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# Residual sleepiness after $N_2O$ sedation: a randomized control trial [ISRCTN88442975]

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## Abstract

**Background:** Nitrous oxide ($N_2O$) provides sedation for procedures that result in constant low-intensity pain. How long do individuals remain sleepy after receiving $N_2O$? We hypothesized that drug effects would be apparent for an hour or more.

**Methods:** This was a randomized, double blind controlled study. On three separate occasions, volunteers (N = 12) received 100% oxygen or 20% or 40% $N_2O$ for 30 min. Dependent measures included the multiple sleep latency test (MSLT), a Drug Effects/Liking questionnaire, visual analogue scales, and five psychomotor tests. Repeated measures analysis of variance was performed with drug and time as factors.

**Results:** During inhalation, drug effects were apparent based on the questionnaire, visual analogue scales, and psychomotor tests. Three hours after inhaling 100% oxygen or 20% $N_2O$, subjects were sleepier than if they breathed 40% $N_2O$. No other drug effects were apparent 1 hour after inhalation ceased. Patients did not demonstrate increased sleepiness after $N_2O$ inhalation.

**Conclusion:** We found no evidence for increased sleepiness greater than 1 hour after $N_2O$ inhalation. Our study suggests that long-term effects of $N_2O$ are not significant.

## Background

Nitrous oxide ($N_2O$) is useful for procedures that result in constant low-intensity pain. Its use has been described in the dentist's office, in the management of orthopedic procedures in the emergency room, for colonoscopy, and for dermatologic procedures [1-7]. Specifically, it is used to control pain and provide sedation.

If patients continue to be sleepy after $N_2O$ inhalation, should they have an escort home and be told not to drive for 24 hr afterwards? In most operating rooms, after any type of sedation, patients are told not to drive or operate heavy machinery for 24 hours. In general dental offices, patients are not told to refrain for 24 hours from driving or operating heavy machinery. Few studies have examined how performance is affected after $N_2O$. Subjective and psychomotor function tests have shown that effects last less than 1 hour after $N_2O$ cessation.

Polysomnographic measures of sedation can detect effects of sedatives not detected by subjective assessment and performance measures [8]. In that study, for example, the multiple sleep latency test (MSLT) demonstrated sleepiness up to 4 hours after injection of one combination of

anesthetic drugs, and in some subjects, sleepiness continued up to 8 hours afterwards; psychomotor function was impaired only at 2 hours after injection of the drug combination.

We hypothesized that sleepiness could be measured for 1 hour or more after $N_2O$ cessation. We sought to establish a basis for decisions concerning discharge requirements and instructions for patients after $N_2O$ for sedation.

## Methods

### *Experimental design*

This was a randomized, double blind, controlled study. The experiment consisted of one practice session and three study sessions. Volunteers were always admitted on the same day of the week for each of the days of drug inhalation. Volunteers were studied after inhaling 100% oxygen, 20% $N_2O$ or 40% $N_2O$. The research technicians and subjects were unaware of the dose of $N_2O$ administered (double-blind), and concentrations were randomized. The anesthesiologist administering the agent was aware of the dose but had minimal verbal contact with the subjects during the session.

### *Subjects*

Our Institutional Review Board approved this study. Candidates who met screening criteria (healthy, non-smoking, age 21–35 years, and within 30% of ideal body weight) and who had normal sleeping habits were scheduled for a screening interview [9]. Informed written consent was obtained from subjects before the first session. During a practice session, subjects were exposed to the different tests in the battery to gain familiarity with them.

Ten men and five women volunteered for the study. On each day of testing, urine pregnancy tests were performed to ensure that female subjects were not pregnant. Subjects were asked to avoid depressants including ethanol (confirmed by measuring exhaled ethanol) and stimulants for 24 hours before study sessions. Subjects were paid for their participation upon study completion.

### *Experimental sessions*

In the first or pre-test day of study, subjects slept in General Clinical Research Center (GCRC) overnight. Their sleep was monitored with an electroencephalogram (EEG) or an activity monitor. The following day, sleep latency measured by the multiple sleep latency test (MSLT) and psychomotor performance were tabulated at 1000, 1200, 1400, and 1600 hours. Subjects were admitted to the study if average sleep latency was ≥10 min and they had no onsets of rapid eye movement (REM) sleep, which is indicative of narcolepsy. One volunteer was excluded from the study because sleep latency was too short; two others declined to participate after the first session for personal reasons. Twelve subjects went on to complete the study.

