Nitrous Oxide in Pediatric Dentistry

A Clinical Handbook

Kunal Gupta
Dimitrios Emmanouil
Amit Sethi
Editors

Springer

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Dedicated
to all the child patients
and
pediatric dentists

Foreword

It is with great pleasure that I write a few words for my colleagues about their exciting new book. This publication provides the reader with theoretical and clinical knowledge on the use of nitrous oxide sedation, a sedation technique used in dentistry for decades, but not available to dentists in all countries. It also highlights the ever-increasing need for knowledge in the field of pediatric sedation worldwide.

India is considered one of the emerging superpowers of the world. This potential is attributed to several indicators, the primary ones being its demographic trends and a rapidly expanding economy. As such, there is a large child population and the growth in demand for dental services has forced professionals to explore and develop techniques used in the field of sedation elsewhere.

Children require specific behavior management techniques to provide them with adequate and compassionate care. Dentists address this clinical requirement with a diversity of non-pharmacological and pharmacological techniques, which differ according to country and resources. Important variables include cultural aspects, current trends in parental expectations worldwide, training and experience in the field of pediatric dentistry, and especially, education in the field of pediatric sedation. Dentists now face many challenges in the management of their young patients.

Dr. Gupta and Dr. Sethi's vision and experience among their colleagues are a sign of the new demands for services in the field of pediatric dentistry. Prof. Emmanouil brings diversity and vast experience in this field. He is a well acclaimed and renowned lecturer internationally and he continues to research on the use of nitrous oxide in our profession. As an experienced pediatric dentist myself, a sedationist and lecturer in the field of pediatric dental sedation, it is heartwarming to see colleagues join forces and edit this publication for the benefit of dentists and children overall.

This publication is a comprehensive book on the history and background, mechanism of action, and the clinical use of nitrous oxide in children. Each chapter addresses different components and the publication is well referenced. Although nitrous oxide has been around for a long time, its use in pediatric dentistry is not widespread worldwide. Increasing demand for the use of sedation in our field makes this book the perfect reference for the clinician learning the use of nitrous oxide.

I am sure this publication will become a great tool for clinicians wanting to expand their knowledge, and a second edition at some stage in future will continue its legacy.

Eduardo A. Alcaino, BDSc (Hons), MDSc (Paeds) MRACDS
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Preface

Pediatric dentistry is one of the most challenging specialities of dentistry because providing good quality clinical work to child patients is dependent not only on the clinical expertise of the operator but more importantly on the behavior guidance skills. Behavior management is an integral part of pediatric dentistry; however, many a time nonpharmacologic techniques are not adequate.

After graduating, I practiced pediatric dentistry without nitrous oxide for quite a few years. Although having seen its use in many countries, and reading about it, I always wondered why was it not used in India. Some dreams do come true, and I got an opportunity to practice this technique. Soon after, I began to realize the change it brought in my clinical practice, and I termed it as the "backbone of pediatric dentistry."

However, it has a stigma attached to it for being a "pharmacologic agent" of behavior management and is commonly but incorrectly kept at the same pedestal as general anesthesia. Aren't we doing operative/surgical procedures which do require the use of pharmacologic agents like local anesthesia? Then why do we shy away from the routine use of nitrous oxide in pediatric dentistry when, with its use, we can make fearful children grow into adults without having fear of dentistry? Why is a pediatric dentist termed an "ideal pediatric dentist" only when he/she uses nonpharmacologic behavior management?

Child is not a miniature adult, and similarly, nitrous oxide in pediatric dentistry is little different from that in adults, mainly because of the lack of adequate communication from children and lower cognitive ability than grown-ups. However, with appropriate use of behavior guidance skills, nitrous oxide can be practiced well in children. And this stimulated me to write this book, because I felt a need to highlight the integration of basic behavior guidance, which starts with recognition of fear, with nitrous oxide-oxygen inhalation sedation. This book, therefore, focusses on the use of nitrous oxide in child patients and is the first book on nitrous oxide exclusively for pediatric dentistry.

The book begins with understanding fear and anxiety. This step is crucial for a clinician to successfully practice nitrous oxide in children because one of the main purposes of nitrous oxide is to bring about anxiolysis. The synergism between basic behavior management and nitrous oxide is explained step-by-step in children with different behaviors. Various aspects of employing this technique in child patients have been supported with videos for better understanding of the readers. A chapter has been dedicated for use of this technique in children with special healthcare needs.

Numerous other dimensions such as the mechanism behind its action, hazards and risks, equipment, and basic properties have been covered, which will make this book an enjoyable read for dentists dealing with children.

Gurugram, India Kunal Gupta
May 2019

Preface

Nitrous Oxide: The Nearly "Ideal" Clinical Sedative

I am pleased to present this book as the product of an international collaboration from authors, experts in the field of inhalation sedation. It has been an honor for me to have worked together with the young generation of India's clinicians on this book.

China and India, nearly 40% of the world's population, have lately introduced nitrous oxide in their inventory of sedation techniques. This book represents an expansion of the chapter I coauthored for the book *Behavior Management in Dentistry for Children* (editors G. Wright, A. Kupietzky, Wiley 2014), which has been translated into Chinese.

My first contact with nitrous oxide was 35 years ago in 1985 when I walked in Dr. Quock's lab at Marquette University Dental School looking for a research subject for my master's thesis. I was captivated by how psychopharmacology could replicate human attributes with animals and the innovative ways there, to test a gaseous agent like nitrous oxide. I felt I had found my calling.

Since then, nitrous oxide research took me from Marquette University to the University of Illinois and Washington State University, USA, working with Dr. Quock's team. I consider myself very fortunate to have chosen this field of study and blessed to have been able to contribute, through my research, some small pieces of the "nitrous oxide" puzzle.

A discussion of the mechanism of action of nitrous oxide, a simple inert compound of only three molecules, has also revealed a long and fascinating history, making it a "laughing gas" not only for patients but also for the researchers trying to decipher its multitude of actions.

Its popularity has been turbulent over time: used as anesthetic, then fell out of favor becoming a recreational drug; came back full force helping anesthesiologists bring faster and painless anesthesia to their patients; used in labor and in dentistry as the favorite analgesic and anxiolytic; today falling out of favor from the anesthesiology departments but gaining favor not only in dentistry but also in the emergency and outpatient hospital departments and at the same time used by young people in today's society as a recreational drug of choice and in "nitrous" bars.

This book is an attempt to bridge the new knowledge of nitrous oxide mechanism of action with its clinical application in pediatric dentistry. There is a lot of material covered with clinical tips and scientific backing, and we have tried to include all the updated literature on nitrous oxide. This book will help the reader advance the knowledge and practice of inhalation sedation with nitrous oxide. Furthermore, the clinician will also have access to videos helping to better understand the concepts of each chapter.

I would like to thank all the contributors for the excellent work on this book and my family for their support throughout the years.

Athens, Greece Dimitris Emmanouil
May 2019

Acknowledgments

First and foremost, I would like to thank God for giving me the strength to undertake this project and pen down my passion of practicing the technique of nitrous oxide in child patients. My heartfelt thanks to my family including my parents, wife Jyotsna, and daughter Kimayra who gave me the power to believe in myself and pursue this dream.

Dr. Justin Lee needs a special recognition for being my mentor for this technique and ensuring that I employ this technique in nearly all my child patients. As a result I could gain good experience in using this technique in child patients and formulating my thoughts.

It was a great privilege and honor to have Dr. Dimitris Emmanouil as a coeditor for this book. Thank you for deciding to trust me, motivate me, and build a professional relationship which will last forever. His vast knowledge on this subject has added value to this book, which the reader will appreciate and benefit from.

I would extend my sincere gratitude to Dr. Amit Sethi who endorsed my idea of this book from its inception to its completion. Each and every contributing author of this book has done a commendable job, especially Dr. Priyanshi Ritwik who left no stone unturned to submit her contributions in time. I would like to thank Prof. Shobha Tandon who has been a constant driving force for me to undertake such projects.

I am grateful to Springer Nature, Switzerland, for consenting to publish this book. My words of appreciation are for Markus Bartels, who gave numerous suggestions to improvise the proposal and also get it approved, Narendran Natarajan and Rajesh for assisting in the production, and Alison Wolf for providing never-ending support and guidance. Mr. Pascali Pascalis from Porter needs a special mention for providing inputs and pictures for chapter on technical considerations.

My words of appreciation for Dr. Meenakshi S. Kher for contributing a video and few pictures; my colleague, Dr. Meha Kohli for her selfless support at various stages of manuscript preparation including photography, videography, referencing; Mr. Rohan Barwal for beautiful artworks, and Ms. Prerita Dobhal for meticulously proofreading the manuscript.

Last but not least, big thanks to all my friends and colleagues who appreciated my practice of nitrous oxide in pediatric dentistry. Many of them directly or indirectly motivated me and stimulated my mind to take up this task.

Gurugram, India
May 2019

Kunal Gupta

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Rationale for Using Nitrous Oxide in Pediatric Dentistry

1

Kunal Gupta and Priyanshi Ritwik

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Learning Objectives

1. Comprehending fear and anxiety in children which forms the basis for using nitrous oxide in children
2. Understanding the purpose of using nitrous oxide in children which will help in increasing its use in children
3. Studying about the indications of using nitrous oxide in children which assists in case selection
4. Knowing contraindications which will help in making this technique more efficacious and safe
5. Realizing the advantages of this technique over other modes of sedation
6. Appreciating the disadvantages of this technique in order to know its limitations

A visit to a dental clinic is always considered to be nerve-racking whether for adults or children. The "smell, the sounds", and the general atmosphere all add up to create an atmosphere which is not exactly perceived to be pleasant by most people. If you add crying children and stressed out parents to the mix, as in case with pediatric dental offices, then the situation becomes even more complex. This means that pediatric dentistry can be demanding for all the people involved and most importantly for child patients. Understanding the basics of fear and anxiety is a stepping stone towards the successful use of nitrous oxide in children as a behavior management tool. The purpose of using nitrous oxide should be clear to the pediatric dentists, in order to ensure that this technique is practiced effectively and efficaciously. It is more of a behavior guidance tool rather than a sedative tool. In this chapter, the indications and contraindications of using nitrous oxide in children shall be discussed as well as the advantages and disadvantages of its use in a pediatric dental office. A thorough knowledge about these will instill confidence in the pediatric dentists about its use in majority of their child patients.

1.1 Understanding Fear and Anxiety

The knowledge and understanding of fear and anxiety not only lays the foundation of our ability to provide the best possible care for children but more importantly allows us to establish a healthy and long-term relationship with them. It helps dentists recognize the signs of fear and anxiety, understand the underlying etiology, and enable them in developing a strategy to interact with such children. It is only after a thorough understanding of fear and anxiety that a dentist can use basic behavior guidance techniques individualized to each pediatric patient and introduce nitrous oxide in an effective manner.

1.1.1 What Is Fear?

Fear is a natural part of a child's development. Overcoming fear helps a child successfully engage and overcome a difficult situation. A child who is able to overcome a fearful situation develops a sense of achievement and becomes more confident. On the other hand, a child who gets overwhelmed by fear often chooses to "run away from the situation." In our case, it means leaving the operatory or if he chooses to stay, he does not allow the dentist to examine or treat him. Such a patient continues to remain "scared of dentists" and becomes more insecure as time passes. This perpetuates future anxiety and reluctance in accepting dental care.

Fear is defined as an unpleasant emotional response to a real or perceived immediate external threat or danger [1]. Fear comprises of psychological and psychophysiological responses. In simple terms, fear is the emotion one experiences, when there is an imminent threat of harm [2]. Fear is a protective emotion and integral to human experience. Fear is caused by specific stimuli in a context-dependent way [3].

> Inability to handle a difficult situation leads to the development of fear.

1.1.2 Ages and Stages of Fear

Fears vary across ages and stages of child development (Fig. 1.1). Typically, fears vary in frequency, intensity, and duration. Fears wax and wane as a child grows; they also tend to differ based on the objects which evoke them in an age-specific and transitory way [4]. Children's fears at various age groups has been detailed in Appendix I. Knowledge about age-specific fears can be useful for the dentists when dealing with children. For eg: In a dental office, separation from parents should not be done for preschoolers as it may induce fear.

1.1.3 Development and Physiology of Fear

The neurobiology of fear remains in its infancy. From an evolutionary perspective, fear is a protective mechanism and enables one to respond appropriately when faced with danger or harm. Fear is considered as an innate function of the subcortical brain, and the amygdala is referred to as the hub of the fear circuit [2]. The role of the amygdala in processing and expressing fear is summarized in Fig. 1.2.

> Amygdala is the core of fear circuit in the brain.

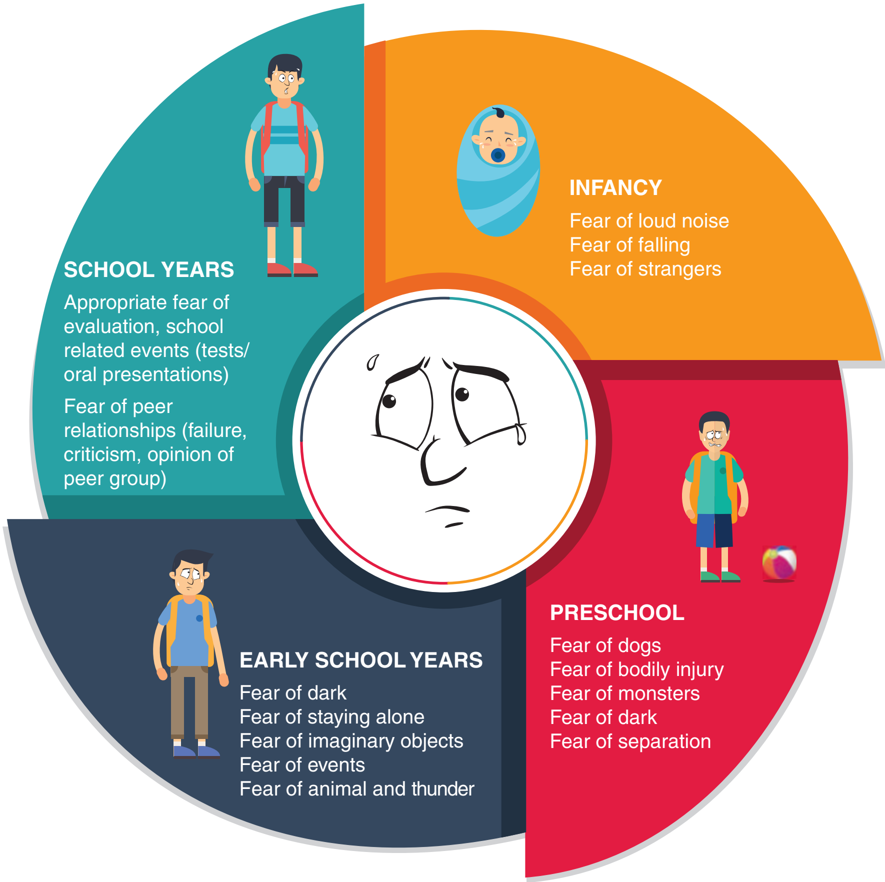

Fig. 1.1 Different kinds of fear at various age groups in a growing child

A child's fear has been explained by several theories. It may be related to the emotional involvement with their parents [5, 6] or may be a conditioned response involving learning, unlearning, and modification of fear through environmental experiences. Gesell states that children [7] go through a series of fears as they mature. Jeffrey Derevensky stated that children's fears are not unrealistic or imaginary [8].

Fear in children is mostly learned through experiences or taught by parents, teachers, siblings, or friends.

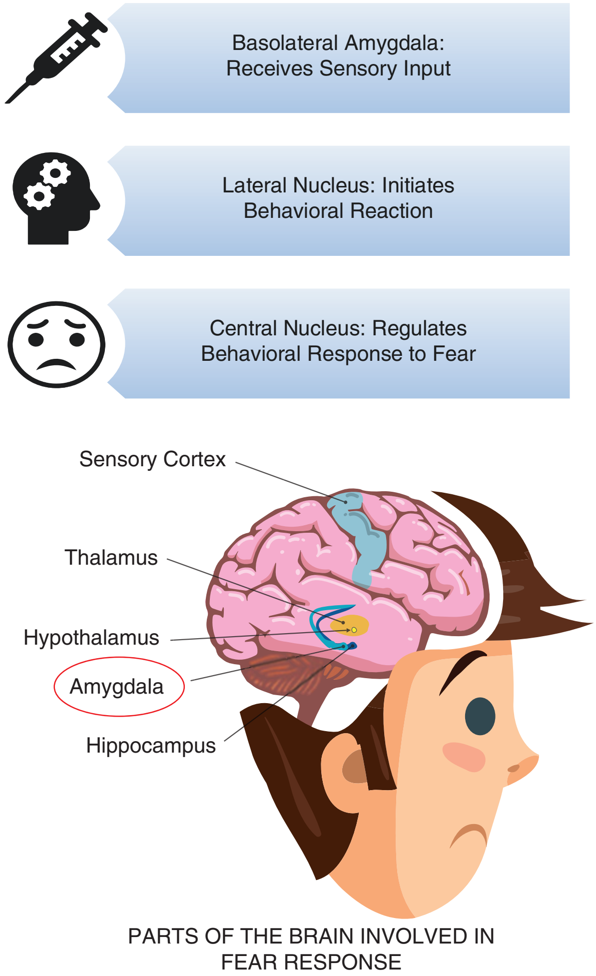

Fig. 1.2 Location and Role of the amygdala in processing and expressing response to fear

1.1.4 Responses to Fear

Stimuli that evoke fear unravel a complex cascade of behavioral, autonomic, endocrine, and cognitive responses. Broadly speaking, fear results in inner feeling/cognitive response, outer behavioral expression, and accompanying physiological changes [4]. The responses to fear are summarized in Fig. 1.3.

Inner feeling/cognitive Response: Negative statements or statements regarding possible danger from fearful situation (e.g., "I feel scared," "The dog will bite me!").

Behavioral Response: Avoidance or escape from the fearful situation, crying, clinging to parents, physical combativeness. The dentist usually has to manage this behavioral response while trying to deliver dental care to a fearful child (Figs. 1.4, 1.5, and 1.6).

A clinician can recognize a fearful child based on behavioral responses.

Physiological: Increased heart rate and respiratory rate, sweating, dryness of mouth, trembling, shaking, changes in respiration.

The emotional response to fear varies from a person to person and is more subjective. The subjective emotional reaction translates to behavioral changes manifesting in characteristic facial expressions, flight, fright, freeze, and/or avoidance [9]. In the long run, stimuli causing fear also lead to the development of particular adaptive behaviors within an individual to avoid or cope with the threat [3].

Fig. 1.3 Different responses to fear

Fig. 1.4 A crying child

Fig. 1.5 A fearful child clinging to mother and covering his mouth

Fig. 1.6 A fearful child wanting to go out of the operatory

1.1.5 Types of Fear

Since fear is evolutionarily related to prevention from harm, there are innate fears, which occur in children, irrespective of their past experiences. Innate fear is not conditioned. It drives the individual's defense when faced by a threat, much like the flight or fright reaction of an animal when it sights its predator. However, an individual's lifetime experiences also shape the development of other fears. Over the course of life, individuals acquire fears. Figure 1.7 provides a visualization of classification of fear into innate and acquired fears in children [10]. The acquired fears are discussed below as conditioned, objective, and subjective fears.

Conditioned fear is the development of fear responses according to the classic Pavlovian conditioning. Classic fear conditioning is described in a historical experiment where a little boy was presented with a white rabbit. At the same time, a suspended steel bar was struck with a hammer to produce a frightening loud noise. The noise caused the boy to tremble and cry. After several pairings of the white rabbit and the noise, the little boy became visibly upset at the sight of the rabbit alone. He also generalized his conditioned emotional reaction to other white, furry objects [11, 12]. Such experiments would no longer be possible to conduct ethically.

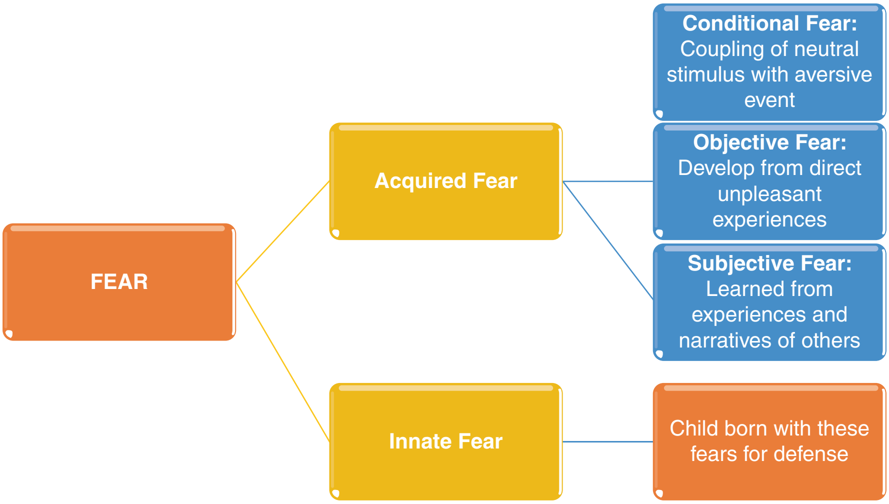

Fig. 1.7 Types of fear and their acquisition in children

However, the implications of conditioned fear in pediatric dentistry are significant. In the dental setting, an example of conditioned fear is the use of topical anesthesia prior to local anesthetic injection. During the first appointment, the child "learns" that the injection follows the application of topical anesthetic. During the second appointment, the child is conditioned to expect the injection after the application of topical anesthetic and may become fearful immediately after the application of topical anesthesia.

Objective fears develop based on one's own experiences. General impatience on part of the dentist while treating a child or lack of clinical skills may instill fear or anxiety in children [13]. An example is the child with an acute dental abscess who may have had a difficult extraction. Should this child need another extraction in the future, he/she will likely have a fear of extraction based on their direct experience at the previous dental visit. In fact, unbearable pain at their first visit to a dentist is a predictor of children developing long-term anxiety and apprehension towards dentists and dental treatment [14].

> A dentist's manner of communication with a child, patience, clinical skills, and use of other behavior management techniques can help in reducing acquired fear in a child.

On the other hand, subjective fear develops based on the experiences or narratives of others. An example would be a child who hears negative feedback from a sibling about the dental treatment. A child's fear can also be initiated on hearing negative words about dental experiences from parents. Many a times, parents tell their children casually that "if you don't brush well, you will end up with a dentist pulling out your teeth." The child now may be fearful at his/her own first dental appointment based on indirect experience or comments of somebody else (child may think that the dentist's job is to pull out teeth). This is similar to developing high levels of fear for a friendly animal for which parents have told threatening narratives to their child.

Mothers who are scared of dentists, often have children who are anxious and fearful about the same [15] and is another example of subjective fear in children.

> It has been found that subjective fears are stronger determinants of dental fears in children than objective fears.

Classification of dental fears into four groups has been carried out by the Seattle system (Table 1.1) (Milgrom 1985) [16]

1.1.6 Levels of Fear

Humans and other species have developed fear as a protective adaptation for survival in response to danger. For most of us, the level of fear is commensurate with the level of threat, and fear response is a dynamic process, adapting to the severity of the threat with effective coping skills. An example is an individual who is fearful of dental procedures, yet he/she decides to receive dental care because the benefits of dental treatment outweigh the threat from the procedure. However, for others, fear is disproportionate to the threat. When fear interferes with normal functions, it leads to maladaptive behaviors, such as avoidance. An example is a child who is extremely fearful of dental procedures and hence avoids dental care until the last moment; this could adversely influence treatment, as a restorable tooth may become non-restorable due to disease progression.

1.1.7 Strategies of Dealing with Fear

Clinicians should be well versed with the developmental aspects of children's fear which are age and stage appropriate [7]. Some important clinically applicable concepts are as follows:

Table 1.1 Table showing types of dental fear (Milgrom 1985)

Type I	Conditioned fear	I am afraid of things that dentists do such as needles, sound, and smell
Type II	Fear of somatic reactions	I am afraid of fainting
Type III	Generally fearful	I am just scared
Type IV	Distrust of dental personnel	I don't trust dentists

- Never make fun of a child's fear.
- Positive reinforcement for a child's good behavior. Ending the dental appointment on a positive endnote enables a child to remember something positive, even about a difficult dental appointment. Constantly highlighting desired behavior can be a much more effective way of promoting the desired behavior and enhancing a child's confidence (Fig. 1.8).
- Try to be supportive and empathetic while talking to a fearful child (Fig. 1.9).
- Help child explore strategies to overcome their fears. Breathing exercises, visual imagery, art therapy, music, and suggestive hypnosis are examples of techniques which can be implemented in the dental clinic (Fig. 1.10).

> A dentist should always make an effort to encourage the child to talk about their fear and its associated feelings.

Three categories of treatment to enable a child overcome dental fear are as follows [7]:

1. *Behavioral procedures*
   - Systematic desensitization
   - Modeling (Fig. 1.11)
   - Contingency management

Fig. 1.8 Positive reinforcement—praising child verbally

Fig. 1.9 Communicating in a supportive and empathetic manner while talking to a fearful child

Fig. 1.10 Using music to overcome a child's fear

Fig. 1.11 Modeling being done on parent to enable child overcome fear

2. *Cognitive behavioral interventions*

   It is a structured and brief psychological treatment based on a combination of psychoeducation, exposure, and homework exercises [17].

