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RECREATIONAL INHALED NITRITE USE AMONG ASIAN MEN WHO HAVE SEX WITH MEN – A REVIEW

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ABSTRACT

Inhaled nitrites are gaining popularity among Asian men who have sex with men (MSM). This review aimed to summarize the current evidence on the prevalence and correlates of inhaled nitrite use among Asian MSM. Besides, the knowledge, perception, and sexual behaviors of nitrite users among MSM were also discussed. Most of the studies on nitrite use among Asian MSM were conducted in major cities of China, with sporadic studies in Japan and Malaysia. The literature showed that inhaled nitrites were one of the most commonly used recreational drugs among Asian MSM. Younger and educated MSM with disposable income were more likely to use inhaled nitrites. MSM used nitrites to enhance sexual pleasure, but most were not sure about their side-effects. Some studies indicated that MSM had low barriers to obtain the substance through various sources. Inhaled nitrites use had been associated with risky sexual behaviors, such as unprotected anal intercourse and multiple sex partners. The use of inhaled nitrites was linked with a higher risk for the infection of HIV and sexually transmitted diseases (STDs). In conclusion, the use of inhaled nitrites among Asian MSM is a serious health concern and demands innovative approaches to address this problem.

Keywords: *HIV; nitrites; poppers; rush; substance abuse*

INTRODUCTION

Inhaled nitrites were traditionally used for the management of angina. The street name "poppers" refers to the crushing sound of glass capsules containing the drugs. Amyl nitrite is the first inhaled nitrite introduced in the market. Following regulation by the authority, butyl nitrite, isobutyl nitrite, and isopropyl nitrite started to proliferate in the market. Pharmacologically, inhaled nitrites are rapid, short-acting potent vasodilators, which produce a warm sensation and facial flushing, or "rush" to the users. This effect is sought after by users to

intensify sexual orgasm. Nitrites also relax the smooth muscle of the anal sphincter, which facilitates anal intercourse, thus are popular among men who have sex with men (MSM).[1]

Inhaled nitrites have a short duration of action, leading to the false perception that they are safe. In reality, they can induce temporary hypotension, reflex tachycardia, dizziness, and syncope.[1] Inhaled nitrites are contraindicated in individuals with hypotensive diseases, glaucoma, and glucose-6-phosphatase dehydrogenase deficiency (with the potential to cause hemolytic anemia).[2,3] They may potentiate the effects of phosphodiesterase-5 inhibitors like sildenafil, causing severe hypotension.[4] Inhaled nitrites can also cause allergic contact dermatitis.[5,6] Some studies suggested that inhaled nitrites were associated with cancers, but the evidence is debatable.[7] Given its oxidative potential, large doses of inhaled nitrite may cause methemoglobinemia, leading to tissue hypoxia and death.[8] Neurological studies in animals also reported that alkyl nitrites were additive and could impair memory, learning, and motor functions.[9,10]

Epidemiological studies on the use of inhaled nitrites started in the 1970s in the United States.[11] Several recent epidemiological studies revealed that inhaled nitrites remain as a popular recreational substance of abuse among MSM in North America and Europe.[12–15] The prevalence of recreational nitrite use was reported to be 46% among Parisian MSM.[14,16] Studies in the United States and European countries demonstrated that inhaled nitrite use was associated with risky sexual behaviors, such as serodiscordant condomless anal sex, concomitant substance use during sex, multiple casual sex partners, and visiting sex-focused venues.[14,15,17–20] Besides, inhaled nitrite use was a strong predictor of HIV and sexually transmitted disease (STD) infection in these populations.[18,21]

Literature reporting the use of inhaled nitrites among Asian MSM communities appeared in the 1990s.[22] Asian MSM may be less knowledgeable on the adverse side effects of inhaled nitrites due to the conservative attitude of most Asian countries towards the gay community, which renders them more vulnerable to the dangers of nitrite abuse. Throughout the years, more studies on the use of poppers among Asian MSM have been reported. This paper aims to provide a comprehensive view of the use of poppers among Asian MSM. The information obtained will be critical in planning strategies to educate Asian MSM on the use of inhaled nitrites.

Literature Search

A literature search was performed using the keywords "nitrites OR poppers OR rush" AND "MSM" with Pubmed and Scopus database from the inception of databases to December 2019 (Figure 1). Original research studies written in English or Mandarin, reporting the prevalence and predictors of nitrites use among Asian MSM were included. Articles written in other languages, review/conference abstract/book chapters, as well as studies that did not distinguish the use of nitrites with other recreational drugs were excluded. A total of 26 articles that fulfilled the criteria were identified and included in this review (Table 1).

Study Design and Subjects

Of all the studies included, three were prospective studies[23–25] while the rest were cross-sectional studies.[22,26–46] The prospective studies aimed to investigate the link between inhaled nitrite use and HIV/STD infection among MSM. A prospective study by Yun et al.[47] was excluded because the cohort is the same as that studied by Chu et al.[23] An intervention study aiming to determine the effectiveness of education and behavior intervention to encourage protective anal intercourse among subjects with a high proportion of inhaled nitrite users was found.[48] The Asian MSM populations studied include those living in the United States,[22] Japan,[26] Malaysia,[32] and major cities in Mainland China.[23–25,27–31,33–46,48] Both the general MSM population and sex workers at night clubs (money boys) have been studied. Data