During the three study sessions, subjects again slept overnight in the GCRC. They were again monitored to ensure 8 hours in bed and adequate sleep efficiency (sleep time > 75% of time in bed). They were in bed by 2230 and were awakened at 0630. At that time, all female subjects had a urine test for pregnancy to verify a negative result. Subjects fasted overnight. At 0700 ECG electrodes, a blood pressure cuff, and oxygen saturation monitor were applied to subjects seated in a chair; ECG and oxygen saturation were measured continuously and blood pressure measurements were made every 5 min during the inhalation period.

Subjects initially inhaled oxygen through a clear anaesthesia facial mask affixed to the face via attached rubber straps that went around the head. Baseline mood and psychomotor tests were performed. Subjects were told at that time that they were not breathing a drug. Subjects were then told that for 30 min they would be breathing air that may or may not contain drug (100% oxygen, 20% $N_2O$ or 40% $N_2O$). At 10 and 20 min after the start of the inhalation period, subjects completed the mood tests and a subset of the psychomotor tests. At the end of the 30-min inhalation period, the mask was removed. At one, 3, 5, and 7 hours after inhalation ended, subjects completed the sleep latency test and tests of mood, and psychomotor performance. The technician who gave the tests was not aware of the drug administered. When no tests were scheduled, subjects were free to engage in sedentary recreational activities, but studying and sleep were not permitted. Room temperature was kept constant. Subjects were allowed to eat a small snack after the Hour-1 test, and lunch after the Hour-3 test.

### *Dependent measures*

The primary dependent variable was daytime sleepiness. Daytime sleepiness was measured with the sleep latency test. Measures of subjective effects, and psychomotor performance were also performed. All tests but the sleep latency test took 5–6 min to complete, and the order of the tests remained the same throughout the experiment. During the time that drug was inhaled, only a subset of tests was administered; these took about 3 min to complete.

### *Multiple sleep latency test (MSLT)*

The procedure for performing the MSLT has been described in detail [8]. At 1, 3, 5, and 7 hours after cessation of drug inhalation, subjects were instructed to lie down on a bed in a dark, quiet room to try to fall asleep. Sleep latency was scored in minutes to the first epoch of

non-wake [10]. Sleep latency was considered the primary dependent variable.

### *Subjective effects*

To assess subjective effects, we used two questionnaires. The Drug Effects/Liking questionnaire (locally developed) with two items assessed the extent to which subjects currently felt a drug effect on a scale of 1 to 5 (1 = "I feel no effect at all"; to 5 = "I feel a very strong effect"). The extent to which subjects liked the drug effect was assessed on a 100-mm line (0 = dislike a lot, 50 = neutral, 100 = like a lot). The Drug Effects/Liking questionnaire was filled out before drug inhalation, 10 min and 20 min into the inhalation, and 1, 3, 5, and 7 hours after inhalation had ceased.

The Visual Analogue Scale (VAS) consisted of twenty-one 100-mm lines, each labelled with one of the following adjectives (locally selected): anxious, coasting, confused, difficulty concentrating, down, drunk, elated, feel bad, feel good, floating, high ('drug high'), light-headed, nauseous, pleasant bodily sensations, pleasant thoughts, sedated, sleepy, stimulated, tingling, unpleasant bodily sensations, unpleasant thoughts. Subjects were instructed to place a mark on each line indicating how they felt now, ranging from "not at all" to "extremely." The VAS was filled out before drug inhalation, 10 and 20 min into the inhalation, and 1, 3, 5, and 7 hours after inhalation had ceased.

### *Psychomotor performance*

Subjects completed five psychomotor tests: auditory reaction time [11], visual reaction time [11], divided attention [11], the digit symbol substitution test (DSST) [12], and the Maddox Wing test [13]. All of the psychomotor tests were performed before and 1, 3, 5, and 7 hours after drug inhalation. The DSST was also performed 10 and 20 min into the inhalation period.

### *Data analysis*

Repeated measures analysis of variance was performed with drug and time as factors. F-values were considered significant for $p < 0.05$ with adjustment of within-factors degrees of freedom (Huynh-Feldt) to protect against violations of symmetry. Post-hoc testing compared the different drug concentrations at corresponding time points in the session using a priori comparisons with Bonferroni adjustments.

## Results

The mean age (±SD) was 25.3 ± 3.3 years. Mean height was 176.5 ± 10.7 cm. Mean weight was 69.9 ± 13.3 kg.