   It is based on changing distorted thinking and dysfunctional behavior. Clinicians should help children learn to identify their triggers, understand how anxiety affects their behavior, and how to replace distorted thoughts using cognitive reframing. Children are taught to replace negative thoughts with positive ones and separate realistic thoughts from unrealistic ones.
3. *Behavioral family interventions*

   This requires involvement of the family, especially the parents. The process involves identifying the problem, trigger for anxiety, and finding a possible solution. It involves stepwise achievement of goals. Positive reinforcement is an integral part of this. Parents need to allocate specific time during the day for this intervention.

1.1.8 Anxiety

Often, the terms fear and anxiety are used loosely or interchangeably. However, while fear is a phasic and transient response to an imminent or immediate threatening stimulus, anxiety is a sustained tonic state, based on the prediction of a threatening stimulus. The term anxiety is used to describe the feeling which occurs when the source of harm is either uncertain or distant in time or space. An individual's emotional response to anxiety and to fear is similar. The difference in fear and anxiety is illustrated in Fig. 1.12.

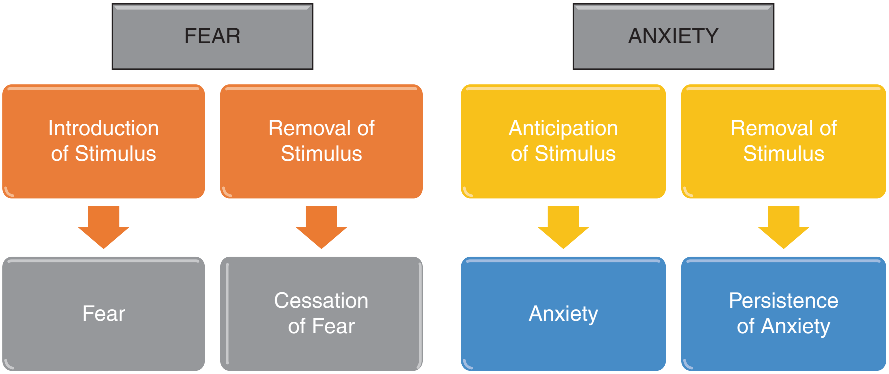

Fig. 1.12 Figure illustrating difference in fear and anxiety

A patient is dentally anxious when he feels that getting dental treatment will result in a negative outcome, and moreover he feels that if and when that happens he will not be able to control the outcome [18]. Dental anxiety has been attributed to factors such as personality characteristics, traumatic or painful past dental experiences in childhood (conditioned experiences), learned attitude towards dental care from fearful family members or peers, perception of body image, fear of bodily injury, coping styles, and pain reactivity [19].

Clinical anxiety in a child regarding a dental visit is a strong predictor of uncooperative behavior [14].

An important distinction between fear and anxiety is that fear is short lived and subsides after the threat or danger passes, while anxiety does not dispel as quickly.

There are various reasons for anxiety in children, as listed below [20]:

- Temperamental disposition
- Physical illness or disability
- Family problems

(A Disagreement between parents, recent parental divorce, parental illness, parents seeking reassurance from children, and parents using excessive threats to control their condition.)

- School/academic worries
- Problems with friends, social circles, and activities out of school

Temperament is a distinct personality of a child. It is an inborn trait which reflects the approach of a child towards the world. Children with different temperaments will have different approaches towards their visit to a dental practice and their acceptability of dental treatment.

Thomas and Chess (1987, 1991) [21] categorized children into three clusters of temperament.

1. ***Easy***—Child is usually in positive mood and adapts easily to new experiences.
2. ***Difficult***—Child reacts negatively, cries frequently, and does not accept new situations easily.
3. ***Slow to warm up***—Child has low activity level and takes time to get adapted to new circumstances.

Rothbart et al. [22] develop Children's Behavior Questionnaire (CBQ) and its derivative Children's Behavior Questionnaire Short Form (CBQ-SF) which serves as an aid to evaluate child's temperament. As per this scale, children with easy temperament which includes children with high effort control (can easily stop an activity when he or she is told "no"), high soothability (easy to soothe when the child gets upset), and low frustration (does not become angry when he or she is asked to go to bed), low activity, and impulsivity (is not in a hurry to get from one place to another or rushing into an activity without thinking about it) will show more success with nitrous oxide sedation.

The physical manifestations of anxiety in children are listed in Table 1.2.

1.1.9 Phobia

Phobia is different from fear in that it is out of proportion, unreasonable, and persistent [23]. Dental phobia is a severe type of dental anxiety which is characterized by marked and persistent anxiety in relation to discernible dental situations/objects (e.g., injections, high-speed handpiece) or to dental situations in general. Dental anxiety and dental phobia represent different points on a continuum, varying from mild dental anxiety on one end to dental phobia on the extreme end of the continuum [24, 25].

> Dental phobia is an extreme form of dental anxiety.

Table 1.2 Physical signs of anxiety in children presenting for a dental appointment

Physical signs of dental anxiety in children
Hiding behind parents
Crying without any reason, screaming, or shivering (Fig. 1.13a)
Not sitting idly
Not making eye contact with the clinician (Fig. 1.13b)
Wanting to use the washroom
Angry or aggressive
Pulling parents out of the clinic

Fig. 1.13 (**a**) Anxious child crying without reason. (**b**) Anxious child not making eye contact with the clinician

1.1.10 Dental Fear and Anxiety in Children

Dental fear and anxiety have been recognized as a public health dilemma in many countries [18, 26].

> Dental fear and anxiety eventually lead to disease progression and exacerbation of the underlying dental problem due to avoidance of dental visits.

Fear of pain is an important predictor of dental anxiety [18]. The nature of fear prominent in a child's life corresponds to the child's age, cognitive ability, and stage of development [18]. In a pre-school child, attachment and separation anxiety play an important role. These children are less likely to become anxious if their parent and favorite toy accompany them into the dental operatory. In children older than 8 years of age, the fear of bodily injury is prominent. The fear of extraction is exaggerated in children in this age group. Teenagers manifest fear of dental treatment, likely due to issues of control and autonomy [18]. Most of these fears in children decrease or disappear as they grow older due to cognitive development and learning appropriate coping skills [18, 26]. Indeed, the prevalence of dental fear and anxiety is higher in younger children [26].

The pooled prevalence of dental fear in children across different countries varies between 10 and 20% [26]. The prevalence and level of dental fear and anxiety in Northern European pediatric populations are lower than in other geographic areas such as Southern Europe, Asia, and the USA. This implies that cultural factors influence dental fear and anxiety. While fear and anxiety in other contexts are socially unacceptable, dental fear is widely accepted and carries little social stigma [27]. Dental fear and anxiety are higher in girls than in boys [26].

Fear of dental treatment in children results in treatment difficulties [18]. Children with dental fear and anxiety exhibit behavioral problems, which can result in a stressful and unpleasant experience for the child, the parents, and the treating dental practitioner [24]. Such behavioral problems are often related to dental factors such as previous negative treatment experiences, particularly extraction, restorative procedures, and injection, which cause the most negative emotional load [18]. Conditioning is an important contributor to dental fear in children of 5–11 years of age [28]. Individuals with dental fear and anxiety have a high likelihood of cancelling dental appointments or failing to show up for scheduled dental appointments [24].

Dental fear leads to avoidance of treatment and high dental anxiety leads to poor oral health-related quality of life.

1.1.11 Etiology of Dental Fear in Children

Dental fear in children can be traced to five basic factors which play a role in its etiology. Dentists treating children should understand the underlying cause of fear as the basis of the uncooperative/fearful behavior exhibited by the child in the dental clinic [29]. These basic root causes of dental fears are summarized in Fig. 1.14.

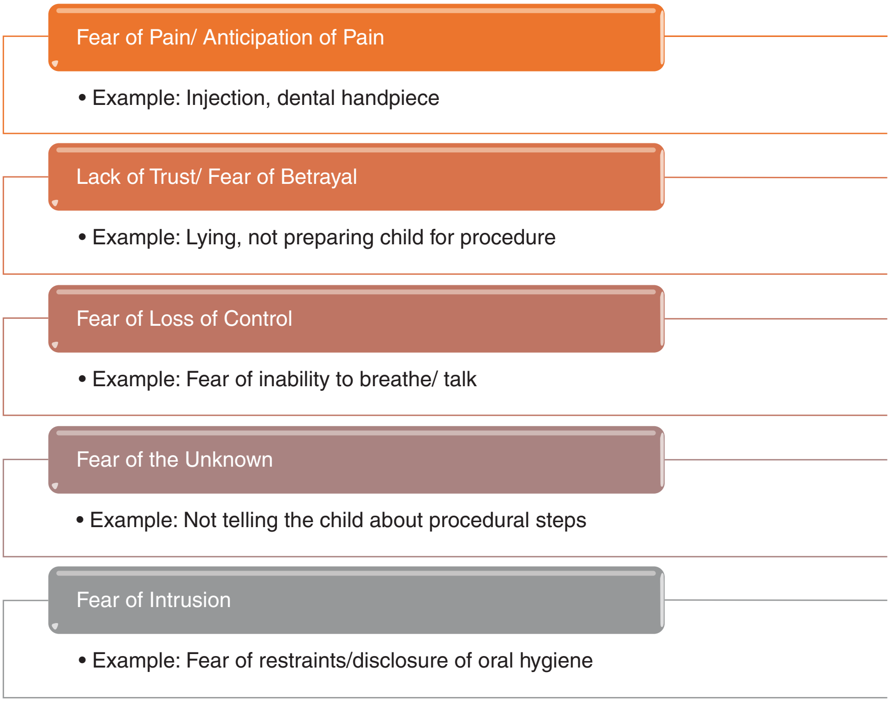

Fig. 1.14 Etiology of fearful behaviors by children during dental appointments

Fear of Pain or Its Anticipation

Dental fear is related to anticipated pain or misinterpreted pain. A logical explanation to the child that pain is different from touch or pressure can help the child in dissociating anticipated or misinterpreted pain from fear. For example, if the child complains of pain even after administering local anesthesia, then use of a probe, to let the child feel the difference in anesthetized and non-anesthetized area, assures the child that he/she will not experience pain.

Lack of Trust or Fear of Betrayal

Trust of the dentist is an important factor in dental fear among adults. However, there is no evidence-based data to demonstrate this in children [29]. Conventional wisdom and classic child psychology literature support building trust between the child and the dentist as the building block to successful dental appointments. Lack of trust in a child may be due to a previous negative experience with a dentist, or medical personnel, and/or learned from behavior/statements of parents, siblings, or peers.

Mistrust can be reduced by proper and honest communication with children. TLC or "tender loving care" is empathetic non-judgmental communication with the child, acknowledging the child's feelings. This mistrust can be reduced by asking the child about his/her feelings. The dentist should ask open-ended questions without words with negative connotations. Therefore, instead of asking the child "are you feeling scared?", the dentist can ask "how are you feeling today?". If the child responds "I am scared," the dentist can ask further open-ended questions such as "can you tell me more about why are you feeling scared today" or "can you tell what makes you scared." This will give the child an opportunity to explain all possible things, which may be a person, a situation, or some objects like a dental explorer which generate fear in his/her mind. To establish trust, it is important that the dentist addresses the matter that the child has identified as the source of distress. Removing or mitigating the stimuli will help the child develop faith and trust in dentist.

> Understanding etiology of fearful behavior can help a dentist form a strategy to deal with a child's fear.

Fear of Loss of Control

Children are fearful that when they open their mouth, the dentist would be in full control of them and they won't be able to stop the dentist in case of any threat to them.

This perceived control can be achieved through tell-show-do technique, offering decisional control (letting the child decide which tooth to polish first or performing polishing only till count of 5) and offering control over noxious stimuli (allowing the child to raise a hand in case of any pain or threat). These techniques are dependent on the cognitive development of a child.

Fear of the Unknown

This fear usually develops when the information is transmitted to the child in an inappropriate manner or certain words are used which may be misleading. An example is, saying “It will not hurt” or “No injection will be given.” Such statements leave ambiguous hints for an anxious child that something is probably going to hurt, or an injection is going to be given. Such statements create misinformation in the mind of an already anxious child, that the dentist may have other “unknown” things which he/she may use during the dental appointment.

Fear of the unknown can be reduced by utilizing the tell-show-do technique. The dentist should explain and show the child in a step-by-step manner, about the upcoming procedure. The child should be shown the instruments/devices used in that procedure. An example of effective tell-show-do technique is when the dentist tells the child “Today I want to count how many teeth you have using a small mirror,” then the dentist shows the mirror, let the child feel the mirror in his/her hand. The dentist can also incorporate modeling on parents/siblings or other children in the clinic by using a mirror to count their teeth. This will make the child understand what he/she is required to do and what instruments will be used for that procedure.

Before performing an oral prophylaxis, a child is shown the slow-speed handpiece with a disposable brush and how the slow-speed handpiece runs. Then a small demonstration is shown on child’s finger which will help make the child familiar with the sound and the vibrations on the finger. Then the prophylaxis can be carried out in the child’s mouth.

Fear of Intrusion

This kind of fear involves impinging on “personal space” or “personal habits” of a child. A child’s mouth, face, and body are considered personal space, and child’s eating habits and oral hygiene habits are personal habits. Fear of intrusion is considered as the most difficult part to handle or address while managing a fearful child.

A child may be fearful of dentist putting instruments in his/her mouth (intruding into the personal space of a child) or being surrounded by dentist and assistants. Child may also be fearful of the dentist knowing about his/her improper brushing or eating habits. It is important for the entire dental team to remain non-judgmental of a child’s dental status.

These five etiologic factors for fear of dentistry in children, usual reactions by children, and some suggested scripts for the dentist are listed in Table 1.3.

1.1.12 Implications of Dental Fear and Anxiety in Children

There is an increasing evidence for relationship between anxiety and pain. Fear of pain is a common phenomenon seen in children visiting pediatric dental practice. Children who are anxious are more likely to complain of pain. This contributes to pain-related avoidance which may further aggravate pain and thereby strengthening avoidance. It has also been found that anxiety has a direct relationship with the intensity of pain experienced by a child [30].

Table 1.3 Examples of etiology of fear and dentist's response

Child's reaction/ response	Fear factor	Dentist's response
"It will hurt"/"this is painful"	Fear of pain or its anticipation	I don't want to hurt you. You may feel some other sensations like pressure, vibration. But still, if you raise your left hand, I will stop immediately
"I know the dentist will put an injection" "I know you will drill my teeth"	Lack of trust/ betrayal	Implement tell-show-do technique to explain what a child can expect or experience. Assure the child that there will be no surprises
"I will faint"/"I won't be able to breathe"	Fear of loss of control	Let's practice taking deep breaths to make your belly-button move. You can keep doing this while I check your teeth. I have a thirsty straw to remove the water and spit from your mouth so that you feel comfortable
"I am just scared"	Fear of unknown	Thank you for telling me how you feel! If you can tell me what scares you, I can let you play with it, and then you will know that there is nothing scary about it. Implement desensitization and tell-show-do
"Don't hold my hands"/"I know I have bad teeth"	Fear of intrusion	When you move your hands, they can hurt me or my assistant. There are also some instruments here, which are sharp and may hurt your hands. If you keep your hands on your belly-button, we do not need to hold them Everybody comes to the dentist to get their teeth cleaned. That does not mean you have bad teeth. But I can certainly make your teeth very clean and healthy

Nitrous oxide has a major role in breaking this vicious cycle by reducing anxiety in a child. Once the anxiety is reduced, child's behavior is improved and the child is willing to accept the dental treatment.

Dental fear and anxiety elicit within the child an urgent need to escape from the dentist [2]. However, since the child is not physically able to escape the dental clinic, he/she starts exhibiting intense emotional responses. These vary from withdrawal, crying, screaming, and not opening the mouth to various levels of physical resistance. An important implication of dental fear and anxiety in children is uncooperative behavior in the dental clinic, which makes delivery of safe and quality dental treatment challenging. Dental anxiety is an important predictor of children's behavior in the dental setting, and there are strong associations between dental anxiety and perceived uncooperative and problem behaviors [31–33]. Uncooperative behavior of children in dental practice creates occupational stress in the dental staff. Stressful moments can also cause moments of discord between the dental professionals and the parents [34].

The sight of a needle and the sound of a dental handpiece are associated with causing highest anxiety in children [35, 36]. Higher levels of dental anxiety have been associated with an increased incidence of dental caries in children [37–39].

Parents who consistently fail to take their children to the dentist report that their children's dental anxiety is one of the influencing factors for their avoidance

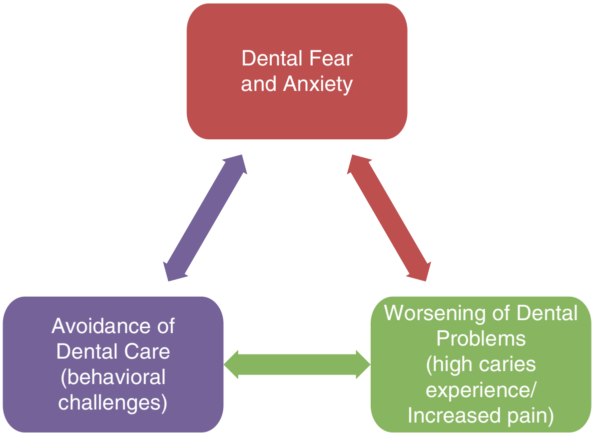

Fig. 1.15 Cycle of dental treatment needs and dental fear and anxiety

behavior [40]. Dental anxiety in children shapes their adult dental behaviors. Research has found that there may be long-term oral health implications resulting from children's dental anxiety, as dentally anxious children are more likely to be symptomatic, rather than proactive, users of dental services in adulthood [41]. The relationship between dental anxiety and dental avoidance is a vicious cycle which exacerbates the unmet dental need (Fig. 1.15). Dental fear and anxiety leads to avoidance of dental treatment. Addressing dental fear and anxiety will prevent treatment avoidance [25]. Besides, impact on dental care, dental fear, and anxiety may also cause sleep disorders, thereby affecting daily life of a child. It can thereby have an impact on the psychosocial functioning of a child.

> Dental fear and anxiety can start a vicious cycle of avoidance and worsening of dental problems such as pain in teeth, which further enhances fear and anxiety.

Dental anxiety in children has financial implications. When advanced behavior guidance techniques, or referral to a pediatric dentist, are necessary to provide dental treatment for anxious children, additional fees and time are direct and indirect costs incurred to the parents.

Dental anxiety in young children influences their pain perception and pain threshold. Research has shown that young children with a low level of dental anxiety show a sensitized reaction trend for self-reported pain over two sequential dental visits, whereas young children with a high level of dental anxiety reported the most pain on the first treatment session [38]. Pain intensity experiences in children, particularly children under 14 years of age, are enhanced by higher dental anxiety [42].

> Dental anxiety increases pain perception and pain exaggerates dental anxiety.

Table 1.4 Basic behavior guidance techniques for pediatric patients [43]

Technique	Description
Communication and communicative guidance	Active and reflective listening to establish rapport, trust, and comfort
Positive pre-visit imagery	Images are shown to children that demonstrate a positive, child-friendly dental environment
Direct observation and modeling	Watching a patient or video that demonstrates desirable dental behaviors
Tell-show-do	Use of age appropriate phrases to tell the child about the dental procedure, demonstration of the dental procedure, and completion of the dental procedure without deviations from assured steps
Ask-tell-ask	Ask the child about the feeling towards planned dental care, explain the treatment planned in age appropriate language, and ask the child again about how he/she feels about the planned care
Voice control	A deliberate alteration of volume, tone, or pace of the dentist's voice to obtain the child's attention and direct behavior
Nonverbal communication	Reinforcement and guidance of behavior through the dentist's facial expressions, body language, and appropriate physical contact
Positive reinforcement and descriptive praise	Reward desired behaviors in the child with positive social reinforcers, such as verbal praise and facial expressions
Distraction	Diverting the child's focus away from a perceived unpleasant procedure
Parental presence	To offer physical and psychological support to the child and decrease anxiety

It can be summarized that addressing dental fear and anxiety in children has multiple immediate and long-term benefits. It enables the child to receive dental treatment in a safe and efficient manner. Allaying dental fear and anxiety enables the child to develop a positive outlook to dental care and grow into an adult who can tolerate dental treatment in an outpatient setting without pharmacologic adjuncts. It shapes an adult who does not avoid dental care. It decreases the burden of dental disease by improving oral health-related quality of life. The overall financial burden to the family and insurance system is decreased by decreasing dental fear and anxiety in the child.

There are several basic behavior guidance techniques that should be utilized to make the dental appointment a positive experience for the child (Table 1.4). When a child exhibits dental fear and anxiety which cannot be reduced by these techniques alone, such basic behavior guidance techniques can be augmented by utilization of inhalational nitrous oxide/oxygen. It is important to keep in mind that nitrous oxide inhalation leads to effective anxiolysis only in conjunction with these basic behavior guidance techniques such as tell-show-do and distraction (Figs. 1.16a, b and 1.17). Most of the times parental presence is also crucial along with basic behavior management techniques especially when parents are over protective or over indulgent (Fig. 1.18).

Basic behavior management techniques form the pedestal for using nitrous oxide sedation in children to reduce fear and anxiety.

Fig. 1.16 (**a** and **b**) Tell-show-do technique for a child

Fig. 1.17 Distraction of child to reduce anxiety

Fig. 1.18 Parental presence can be allowed during nitrous oxide sedation

1.2 Purpose of Nitrous Oxide in Children

Purpose of using nitrous oxide inhalation sedation should be clear to make it effective. It is an invaluable tool for behavior management (rather behavior guidance) in children [44, 45]. Since it brings about some sedation, it does not mean that it should be used only for children who are not cooperative for dental treatment. It has various purposes in children.

1.2.1 Reduce Fear and Anxiety

Nitrous oxide has euphoric and anxiolytic properties because of which it has a role in reducing fear and anxiety in children. Due to previous unpleasant experience of the child or parents, child may have developed fear of visiting a dentist. This initiates a vicious cycle as fear may lead to avoidance of treatment which further aggravates the caries status of the child. Use of nitrous oxide helps in breaking this vicious cycle, thereby preventing the child from having a poor oral health which in turn may affect his general health.

1.2.2 Enhance Communication of a Child with the Dentist

Many a times, a dentist is unable to address the anxiety of the child because of lack of communication from the child. This lack of communication may be due to the lack of trust ("unpleasant experiences" shared by parents or friends) or shy behavior of the child. With the use of nitrous oxide gas, child's anxiety gets reduced. The child sheds barrier formed around him and begins to interact with the dentist. The dentist may then be able to ascertain the reason for the lack of trust and fear in the mind of the child. This helps dentist in dealing with the child by addressing his/her concerns (Fig. 1.19).

Fig. 1.19 Using nitrous oxide on a fearful child enhances communication with the child

1.2.3 Instills a Positive Dental Attitude in Children for the Dentist and Dental Treatment

Even though a child may be cooperative for dental treatment, but he may not like visiting a dentist for complete treatment or preventive treatment. This is because of some sensitivity during treatment, tiredness of keeping mouth open, irritation with the sound of dental drills or suction, etc. Since nitrous oxide has euphoric and analgesic properties, children enjoy getting the treatment done and may look forward to subsequent visits. This instills a positive dental attitude in the child for the entire life.

> Main purpose of using nitrous oxide in pediatric dentistry is to not only reduce fear and anxiety in children and parents towards dentists and dental treatment but also build a positive dental attitude. This helps in building trust and confidence of children and parents.

1.2.4 Improves the Quality of Dental Treatment Rendered to Children

Many dentists struggle treating a child and would like to complete the work in the shortest possible time, thereby compromising on the quality of treatment rendered to a child. Since nitrous oxide is used to bring about minimal sedation, unwarranted tongue and lip movements are reduced. These factors contribute towards improving the quality of dental treatment.

1.2.5 Increases Efficiency of the Operator

A dentist is able to accomplish more work in a single appointment with nitrous oxide gas than without because less time is spent in managing the behavior of the child. As there is lesser unwarranted movement of the child, the operator is able to practice quadrant dentistry, which in turn decreases the number of future visits.

1.2.6 Reduces Fatigue

With the use of nitrous oxide gas, less talking or verbal distraction is required, which reduces the fatigue of the operator. This, in turn, improves the overall efficiency of the dentist, as he/she is able to treat more number of patients on a particular day without getting tired.

1.2.7 Reduces Gag Reflex

Gagging is a normal reflex response in a healthy child. It may, however, interfere with various dental procedures such as taking X rays, making impressions, and restorative treatment. Sometimes, this response is so strong that it may lead to an avoidance of the dental treatment.

There are various causes of gagging such as systemic disorders, drug induced, physiologic, psychological, and iatrogenic [46]. In children, mostly the cause of gagging is psychological, that is fear [47].

Nitrous oxide oxygen sedation has use in reducing the gag reflex in a child. This is because gagging is related to specific fear, anxiety, which gets reduced by nitrous oxide due to its anxiolytic property [48]. Langa [49] states that although "nitrous oxide sedation does not totally eliminate gagging in extreme cases, it depresses the gag reflex sufficiently that a good impression is obtained at first attempt in all instances."

