

# Poppers: Epidemiology and Clinical Management of Inhaled Nitrite Abuse

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Commonly referred to as “poppers,” inhaled nitrites have a long history of abuse. Poppers are rapid-onset, short-acting potent vasodilators that produce a rush characterized by warm sensations and feelings of dizziness. Poppers sometimes are used to facilitate anal intercourse because of their actions on the anal sphincter. Epidemiologically, the frequent use of nitrites by men who have sex with men has led some experts to implicate these chemicals in the pathogenesis of Kaposi’s sarcoma and acquired immunodeficiency syndrome. Controlled clinical trials to examine this potential correlation have not been conducted, and the use of nitrites simply may be a marker for other high-risk behaviors such as unprotected sex. Although regulated in the United States, many nitrite compounds and isomers are sold at various venues including bars, bookstores, and over the Internet. Adverse effects associated with these products vary from mild allergic reactions to life-threatening methemoglobinemia. The potential for drug-drug interactions and a propensity toward unsafe sex also exist. Clinicians should be familiar with the populations most likely to abuse these agents and with the clinical effects and management guidelines for acute ingestions.

**Key Words:** poppers, inhaled nitrites, drug abuse.  
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## OUTLINE

History  
Epidemiology  
Kaposi’s Sarcoma and Human Immunodeficiency  
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Clinical Effects and Considerations  
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Conclusion

Drugs such as 3,4-methylenedioxy-methamphetamine (MDMA, Ecstasy),  $\gamma$ -hydroxybutyric acid (GHB), methamphetamine, and ketamine are popular substances of abuse in social settings

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such as bars and dance clubs.<sup>1,2</sup> For this reason, these substances commonly are referred to collectively as “club drugs.” Club drugs first gained popularity in Europe and later in the Americas with the introduction of raves, all-night parties with a prolonged style of dance to fast-paced, repetitive music often accompanied by laser light shows. These substances are used in a recreational fashion to enhance social experiences.<sup>1,2</sup> Typically, they produce social disinhibition, provide energy boosts, and heighten sexual experiences. In some instances, these club drugs have been used to facilitate date rape.

Inhaled nitrites (“poppers”) are also a common class of drugs that have a long history of being abused in social settings, particularly among gay and bisexual men.<sup>3,4</sup> The abuse of nitrites may be associated with a number of health implications and may decrease use of safer sexual practices designed to help prevent human immunodeficiency virus (HIV) infection and

other sexually transmitted diseases (STDs).<sup>3, 5, 6</sup> In the early years of the acquired immunodeficiency syndrome (AIDS) epidemic, nitrite abuse was hypothesized to be a potential vector of HIV acquisition.<sup>6</sup> At that time, nitrite abuse was also believed by some to be associated with the common opportunistic infection Kaposi's sarcoma.<sup>7-9</sup> Many researchers have provided evidence to disclaim these associations, but within the popular media, nitrites may continue to be perceived as linked to these diseases.

### History

In 1859, amyl nitrite was first described to cause flushing of the skin on the face and neck after inhalation.<sup>10</sup> Subsequent to this discovery, amyl nitrite was first prescribed therapeutically for the management of angina in 1867.<sup>11</sup> Originally, nitrites were available in crushable mesh-enclosed glass capsules called pearls. The pearls were crushed with the fingers, creating a popping sound, and subsequently inhaled by the patient.<sup>10</sup> The characteristic popping sound generated by this process is thought to be the origin of the term "poppers," which has become the common street name for the nitrites. In the 1880s, butyl nitrite, which has the same chemical properties as amyl nitrite, was investigated as an alternative to amyl nitrite but never gained widespread use.<sup>10</sup>

Amyl nitrite remained a prescription drug product until September 1960 when the United States Food and Drug Administration (FDA) waived this requirement.<sup>10</sup> After deregulation of the drug, both pharmacists and drug manufacturers noted widespread purchases of the agent by apparently healthy, young adults. Based on reports that abuse of the drug had become commonplace, the FDA reinstated the original prescription requirement in 1969.<sup>10</sup>

After reinstatement of the prescription requirement, the unavailability of amyl nitrite led to a proliferation of the nonregulated chemicals butyl and isobutyl nitrite in the 1970s.<sup>10</sup> In 1988, the United States Congress enacted a ban on the manufacture and retail sale of butyl nitrites in the Anti-Drug Abuse Act.<sup>12</sup> After this legislation, dealers began to sell other alkyl nitrites, such as isopropyl nitrite, which were purported to be "new and improved" products. In 1990, the Omnibus Crime Bill outlawed the sale of all alkyl nitrites.<sup>12</sup> Butyl, isobutyl, and other nitrite compounds continue to circumvent FDA regulation today and commonly are sold over the

