Published in final edited form as:

Drug Alcohol Depend. 2008 November 1; 98(1-2): 163–168. doi:10.1016/j.drugalcdep.2008.06.001.

Choice of Nitrous Oxide and Its Subjective Effects In Light and Moderate Drinkers

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Abstract

Background—Alcohol-drinking status has been shown to modulate the reinforcing and subjective effects of a number of drugs. We have previously published two studies on the modulating effects of alcohol-drinking status on choice for, and subjective effects of, nitrous oxide, but the results were equivocal. Using a methodology different from our previous studies, we sought to determine in a more definitive fashion the degree to which the choice of nitrous oxide and its subjective effects were modulated by drinking status.

Methods—Four concentrations of nitrous oxide (0, 20, 30, 40%) were administered to 16 moderate drinkers (MDs) and 16 light drinkers (LDs) across four 3.5-h sessions. During experimental sessions, subjects first completed two 10-min sampling trials in which one of the nitrous oxide concentrations and placebo (100% oxygen) were inhaled. Subjective and psychomotor tests were given 5 min into each sampling trial. During the subsequent choice period, subjects were allowed to choose what they wanted to inhale (drug, placebo, or “drug-free air”) on nine contiguous 5-min choice trials.

Results—Choice of nitrous oxide was modulated by drinking status: MDs but not LDs chose nitrous oxide significantly more times than placebo, and MDs also chose nitrous oxide significantly more times than did LDs. At each active nitrous oxide concentration, MDs reported more abuse liability-related subjective effects, especially at the 20% and 30% concentrations.

Conclusions—The results of the present study provide more conclusive evidence that choice as well as subjective effects of nitrous oxide are modulated by alcohol-drinking status.

Keywords

Nitrous oxide; Preference; Choice; Reinforcing effects; Subjective effects; Psychomotor; Inhalants; Human

1. Introduction

Inhalants are abused (Substance Abuse and Mental Health Services Administration, 2007) and associated with morbidity and mortality (Chalmers, 1991; Winek et al., 1995; Lubman, et al., 2006). It is therefore important to characterize the abuse liability of inhalants, as well as determine what variables may modulate their abuse liability. Over the last 15 years our

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laboratory has conducted such research with inhaled gaseous and volatile general anesthetics and have established that both classes of anesthetics have abuse liability in healthy volunteers. We have also documented individual differences in the degree to which volunteers choose the inhaled anesthetic over placebo, as well as the extent to which they experience positive, or abuse liability-related, subjective effects (Dohrn et al., 1993; Walker and Zacny, 2002; Walker et al., 2004). Individual differences could be related to a host of variables, including organismic and environmental factors. One variable that has been demonstrated to modulate drug effects in both nonhumans and humans is drug history (e.g., Young and Woods, 1981; Horger et al., 1992; Evans et al., 1996). A number of studies have examined the role that alcohol-drinking status has on modulating the reinforcing or subjective effects of drugs. It has been shown with several different drugs, including amphetamine, diazepam, sevoflurane (an inhaled volatile general anesthetic), and alcohol itself, that heavier drinkers choose these drugs more often, and/or present with a more positive profile of subjective effects of those drugs, than do lighter drinkers (de Wit et al, 1989; de Wit and Doty, 1994; Evans et al., 1996; Holdstock et al., 2000; King et al., 2002; Stoops et al., 2003; Zacny et al., 2008).