Malamed is also of the opinion that using nitrous oxide and oxygen sedation can help with reducing the hypersensitive gag reflex [50].

The mechanism by which nitrous oxide obtunds the gag reflex is not clear. It may be proposed that the anxiolytic (sedative) properties of nitrous oxide play a major role in the reduction of the gag reflex [51].

1.2.8 Reduce Stressful Environment

Pediatric dental practice can create a stressful environment due to crying children, clashes with interfering parents, and difficult access in small mouth of children. Nitrous oxide can help in creating a peaceful, stress-free, and relaxing environment in a pediatric dental practice.

> Using nitrous oxide is not only beneficial for the child but also for pediatric dentist and staff because it reduces stressful environment usually present in a pediatric dental practice.

1.2.9 Role of Basic Behavior Management Technique

The dentist should be able to judge the expected level of cooperation during the first dental visit and accordingly decide to use nitrous oxide inhalation sedation. Nitrous oxide sedation for child patients is ineffective in the absence of basic behavior management techniques.

Basic behavior management techniques are essential for building a rapport with the child so that the child is able to interact with the dentist. This is essential for introducing the nasal hood to the child effectively.

However, if basic behavior management techniques are used alone initially for children who are not willing for dental treatment, then making them use inhalation sedation mask later within the same setting, with the same dentist, becomes almost impossible because the child would have already developed some anxiety or fear for that setting and person.

Another common mistake or misconception is that children in precooperative age are considered for nitrous oxide inhalation sedation. The pediatric dentist should realize that if a child is not accepting basic behavior management technique, then making them accept nasal hood is not possible.

1.2.10 Purpose of Nitrous Oxide in Children with Different Behaviors

Nitrous oxide inhalation sedation has a purpose for children who are not only fearful but also the so-called cooperative for dental treatment.

Based on the FrAnkl's [52] behavior rating scale, the purpose of using nitrous oxide inhalation sedation for each of the category is mentioned below.

- **Definitely positive**—improves the efficiency of the operator, thereby reducing the time required to complete dental procedures. It also plays a major role in practicing quadrant dentistry for pediatric patients. It also helps in improving the quality of dental work provided to the child.
- **Positive**—instills a positive dental attitude and help in creating a "Happy child." Children will look forward towards their dental appointment. This, in turn, helps in instilling a positive attitude for dental treatment in parents. Parents will be more willing to accept the preventive treatment in children because they see that their children are comfortable during the dental procedures. They will also not focus only on the chief complaint rather will get all the teeth affected by dental caries treated.
- **Negative**—removes fear and anxiety of dentist/dental treatment. It thereby ensures an unpleasant procedure to be carried out in a child which would have otherwise caused distress in a child.
- **Definitely negative**—it reduces the number of cases being treated under general anesthesia. It also helps in treating an anxious or phobic child who would otherwise be denied access to dental treatment.

1.3 Indications of Using Nitrous Oxide in Pediatric Dentistry

1. ***Apprehensive and fearful children***

   Use of nitrous oxide is best indicated in children who are apprehensive, nervous, or uneasy about the upcoming dental treatment. Nitrous oxide will help in reducing this worrying feeling, thereby decreasing the hurdles posed by children during the treatment such as frequent movement, closure of the mouth, and asking for breaks.

   At the same time, if the level of fear is severe, then nitrous oxide may not be of great help during the dental treatment of such children. Anxiolysis brought about by nitrous oxide may not be sufficient enough to overcome fear in such children [53].

2. ***Examination of a child with a previous negative dental experience***

   A child who previously had a negative experience during a dental visit may not be willing to even sit on a dental chair. In such children, examination also becomes difficult and convincing them to accept dental treatment is nearly impossible. If the dentist is able to recognize the reason behind fear and introduces nitrous oxide even before attempting examination, then a proper examination becomes much easier (a proper examination involves use of compressed air to dry the tooth for visual inspection of a carious tooth and taking radiographs).

3. ***Examination for preschoolers***

   Examination of preschoolers is many a times challenging due to their cognitive ability or anxiety. If a dentist is able to encourage the use of nitrous oxide mask, then a thorough examination can be carried out under the influence of nitrous oxide.

> Intra-oral examination should be done using nitrous oxide in children who appear to be anxious in the first appearance. Attempting examination without nitrous oxide may further increase anxiety in such children.

4. ***Examination in special children***

   Children with special health care needs such as autism spectrum disorder, attention deficit hyperactive disease, and cerebral palsy have higher levels of anxiety due to the pre-existing medical or behavioral conditions. Use of nitrous oxide in such children, at the first instance before examination, will help in reducing their anxiety and building trust as well as confidence with the dentist [54, 55].

5. ***To reduce the perception of time and reduce fatigue***

   During the course of treatment, even a cooperative child may say that he/she is tired and doesn't want to get more treatment done. This can pose a problem in completing the planned treatment or practicing quadrant dentistry for a child [56].

   Using nitrous oxide alters the sense of time in children and thereby assists dentist in performing uninterrupted treatment for children.

6. ***To control gagging***

   Gag reflex is common in children, which poses difficulty while taking radiographs, making impressions, taking photographic records, or even examination with a mouth mirror in certain instances. Nitrous oxide reduces the gag reflex and thereby makes it possible for a clinician to perform these tasks effectively [48, 57, 58].

7. ***To perform a procedure for which profound anesthesia cannot be achieved***

   Many a times, extraction of an abscessed maxillary tooth, pulp therapy in a tooth with acutely inflamed pulp can pose a challenge because the local anesthesia administered using the infiltration technique may not be effective enough to perform the procedure without causing pain. In these scenarios, use of nitrous oxide can be of great benefit because of its analgesic properties.

8. ***Age***

   Although there is no minimum age requirement for the use of nitrous oxide, its success is dependent on the concurrent use of behavior management techniques. Some authors have recommended 4 years [54] as cutoff age, and others have suggested 6 [55] or 8 [59] years as minimum age for practice of nitrous oxide (The reason cited was that the behavior management skills were sufficient to manage most of the children and children below these ages needed other form of sedation [59]). It has been mentioned earlier in this book that nitrous oxide is used for behavior guidance and therefore, has some purpose in children of all age groups, provided they are able to accept the nasal hood.

9. ***Medical History***

   Nitrous oxide sedation is best suited for children falling under ASA category I and II. For children under ASA III, prior consultation and opinion from primary care physician or consulting medical specialist is necessary. **(ASA Classification is described in Appendix II.)**

1.4 Contraindications for the Use of Nitrous Oxide in Children

1.4.1 Systemic or Behavioral Causes

1. **Chronic obstructive pulmonary disease**

   Although COPD is usually seen in adults, in extremely rare cases, children may get COPD due to the genetic disorder alpha-1 antitrypsin deficiency [60]. Children will experience similar symptoms, including difficulty in breathing and shortness of breath. In this condition, there is a poor exchange of gases in the lungs leading to hypoxemia and hypercarbia. Poor exchange could be due to reversible bronchospasm and irreversible bronchial obstruction. This has two consequences.

   (a) As a result of poor exchange of gases into and out of the lungs, it is more difficult to administer nitrous oxide/oxygen gases to the child and also recover them back. This may compromise the safety factor of nitrous oxide/oxygen sedation.

(b) There is a hypoxemic drive (compensatory mechanism in which reduced oxygen in the blood due to poor alveolar exchange stimulates breathing) which helps in compensating for hypoxemia. However, with the use of nitrous oxide sedation which delivers high concentration oxygen, hypoxemic drive can be reduced. The patient can lose much or all of the respiratory drive. This potential for apnea, fortunately, is more theoretical and rarely becomes a clinical problem [61].

History of asthma is not a contraindication for the use of nitrous oxide since nitrous oxide is not irritating to the tracheo-bronchial tree. Nitrous oxide decreases emotional stress, thereby reducing the precipitating factor for asthma.

2. **Bowel obstruction or abdominal pain**

   Since nitrous oxide gas readily replaces nitrogen in air-filled cavities, hence when used in cases of bowel obstruction, it may cause abdominal pain due to distention of abdomen. When a child is having constipation, it may also cause abdominal pain during the nitrous oxide sedation. A meta-analysis found that nitrous oxide resulted in a time-dependent increase in bowel distention [62]. The amount of increase in pressure in bowel is also related to the partial pressure of nitrous oxide and the intestinal blood flow [63].
3. **Middle ear surgery/infections/otitis media**

   Nitrous oxide can increase intratympanic pressure during sedation and cause negative pressure after it is discontinued, mainly in patients with eustachian tube dysfunction. Increase in intratympanic pressure is related to the property (fast entry into air-filled cavities) of nitrous oxide gas. In children, eustachian tube pressure is slightly negative compared to an adult. Most children, even those who are not suffering from middle ear disease, have difficulty in maintaining appropriate pressure. Stiffness of eustachian tube is responsible for maintaining appropriate pressure which is relatively pliable in children. This leads to an increased incidence of middle ear disease in children. As soon as the nitrous oxide gas administration is stopped, it rapidly displaces out of the middle ear, creating a higher negative pressure which may promote insufflations, aspiration, or reflux of nasopharyngeal secretions into the middle ear. Thus, some children may report of ear pain after the procedure [64–66].

   There has been a report of multiple episodes of postoperative hearing loss in a child suffering from Crouzon's syndrome after she received nitrous oxide as a part of general anesthetic. Narrowing of the internal acoustic meatus in this syndrome may make these patients more susceptible to increased middle ear pressure secondary to inhalation of nitrous oxide, thus increasing their risk for hearing loss.
4. **Severe emotional disturbances/psychiatric disorders or drug-related dependencies**

   Many psychiatric patients are not able to handle the dental treatment due to higher anxiety. Such patients may be receiving psychotropic drugs which usually alter the cerebral cortex function. They may also be on medication bringing about some sedation. Therefore, nitrous oxide sedation should be carefully administered in such children who may need close monitoring since their reaction may be unpredictable [55, 67, 68].

5. **Treatment with bleomycin sulfate**

   Bleomycin is an antineoplastic antibiotic used in the treatment of certain neoplasms such as Hodgkin's and non-Hodgkin's lymphoma. This is used as an adjunct to surgery and radiation therapy. Ten to twenty percent of patients receiving bleomycin therapy may develop interstitial pneumonitis which is considered as the most toxic effect of bleomycin. Although pulmonary toxicity most frequently occurs in older patients, it is unpredictable and may develop in younger patients and with low-dose therapy. Thus, there is an increased risk of developing pulmonary toxicity when oxygen is administered to patients who have received bleomycin [58, 69].

   It is reported that patients can develop respiratory failure when exposed to oxygen in a concentration greater than 25% [7]. Since during nitrous oxide sedation, oxygen concentrations vary from 100 to 30%, such patients will be at high risk of respiratory failure.

6. **Autoimmune disorders or children on immunosuppressive therapy**

   Nitrous oxide is believed to cause depression of bone marrow activity which can lead to a reduction in production of erythrocytes and leukocytes. Since bone marrow has a reserve of mature cells, a single exposure to nitrous oxide will not be of clinical significance because the bone marrow reserve will replenish the need of erythrocytes and leukocytes. This depression of marrow activity bounces back in 3–4 days. If nitrous oxide is administered repeatedly during this period, it may extend the inhibition of synthesis which may exceed the safety factor of stored cells. Therefore, the use of nitrous oxide gas, repeatedly at less frequent intervals, may cause further reduction in immune response of the body.

7. **Cobalamin deficiency**

   Vitamin B_{12} is a bound coenzyme of methionine synthase and has a tetrapyrrole ring with monovalent cobalt at the center. The cobalt functions as a methyl carrier in the transmethylation reaction. The sole biochemical effect of nitrous oxide is to block the transmethylation reaction as it converts monovalent cobalt to an inactive trivalent form. Methylation reactions have a role to play in DNA/RNA synthesis (turning on/off genes), brain chemical production (e.g., dopamine, serotonin, epinephrine), hormonal breakdown (e.g., estrogen), creation of immune cells (e.g., NK cells, T cells), creation of protective coating on nerves (i.e., myelin formation), and processing of chemicals and toxins (detoxification).

   Thus, nitrous oxide is contraindicated in cases of methionine synthase deficiency, methylene tetrahydrofolate reductase deficiency, or vitamin B_{12} deficiency which may further decrease the methionine levels required for protein synthesis and methylation reactions.

8. **Children who are in precooperative stage**

   The children do not have cognitive ability developed enough to understand the use of nasal hood. A child who is less than 30 months old usually will not understand putting a mask on the nose. Even if they allow, they may not let it stay there for more than few minutes. If the mask is put forcefully on the child's nose by using restraint, then the child may get more anxious [53].

A clinical tip is that if the child has used nebulization mask and is comfortable using it at home, then the child may use the nitrous oxide nasal hood easily.

9. **Extremely anxious and fearful children who are crying uncontrollably**
   It is very difficult to explain the process of using nitrous oxide in such children and hence this technique may not be successful. A child who is usually unresponsive to audiovisual distraction will usually not inhale nitrous oxide efficiently. Sometimes, resorting to basic behavior management techniques, over a period of 1–3 visits, may make them develop rapport with the dentist, thereby making it possible to use nitrous oxide nasal hood [70].

A clinical tip is that if a child is not willing to enter the dentist office or is extremely fearful of external factors, such as a hair cut, then the child may not be a good patient for using this technique.

10. **Children who are unable to communicate**
    Children who are otherwise cooperative but unable to communicate because of systemic disorders or mental delays may not respond well to verbal commands during nitrous oxide sedation. This may make it difficult for the operator to seek purposeful response to verbal commands thereby misjudging the level of sedation [56, 71].
    Also, children who speak and comprehend language other than that used by the clinician, may face challenges in understanding.
11. **Child wants to get treatment done using nitrous oxide**
    Once exposed to nitrous oxide, a child may demand its use, even though no treatment is required. This is because of the euphoric potential of nitrous oxide. In such situations, dentist should counsel the child against its unnecessary use.
12. **Children with behavioral issues**
    Hysterical, stubborn, or defiant patients may be difficult candidates for introducing nitrous oxide mask.
13. **Child suffering from multiple sclerosis**
    Frequent exposure to nitrous oxide for performing dental treatment in a child suffering from multiple sclerosis is not recommended as it may cause neuropathies. Patients with multiple sclerosis suffer from nerve demyelination, and the symptoms may worsen by nitrous oxide-induced neuropathy [72].

1.4.2 Local Causes

1. **Surgery involving the anterior surface of maxilla**
   Nitrous oxide sedation requires a nasal hood to rest on the upper lip throughout the dental procedure. If any surgery has to be carried out in the anterior surface of maxilla such as extraction of an impacted tooth, removal of odontomes, and cysts, it becomes difficult to retract the upper lip for surgical access. Hence, nitrous oxide nasal hood poses a challenge for surgical procedures involving the anterior surface of maxilla [73] (Fig. 1.20).
2. **Mouth breather**
   A child, who is a mouth breather because of obstructive causes such as nasal polyps, deviated nasal septum, or enlarged adenoids may find it difficult or impossible to breathe through the nose. It may be futile to use nitrous oxide sedation through the nasal hood in such patients as they won't be able to breathe through the nose, thereby making nitrous oxide sedation ineffective [74, 75].
3. **Difficulty in breathing through nose or upper airway infection**
   A child who is otherwise able to breathe normally through nose but is unable to do so on a particular day because of nasal congestion or upper airway infection may find it difficult to breathe through nose, thereby causing nitrous oxide sedation ineffective [73].

Nitrous oxide has no absolute contraindications and is a useful alternative to general anesthesia [76]. Table 1.5 enlists various conditions in which use of nitrous oxide may or may not be contraindicated.

Fig. 1.20 Difficulty in administering local anesthesia in the maxillary anterior region due to the nasal hood

Table 1.5 Categorization of contraindications

No contraindications	Possible contraindications	Absolute contraindications
Cardiovascular system Heart murmur, congenital conditions, rheumatic fever, transplant	Sinus infection/congestion—may need postponement of appointment	Recent eye surgery
Central nervous system Seizure disorders	Tuberculosis or upper respiratory infection	Recent ear surgery
Respiratory system Asthma—N_2O is not contraindicated as it reduces the stress-provoking stimuli which usually precipitate asthma	Ear infection—may require postponement of appointment	Latex allergy
Hematological disorders Anemias, methemoglobinemia, sickle cell anemia, leukemia, hemophilia, polycythemia vera	Mental illness, autism, psychiatric disorders	Bleomycin therapy
Hepatic diseases Hepatitis, jaundice	Stomach pain May require postponement	
Endocrine system Thyroid/adrenal dysfunction, diabetes	Claustrophobia	
Kidney diseases No effects of nitrous oxide		
Neuromuscular system Multiple sclerosis, muscular dystrophy, cerebral palsy, myasthenia gravis		
Cancer N_2O creates a sense of well-being and relaxation		

Source: Paarmann C, Royer R. Pain control for dental practitioners: An interactive approach [77]

1.5 Advantages of Using Nitrous Oxide in Children

Nitrous oxide inhalation sedation has various advantages to other sedative techniques used in children such as oral, intramuscular, intranasal, or intravenous.

1.5.1 Fast Onset

The onset of subjective symptoms using nitrous oxide sedation is much faster compared to other sedative techniques especially oral technique. There is always a lag period after administration of oral sedative because of the time required for the drug to be absorbed by the stomach mucosa [33].

Fast onset of nitrous oxide gas is attributed to its low blood gas partition coefficient (Refer Chap. 2).

1.5.2 Ease of Administration

If a child is willingly accepting a nasal hood, then the ease of administration of nitrous oxide sedation is much higher compared to other techniques. During oral administration of a sedative drug, the child may not completely ingest the drug. He/

she may spit out a part of the drug mixed with saliva making it difficult for the operator to determine the exact dose of sedative administered to the child. Intranasal administration is also not easy as putting the drug in the nose causes a lot of irritation to the child. Again, the exact desired amount of drug may not be delivered to the child. Intravenous/intramuscular is definitely not convenient for a child as it employs the use of a needle.

1.5.3 Sedation Level Can Be Adjusted Based on Response (Titratable)

This property is of great benefit in a non-hospital setting as the sedation level could be reduced by reducing the concentration of the drug delivered to the child. This is also related to its property of fast onset and fast recovery, as for other techniques, the sedation level cannot be adjusted once the drug is administered through other routes because the entire amount of drug is delivered inside the body in one go. Thus, after the administration of the drug, sedation response cannot be reduced.

On the other hand, more drug cannot be administered to the child if the sedation response is less than desired because the sedative drug is administered based on the body weight of a child. If more drug is administered, then the additive effect might lead to a deeper level of sedation.

1.5.4 Quick Recovery

Similar to fast onset, nitrous oxide gas has a quick recovery period, making it safer compared to other sedative agents and also prevents the need for any postoperative recovery period [67].

1.5.5 Ability to Communicate During Procedures

Since nitrous oxide sedation causes only minimal to moderate level of sedation, the child will be able to communicate during the procedure making it safer compared to other sedative agents (Fig. 1.21). This has a psychological impact on the parents because they feel that the child is well in control of the situation and has not gone into a state where they cannot carry out a meaningful dialogue with the child.

1.5.6 Safe Compared to Other Agents

Safety index of nitrous oxide sedation is much higher compared to other sedative agents. Nitrous oxide sedation is believed to have a safety record of more than 100 years.

Fig. 1.21 Operator can communicate with the child during the procedure

1.5.7 No Impact on Daily Duties

A child can go to school, play outdoors or indoors, study or carry out any other activity soon after the dental procedure under nitrous oxide sedation. This has a major impact on the minds of the parents because it is then considered equivalent to a normal dental procedure. It does not affect their schedule also as they are not required to stay back with the child leaving their work. However, with other sedative techniques, this is not achievable because it requires varying periods of postoperative monitoring in the clinic depending on the sedation. This definitely has to be followed with the need of parents accompanying their child at home for a few hours after the procedure.

> Main advantage of nitrous oxide sedation is related to its property of fast onset and fast recovery.

Other modes of sedation have clear disadvantages over nitrous oxide sedation (inhalation sedation) which have been summarized in Table 1.6.

1.6 Disadvantages of Nitrous Oxide in Children

Nitrous oxide inhalation sedation has certain disadvantages associated with it such as follows:

1. ***Poor acceptance of the nasal mask***
   Children who are extremely anxious may not accept the nasal mask readily (Fig. 1.22). Acceptance of nasal mask is of utmost importance for nitrous oxide inhalation sedation. Also during the procedure, child may not keep the mask

Table 1.6 Disadvantages of other modes of sedation over inhalational mode (nitrous oxide)

Route of administration	Disadvantages over nitrous oxide sedation
Oral	• Cannot titrate the drug • Delay in onset • Varying response due to difference in gastric absorption • No oral reversal drug present • Longer pre-procedural fasting required
Intramuscular	• Difficult for patients who are needle phobic • Can cause muscular pain • Over sedation possible • Longer pre-procedural fasting required
Intravenous	• Difficult for patients who are needle phobic • Over sedation possible • Longer pre-procedural fasting required
Intranasal	• Difficult to administer • Can cause burning sensation in nasal mucosa • Over sedation possible

Fig. 1.22 Poor acceptance of nasal mask in extremely anxious children

untouched and undisturbed. He/she may move the mask or move his/her face disturbing the position of the mask which reduces the efficacy of nitrous oxide sedation. This disadvantage can be overcome by the use of basic behavior management techniques.

2. ***Relative weak potency of nitrous oxide/oxygen***

   Nitrous oxide gas also has biovariability associated with it. Hence, in few of the children, the effect of nitrous oxide sedation is not clinically evident. Even at a higher concentration of nitrous oxide, the child may not have reduced anxiety or may not have clinically desired level of sedation. In many instances, using basic behavior management techniques usually helps in overcoming this disadvantage.

3. ***Difficulty in introducing nasal mask in children of precooperative age***

   Children who are less than 3 years old usually do not have cognitive ability developed enough to understand the use of a nasal mask (Fig. 1.23). Hence, they may not allow the mask to be used because of which, nitrous oxide sedation has a smaller role in children who are less than 3 years old [53].

> There may be a few children less than 3 years old who may willingly accept the mask and hence can be considered for nitrous oxide sedation.

Fig. 1.23 Difficulty in introducing nasal mask in children in precooperative age

4. ***Associated with nausea or vomiting***

   Few children develop nausea or vomiting on using nitrous oxide sedation. This is seen more in children who have motion sickness or have taken fatty food before the appointment.
5. ***No role in post-treatment pain***

   Children who are very comfortable during the treatment because of analgesic properties suddenly start crying at the end of the procedure because of loss of analgesic properties which are diminished as the nitrous oxide concentration is reduced to zero. This is usually seen after placement of stainless steel crowns without local anesthesia. A heightened response is also seen with local anesthesia. During the course of nitrous oxide sedation, the child will not realize numbness associated with local anesthesia, but as soon as nitrous oxide is reduced child realizes numbness and may start showing unhappiness over numb feeling.
6. ***Children with behavioral problems***

   Children who suffer from anxiety disorders, may start shouting or crying suddenly during the course of nitrous oxide sedation because they are not able to understand the subjective symptoms such as tingling in extremities or light headedness. This disadvantage can be overcome by explaining the expected feelings before starting the use of nitrous oxide.
7. ***Dependence on psychological assurance***

   Nitrous oxide efficacy is largely dependent on psychological assurance. The child has to be told about expected feelings and reassured that such feelings are expected. Many a times, such feelings should be associated with euphemisms.
8. ***Occupational hazard for the dental personnel***

   Chronic exposure of nitrous oxide gas to the dental personnel in an unscavanged operatory poses some health risk to the dentists and their staff [69].
9. ***Cost of equipment***

   Nitrous oxide sedation usually requires the use of specialized equipment like flowmeters. Also there is a recurring need for nitrous oxide and oxygen cylinders which have to be procured from a medical gas supplier on a regular basis. This may be difficult at times considering the weight of the cylinders, making it challenging to transport the cylinders [73, 78].
10. ***Not an alternative to local anesthesia***

    Although nitrous oxide has analgesic properties, it cannot substitute local anesthesia completely. It only serves as an adjunct to local anesthesia [79].

Hence, the advantages of using nitrous oxide sedation in children usually outweigh its disadvantages.

1.7 Conclusion

At the end of this chapter, we realize that recognizing as well as dealing with fear and anxiety is crucial for effectively introducing the technique of nitrous oxide sedation in children. In 2003, the American Academy of Pediatric Dentistry introduced the term **"behavior guidance"** in lieu of "behavior management." This was done to emphasize that the goal is not to “deal” with a child’s behavior but to “enhance communication with the parent and child to promote a positive attitude and good oral health.” In conjunction with **behavior guidance** techniques, nitrous oxide, due to its anxiolytic and analgesic properties, can promote “positive experiences,” thereby helping the child to not only maintain a good dental health at a young age, but also help him/her develop a positive dental attitude, which, in turn, may help in improving the dental health of the community as a whole. Nitrous oxide sedation is safer and reliable compared to other forms of sedation and can help in reducing the number of children being treated under general anesthesia for dental rehabilitation.