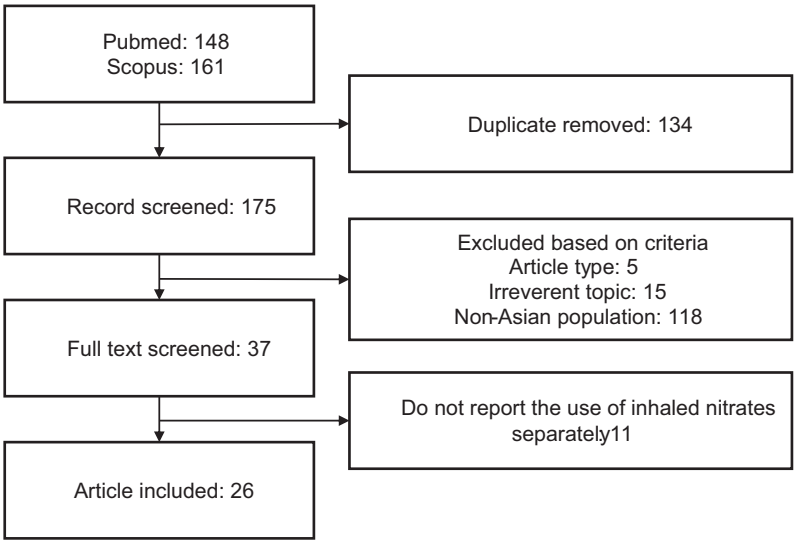

FIGURE 1 Flow chart of article selection.

collection of the studies were performed through internet-based surveys, face-to-face interviews, and a mixture of both techniques. Since homosexuality is a taboo in most Asian countries, most of the subjects were recruited using snowball sampling or peer referral. In a Japanese study, subjects were recruited through gay websites, magazines, and internet email listing.[26] A study in Hunan China recruited subjects through gay dating websites and most of the subjects were money boys.[36] Recruitment at HIV/STD testing and consultation facilities, gay-oriented venues (bar, night club, tea bar, sauna, and bath) were performed.[25,28,30,31,35,40,43,44]

Prevalence of inhaled nitrite use

Inhaled nitrites were the most commonly used recreational drugs among MSM in many major cities of China.[29–31,36,37,41,44] Among 3830 MSM in six major cities (Kunming, Jinan, Changsha, Zhengzhou, Nanjing, and Shanghai) of China, 28% reported the use of at least one type of substance, of which 26.5% used inhaled nitrites, followed by ecstasy (2.8%) and ice (2.5%).[30] Similarly, in a nationwide online survey in China (n = 1142), 77.3% of MSM studied reported the use of recreational drugs in their lifetime, of which 21.3% used inhaled nitrites, 2.4% used crystal meth, and 1.0% used ecstasy.[41] In a recent nationwide study in China involving 16 cities (n = 3135), 96.3% of the MSM who used synthetic tried inhaled nitrites in their lifetime.[45] Inhaled nitrites were also the most common recreational substance used among money boys in Changsha, a highly developed entertainment city in China, whereby 36.6% of the substance users reported ever use in the last 3 months of the survey.[36] Researchers suggested that the low cost of inhaled nitrites and high accessibility through online market and adult stores contributed to the prevalent use of inhaled nitrites in China.[29,37] The status of inhaled nitrite in China is ambiguous compared to other substances that are outright illicit.[33,37] A higher tolerance towards homosexuality in major cities of China might also drive higher usage of nitrite inhalants.[35]

In Japan, Hidaka et al.[26] indicated that amyl nitrites (63.2%) were the most commonly used substances among 2062 MSM studied, followed by 5-methoxy-diisopropyltryptamine (9.3%) and marijuana (5.7%). The researchers suggested that

TABLE 1 Studies on Inhaled Nitrite Use among Asian MSM.

Authors	Study design	Characteristics of subjects and sampling methods	Findings regarding the use of inhaled nitrites*
Choi et al.[22]	Cross-sectional study. Face-to-face interviews.	496 Asian and Pacific Islander MSM in San Francisco, USA met at gay-identified venues. Nationality breakdown as the following: 28% Filipino, 27% Chinese, 16% Vietnamese, 4% Japanese, 4% Thai, 3% Korean, 10% multi-ethnic, and 8% other Asian or Pacific Islander. Subject sampled through venue-based, time-space sampling procedures.	• The most common drugs used: ecstasy 19%; marijuana 14%; inhalant nitrites 11%; crystal methamphetamine 10%. • Frequent attendance to gay venues and circuit party were associated with being high or buzzed with substances, including poppers. Popper use was associated with multiple sex partners.Poppers are the single drugs associated with unprotected anal sex ((Odds ratio (OR): 3.29, 95% confidence interval (CI): 1.50–7.25), along with being buzzed or high (OR = 2.62, CI: 1.37–5.02)).
Hidaka et al.[26]	Cross-sectional study. Lifetime substance use was asked using an online questionnaire.	2062 Japanese MSM recruited from gay websites, magazines, and internet email listing.	• 34.5% never used a substance, 45% used one type of substance9.6% used >1 type of substance.The most common substance: amyl nitrite 63.2%; 5-methoxy-N,N-diisopropyltryptamine (5-MeO-MiPT) 9.3%; and marijuana 5.7%.
He et al.[27]	Cross-sectional study. The mode of administering the questionnaire was not mentioned.	200 HIV-positive MSM (mean age 36.29+10.09 years) in Shanghai. Snowballing method.	• Unsafe sex (anal/vaginal) was associated with getting drunk during sex, the use of amyl nitrites, having a casual male partner and an HIV diagnosis in the last 6 months.
Li et al.[28]	Cross-sectional study. A self-administered questionnaire using computer-assisted self-interviewing technology. HIV status screened using enzyme-linked immunoassay (ELISA) and confirmed using Western blot.	400 MSM (71.5% homosexual, 24.5% bisexual) in Beijing (mean age 30 ± 7.1 years). Recruited from websites, gay venues STD clinics, and via peer referral.	• 47.3% ever used nitrite inhalants, 42.3% used nitrite inhalants in the past year. The use of nitrite inhalants was associated with age <25 years, higher education, seeking sex via the internet, having casual partners in the past 3 months, and being HIV positive. • Recent use (for the past 3 months) was associated with higher education levels, seeking sex partners via the internet and having multiple partners.

