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Nitrous Oxide Inhalation Among Adolescents: Prevalence, Correlates, and Co-Occurrence with Volatile Solvent Inhalation

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Abstract

Few studies have examined the prevalence of nitrous oxide (NO) inhalation or co-occurrence of NO and volatile solvent (VS) use in adolescents. Study aims were to (1) describe the independent and conjoint prevalence of NO and VS use in incarcerated youth, (2) compare adolescent users of both NO and VS inhalants (NO+VS) to users of NO-only, VS-only, and nonusers of NO and VS (NO/VS nonusers) with regard to demographic, psychological, and behavioral characteristics, and (3) conduct logistic regression analyses identifying correlates of NO use. Residents (N = 723) of Missouri Division of Youth Services were assessed with standardized psychosocial measures. Participants averaged 15.5 (SD = 1.2) years of age, were ethnically diverse and predominantly male. Lifetime prevalence of NO use was 15.8%. NO+VS users evidenced greater impairments compared to NO+VS nonusers. VS-only users evidenced impairments that were similar in kind but at lower prevalences compared to those displayed by NO+VS users, whereas NO-only youth had profiles that were similar to those of NO/VS nonusers. Psychiatric disorders, polydrug use, and temperamental fearlessness were correlates of NO use. NO+VS users were at high risk for behavioral and emotional problems. Screening and interventions for NO and VS inhalant use should be implemented in juvenile justice facilities.

Keywords

co-occurring disorders; juvenile justice; nitrous oxide; substance abuse; volatile solvents

Since the late eighteenth century, nitrous oxide (NO) has been inhaled to induce altered states of consciousness. Luminaries such as Samuel Taylor Coleridge, William James, and James Watt (inventor of the steam engine) self-administered the gas to facilitate metaphysical exploration. Although its abuse liability has been a matter of contention (e.g. Gillman 1995, 1992; Zacny et al. 1995), NO has become a significant drug of abuse among U.S. adolescents. NO users inhale the gas from balloons filled by tanks used in dental or automotive supply, from whipped cream dispensers that release gas stored in “chargers” or steel cartridges used as a propellant in whipped cream, or directly from whipped cream containers that are purchased at grocery stores. NO intoxication is characterized by euphoria, incoordination, dissociation, and hallucinatory experiences (Brouette & Anton 2001). While the current pattern of usage in teens is poorly understood, deleterious

biopsychosocial sequelae associated with recurrent NO use have been described in the literature and are discussed below.

NO is a simple molecular compound comprised of two nitrogen atoms to every one oxygen atom. An odorless and colorless gas with analgesic and anesthetic properties, NO has been used to allay anxiety and reduce discomfort during brief, painful medical procedures, such as those commonplace to dentistry (Malamed & Clark 2003). NO's therapeutic properties are thought to derive from its activation of *mu* and *kappa* opioid receptors in the dopamine circuitry of the nucleus accumbens (Lichtigfeld & Gillman 1996) and modulation of noradrenergic neurons in the brainstem (Sawamura et al. 2000). As an alternative to benzodiazepines, NO also has therapeutic potential as a treatment for mild to moderate alcohol (Gillman, Lichtigfeld & Young 2007), cannabis (Gillman, Harker & Lichtigfeld 2006), and cocaine (Gillman, Lichtigfeld & Harker 2006) withdrawal symptoms. While NO has accepted clinical utility, professionals who have ready access to the substance (e.g. dentists, medical students, and hospital staff) are at elevated risk for NO misuse, abuse, and dependence (Blanton 2006; Rosenberg, Orkin & Springstead 1979; Seidberg & Sullivan 2004).

Clinical case studies reveal the potential neurotoxicity of NO abuse. Putative mechanisms of neurotoxic effects have been postulated, including inactivation of vitamin B₁₂ resulting in neuronal demyelination (Cartner, Sinnott & Silburn 2007; Doran et al. 2004) and disruption of DNA synthesis (Stacy, Di Rocco & Gould 1992), as well as inhibition of NMDA receptors, stimulation of dopaminergic and noradrenergic neurons, and adrenergic sympathetic activation (Waters et al. 2005; Stacy, Di Rocco & Gould 1992). Spinal myoclonus (Wu et al. 2007), sensorimotor polyneuropathy (Lin et al. 2007), paralysis (Cartner, Sinnott & Silburn 2007), abnormal brainstem activity (Lin et al. 2007), cervical myelopathy (Diamond et al. 2004), and other neurological abnormalities (Iwata, O'Keefe & Karanas 2001) have been associated with acute and chronic NO abuse. NO abuse has been observed in conjunction with cognitive problems including memory (Duarte et al. 2008) and attentional (Estrin et al. 1988) impairments. Serious psychological consequences have been associated with NO intoxication, including depression (Brouette & Anton 2001), other mood disorders (Grigg 1988), and psychosis (Brodsky & Zuniga 1975; Sethi et al. 2006).

