# Nitrous Oxide/Oxygen Sedation and the Single-dose Sedative

Used in combination, these two agents form a powerful partnership.

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## ABSTRACT

The link between patient fear and dental avoidance has been documented in cultures around the world. Nitrous oxide is among the oldest and safest dental analgesics. When used as a monotherapy, however, nitrous may not provide adequate sedation for the highly anxious and phobic patient. Modern oral sedatives—medications benefiting from decades of rigorous study—offer consistent relief of anxiety as well as sedation to complement the analgesic properties of nitrous. This article examines the pairing of nitrous oxide and the single-dose sedative and identifies factors in the creation of a safe clinical environment. Adherence to established protocols for nitrous and the single-dose oral sedative can plausibly reduce patient anxiety and the multitude of patients failing to seek care, as well as reduce expenses related to deferred oral health.

## LEARNING OBJECTIVES

- Discuss the advantages of nitrous oxide and oxygen analgesia/sedation and reasons for pairing it with common oral sedatives.
- Identify the different types of sedation.
- Learn the importance of taking a patient's medical history to assess his or her suitability as a sedation candidate.

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Overwhelming desire for pain relief is often the trigger that prompts patients to seek medical or dental care, yet the link between patient fear and dental avoidance has been well documented globally.[1-4] For this reason, treating pain has assumed a central place in the practice of modern dentistry. Of course, attempts to mitigate pain are hardly new; they are as old as the art of healing. The use of morphine from opium poppies dates back to prehistoric times; Homer refers to the drug in *The Odyssey*.[5] Alcohol has served as a mainstay on the battlefield for hundreds of years. The Romans relied upon the mandrake root as an anesthetic.[6] Today's pain control arsenal recognizes both the multifaceted aspects of the myriad sources of pain along with the unique attributes of individual response. Current palliative care provides not only pharmacological tools but psychological and physiological ones, including exercise; therapy; desensitization; acupuncture; transcutaneous electrical nerve stimulation, and many other treatments and resources.

In dental practice proficient local anesthetic technique is imperative for obtaining desired pain control. The use of nitrous oxide—either alone or in combination with sedatives or analgesics—cannot substitute for this proficiency. Nitrous oxide is among the oldest and safest dental analgesics. When used as a monotherapy, however, nitrous may not provide adequate sedation for the highly anxious and phobic patient.[7] However, nitrous oxide provides a vital addition to the dental practitioner's armamentarium that directly treats pain, discomfort, anxiety, and needle or other phobias unrelieved by the use of local anesthesia alone.

While contemporary analgesic agents are vastly superior to their primitive predecessors, each still carries singular advantages and limitations. Paradoxically, despite ongoing advancements and the widespread adoption of policies guaranteeing the right to timely pain relief, evidence suggests widespread disparities persist. The Institute of Medicine recently labeled inconsistent pain control a public health threat and called for a multidisciplinary "transformation" in the nation's priorities and attention.[8]

## Nitrous Oxide's Long Reach

Among the oldest and most reliable sources of pain relief is nitrous oxide. England's Sir Humphry Davy first published the results of his experiments with this odorless, colorless gas in 1800. By the 1840s, New York dentist Horace Wells would successfully address the pain patients experience during extractions with nitrous. (Wells, of course, used 100% nitrous; this method would never be applied today because it poses a high risk of hypoxemia.) While the following decades would see many other innovations in anesthesia—ether, chloroform, and lidocaine to name a few—nitrous oxide would remain a popular vehicle in the medical field generally but particularly in dentistry. A study of nitrous administration in dental offices reported that around 75% of the respondents had used nitrous oxide in the previous year.[8,9]

The popularity of nitrous is all the more remarkable given that understanding of its underlying mechanisms remains incomplete. Its numerous advantages are very clear. Many studies equate the benefits of 30% to 50% nitrous oxide/oxygen with 10 mg to 15 mg morphine.[10] Nitrous is relatively straightforward to administer and titration is easily accomplished. Nitrous