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Basic Properties of Nitrous Oxide Gas

2

Amit Sethi, Sumati Bhalla, and Kunal Gupta

Contents

Learning Objectives

1. Understand the manufacturing process of nitrous oxide gas
2. To be well versed with storage of nitrous oxide gas, cylinder specifications and important precautions to be taken during their storage and handling
3. To have good grasp over pharmacodynamics and pharmacokinetics of nitrous oxide gas

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The discovery, history, and evolution of “office-based anesthesia is a colorful mix of men, motives, medications and machines” [1]. We would not be wrong at all to add “gases” to the statement above. The first gas found to have analgesic, anxiolytic, and “euphoric” properties and which introduced the concept of anesthesia to the world was nitrous oxide. This chapter dwells into the history of production of nitrous oxide, the manufacturing process, its storage (in cylinders), and its properties. A good understanding about pharmacological properties of nitrous oxide gas will instill confidence in readers about the safety of this gas, use of this gas effectively for child patients, and also about the mechanism behind minor adverse events which they may encounter.

2.1 Manufacture and Storage of Nitrous Oxide

2.1.1 A Brief History of Production of Nitrous Oxide

Joseph Priestly is credited with synthesis of nitrous oxide in 1772. Priestly was working to study what he called the “Nitrous Air” in more detail when he discovered nitrous oxide by serendipity [2]. One of these experiments involved “adding in water a quantity of nitrous air (NO) phlogisticated with iron fillings and brimstone (sulfur).” He would go on to say that “most unexpected change was made…and it was transformed into a species of air in which a candle burns quite naturally and freely, and which is yet in the highest degree noxious to animals” [3].

He named the gas “dephlogisticated air,” and the same would later be called nitrous oxide or the “laughing gas” (Fig. 2.1).

$$2NO + H_2O + Fe \longrightarrow N_2O + Fe(OH)_2.\ (\text{Eq. } 2.1) \qquad 2.1$$

> Nitrous oxide was termed as “nitrous air, diminished” by Joseph Priestley because it was prepared by allowing nitric oxide (nitrous air) to remain in contact with moist iron fillings.

This “dephlogisticated nitrous air” was a nod to the predominant chemical theory at that time, “phlogiston theory.” This theory postulated that a fire like element called “phlogiston” is contained within combustible bodies and is released during combustion. The theory was later disapproved, and processes like combustion and rusting were explained by oxidation.

Humphrey Davy gained fame due to his work on nitrous oxide, and as part of his experiments he synthesized and inhaled small quantities of it without any

Fig. 2.1 Joseph Priestley's apparatus for conducting experiments on gases. (**Source**: https://www.beautifulchemistry.net/priestley)

adverse effects [2]. In the very beginning, Davy used Priestly's method to synthesize the gas as in Eq. 2.1 above, but he soon found out that it took longer and produced smaller quantities. Looking for a more efficient method, he switched to technique advocated in 1785 by a French chemist and physician, Claude Louis Berthollet, in which the decomposition of ammonium nitrate crystals is used to produce nitrous oxide.

Nitrous oxide, actually synthesized in 1772, soon faded into background until it was revived by Humphrey Davy of Pneumatic Institute, Bristol, England.

$$NH_4NO_3 \xrightarrow{\Delta} N_2O + 2H_2O \tag{2.2}$$

Davy used crystals of ammonium nitrate placed in distilling glass and heated these up to 350 °C (Fig. 2.2). The nitrous oxide thus released was captured by water-cooled, hydraulic air bag like sacs (bellows) (Fig. 2.3). To minimize violent exothermic reactions and toxic by-products such as nitric acid which appeared at high temperatures, the temperature was maintained between 240 and 480 °C.

The nitrous oxide produced was stored in reservoir tanks. At that time, silk bags were used to help people "inhale the gas during sessions" [2]. The gas continued to be used to amuse people with its euphoric effects at various public gatherings and exhibitions.

> Fifty years after the discovery of nitrous oxide, its analgesic and anesthetic properties were not realized. It was mainly used for euphoric purpose till then.

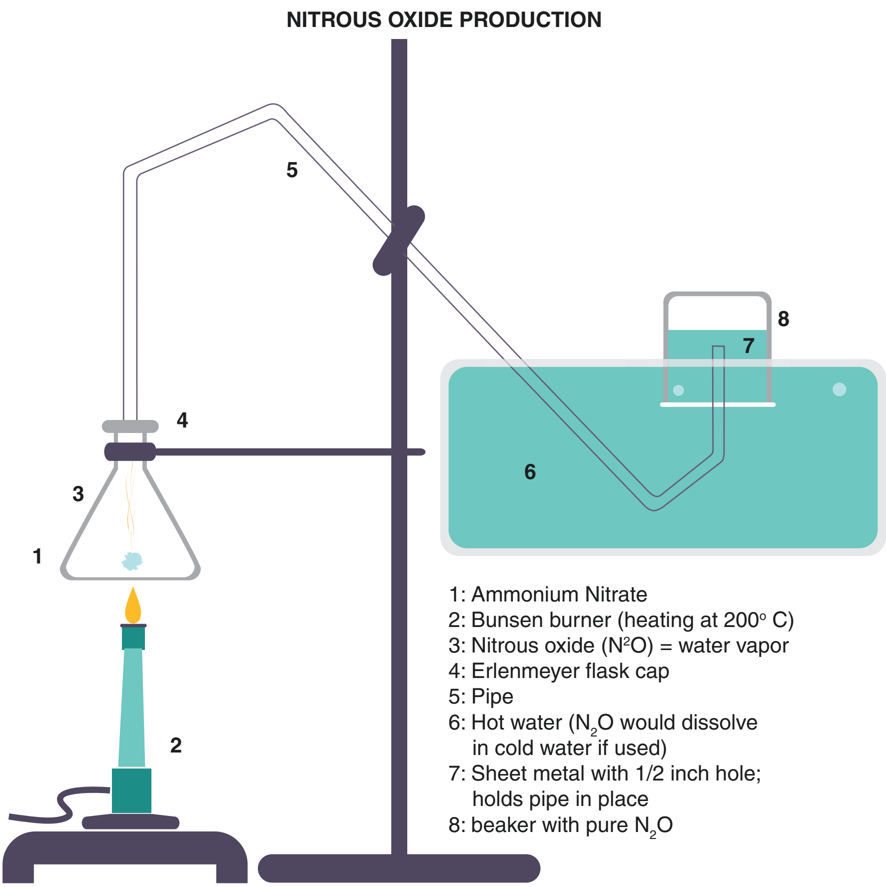


Fig. 2.2 Production of nitrous oxide using ammonium nitrate crystals. (*Modified from: https://www.thoughtco.com/make-nitrous-oxide*)

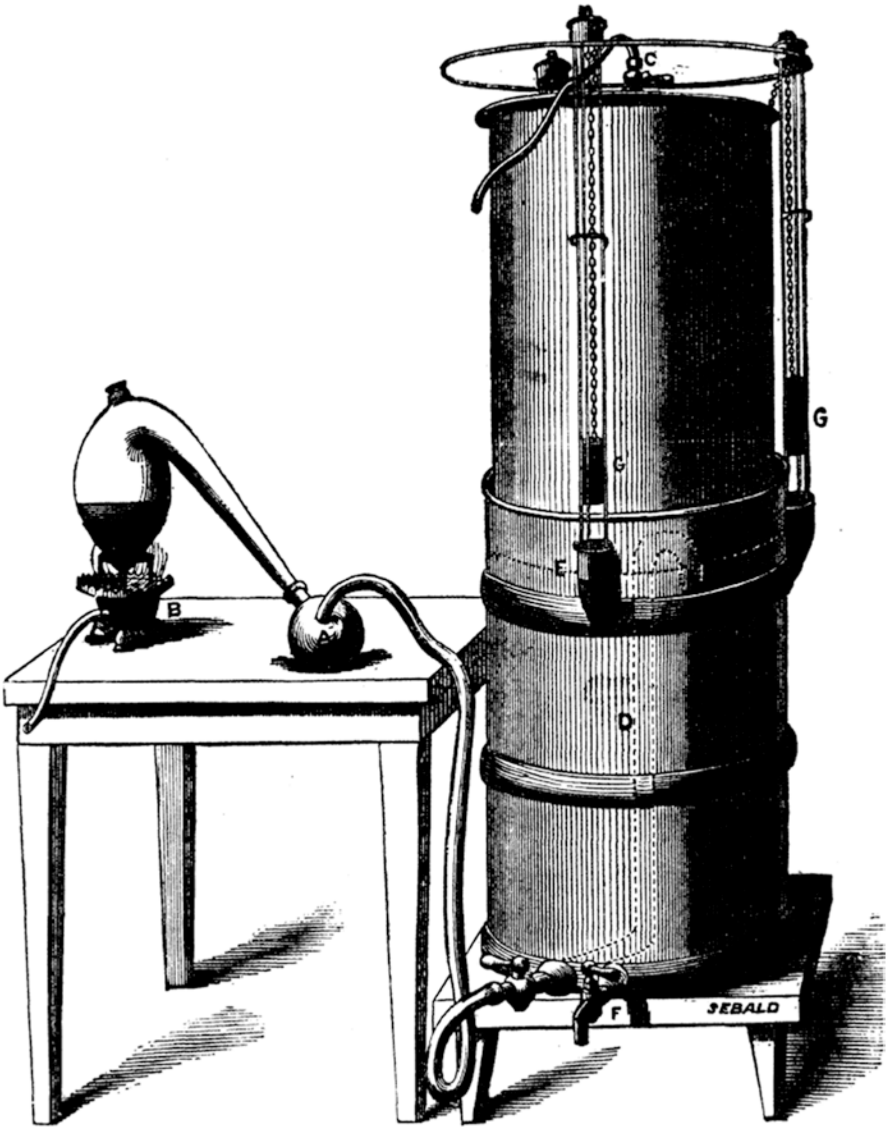


Fig. 2.3 Figure showing hydraulic air bag like sacs in which nitrous oxide was stored. (Source: Smith WDA. A history of nitrous oxide and oxygen anaesthesia part x: the early manufacture, storage and purity of nitrous oxide. British Journal of Anaesthesia. 1967 May;39 (5):351–81)

2.1.2 Modern Processes for the Manufacture of Nitrous Oxide

Production from Ammonium Nitrate Solution

In this method, a solution of ammonium nitrate and water, known as liquid ammonium nitrate (80–93% ammonium nitrate by weight), is heated to approximately 250 °C. Two reactions occur at this temperature—decomposition and dissociation.

The decomposition reaction is as below and results in production of the desired gas with high degree of purity [2].

$$NH_4NO_3 \xrightarrow{\Delta} N_2O{+}2H_2O \text{ (same as Eq. 2.2 above)}$$

The dissociation reaction produces undesirable by-products and is as under:

$$NH_4NO_3. \xrightarrow{\Delta} NH_3 + HNO_3$$ [1]

In order to remove the ammonia, this gas mixture is passed through sulfuric acid scrubber and a water scrubber.

The other toxic impurity which often accompanies the production of nitrous oxide is nitric oxide, and its removal is accomplished by washing/scrubbing the gas mixture by an alkaline potassium permanganate solution.

$$NO{+}KMnO_4. \xrightarrow{\Delta} KNO_3 + MnO_2$$

The final drying of nitrous oxide is achieved with potash (KCO_3, KOH).

The dried and compressed (38 atm) gas is liquefied, degassed, passed through dryers again, and stored in the storage tanks.

The composition of gas obtained must confirm to standards of U.S. Pharmacopeia as below [4].

Nitrous oxide	99.0% minimum in liquid
Carbon monoxide	10 ppm maximum in vapor
Nitrogen dioxide	1 ppm maximum in liquid
Halogens	1 ppm maximum
Carbon dioxide	300 ppm maximum
Ammonia	25 ppm maximum
Water per 20 L	3 mg maximum

Production from Solid Ammonium Nitrate

Solid ammonium nitrate is placed into a preempting vat, while in the next chamber, the retort is capped and heated. The ammonium nitrate loaded into the vat is heated to 163 °C and on melting is converted to the liquid form which is then transferred into the retort. The hot gas leaving the retort contains water vapor, acids, and oxides of nitrogen. The water-cooled condenser, scrubber, and caustic soda solution in the subsequent chambers work to cool the gas and remove acidic impurities and oxides of nitrogen. The reaction that occurs in scrubber with caustic soda solution is as follows.

> The use of solid ammonium nitrate for producing nitrous oxide gas dates back to early 1900s and is still used in some countries.

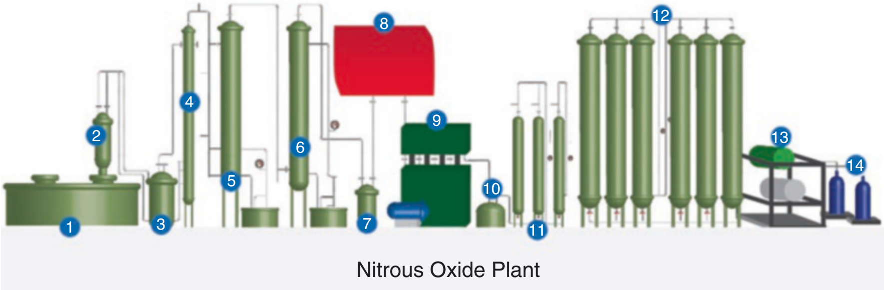


Fig. 2.4 Parts of nitrous oxide plant. (**Modified from**: https://www.hitechgas.com/nitrous-oxide/nitrous-oxide-plants/how-nitrous-oxide-plant-works/)

$$2NO_2 + 2NaOH \rightarrow NaNO_2 + NaNO_3 + H_2O$$

After this, the gas travels through towers filled with iron borings to remove the last traces of higher oxides of nitrogen. Sulfuric acid scrubber removes all traces of ammonia and other alkaline impurities. To make sure that there is no acid carried over and to decrease the moisture content, the gas is passed through a tower containing caustic soda and is then collected in a reservoir. Then the gas is drawn from the reservoir, compressed to 550–950 psi, and is finally drawn into a brine tank where liquid nitrous oxide accumulates at the bottom of the refrigerated cylinder and non-condensable gases accumulate on top. The cold liquid nitrous oxide is piped into cylinders that are used to distribute it for anesthetic purposes [4].

Main parts of nitrous oxide plant and their purposes are as follows [4] (Fig. 2.4):

1. **Melter**—Heats the solid ammonium nitrate to a temperature of 163 °C and converts it into a liquid (molten state).
2. **Retort/Reactor**—The liquid/molten form from the melter is transferred to the retort as needed where ammonium nitrate is decomposed based on chemical reaction mentioned above.
3. **Condenser**—Eliminates the water vapor.
4. **Water scrubber**—Washes the gas–steam mixture with fresh water, condensing the steam, and absorbing unwanted oxides of nitrogen.
5. **Sodium hydroxide scrubber**—Removes acidic impurities and higher oxides of nitrogen.
6. **Acid scrubber**—Removes traces of ammonia and alkaline impurities.
7. **Moisture separator**—Removes traces of moisture.
8. **Gas holder**—Liquid nitrous oxide collects at the bottom of the tank.
9. **Nitrous oxide compressor**—Gas is compressed to 37–65 atm of pressure.
10. **Purge bottle**—Removes the non-condensable gases which collect at the top and purges them to atmosphere.
11. **Drying units**—This part helps in final drying of the gas.

12. **High pressure buffer storage**—This part stores nitrous oxide before it is liquified and in situations where surge in demand exceeds the capacity of the cooling system.
13. **Liquefaction unit**—The nitrous oxide is liquified in this unit.
14. **Cylinder filling ramp**—Finally, gas is transferred into cylinders to facilitate transport.

2.1.3 Manufacturing Hazards

The potential for a possible explosion is increased if ammonium nitrate is contaminated by any organic matter. A contamination of as little as 1.5% organic matter will cause ammonium nitrate to explode at temperature of 150 °C and 17 atm. To put this in perspective, pure ammonium nitrate explodes at 230 °C and 170 atm. Explosion at high temperatures results from breakdown of ammonium nitrate into ammonia and nitric acid, thus increasing gas pressure and generating heat, which increases the intensity of the decomposition reaction. Over the years, more than 5000 people have lost their lives in more than 25 major explosions involving over 12,000 tons of ammonium nitrate [4].

2.1.4 Toxicity of the Impurities in Nitrous Oxide

Some of the impurities can get incorporated into nitrous oxide at the time of manufacture [4].

1. **Nitric Oxide**
   A colorless gas which readily combines with air to form the highly poisonous nitrogen dioxide and dinitrogen tetroxide. One of the main causes for concern with this gas is that the damage produced by it may not be noticed for several hours. The pulmonary edema, which may be caused by exposure to more than 25 ppm of oxides of nitrogen for more than 8 h, may not develop till 72 h later.
2. **Nitrogen Dioxide**
   This gas which is red in color is one of the most insidious gases. It causes severe pulmonary damage which though may not even be noticeable in the beginning but still can result in death of the person exposed. The threshold limit value (TLV) for nitrogen dioxide is 5 ppm.
3. **Ammonia**
   Ammonia does not have any known systemic toxicity, but its inhalation may cause possible irritation of upper respiratory tract, laryngospasm, bronchospasm, and apnea. Occupational health and safety have recommended a TLV of 50 ppm for ammonia.
4. **Chlorine**
   The source of chlorine is through contamination of ammonium nitrate. It has a suffocating odor, and higher concentrations can cause symptoms of suffocation,

constriction in chest, and tightness in throat. The recommended TLV for chlorine is 1 ppm.

5. **Carbon Monoxide**
   This is an inflammable, colorless, tasteless, and odorless gas which can combine with hemoglobin to form carboxyhemoglobin which can interfere with oxygen carrying capacity of blood, thereby causing dizziness, nausea, loss of muscular control, collapse, and even death. The gas concentration, exposure time, and physical activity of the inhaler determine the percentage of hemoglobin converted to carboxyhemoglobin. Occupational health and safety recommends a TLV of 35 ppm for a sedentary non-smoker.
6. **Water**
   Presence of water represents a mechanical problem and is not a health hazard. Condensation of water vapor and ice in cylinder and manifold valves may produce an uneven flow of gases. The modern day production of nitrous oxide does away with most of the moisture by passing the gas through multiple drying cycles.

With modern manufacturing techniques, impurities in nitrous oxide gas have been reduced to negligible.

2.1.5 Storage of Nitrous Oxide

Once it is manufactured, nitrous oxide is stored in highly pressurized gas cylinders. Medical gas cylinders were traditionally made of low carbon steel (Fig. 2.5), but now they are constructed from light weight chrome molybdenum steel, aluminum (Fig. 2.6), or a composite such as aluminum wrapped in carbon fiber. In MRI rooms, special cylinders made of aluminum are used. Typical wall thickness of steel cylinder is 3 mm and that of aluminum alloy is 6 mm [5]. A typical cylinder is formed of a body and the valve which is attached to it.

Fig. 2.5 Nitrous oxide cylinder made of steel

Fig. 2.6 Aluminium cylinders of nitrous oxide and oxygen

Body

Body forms the bulk of the part of cylinder. The body continues into neck which is the narrower part. It is the neck which has a tapered screw at the end and connects to the valve. When the valve is screwed to the cylinder neck, a fusible material (Wood's metal) is used to seal leaks between the valve and cylinder. This material will melt if the cylinder is exposed to intense heat, thereby allowing the gases to release and reduce the risk of explosion [5].

> Nitrous oxide cylinder's body is colored blue internationally and light blue in the USA. Body of oxygen cylinder is colored white internationally, green in USA, and is colored black in India.

Valve

The valve provides a means of connection to the yoke assembly on anesthesia machines. The valve which is made out of bronze or brass, allows the gas to exit through the cylinder, and this is facilitated by opening of a stem or shaft (Fig. 2.7).

Perhaps the most important characteristic of valve is the pin index system. It is a one of its kind, configuration of holes and pins, which is like a key and lock. This is designed to eliminate connection of the wrong cylinder to the equipment, thereby

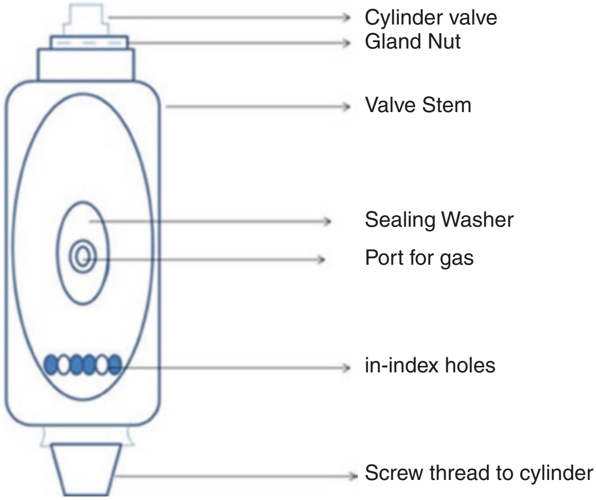


Fig. 2.7 Parts of cylinder valve

Fig. 2.8 Pin index system for oxygen on cylinder and yoke of portable nitrous oxide delivery system

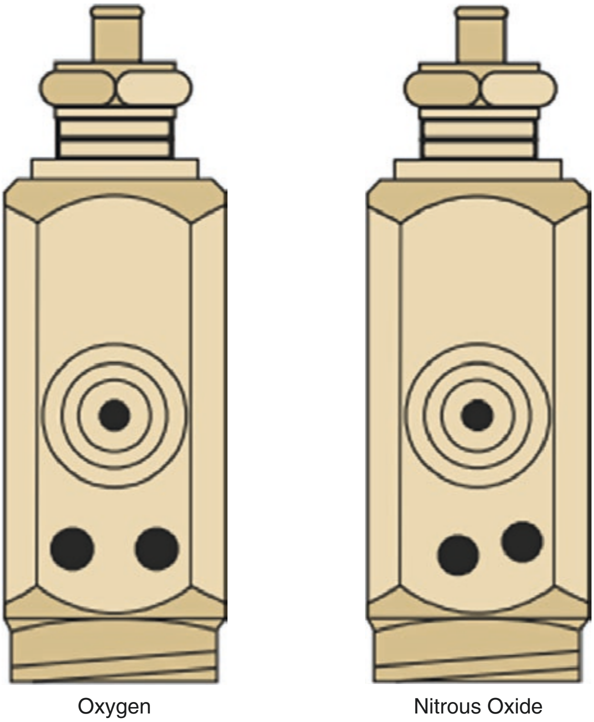
preventing delivery of wrong gas to the patient. This also ensures that a cylinder can be only connected to a yoke with matching pair of pins. Pin index valves are fitted in small cylinders which are commonly connected directly to anesthesia machines (Figs. 2.8, 2.9, and 2.10).

Storage of Gases in Cylinders

Compressed gases (oxygen, air, nitrogen) are stored in cylinders. These gases do not liquify at ordinary ambient temperature regardless of the pressure applied [6]. These cylinders are filled up to service pressure (maximum pressure to which cylinder

Fig. 2.9 Pin index system for nitrous oxide on cylinder and yoke of portable nitrous oxide delivery system

Fig. 2.10 Pin index on valves for oxygen and nitrous oxide. (Source: https://www.bochealthcare.co.uk/en/images/cylinder_data_med309965_2011_tcm409-54065.pdf)



may be filled at 70 °F) but are designed to tolerate 1.66 times the service pressure. The service pressure is usually 2000–2015 psi for oxygen and 750 psi for nitrous oxide [7]. The quantity of gas in these cylinders can be estimated by using the pressure gauge since the quantity is directly proportional to the pressure in the cylinder (*however, this does not happen with nitrous oxide as described in the following subsection*).

Oxygen is stored as compressed gas in cylinder, but nitrous oxide is liquefied under pressure.

Nitrous Oxide Cylinders

A major difference between nitrous oxide and other gases is that the former liquifies at the pressures at which cylinders are filled. The pressure of nitrous oxide vapor floating above the liquid nitrous oxide is 750 psi. As the gaseous nitrous oxide escapes, more of liquid nitrous oxide vaporizes to replace it. The pressure of this new gas is 750 psi. This process continues till no more liquid remains to convert to gas. Therefore, the pressure gauge in nitrous oxide cylinders cannot be used to accurately predict the amount of gas remaining in the cylinder [8] (Fig. 2.11).

In contrast, the entire oxygen cylinder is filled with oxygen gas, and as a result the pressure gauge will show gradual reduction as the gas in the cylinder empties.

To make space for the vapors of the gas, nitrous oxide cylinders are filled at about 90–95% of the capacity with liquid nitrous oxide. Partially filling the cylinders allows some leeway in an event of exposure to sudden high temperatures, which could result in bursting of cylinders, as a result of increased pressure. Hence, these cylinders are only partially filled with liquid depending on the climate in which they are used [9].

As the cylinder is opened for use and nitrous oxide discharges, liquid nitrous oxide will vaporize and in doing so it will take heat from the cylinder and the immediate surroundings, thus cooling the cylinder.