We have conducted two studies with nitrous oxide, an inhaled gaseous general anesthetic, to determine if choice of nitrous oxide and/or its subjective effects were modulated by alcohol-drinking status (Cho et al., 1997; Walker and Zacny, 2001a). We obtained equivocal results. In the Cho et al. (1997) study, concentrations of 10, 20, 30, and 40% nitrous oxide were studied, using a within-subjects design. Subjects (9 LDs and 10 MDs) first sampled a given concentration of nitrous oxide and placebo (100% O₂), each for 30 min (separated by 60 min recovery). The choice procedure used in this study allowed subjects to then choose what they wanted to inhale during the subsequent 30-min choice trial. More MDs chose nitrous oxide than did LDs at each concentration, but the differences were not statistically significant. Cho et al. (1997) attributed the lack of statistical significance to the small sample size, which decreased the power to detect differences between groups within a given concentration. Using post hoc testing, we collapsed across concentrations to increase number of choices for each subject (4), and the median number of times nitrous oxide was chosen was significantly greater in the MD group (3 times) than in the LD group (1 time). Although a few subjective effects of nitrous oxide were modulated by alcohol-drinking status, none of these effects could be considered abuse liability-related. In the Walker and Zacny (2001a) study, the effects of ethanol pretreatment and alcohol-drinking status on choice for, and subjective effects of, nitrous oxide were examined. A different choice procedure was used than that used by Cho et al. (1997). Subjects (8 LDs and 8 MDs) first sampled 30% nitrous oxide and placebo for 5 min each (separated by 30 min), and then completed six 5-min choice trials in which they chose between the two sampled agents. Alcohol-drinking status did not modulate the number of times nitrous oxide was chosen, or its subjective effects. Both study designs had methodological weaknesses related to the way choice was assessed (see Walker and Zacny, 2002). Briefly, in the Cho et al. (1997) study, quantitative differences in reinforcing efficacy of different doses were impossible to observe because only one choice trial per dose was conducted. In the Walker and Zacny (2001a) study, quantitative analyses were possible, but only one dose was tested and a forced choice procedure was used that may have underestimated the reinforcing efficacy of nitrous oxide (Spiga and Roache, 1997). In addition, both studies employed small sample sizes.

Given the equivocal results, with one study providing some evidence for modulation, and the other study providing no evidence, we conducted the present study with a larger sample size and a more methodologically sound choice procedure (Spiga and Roache, 1997; Walker and Zacny, 2002), i.e., multiple doses, multiple choices, and inclusion of a drug-free (i.e., neither) option. In conducting the present study, we sought to determine in a more definitive fashion than our previous two studies whether choice for, and subjective effects of, nitrous oxide were modulated by alcohol-drinking status.

2. Methods

Subject screening and recruitment procedures, inclusion and exclusion criteria (apart from alcohol usage), study procedures, and dependent measures used in the current study are described in a previous study (Walker and Zacny, 2001b) and will therefore be briefly summarized below.

2.1. Subjects

Requirements for participation in this IRB-approved study included age between 21–39 years, a high school diploma or the equivalent, verbal fluency in English, and some current level of alcohol use. Exclusion criteria included total abstinence from drugs and a history of substance abuse disorders (American Psychiatric Association, 2000) or significant medical events. Written informed consent was obtained for subjects who met the inclusion criteria. The subject population included 32 individuals, 16 classified as light drinkers (LDs) and 16 as moderate drinkers (MDs), with an equal number of males and females in each group. Mean age ($\pm$ SD) in the LD group and MD group were 22.9 (2.4) and 24.7 (3.9) years, respectively. LDs had to meet two criteria: 1) consume at least one but no more than four drinks/month and 2) drink two or fewer drinks/occasion. MDs had to meet two or more of the following criteria (Evans et al., 1996; Stoops et al., 2003): 1) ingest at least seven drinks/week, 2) drink at least three drinks/occasion at least once/week, and/or 3) consume alcohol at least four days/week. There were no significant differences between the groups in age, body mass index, race, or ethnicity. With regard to lifetime recreational drug use, there was only a significant difference between LDs and MDs in the number of participants who had used marijuana, 7 and 16 respectively. Current drug use (last 30 days) between the two groups differed significantly in weekly consumption of alcohol and caffeine. LDs consumed an average of 0.8 alcoholic drinks/week and 5.3 caffeinated beverages/week while the MDs consumed an average of 11.1 alcoholic drinks/week and 8.3 caffeinated beverages/week.

2.2. Experimental design, drugs, and experimental sessions

A double-blind, placebo-controlled, randomized, crossover design was utilized. Across four 3.5-hour sessions, each subject received one of four concentrations of nitrous oxide: 0, 20, 30, and 40% nitrous oxide in oxygen. The 0% nitrous oxide condition was 100% oxygen. Sessions were spaced at least 3 days apart. Each experimental session consisted of one sampling period made up of two 10-min sampling trials and one 45-min choice period. Thirty min separated each period (i.e. recovery). During the two sampling trials, one of the four nitrous oxide concentrations and placebo (100% oxygen) were administered. Order of concentration conditions was randomized across subjects. Within subjects, the order of nitrous oxide and placebo sampling trials was counterbalanced across sessions. During the sampling period, subjects were given a letter code to identify each agent. Before each sampling trial, subjects were told, "For the next 10 min you will be inhaling agent_, which may or may not contain a drug." During the subsequent choice period subjects were allowed to select what they wanted to inhale: one of the sampled agents (i.e., either drug or placebo), or a "drug-free air" option (100% oxygen). Subjects completed nine choice trials in which they were asked every five min to choose what they wanted to inhale for the next five min. A 60-minute recovery period followed the 45-minute choice period.