While breathing 20 or 40% $N_2O$, there was a clear drug effect. A significant interaction between drug concentration and time was observed on the drug effect rating ($p < 0.0001$) (figure 1). Post-hoc testing revealed significant concentration effects during drug inhalation (0% vs. 20% $N_2O$ $p < 0.0002$; 20% vs. 40% $N_2O$ $p < 0.0002$). Significant interaction between drug concentration and time was observed on the ratings for "difficulty concentrating" ($p < 0.025$) and "tingling" ($p < 0.05$). Significant differences on post-hoc testing during the inhalation period between 0% and 20% $N_2O$ were seen with the rating "tingling" ($p < 0.05$) and between 20% and 40% $N_2O$ with the ratings "anxious" ($p < 0.02$), and "high" ($p < 0.05$). A significant interaction between drug concentration and time was observed on the DSST test. Post-hoc testing revealed significant concentration effects during drug inhalation (0% vs. 20% $N_2O$ $p < 0.02$; 20% vs. 40% $N_2O$ $p < 0.0002$).

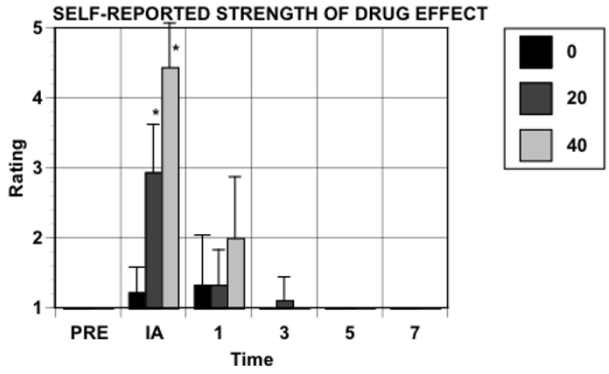


**Figure 1**

**Self-reported drug effect**. Self-reported strength of drug effect of 0%, 20% or 40% $N_2O$ is shown as a function of time. The solid bars indicate the average response time; whiskers indicate SD. PRE refers to the measure taken at baseline; IA refers to the averaged value during inhalation; 1, 3, 5, and 7 refer to hours after inhalation ceased. An asterisk represents a significant difference between a value at a given concentration at a particular time during inhalation and the lower adjacent concentration at the same time point.

After inhalation ceased, residual sleepiness was measured after 100% oxygen and 20% $N_2O$, but not after 40% $N_2O$. With the MSLT, there was a significant time effect ($p < 0.05$) and a significant drug time interaction after 100% oxygen ($p < 0.05$). When the volunteers breathed 100% oxygen, they were sleepier 3 hours after inhalation than 1 hour after inhalation ($p < 0.025$). After breathing 20% $N_2O$, volunteers took longer to fall asleep at 1 hour than at 3 hours ($p < 0.025$) (Figure 2).

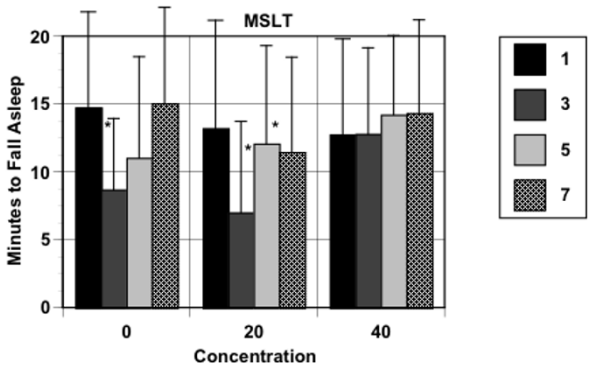


**Figure 2**
**Multiple sleep latency test**. Effects of time (1, 3, 5, and 7 hours after inhalation ceased) as a function of $N_2O$ concentration for multiple sleep latency test is illustrated. The solid bars indicate the average response time; whiskers indicate SD. An asterisk represents a significant difference between a value at a given concentration and time after inhalation ceased and the lower adjacent time point at the same concentration.

After inhalation ceased, no tests of psychomotor performance or subjective effects were significant. No significant differences were seen with auditory, visual, or divided attention reaction times, incorrect responses, or the Maddox Wing test. Figure 3 demonstrates how the subjective tests showed significant change during inhalation but not at any time after inhalation ceased.