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**TABLE 1**

### Contraindications to Nitrous Oxide Use

| ABSOLUTE CONTRAINDICATIONS | RELATIVE CONTRAINDICATIONS |
|---|---|
| Methionine synthase pathway enzyme deficiencies | Pulmonary hypertension |
| Possible gas-filled spaces | Prolonged anesthesia (> 6 hours) |
| • Emphysema | First-trimester pregnancy |
| • Pneumothorax | High-risk nausea and vomiting |
| • Middle ear surgery | Risk of myocardial ischemia (putative) |
| • Air embolus | |
| Raised intracranial pressure | |

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takes effect in as few as 30 seconds, with peak effects occurring in less than 5 minutes. Recovery is comparably rapid, also averaging 5 minutes. Protective reflexes such as coughing and gagging continue intact. Training requirements correspond to guidelines for the administration of minimal sedation.[11] And nitrous is also tolerated by a wide variety of patients. Nitrous is completely eliminated from the body when 100% pure oxygen is applied after its termination. It is not metabolized in the body.

The few disadvantages to nitrous oxide include central nervous system depression, nausea, and vomiting; these factors are usually the result of higher concentrations over longer exposure. Absolute and relative contraindications are easily avoided in office-based dentistry with proper screening (Table 1).[12]

Many studies have raised questions about the place of nitrous in modern healthcare, citing an association with a higher incidence of postoperative complications.[13] Others question the methodology of these studies and say the evidence is not only scant but also inadequate to ban such a longstanding tool. They maintain that, in or out of the dental office, there simply exists no viable alternative to this effective and affordable analgesic/sedative. Moreover, other research suggests that appropriate training in the use of nitrous oxide—rather than type of practitioner—represents the most significant factor in safe patient outcomes.[14,15]

## Oral Sedatives and Nitrous: A Marriage of Convenience

As an analgesic/sedative, nitrous boasts only a short duration of action. Thus, it represents a less than perfect palliative. The pairing of nitrous with other pharmacologic sedatives deepens the effects of each, magnifying what one provides alone. It is important to stress that in the dental office, this combination is meant to achieve anxiolysis, the mildest form of sedation. The patient continues to stay alert and respond to cues, but experiences greatly reduced anxiety. Others find that taking a sedative the evening before ensures a restful sleep prior to the dental appointment, and thus produces a less stressful encounter.

Around the world, sedatives are most often administered orally (Figure 1). Routes of drug administration include enteral (absorption across the enteric membranes of the gastrointestinal tract) or parenteral (bypassing the enteric membranes). Enteral routes can involve either the oral and rectal pathways, while parenteral may be accomplished via intramuscular (IM), intravenous (IV), subcutaneous (SC), or inhalation methods.

Among the advantages of oral sedatives are their ease of administration, universal acceptance, low cost, decreased number and severity of adverse reactions, and lack of reliance upon syringes or specialized training. Disadvantages include dependence on patient compliance, a prolonged latent period, erratic absorption from the gastrointestinal tract, inability to titrate, prolonged duration of action, and inability to readily lighten or deepen the level of sedation.

Levels of sedation correspond to the degree of depression of the central nervous system. Older, more traditional terms such as *anxiolysis* and *conscious sedation* have been largely replaced by terms more consistent with those used in medical practice, for example, *minimal* and *moderate sedation*. The definition of moderate sedation is a depressed state allowing a patient to respond purposefully to verbal stimuli. No interventions are needed to maintain the airway. Spontaneous ventilation is adequate and cardiovascular functions are usually maintained. In deep sedation, the patient may not respond to physical or verbal stimuli, be able to maintain reflex mechanisms, or breathe without assistance. Under general anesthesia, individuals are rendered unconscious, unable to respond to physical or verbal stimuli or breathe on their own (Table 2).

**TABLE 2**

### Glossary of Sedation Terms (from the American Dental Association)

**ANXIOLYSIS** is the diminution or elimination of anxiety.

**CONSCIOUS SEDATION** represents a minimally depressed level of consciousness that retains the patient's ability to independently and continuously maintain an airway and respond appropriately to physical stimulation or verbal command; it is produced by a pharmacological or non-pharmacological method or a combination thereof.

**MINIMAL SEDATION** means a minimally depressed level of consciousness, produced by a pharmacological method, that retains the patient's ability to independently and continuously maintain an airway and respond normally to tactile stimulation and verbal command. Although cognitive function and coordination may be modestly impaired, ventilatory and cardiovascular functions are unaffected.