Recent psychopharmacological research indicates that NO may have mechanisms of action that are distinct from those of volatile solvent (VS) inhalants (e.g., toluene) and NO reportedly produces markedly more pleasant, psychedelic experiences (Beckman, Zacny & Walker 2006). This distinctive psychopharmacological profile may lend to its appeal as a recreational drug of abuse for youth. Among a sample of first-year college students in New Zealand, 12% reported using NO only episodically, whereas 3% reported using the drug monthly (Ng et al. 2003). According to data from the 2000/2001 National Household Survey on Drug Abuse, approximately 9.0% of U.S. 12- to 17-year-olds had used inhalants and, of these, 21.7% reported lifetime NO use, making NO use the fourth most prevalent specific class of inhalants used nationally among adolescents, with a lifetime prevalence of use estimated at 2.0% (Wu, Pilowsky & Schlenger 2004). Few studies have described the epidemiology of NO use generally or in juvenile justice or adolescent clinical populations (Sakai et al. 2004; McGarvey, Canterbury & Waite 1996), and to our knowledge, none have attempted to discriminate the sociodemographic and psychosocial profiles of adolescent NO and VS users. This lack of differentiation in the inhalant literature is unfortunate, given the potential pharmacological distinctiveness of NO and VS inhalants (Duarte et al. 2008; Beckman, Zacny & Walker 2006) and the claims for NO's low abuse potential (Gillman 1995).

To help fill this gap in the literature on adolescent NO and VS inhalant use, this report presents findings from a relatively large and a detailed assessment of polyinhalant use in adolescents. The aims of the investigation were to (1) describe the prevalence of NO use in a state population of youth in residential care for antisocial behavior, including NO use independent of and co-occurring with VS inhalant use, (2) compare youth with histories of both lifetime NO and VS inhalant use (NO+VS), to users of NO-only, VS-only, and youth who had never used nitrous oxide or volatile inhalants (NO/VS nonusers) with regard to sociodemographic, psychiatric, behavioral, and attitudinal characteristics, and (3) conduct multivariable logistic regression analyses identifying correlates of lifetime NO use.

Methods

Study Sample

Residential rehabilitation services of the Missouri Division of Youth Services (DYS) are provided at 27 facilities statewide. Facilities range in size from eight to 102 beds. DYS is the legal guardian of residents ages 13 to 17 committed to its care by the state's juvenile courts. The DYS client population is representative of incarcerated youth nationally with regard to the age, gender and number of state youth incarcerated per 100,000 adolescents (Sickmund 2002).

The 4 DYS regions were targeted for interviewing in sequential order. Within regions, residential facilities were surveyed sequentially. All residents at a facility were recruited for participation at the time interviewing at that facility commenced. No youths who had completed the interview at one facility were reinterviewed at another facility. Interviewing was completed over a three-month period in 2004. Youth completed the interview in one 30 to 90 minute session, the length depending principally on the respondent's inhalant use history. Youth were allowed brief breaks during the interview if they became fatigued.

All current DYS residents (N = 740) were eligible to participate in the study. A total of 723 youth were available to be interviewed, agreed to participate, and completed the interview. Youth who completed the interview constituted 97.7 % of DYS residents at the time interviewing was conducted.

Interviews were conducted by graduate social work student interviewers; seven core interviewers completed 530 (73.3 %) interviews. Interviewers completed an intensive training session and an interview editor was on-site at each facility as youth were interviewed to minimize interviewer errors. Interviews were conducted in large rooms at each facility that provided private areas where confidential one-on-one interviews could be conducted. Youth signed informed assent forms and were provided with \$10.00 to their facility monetary accounts (and a receipt for such) for completion of the interview. The informed assent form and interview protocol provided residents with detailed information about the study, name and telephone number for a nonstudy or university-affiliated advocate who they could call for more information about the study, assured youth that they were not required to participate, could cease participation at any point, and that their legal status would not be affected by their participation or nonparticipation in the study. As legal guardian of all youth, DYS provided formal permission for youths to participate in the study. The informed consent and study protocols were approved by the Missouri DYS IRB, Washington University Human Studies Committee IRB, federal Office of Human Research Protection, and were granted a Certificate of Confidentiality by the National Institute on Drug Abuse.

VSSI Measures

All youth completed the Volatile Solvent Screening Inventory (VSSI), an interview developed by Howard and colleagues (2008) assessing demographic characteristics, medical history, lifetime/annual use of 65 inhalants, other drug use and substance-related problems, current psychiatric symptoms, thoughts of suicide/actual suicide attempts, trauma history, antisocial traits and delinquent behavior. The following measures were used in the analyses reported below.

Demographic factors—Gender, age, self-reported racial status, family receipt of public assistance, and geographical area of family residence (i.e., urban, suburban, small town, rural) were recorded for each youth.

Neuropsychiatry history—Respondents were asked whether (yes or no) they had ever experienced a head injury with extended loss of consciousness, been diagnosed with a mental disorder by a psychiatrist or other doctor, or “heard voices of people who were not actually there.” Respondents were also asked to report all currently prescribed psychotropic medications they were taking.

Nitrous oxide use—NO use was assessed with the following three items from the VSSI inhalant assessment: “Have you ever inhaled or ‘huffed’ nitrous oxide (‘laughing gas’) through your nose or mouth in an effort to get high? (note to interviewer: ensure that NO use was *not* at the dentist and was *not* actually helium use); “Have you ever inhaled or ‘huffed’ whippets (i.e. carbon dioxide canisters containing nitrous oxide) through your nose or mouth in an effort to get high?; and “Have you ever inhaled or ‘huffed’ gas from whipping cream cans through your nose or mouth in an effort to get high? Respondents answering affirmatively to one or more of these three items were considered lifetime NO users. Most youth were familiar with the term “huffing” and few respondents evidenced any difficulty in understanding the meaning of the NO use questions. Interviewers were carefully trained to record only illicit NO use occurring in conjunction with an acknowledged intention to get high.