Internet, at adult bookstores, and in bars under the guise of incense or room-odorizing products.<sup>10, 13</sup> Other pretenses for the sale of nitrites include labeling the product as video head cleaner, boot cleaner, or leather cleaner. Typically, these products are sold in small, amber glass ampoules containing 10–30 ml of the drug, at an average cost of \$10–20 each.<sup>10, 13</sup> Interestingly, amyl nitrite is used in emergency kits developed to treat cyanide poisoning. One report describes the theft of amyl nitrite capsules from a cyanide antidote kit, making them unavailable for an emergency situation.<sup>14</sup>

### Epidemiology

Limited epidemiologic information is available regarding the frequency and prevalence of nitrite abuse among the general United States population. Most national substance abuse data subclassify nitrites under the general category of inhalants, and information regarding abuse is summated with other similar volatile solvents such as lighter fluid, gasoline, cleaning solutions, paint, and glue. According to the 2002 Monitoring the Future Study (MFS), 11.7% of 12th graders, 13.5% of 10th graders, and 15.2% of 8th graders took an inhalant in their lifetime.<sup>15</sup> In 2002, 1.5% of high school seniors, 2.4% of 10th graders, and 3.8% of 8th graders took inhalants in the past month. The MFS reported nitrite-specific abuse rates for 12th graders. Lifetime prevalence was 1.5% in both 2001 and 2002. Among college students surveyed in 2001, 9.6% reported taking inhalants during their lifetime, and 0.4% reported use during the previous 30 days.<sup>16</sup> Nearly 13% of young adults aged 19–28 years who were surveyed in 2001 reported taking inhalants in their lifetime and 0.4% within the previous 30 days.<sup>15</sup> In examining cumulative data for trends since 1976 among 8th, 10th, and 12th graders, overall inhalant use appears to have declined since a peak in 1996.<sup>15, 16</sup> The total number of emergency department mentions of incidents involving inhalants decreased by 56%, from 1522 in 2000 to 676 in 2001.<sup>15</sup> The reasons for these declines remain unclear, although misclassification of the many substances involved may be one explanation. The summated approach to data reporting for inhalants places all chemicals into one drug category, making it difficult to discern trends for specific individual substances such as nitrites.

Most epidemiologic information concerning nitrite abuse is found in subgroup studies of men

who have sex with men (MSM). This is likely due to a perceived propensity for this population to engage in nitrite abuse.<sup>4, 6, 7, 10</sup> Because nitrites seem more commonly associated with gay culture and use of the substances has been associated with specific sexual practices more common among MSM, most published epidemiologic studies regarding nitrites focus on use by gay and bisexual men. Use of nitrites was also at one time anecdotally linked to the etiology of HIV. This association has never been scientifically demonstrated. Reports of nitrite abuse in the homosexual population began appearing in the medical literature as soon as the early 1980s.<sup>3, 4, 7, 10, 17</sup> One group of authors<sup>18</sup> delivered a self-administered questionnaire to homosexual and bisexual men seeking care at a local AIDS unit. Data from the questionnaires were then correlated to clinical laboratory findings that included HIV serostatus. The researchers found that within a cohort of 1348 gay and bisexual men surveyed in West Berlin, Germany, 477 (35.4%) reported taking nitrites.<sup>18</sup> Of 364 of these subjects who tested positive for HIV, 194 (53.3%) were regular users of butyl nitrite. This information was limited by its self-report nature and the clarity of the self-administered questionnaire.

Another group<sup>19</sup> described the extent of recreational drug use among a cohort of homosexual men participating in the Chicago Multicenter AIDS Cohort Study (MACS). Marijuana and nitrites were the two most frequently used drugs throughout the study period, which lasted from 1984–1990. Men who did report nitrite use in the MACS cohort were consistently more likely to participate in high-risk sexual activities as compared with nonusers. Receptive anal intercourse without a condom was 1.5–2.0 times greater in the nitrite group ( $p < 0.0001$ ). The investigators concluded that a significant association exists between nitrite use and high-risk sexual behavior. The report emphasized that nitrite use is particularly associated with unprotected receptive anal intercourse and a significantly higher HIV seroconversion rate. The investigators commented that continued nitrite use might prevent modification of preexistent high-risk sexual behaviors. Similar to the previously mentioned study,<sup>18</sup> this trial<sup>19</sup> was limited by the self-reporting of data that was required of the subjects.