**MODERATE SEDATION** is a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.

## Benzodiazepines

Benzodiazepines constitute the largest class of medications currently used for oral sedation.[16] They lack analgesic properties, and profound local anesthesia is required to perform painful dental procedures. Benzodiazepines were first introduced in the 1960s and possess sedative as well as hypnotic properties. Their efficacy is equivalent to or greater than any of the other classes of sedatives and their safety profile is excellent.[16] Virtually all effects of the benzodiazepines result from their specific actions on the central nervous system. All benzodiazepines affect gamma-aminobutyric acid (GABA) receptors. GABA is an inhibitory neurotransmitter. Because GABA is an inhibitory neurotransmitter, and GABA reduces the activity of nerves in the brain, benzodiazepines are thought to work by increasing the effects of GABA in the brain.[17] Benzodiazepines decrease the activity of interneurons containing GABA-receptor complexes involved in regulating central nervous system circuits associated with arousal, attention, anxiety, and pain perception.[18]

Common examples of the benzodiazepine class of drugs include triazolam (Halcion®), lorazepam (Ativan®), and diazepam (Valium®). According to the Food & Drug Administration, among the contraindications of one or more of these medications are pregnancy, known hypersensitivity, acute narrow-angle glaucoma, and impaired renal function.

Adverse events from the use of oral sedatives in the dental facility are exceedingly rare, particularly when contrasted with other settings and regimens. In American hospitals, for example, the mortality rate associated with general anesthesia is 1 in 200,000.[19] Respiratory depression represents the principle negative that is introduced with any sedation.

## Assessing Patients, Ensuring Safe Candidates

As already discussed, the use of nitrous oxide and oxygen sedation and single-dose oral sedatives has proven to produce few unwanted consequences. Nevertheless, standard practice dictates that the patient's medical situation be carefully explored before administration of any analgesia or sedation. Dentists should document evidence of existing medical conditions; the presence of major system abnormalities; any history of previous adverse sedation or anesthesia reactions; known allergies; and any indication of alcohol, tobacco, or substance abuse, among other factors.

Classifications developed decades ago by the American Society of Anesthesiologists, such as the ASA Physical Classification System, remain useful in the process of patient selection. These assess individuals from ASA I (those without systemic disease) along a continuum to ASA IV and E (people either suffering from life-threatening conditions or likely near death). The system of categorization remains helpful in determining whether or not a patient is a good candidate for sedation.

Clinicians should always choose the sedative agent that best suits the patient based on age, weight, and medical history; this important decision should never be based solely upon the length of

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time required for the dental treatment.

Before any sedation, and even where law does not require such consent, the patient should be informed about the intent of the procedure and how it will be accomplished. This discussion should include the risks, benefits, and alternatives to the use of nitrous oxide and sedatives and allow the opportunity for the patient to ask questions. Informed consent should be obtained from the patient and/or the patient's legal guardians if the patient is a minor.

## Medically Complex Population

Among the most rapidly growing populations in healthcare is the medically complex patient. Fueled by an aging demographic, the number of those who suffer from more than one chronic condition—and who regularly take more than three medications—is increasing quickly.[20] This phenomenon makes an overwhelming case for the ready availability of sophisticated real-time desktop drug-interaction software. Various comprehensive reviews, which include potential adverse drug interactions with oral benzodiazepines, have been recently published in the dental literature.[21,22]

Consultation with the medical doctor may be warranted in order to understand any treatment the patient is undergoing and the extent to which their underlying conditions are in control. While patients with complex medical problems require careful evaluation as sedation candidates, this does not mean they are inappropriate recipients. In fact, they often signify sedation's biggest beneficiaries.

The reason is the likelihood that anxiety and pain will accelerate the heart rate and blood pressure of these patients. This leads to increased oxygen demand of the myocardium. With coronary artery disease, this heightened oxygen requirement may not be met. Episodes of angina and dysrhythmias can result. Therefore, use of sedation in addition to provision of profound local anesthesia during the procedure becomes extremely important. Decreased stress provided by oral sedation can greatly benefit these patients, especially during long or traumatic appointments. Prudent use of postoperative analgesics has the goal of continuing this process.