2.3. Dependent measures

Dependent measures included number of nitrous oxide and placebo choices, and subjective and psychomotor effects. In the choice period, number of times the drug-free air option was chosen at each concentration was recorded but was not included in the data analysis, because the key question of interest was whether nitrous oxide was preferred over placebo (Walker and Zacny, 2002). Subjective effects were measured five min into each sampling trial with a visual

analog scale (VAS), drug effects/drug liking/inhale again questionnaire (DEL/IA), and an odor detection/liking questionnaire. Two variants of the DEL/IA questionnaire were used: one was completed at the end of the session, and the other was to be completed 24 h after the conclusion of the session. On both forms, subjects were asked to rate overall drug liking and overall “want to inhale drug again” of the two agents inhaled in the session. An inhalant effects checklist (IEC) (Atkinson et al., 1977; Block et al., 1990) was given to subjects five min after each sampling trial. Psychomotor performance was assessed five min into each sampling trial using the Digit Symbol Substitution Test (DSST) (Wechsler, 1958).

2.4 Data analysis

Dependent measures were analyzed by a mixed model analysis of variance (ANOVA) with drinking status (LD vs. MD) as the grouping factor and drug concentration (0, 20, 30, and 40% nitrous oxide) and sample drug (nitrous oxide and placebo) as the repeated measures. When appropriate, Tukey post hoc testing was performed.

3. Results

Figure 1 (left frame) shows choice of nitrous oxide versus placebo as a function of alcohol-drinking status and concentration. Alcohol-drinking status influenced nitrous oxide choice (Group×Sample Drug: $p<0.01$): post hoc analyses revealed that MDs chose nitrous oxide significantly more times than placebo, and also chose it more than LDs. The Group×Concentration×Sample Drug interaction was not significant. The Group×Sample Drug interaction remained significant when the 0% concentration (in which both “drug” and placebo were 100% O₂) was removed from the analysis. Nitrous oxide had a number of subjective effects, but for the sake of brevity, Table 1 shows only those effects in which a Group×Concentration×Sample Drug interaction was found. In general MDs showed more effects than did LDs, although the most consistent differences were found with the measures of drug liking (Figure 1, right frame) and desire to inhale the drug again which were measured during inhalation, at the end of the session, and 24 h after the session. In each of the nitrous oxide conditions, with the exception of the 24-h “inhale again” ratings, MDs in the active-drug sampling trial had significantly elevated ratings relative to LDs. In the 20% and 30% nitrous oxide conditions, differences in these ratings between the active-drug sampling trial and the placebo sampling trial (including the 24-h “inhale again” ratings) in the MDs were significant. In the 30% nitrous oxide condition, increased VAS ratings of “elated,” “feel good,” and “pleasant thoughts” and increased scores from the IEC Euphoria scale in the active-drug sampling trial, relative to the placebo sampling trial, were significant only in MDs. With the latter three measures, MDs had significantly higher ratings or scores relative to LDs. LDs reported significantly higher ratings of “sedated” and “elated” in the active-drug sampling trial relative to the placebo sampling trial in the 30% and 40% nitrous oxide conditions, respectively. There was a significant Group×Sample Drug interaction on number of symbols drawn, and drawn correctly, on the DSST, with MDs showing less impairment from nitrous oxide than LDs. Specifically, MDs drew on average 5.4 fewer symbols when inhaling nitrous oxide relative to inhaling placebo (100% O₂), as compared to LDs who drew on average 8.6 fewer symbols ($p<0.05$). Although there was not a significant Group×Concentration×Sample Drug interaction, the impairment, and differences in impairment between the groups, were in the 20–40% nitrous oxide conditions. Number of symbols drawn correctly showed the same difference in magnitude of impairment between the MDs and LDs.

4. Discussion

MDs, but not LDs, preferred nitrous oxide over placebo, and also chose nitrous oxide more often than did LDs. These effects were not concentration-related in the range from 20–40%

nitrous oxide. MDs were also more likely than LDs to report abuse liability-related subjective effects of nitrous oxide that achieved statistical significance (Table 1). Curiously, this was not apparent at the 40% nitrous oxide concentration when examining the VAS ratings, even though differences between MDs and LDs were apparent on measures of liking, “inhale again,” and drug choice. In general, however, there was concordance between the abuse liability-related subjective effects reported by the MDs and their choice behavior (Figure 1).