## Discussion

We hypothesized that after 30 min of $N_2O$ inhalation, drug effects, particularly our primary variable sleep latency, could be measured at least 1 hour afterwards and perhaps longer. If our hypothesis were true, it would support the (hospital) practice of not allowing patients to drive home after inhaling nitrous oxide. Proscribing certain activities (e.g., driving, operating heavy machinery, or cooking for the remainder of the day) after $N_2O$ inhalation would also apply. Our hypothesis, though, was disproved. During $N_2O$, inhalation subjects had mood and psychomotor effects. Depending on the concentration, subjects felt a drug effect and were anxious; had difficulty concentrating; felt high, light-headed, and tingling; and showed impairment on the DSST. One hour after inhalation stopped, these effects were not significant.

Despite no evidence of sleepiness 1 hour after $N_2O$ inhalation, 3 hours after drug inhalation subjects were sleepier than at 1 hour after inhalation, particularly when no or 20% $N_2O$ was inhaled. This result may be attributed to the fact that sleep propensity follows temperature rhythms and has a moderate nadir in the middle of the day [14]. Why we did not find this effect after 40% $N_2O$ is unclear. Rebound insomnia is known to occur after depressants such as alcohol and benzodiazepines [15].

We did not measure end-expired concentrations of $N_2O$, measurements that are not reliable when a facemask is used. Our anaesthesia machine was calibrated, although room air may have leaked in through the facemask during inhalation. Yet, our results are similar to those of others who have studied the effects of inhaled $N_2O$. In one study, 22 min after subjects inhaled 30% $N_2O$, psychomotor performance had returned to baseline [16]. In another study, when 40% $N_2O$ was inhaled for 30 min, self-reported strength of drug effect was significant and subjects felt drunk, spaced out, and high [17]. By 60 min after drug inhalation had ceased the drug effect disappeared. In a previous study, we found that, although psychomotor function tests indicated no effect 2 hours after drug injection, shorter sleep latency times were significant for at least 4 hours after injection of midazolam and fentanyl for sedation [8]. Although we hypothesized similar results with $N_2O$, the results were not similar.

In many areas of healthcare, 40% $N_2O$ has been used with a great degree of safety. 20% $N_2O$ is not typically used. We included the lower $N_2O$ concentration in our study to see if there was a linear dose response.

Many procedures in ambulatory care facilities are performed on patients who have concomitant disease, chronic obstructive pulmonary disease and sleep apnoea. Our results may not be applicable to these patients and may not be generalized because other variables were not considered. Patients may experience pain because of a procedure, and our volunteers did not. Nitrous oxide inhalation may be needed for longer than 30 minutes for procedures. Nitrous oxide might also be used with other drugs. Shift workers may be tired during the day and this sleepiness might interact with the effects of the drugs. Similarly, individuals might not sleep well prior to their procedure, and we only studied individuals who slept normally prior to receiving $N_2O$.

In many studies, $N_2O$ performance, memory, or mood with $N_2O$ have been measured during $N_2O$ inhalation, not after. When painful transcutaneous electrical stimulation and somatosensory evoked potentials were used to examine the time course of function for up to 35 minutes after 50% $N_2O$ inhalation, impairment lasted as long as 35 minutes afterwards and was as great as impairment during inhalation [18]. In another study in which a driving simulator was used, errors increased 15 minutes after exposure to 50% and 70% $N_2O$ [19]. Mood changes