If youth answered affirmatively to a specific question about NO use, they then were asked whether they actually got high when they used NO in that manner (yes or no), the number of days they had used NO in that manner in their lifetime (less than five, five to 10, 11 to 99, 100 or more), and about the frequency of their NO use in that manner in the year preceding their current treatment episode (once, two to four times, five to 10 times, once a month, every two to three weeks, once a week, two to three times a week, once a day, and two to three times a day).

Volatile solvent use—Respondents were also questioned about their use of 55 VS inhalants. For each VS inhalant, youth were asked, “Have you ever inhaled or ‘huffed’ [inhalant] through your nose or mouth in an effort to get high?” Among the VS inhalants assessed were categories of paint-related products (e.g., paint thinner), glues or cements (e.g., airplane or model glue), shoe products (i.e., shoe shine/polish), gases (e.g., propane), aerosols (e.g., air freshener), cleaning agents (e.g., spot remover), and miscellaneous volatile solvents including nail polish, nail polish remover, correction fluid, gasoline, permanent markers, and carburetor cleaner. Respondents who reported any use of one or more of these 55 VS inhalants with the intention of getting high were considered lifetime VS inhalant users. Inhalation of nitrites and nonpsychoactive gases (e.g., helium, bottled oxygen) was assessed but was not, for the purposes of this investigation, considered VS inhalant use consistent with current diagnostic practices (APA 2000).

Other substance use—Use of 20 categories of psychoactive substances (e.g., cocaine) was assessed. For each psychoactive agent, youth reported whether or not they had ever used the drug (yes or no) and their age at first use of the drug. Total lifetime use of drugs used was computed by summing the number of affirmative responses across all 20 categories of use.

Other Measures

Substance-related problems—Lifetime substance-related problems were assessed with the eight-item Alcohol/Drug Use Problems Scale of the Massachusetts Youth Screening Instrument—2nd Version (MAYSI-2; Grisso & Barnum 2000) developed for use with juvenile justice populations. Youth responded “yes” or “no” to questions about whether they had ever been drunk or high at school, had used alcohol and other drugs at the same time, had ever been so drunk or high they couldn't remember what happened, used alcohol or other drugs to help them feel better, had gotten into trouble while high or drinking, (if yes) whether or not that trouble had been fighting, had done anything they wished they hadn't while drunk or high, or had their parents think they drink too much. Scores could range from zero to eight. Grisso and Barnum (2000) found the scale to be internally consistent ($\alpha = .86$) in their norming sample; the α coefficient in this study was .83.

Suicidal ideation and attempts—Youth completed the 5-item MAYSI-2 Suicide Ideation scale, which requires youth to respond “yes” or “no” to questions assessing whether or not they have ever wished they were dead, have felt like life was not worth living, have felt like hurting themselves, have felt like killing themselves, and have ever given up hope for their life. Grisso and Barnum (2000) reported a α reliability of .83; the α coefficient in this study was .91.

Lifetime trauma—All respondents completed a four-item Traumatic Experiences scale adapted from the MAYSI-2 ($\alpha = .69$ in the current study). Youth were asked to indicate whether or not (yes or no) they had ever seen someone severely injured or killed in person (not in the movies or on TV), had a lot of bad thoughts or dreams about a bad or scary event that happened to them, had ever been badly hurt, or been in danger of getting badly hurt or killed, and had ever in their whole lives had something very bad or terrifying happen to them.

Current psychiatric symptoms—All respondents completed the Brief Symptom Inventory (BSI; Derogatis 1993), consisting of 53 items assessing the extent to which youth were “bothered or disturbed” (0 = not at all; 4 = extremely) by a variety of thoughts or feelings “over the last seven days including today.” The BSI yields a global index of overall current psychiatric distress (possible range = 0 to 212, $\alpha = .96$ in current study). For this study, raw scale total scores were calculated for four of the nine primary symptom dimensions: depression, anxiety, obsessive-compulsive, and psychoticism. Raw scale total scores were used; subscale α reliabilities ranged from .70 to .83.

Antisocial traits—Youth completed the Antisocial Process Screening Device (APSD, Vitacco, Rogers & Neumann 2003), a 20-item scale assessing features of juvenile psychopathy, including subscales assessing narcissism, impulsivity, and callous unemotionality. Respondents were read 20 statements and asked to indicate to what extent each statement describing characteristic attitudes or behaviors was true of them (0 = not at all true, 1 = sometimes true, 2 = definitely true). The APSD also yields a total psychopathy score ($\alpha = .70$).

Study participants also completed the 56-item Psychopathic Personality Inventory—Short Version (PPI-SV; Lilienfeld & Andrews 1996). Youth were asked to decide to what extent each of the personality characteristics described in each statement were false or true as applied to them (1 = false, 2 = mostly false, 3 = mostly true, 4 = true). Total scores could range from 56 to 224 ($\alpha = .76$). In addition to the total score, two of the eight subscales of the PPI-SV were selected for use in this study, including Fearlessness and Impulsive Nonconformity.

Delinquent behavior—The Self-Report of Delinquency (SRD; Elliott, Huizinga & Menard 1989) was used to assess how many times in the year before they were incarcerated youth engaged in seven nonviolent and 10 violent crimes. Responses could range from 0 (never) to 8 (two to three times a day) for each item. Total SRD scale scores could range from 0 to 136 ($\alpha = .84$).