We have conducted three studies with nitrous oxide to determine whether alcohol-drinking status modulated its effects. We believe that the present study using a more methodologically sound choice procedure, and larger sample sizes, than the previous two studies (Cho et al., 1997; Walker and Zacny, 2001a) presents compelling evidence that alcohol-drinking status modulates choice and some subjective effects of nitrous oxide. It should be noted, though, that MDs differed from LDs on lifetime marijuana use and current caffeine intake in the present study, and these and other differences that might exist between heavier and lighter drinkers may have played a role in the results obtained in this study. However, the study results are consistent with the extant literature demonstrating that alcohol-drinking status modulates choice and/or subjective effects of psychoactive drugs from a number of different classes. Whether there is a common mechanism underlying this modulating effect that occurs with drugs from different pharmacological profiles is not known, but deserves further exploration.

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Figure 1.

Mean ($\pm$ SEM) number of placebo (P) and nitrous oxide (N) choices (left frame) and mean ($\pm$ SEM) liking ratings in the P and N sampling trials (right frame) for each of the four nitrous oxide concentrations (0, 20, 30, 40%) in light drinkers (LDs) and moderate drinkers (MDs). Total number of choices that could be made was nine per concentration. Choice of the drug-free air option was not included in the analysis. Drug liking was rated on a 100-mm bipolar VAS (0=dislike a lot, 50=neutral, 100=like a lot). Asterisks in the right frame indicate that liking ratings were significantly higher in the N sampling trial compared to the P sampling trial in the 20% and 30% nitrous oxide concentrations. Daggers indicate that MDs had significantly higher liking ratings than LDs in the N sampling trial in the 20%, 30%, and 40% nitrous oxide concentration conditions.

Table 1

Mean subjective effects and psychomotor values in which a significant Group (light [LD] vs. moderate drinking [MD] history) x Nitrous Oxide Concentration (0, 20, 30, 40%) x Sample Drug (placebo [PLC], nitrous oxide [N₂O]) interaction was found.

Nitrous Oxide Concentration: History Drug	20%			30%			40%					
	PLC	LD	N ₂ O	PLC	MD	N ₂ O	PLC	LD	N ₂ O	PLC	MD	N ₂ O
VAS ^{a,b}												
Elated (very happy)	2.4		11.0	2.2		19.1	3.7		36.0		4.0	
Feel Good	33.9		37.1	32.8		55.3	36.1		61.1 ^c		37.5	
Pleasant thoughts	19.4		25.4	25.9		39.3	24.4		44.7 ^c		21.0	
Sedated												
(calm, tranquil)	11.9		18.3	10.8		30.0	10.1		18.4		11.6	
DELIA												
Liking												
(within session) ^{b,d}	47.2		47.8	47.9		69.9 ^c	49.0		75.6 ^c		53.3	
Sedated												
(end of session) ^d	49.1		44.1	49.2		74.6 ^c	51.3		74.4 ^c		52.6	
Liking												
(24-h assessment) ^d	50.7		43.1	47.9		74.6 ^c	49.5		72.0 ^c		52.7	
Inhale again												
(within session) ^{b,d}	51.1		46.8	50.8		73.7 ^c	53.6		71.0 ^c		61.1	
Inhale again												
(24-h assessment) ^d	48.1		37.3	39.1		66.7 ^c	46.9		67.0 ^c		47.5	
Odor detection/liking												
Liking ^{b,d}	50.4		48.2	46.4		53.1	51.5		55.5		51.8	
Inhalant Effects Checklist												
Euphoria ^c (10 statements)	0.1		2.6	0.3		2.8	0.1		5.4 ^c		0.4	

For the sake of clarity the 0% nitrous oxide condition is omitted. Numbers in bold font indicate that values differ significantly from placebo as determined by Tukey post hoc testing.

^aEndpoints of 100-mm VAS: 0=not at all; 100=extremely.

^bMeasures assessed at 5 min into the sampling period in which subjects were asked to rate their response based on how they currently felt.

^cTukey post hoc testing revealed significant differences existed between light drinkers (LD) and moderate drinkers (MD).

^dResponses were made on a 100-mm bipolar VAS. For "drug liking" and "odor liking," 0=dislike a lot; 50=neutral; 100=like a lot, and for "inhale again," 0=definitely would not; 50=neutral (don't care); 100=definitely would.

^eDependent measure assessed 5 min after sampling periods; numbers represent mean number of statements endorsed out of a possible 10.