## Red Flags

In addition to pre-existing medical conditions, a red flag for the practitioner is simply age. For geriatric patients (defined as 65 or older), many physiological and psychological changes take place, such as decreases in cerebral blood flow, cardiac output, renal and hepatic blood flow, and pulmonary function. Furthermore, these individuals tend to suffer from at least one chronic condition such as heart disease, hypertension, arthritis, osteoporosis, and noninsulin-dependent (type 2) diabetes mellitus, all requiring long-term control with drug therapy and, occasionally, surgery.[16] As well, this group tends to metabolize and excrete drugs differently. Thus, they are more likely to develop adverse drug reactions. Recommendations for this group are lower dosages and shorter-acting medications (such as triazolam) to reduce the possibility of oversedation.[16]

Patients of any age whose chronic conditions are not under adequate control should also raise an alarm. Diabetics, for example, are much more likely to experience an infection that is difficult to control. The presence of chronic obstructive lung disease presents an increased risk for hypoxemia. Obesity has reached endemic proportions and may be associated with undiagnosed diabetes, hypertension, exercise intolerance, vascular heart disease, some cancers, and sleep apnea.[23] Obesity is defined as a body mass index (BMI) of greater than 30. The BMI is the patient's weight measured in kilograms divided by height (in meters) squared. When the patient has a BMI higher than 35, a diagnosis of morbid obesity is made; this increases the severity of the above medical conditions. Ventilation problems with sleep apnea can result from decreased lung volumes, decreased anatomical patency of the airway, and dysfunction of respiratory drive.[24] Obesity, the presence of chronic obstructive pulmonary disorder, and sleep apnea each pose a greater danger of airway emergency.[25]

## Protecting the Airway

When providing sedation, the airway is always of chief concern, regardless of the level provided. While it is unlikely that appropriate doses of the drugs commonly used for oral sedation to produce anxiolysis will produce significant respiratory depression, this should not be confused with airway obstruction. Obstruction and respiratory depression are not synonymous. For example, a patient's airway may become obstructed by depression of the mandible during treatment. Until this occurs, a sedated patient may breathe normally, but fail to initiate ventilatory effort sufficient to overcome this obstruction; thus, hypoxemia can occur. The risk of obstruction is a consideration when using any central nervous system (CNS) depressant, regardless of its ability to actually depress the medullary respiratory drive.

The sedation team must continually observe the position of the patient's airway, as well as the rise and fall of the chest; breathing sounds, with or without a stethoscope; and skin and mucosa color (hypoxia lends the skin a blue tint).

## Monitoring

The standard of care for the anesthesia community involves monitoring vital signs before, during, and after the operative procedure. Regulatory agencies publish similar requirements, for example, the American Society of Anesthesiologists has its own "Standards & Guidelines," in which it recommends that evaluation include the level of consciousness, pulmonary ventilation, oxygenation, and hemodynamics.

Depending on the clinical setting and the treatment performed, some vital signs will be evaluated more frequently than others. Blood pressure, pulse, and respiration are the most dynamic vital signs. The oxygen saturation level is a critical statistic during sedation procedures, and therefore monitoring of pulse oximetry is an absolute necessity. The patient's weight, especially if the patient is obese, relates directly to the risk to airway patency and maintenance. Obesity is best measured by body mass index (BMI) as defined above.

Postoperative vital signs serve as a measure of recovery. These values are compared with those obtained preoperatively and are assessed for the degree of variation. Vomiting should not occur when nitrous oxide and oxygen sedation is appropriately administered. The clinical team must be prepared for this adverse event; however, it is more frequently associated with moderate sedation. Levels of consciousness can be monitored by the patient's response to verbal stimulation. Monitoring ventilatory function can be accomplished by observation and/or auscultation. Pulse oximetry reports oxygen desaturation and can detect early hypoxemia. Early detection of hypoxemia through the use of a pulse oximeter decreases the likelihood of severe adverse reactions.