In 402 homosexual men who were enrolled in a longitudinal cohort study in Amsterdam,

researchers found a correlation between nitrite use and the lapse in time from safe sexual practices to unsafe sexual practices.<sup>20</sup> During the study, each subject underwent prospective analysis for clinical markers of HIV disease. Subjects completed a questionnaire on behavioral data, which included sexual and substance-abuse history, every 6 months. All the subjects reported previous safe sexual practices of at least 12 months' duration. These researchers hypothesized that nitrite abuse may be common in the context of anal intercourse because the drugs are known to reduce anal sphincter tone.

Collecting survey data among a cohort of 87 homosexual men, another group of authors found that nitrites and cannabis were the most common substances abused.<sup>21</sup> Twelve (60%) of 20 HIV-seropositive patients and 40 (60%) of 67 HIV-seronegative patients reported regular use of the substances. Patients who were available at follow-up were reassessed 6 months after the baseline study, at which time 10 (63%) of 16 HIV-seropositive patients and 23 (46%) of 50 HIV-seronegative patients reported continued use of nitrites. This trial was limited by its small sample.

In a study conducted in 1995,<sup>22</sup> the authors examined data from 3553 repeat anonymous HIV tests among MSM in the San Francisco Bay area. The HIV seroprevalence was estimated for the cohort, and predictors of HIV seroconversion were derived. Amyl nitrite use was one of six variables found to be a statistically significant independent predictor of increased HIV seroprevalence. This study was limited by the hypothetical models used to estimate seroprevalence, as well as subject-associated recall bias and potential hesitancy to divulge information.

Another group<sup>23</sup> used a survey to study a cohort of 525 homosexual and bisexual men (156 were HIV seropositive and 369 were HIV seronegative) and determine what factors might lead individuals to practice unprotected sex and potentially place others at high risk for HIV acquisition. The sample group was derived from subjects enrolled in the Pittsburgh Multicenter AIDS Cohort Study. Regardless of serostatus, the researchers found that among other variables, frequent users of nitrites (e.g., at least monthly) were more likely to engage in risky sexual behaviors. Similar to the previous trials examining sexual activity among subjects, this trial was limited by recall bias and willingness to divulge information.

In another study,<sup>5</sup> a cohort of 578 HIV-

seronegative MSM were evaluated to determine the prevalence of STDs and the frequency of and risk factors for STDs. Unprotected insertive anal sex with an HIV-seropositive or unknown-serostatus partner in the past 6 months and nitrite inhalant use were independently associated with acquiring an STD. When unprotected insertive anal sex was removed from the statistical model, the number of partners and nitrite inhalant use were independently associated with incident STD. Although not statistically significant, men with an STD who reported nitrite use were more than 4 times as likely to report having had sex in a bathhouse when compared with those not using nitrites. The use of nitrite inhalants was associated with a greater than 2-fold increased likelihood of acquiring an STD. Similar to other researchers, the authors of this study hypothesized that nitrite use may be a marker for other high-risk sexual practices.<sup>5</sup>

As part of a 1996–1997 HIV vaccine feasibility and suitability study for young gay men, data were collected regarding a cohort of 2189 young gay men.<sup>24</sup> The participants were recruited from three large cities (Atlanta, Denver, and San Francisco). Eighteen percent of the subjects aged 18–25 years and 24% of the subjects older than 25 years reported using nitrites within the previous 6 months.

In a trial involving 719 young gay and bisexual men, the authors reported on two cohorts: one very young (aged 15–17 yrs, 100 subjects) and one slightly older (18–22 yrs, 619 subjects).<sup>25</sup> Each participant was asked to report on the frequency of nitrite use according to the following scale: 1 = never, 2 = less than once/month, 3 = about once/month, 4 = 2–3 times/month, 5 = about once/week, 6 = 2–3 times/week, and 7 = every day or almost every day. The mean  $\pm$  SD responses for the cohort aged 15–17 years and the cohort aged 18–22 years were  $1.14 \pm 0.49$  and  $1.18 \pm 0.66$ , respectively. The difference between the groups was not statistically significant. Among these age groups, 10.8% of all subjects reported having used nitrites within the previous 6 months. The researchers concluded that interventions designed to encourage safer sexual practices in these groups should address recreational drug use, particularly nitrites.