Study Subgroups

Responses on the VSSI to nitrous oxide and volatile solvent use items were used to define four mutually exclusive study subsamples of interest: youth with lifetime use of both NO and VS inhalants (NO+VS, $N = 103$), youth who had used NO but not VS inhalants (NO-only, $N = 11$), youth who had used VS but not NO inhalants (VS-only, $N = 164$), and youth who had used neither NO nor VS inhalants (NO/VS nonusers, $N = 445$).

Data Analysis

Bivariate comparisons of the four subgroups were conducted using chi-square tests and Fisher's exact tests for categorical variables and one-way analysis of variance (ANOVA) with Bonferroni post-hoc comparisons for continuous variables. Associations were also tested using multivariate logistic regression analyses. Because of the exploratory nature of this study, we believed it was overly conservative to apply corrections for multiple comparisons. Instead, we summarized significant relationships using effect size estimates (i.e., Cramer's V and partial eta-squared).

Results

Characteristics of Overall Sample and NO and VS Inhalant User Subgroups

Overall sample—The average age of the total sample of 723 was 15.5 ($SD = 1.2$). Most participants were male (87.0%) and lived in urban (39.1%) or small town (39.6%) areas. Participants were racially diverse ($N = 400$ Caucasian, 55.4%; $N = 238$ African American, 33.0%; $N = 28$ Hispanic, 3.9%, and $N = 56$ bi/multi-racial, 7.7%) and a substantial minority (40.3%) reported that their families currently received public assistance. Medical histories that included head injury with loss of consciousness (18.3%) and mental illness diagnosed by a psychiatrist or other physician (51.4%) were relatively common. A large percentage (42.3%) of youth was currently taking prescribed psychotropic medication.

NO and VS inhalant user subgroups—Table 1 provides information about the study inhalant users subgroups. NO/VS inhalant nonusers constituted 61.5% of the overall sample, whereas NO+VS, NO-only and VS-only inhalant users constituted 14.2%, 1.5%, and 22.7% of the total sample, respectively. In the total sample, lifetime VS use was 2.3 times more common than lifetime NO use ($Ns = 267$ vs. 114, respectively). Approximately 38.5% of VS users had used NO, whereas 90.0% of NO users had used VS inhalants.

Large inhalant subgroup differences were observed with respect to neuropsychiatric history variables, with approximately four in five NO+VS users (77.7%) having received a mental disorder diagnosis followed by 58.9% of VS-only, 42.9% of NO/VS nonusers, and 36.4% of

NO-only users. Among all the variables examined at the bivariate level, this association had the strongest effect size ($V = .25$). Findings for a history of hearing voices followed the same sequence with the highest prevalence rates observed for NO+VS (24.3%) and VS-only (20.1%) inhalant users, followed by NO/VS inhalant nonusers (10.6%) and NO-only users (9.0%), although this effect size was smaller. Rates of head injury with loss of consciousness were highest for NO+VS youth, followed by VS-only, NO/VS nonusers, and NO-only users. NO-only users were more likely to reside in urban and suburban locations, and less likely to live in a family that received welfare. Youth in the NO+VS and VS-only groups tended to reside in small town and nonurban settings. NO/VS nonusers tended to be disproportionately black and to have comparatively low rates of diagnosed mental health disorder approximate to those of NO-only youth.

Lifetime Nitrous Oxide Use

Prevalence and types of use—The lifetime prevalence of NO use in the total sample was 15.8%. Of the 114 NO users, 57.0% had used NO from whipped cream chargers (i.e., “whippets”), 38.6% had used NO directly from whipped cream cans, and 39.5% had inhaled NO through their nose or mouth in some other manner such as from balloons (note: multiple modes of NO use were reported by many NO users; thus, percentages of users by manner of use total more than 100%). Among both NO+VS and NO-only users, whippets were the most prevalent mode of NO administration.

Recency of use—Overall, 88 (77.2%) lifetime NO users reported NO use in the year prior to their current treatment episode.

Perceived intoxication and addiction liability—Most NO+VS users of whippets (84.2%) reported getting high when they used them, as did 67.4% of NO+VS users who inhaled NO from whipped cream cans and 97.7% of NO+VS users who inhaled NO through their nose or mouth in an otherwise unspecified manner. Seven of eight (87.5%) NO-only users of whippets and one of three (33.3%) NO-only users of whipped cream cans reported getting high when they used NO in these manners.

All NO-only users reported less than five days of lifetime NO use. In contrast, 9.7% of NO+VS users reported using whippets on 100 or more days in their lifetime, 4.8% of NO+VS users reported inhaling NO through their nose or mouth in an unspecified manner on 100 or more days, and 1.9% of NO+VS users of NO from whipped cream cans reported 100 or more days of NO use in this manner.

Patterns of lifetime VS inhalant use in NO+VS users and VS-only users

Lifetime prevalence rates for the 15 most commonly used volatile solvents are presented in Table 2. NO+VS users reported significantly higher lifetime prevalence rates for 10 of 15 of these agents relative to VS-only users, with particularly large differences observed for use of PC duster sprays, paint remover/stripper, spray paint, butane, and air freshener.

Differences between NO and VS Inhalant User Subgroups across Psychosocial and Psychiatric Factors

Univariate contrasts—NO+VS users evidenced significantly higher rates of psychiatric symptoms than NO/VS nonusers across all four BSI subscales of interest, as well as the BSI Global Severity Index (see Table 3). NO+VS users also endorsed significantly higher rates on these subscales and the GSI compared to VS-only users. NO+VS users had significantly higher scores than NO-only users on the Anxiety and Obsessive-Compulsive subscales.