## Emergency Preparedness

Healthcare personnel in any setting should possess a basic knowledge of the pharmacokinetics and pharmacodynamics of any medications they supply. They should know how to recognize complications and quickly respond to them. In addition, practitioners should be certified in basic life support, including CPR and the management of airway obstruction for adults, children, and infants. In the case of sedation practitioners, more advanced airway certification should be obtained through the American Dental Association (ADA) or

EXAMPLES OF ORAL SEDATIVES

| | Brand Name | Duration | 1/2 Life | MRD | Dosage | Generic Name |
|---|---|---|---|---|---|---|
| | | in hours | | milligrams | | |
| | Valium® | 6-8 | 20-100 | 10 | 2.5-10 | diazepam |
| | Halcion® | 2-3 | 1.5-5 | 0.5 | 0.125-0.75 | triazolam |
| | Ativan® | 6-8 | 12-14 | 3 | 1-4 | lorazepam |

**FIG. 1**

**SEDATIVE DRUGS BY CLASS (1.)** The three most commonly prescribed sedatives and their durations and dosages.

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the American Heart Association (AHA).

The automated external defibrillator is increasingly required in dental offices (most recently the state of New York mandated acquisition of the AED). Even when moderate sedation is not the intent, the provider should be prepared to handle sedation one level beyond the intended level of consciousness as well as be trained to address emergency situations.

Other recommended equipment includes a positive-pressure ventilation system, adequate suction to clear an airway, and advanced airway equipment. Flumazenil is a specific antagonist of the effects of benzodiazepines and should always be available for nitrous/oral benzodiazepine sedation procedures. It must be given parenterally (intravenously or intramuscularly), and practitioners should be trained on how to administer it.

## Nitrous Technique: Titration

It is important that operators are confident in their ability to administer nitrous oxide. The key to technique is careful titration combined with keen observation of patient response (Figure 2). Occasional cases are reported during which patients' experience with nitrous is negative. In these instances the operator very likely did not titrate properly. For this reason, the importance of learning to titrate competently is among the most valuable skills a nitrous-oxide/oxygen-sedation clinician can learn.

*Titration* refers to the administration of a drug in increments toward a desired endpoint. For nitrous oxide and oxygen analgesia and sedation, nitrous oxide is provided incrementally until the patient has reached a state that is relaxed and comfortable. The ability to titrate a drug represents an important advantage because it allows a specific amount to be delivered, and the patient does not receive any more of the drug than is necessary.

## Oversedation

A wide range of responses has been associated with nitrous-oxide sedation.[26,27] Individual variability causes some to experience many sensations, others fewer. Patients may notice discomfort but not remark about the unpleasant feelings until afterward. Also reported are dreams, hallucinations, and/or sexual fantasizing. Signs of relaxation can disappear and then be replaced by restlessness and even combativeness (known as disinhibition).

Oversedated patients may want to sleep and find it difficult to keep their eyes open. Their eyes may turn fixed and nonresponsive. Fits of uncontrollable laughter have been reported. Words may be slurred or repeated, and sentences turn incoherent. The patient may not be able to respond to verbal commands. Vomiting may occur, especially in children.

## Scavenging Systems

When used properly, nitrous oxide is a safe inhalation anesthetic. However, chronic exposure by health personnel has been the source of study for decades. Evidence has linked chronic exposure of high levels of nitrous to harmful effects on reproduction.[24] But to date, no direct causal relationship has been proved between reproductive health and scavenged low levels of nitrous.

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Nevertheless, the use of proper scavenging systems is highly recommended. These systems include accurate flowmeters, scavenging masks, and a vacuum system able to eliminate gases at least 45 liters per minute. The gases should vent to the outside. Types of scavenging systems have been evaluated with variation reported among different manufacturers.[28]

Safety guidelines range from a maximum of 25 parts per million of air from the National Institute of Occupational Safety and Health (NIOSH)[29] to 50 ppm from the American Conference of Governmental Industrial Hygienists (ACGIH).[30] Routine use of a dental safety mask reduces exposure to nitrous oxide as does keeping the patient's talking to a minimum.

Once the nitrous flow is terminated, patients should continue to receive 100% oxygen during the final minutes of the operative procedure. This begins the required postoperative oxygenation period of 5 minutes minimum. Should the patient report any lethargy, dizziness, lightheadedness or headache, continue the 100% oxygen for additional minutes until symptoms are eliminated and the patient feels normal. When that is achieved, the nasal hood can be removed and the patient returned to breathing normal room air.