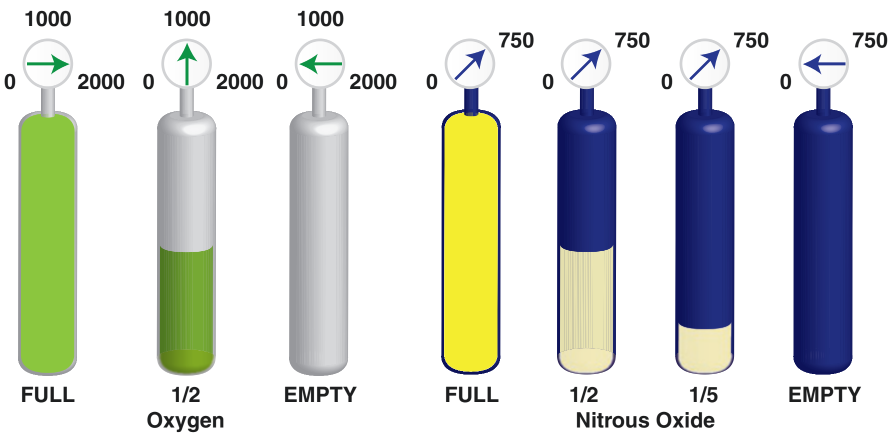


Fig. 2.11 Pressure indicators show reduction in cylinder pressure as gas reduces in oxygen cylinder (green colored), whereas in nitrous oxide cylinders (blue) the pressure indicator remains same till the nitrous oxide gets exhausted

Table 2.1 Table showing characteristics of E sized oxygen and nitrous oxide cylinders (USA)

Characteristics	Oxygen	Nitrous oxide
Cylinder contents	625	1590
Cylinder weight, empty kg	5.90	5.90
Cylinder weight, full kg	6.76	8.80
Cylinder pressure, full psi	2000	750

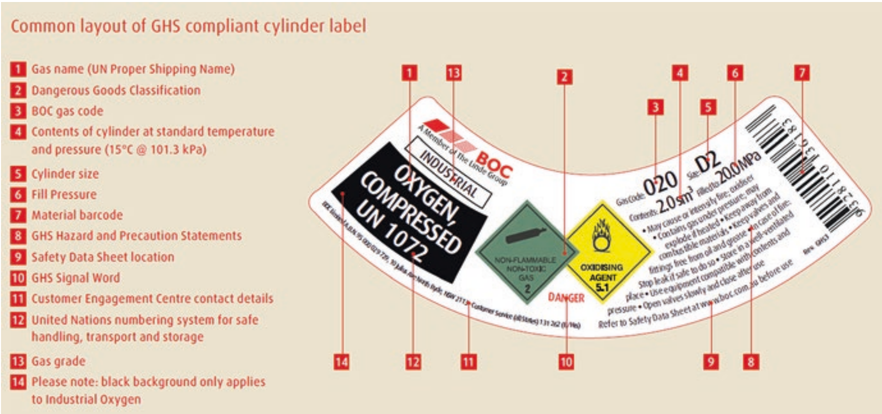


Fig. 2.12 Components of globally harmonized system of classification

Cylinder Size

Size of cylinder is defined by its ability to hold water and ranges between 1.2 and 6550 L. The cylinders, depending on their size, are alphabetically designated. The most commonly used cylinder in dental offices which do not have a central supply is small-sized cylinder. This is also the most commonly used cylinder for anesthesia machine and patient resuscitation.

In most dental offices, nitrous oxide is delivered in combination with oxygen through a portable machine and size E (USA) is the most common cylinder used (Table 2.1).

Cylinder size specifications for India, the USA/Canada, the United Kingdom, Australia, and New Zealand have been detailed in Appendix III–VI. Safety data sheet for nitrous oxide is detailed in Appendix VII.

> Most dental offices using portable nitrous oxide delivery system require size E cylinders and those with centralized supply need size H cylinders.

Labeling of Cylinders

Globally harmonized system of classification is an internationally agreed system of chemical classification and hazard communication through labeling and safety data sheets. Components of this can be seen in Fig. 2.12.

Handling Instructions for Cylinders [9] (Fig. 2.13)

Before Movement

1. Valves should be properly closed.
2. Valve protection cap is properly secured.

During Movement

1. Cylinders should never be dropped or be allowed to strike against each other violently.
2. Cylinders should be strapped or clamped during transport in a vehicle.
3. Do not lift cylinders by the cap.
4. Avoid dragging or sliding cylinders.
5. Cylinders should always be carried on trolleys which have a mechanism to prevent its slippage from trolley (Fig. 2.14).

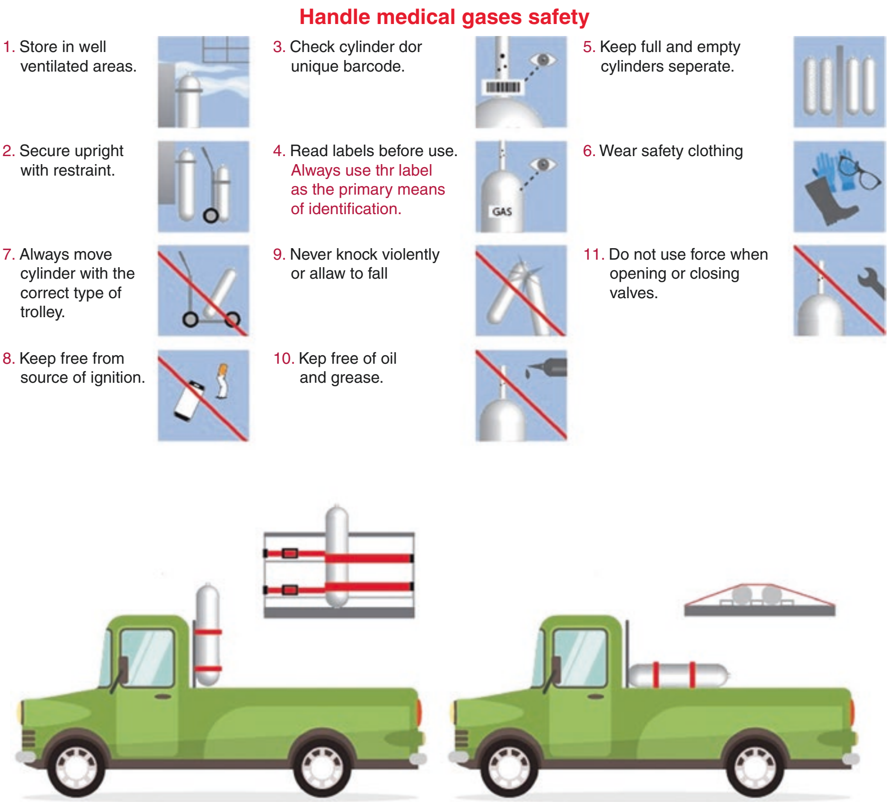


Fig. 2.13 Precautions to be taken during handling and storage of medical gas cylinders

Fig. 2.14 Cylinder should be carried on trolley with a bar in place to prevent slippage

Fig. 2.15 Seal over the valve

During Storage

1. Cylinders should be stored in well-ventilated and locked areas.
2. Cylinders should not be stored in areas where temperatures are in extreme.
3. Cylinders should be checked for label and color.
4. Cylinders should be stored on leveled floor which is clean and dry.
5. Large cylinders should be stored vertically and small cylinders stored horizontally.
6. Cylinders are placed in such a way that they do not fall and cause damage to surroundings.
7. During fall off cylinders, valves may get damaged and may cause leakage from cylinders.
8. A single cylinder may cause falling of other cylinders and hence each cylinder should be secured in place.
9. Cylinders should not be stored along with inflammable material.
10. Cylinders should not be stored in areas where movement of people takes place.
11. Cylinders should be labeled as "empty," "filled," or "in use."

Opening and Closing Valves

1. Handling should be done by a trained staff.
2. Seal over the valve should not be tampered with and should be opened just before connecting the cylinders to the yolk or manifold (Fig. 2.15).
3. Most appropriate way of opening the cylinder valve is to open the valve momentarily and then close it. After this, the valve should be opened slowly (Fig. 2.16). This process is known as "cracking" the valve. This allows the equipment to get adjusted to full pressure.
4. Valve should not be over opened.
5. Valve should not be over closed at the end of the day.

While opening the cylinders, "cracking the valve" technique should be followed.

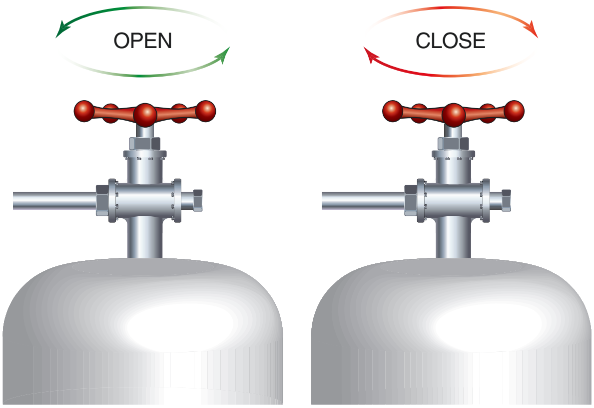


Fig. 2.16 Correct way of opening and closing the valves. (**Source**: "WHS UNIT Storage and Handling of Gas Cylinders Guidelines" https://smah.uow.edu.au/content/groups/public/@web/@ohs/documents/doc/uow136686.pdf)

Inspection of Cylinders Before Use

1. Inspect the cylinders for any damage.
2. The valve seal should be intact.
3. The valve should be free of dust or oil (oil and grease can react with oxygen to cause explosion; dust can cause a spark when in contact with high velocity gas).
4. Check the valves for leakage.

Despite all the precautions, many accidents have been reported throughout literature which involve incorrect tank (despite pin index safety system), incorrect contents, incorrect valves, wrong color, damaged valves, explosion of tanks, contamination, theft of nitrous oxide cylinders for recreational use, and last but not the least trauma to patients due to falling cylinders and accidents with steel cylinders in MRI room.

Despite many inbuilt safety features, accidents do occur and can be prevented by adhering to the recommended guidelines, cross-checking the label on the cylinder, and as always to have a degree of suspicion if something does not feel right.

2.2 Physico-Chemical Properties of Nitrous Oxide

Nitrous oxide enjoys immense popularity as an anxiolytic, and its use has increased among general dentists as well as other specialists over the years. Simplicity of use, cost-effectiveness, and very high safety index are its hallmarks. However, even after more than 150 years of its discovery, there is a lack of clear understanding on how it works [10]. The mechanism of action is discussed in detail in a separate chapter, but before we dwell into that it is important to know the basic properties of the gas.

Nitrous oxide (dinitrogen monoxide) has the molecular formula of N_2O (Fig. 2.17). It is a nonirritating, sweet-smelling, slightly sweet-tasting, and colorless gas [4, 11]. Its molecular weight is 44 with a specific gravity of 1.53 vs air (which has specific gravity of 1); it is about one and a half times heavier than air. It is not inflammable but supports combustion because at temperatures above 450 °C it breaks down into nitrogen and oxygen and the latter will support combustion. It is very stable and rather inert at room temperature.

Nitrous oxide is a sweet-smelling non-irritating gas.

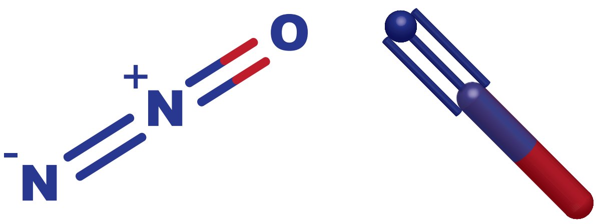


Fig. 2.17 Two-dimensional and three-dimensional structure of nitrous oxide

The boiling point of nitrous oxide is −89 °C. It is water soluble, oil water solubility quotient is 3.2, and with a blood gas partition coefficient of 0.47, nitrous oxide is relatively insoluble in blood. It is carried in blood without combining with any other constituents of blood [11]. In olden days, it was believed that the oxygen molecule attached to nitrogen was capable of providing oxygen to the tissues, but further studies, research, and numerous episodes of hypoxia which occurred then with higher concentrations of nitrous oxide proved that nitrous oxide does not break down under physiologic conditions and oxygen is not available for use by the tissues [12].

2.3 Pharmacokinetics of Nitrous Oxide

In this part of the chapter, we will try to understand the physiological basis of the interaction of nitrous oxide and the human body. In order for our readers to better understand the pharmacokinetics, it is important that we first look into the details of a few of its significant properties.

The uptake and distribution of anesthetic gas are dependent on the pressure gradients of the gas within alveolus, blood, and tissue. Equilibrium is achieved when the tension or the partial pressure of inspired gas becomes same as that of blood and tissue.

2.3.1 Solubility of Nitrous Oxide

The solubility of an anesthetic gas in the blood is the primary factor in determining its uptake and distribution. Anesthetic solubility is most commonly expressed as (1) **partition coefficient** or (2) **Ostwald solubility quotient**.

A "**partition coefficient**" is a general term, and it is the ratio of "anesthetic concentrations in each of the two compartments when equilibrium exists (partial pressure of the agent in both the compartments is same) between these compartments". For example "if the concentration of an anesthetic is 1 ml per ml of blood and this is in equilibrium with a tissue which has 2 ml of agent per ml of tissue, then tissue/blood partition coefficient would equal 2/1 or 2." It is most commonly expressed as $P_{\text{blood/tissue}}$ or $P_{\text{tissue/blood}}$ [13] (Table 2.2).

Table 2.2 Table showing blood gas partition coefficient of various inhalational anesthetic gases

Inhalation agent	Blood gas partition coefficient
Desflurane	0.42
Nitrous oxide	0.47
Sevoflurane	0.68
Isoflurane	1.40
Enflurane	1.91
Halothane	2.36
Chloroform	10.30
Diethylether	12.10

Since it is only a ratio, hence it has no units. Also, the coefficients are measured at 37 °C.

Nitrous oxide gas has a low blood gas partition coefficient as compared to other inhalational anesthetic gases thus facilitating rapid uptake into blood stream and rapid delivery to the brain.

Ostwald solubility coefficient is the other expression used to express the solubility of anesthetic solubility, and it is the "volume of gas dissolved per unit volume of blood or tissue, when equilibrium is attained between blood or tissue and the pure gas." Nitrous oxide was found to have a blood/gas partition coefficient of 0.468 as reported by Katy et al. in 1948 [14]. In the case of nitrous oxide, it means "that if pure nitrous oxide is equilibrated with blood and 0.468 ml of gas dissolves in each ml of blood then the Ostwald coefficient will be 0.468."

Before we look at the clinical implications of the solubility quotients and how it influences the behaviors of anesthetic agents, in particular nitrous oxide, there is one more physiological parameter to consider and that is the alveolar concentration of an anesthetic. The alveolar concentration is "the balance of anesthetic gas between that introduced into lungs by ventilation and that removed through uptake by blood." "The alveolar concentration is of particular interest to anesthetist because it is (after a time lag) equivalent to the brain tension" [13].

The clinical agents with higher blood gas partition coefficient will have more molecules being soluble in blood, and alveolar concentration of the gas remains low as most of the gas is taken up by the blood. Since blood can accommodate more of gas molecules due to its higher solubility, it takes a longer time for blood to get saturated with the gas molecules. Once the blood gets saturated with anesthetic molecules, the alveolar concentration of the gas begins to rise and the additional molecules get transferred to the brain. This explains for a delayed onset of the anesthetic effect (Fig. 2.18).

On the other hand, in case of agents with lower blood gas partition coefficient and lower solubility (nitrous oxide), only a small quantity is absorbed by blood and the alveolar concentration rapidly rises towards inspired concentration and the anesthetic agent molecules are readily transferred to the brain. This indicates a faster onset of action for the anesthetic agent (Fig. 2.19).

The anesthetic agent will fill the alveoli as it enters the lungs, and these alveoli are surrounded by a dense network of pulmonary capillaries around them. When the gas first fills the alveoli, the pulmonary capillaries have none of it, and by virtue of the difference in partial pressure between the two media, the gas will diffuse from the alveoli into capillaries. Alveolar concentration is the result of balance between the concentration of anesthetic gas introduced into the lungs and that removed by uptake from the blood. If the gas has zero solubility (Ostwald coefficient/blood–gas partition is zero), then no gas will diffuse into the capillaries and the alveolar concentration will start to rise, till it equals the amount of gas being inspired.

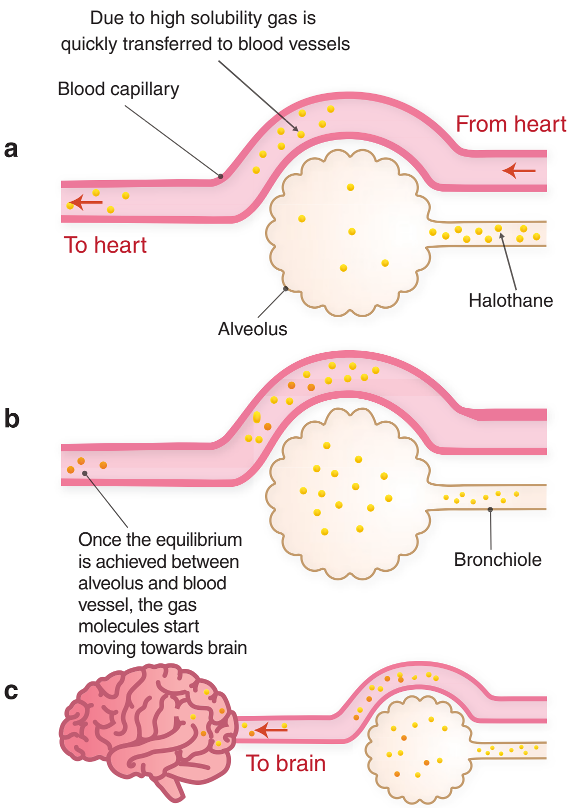


Fig. 2.18 (**a**) Halothane gas is rapidly taken up by blood from alveolus due to its higher solubility, which reduces the partial pressure of gas in alveolus in comparison to that of inspired air; (**b**) halothane begins to be delivered to brain only when partial pressure in blood vessels, alveolus, and inspired air achieves near equilibrium, which takes longer than nitrous oxide; and (**c**) halothane reaches brain tissue for uptake after a lag period

Nitrous oxide, with a partial pressure coefficient of 0.47, is among the least-soluble anesthetic gases, and hence, as the gas fills the alveoli, only a small quantity is absorbed and as a result alveolar concentration rises rapidly [11]. Studies have shown that after a patient breathes a low concentration of nitrous oxide for 1 min, the alveolar concentration reaches 60–80% of the inspired concentration [15]. The small quantity of gas, which is diffused into capillaries, reaches the vessel-rich group which includes the brain, heart, and kidney. Since the solubility of nitrous oxide is low, it equilibrates rapidly with these tissues (10–15 min). These tissues are supplied by 75% of the cardiac output, which means that three-fourth of blood in human body returning to heart after 10–15 min will not be capable of taking up nitrous oxide. This reduction in uptake will push the alveolar concentration even higher. After this, nitrous oxide equilibrates in less perfused tissues, such as muscle and fat. Here also because of less solubility of nitrous oxide, equilibrium is reached fairly quickly and uptake by muscle and fat also drops down at a rapid rate.

Within 1–2 min, equilibration of alveolar and inspired concentrations of nitrous oxide reaches almost 95%.

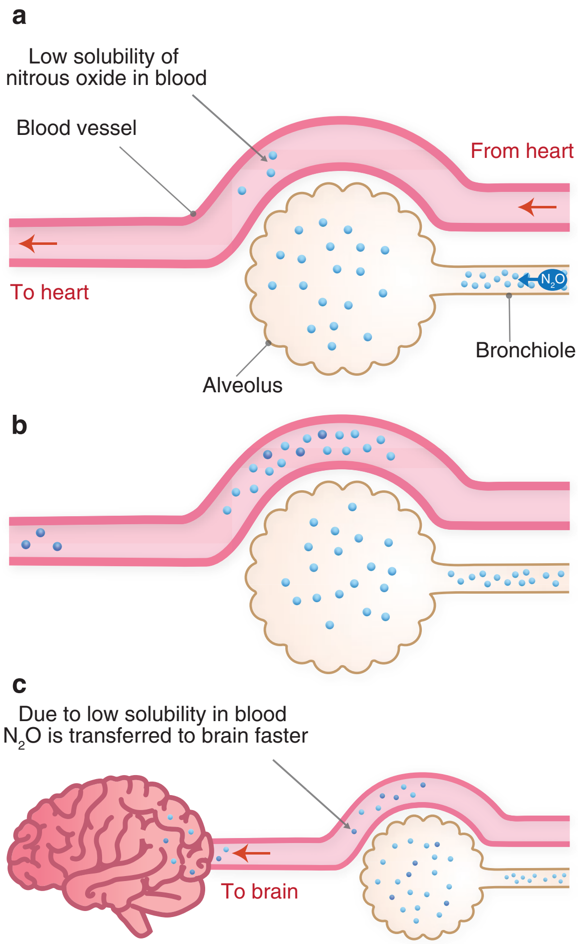


Fig. 2.19 (**a**) Due to lower solubility of nitrous oxide in blood, partial pressure of alveolus and inspired air remains in near equilibrium without any lag; (**b**) additional molecules of nitrous oxide gas are taken up by blood and delivered to brain due to low solubility in brain; and (**c**) nitrous oxide reaches brain tissue for uptake in a shorter period of time

Decreased solubility also means that recovery from nitrous oxide anesthesia is faster because the tissues are "less saturated with nitrous oxide" [13] and there is less reservoir for the gas, which means that it is cleared efficiently and effectively, thereby minimizing the recovery time from nitrous oxide anesthesia.

In dental and other outpatient clinics which use nitrous oxide–oxygen sedation, this translates to faster induction and also a safe and quick recovery from the effects of the gas.

Nitrous oxide, once absorbed from alveoli, enters the pulmonary circulation and "primary saturation of blood and brain" [11] with the gas occurs primarily by displacement of nitrogen by nitrous oxide which takes about 3–5 min. This becomes significant when nitrous oxide–oxygen sedation is used for the first time on a patient. In order to determine what concentration of inspired gas mixture will have the desired effect of anxiolysis, yet maintain high safety index in dental offices, we should start the patients on low concentrations (20–25% nitrous oxide) and allow them to stay at this percentage for 3–5 min before increasing the concentration in order to allow the gas to have the desired effect. This will give a fair idea of the suitable level for a particular patient, and on subsequent visits the operator can directly administer the previously determined concentration of the mixture.

> Nitrous oxide should be delivered at a particular concentration for 3–5 min before increasing the concentration, to understand the right concentration for achieving the desired clinical signs in a child.

The rapid uptake of nitrous oxide causes two distinct but interesting phenomena which we will try to understand next.

2.3.2 Concentration Effect

In simple terms, it means that "higher the inspired concentration of nitrous oxide, more rapidly the alveolar concentration approaches the inspired concentration" [16].

> At higher concentrations of nitrous oxide, uptake of nitrous oxide is even faster. This property is used in rapid titration technique in dentistry.

Concentration effect is seen most commonly when a higher concentration of gases are administered. In case of nitrous oxide when higher concentration of gas is administered, it rapidly raises the alveolar tension of the gas. This in turn means that a larger volume gets removed from lungs into the blood stream, and this potentially creates a vacuum, thereby resulting in more nitrous oxide being drawn from the machine into the lungs [11]. The principles which are responsible for concentration effect are seen with all anesthetics; however, they are mostly marked with nitrous oxide because the gas is administered over a wide range of concentrations [13]. This phenomenon usually, does not play out very significantly in dentistry because the concentration of gas used is lower when compared to general anesthesia [11] (Fig. 2.20).

2.3.3 Potency of Nitrous Oxide (MAC)

MAC or minimum alveolar concentration is analogous to ED_{50} and signifies "the concentration of the gas in alveolus at 1 atmospheric pressure that will render 50% of patients unresponsive to a surgical stimulus". It is also a measure of the potency of anesthetic gases. Nitrous oxide with a MAC of 104 is least potent of all the anesthetic gases. A MAC of 104 is not possible to achieve unless hyperbaric conditions are used. Clinically, this means that nitrous oxide cannot be used to produce adequate surgical anesthesia unless an adjunctive agent is used. This may be an

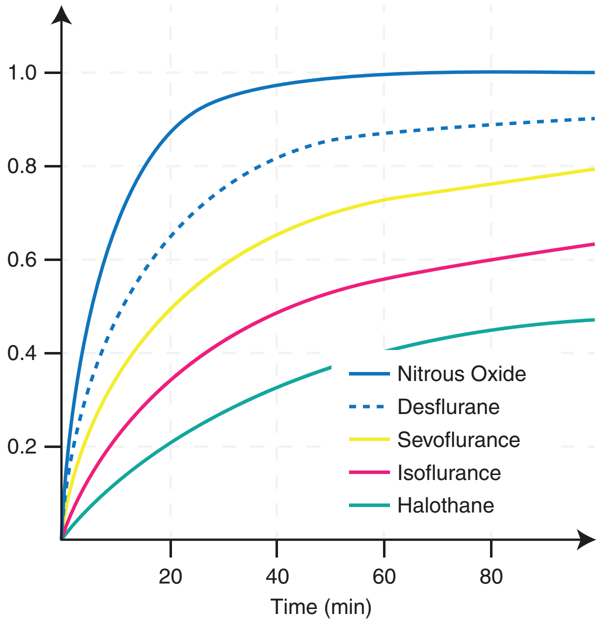


Fig. 2.20 Graph showing that nitrous oxide reaches near equilibrium of inspired air and alveolar air in the shortest duration of time. (Source: Butterworth JF, Mackey DC, Wasnick JD. Morgan and Michail's Clinical Anesthesiology. 5th ed. www.accessmedicine.com)

intravenous (propofol) or inhalation (sevoflurane) agent [11, 17]. However, when combining with other agents caution is advised as these may not only lower the MAC for nitrous oxide but work synergistically in depressing respiratory and cardiovascular function.