			• 40.5% of users reported having sex with one person after use. 4.5% reported having sex with >1 person. 37.8% reported no change in the number of sexual partners. 36% reported an increase in sexual pleasure after use. 76.1% reported no change in the frequency of having sex after use. The prevalence of HIV was higher among ever users but the prevalence of syphilis was similar between users and nonusers.
Xu et al.[29]	Cross-sectional study. Face-to-face interviews using a structured questionnaire.	625 MSM in Shenyang, China. Snowballing method.	• 23.2% ever used recreational drugs. Alkyl nitrites 19.2%, methylmorphine 5.1%, methamphetamine 4.0%, ketamine 0.8%. In univariate analysis, the odds of HIV infection among popper users was 4.1 times higher (CI: 2.3–7.2) compared to nonusers. The odds of methamphetamine users were 1.8 times higher compared to nonusers.
Xu et al.[30]	Cross-sectional study. Face-to-face interviews using a structured questionnaire.	3830 MSM in six major cities in China (Kunming, Jinan, Changsha, Zhengzhou, Nanjing, and Shanghai). Recruited from websites, gay venues, STD clinics, and via peer referral.	• 28% ever used >1 substance in the past 6 months: Popper 26.5%, ecstasy 2.8%, ice 2.5%, amphetamine 0.7%, tramadol 0.4%, and ketamine 1.0%.
Chen et al.[31]	Cross-sectional study. Self-administered questionnaire.	826 MSM from Changsha. Recruited from gay-oriented venues (bars, night clubs, tea bars), internet, and sauna/bath/park.	• 21.4% had used club drugs prior to or during sex in the past 6 months. Poppers were the most popular drugs used (86.9%) among single drug users, followed by codeine phosphate (5.2%), ketamine 3.3%, methamphetamine 2.6%, and 2.0% ecstasy.
Lim et al.[32]	Cross-sectional study. Online survey.	1235 Malaysian from a multinational online survey, with a mean age of 33.98 ± 9.55 years. 55% had at least a college degree. Recruitment through a gay-oriented website.	• The most popular recreational drugs used were ecstasy 10.8%, erectile dysfunction medication 9.1%, crystal meth 7%, and poppers 6.5%. 13% consumed drugs before sex and 7.9% consumed alcohol before sex. 83.9% were negligible users, 8.7% were soft substance users (poppers/ecstasy), 7.5% were amphetamine-type stimulant users (ecstasy, crystal meth, GHB, and ketamine).

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TABLE 1 (*Continued*)

Authors	Study design	Characteristics of subjects and sampling methods	Findings regarding the use of inhaled nitrites*
Wang et al.[33]	Cross-sectional study. Face-to-face interviews.	576 MSM in Beijing, China. Snowballing method.	• 49.8% heard of rush/inhaled nitrites. The awareness was associated with being single (OR: 1.75, 95% CI: 1.03–2.96), cohabitation with men (OR: 3.83, 95% CI: 1.92–8.06) (both vs married to women), high education level (postgraduates vs senior high or lower-OR: 1.85, 95% CI: 1.07–3.20), and multiple male sex partners (OR: 1.66, 95% CI: 1.18–2.33). 28.3% of all subjects used the substance in the last 3 months. The proportion was 56.8% among those with the knowledge of rush. • Age group of 26–35 years (OR: 3.91, 95% CI: 1.67–9.17), <25 years (OR: 3.05, 95% CI: 1.44–6.46), multiple male sex partners (OR: 2.29, 95% CI:1.40–3.76) were associated with the use of inhaled nitrites. 70% believed long-term use of rush caused harm, 50–56.4% perceived some forms of sexual benefits (apart from maintaining an erection – 29.6%). • Perceived barriers to rush was generally low (6.2–15.7%), 60.3 and 54.7% stated that their male sexual partners and peers asked them to use rush. • Less than half state they could refuse rush if being asked (44.3–45.6%).
Chen et al.[34]	Cross-sectional study. Online questionnaire.	825 MSM in Guangdong Province >16 years (range 21–27 years), mostly with tertiary education. Recruited through a gay website.	• 14.8% reported the use of poppers in the past 3 months. The rate of use was higher among HIV positive individuals, subjects with anal intercourse in the last 3 months, and multiple sexual partners (two or more) in the past 3 months, had a casual partner, had an STD. • HIV testing (OR: 1.70, CI: 1.07–2.70), having a casual partner (OR: 1.67, CI: 1.12–2.50) and being sexually active with other men >5 years (OR: 1.87, CI: 1.05–3.31) was associated with popper use.