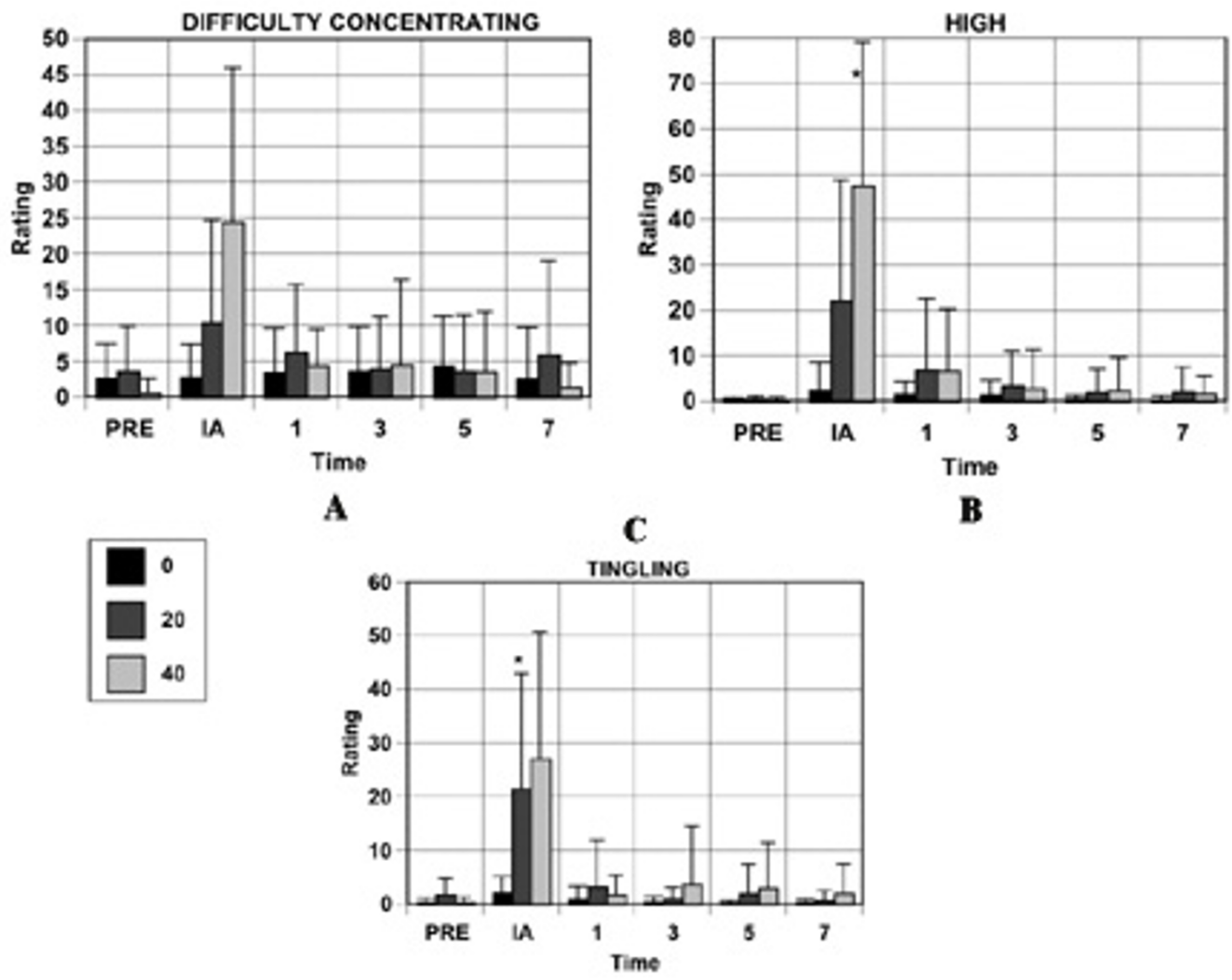


**Figure 3**

**Other drug effects**. Effects of 0%, 20% or 40% $N_2O$ as a function of time for having difficulty concentrating (figure 3a), feeling high (figure 3b), and tingling (figure 3c) are illustrated. The solid bars indicate the average response time; whiskers indicate SD. PRE refers to the measure taken at baseline; IA refers to the averaged value during inhalation; 1, 3, 5, and 7 refer to hours after inhalation ceased. An asterisk represents a significant difference between a value at a given concentration at a particular time during inhalation and the lower adjacent concentration at the same time point.

(mental and physical sedation) were evident up to 15 minutes after 25% $N_2O$ inhalation, although no impairment was found during the recovery period by objective tests. According to a series of tests that take about five minutes to perform, memory returned to baseline after 20 minutes, but subjective effects of $N_2O$ extended for up to 8 hours [20]. Others who studied the possible interaction of $N_2O$ with ethanol, found a drug effect for at least one hour after 30% $N_2O$ inhalation ceased [21]. Performance effects in other studies lasted only five minutes [16,22].

## Conclusions

In conclusion, we found no evidence for increased sleepiness 1 hour or greater after $N_2O$ inhalation. Our study suggests that long-term effects of $N_2O$, particularly sleepiness, are not significant. Patients should be advised to avoid activities shortly after $N_2O$ inhalation that might

harm themselves or others. After one hour, though, there is no evidence for abstaining from normal activities. The data presented in this study only applies to $N_2O$ given alone. No inference regarding $N_2O$ with additional sedatives can be made regarding post-administration impairment. Further study is warranted in patients with concomitant disease or in those who have inhaled $N_2O$ for longer periods.

## Competing interests

None declared.

## Authors' contributions

JLL conceived of the study and participated in its design and coordination. BSL participated in the coordination of the study. MBZ performed the statistical analysis. All authors read and approved the final manuscript.