Circuit parties are typically 3–4-day weekend events that are marked with many social gatherings that culminate in one large concluding party. Since circuit parties often are attended by

MSM and have been reported to be venues where drug abuse is common, some researchers have investigated the extent of use of inhaled nitrites at these events.<sup>2</sup> One group of authors surveyed a nonrandom sample of 1169 circuit party attendees.<sup>25</sup> Thirty-nine percent of party attendees reported nitrite use in the last 12 months. Nitrite use was also statistically significantly associated with unsafe sexual behavior in the previous 12 months and while at the party event itself. Among all drugs examined (MDMA, ketamine, GHB, crystal methamphetamine, cocaine), nitrites demonstrated the strongest association with unsafe sex. This was thought to be because of the nitrites' specific use to facilitate anal intercourse.

Another group<sup>27</sup> compared the use of various recreational drugs among a cohort of circuit party and noncircuit party attendees. Two hundred ninety-five gay and bisexual men from the San Francisco Bay area were recruited to complete an anonymous survey. During their most recent circuit party weekend, 12% of subjects reported the use of nitrites. Five percent of respondents reported using nitrites while attending dance clubs on weekends, and 5% reported using nitrites independent of any events, parties, or clubs. Use of nitrites was found to be an independent predictor of unprotected anal intercourse with opposite- or unknown-HIV-serostatus partners. The authors concluded that substance abuse and high-risk sexual behaviors are correlated and common in various venues including circuit party weekends and that preventative programs must address these factors.

In another study, the authors examined substance abuse and unsafe sex among homosexual men in Edinburgh, Scotland.<sup>28</sup> Five hundred six homosexual and bisexual men were recruited from bars, cafes, saunas, and a "cruising ground" to complete an anonymous questionnaire regarding substance abuse and unsafe sexual practices. Unsafe sex was defined as anal intercourse without a condom and with a partner of unknown HIV serostatus. Three hundred respondents (65.6%) reported having used nitrites in their lifetime, 193 (37.1%) had used nitrites within the previous 3 months, and 66 (13.1%) used nitrites once/week or more within the previous 3 months. Respondents also were asked about nitrite use as it related to sexual practices. Forty-one (9%) had used nitrites immediately before or during sex, none reported using nitrites less than 2 hours before sex, and one respondent said he used nitrites more than 2

but less than 12 hours before sex. Among users, nitrites were significantly associated with unsafe sexual practices ( $p < 0.05$ ). Similar to previous reports, the investigators commented that these results were not surprising given the close association of nitrites with heightened sexual experiences. In addition, the researchers recommended that nitrite users be targeted for preventive and educational efforts regarding safer sexual practices.

Another group compared substance abuse among MSM with a nationally representative sample of heterosexual men in 2000.<sup>29</sup> The MSM group contained 3212 subjects, whereas the heterosexual representative sample contained 2481 subjects. The three most commonly abused substances in the MSM group were alcohol (88.8%), marijuana (49.4%), and nitrites (29.1%). Among the heterosexual group, the three most common substances of abuse were alcohol (79.5%), marijuana (15.3%), and stimulants (i.e., cocaine, methamphetamines, 4.64%). Prevalence of nitrite use was 1.35% among the heterosexual group. The higher rate of substance abuse among the MSM group was thought to be partially attributed to their higher likelihood of attendance at raves or circuit parties. The specific disparate finding of nitrite abuse may be due to a greater likelihood of abuse by the MSM population with regard to anal intercourse.

### **Kaposi's Sarcoma and Human Immunodeficiency Virus**

In the early years of the HIV epidemic, little regarding the etiology of AIDS and its associated opportunistic infections, including Kaposi's sarcoma, was understood. Many etiologic theories were proposed. The widespread and publicized use of nitrites among homosexual men led some investigators to examine a potential role of nitrites in the pathogenesis of this disease and its complications.<sup>7, 30, 31</sup>

Many theories were developed to describe a potential relationship between Kaposi's sarcoma and the nitrites. Some hypothesized that nitrite use produced immune dysregulation, which in turn allowed for expression of a previously suppressed oncogenic virus.<sup>7, 32</sup> Other researchers hypothesized a local carcinogenic effect due to inhaled nitrite vapor contact with skin and oral mucosa, rather than by means of systemic distribution.<sup>10</sup> Still other researchers speculated that nitrite use was simply a strong

confounder of studies of HIV and Kaposi's sarcoma and represented a marker for other ongoing risk factors such as sexual activity.<sup>33</sup>

In 1982, a group of authors evaluated the effects of nitrites on T cells in homosexual men.<sup>7</sup> Data were collected from two homosexual patients with Kaposi's sarcoma and 15 men without the opportunistic infection. Both patients with Kaposi's sarcoma had taken nitrites regularly and also had low helper:suppressor T cell ratios. Eight of the 15 patients without Kaposi's sarcoma reported regular nitrite use, seven of whom had low helper:suppressor T cell ratios. Among both patient groups, altered T cell ratios correlated with higher than normal cytomegalovirus antibody titers. The authors claimed that these data suggested nitrites might be immunosuppressive, especially in the setting of repeated antigenic stimulation, and might contribute to the high frequency of Kaposi's sarcoma and other opportunistic infections among homosexual men. This initial report included a very small sample and was incompletely controlled, yet it fueled further research in this area.