Lei et al.[35]	Cross-sectional study. The assisted questionnaire developed by the research team. HIV status screened by ELISA and confirmed by Western blot.	625 MSM in Changsha (aged 28.2 ± 6.4 years, range 17–68 years). 72.4% had tertiary education. 62.3% homosexual. Recruited from attendees of HIV testing and counselling services.	• 29.8% ever used poppers, and 18.8% among those were HIV positive. Among nonusers, 10.5% were HIV positive. Those with one-night-stand (ONS) 6–10 times in the past 6 months had 4.32 times odds (CI: 1.77–10.57) using poppers compared to those without ONS experience. Subjects self-identified as bottom or versatile had 2.99 (CI: 1.52–5.86) and 3.60 (CI: 2.13–6.09) times odds of using poppers compared to the top. The odds of those who used or ever used poppers to infect HIV was 1.88 (CI: 1.12–3.16).
Yang et al.[36]	Cross-sectional study. Self-administered questionnaire. HIV status was self-declared.	205 Hunan money boys recruited from gay dating websites. Respondent-driven sampling approach.	• 39% of the money boys used drugs in the last 3 months, of which poppers use was the highest 36.6%, followed by methamphetamine (12.7%). HIV testing and status were not related to drug use in this study.
Zhang et al.[37]	Cross-sectional study. Interviewer-administered questionnaire.	3588 MSM in Beijing aged 30 years (range 18–75 years), 71.9% had at least a college degree. Convenient sampling.	• 27.5% of men had used at least one type of drugs in the past 3 months, of which 26.8% used poppers. 63.7% of the popper users used poppers 1–3 times in the past 3 months. • Compared to nonusers, popper users were younger, never married, having higher education, higher income, seeking male partners through the internet. • Popper users had higher odds of being HIV positive (OR: 1.38, CI: 1.11–1.70) but not syphilis (OR, 1.06; CI, 0.80–1.40). Polydrug users had higher odds of being infected with HIV and syphilis. • Younger age (18–34 years vs 35–75 years) [adjusted OR (AOR): 1.56, CI: 1.25–1.94], higher education (college vs lower) (AOR: 1.61, CI: 1.33–1.96), alcohol use before sex (AOR: 1.32, CI: 1.10–1.60), seeking male partners via the internet (AOR: 1.60, CI: 1.28–2.00), multiple male sex partnership (AOR: 2.22, CI: 1.90–2.60), and unprotected receptive anal intercourse (AOR: 1.52, CI: 1.28–1.81) were associated with poppers used. Heterosexual partnership was negatively associated with popper use (AOR, 0.66; CI, 0.49–0.89).

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TABLE 1 (*Continued*)

Authors	Study design	Characteristics of subjects and sampling methods	Findings regarding the use of inhaled nitrites*
			• Popper use was not linked to male commercial sex 1.24 (0.80–1.90) and unprotected insertive anal sex 0.93 (0.53–1.62).
Zhang et al.[38]	Cross-sectional study. Online questionnaire.	501 HIV positive MSM with a mean age of 30.24±7.7 (18–63 years) years from Chengdu, Chongqing, Guangzhou. 63.5% of them had at least a college degree. Snowballing methods.	• Using alcohol (OR: 3.00, CI: 1.37–6.62) and poppers (OR: 3.53, CI: 1.71–4.33) during sex were associated with unprotected sex in the past 6 months. • At baseline, 29.8% had ever used nitrate inhalants during sex in the past 6 months. 1.6% reported the use of more than one drug. Compared to nonusers, nitrite inhalant users were younger, better educated, never married, had a higher monthly income, more likely in Beijing, drink alcohol and were infected with STI. More nitrate inhalant users sought sex partners via the internet, had fewer than 10 lifetime-sex partners, went to a clinic to have their nonregular sex partners tested for HIV or used condoms, not knowing their last nonregular male sex partners HIV status, and not having heterosexual intercourse. More users also had multiple sex partners, engaged in group sex, did not inform male sex partners of their own HIV serostatus. • The use of nitrate inhalant was associated with HIV infections (OR 2.0, 95% CI 1.1–3.7), but not syphilis infection (OR 1.0, 95% CI 0.5–2.0). In logistic regression, never married (AOR 3.0, 95% CI 1.0–8.7), residing in Beijing (AOR 3.9; 95% CI 1.6–9.3), not willing to test HIV with oral self-test (AOR 4.3, 95% CI 1.5–12.2), and seeking male sex partners via the internet (AOR 20.4, 95% CI 2.2–192.1) were associated with nitrate use. • At follow up, 63% MSM who used nitrate inhalants had sex without a condom compared with 50.9% of the nonusers.
Wang et al.[25]	Prospective study. Face-to-face interviews. HIV status screened using ELISA and confirmed by Western blot. Syphilis status screened using rapid plasma reagin and confirmed by ELISA.	510 (baseline) MSM with a median age of 28 (range 18–70) years. 50.4% had at least a college degree. Recruited in HIV clinics in Beijing and Nanning, China.	