While VS-only users reported significantly higher levels of antisocial traits as measured by the APSD than NO/VS nonusers, their scores on the APSD did not significantly differ from those of NO+VS users. The only significant difference on the SRD measure of delinquency was between NO+VS users and NO/VS nonusers. On the PPI, NO+VS users had significantly higher total scores than VS-only users or NO/VS nonusers, as well as significantly higher scores on the Impulsive Nonconformity and Fearlessness subscales. VS-only users also had significantly higher total PPI, Fearlessness, and Impulsive Nonconformity scores than did NO+VS nonusers.

NO+VS inhalant users had significantly higher scores than NO/VS inhalant nonusers on the Traumatic Experiences and Suicidal Ideation scales and significantly elevated suicidal ideation compared to NO-only users. VS-only users had significantly more suicidal ideation compared to NO+VS nonusers. NO+VS users reported significantly more polysubstance use and an earlier age of onset of marijuana use than any other group. NO+VS users also reported using alcohol significantly earlier in life than NO-only and NO/VS nonusers and evidenced significantly greater lifetime substance-related problems than NO/VS nonusers. VS-only inhalant users reported significantly greater suicidal ideation, lifetime polydrug use, and an earlier age at onset of alcohol use than NO/VS inhalant nonusers. Overall, NO+VS and VS-only users had significantly more problematic and extensive substance abuse histories than nonusers.

NO-only users appeared to present a less impaired psychiatric and behavioral profile than did NO+VS or VS-only inhalant users; however, the small size of the NO-only group reduced statistical power and many of these differences did not reach statistical significance. NO-only users had significantly lower BSI Anxiety and Obsessive-Compulsive subscales scores compared to NO+VS inhalant users. BSI scale and subscale scores of NO-only users and NO/VS inhalant nonusers were generally similar. As indicated above, NO-only users had significantly less suicidal ideation and polydrug use, and a later onset of alcohol and drug use than did NO+VS inhalant users.

Predictors of Lifetime NO Use

A multivariable logistic regression model was used to identify biopsychosocial correlates of lifetime NO use while controlling for potentially confounding factors (see Table 4). Using findings from the univariate contrasts presented above as a guide, 11 covariates were entered simultaneously in the analysis: race/ethnicity, family receipt of welfare, SRD Total Delinquency Score, history of mental illness, BSI-Global Severity Index, PPI-Fearlessness, PPI-Impulsive Nonconformity, APSD-Total Score, MAYSI-2 Suicide Ideation scale and Traumatic Experiences scale, and lifetime total number of drug types used.

Youth who had been diagnosed with psychiatric disorders were 91% more likely than their counterparts who did not receive psychiatric diagnoses to report lifetime use of nitrous oxide. Adolescents with fearless temperaments and who reported lifetime use of a larger number of illicit drug types were significantly more likely to use NO than their counterparts. For each additional illicit drug class used by a given youth in the sample, the odds that that youth would report NO use were increased by 73%, after controlling for the influence of other variables in the model.

Discussion

Approximately one in six (15.8%) adolescents in this state population of youth in residential care for antisocial behavior reported lifetime NO use. This prevalence estimate is approximately eight times greater than the 2.0% figure for U.S. adolescents reported in the 2000/2001 National Household Survey on Drug Abuse (Wu, Pilowsky & Schlenger 2004).

NO use occurring in conjunction with VS use was associated with significant psychiatric and substance-related impairments, whereas use of only NO inhalants appeared relatively benign in relative terms. VS-only users evidenced significant dysfunction across a range of psychiatric and substance-related measures, although not as extreme as that found in NO+VS users. These differences suggest the existence of a risk spectrum in this population, with NO+VS users being the most at-risk for psychological, behavioral, and substance abuse problems, followed by VS-only inhalant users and then NO-only users, the latter differing little clinically from youth who had used neither NO nor VS inhalants. Although these findings do not settle the debate about the abuse potential of nitrous oxide, they do suggest that incarcerated youth who have used both NO and VS should be the target of redoubled assessment and intervention efforts due to their heightened vulnerability for a variety of disorders.

Among all respondents sampled, NO+VS inhalant users had the highest rates of global psychiatric symptomatology. NO+VS users reported significantly greater obsessive-compulsive, depressive, anxious, and psychoticism symptoms than VS-only users, who themselves were at elevated risk for psychological problems (Howard et al. 2008). The observation that NO+VS users had significantly greater scores on the BSI Obsessive-Compulsive and Psychoticism scales, which contain items pertaining to “trouble remembering things,” “your mind going blank,” “trouble concentrating,” and “the idea that something is wrong with your mind” suggests that combined use of NO and VS may produce neurotoxic effects, leading to cognitive impairments. Additionally, NO+VS users were significantly more likely to have received a psychiatric diagnosis than any other group. While causality cannot be inferred from cross-sectional analyses, this finding suggests that youth who use both NO and VS may suffer from affective dysregulation and cognitive impairments. Whether such elevated risk stems from substance-related neurotoxicity or whether more psychiatrically-disordered individuals tend towards polyinhalant use, or both, the presence of this specific pattern of inhalant use is an important risk factor in predicting psychological vulnerability.