In 1983, a national case-control study of Kaposi's sarcoma in homosexual men found that nitrite use was a relatively unimportant factor in acquisition of Kaposi's sarcoma.<sup>9</sup> Rather, the number of male sex partners/year was the most common factor associated with the opportunistic infection. The authors did comment, however, that during pretesting of their survey, most participants often were unsure if they specifically used nitrite products.

One group of authors<sup>30</sup> attempted to identify risk factors that determine the major manifestations of AIDS by analyzing data from three epidemiologic studies conducted by the Centers for Disease Control and Prevention (CDC). Eighty-seven cases were available for analysis, including interviews and laboratory testing. Compared with patients who had only *Pneumocystis carinii* pneumonia, patients with Kaposi's sarcoma and those with both Kaposi's sarcoma and *P. carinii* pneumonia had more sexual partners and used more recreational drugs. Multivariate analysis showed that the variable most strongly associated with Kaposi's sarcoma was the use of large quantities of nitrite inhalants. The authors hypothesized that nitrites may be a promoter of Kaposi's sarcoma carcinogenesis, which in the presence of an initiating event (e.g., immunosuppression from HIV or AIDS) results in clinical disease. This

study had several limitations including its small sample and retrospective nature. Experts cautioned that nitrite inhalation may have represented a correlation (rather than an etiologic association) and could be merely a marker for other behaviors that place patients at risk for Kaposi's sarcoma, HIV, or AIDS.

The authors of a retrospective study proposed that the occurrence of Kaposi's sarcoma actually was related to sexual practices associated with fecal contact among HIV-infected men.<sup>34</sup> The investigators distributed a questionnaire to 65 homosexual men, all of whom had AIDS as defined by the CDC classification system in 1986. Data regarding time of diagnosis, frequency of disease manifestations, sexual practices, and recreational drug use were collected. Thirty patients (46%) had a diagnosis of Kaposi's sarcoma. Insertive oral-anal intercourse ("rimming") was statistically significantly associated with Kaposi's sarcoma, yet use of nitrites was not. Nitrite use however was related to insertive rimming. Approximately one half of all the men who had never used nitrites or had used them less than once/month reported practicing insertive rimming, whereas most men who used nitrites at least once/week practiced insertive rimming. Stratification of the data by insertive rimming as a risk factor demonstrated no association between Kaposi's sarcoma risk and nitrite use. The authors postulated that sexual practices are the most important determinant of Kaposi's sarcoma transmission or infection. Particularly risky are sexual activities that involve fecal matter. They speculated that fecal matter might be a vector for transmission of an infective organism involved in the acquisition of Kaposi's sarcoma. These authors also hypothesized that an alteration in sexual practices (e.g., reduced frequency of oral-anal activity) among MSM might lead to a reduction in the frequency of Kaposi's sarcoma. This study was limited by its small sample, retrospective nature, and use of older criteria for the diagnosis of AIDS. Furthermore, survey data regarding sexual practices were limited by the respondents' comfort level with specific questions and the extent of honest answering.

Studies that subsequently examined the frequency and epidemiology of Kaposi's sarcoma in later years of the HIV epidemic found that the cancer most likely was related to infection with human herpesvirus 8 (HHV-8).<sup>35</sup> Current CDC HIV and opportunistic infection treatment guidelines recognize HHV-8 as the primary cause

of Kaposi's sarcoma.<sup>36</sup> Although HHV-8 is uncommon in the general population in North America, among MSM 11–20% of those who are HIV seronegative and 30–54% of those who are seropositive have detectable antibodies against HHV-8.<sup>37, 38</sup> The frequency of HHV-8 among the MSM population is greatest among those with multiple sexual partners, highlighting the role of sexual transmission.<sup>37, 38</sup> Human herpesvirus 8 appears to be more seroprevalent in the oropharynx than in the genital tract, suggesting that oral exposure is the most common mode of disease transmission.<sup>39</sup> Injection-drug use also has been shown to transmit HHV-8 effectively. One study demonstrated that among a cohort of 1905 injection-drug users, HHV-8 seroprevalence increased with the number of years of injection-drug use.<sup>40</sup> Taken together, these new data effectively have silenced the proponents of the hypothesis that inhaled nitrites "cause" Kaposi's sarcoma; nevertheless, the association suggests that the use of inhaled nitrites facilitates unsafe sexual practices that promote transmission of HHV-8 and thus indirectly increases the risk of Kaposi's sarcoma.