Zhang et al.[40]	Cross-sectional study. Interviewer-administered questionnaire. Sexually transmitted diseases screened using ELISA. HIV status was confirmed using Western blot. Syphilis was confirmed using *Treponema pallidum* particle agglutination test.	500 MSM from Tianjin with a mean age of 29.7 ± 8.1 years (range 18–68 years). 86% were homosexual and 14% were bisexual. Recruited from volunteer groups, MSM venues, and HIV consultation clinics.	• 64% knew rush could increase sexual pleasure, 38.6% used rush at least once, of which 67.4% used within the recent 1 year. The mean duration of use was 1.5 years. Among those familiar with a rush, 60.0% heard about it after 2011, 35% between 2009 and 2011. 55% learnt about it through the internet, 38.8% knew it from homosexual partners, 36.9% from friends, and 49.4% had introduced rush to their friends. 55.4% did not know if rush had side effects, 30.6% thought it might have, and 2% thought it was safe. 42.2% were familiar with the side effects of rush, such as dizziness, severe palpitations, shortness of breath, blurred vision, erectile dysfunction, confusion, tinnitus, and vomiting. Reasons for using rush included increasing sexual pleasure 67.4%, required by partners 63.7%, pain relief during sex 33.7%, as sexual stimulus 17.1%, and drug dependence 14.0%. Source of rush: online shop 69.5%, friends 35.8%, overseas 7.4%, adult stores 3.2%. 67.4% used rush to increase voluptuous. No association between rush use and HIV and syphilis infection. • Rush users were more likely to work in companies (OR: 2.61; 95% CI: 1.65–4.12), live with homosexual partners (OR: 1.88, CI: 1.19–2.92), not live alone (OR: 2.26; 95% CI: 1.29–3.96), smoke cigarettes (OR: 1.49; 95% CI: 1.02–2.17), use alcohol (OR: 1.63; 95% CI: 1.12–2.39), seek sexual partners on the internet (OR: 2.59; 95% CI: 1.50–4.50).
Zhao et al.[41]	Cross-sectional study. Online questionnaire.	1142 MSM with a mean age of 25.5± 6.8 years, 68% had at least a college degree, 72.9% identified as gays. Recruited through a nationwide online survey.	• 77.3% of subjects reported ever use of recreational drugs in their lifetime. 21.3% used poppers, 2.4% used crystal meth, and 1.0% used ecstasy. • Compared to non-popper users, users are more likely to be tested for HIV (AOR: 1.50, CI: 1.15–1.96) and other STIs (AOR: 1.65, CI: 1.26–2.17), engaged in group sex (AOR: 2.63, CI:1.80–3.86), commercial sex (AOR: 1.86, CI:1.13–3.06), and used mobile apps to seek sexual partners (AOR: 2.10, CI:1.58–2.80). They were also more likely to be the receptive partners (AOR: 1.56, CI: 1.16–2.12). • 19.3% had ever used poppers. The prevalence of use showed an increasing trend (12.6, 27.6, and 20.8% between April 2014 and June 2015).

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TABLE 1 (*Continued*)

Authors	Study design	Characteristics of subjects and sampling methods	Findings regarding the use of inhaled nitrites*
Zhu et al.[42]	Cross-sectional study. Face-to-face interviews. HIV status screened using ELISA and confirmed using Western blot.	1721 MSM collected in three rounds of survey in Nanjing (Apr–June 2014, Oct–Dec 2014, Apr–June 2014). Recruited through community center, telephone, website.	• Poppers were linked with HIV infection (OR:1.676, 95% CI:1.201–2.339) but not syphilis and hepatitis C. • Popper users mainly aged <30 years, were not married, had at least a college education, lived in Nanjing less than 2 years, sought sex partners through the internet, and identified themselves as homosexual. Age <30 years, more than two sex partners in the past 6 months, diagnosed with STDs in the previous 1 year, using traditional drugs.
Duan et al.[39]	Cross-sectional study. Self-administered computer-based questionnaire. HIV status screened using rapid test and ELISA, and confirmed with Western blot. Syphilis screened using rapid test and *Treponema pallidum* particle agglutination test.	1935 MSM (mean age 29.3+/-8.4 years, range from 16 to 76 years) from Shenzhen 85.8% had at least senior high school education. Snowballing, time and location sampling, and respondent-driven sampling.	• 12.7% reported drug use in the past 6 months, 0.8% had used multiple drugs. 10.6% were using poppers. Drug use was associated with unmarried (AOR:1.83, CI:1.04–3.20), non-Han ethnicity (AOR: 2.46, CI: 1.05–5.78), having a higher education background/at least senior high school (AOR:1.95, CI:1.07–3.57), tested for HIV (AOR:1.52, CI:1.02–2.27) seeking male sex partners through the internet (AOR: 2.16, CI: 1.42–3.28), having two or more sex partners (AOR: 2.58, CI: 1.82–3.68), role as receptive during anal sex (AOR: 1.86, CI: 1.31–2.63), role as versatile (AOR: 1.93, CI: 1.25–2.99), having unprotected anal intercourse (AOR:1.37, CI:1.01–1.87). It is also related to a higher risk for HIV and syphilis infection. Popper use was associated with seeking male sex partners via the internet (AOR: 2.43, CI: 1.56–3.78), having multiple sex partners (AOR: 3.65, CI: 2.60–5.11), practising receptive sexual role (OR: 1.57, CI: 1.15–2.13) and unprotected anal intercourse (AOR: 1.46, CI: 1.08–1.98), and having HIV infection (AOR: 1.76, CI: 1.16–2.68), and syphilis infection (AOR: 1.82, CI: 1.23–2.70).