## The Case for Compassionate Care

The aging population brings with it a new universe of issues with regard to dentition. The exploding rate of caries—which affects all ages—has been called a public health crisis.[31] These escalating numbers and challenging problems are potent reminders of the need for more dental services, rather than less. Yet 50 years of effort has not appreciably altered the percentage of the population that avoids dental care due to fear. Anxiety has not abated despite extraordinary innovations in pain control and dental materials.[32]

Studies throughout the world indicate that the achievement of minimal sedation through oral sedation enjoys a wide margin of safety.[33,34] While these are neither sufficiently numerous nor persuasively large enough to establish scientific certainty, they make a strong case for the widespread availability of minimal sedation, which has been demonstrated to help a variety of underserved groups.

A 2007 study examined the practices of the members of DOCS Education; the report included the largest number of subjects so far in the literature of enteral sedation. (Founded in 1999 by the author and Dr. Anthony Feck, DOCS Education has taught courses across the United States and Canada in oral, pediatric, and IV sedation to more than 18,000 dental professionals.) Its conclusion was that a compelling connection existed between safe outcomes and trained practitioners who monitor patients with pulse oximetry, blood pressure measurement, and direct observation.[35]

## Conclusion

The gap between people in need and the number of trained sedation dentists remains uncomfortably large. More clinical studies can—and will—shore the foundation of safety. But the practitioner can also play a role. Just as the Institute of Medicine has recommended, doctors might better heed the call from their patients for relief from pain. Additional didactic and hands-on training by clinicians in sedation techniques will only improve the efficacy and safety of pain and anxiety control in the outpatient dental setting.

***Disclosure***

Dr. Silverman is one of the founders and is an employee of DOCS Education, which conducted one of the studies cited in this article. Dr. Hexem receives speaker's fees from DOCS Education.

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FIG. 2

**MAINTAIN VIGILANCE (1.)** Patient reaction should be carefully monitored during the administration of nitrous oxide.

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**Please fill out the Answer Sheet on page xx or your answers will not be valid.**

**1** What are the respective timepoints for nitrous taking effect?

- **A.** 30 seconds, with peak occurring in less than 5 minutes
- **B.** 2 minutes, with peak occurring in 10 minutes
- **C.** 5 minutes, with peak occurring in 10 minutes
- **D.** 10 minutes, with peak occurring in 20 minutes

**2** The disadvantages to nitrous oxide include:

- **A.** central nervous system depression.
- **B.** nausea.
- **C.** vomiting.
- **D.** all of the above

**3** Sedatives are most often administered:

- **A.** rectally.
- **B.** sublingually.
- **C.** orally.
- **D.** intravenously.

**4** Which of the following is the largest class of medications currently used for oral sedation?

- **A.** tetracyclines
- **B.** benzodiazepines
- **C.** barbiturates
- **D.** morphine

**5** When assessing a patient for sedation, dentists should document any evidence of:

- **A.** existing medical conditions.
- **B.** major system abnormalities.
- **C.** history of substance abuse.
- **D.** all of the above

**6** In addition to pre-existing medical conditions, what is a red flag for using oral sedation?

- **A.** Age
- **B.** Gender
- **C.** Ethnicity
- **D.** all of the above

**7** Obesity is defined as a body mass index (BMI) greater than:

- **A.** 10.
- **B.** 20.
- **C.** 30.
- **D.** 40.

**8** Which of the following should be monitored closely while oral sedation is being administered?

- **A.** Heart rate, pupil reaction, respiratory rate
- **B.** Blood pressure, pulse, respiration, oxygen saturation level
- **C.** Body temperature, pupil reaction, heart rate, skin color
- **D.** Skin color, blood pressure, heart rate, pupil reaction

**9** Among the signs of nitrous oxide/oxygen oversedation is:

- **A.** eyes that appear fixed and nonresponsive.
- **B.** uncontrollable laughter.
- **C.** slurred, incoherent speech.
- **D.** all of the above

**10** With regard to nitrous exposure, the following is the maximum recommended in a dental operatory by the National Institute for Public Health and Safety:

- **A.** 5 parts per million of air.
- **B.** 10 parts per million of air.
- **C.** 25 parts per million of air.
- **D.** 50 parts per million of air.

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Inside Dentistry

**September 2011**

**Nitrous Oxide/Oxygen Sedation and the Single-dose Sedative**

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Please circle your level of agreement with the following statements.
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| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
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