In contrast, NO use independent of VS use was associated with markedly less severe psychiatric symptomatology than co-occurring NO and VS inhalant use or VS-only inhalant use. Again, it is impossible to discern whether this diminished risk is due to the pharmacological profile of NO or to a spurious third variable—e.g., sensation-seeking (Zuckerman 1996; Zuckerman et al. 1972). The youth in our sample who had used NO but not VS inhalants may have had less sensation-seeking temperaments compared to NO+VS users. Youth with comparatively low levels of sensation seeking may have lower rates of psychiatric illness or antisocial behavior (Gabel et al. 1994) and also tend toward less severe polysubstance use (Martin et al. 2004; Sutker, Archer & Allain 1978). In the present sample, youth who had used NO but not VS inhalants were experimental users with few lifetime episodes of use. However, approximately 10% of youth who had used both NO and VS inhalants reported 100 or more occasions of NO use. More psychiatrically-disordered persons may tend toward patterns of comparatively frequent, intensive, and solitary polyinhalant and other drug use indicative of serious addiction (Skinstad & Swain 2001; Sumnall, Wagstaff & Cole 2004). Indeed, the data clearly demonstrate that in this state population of youth in mandated treatment for antisocial behavior, VS inhalant use was prevalent and in a substantial minority of cases included comorbid NO use, whereas almost all NO users had tried VS inhalants. It is unclear to what extent this asymmetrical relationship may be due to lesser availability of NO relative to VS inhalants (which are ubiquitous in the physical environment).

These differential patterns of drug use may relate to overall differences in the personality profiles and antisocial behaviors of NO+VS users and their counterparts. On the whole, NO

+VS users appeared to be the most fearless subgroup, and reported the highest levels of criminality. The presence of these characteristics suggests a proclivity towards risk taking that may be explained by neurotoxic effects or other factors such as deficits in prefrontal cortical circuits responsible for impulse control (Davidson, Putnam & Larson 2000).

The co-occurrence of psychosocial liabilities with the polysubstance use observed among incarcerated NO+VS inhalant users suggests a possible intention driving this pattern of drug abuse. Given the high rates of traumatic experiences and suicidal ideation in this population, comorbid NO+VS use may represent an attempt at self-medication. Prolonged or repeated activation of the nervous system due to stressful social-environmental stimuli may lead to an allostatic state, a chronic deviation of self-regulatory mechanisms from their normal mode of operation that leads to heightened sensitivity and vulnerability to future stressors (McEwen 2000, 1998). The self-administration of drugs may momentarily regulate stress-enhanced sensitivity, but ultimately results in a shift in the neurobiological reward set point towards reward insensitivity (Koob 2003; Koob & Le Moal 2001). This shift in the set point elicits increased substance use as a means of achieving hedonic allostasis (Koob 2003). Hence, chronic use may be a form of emotion regulation, whereby the powerful psychoactive effects of inhaled gases temporarily alleviate dysphoria. Negative reinforcement resulting from substance-related reduction of affective distress may result in habitual, addictive use (Baker et al. 2004). Indeed, the NO+VS users sampled in this study exhibited the most extreme psychosocial distress and substance use patterns in this population of incarcerated youth.

This study is, we believe, the first to describe the conjoint prevalence and correlates of NO and VS polyinhalant use in the current or any other service population of youth. Among the strengths of the research are the reasonably large sample size and high participation rate. However, this study is limited by its reliance on self-report measures, an assessment approach that is normative in substance abuse epidemiology but one that warrants caution in interpreting results. It is possible that reports of substance use or psychiatric symptomatology were influenced by some form of desirability bias (Shadish, Cook & Campbell 2002). A second limitation is the small size of the subsample of NO users, which reduced the study's statistical power to detect significant differences between this group and others. A final limitation of the study is its cross-sectional nature, which precludes causal inferences. Future research should track adolescent NO users longitudinally to examine change trajectories of the relevant psychological, behavioral, and criminological parameters outlined by these findings.

Study findings have implications for prevention and treatment efforts aimed at substance-using youth exhibiting antisocial behavior and psychiatric symptoms. Screening for NO use (particularly adolescents with comorbid NO and VS inhalant use) may help to identify potentially vulnerable individuals who would benefit from targeted treatment and prevention interventions. In the hands of nineteenth century luminaries, NO may have catalyzed "intense metaphysical illumination" (James 1969), but among the troubled youth of today, its use may instead yield only "bewilderment, puzzle, confusion ... with nothing particular left to be bewildered at save the bewilderment itself" (James 1969).

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TABLE 1
Sociodemographic and Neuropsychiatric Characteristics of 723 Adolescent Inpatients in 27 Missouri Division of Youth Services Treatment Facilities