> Higher MAC value of 104 signifies lower anesthetic potential of nitrous oxide, thereby enhancing its safety margin for use in dentistry.

It is also important to realize that the low potency of nitrous oxide has proved to be extremely useful in situations where we do not desire anesthesia but require anxiolysis and some analgesia. Dental outpatient procedures provide ample opportunity for us to exploit these properties of nitrous oxide, yet stay safe.

Variables Affecting MAC

MAC decreases with increasing age. For nitrous oxide, MAC is 133 during infancy, 104 at 40 years, and 81 at 80 years (Table 2.3). MAC is increased in fever and during use of CNS stimulants. Hypothermia, CNS depressants, and severe hypercapnia ($PaCO_2 > 90$) cause a decrease in MAC.

Effects of Below MAC Concentrations

Subanesthetic concentrations of nitrous oxide cause analgesia and amnesia. They may also cause decrease in judgment and motor performance. Impairment in learning is observed at 30% nitrous oxide, and amnesia appears at 20% and increases at

Table 2.3 Table showing changes in MAC (minimum alveolar concentration) values at different ages for various inhalational anesthetic agents

Inhalation agent	1 year	40 years	80 years
Halothane	0.95	0.75	0.58
Isoflurane	1.49	1.17	0.91
Enflurane	2.08	1.63	1.27
Sevoflurane	2.29	1.80	1.40
Desflurane	8.3	6.6	5.1
Nitrous oxide	133	104	81

40%. These are of interest to us since these concentrations are mostly used during sedation in dentistry.

2.3.4 Second Gas Effect

Though this effect is more significant when nitrous oxide is used in combination with another anesthetic agent, for example, sevoflurane, it is discussed here for academic interest.

If nitrous oxide is used as the first gas, then it has a unique ability to increase the uptake of the second inhalation agent [13]. This is used by anesthetists to their advantage by using higher concentrations of nitrous oxide at induction which leads to an increase in the alveolar concentration of the second inhalation agent and oxygen [18]. Including nitrous oxide in gas mixtures decreases the amount of volatile anesthetics needed. This effect which has also been termed as “MAC sparing effect” [18] is attributed to the fact that nitrous oxide gets taken up in such large volumes by the alveoli that the second gas is able to get concentrated in a smaller volume [13].

> Second gas effect is of significance in anesthesia when another inhalational agent is administered along with nitrous oxide gas, making use of the property of rapid uptake of nitrous oxide.

Exact reversal of this effect is seen during recovery from anesthesia mixture. The elimination of nitrous oxide at the end of the procedure causes a rapid outward diffusion of the accompanying inhalation agent. This is attributed to the fact that nitrous oxide dilutes the alveolar concentration of the other agent which in turn gets exhaled faster. This effect has been termed as “reverse second gas effect” [19].

Significance of low solubility and concentration effect of nitrous oxide on onset and maintenance of sedation in dentistry:

1. Nitrous oxide achieves its maximum effect in the brain in a much shorter time when compared to other anesthetic agents. Hence, it has the advantage of quick onset and quick recovery.

2. The similarities in the concentration of the inspired gas and alveolar concentration mean that the "precision with which the anesthetic effect of nitrous oxide can be controlled is greater than any other inhaled anesthetic." [13]This also makes it safe for use in dentistry.
3. When we want to "reverse the sedation" or stop sedation, then the reverse is true as well. When the flow of the gas is stopped, the concentration in alveoli will approach zero sooner than later. Hence, recovery from sedation is much quicker, and child patient can resume normal activities soon after.

2.3.5 Transfer of Nitrous Oxide to Closed Gas Spaces

There is a marked distinction between the way nitrous oxide and nitrogen move into and out of the tissues. The reason for this distinction is the difference between the solubility of two gases. The blood gas partition coefficient for nitrous oxide is 0.46 whereas that of nitrogen is 0.015. In simple terms, this means that at a particular partial pressure, compared to nitrogen gas "far more nitrous oxide can be carried to or removed from a closed gas space" [15] (Fig. 2.21).

A closed gas space contains air (nitrogen) and when such space is exposed to nitrous oxide by means of sedation/anesthesia, the rate at which nitrous oxide enters the space is much faster than the rate at which nitrogen can exit. This results in an increase in the pressure and volume of such spaces, resulting in some of the side effects we see with nitrous oxide.

Nitrous oxide causes an increase in pressure of air-filled closed cavities in the body due to its rapid uptake in these spaces.

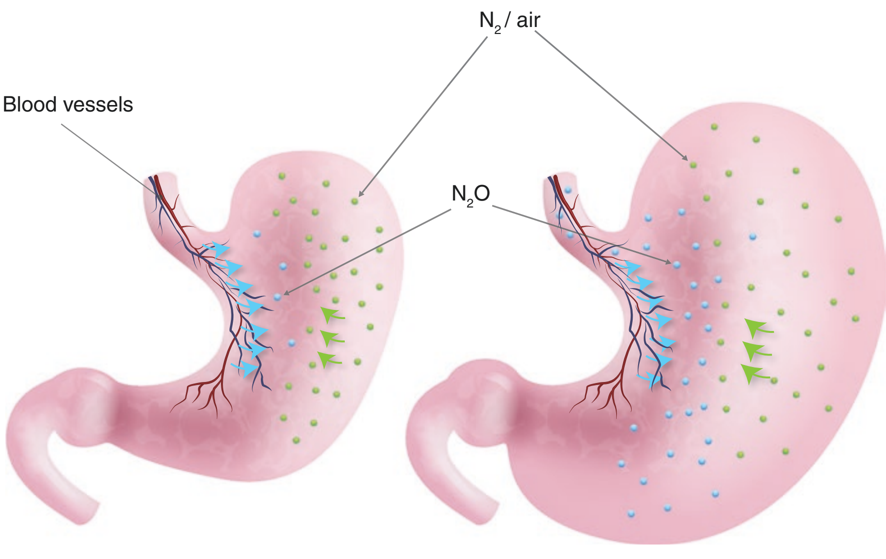


Fig. 2.21 Figure showing rate of nitrous oxide uptake being higher than the rate at which air (N_2) is removed causing pressure build up inside closed air-filled cavities like stomach

Such effects on volume change are most marked in cases where patients have an existing pneumothorax. Sadman and Eger in their study in 1965 showed that inhaling 75% nitrous oxide increased the size of pneumothorax two times in 10 min and up to three times in 30 min [20]. These effects of nitrous oxide are the reason behind contraindication for its use in patients with pneumothorax.

The rapid diffusion of nitrous oxide may also be a problem in patients who have undergone vitreoretinal surgery. In such patients, a gas bubble (filtered room air, sulfur hexafluoride (SF6), and perfluoropropane) is deliberately left within the eye for about 70 days in order to keep the retina attached while natural adhesions develop. If nitrous oxide is administered during this time, the bubble will rapidly expand, thus increasing risk for retinal and optic nerve ischemia, which could lead to loss of vision [21]. Nitrous oxide is absolutely contraindicated for up to 3 months in such patients. Similar problems may be encountered in patients who have existing sinusitis (increased pain), have had middle ear surgery or tympanoplasty graft placed, and those who have increased intestinal distention in the presence of bowel obstruction [11].

2.3.6 Systemic Effects of Nitrous Oxide

Central Nervous System

Nitrous oxide depresses all forms of sensation including sight, hearing, smell, and touch. As long as administered with more than 20% oxygen, the effects on central nervous system are limited to a mild depression of cerebral cortex [11]. Vomiting center in medulla is not affected by nitrous oxide as long as physiological concentrations of oxygen are maintained.

Respiratory System

As long as it is used alone, nitrous oxide does not affect respiration adversely (Table 2.4). However, when combined with oral or intravenous sedative agents, respiratory depression may be seen. The use of nitrous oxide with any other mode of sedation qualifies as “moderate sedation” and requires much more rigorous monitoring of the patient. Nitrous oxide is similar to other inhalation agents when it comes to producing a dose-dependent depression of ventilatory drive, and it has a greater influence on the ventilatory response to decreased levels of oxygen rather than to increased levels of carbon dioxide. This becomes significant in patients

Table 2.4 Effects of nitrous oxide on physiological parameters

Inhalation agent	Nitrous oxide
Blood pressure	No change
Heart rate	No change
Tidal volume	Decrease
Respiratory rate	Increase
Net ventilation	Increase/no change

Source: Becker ED, Rosenberg M. Nitrous Oxide and the inhalation anesthetics. Anesth Prog 2008;55:124–131 suffering from COPD since they depend entirely on decreased blood oxygen levels (hypoxemia) to drive their respiration. This coupled with the fact that nitrous oxide is often administered with high levels of oxygen may further decrease the respiratory drive. The above factors have led some authors to recommend that nitrous oxide should be avoided in patients suffering from COPD [22].

> Nitrous oxide gas has no significant effects on cardiovascular and skeletal systems and has minimal effect on respiratory system by decreasing the respiratory drive.

Cardiovascular System

Unlike most inhalation anesthetics which produce a dose-dependent decrease in mean arterial pressure, nitrous oxide is not known to produce any changes in heart rate or blood pressure (Table 2.4) [11, 22]. Nitrous oxide may, however, cause cutaneous vasodilation, and this can be used to "help finding veins in patients who are anxious or in whom superficial veins are hard to find" [11].

Skeletal System

Isoflurane, desflurane, and sevoflurane are known to cause skeletal muscle relaxation, and this is desirable for most surgeries. Nitrous oxide, however, has no such effect on skeletal muscles [22].

2.3.7 Recovery from Nitrous Oxide Anesthesia

Unlike induction, where all patients start at the same baseline in terms of anesthetic gases administered (zero to start with), the recovery may be lengthened in some patients due to the "duration of anesthesia" they receive. A greater duration of anesthesia will mean a longer recovery period due to increased amounts of anesthesia stored in various body compartments and tissues. However, the low solubility of nitrous oxide means that the tissues have a "lesser ability" to hold it when compared to more soluble agents. Once nitrous oxide is switched off, the venous blood returning to lungs is rich in nitrous oxide whereas alveoli have almost none of it. Thus nitrous oxide diffuses out of blood into the alveoli and is eliminated through the lungs [11]. The recovery from nitrous oxide is usually rapid and complete, and the patient may be permitted to leave the office unaccompanied [11]. There are no residual effects seen after nitrous oxide anesthesia, and this is one of the main reasons for its widespread popularity.

> Recovery from nitrous oxide is as rapid as its uptake and allows the child patient to resume normal activities soon after the procedure.

However, escape of large volume of nitrous oxide may cause another interesting phenomenon which is called "diffusion hypoxia" or "diffusion anoxia."

2.3.8 Diffusion Hypoxia

As large volumes of nitrous oxide diffuse out of the alveoli, increased nitrous oxide is taken up by the alveoli at an even faster rate. This results in "reverse concentration effect" which simply means that the rapid escape of nitrous oxide from the blood and alveoli causes other gases to escape as well, including carbon dioxide. The escape of carbon dioxide from blood lowers the CO_2 tension of blood which in turn decreases the stimulus for breathing and lowers the respiratory drive [11]. Another phenomenon which occurs is the dilution of oxygen in alveoli (Fig. 2.22). Both these phenomena may cause a transient hypoxia, and this has been found to be responsible for most cases of "headache, nausea, and lethargy" seen after nitrous oxide administration [11].

This unwanted side effect can be avoided by administering 100% oxygen for 3–5 min at the termination of the procedure.

This diffusion hypoxia is of higher significance when nitrous oxide is used as an anesthetic using a full coverage mask or an endotracheal tube and not when it is used in dentistry using a nasal mask.

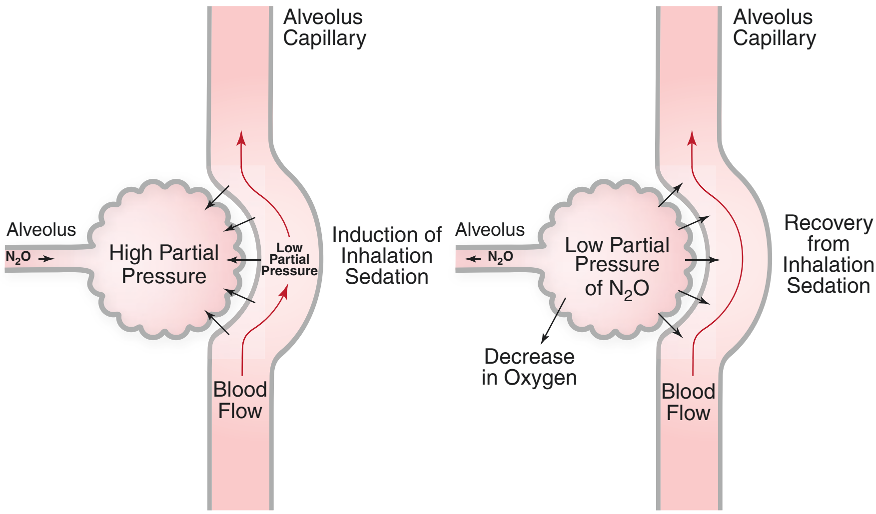


Fig. 2.22 Figure showing depletion of oxygen tension in alveolus during recovery from nitrous oxide sedation

2.3.9 Metabolism of Nitrous Oxide

Most nitrous oxide is eliminated by lungs within 3–5 min after stopping its delivery. Close to 1% of inhaled nitrous oxide will be eliminated through the skin over the next 24 h [11]. About 0.004% of nitrous oxide taken up during anesthesia will be metabolized by anaerobic bacteria in the human intestine through a reductive pathway. This pathway can lead to the formation of free radicals and per oxidized lipids. These free radicals have not been associated with any harmful side effects [23].

2.4 Conclusion

At the end of this chapter, readers will appreciate that with the advancements in manufacturing process, impurities in nitrous oxide gas have been reduced. Following manufacturing, they should be properly handled and stored in color-coded cylinders. Lower solubility of nitrous oxide gas in blood and high MAC values are two important properties which make use of this gas as a safe anxiolytic or sedative agent in pediatric dentistry.

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Mechanism of Action of Nitrous Oxide

3

Dimitrios Emmanouil

Contents

Learning Objectives

1. Recapitulating pain pathway
2. Gaining in-depth knowledge on neurophysiology of nitrous oxide's analgesic action
3. Understanding anxiolytic and analgesic properties of nitrous oxide
4. Ability to distinguish between various levels of sedation
5. Recognizing various clinical effects of nitrous oxide in children

The discussion for the mechanisms of action for N_2O has a long and fascinating history making it a "laughing gas" not only for patients but also for the researchers trying to decipher its multitude of actions. Adding to this, N_2O is a simple inert compound of only three molecules, a fact that makes it even more intriguing.

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Despite it being known and used for two centuries, only recently valuable information about the gas is beginning to emerge as researchers learn about its wide ranging influence on the complex operations of the central nervous system. For nearly 150 years since its discovery, N_2O has been used by clinicians without a clear knowledge of its mechanisms of action. Only over the last 30 years has there been any significant research elucidating the mechanisms of the analgesic, antianxiety, and anesthetic effects of N_2O.

The use of nitrous oxide sedation can reduce the anxiety associated with the treatment of children in the dental office. The emotions of the dentist, staff, and the child's parents are influenced by the child's response to the dental experience. Nitrous oxide helps produce a relaxed atmosphere in the dental office, and it can benefit everyone involved. This is the reason that N_2O is actually considered a behavior modification technique rather than a pure sedation technique [1].

Pain, with physiological and psychological components, can be somewhat difficult to define in the clinical setting. In modern dentistry, children should not experience real physical pain. Many procedures, however, are less than pleasurable, and children may perceive minor discomforts as painful. Some children also may become tired when asked to sit for an extended time period. Analgesia/anxiolysis is defined as the diminution or elimination of pain and anxiety in a conscious patient [2].

3.1 Mechanism of Action

The first person to recognize N_2O analgesic properties was Humphry Davy as early as 1800. He wrote "As nitrous oxide in its extensive operation appears capable of destroying physical pain, it may probably be used with advantage during surgical operations in which no great effusions of blood have taken place."

In 1985, Eger published the first comprehensive book on N_2O, gathering all available information up to that time and providing an excellent summary of clinical and research issues. In 2012, Mark Gillman published an equally interesting book "Nitrous oxide and Neurotransmission" where he made some interesting hypotheses on its function, gathering all available research up to date.

3.1.1 Neural Pathway of Pain

Pain sensations travel from the site of injury to the sensory cortex of brain via the ascending tracts. Brain continues into brain stem which consists of mid brain, pons, and medulla through which the nerve filers carrying pain sensations pass. Brain stem continues into spinal cord which has nerve fibers entering it through posterior root (dorsal horn) and exiting from anterior root.

Prostaglandins and cytokines produced as a result of inflammation activate sensory nerve fibers (first order neuron) to carry pain signals to the dorsal horn of spinal cord where it synapses with second-order neuron. This area of spinal cord is referred to as the substantia gelatinosa where the synapse takes place between the first-order and second-order neuron. First-order neuron passes pain impulses to second-order neuron through substance P in the synaptic area. Second-order neuron, as a part of spinothalamic tract, passes through brain stem and reaches the sensory cortex (Fig. 3.1).

> Inhibition of pain transmission takes place by release of various neurotransmitters in substantia gelatinosa located in the dorsal horn of spinal cord.

Descending pathway has a role in controlling or inhibiting the ascending pathway to prevent perception of pain by the brain. The descending pathway arises from

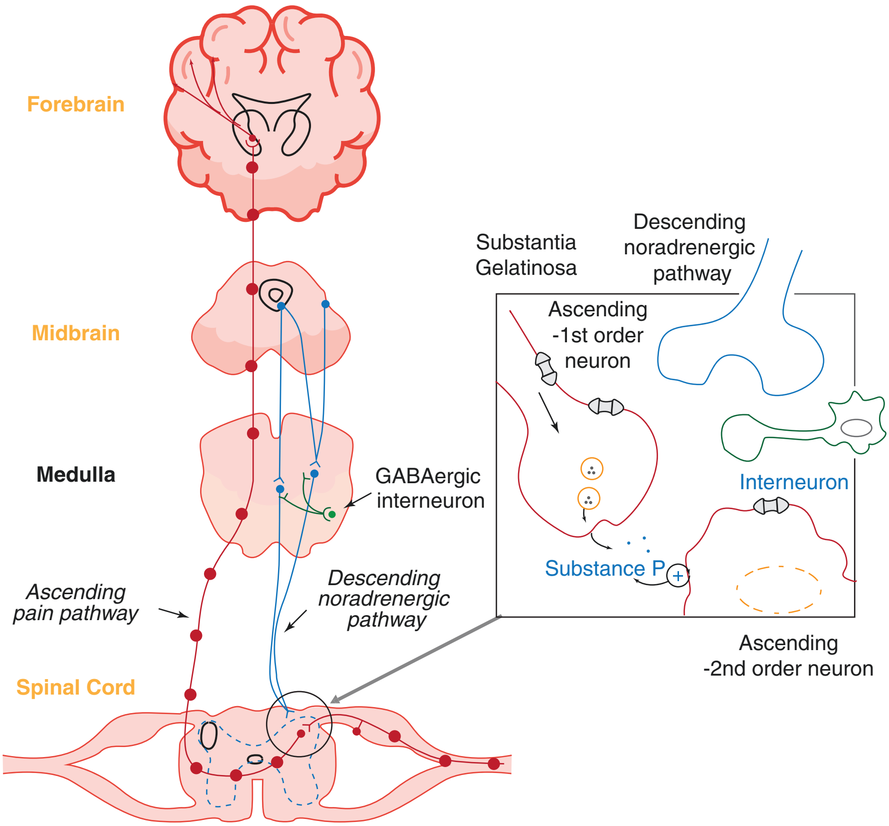

Fig. 3.1 Ascending pain pathway activated following nociceptive stimuli. First-order neuron synapses with second-order neuron. First-order neuron releases substance P activating the second-order neuron

Table 3.1 Table showing various neurotransmitters and their role in pain pathway

Neurotransmitter	Role
Glutamate/aspartate	Excitatory
Serotonin 5-Hydroxytryptamine (5-HT)	Excitatory
Dopamine	Inhibitory
Norepinephrine	Excitatory a1 and B Inhibitory a2
Endorphins	Inhibitory
Enkephalins	Inhibitory
Dynorphins	Inhibitory
Substance P	Excitatory
Nitric oxide	Excitatory/inhibitory

periaqueductal gray matter of pons and synapses with second-order descending neuron in nucleus raphe magnus of medulla. Second-order neuron of descending pathway is serotonergic or noradrenergic neuron which plays a role in inhibiting the ascending pain pathway in the dorsal horn of spinal cord (Table 3.1).

> Descending pain pathway is mainly responsible for inhibiting transmission of pain impulses to the brain.

Serotonin or noradrenaline being released by second-order neurons of descending pain pathway **inhibits** release of substance P from first-order neuron of ascending pain pathway and stimulates the interneuron to release endogenous opioids or enkephalins (Table 3.1). Enkephalins will have two roles, that is, to inhibit release of substance P from presynaptic neuron of ascending pain pathway and prevent depolarization of second-order neuron of ascending pain pathway, thereby preventing the pain impulses from being carried to the brain.

3.1.2 Nitrous Oxide: The Nearly "Ideal" Clinical Sedative

Nitrous oxide is a non-irritating, colorless gas with a faint sweet taste and odor. It is an effective analgesic/anxiolytic agent causing central nervous system (CNS) depression and euphoria with little effect on the respiratory system. It has rapid uptake, being absorbed quickly from the alveoli and held in a simple solution in the serum; dissolved and transported in blood; does not combine with hemoglobin, and it does not undergo biotransformation.

It is relatively insoluble, producing a rapid equilibration between inspired and expired concentrations. Elimination of nitrous oxide occurs by means of expiration in a manner that is precisely the reverse of uptake and distribution, and its low solubility allows it to be removed rapidly having very little effect on kidney and liver function [3].

Today we know that N_2O has strong analgesic properties along with its anesthetic ones. N_2O analgesia has a long history of use in obstetrics for relief of labor pain [4]. It is also being used for self-administered analgesia in cancer patients [5] to alleviate pain and discomfort associated with a number of medical procedures and emergency dept. lacerations and orthopedic procedures [6].

CNS Effects
Nitrous oxide has multiple mechanisms of action that underlie its varied pharmacological properties. Subanesthetic concentrations of N_2O produce only analgesic and anxiolytic effects without unconsciousness [7]. The anesthetic effect of N_2O appears to be caused by inhibition of NMDA glutamate receptors, removing its excitatory influence on the nervous system.

> Although nitrous oxide is an inhalational anesthetic agent, in dentistry it is being used in subanesthetic concentrations to achieve analgesia and anxiolysis.

3.1.3 Mechanism of Analgesia Produced by Nitrous Oxide

Although its analgesic properties have been known since the eighteenth century, it is only relatively recently that we have begun to understand the underlying mechanism of its analgesic actions. Our better understanding of these mechanisms began after the discovery of the endogenous opioid system in the 1970 [8]. It is important here to make a distinction between the high anesthetic concentrations of nitrous oxide producing unconsciousness and the much lower doses that are associated with consciousness, analgesia, anxiolysis, and euphoria, a term that is described as PAN (psychotropic actions) [8].

The Opioid Hypothesis of N_2O Antinociceptive Action (Fig. 3.2)
Chapman et al. [9] were the first to report that the analgesic effect of N_2O was comparable to that of opioid analgesic drugs—30% of N_2O was deemed to be equieffective as 10–15 mg of morphine. Thirty years later, Berkowitz et al. in mice and rats [10, 11] and others in human subjects reported that N_2O-induced analgesia was sensitive to blockade by the narcotic antagonist naloxone [12–14] (Fig. 3.2). Quock et al. [15] provided the first chemical evidence that N_2O releases opioid peptides.

Apart from the opioid system, other receptor systems have also been implicated in the analgesic action of nitrous oxide, including the GABAergic, adrenergic, and even possibly the glutaminergic systems [3, 16]. Nonetheless, the opioid system was the first neurotransmitter system to be identified as being involved in the analgesic actions of nitrous oxide [10]. One of the first important differences between the analgesic and anesthetic actions of nitrous oxide as far as the mechanisms of action was the lack of opioid system involvement in the anesthetic actions, whereas opioid mediation was required for the analgesic properties of nitrous oxide [8].

