies can rule out intracranial hemorrhage and occult fractures.

Assessment Following Stabilization

DIAGNOSING INHALANT USE DISORDER

Before and during assessment, it is important to attempt to build a relationship of trust with the patient, as a confrontational approach is not typically effective. Both the patient and family should be approached gently. Obtain a history from the patient, including information on products used, amount, frequency, duration, time of last use, methods of use, acute symptoms, and use of alcohol and/or other drugs. Obtain information regarding any cardiac, pulmonary, gastrointestinal, renal, neuropsychiatric, or behavioral symptoms. It is also important to review past medical history, past attempts to discontinue use, toxicities, and current motivation (if any) to change. Ask the patient's permission to determine whether collateral history regarding inhalant use can be obtained from family or friends. This collateral information could

involve empty adhesive tubes; aerosol spray cans; cigarette lighter refills; nitrous oxide cartridges; or paper, plastic, or potato chip bags at the scene of an accident. Obtain further information on the pattern of use and social and functional aspects to determine whether chronic users have a diagnosis of inhalant use disorder according to *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria.²⁸ Only 2 of the following criteria are needed to reach this diagnosis: the patient 1) uses inhalants in larger amounts or for a longer time than intended; 2) wants to cut down on inhalant use but has difficulty doing so; 3) spends a lot of time getting the inhalants, using them, or recovering from the effects; 4) has cravings or strong desire or urges to continue use of the inhalant substance; 5) fails to carry out important tasks related to home, school, or work because the inhalant use is adversely affecting their functioning; 6) exhibits recurrent use of inhalant substances despite social, interpersonal, physical, or psychological problems; 7) exhibits risk taking in inhalant use (easy to establish, as these substances are toxic poisons); or 8) exhibits tolerance to inhalants (more of the substance is needed to get the same effects).²⁸

PHYSICAL EXAMINATION

Key components of physical examination are listed in Table 4.

LABORATORY TESTING AND IMAGING STUDIES

Further laboratory testing after the patient is medically stable includes serum chemistry (electrolytes, calcium, phosphorus) and liver and kidney function to assess acid-base regulation and to rule out renal tubular acidosis, azotemia, and hepatic inflammation. A comprehensive urine toxicology screen is strongly suggested to exclude the use of alcohol and/or other illicit drugs. Cardiac muscle enzyme analysis should be ordered for suspected cardiac injury. A pregnancy test should be performed on all females of childbearing age to assess the chance of embryopathy. In patients using methylene chloride, high carboxyhemoglobin is expected. In suspected chronic nitrous oxide use, testing should reveal hyperhomocysteinemia and decreased vitamin B₁₂ levels. In fact, measurements of homocysteine and vitamin B₁₂ levels can be considered as biologic markers for nitrous oxide abuse. For patients with suspected myelopathy secondary to chronic nitrous oxide use, early diagnosis is important, as irreversible neurological damage can result without treatment. Urinary metabolites of some solvents can be analyzed for monitoring and determining treatment compliance in patients already in treatment for inhalant use disorders. These metabolites include urinary benzene metabolites (phenol, *t,t*-muconic acid, and

System	Examination component	Notes
General	Dazed look, apathy, chemical odor on breath, cyanosis	Cyanosis may indicate methemoglobinemia due to nitrite use or carboxyhemoglobinemia due to methyl chloride use
Skin	Paint, glitter, or other stains on face, hands, fingernails, or clothes, thermal burns, contact dermatitis, periorbital eczema, rashes on face	Look for huffer's rash or glue sniffer's rash
Eyes	Diplopia, injected sclera, photophobia, blurred vision	Visual loss due to toluene use, "poppers maculopathy" in nitrite users with central visual loss
Ears/nose/throat	Orofacial and nasal frostbite, airway compromise, rhinorrhea, sores around the mouth, oral or airway burns	Frostbites seen with chlorofluorocarbon propellants, burn injuries seen with butane and propane
Lungs	Cough, dyspnea, wheezing, rhonchi, or rales	Pneumonitis or aspiration
Heart	Bradycardia, tachycardia, irregular rate, hypotension	Dysrhythmias occur with volatile solvents and can cause sudden death
Abdomen	Jaundice, abdominal pain, flank pain	Hepatic injury may cause jaundice and right-upper-quadrant abdominal pain, renal injury can cause flank pain
Musculoskeletal	Muscle weakness	Rhabdomyolysis or hypokalemia
Neurologic	Dizziness, ataxia, tremor, neuropathy, slurred speech, decreased memory, nystagmus, muscle weakness	Region-specific brain white-matter abnormalities, myelinated sheath degeneration
Psychiatric	Anxiety, psychosis, euphoria, psychomotor retardation, disorientation, distortion of time and space	Drug-induced psychosis includes hallucinations and thought disturbance