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## References

1. Weinstein P, Milgrom P, Ramsay DS: **Treating dental fears using nitrous oxide oxygen inhalation and systematic desensitization.** *Gen Dent* 1988, **36:**322-326.
2. Ward KR, Yealy DM: **Systemic analgesia and sedation in managing orthopedic emergencies.** *Emerg Med Clin North Am* 2000, **18:**141-66, vi.
3. Saxen MA, Newton CW: **Managing the endodontic patient with disabling anxiety or phobia.** *J Indiana Dent Assoc* **78:**21-23. 1999–2000
4. Luhmann JD, Kennedy RM, Porter FL, Miller JP, Jaffe DM: **A randomized clinical trial of continuous-flow nitrous oxide and midazolam for sedation of young children during laceration repair.** *Ann Emerg Med* 2001, **37:**20-27.
5. Forbes GM, Collins BJ: **Nitrous oxide for colonoscopy: a randomized controlled study.** *Gastrointest Endosc* 2000, **51:**271-277.
6. Maloney JM 3rd: **Nitrous oxide-oxygen analgesia in dermatologic surgery.** *J Dermatol Surg Oncol* 1980, **6:**447-449.
7. Otley CC, Nguyen TH: **Safe and effective conscious sedation administered by dermatologic surgeons.** *Arch Dermatol* 2000, **136:**1333-1335. 8.31–41
8. Lichtor JL, Alessi R, Lane BS: **Sleep tendency as a measure of recovery after drugs used for ambulatory surgery.** *Anesthesiology* 2002, **96:**878-883.
9. Carskadon MA, Dement WC: **Nocturnal determinants of daytime sleepiness.** *Sleep* 1982, **5(Suppl 2):**S73-81.
10. Rechtschaffen A, Kales A, ed: *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects* Washington D.C.: Public Health Service; Bethesda: National Institutes of Health; 1968.
11. Nuotto EJ, Korttila KT: **Evaluation of a new computerized psychomotor test battery: effects of alcohol.** *Pharmacol Toxicol* 1991, **68:**360-365.
12. Wechsler D: *The measurement and appraisal of adult intelligence* Baltimore, MD, USA: Williams and Wilkins; 1958.
13. Hannington-Kiff JG: **Measurement of recovery from outpatient generalanaesthesia with a simple ocular test.** *Br Med J* 1970, **3:**132-135.
14. Roehrs T, Zorick FJ, Roth T: **Transient and short-term insomnias.** In *Principles and practice of sleep medicine* third edition. Edited by: Kryger MH, Roth T, Dement WC. Philadelphia, PA: W. B. Saunders Company; 2000:624-632.
15. Roehrs T, Roth T: **Hypnotics, alcohol, and caffeine: relation to insomnia.** In *Understanding sleep: the evaluation and treatment of sleep disorders* Edited by: Pressman MR, Orr WC. American Psychological Association; 1997:339-355.
16. Korttila K, Ghoneim MM, Jacobs L, Mewaldt SP, Petersen RC: **Time course of mental and psychomotor effects of 30 per cent nitrous oxide during inhalation and recovery.** *Anesthesiology* 1981, **54:**220-226.
17. Zacny JP, Sparacino G, Hoffmann P, Martin R, Lichtor JL: **The subjective, behavioral and cognitive effects of subanesthetic concentrations of isoflurane and nitrous oxide in healthy volunteers.** *Psychopharmacology (Berl)* 1994, **114:**409-416.
18. Herwig LD, Milam SB, Jones DL: **Time course of recovery following nitrous oxide administration.** *Anesth Prog* 1984, **31:**133-135.
19. Moyes D, Cleaton-Jones P, Lelliot J: **Evaluation of driving skills after brief exposure to nitrous oxide.** *S Afr Med J* 1979, **56:**1000-1002.
20. Cheam EW, Dob DP, Skelly AM, Lockwood GG: **The effect of nitrous oxide on the performance of psychomotor tests. A dose-response study.** *Anaesthesia* 1995, **50:**764-768.
21. Zacny JP, Camarillo VM, Sadeghi P, Black M: **Effects of ethanol and nitrous oxide, alone and in combination, on mood, psychomotor performance and pain reports in healthy volunteers.** *Drug Alcohol Depend* 1998, **52:**115-123.
22. Zacny JP, Lichtor JL, Coalson DW, Apfelbaum JL, Flemming D, Foster V: **Time course of effects of brief inhalations of nitrous oxide in normal volunteers.** *Addiction* 1994, **89:**831-839.

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