Before the identification of HIV in the mid-1980s, nitrites were a suspected cause of the immune suppression observed in homosexual men with AIDS.<sup>6, 7, 10</sup> Despite the identification of HIV and the relative lack of nitrite use in some heavily HIV-infected areas (e.g., Africa), some groups continued to promulgate etiologic theories of AIDS that involved nitrite use. Certain researchers have used the previously described theory of nitrite-induced immunosuppression to explain a potential role for nitrites in the etiology of HIV.<sup>7</sup> The debate surrounding the role of nitrites in HIV will certainly continue, given that nitrite abuse is more prevalent among MSM than in the general population. The high prevalence of nitrite abuse and the association with high-risk sexual practices highlight the importance of recognizing that nitrites are often a strong confounder in many HIV epidemiologic studies.<sup>33</sup>

### Clinical Effects and Considerations

Inhaled nitrites rapidly and effectively are absorbed into the bloodstream, with the onset of effects being in the order of seconds.<sup>10, 13</sup> Subsequently, the nitrites are rapidly metabolized by the liver, kidneys, lungs, intestinal mucosa, and vascular tissue, with effects lasting only minutes. Most of the metabolism occurs

hepatically by the enzyme glutathione-organic nitrate reductase. Tachyphylaxis to nitrites may develop in any individual, leading the subject to inhale progressively increased amounts of the drug to produce the same desired effects.

Users of nitrites report that the drug enhances sexual perception and pleasure.<sup>10, 13, 41</sup> Vasodilation of cerebral blood vessels along with warm sensations and facial flushing are common and contribute to the users' perceptions of a rush or high.<sup>42</sup> Users report inhaling nitrites just before sexual orgasm for a number of reasons. The rush or high experienced by users is perceived to augment and intensify sexual orgasm. Nitrites also are believed to dilate the anal sphincter, thus facilitating anal intercourse.<sup>10, 13, 41</sup>

As previously discussed, the nitrites are potent vasodilatory substances. The vasodilatory effects are accomplished by relaxing involuntary muscles of the vasculature.<sup>10, 13</sup> After inhalation, vasodilatation often results in temporary reductions in blood pressure accompanied by tachycardia, lightheadedness, and syncopal feelings. Medicinal nitroglycerin products (i.e., isosorbide dinitrate, isosorbide mononitrate) are organic nitrates and do not immediately result in many of the same clinical and pharmacologic properties of the volatile nitrites and thus are not considered substances of abuse.<sup>10, 13</sup> Hypotension, lightheadedness, and flushing may occur as a result of medicinal nitroglycerin therapy, but the delayed onset of these effects compared with those of volatile nitrites makes them less desirable.

Frequent use of inhaled nitrites is associated with a myriad of adverse effects. Crusty skin lesions with a distinctive yellow tint have been reported around exposure areas including the nose, mouth, lips, and face.<sup>10, 13, 17, 43</sup> These lesions may be misdiagnosed as impetigo or severe seborrheic dermatitis. Dermatologic eruptions usually resolve within 7–10 days of drug discontinuation.<sup>17</sup> The irritating and volatile properties of the inhaled nitrites also may result in sinusitis and, in some cases, trigger allergic reactions accompanied by wheezing and dyspnea.<sup>17</sup> Clinicians should be aware that many nitrite compounds are scented with various fragrances before sale, and these perfume additives may cause allergic-type reactions. Headaches of varying severity are a common result of cerebral vasodilatation.<sup>10, 13, 41</sup> Also, nitrites may produce transient elevations in intraocular pressure, which may be of special concern to patients with underlying glaucoma.<sup>10, 13</sup>

A serious adverse effect of large nitrite

exposure is methemoglobinemia.<sup>10, 13, 44</sup> In varying doses, nitrites can enter red blood cells and oxidize hemoglobin, forming methemoglobin. In cases of cyanide toxicity, induction of methemoglobin may actually play a beneficial role by displacing cyanide from the heme group of cytochrome oxidase.