Chen et al.[43]	Cross-sectional study. Paper-based self-administered questionnaire. HIV status and test history were self-declared.	MSM in three cities (Deyang, Xichang, and Yibin) of Sichuan province, with a mean age of 30±9 years. 44.1% at least have a college education. Sampling through community-based organization during consultation and testing service and outreach program, and peer-referral.	• 27.7% of subjects reported the use of at least one recreational drug, of which 36% were polydrug users. Of these subjects, 24.1% reported the use of poppers, followed by methamphetamine 7.1%, zero capsules 6.1%, and magu 2.0%. • Popper users tend to be younger, single, more likely to find sex via the internet, prone to practice unprotected anal intercourse with regular sex partners in the past 12 months, engaged in group sex and showed a higher prevalence of self-reported STI (gonorrhea, condyloma acuminate, or syphilis infection, excluding HIV). • It is not related to education level (college vs below). Popper use was associated with risky sex behaviors, including group sex (OR: 1.88, CI: 1.25–2.83) and unprotected anal intercourse with nonregular partners (OR: 1.44, 95% CI: 1.01–2.05).
Chu et al.[23]	Longitudinal study. Face-to-face interviews. HIV status screened using ELISA and confirmed using RT-PCR. Syphilis status screened using rapid test and confirmed using the *Treponema pallidum* particle agglutination test.	475 HIV-negative MSM from Shenyang (Liaoning Province). Recruited through voluntary counselling and testing center.	• 23.4% were ever popper users, 4.8% ever used methamphetamine. 18.9% used poppers in the recent 3 months, and 2.9% methamphetamine. • Age <30 years (AOR: 2.3, CI: 1.2–4.3), residence outside Liaoning (AOR: 2.0, CI: 1.1–3.6), ever in commercial sex (selling sex) (AOR: 3.4, CI: 1.4–8.0), seeking sex via the internet (AOR: 2.8, CI: 1.5–5.1), group sex in the past 3 months (AOR: 23.1, CI: 4.1–130.6) were predictors of popper use. • In the follow-up, people who used or ever used poppers had higher bacterial STI (syphilis) infection than the never-use group. The HIV incidence was higher among popper users over the 2 years follow-up (three times higher compared to nonusers: 15.5 vs 4.6/100). • Popper use, having >1 male partner, group sex, unprotected anal intercourse (inconsistent use condom) with regular or casual male partners, and baseline syphilis positivity predicted HIV seroconversion.
Guo et al.[24]	Longitudinal study. Face-to-face interviews. HIV and syphilis status screened using ELISA. HIV confirmed with Western blot, syphilis using tolulinized unheated serum test.	4305 MSM followed during 2013–2015. Subjects recruited in Tianjin, Harbin, Chong Qing, Nan Jing, and Xi An. Their mean age at baseline was 29.87±9.29 years. Recruited through gay-oriented values and website.	• 15.3% (of 1186), 21.9% (of 2567), and 21.6% (of 552) of the subjects seeking partners at bars, through the internet and baths used poppers. Poppers' use was associated with higher HIV seroconversion (new case) after multiple adjustments (OR: 1.55, CI: 1.10–2.17).

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TABLE 1 (*Continued*)

Authors	Study design	Characteristics of subjects and sampling methods	Findings regarding the use of inhaled nitrites*
He et al.[44]	Cross-sectional study. Face-to-face interviews. HIV status screened using ELISA and confirmed using Western blot.	555 MSM recruited in Hangzhou with a median age of 31 years (IQR=26–40 years). 59.35% were bisexual, 38.9% were homosexual. Snowballing method at counselling and testing centers, baths, bars, social media, and other gay venues.	• 18.2% used a drug in the past 3 months, of which 65.3% used poppers, and the others used ketamine 10.9%, methamphetamine 8.9%, ecstasy 5.9%, and the rest used combinations. Popper used was not related to HIV infection.
Luo et al.[45]	Cross-sectional study. Face-to-face interviews. HIV status screened using ELISA and confirmed using Western blot.	3135 MSM from 16 cities (Beijing, Tianjin, Changchun, Harbin, Shanghai, Nanjing, Hangzhou, Wuhan, Guangzhou, Shenzhen, Nanning, Chengdu, Chongqing, Kunming, Xi'an, and Wulumuqi). Recruited from HIV counselling and testing services at the selected community-based organization.	• 39.8% reported ever use of synthetic drugs. 96.3% reported the use of inhaled poppers. Drug users tend to be younger (<30 years), single, more educated (at least college education) and have MSM activity more than once per week, >1 sexual partner, participated in male group sex, penetrative sexual behavior >20 min, and consistent condom use with male partners. Drug users (10.6%) were more likely to be infected with HIV compared to nonusers (6.0%) (adjusted OR: 2.04, CI: 1.56–2.70).
Zhou et al.[48]	Intervention study-education and behavior intervention to encourage protective anal intercourse. Face-to-face interviews.	1007 Tianjin MSM followed up for 6 months. Recruited from MSM venues, websites, and social applications.	• 184 out of the 823 subjects used poppers. Popper use was associated with unprotective anal intercourse during the follow-up period.
Tuo et al.[46]	Cross-sectional study. Online questionnaire. HPV infection was confirmed using the genotyping of swab samples.	651 MSM in Urumqi recruited publicly or through the internet.	• Poppers' use was associated with human papillomavirus infection (OR: 2.21 CI: 1.53–3.19) after multiple adjustments.

**The terms "poppers", "rush", "nitrites inhalant", and "inhaled nitrites" refers to the same substance.*

the highest usage was attributable to the efficacy of inhaled nitrites, a false sense of security among the users due to the ambiguous legal status of the drugs, and false perception of their medical safety.[26] An online study in Malaysia (n = 1235) reported that 6.5% of the MSM acknowledged taking inhaled nitrites before sex. The usage was lower compared to ecstasy (10.8%), medication for erectile dysfunction (9.1%), and crystal meth (7%).[32] Among Asian and Pacific Islander MSM in San Francisco, USA (n = 496), the usage of inhalant nitrites (11%) ranked below ecstasy (19%) and marijuana (14%).[22] However, this study excluded non-English speakers who did not visit gay venues.