Table 4: Physical examination in patients with inhalant abuse

S-phenylmercapturic acid), urinary toluene metabolite (hippuric acid), urinary xylene metabolite (methyl hippuric acid), urinary trichloroethylene metabolite (trichloroethanol), and urinary tetrachloroethylene metabolite (trichloroacetic acid).²⁹⁻³¹ Characteristic imaging may show abnormal signals in the posterior columns of the cervical spinal cord and prompt treatment with vitamin B₁₂ may be needed. For chronic users of volatile inhalants, magnetic resonance imaging of the brain can be useful in detecting signs of cerebral or cerebellar atrophy.

Treatment of Inhalant Use Disorder

PHARMACOLOGIC TREATMENT FOR VOLATILE INHALANTS

Volatile inhalant withdrawal symptoms can develop in chronic inhalant users. Symptoms may include anxiety, irritability, diaphoresis, nausea, vomiting, tachycardia, insomnia, hallucinations and delusions.²² Because of cross-tolerance between inhalants and alcohol, use of benzodiazepines has been suggested as a first line of treatment.¹⁹ In addition, a Barbiturates (ie, Pheno-barbital) was found to be useful in an animal study for the treatment of inhalant withdrawal.³² Another agent found to be useful is baclofen at doses of up to 50 mg orally per day, which effectively reduced both withdrawal symptoms and cravings in a case series.³⁵ Other pharmacotherapy treatments are focused on

reducing cravings, urges, and drive for inhalants, to promote abstinence. Such agents that might reduce cravings and addictive drive for inhalants have been suggested, including lamotrigine at 100 mg orally per day,³⁴ buspirone at 40 mg orally per day (reduced cravings for petrol inhalation abuse in a case report),³⁵ and risperidone at 0.5 mg orally twice per day (reduced cravings in another case report).³⁶ Pharmacologic agents can also be helpful for the treatment of comorbid psychiatric conditions and/or neuropsychiatric consequences of volatile substance use. Long-term use of risperidone at higher doses (1 mg orally twice per day) was found to be useful in lowering psychotic symptoms in the same case report as cited earlier.³⁶ A randomized clinical trial showed that treatment with antipsychotic medications carbamazepine or haloperidol reduced psychiatric symptoms such as psychosis, anxiety, mood changes, and depression in patients with inhalant use disorder.³⁷ Case analysis found that aripiprazole can be an effective therapy for adolescent patients with inhalant use disorder who also have conduct disorder, as it both controlled the psychiatric symptoms and reduced the frequency of substance use in such patients.³⁸

BEHAVIORAL INTERVENTIONS

Behavior interventions for inhalant use disorder are similar to interventions associated with other substances of abuse. Treatment should address the emotional, social, academic, cultural, and demographic factors related to inhalant abuse. Treatment options

include cognitive-behavioral therapy, dialectical behavior therapy, group therapy, individual therapy, family therapy, and motivational enhancement.

NEUROPSYCHOLOGICAL ASSESSMENT

Patients with a history of inhalant abuse who have had prolonged cognitive dysfunction lasting 6 weeks or longer should be referred for formal neuropsychological assessment using standardized psychometric tools. These tests are useful for assessing the extent of neurologic damage and determining the areas of the brain impacted by the inhalant injury. Neuropsychological assessments can be helpful in evaluating cognitive deficits, measuring the severity of neurologic vs psychiatric impairments, and making decisions regarding appropriate potential rehabilitation treatments. In addition, this type of assessment can be useful in determining whether the patient is a candidate for higher-level substance abuse treatments such as cognitive-behavioral and/or motivational enhancement therapies.