One report describes the case of an otherwise healthy 29-year-old man who came to an emergency department slumped over in a wheelchair and complaining of extreme lethargy, with circumoral cyanosis.<sup>44</sup> He reported inhaling amyl nitrite just before the onset of his symptoms. Vital signs revealed tachycardia to 112 beats/minute and blood pressure 100/60 mm Hg. Respiratory rate was 12 breaths/minute and pulse oximetry 56% on 100% oxygen delivered by nonrebreather mask. Intravenous naloxone and dextrose with thiamine were administered with no change in the patient's mental status. Blood drawn for laboratory studies was found to be chocolate brown. A tentative diagnosis of methemoglobinemia was made, and intravenous methylene blue was administered. Ten minutes after methylene blue administration, the patient became alert and more responsive, with a pulse oximetry reading of 74%. Forty-five minutes after methylene blue administration, the patient was awake and oriented to person, place, and time. Oxygen saturation improved to 98%. This case demonstrated the classic and potentially life-threatening effects of nitrite-induced methemoglobinemia, which responded to appropriate treatment with methylene blue. Note that methemoglobinemia can cause pulse oximetry readings to be falsely elevated, and subsequent administration of methylene blue can cause dramatic decreases in pulse oximetry readings. Therefore, clinicians treating patients with methemoglobinemia should be careful not to rely solely on pulse oximetry readings and should always consider the clinical status of the patient.

Nitrite inhalation also has been associated with hemolytic anemia in patients deficient in glucose-6-phosphate dehydrogenase (G6PD).<sup>10, 13, 45</sup> One group of authors<sup>45</sup> described the case of a 19-year-old man who was admitted with complaints of severe headache and jaundice. The patient reported having inhaled nitrites the previous day, which he referred to as poppers. The patient's medical history was unremarkable except for Kawasaki disease at age 10 years, and he was receiving no drug therapy. His initial hemoglobin level was 13.0 mg/dl (normal range 13.5–17.3 mg/dl). Also noteworthy were total

serum bilirubin 12.4 mg/dl (0–1.0 mg/dl) and serum lactate dehydrogenase 430 U/L (90–250 U/L). The following day the patient was severely icteric, and the hemoglobin level had decreased to 11.0 mg/dl. Results of a direct Coombs' test were negative, and qualitative G6PD assay demonstrated deficiency of the enzyme. The patient's condition stabilized, and he was discharged 3 days after admission. The cause of anemia was believed to be oxidative red blood cell stress elicited by nitrite use and exacerbated by a deficient G6PD enzyme system.

Since the earliest reports of nitrite abuse, some clinicians have expressed concerns that these substances might be carcinogenic. Inhaled nitrites may interact with endogenous trivalent nitrogen compounds to produce nitrosamines, some of which are known to be carcinogens.<sup>10</sup> Whether clinically significant amounts of nitrosamines are formed after inhaling these nitrites and how much exposure by inhalation would be required to produce a significant risk of cancer remain to be determined. Some investigators have demonstrated that, at least in vitro, butyl nitrites appear able to form reactive nitrosamines that may become carcinogenic.<sup>32</sup>

Comorbid conditions place some patients at special risk of adverse consequences from inhaled nitrites. Patients with ocular conditions, particularly glaucoma, should be especially cautioned to avoid inhalation of any nitrite product.<sup>13</sup> Nitrite abuse also may aggravate preexistent cardiovascular disease, particularly in patients with arrhythmias or hypotensive disease. Severe headaches are a common consequence of nitrite abuse and may be misdiagnosed in this patient population.

Patients with HIV and those with a high risk of disease acquisition (e.g., MSM) should be questioned routinely regarding the use of nitrites, as well as other recreational drugs.<sup>1,2</sup> Clinicians, particularly those involved in the care of HIV-infected or high-risk patients, should be familiar with the effects of these agents and their association with high-risk sexual practices. Patients who are HIV seropositive with preexistent G6PD deficiency, which often results in sulfa drug intolerance, may be predisposed to the hemolytic effects of even small amounts of nitrites and should be counseled accordingly.

Clinicians should recognize the risks of increased disease transmission associated with nitrite abuse. Given that the agents are used frequently to facilitate specific sexual practices, nitrite inhalation is particularly concerning with

regard to STDs. The high produced by nitrites may increase libido and reduce the likelihood that safe sexual practices are used.<sup>10</sup> In addition, nitrites are known to cause vasodilatation of smooth muscle, particularly of the anal sphincter.<sup>10,13,41</sup> These effects may facilitate more forceful anal intercourse. Also, the pain caused by microtears in the rectum may be less recognized by individuals impaired by the effects of nitrites. Vasodilatation of perianal blood vessels may result in increased blood flow to the anal cavity.<sup>41</sup> Given the traumatic nature of anal intercourse, increased blood flow may result in more efficient acquisition of blood-borne diseases such as HIV or hepatitis B.