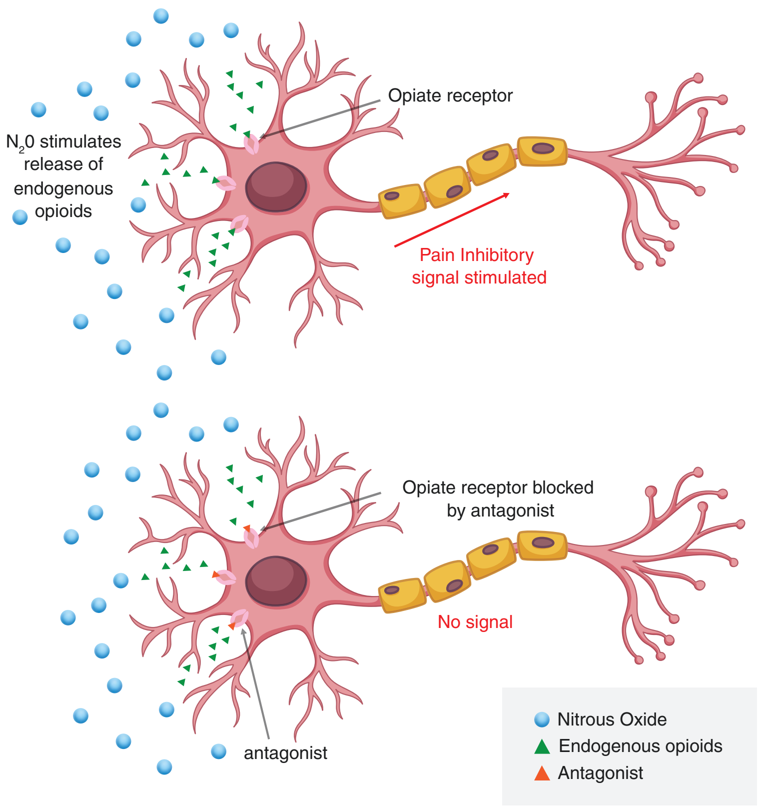

Fig. 3.2 N_2O stimulates release of endogenous opioids blocking pain signal to be transmitted. When using opioid receptor antagonists, pain inhibiting signal gets blocked evidence that nitrous oxide analgesic action is mediated by opioid receptors

> Analgesic action of nitrous oxide lies in its ability to stimulate release of endogenous opioids.

The Neural Pathways Mediating the N_2O Analgesia (Table 3.2)
Emmanouil and Quock [17] were the first to link GABA receptors to the antinociceptive action of nitrous oxide by showing that the inverse agonist noreleagnine reduced the analgesic actions of nitrous oxide. This was also confirmed by Okuda et al. [18] who showed that flumazenil, the benzodiazepine antagonist, attenuated nitrous oxide antinociceptive responses in feline spinal cord. More evidence for the involvement of GABA receptors in the analgesic actions of nitrous was shown at the selective activity towards Fisher strain rats, known to be sensitive to nitrous oxide antinociception, in comparison to Lewis strain rats (non-sensitive). It was demonstrated that nitrous oxide exposure increased synaptic activity in spinal GABAergic neurons, identified by c-Fos used as a marker of synaptic activity [19].

Table 3.2 Summary of various hypotheses suggesting role of nitrous oxide in analgesia

Hypothesis	Evidence
Nitrous oxide-induced analgesia is related to opioid receptor	Nitrous oxide analgesia sensitive to blockade by narcotic antagonist
GABA receptors involved in nitrous oxide analgesia	– Nitrous oxide analgesia sensitive to blockade by GABA antagonist, noreleagnine – Antinociceptive response of nitrous oxide is attenuated by benzodiazepine antagonist, flumazenil
Nitrous oxide stimulates release of noradrenaline at dorsal horn of spinal cord	– Depletion of noradrenaline causes reduction of nitrous oxide analgesia – Nitrous oxide analgesia reduces after systemic administration of α2 adrenal receptor antagonist – Spinal transection eliminated nitrous oxide analgesia
Spinal α2b receptor involved in nitrous oxide analgesia	Dexmedetomidine, which is α2b agonist synergizes with nitrous oxide
Nitrous oxide stimulates α1 adrenoceptors	Nonspecific α1 blocker prazosin antagonizes nitrous oxide analgesia
Nitric oxide has a role in analgesic action of nitrous oxide	– Analogues of L-arginine which inhibit nitric oxide synthase, antagonized nitrous oxide analgesia – Nitrous oxide stimulated nitric oxide synthase more in mice sensitive to nitrous oxide analgesia – Injection of nitric oxide synthase inhibitor antagonized nitrous oxide analgesia

Stimulation of opioid receptors by nitrous oxide released opioid peptides inhibits the inhibitory GABAergic pathway.

Fujinaga and Maze [20] showed that the extrinsic action could occur by the stimulatory action of nitrous oxide on non-opioid neurons outside the PAG like substance P and neurotensin. They then hypothesized that the release of endogenous opioid peptides and the subsequent stimulation of opioid receptors activate descending pathways that modulate nociceptive processing in the spinal cord (Fig. 3.3).

Activation of descending pain pathways leads to inhibition of release of substance P from first-order neuron of ascending pathway, thereby preventing activation of second-order neuron transmitting pain impulses to higher centers. This results in analgesia.

Sawamura et al. [21] have shown that a corticotrophin-releasing factor antagonist, given by intracerebroventricular injection, almost completely abolishes nitrous oxide analgesia but not the analgesic action of dexmedetomidine. N_2O also produces a dose-dependent increase in c-Fos expression in corticotropin-releasing factor containing cells in the paraventricular nucleus of the hypothalamus, indicating a specific role for corticotropin-releasing factor in nitrous oxide analgesia.

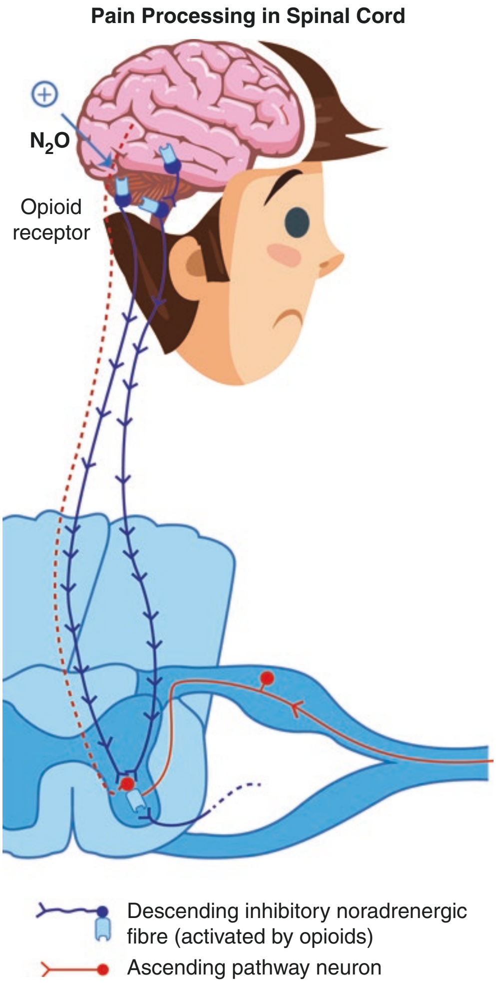

Fig. 3.3 Stimulation of opioid receptors activates the descending pathway causing analgesia

Whatever the actual mechanism, stimulating opioid receptors in the PAG, Sanders et al. [16] have suggested that the following pathways are involved in the analgesic actions of nitrous oxide (Fig. 3.4).

All these studies indicate that the GABA receptor, most probably the $GABA_A$ receptor, is involved in the analgesic actions of nitrous oxide. Orii et al. [22] also found that **spinal** GABAergic neurons in the spinal cord act in the opposite direction to those at the **supraspinal** level in mediating nitrous oxide analgesia. The same neurotransmitter may have diametrically opposite actions depending on its site of action. So nitrous oxide analgesia depends on inhibition of supraspinal and activation of spinal GABAergic receptors [16].

Role of Adrenergic Pathway (Table 3.2)

There is additional indirect evidence, although controversial, of the involvement of adrenergic pathways in the analgesic actions of nitrous oxide. Nitrous oxide

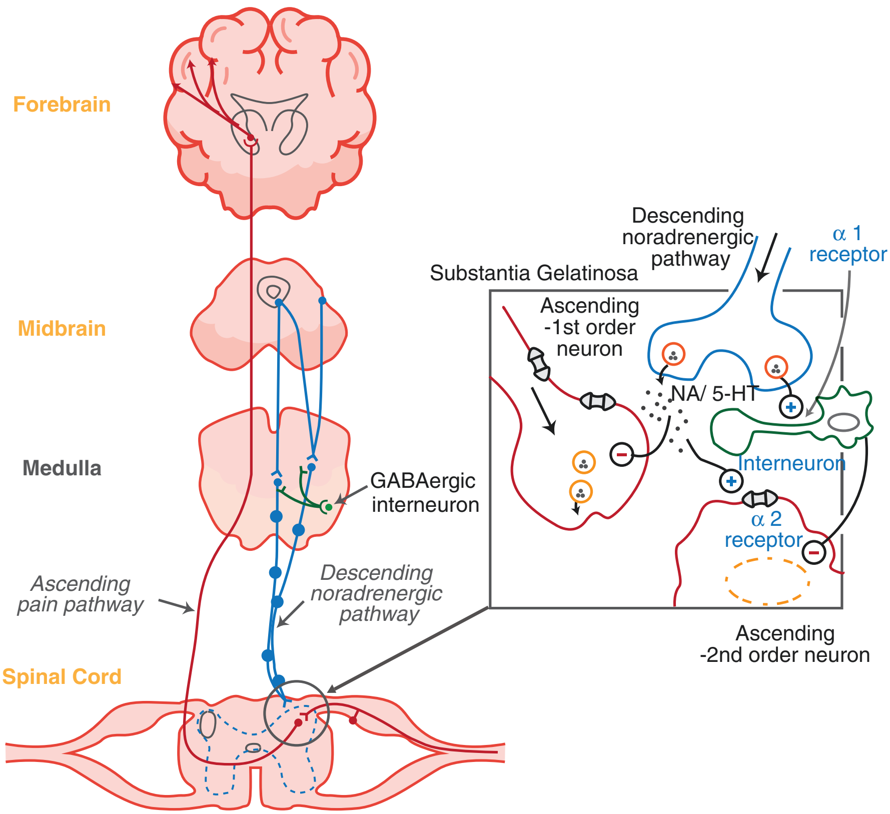

Fig. 3.4 Nitrous oxide activates GABAergic interneuron which activates (disinhibits) descending adrenergic pathway, releasing noradrenaline in substantia gelatinosa which in turn inhibits activation of second-order neuron of ascending pathway, thereby blocking pain. It appears that once the opioid receptors on GABAergic interneuron have been activated, these GABA interneurons are inhibited, thus disinhibiting descending adrenergic neurons arising in the pons and medulla. These descending noradrenergic neurons have an inhibitory effect by releasing noradrenalin in the spinal cord onto at least two types of adrenergic receptors: α_{2B}-adrenergic receptors found postsynaptically on second-order neurons and α_1-adrenergic receptors on GABAergic interneurons. Stimulation of these adrenergic receptors results in reduced firing of second-order afferent neurons. The net effect is a reduction of pain impulses reaching supraspinal regions mediating pain. Adapted from Sanders et al. [16]

stimulates the release of noradrenalin at the dorsal horn of the cord, and its depletion interferes with nitrous oxide analgesia [23]. Systemic administration of the α_2-adrenal receptor antagonists attenuates nitrous oxide analgesia. Similarly, intrathecal atipamezole blocks nitrous oxide analgesia. On the other hand, intracerebroventricular atipamezole fails to do so [24]. Other investigators have also shown that systemic yohimbine can antagonize nitrous oxide analgesia [25]. Furthermore, spinal transection also eliminated nitrous oxide analgesia [23]. Work on transgenic mice further indicates that spinal α_{2B}-adrenoreceptors are the most likely receptor involved in nitrous oxide analgesia [21]. Further collaborating evidence, a combination of intrathecal dexmedetomidine, an α_2-adrenoreceptor agonist [26], synergizes with nitrous oxide, indicating the role of spinal α_2-adrenoreceptors in the synergism [27]. On the other hand, dexmedetomidine does not produce analgesia at a supraspinal level since it actually antagonizes the action of nitrous oxide by blocking its action in the locus coeruleus [27]. All these factors seem to imply that the synergism between nitrous oxide and dexmedetomidine occurs at spinal level.

It has been also shown that nitrous oxide stimulates c-Fos expression in the spinal cord via activation of α_1-adrenoreceptors [22] and the nonspecific α_1-blocker prazosin antagonizes nitrous oxide analgesia implicating these receptors as well [28].

The role of serotonin in nitrous oxide analgesia is still unclear [22, 29].

> In early childhood, neurons of descending pain pathway are immature and hence may have reduced sensitivity to antinociceptive effects of N_2O.

The most important finding though in these experiments is that descending noradrenergic inhibitory neurons are immature and not functional at birth and take at least 3 weeks to fully develop in rats [30]. It has been suggested that the central nervous system of a 3-week-old rat is equivalent to that of a human at the toddler stage [31]. This may explain experimental observations that rats do not exhibit sensitivity to the antinociceptive effects of N_2O before 4 weeks of age [20, 32]. Although we cannot take these findings literally (species differences confound comparisons of the development of the human and rat nervous systems), these results suggest that N_2O may not be efficacious as an analgesic agent in early childhood.

Role of Glutamate (Table 3.2)

Fifty percent of nitrous oxide blocks both NMDA and AMPA glutaminergic receptors in the substantia gelatinosa of the dorsal horn of the spinal cord, an area of the cord that is known to be intimately involved in pain processing (Fig. 3.5). It is possible that glutaminergic neurons are also involved in nitrous oxide analgesia [33].

Involvement of Nitric Oxide in N_2O Antinociception (Table 3.2)

Nitric oxide (NO) is a naturally occurring gas that only recently has been recognized as an endogenous biological regulator of great significance. Science magazine declared NO as “The Molecule of the Year” for 1992. There is evidence that NO released from nitrergic neurons seems to regulate the release of a variety of transmitters (acetylcholine, catecholamines, excitatory and inhibitory amino acids, serotonin, histamine, and adenosine) in the brain [34].

> Nitrous oxide stimulates nitric oxide synthase, thereby producing nitric oxide which provokes release of endogenous opioids, which in turn activates descending pain pathway.

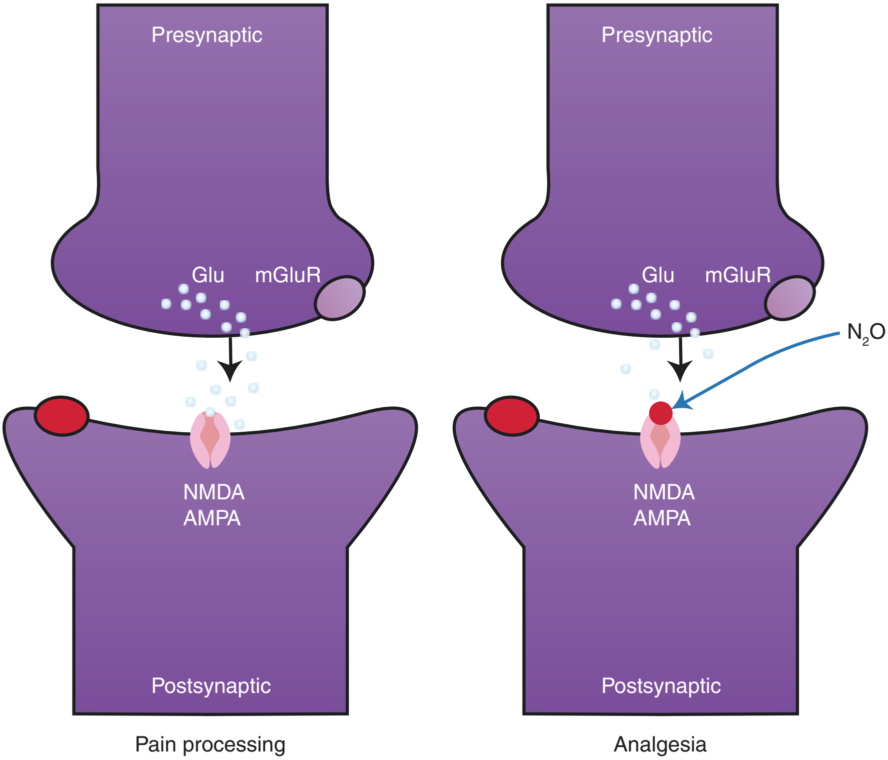

Fig. 3.5 Nitrous oxide is responsible for blocking glutaminergic (pain stimulatory) receptors in substantia gelatinosa, thereby causing analgesia

Quock's group was again the first to implicate nitric oxide in the analgesic actions of nitrous oxide. They showed that various analogues of L-arginine, which inhibit nitric oxide synthase, antagonized nitrous oxide analgesia. They demonstrated that antagonism of analgesia was stereospecifically reversed by L-arginine but not by its inactive stereoisomer D-arginine. It was also shown that L-arginine in mice, but not in rats, potentiated nitrous oxide analgesia [35]. NO also provokes the release of endogenous opiates (DYN peptides) in the region of the PAG playing a mediatory role in the antinociceptive effect of N_2O [36]. In another study, they found that nitrous oxide stimulated nitric oxide synthase more in mice sensitive to nitrous oxide analgesia (C57BL/6 mice) than those insensitive to the gas (DBA/2 mice) [36]. This correlation between sensitivity to nitrous oxide analgesia and increase in nitric oxide synthase activity has been also shown by Henry et al. [37]. Evidence has been provided indicating that the neuronal rather than the endothelial or inducible forms of nitric oxide synthase is involved in nitrous oxide antinociception [38, 39].

Genetic analysis identified two markers on mice chromosome 2 and 5, highly correlated to nitrous oxide analgesia and another possible marker on chromosome 18 [40, 41]. It is also interesting that the neuronal form of nitric oxide synthase has been localized to mice chromosome 5 [42].

Intracerebroventricular β-endorphin stimulates the spinal release of met-enkephalin [43, 44]. Met-enkephalin release is potentially mediated by nitric oxide [45]. Confirming this hypothesis, nitrous oxide inhalation stimulates an increase in both β-endorphin and nitric oxide metabolites antagonized by nitric oxide synthase blockade [46, 47]. Cope et al. [48] extended these findings by showing that both supraspinal and spinal nitric oxide are required for nitrous oxide analgesia.

There is substantial evidence that both nitric oxide and opioid receptors localized in the periaqueductal gray (PAG) are involved in nitrous oxide analgesia.

The mechanism of activation of opioid receptor in periaqueductal gray matter could be intrinsic (direct occupation of the receptor), extrinsic, or both. Emmanouil et al. [49] have found that that injection of a nonspecific opioid antagonist or an inhibitor of nitric oxide synthesis into the PAG antagonizes nitrous oxide analgesia. Nitrous oxide exposure also increased both β-endorphin and nitric oxide oxidation products in dialysates recovered from the arcuate nucleus and periaqueductal gray [46]. Pre-treatments that increased brain levels of L-arginine or NO restored sensitivity of N_2O-insensitive D2 mice to N_2O-induced antinociception. This also indicates that the NOS enzyme in D2 mice is functional and that the insensitivity of D2 mice to N_2O may lie in some other component or function related to NO, possibly the availability or utilization of L-arginine [50]. All the above work suggests that nitric oxide plays a crucial intermediate role in the release of analgesic endogenous opioids following exposure to nitrous oxide but also other possible mechanisms, that is, nitric oxide might increase the sensitivity of opioid receptors [49].

Tolerance to N_2O Antinociception

As with many centrally mediated drug effects, continuous administration of N_2O results in the development of tolerance to the antinociceptive effect of N_2O in experimental animals [50] and to the analgesic effect of N_2O in human subjects [51]. The opioid mechanism has been confirmed from reports of morphine-tolerant animals being cross-tolerant to N_2O [11, 52]. Interestingly, N_2O-tolerant animals were not cross-tolerant to morphine, and this led Berkowitz et al. [52] to hypothesize that N_2O might work through stimulating the neuronal release of endogenous opioid peptides. Chronic treatment with morphine results in desensitization of opioid receptors and/or signal transduction mechanisms, hence resulting in cross-tolerance to N_2O, which relies on the same opioid receptors. Chronic treatment with N_2O results in a tolerance due to excessive depletion of endogenous opioid peptide stores that a subsequent exposure to N_2O is unable to release enough opioid peptides to cause antinociception.

Tolerance to nitrous oxide is related to its role in release of endogenous peptides.

Table 3.3 Summary of hypothesis suggesting role of nitrous oxide in anxiolysis

Hypothesis	Evidence
Anxiolytic effect of nitrous oxide involves activation of GABA receptor through benzodiazepine binding site	Benzodiazepine binding site blocker, flumazenil, antagonizes nitrous oxide anxiolytic behavior Tolerance due to daily treatment with escalating dose of chlordiazepoxide causes cross-tolerance to nitrous oxide

3.1.4 Mechanism of Anxiolysis Produced by Nitrous Oxide

There is evidence that the anxiolytic effect of N_2O is independent of its analgesic action. The mechanisms involved though are not yet completely understood.

The Benzodiazepine/GABA Receptor Hypothesis of N_2O Anxiolysis

The anxiolytic effect of N_2O involves activation of the $GABA_A$ receptor through the benzodiazepine binding site. It is not clear whether N_2O acts directly or indirectly on it. The anxiolytic pathway stimulated involves a sequence of three enzymes, NOS, soluble guanylyl cyclase, and PKG. N_2O in its behavioral response mimics the effects of benzodiazepines in different animal models of experimental anxiety [53–57]. N_2O- and benzodiazepine-induced anxiolytic-like behaviors were sensitive to antagonism by the benzodiazepine binding site blocker flumazenil [54]. Mice rendered tolerant to benzodiazepines by daily treatment with escalating doses of chlordiazepoxide are cross-tolerant to the anxiolytic-like behavioral response to N_2O [54, 55]. All these findings strongly suggest that the anxiolytic effect of N_2O is associated with brain benzodiazepine mechanisms (Table 3.3).

> $GABA_A$ receptor is involved in anxiolytic action of nitrous oxide.

Signaling Pathway That Mediates Anxiolytic-Like Activity

Since benzodiazepines act through facilitation of GABA-ergic inhibitory neurotransmission, research was conducted to determine the involvement of $GABA_A$ receptors in N_2O anxiolysis [56]. Consistent with the known interaction between benzodiazepine and $GABA_A$ receptors, these findings indicate that $GABA_A$ receptors mediate the anxiolytic-like effects caused by chlordiazepoxide and N_2O activation of benzodiazepine receptors. N_2O- and benzodiazepine-induced anxiolytic-like effects in animal models of anxiety are also sensitive to antagonism by inhibition of nitric oxide synthase (NOS), a family of enzymes responsible for the synthesis of nitric oxide (NO). These findings suggest that NO plays a key role in the anxiolytic signaling mechanism downstream from the benzodiazepine/$GABA_A$ receptor complex [56, 58, 59]. In a manner similar to how N_2O activates opioid receptors, it is plausible that N_2O may induce neuronal release of endogenous benzodiazepine factors that then stimulate the $GABA_A$ receptor.

Nitric oxide also has a role in anxiolytic mechanism of nitrous oxide besides having a role in its analgesic property.

Based on the above studies, Emmanouil and Quock [3] proposed a possible mechanism for nitrous oxide anxiolytic actions at a cellular level with the following steps;

> *N_2O activates the benzodiazepine binding site of the $GABA_A$ receptor, since flumazenil blocks nitrous oxide anxiolysis. This facilitates the binding of g-aminobutyric acid resulting in an influx of Cl-, which causes activation of calmodulin. Calmodulin in turn activates nitric oxide synthase, which catalyzes the conversion of L-arginine to L-citrulline with the liberation of nitric oxide. Nitric oxide then stimulates enzyme soluble guanylyl cyclase, resulting in the production of the second messenger cyclic guanosine monophosphate[cGMP]. cGMP then stimulates a cyclic GMP-dependent protein kinase [PKG] resulting in anxiolysis* (Fig. 3.6).