Overall, inhaled nitrites were the most common recreational substance used among Asian MSM, but in the Western countries, they ranked behind marijuana.[13,49] Bias in the reporting of the prevalence of inhaled nitrite use is possible since substance use and homosexuality are still a taboo in Asian countries. In general, social desirability bias may prevent the subjects from disclosing the use of substances truthfully. Due to the illegal status of other substances, the over-representation of nitrites in the substance used by Asian MSM cannot be neglected. The difference in "recent use" and "lifetime use" has also influenced the prevalence values.

Correlates of inhaled nitrite use

The use of inhaled nitrites was more prevalent among younger MSM. Multiple studies of cities in China reported that younger age was associated with increased inhaled nitrite use.[23,25,28,37,42,43] Specifically, Zhang et al.[40] reported that more MSM in Beijing aged 18–34 years were users compared to 35–75 years. Other studies reported that more MSM nitrite users belonged to the age group of <25 years or <30 years compared to other age groups.[23,28] This was in line with the general age trend of MSM substance users (including nitrites) in China.[29–31] The study in Japan indicated that significantly more MSM aged 30–39 years were users compared to those aged 14–19 years.[26]

Inhaled nitrite use was also associated with a higher education level in most of the studies.[25,28,33,37,42] A study in Beijing, China (n = 576), reported that MSM with a postgraduate degree were more likely to use inhaled nitrites compared to those with senior high school education.[33] Whereas in Nanjing, China (n = 1721), MSM with at least a high school education were more likely to be users.[42] Younger age and better education levels may imply better technical ability to source inhaled nitrites through the internet.[28] In contrast, the trend of overall substance use (including inhaled nitrites) with respect to education level was more heterogeneous, whereby it was linked with a higher[39,44,45] or lower education level.[26,31] Two studies highlighted that increased income was associated with inhaled nitrite or substance (inclusive of nitrites) use among MSM.[25,30] Zhang et al.[40] also reported that poppers users were more likely to be corporate workers. Overall, these studies suggest that young professional population with disposable income are more likely to engage in inhaled nitrite use.

Major cities in China with a large immigrant population also reported high inhaled nitrite use. In Beijing, the capital of China, the MSM population was suggested to be more educated, internet-savvy, and had a higher income, thus was technically and financially capable of sourcing inhaled nitrites.[25] In Shenzhen, China, substance use (including nitrites) among MSM was associated with the immigrant population of the city, whereby the non-Han MSM population was 2.5 times more likely to use the substance.[39] In Shenyang, China, immigrants from other cities were two times more likely to be inhaled nitrate users.[23]

Besides, studies identified that inhaled nitrites were commonly used together with other substances. Alcohol use before sex was associated positively with inhaled nitrite use among 3588 Beijing MSM.[37] Similarly, a two-city study (Beijing and Nanning, n = 1721) reported that alcohol use was related to nitrites use.[42] The concurrent use of substances like alcohol with inhaled nitrites may preclude a rational

judgment of the users, leading to high-risk behavior during intercourse.

A study among money boys in Hunan reported that having a wider social network was a risk factor of substance use (including inhaled nitrites).[36] The researchers hypothesized that a wide social network indicated higher exposure to negative elements from friends and higher peer pressure to use inhaled nitrites.[36]

Knowledge and perception of users towards inhaled nitrites

A study by Zhang et al.[40] (n=500) in Tianjin reported that 60% of MSM learned about inhaled nitrites after 2011. This observation implies that the proliferation of inhaled nitrites in China is rather recent compared to Japan and the West. The study also identified that the internet was the most important source of knowledge on nitrites (55%), followed by homosexual partners (38.8%) and friends (36.9%).[40] Peers played a critical part in the propagation of nitrite use among MSM because 49.4% of the surveyees had introduced the substances to their friends.[40] Alarmingly, 55.4% of MSM did not know whether inhaled nitrites had side effects, whereas 42.2% were familiar with the side effects of nitrites, such as dizziness, severe palpitations, shortness of breath, blurred vision, erectile dysfunction, confusion, tinnitus, and vomiting.[40] Reasons to use nitrites as indicated by subjects included increasing sexual pleasure (67.4%), requested by partners (63.7%), reducing pain during sex (33.7%), as sexual stimulus (17.1%), and drug dependence (14.0%).[40] The subjects sourced inhaled nitrites through online shops (69.5%), friends (35.8%), overseas (7.4%), and adult stores (3.2%).[40]

On perception, 36% of MSM in Beijing (n = 400) reported increased sexual pleasure after the use of inhaled nitrites.[28] Similarly, in another study by Wang et al.[33] in Beijing (n = 576), 50–56.4% of MSM nitrite users perceived some forms of sexual benefits after using nitrites. Only 29.6% indicated that it helped to maintain the erection.[33] On perceived severity of nitrites, 70% believed long-term use could cause harm to their body. Another 6.2–15.7% mentioned a low barrier to obtain inhaled nitrites.[33] In addition, 60.3 and 54.7% of MSM revealed that their male sexual partners and peers asked them to use nitrites, and less than half (44.3–45.6%) perceived that they could refuse when being asked.[33]

Overall, a significant proportion of MSM did not know about the side effects of inhaled nitrites. Apart from sexual pleasure, many of them were motivated by their partners or peers to use nitrites and they could not refuse the offer. Previous studies did not further investigate the reasons for this, but loneliness and fear of rejection/exclusion may play a role.