Prevention of Inhalant Abuse

Prevention measures such as educating children, parents, and teachers and reducing the environmental supply are essential in limiting inhalant abuse. Screening teenagers for inhalant abuse is also important in prevention and early detection. Questions regarding inhalant abuse such as huffing or sniffing glue, paint thinner, and similar products can be added to those that may already be in use for tobacco, cannabis, alcohol, and other drugs. Psychoeducation and skills training should focus on the dangers of inhalant use including sudden death, burns, flash fires and brain damage.

Conclusions

Inhalant abuse is a dangerous yet popular behavior because of easy access to commonplace household items. It tends to occur disproportionately among adolescents and young adults in impoverished or marginalized cultural groups.¹ It is associated with a diverse array of medical and psychiatric complications including cardiac, pulmonary, renal, hepatic, dermatologic, hematologic, neurologic, and psychiatric disorders. Inhalants are toxic poisons with high liability potential, yet they receive little research attention. The multitude and diversity of these agents makes studies of the structural categorization, mechanism of action, pharmacologic effects, and toxicity highly challenging. More studies are needed regarding the identification

of molecular targets and clarification of the mechanisms of action of volatile solvents and anesthetic gases. Acute effects of inhalants include sudden death, cardiac arrest, burns, and brain damage. Chronic use can alter the development of the adolescent brain, including altering synaptic transmission in brain pathways, the mesolimbic dopamine system, and the medial prefrontal cortex. Inhalants are psychoactive chemicals with addictive and reinforcing properties. They can induce neuroadaptations in the regions of the brain related to the addiction neurocircuit. Clinicians should keep a high index of suspicion for young, intoxicated patients who have otherwise normal laboratory findings including urine toxicology and alcohol screening. Understanding the pharmacology, effects, and toxicity of these agents would greatly aid all clinicians in performing clinical assessments and referral to specialists in addiction medicine. As of now, the treatment of acute inhalation-related injury is supportive, whereas the treatment of inhalant use disorder involves participation in a substance abuse treatment program. Notably, prevention measures such as educating children, parents, and teachers are essential in limiting inhalant abuse.

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Definitions

Bagging: inhaling fumes from saturated cloth sprayed with euphoria-inducing substances and deposited inside a paper or plastic bag.

Ballooning: inhaling a gas (usually nitrous oxide) from a balloon.

Chroming: spraying paint from an aerosol can into a plastic bag and then breathing the vapors from the bag.

Dusting: spraying an aerosol directly into the nose or mouth.

Gladding: inhaling air-freshener aerosols sprayed in the proximity of face.

Glue sniffer's rash/huffer's rash: an eczematous dermatitis with inflammatory changes and pyodermas seen mainly in the perioral area extending to the midface caused by the drying effects of inhalants, especially hydrocarbons dissolving dermal lipids from skin.¹

Huffing: inhaling a substance from a cloth or rags that have been soaked or saturated and are held close to the face.

Poppers/snappers: amyl nitrite packaged in small bottles that are opened to release the vapors; sold under trade names Super Rush, Locker Room, Bolt, Jungle Juice, Quick Silver, and Extreme Formula.²

Popper's maculopathy: toxic maculopathy due to the use of alkyl nitrites, which can cause structural

changes in the architecture of the retinal fovea resulting in loss of central vision.³

Sniffing/snorting: inhaling a substance from an open container directly through the mouth or nose.

Snotballs: inhaling smoke from the combustion of rubber cement, where the adhesive is usually rolled into balls then burned to release the fumes.⁴

Whippets: vials of nitrous oxide gas, most commonly from whipped cream aerosol canisters. The nitrous oxide can be extracted following whipped cream discharge, after which the released gas can be inhaled at close range or transferred to a balloon and then inhaled.

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