For HIV-infected patients, considerations should be given to the effects of inhaled nitrites on adherence to antiretroviral drug regimens. Although the rush created by nitrites appears to be short-lived, long-term abuse of these agents places the patient at risk of missed antiretroviral doses, thus facilitating the development of resistant viral strains. Some authors have described the potential for serious drug-drug interactions involving nitrites. Sildenafil (Viagra; Pfizer, Inc., New York, NY) has been well established to interact with various nitrate products that are taken orally for the relief of anginal pain.<sup>46</sup> Sildenafil often is taken by recreational drug users to counteract the impotence-inducing effects of certain agents (i.e., Ecstasy).<sup>47</sup> Concurrent use of sildenafil and nitrates may result in life-threatening hypotension; indeed, the product package insert warns against the use of this product with any nitrate product. Although nitrites have not been tested specifically in combination with sildenafil, it would appear prudent to avoid concurrent use of these agents.

## Management

Clinicians may be more familiar with newer recreational drugs (e.g., Ecstasy, GHB); however, nitrite inhalation remains popular especially among MSM. Practitioners should be familiar with the effects of nitrite inhalation and the associated risks. Patients, and particularly MSM and those with a history of drug abuse, should be questioned with regard to nitrite use. Regular abusers should be referred to appropriate substance-abuse specialists, and all users should receive detailed counseling regarding the potential effects of inhalation and the correspondent risks.

Clinicians should be cognizant of the fact that nitrite solutions may contain unknown impurities,

some of which may be toxic. Acute toxic ingestions, while relatively rare, are possible. Small ingestions resulting in headache, blurred vision, postural hypotension, syncope, transient hypotension, or tachycardia may be managed symptomatically.<sup>8, 10</sup> Topical exposure to nitrites may result in chemical burns and should be treated symptomatically with copious water and soap rinsing and flushing.<sup>17, 43</sup> Also, nitrite solutions are extremely flammable; burns should be managed with standard burn protocols.<sup>13</sup> Oral ingestions should be treated with immediate administration of activated charcoal.<sup>10, 13, 41</sup>

Larger or continued exposures can result in serious, life-threatening methemoglobinemia. Diagnosis can be made based on patient history in conjunction with physical findings of cyanosis, arterial blood gas readings, and methemoglobinemia concentrations.<sup>44</sup> Blood drawn from patients with methemoglobinemia often will reveal a distinctive chocolate-brown color. Cyanosis related to methemoglobinemia often does not respond to therapy with oxygen and requires the administration of methylene blue. Methylene blue 1% should be given parenterally at a dose of 1–2 mg/kg. Based on response, additional dosages may be required but should not exceed 7 mg/kg/day.<sup>44</sup> Daily doses of methylene blue that exceed 7 mg/kg may actually promote methemoglobinemia.

## Conclusion

Unlike many current recreational drugs, the nitrites have a long history of abuse dating to the 1960s. Inhaled nitrites, commonly known as poppers, are often used to facilitate specific sexual practices, especially anal intercourse. Observations of the frequent abuse of nitrites by MSM have led some researchers to speculate about a possible role of nitrites in the pathogenesis of various diseases including HIV or AIDS and Kaposi's sarcoma, but the associations between these diseases and nitrite abuse have not been demonstrated in controlled clinical trials. Although the substances do not appear to be directly correlated with the pathogenesis of HIV or Kaposi's sarcoma, significant risks do exist for users of inhaled nitrites. For patients with preexistent HIV or other diseases, nitrite abuse may affect the ability to adhere to drug regimens. Nitrite abuse may cause a temporary loss of social inhibitions, thereby promoting higher risk sexual practices. Pharmacologically, the nitrites may act to facilitate the transmission of certain

sexual diseases through their actions on the anal sphincter. Serious interactions exist with other drugs that often are used to facilitate sexual activity, and patients always should be questioned regarding concurrent use. Inhalation of nitrites can result in local irritation, allergic reactions, symptoms due to vasodilation, and even potentially life-threatening methemoglobinemia. Clinicians should be able to recognize the populations most likely to abuse nitrites and be prepared to counsel them regarding the risks of this prevalent form of substance abuse.

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