Variables	A. Lifetime NO ² +VS Users N = 103*	B. Lifetime NO-Only Users N = 11**	C. Lifetime VS-Only Users N = 164***	D. NO/VS Nonusers N =445****	p-Value	Cramer's V	Post-hoc Contrasts ^b
Demographics							
Age (M, SD)	15.7 (.89)	16.1 (.54)	15.4 (1.3)	15.5 (1.3)	F(3,719)=2.4 (.067)	-	-
Gender N (%)					.309	.06	-
Male	89 (86.4)	9 (81.8)	137 (83.5)	394 (88.5)			
Female	14 (13.6)	2 (18.2)	27 (16.5)	51 (11.5)			
Race N (%)					.000	.25	AD, CD
White	78 (75.7)	8 (72.7)	122 (74.4)	192 (43.1)			
Black	6 (5.8)	2 (18.2)	14 (8.5)	216 (48.5)			
Hispanic	6 (5.8)	0 (0.0)	14 (8.5)	8 (1.8)			
Biracial	10 (9.7)	1 (9.1)	9 (5.5)	25 (5.6)			
Other	2 (1.9)	0 (0.0)	5 (3.0)	4 (0.8)			
Geographic Area of Family Residence							
N (%)					.000	.15	AD, CD, BC
Urban	30 (29.1)	6 (54.5)	40 (24.4)	207 (46.5)			
Suburban	19 (18.4)	3 (27.3)	15 (9.1)	63 (14.2)			
Rural	7 (6.8)	0 (0.0)	14 (8.5)	33 (7.4)			
Small town	47 (45.6)	2 (18.2)	95 (57.9)	142 (31.9)			
Welfare N (%)					.002	.13	BD, BC, AB, AC
Yes	33 (32.0)	0 (0.0%)	76 (46.9)	179 (40.7)			
No	70 (68.0)	10 (100%)	86 (53.1)	260 (59.2)			
Head Injury with Extended Loss of Consciousness N (%)							
Yes	28 (27.2)	1 (9.1)	36 (22.0)	67 (15.2)	.015	.12	AD
No	75 (72.8)	10 (90.9)	128 (78.0)	375 (84.8)			
History of Mental Illness Diagnosed by a Psychiatrist or Other Physician N (%)							
Yes	80 (77.7)	4 (36.4)	96 (58.9)	190 (42.9)	.000	.25	AD, CD, AB, AC

Variables	A. Lifetime NO ² +VS Users N = 103*	B. Lifetime NO-Only Users N = 11**	C. Lifetime VS-Only Users N = 164***	D. NO/VS Nonusers N =445****	p-Value	Cramer's V	Post-hoc Contrasts ^b
No	23 (22.3)	7 (63.6)	67 (41.1)	253 (57.1)			
History of Hearing Voices N (%)					.000	.16	AD, CD
Yes	25 (24.3)	1 (9.1)	33 (20.1)	47 (10.6)			
No	78 (75.7)	10 (90.9)	131 (79.9)	398 (89.4)			

* N's ranged from 102 to 103 across row variables;

** N's ranged from 10 to 11;

*** N's ranged from 162 to 164;

**** N's ranged from 439 to 443.

^aNO = Nitrous Oxide; VS = Volatile Solvents.

^bAB = Lifetime Users of NO and VS Inhalants vs. Lifetime Users of Only NO. AC = Lifetime Users of NO and VS Inhalants vs. Lifetime Users of Only VS Inhalants. AD = Lifetime Users of NO and VS Inhalants vs. NO/VS Inhalant Nonusers, BC = Lifetime Users of Only NO vs. Lifetime Users of Only VS Inhalants, BD = Lifetime Users of Only NO vs. NO/VS Inhalant Nonusers, CD = Lifetime Users of Only VS Inhalants vs. NO/VS Inhalant Nonusers. Bold font = $p < .05$.

TABLE 2
Lifetime Prevalence of Specific Types of Volatile Solvent Inhalant Use Among
Adolescents with a History of Nitrous Oxide and Volatile Solvent Use (NO +VS, N = 103)
and Adolescents with a History of Volatile Solvent Use but no History of Nitrous Oxide
Use (VS-Only, N = 164)*

Inhalant Product	Lifetime Prevalence NO+VS Users N(%)	Lifetime Prevalence VS-Only Users N(%)	<i>p</i> -Value**	Effect Size: Cramer's V
Gasoline	65 (63.1)	94 (57.3)	.348	.06
PC Duster Sprays	59 (57.3)	47 (28.7)	.000	.29
Permanent Markers	49 (47.6)	57 (34.8)	.037	.13
Spray Paint	46 (44.7)	37 (22.6)	.000	.23
Paint Thinner	33 (32.0)	27 (16.5)	.003	.18
Air Freshener	32 (31.1)	26 (15.9)	.003	.18
Butane	30 (29.1)	20 (12.2)	.001	.21
Nail Polish	28 (27.2)	33 (20.1)	.181	.08
Nail Polish Remover	28 (27.2)	35 (21.3)	.274	.07
Freon	23 (22.3)	21 (12.8)	.041	.13
Airplane/Model Glue	21 (20.4)	18 (11.0)	.034	.13
Correction Fluid	21 (20.4)	31 (18.9)	.785	.02
Rubber Cement	20 (19.4)	15 (9.1)	.015	.15
Paint Remover/Stripper	19 (18.4)	6 (3.7)	.000	.25
Hairspray	16 (15.5)	13 (7.9)	.052	.12

* Specific volatile solvent inhalants for which no use was reported are not included in this table; nitrite inhalants and nonpsychoactive inhalants such as helium are also not included in this table, although they were assessed in this study using the Volatile Solvent Screening Inventory (Howard et al. 2008).