Sexual behaviors of nitrites users

Inhaled nitrites were commonly used by MSM who are receptive or versatile.[35,39,41] A study among MSM in Changsha (n = 625) demonstrated that receptive partners were three times, and those who were versatile were 3.6 times more likely to use inhaled nitrites compared to insertive partners.[35] This observation may be related to the pharmacological action of inhaled nitrites, which relax the anal sphincter and results in reduced pain during anal intercourse.

Inhaled nitrites have also been associated with risky sexual behavior, for instance, unprotected sexual intercourse.[37,39,43,48] Specifically, it had been linked to unprotected receptive intercourse rather than unprotected insertive intercourse.[37] Considering the duration of action for nitrites is short, they may not impair the judgment of users significantly. Therefore, inhaled nitrites use may be an indicator of risky sexual behavior and concomitant substance use rather than the cause. Correspondingly, nitrites users were more likely to have multiple sex partners,[25,33,37,39,42] casual sex partners,[28,34] be involved in group sex.[23,25,41,43] As nitrite users were likely to be internet savvy, they were prone to find sexual partners through the internet or mobile applications.[23–25,28,37,39–43] Nitrite users also identified their sexual partners in gay baths and

bars.[24] The users were also less likely to mention their HIV serostatus to their male sex partners or to ask the HIV status of their sexual partners.[25]

Concerning involvement in commercial sex, some studies identified that it was linked with inhaled nitrite use[23,41] but others did not.[37] The type of commercial sex might influence the pattern of drug use. Yang et al.[36] suggested that money boys in Hunan province, China, who serviced in gay clubs used soft drugs (including inhaled nitrites) while street sex workers used hard drugs more commonly. The money boys indicated that the request of clients and the need to approach clients without emotional connection were reasons for substance use.[36] In a study conducted in Shenzhen, China, 26.3% of the surveyed MSM were money boys, but the prevalence of substance use was surprisingly low (2.9%) compared to the general MSM population (16.1%).[39] This might be due to a higher perceived risk in this population.[39]

Some studies demonstrated inhaled nitrite users were more likely to be diagnosed with HIV, syphilis, human papillomavirus, and other STDs.[23–25,27,28,37,39,41–43,46] In a prospective study in Shenyang (n = 475), MSM subjects who indicated ever use of inhaled nitrites had a higher rate of syphilis and HIV infection after 2 years.[23] Again, this may be an indicator of users' risky sexual behavior. Researchers highlighted that nitrite users might be more knowledgeable about HIV and more likely to go for HIV testing.[25,34] This might be related to their higher perception of the susceptibility of HIV among nitrites users due to their risky sexual behaviors. This observation has been reported by other studies in the West, whereby nitrite users were more likely to use pre-exposure prophylaxis to prevent HIV infection.[16,50] A study suggested that repeated testing could create a false sense of safety, leading to risky sexual behaviors.[25]

Perspectives

The literature search revealed that studies on the use of inhaled nitrites among the Asian population are very limited. Most of the studies were performed in Chinese cities and sporadic studies in Japan and Malaysia were found. Because of this limitation, the readers should be cautious that these sporadic studies should not be generalized to represent the whole country. We do not exclude the possibility that literature published in non-indexed local journals or other languages may be overlooked. The lack of studies may also stem from the fact that homosexuality and substance use remains a taboo subject in conservative Asian societies. Social stigma and discrimination could result in the isolation of MSM and the homosexual population. Previous studies also reported that internalized homophobia due to societal discrimination could lead to substance use and risky sexual behaviors.[51,52] Thus, substances to enhance sexual experience may provide a temporary escape for these populations. The fear of rejection makes turning down offers to use substances before sex a challenge.[33] Anti-discrimination education towards homosexuality, promoted by either government and nongovernmental organizations, could reduce stigmatization and risky health behaviors among MSM.

Proper legislation on the development, production, distribution, sales, and possession of inhaled nitrites may be a straightforward approach to deal with the abuse of this substance. However, the experience of regulating inhaled nitrites in the United States revealed that manufacturers would always adopt innovative approaches to circumvent any new rules as long as there is a demand for similar substances. Following the outlaw of amyl nitrites and alkyl nitrites, similar products were now sold in the disguise of performed and tape cleaners.[1]

Hence, it is important to educate Asian MSM, who are recently introduced to inhaled nitrites, regarding the safety and adverse side effects of this substance. However, it is impossible to depend on governments that are generally unfriendly to homosexuality and MSM on this task. Local nongovernment organizations with a concern about health issues among MSM should take an active part in this regard. Since nitrite users tend to be younger and internet savvy, creative social marketing via mobile apps, and the internet

may be a viable method to engage and educate this population about inhaled nitrites. Community and peer-lead intervention programs may be beneficial to MSM substance users who felt isolated.[53]

CONCLUSIONS

The current review demonstrated that inhaled nitrites are one of the most popular recreational substances in the Asian region, at least among major cities in China, since its emergence and it is popular among young MSM with high accessibility to the internet. A substantial proportion of MSM is not aware of the adverse side effects of inhaled nitrites, which might lead to numerous health issues in the long run. Nevertheless, more research on nitrites use in Asian countries with diverse cultural backgrounds is needed. Inhaled nitrite use is also reflective of risky sexual behavior and predicts HIV seroconversion and STD infection. The hidden nature of MSM in Asian societies demands innovative methods to address this problem.

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