** χ^2 used for statistical comparison of inhalant use of NO+VS and VS-only users. Bold font = $p < .05$.

TABLE 3
Unadjusted Univariate Contrasts of Lifetime Users of Nitrous Oxide and Volatile Solvents, Users of Nitrous Oxide Only, Users of Volatile Solvents Only, and Users of Neither Nitrous Oxide nor Volatile Solvents Across Mental Health, Health, Attitudinal, Criminological and Substance Use Measures

Variables	A. Lifetime NO +VS Users N = 103	B. Lifetime NO-Only Users N = 11	C. Lifetime VS-Only Users N = 164	D. NO/VS Nonusers N = 445	Test Statistic	Partial eta Squared [†]	Post-hoc Contrasts
Brief Symptom Inventory M (S.D.)							
Global Severity Index	63.3 (41.5)	36.2 (23.3)	49.2 (33.8)	37.5 (31.7)	F (3,719) = 18.4***	.07	AC, AD, CD
Depression	7.3 (6.3)	4.0 (3.1)	5.5 (4.9)	3.9 (4.4)	F (3,719) = 12.34***	.06	AC, AD, CD
Anxiety	7.2 (6.0)	2.4 (1.6)	5.0 (4.4)	3.5 (4.1)	F (3,719) = 18.7***	.09	AB, AC, AD, CD
Obsessive-Compulsive	10.4 (6.3)	5.9 (3.8)	7.4 (5.1)	5.8 (4.7)	F (3,719) = 21.2***	.10	AB, AC, AD, CD
Psychoticism	6.1 (4.8)	3.7 (4.4)	3.7 (3.6)	3.0 (3.2)	F (3,719) = 17.2***	.09	AC, AD, CD
Antisocial Process Screening Device Total M(S.D.)	17.5 (4.7)	16.5 (4.0)	17.9 (5.7)	16.1 (5.5)	F (3,718) = 4.3**	.02	CD
SRD (Total Delinquency) M(S.D.)	31.0 (19.5)	16.8 (6.1)	27.3 (18.9)	25.3 (17.8)	F (3,719) = 3.5*	.02	AD
Psychopathic Personality Inventory M(S.D.)							
Total	145.4 (14.6)	143.2 (16.4)	139.7 (15.3)	134.3 (12.7)	F (3,719) = 17.5***	.086	AC, AD, CD
Fearlessness	20.2 (4.8)	18.5 (3.1)	18.5 (4.7)	15.9 (5.0)	F (3,719) = 24.3***	.115	AC, AD, CD
Impulsive Nonconformity	17.1 (4.3)	15.1 (5.3)	15.6 (4.7)	14.1 (3.6)	F (3,719) = 13.8***	.069	AC, AD, CD
Massachusetts Youth Screening Inventory M (S.D.)							
Traumatic Experiences	3.5 (1.5)	3.3 (1.8)	3.1 (1.6)	2.8 (1.6)	F (3,718) = 4.1**	.021	AD
MAYSI-Suicidal Ideation	3.5 (2.5)	1.5 (2.4)	3.4 (2.4)	1.5 (2.1)	F (3,718) = 33.4***	.152	AB, AD, CD
Substance Use and Related Problems							
MAYSI-Alcohol/Drug Problems Scale M (S.D.)	5.9 (1.2)	4.6 (2.1)	5.0 (1.9)	4.3 (5.8)	F (3,702) = 3.4*	.018	AD
Lifetime # of Drug Types Used M(S.D.)	7.9 (2.4)	6.1 (2.5)	5.3 (2.3)	3.6 (1.8)	F (3,717) = 112.3***	.376	AB, AC, AD, CD
Lifetime Alcohol Use N(%)	99 (96.1%)	11 (100.0%)	155 (94.5%)	348 (78.2%)		.233	AD
Age at Onset of Alcohol Use (Years) M(S.D.)	10.7 (2.7)	13.1 (1.6)	11.3 (2.9)	12.1 (2.5)	F (3,609) = 8.0***	.041	AB, AD, CD
Lifetime Marijuana Use N(%)	99 (96.1%)	11 (100.0%)	156 (95.1%)	360 (80.9%)		.212	AD

Variables	A. Lifetime NO- +YS Users N = 103	B. Lifetime NO- Only Users N = 11	C. Lifetime VS- Only Users N = 164	D. NO/YS Nonusers N = 445	Test Statistic	Partial eta Squared [‡]	Post-hoc Contrasts
Age at Onset of Marijuana Use (Years) M(S.D.)	10.4 (2.3)	12.3 (2.2)	11.3 (2.2)	11.4 (2.1)	F (3,621) = 5.9***	.030	AB, AC, AD

* $p < .05$
 ** $p < .01$
 *** $p \leq .001$

[‡] Cramer's V reported as an effect size estimate for dichotomous bivariate comparison

TABLE 4
Multiple Logistic Regression Analysis (with Simultaneous Entry of Covariates)
Examining Correlates of Lifetime Nitrous Oxide Use in the Total Sample of 723 Youth in Residential Treatment

Variables	AOR	95% CI
Race/Ethnicity	1.02	.78 – 1.33
Family Receipt of Welfare	.58	.33 – 1.02
SRD-Total Delinquency Score *	.98	.97 – 1.00
Prior Receipt of a Mental Illness Diagnosis	1.91	1.07 – 3.42
BSI- Global Severity Index	1.01	1.00 – 1.02
PPI-Fearlessness	1.10	1.04 – 1.16
PPI-Impulsive Nonconformity	1.03	.96 – 1.09
APSD Total	.95	.90 – 1.00
MAYSI Suicide Ideation Scale	.99	.88 – 1.12
MAYSI-2 Traumatic Experiences Scale	.89	.73 – 1.09
Total Number of Drug Types Used	1.73	1.55 – 1.94

* Note: AOR = Adjusted odds ratio, CI = Confidence interval, SRD = Self-Report of Delinquency Scale, BSI = Brief Inventory Scale, APSD = Antisocial Process Screening Device, MAYSI = Massachusetts Youth Screening Inventory. Adjusted odds ratios in bold are significant based on a 95% confidence interval that does not bound the value 1.00.