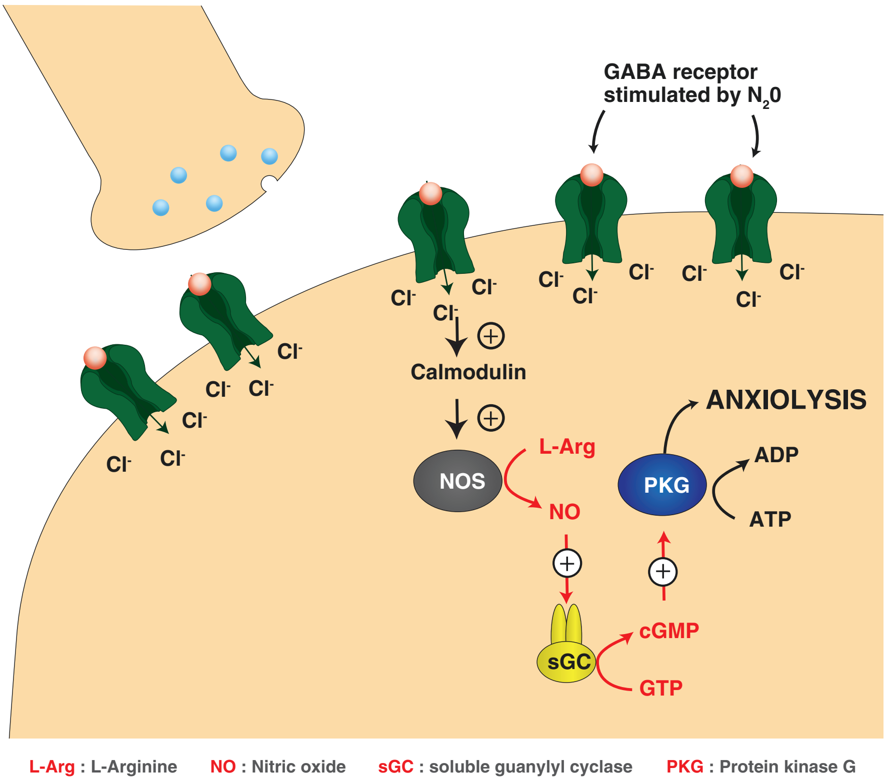

Fig. 3.6 Stimulation of GABA receptors by nitrous oxide which in turn activates a cascading reaction causing anxiolysis

3.1.5 Mechanism of Anesthesia Produced by Nitrous Oxide

N_2O has a well-known role in medical history because it was the first drug used for surgical anesthesia. It is a true general anesthetic but the least potent of all anesthetic gases in use today. The minimum alveolar concentration, if it was to be used as a sole agent, is >100% but varies from species to species (104% MAC at 1 atm in humans, unknown for children) (MAC = minimum alveolar concentration of anesthetic required to prevent movement in 50% of patients subjected to a noxious stimulus), and then it would require high volume percentage and hyperbaric conditions to achieve anesthesia [60]. As a result, N_2O cannot be administered alone to produce anesthesia and is used along with other volatile anesthetics and a sufficient concentration of oxygen (33% is advised) to prevent hypoxia. Despite its limited anesthetic potency, N_2O is the most widely used general anesthetic agent because in clinical practice, N_2O is generally used to reduce the minimum alveolar concentration of a second inhalation agent for anesthesia and increase the rate of induction (i.e., the second gas effect) [61] and to provide or augment the analgesic component of general anesthesia.

> N_2O is weak anesthetic agent due to its high MAC value. In anesthesia, its use is to potentiate induction of other inhalational agents.

General anesthetics like N_2O have long been hypothesized to act in a nonspecific manner on neuronal membranes, alter membrane fluidity, and/or influence ion channels. In contrast to most other anesthetic agents, which exert their actions as gamma-aminobutyric acid agonists, there is now enough evidence supporting the fact that N_2O is predominantly an *N*-methyl-D-aspartate receptor antagonist [62]. However, a great deal of work is required before the molecular and neural pathways involved in mediating nitrous oxide anesthesia are fully determined [16, 63]. It is suggested that a common property of NMDA receptor antagonism may underlie the similar pharmacological profiles of N_2O and ketamine, an intravenous dissociative anesthetic. The two drugs, in fact, produce synergistic neurotoxicity when used together [64].

> Anesthetic mechanism of action of nitrous oxide is related to its antagonism of NMDA receptor.

3.1.6 Stress and Nitrous Oxide

There is little doubt that nitrous oxide has antistress actions. A typical stress response results in the release of various hormones like corticotropin-releasing factor, β-endorphin, and ACTH [65]. At the same time, the sympathetic nervous system is activated releasing adrenalin, noradrenalin, and dopamine [66]. There is some

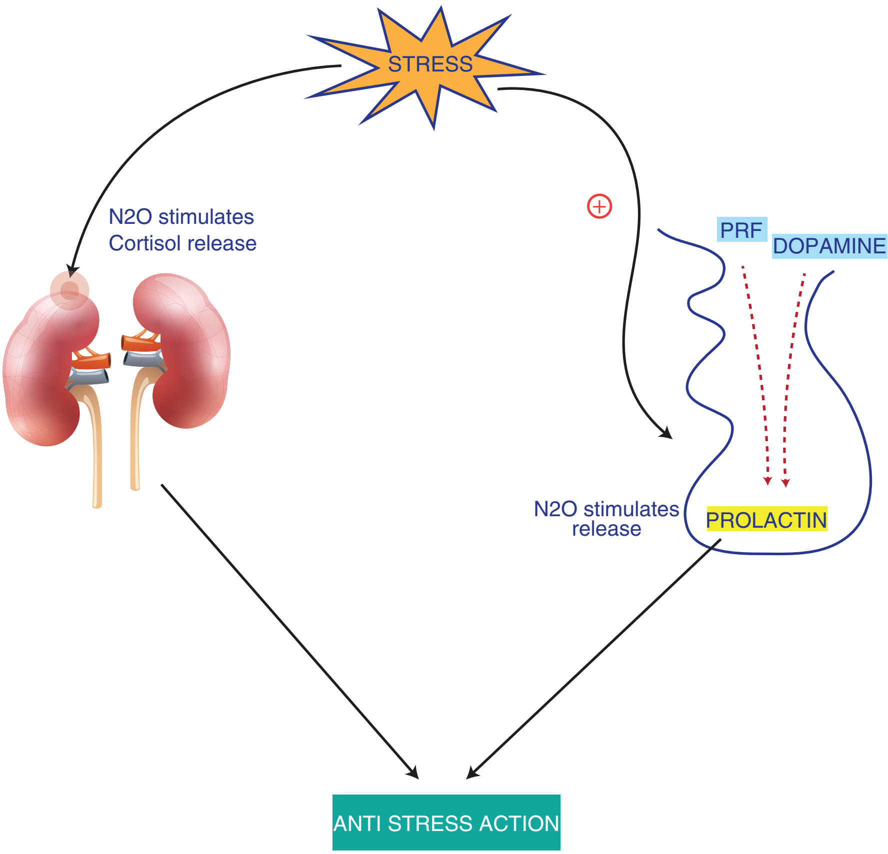

Fig. 3.7 Nitrous oxide stimulating cortisol and prolactin release in conditions of stress

evidence that nitrous oxide exerts its antistress actions via the release of cortisol and of prolactin [67] shown to have an antistress action [68] (Fig. 3.7).

Acute stress appears to induce an anxiogenic-like behavioral profile in the mouse light/dark exploration test. Exposure to N_2O normalizes this behavior to the non-stressed status but does not produce anxiolytic-like effects as it does in non-stressed animals. Chronic stress appears to have no effect on anxiety, but exposure to N_2O of chronically stressed animals does not produce the anxiolysis expected. While exposure of non-stressed mice to N_2O produces a marked analgesia as expected, chronically stressed mice exposed to N_2O show a marked hyperalgesia [69]. This may be of clinical significance in the use of N_2O in patients with acute or chronic stress. Further investigation in the influence of stress on N_2O function needs to be carried out.

Although nitrous oxide causes analgesia and anxiolysis, in already stressed children, it may not produce the desired result.

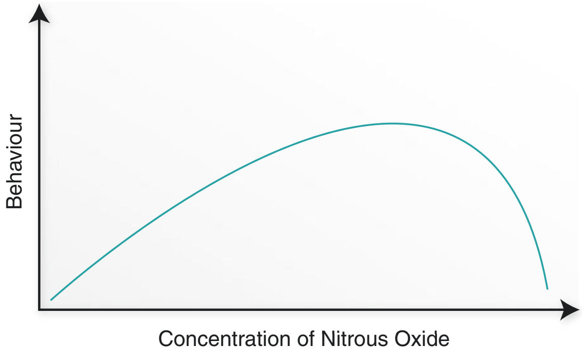

Fig. 3.8 A schematic representation of bitonic behavioral effects of nitrous oxide

Frequently, behavioral effects of drugs, including reinforcing effects, are bitonic; that is, low to moderate doses increase behavioral effects, and higher doses decrease effects, resulting in an inverted U-shaped dose–response function [70, 71] (Fig. 3.8). N_2O shows also bitonicity of effects in humans [72].

3.1.7 Nitrous Oxide and Amnesia

In addition to analgesia, anxiolysis, and anesthesia, N_2O can also cause amnesia or memory loss. Few studies have investigated the clinical amnesic effects of N_2O, but they do support that inhalation of N_2O affects learning [73, 74]. In humans, it has been discovered that almost twice as many acquisition trials were required to reach the criterion of learning when participants received 30% N_2O rather than a placebo gas [75]. Aged rats exposed to 70% N_2O [76] as well as the common clinical combination of isoflurane and N_2O [76] leads to lasting impairment in spatial working memory. A possible mechanism of N_2O and impaired memory was explored in a study analyzing the cyclic AMP (cAMP) response element–binding protein (CREB), which has been extensively implicated in learning and memory [77]. The T-Maze Spontaneous Alternation Task (T-SAT) testing spontaneous alternation behavior (SAB) and, therefore, spatial working memory has been used, confirming that 70% N_2O reduced spatial working memory in mice, which could be improved independently by flumazenil and HBO_2. This study implied that N_2O possibly affect the $GABA_A$ receptor complex in inhibiting spatial working memory [78].

> Nitrous oxide is believed to have amnesic property as well besides analgesic, anxiolytic, and anesthetic properties.

The research presented here has several limitations when trying to project animal research to the clinical actions of nitrous oxide. The mechanism of the analgesic effect of N_2O is gradually being clarified through elucidation of its antinociceptive effect in animals. Ideally, the term analgesia should be used only for humans that have the capacity to communicate the entire experience of pain including the emotional component. On the other hand, animals cannot report a reduction in the sensation of pain so analgesia is determined in animals as antinociception or a diminished responsiveness to a noxious stimulus [79]. It is also important to point out here that since most of the pioneering work at Quock's laboratory was conducted on mice, findings from one species cannot necessarily be extrapolated to other species, and thus their findings may only apply to mice [63].Genetic differences between strains or species may also be responsible for conflicting research results [16, 63].

3.2 Levels of Sedation and Clinical Effects

The use of nitrous oxide can help many children learn to cope with the stressful environment by bringing about sedation.

Emotions and the threshold for pain are interwoven. There is a positive association between anticipatory anxiety and procedural pain. Task-specific anxiety is an important predictor of pain report and, in certain cases, pain tolerance. Interventions designed to reduce task-specific anticipatory anxiety may help reduce pain responses in children and adolescents [80].

When a child is fearful, anxious, or apprehensive, has a lower pain threshold. Nitrous oxide sedation eliminates or reduces fear and anxiety raising the pain reaction threshold and reducing fatigue [81]. Both pain sensitivity and pain reaction are altered. In addition, the pain threshold can be raised with attention and distraction tasks. By involving the child in the equipment for inhalation sedation, some distraction is provided. When this placebo effect of distraction is combined with the sedative properties of nitrous oxide, the injection experience, which often is a major psychological hurdle for children, is reasonably pleasant. Most of the children report dreaming or being on a "space-ride" [82].

Langa (1968) [83] describes the child under nitrous oxide sedation as being in "suspended animation." The child's body does not move. His head and extremities remain relaxed. There is an elimination of sudden movements commonly associated with children. The child is in a relaxed state.

> A dentist using nitrous oxide sedation can provide optimum treatment for a child with a minimum of trauma to both himself and his patient.

3.2.1 Levels of Sedation

Sedation means "use of a drug or other means to make someone calm or make them go to sleep."

Sedation is a continuum, meaning that there are no fixed boundaries demarcating different levels of sedation. Various levels of sedation as per American Dental Association and American Academy of Pediatric Dentistry are as follows:

Table 3.4 Table showing responsiveness, airway, ventilation, and cardiovascular system at various levels of sedation

	Minimal sedation	Moderate sedation	Deep sedation	General anesthesia
	Drug-induced state	Drug-induced depression of consciousness	Drug-induced depression of consciousness	Drug-induced loss of consciousness
Responsiveness	Normal to verbal stimulus, coordination may be impaired	Purposeful response to verbal alone or accompanied by tactile stimulation	Purposeful to repeated verbal or painful stimulus	Unarousable, even to painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be required

Source: American society of Anesthesiologists

- **Minimal sedation** (old terminology "anxiolysis"): It can be defined as a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected (Table 3.4). Nitrous oxide is used to bring about minimal sedation.
- **Moderate sedation** (old terminology "conscious sedation" or "sedation/analgesia"): It is a drug-induced depression of consciousness during which patients respond purposefully to verbal commands (e.g., "open your eyes" either alone or accompanied by light tactile stimulation such as a light tap on face, forehead, or shoulder) (Table 3.4).

  For older child patients, this level of sedation implies an interactive state, whereas for much younger child patients, age-appropriate behavior like crying can be expected.

  Further, patients whose only response is reflex withdrawal from repeated painful stimuli would not be considered to be in a state of moderate sedation (Malamed 2010) [84].
- **Deep sedation** (deep sedation/analgesia): It is a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully after repeated verbal or painful stimulation like tapping hard on shoulder, shaking the child, or tapping on the chest. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained. A state of deep sedation may be accompanied by partial or complete loss of protective reflexes (Table 3.4).
- **General anesthesia**: It can be defined as a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired (Table 3.4).

A clinician should be well aware about the various stages of sedation and should be able to recognize and rescue a child from a deeper level of sedation than intended. Using nitrous oxide, a child patient should be maintained in minimal sedation.

3.2.2 Stages of Anesthesia

Four stages of general anesthesia were recognized in Guedel's classification (Fig. 3.9).

1. Induction (also referred to as analgesia)
2. Excitement stage
3. Surgical anesthesia
4. Overdose (Guedel 1937) [85]

Stage I of anesthesia begins with the induction of anesthesia and ends with a patient's loss of consciousness. Patients still feel pain in this stage. During N_2O inhalation sedation, the patient always remains at the first stage of anesthesia.

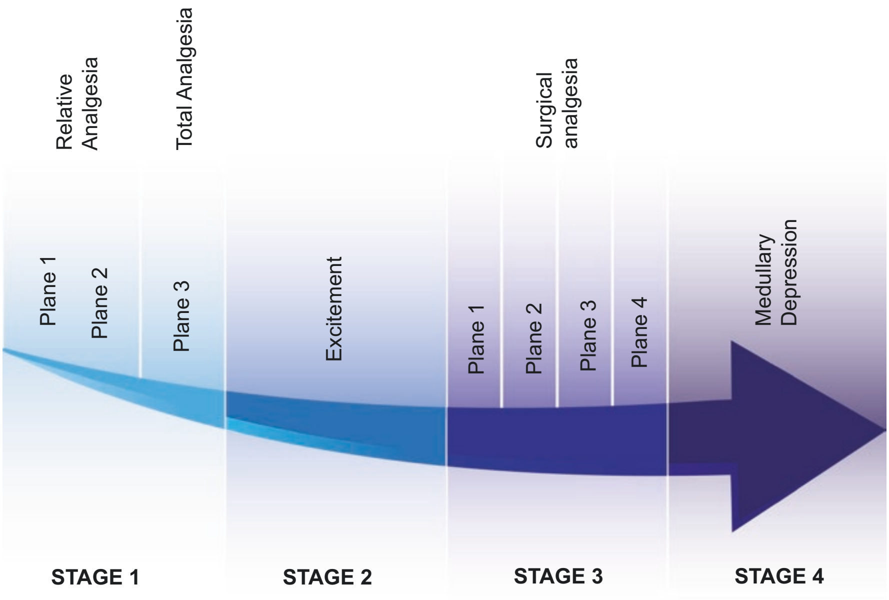

Fig. 3.9 Figure showing stages of anesthesia and planes of nitrous oxide sedation in stage 1

In the first stage of anesthesia with N_2O, Carnow (1969) [86] described four plateaus.

These are the paresthesia, vasomotor, drift, and dream plateaus. Characteristic patient responses in each of these plateaus are as follows:

- **Paresthesia Plateau**: Tingling sensation in the fingers and toes. Sometimes sensations extend through whole body.
- **Vasomotor Plateau**: Warm or flushed sensations over whole body.
- **Drift Plateau**: A generalized feeling of euphoria and sensations of drifting or floating. Patients' pupils are centrally fixed and face is void of expression. (Staring ahead with a "far away" look.)
- **Dream Plateau**: Patients' eyes are generally closed, and there is difficulty in speaking.

The paresthesia and vasomotor plateaus are of short duration, whereas the drift and dream plateaus can be maintained for several hours until nitrous oxide inhalation is terminated. Children in the drift or dream plateau usually respond to questions by moving their head rather than talking. Their facial features as well as arms and legs are noticeably relaxed.

The drift and dream plateaus are the desired level of N_2O/O_2 sedation. These plateaus are usually in the 30–40% range.

3.2.3 Relative Analgesia

In 1968, Langa [83] introduced a term to represent N_2O inhalation sedation, relative analgesia (RA). Langa proposed that there were three planes of analgesia in the first stage (Fig. 3.9). The planes vary from moderate to total analgesia and are dependent on the concentration of nitrous oxide in the mixture and the signs and symptoms shown by patients.

- **In Plane 1 (5–25% N_2O)**: The patient appears normal, relaxed, and awake; may feel slight tingling in toes, fingers, tongue, or lips; and may giggle. Vital signs remain normal. There are no definite clinical manifestations.
- **In Plane 2 or relative analgesia (26–55% N_2O)**: The patient may have a dreamy look, eyes appear "glassy" occasionally with tears, reactions are slowed, and voice may sound "throaty." Patient will feel warm and drowsy, may drift in and out of environment, and hear pleasant ringing in ears. Partial amnesia may occur. Vital signs remain normal. Pain is reduced or eliminated, but touch and pressure are still perceived. Patient is less aware of surroundings; sounds and smells are dulled. The term psychotropic analgesic nitrous oxide (PAN) was introduced by Gillman and Lichtigfeld (1994) [87] to describe plane 2 of analgesia. This term clearly distinguishes the concentrations of nitrous oxide used for anxiolysis/analgesia from the much higher doses used for anesthesia wherein the patient is totally unconscious.

Table 3.5 Average effects of nitrous oxide/oxygen with various concentrations of nitrous oxide

Concentration of nitrous oxide (%)	Effect
100	Will produce anoxia
80	Will produce hypoxia with hallucinations and bizarre dreams
65	Can cause patients to enter the excitement stage
35	Usually provides maximum analgesia and anxiolysis with maintenance and cooperation of the patient
25	Its analgesic is equal to 10 mg morphine sulphate

- **In Plane 3 (55–70% N_2O)**: Patients become angry with hard stare, pupils usually are centrally fixed and dilated, mouths tend to close frequently, unaware of surroundings, patients may hallucinate. When patients are in plane 3, Roberts (1990) [88] reported that they may experience sensation of flying or falling, uncontrolled spinning, or the chest may feel heavy, and the patient no longer cooperates.

Effects produced at various concentrations of nitrous oxide are outlined in Table 3.5.

Plane 2 provides adequate N_2O sedation and allows dentist–child communication, although some clinicians prefer the dream period, usually characterized by closed eyes and difficulty with speech.

Plane 1 usually is of short duration. Plane 2 can be maintained for several hours. Children in plane 2 usually respond to questions by moving the head rather than speaking. Facial features are relaxed and the jaw usually sags open and remains open without mouth props. The eyes are usually closed but will open in response to questions. The arms are heavy and will stay where placed, and the hands are open. The legs often slide off the side of the chair. All vital signs are stable. The objective of the sedation should be to reach, but not pass, this plane. This is the desirable sedation plane when performing N_2O sedation.

There is no significant risk of losing protective reflexes, and the child is able to return to pre-procedure mobility.

3.2.4 Levels of Nitrous Oxide Analgesia

The degree of analgesia is directly proportional to the concentration of nitrous oxide being inhaled [89]. Therapeutic range of nitrous oxide can be broadly divided into two planes of analgesia and amnalgesia (amnesia along with analgesia) [89] (Fig. 3.10). These planes can be further subdivided into two zones each.

1. Analgesia
   (a) Moderate analgesia
   (b) Dissociative analgesia
2. Amnalgesia
   (a) Analgesic anesthesia
   (b) Light anesthesia

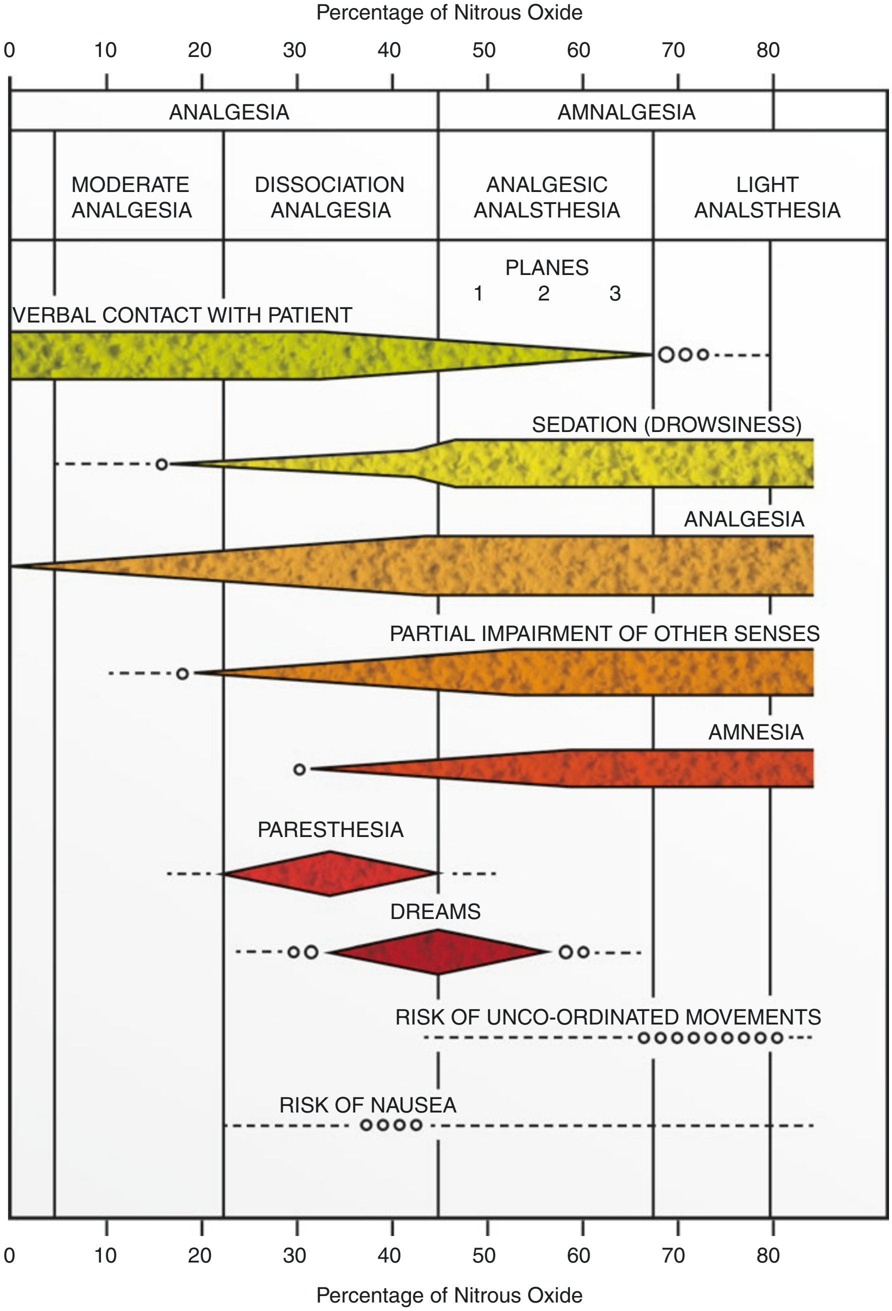

Fig. 3.10 Figure showing various effects produced at varying concentrations of nitrous oxide. (**Source**: Parbrook GD. Therapeutic uses of nitrous oxide. Brit J Anaesth. 1968;40:365–372)

Zone 1: Moderate Analgesia (6–25% Nitrous Oxide)
Clinician is able to maintain full contact with the patient with patient experiencing a feeling of relaxation. This zone may also cause euphoria. However, nausea does not occur in this zone. Psychomotor activity may be slightly affected with impairment of other sensations such as touch, hearing, vision, and proprioception.

Zone 2: Dissociative Analgesia (26–45% Nitrous Oxide)
Pleasant effects of nitrous oxide are experienced in this zone with a sense of dreaminess, detachment, and lack of ability concentrate. Marked analgesia is experienced in this zone along with slight sedative effect. An altered time sense is present at these concentrations of nitrous oxide. Marked sedation or drowsiness is experienced towards the higher end of this zone. Slight amnesia, paresthesia, is present in this zone with dizziness and auditory effects being side effects. One to two minutes after commencing of inhalation, these effects are more prominent. Nausea is not so frequent in this zone, but repeated "see sawing" between high and low concentrations could precipitate nausea.

Zone 3: Analgesic Anesthesia (46–65% Nitrous Oxide)
Amnesia is more marked in this zone which lies between analgesia and anesthesia. Loss of consciousness may occur towards the upper end of this zone. Nausea is more common in this zone.

Zone 4: Light Anesthesia (>66% Nitrous Oxide)
Amnesia is complete and contact with the patient may be lost in this zone.

> These zones can be identified by the clinical signs rather than the fixed concentrations of nitrous oxide.

3.2.5 Clinical Signs and Effects

Clinical signs and symptoms may vary from child to child during nitrous oxide sedation. These can be described as follows:

1. General appearance
   (a) Child may appear to be relaxed.
   (b) Few children may comment that they are feeling less scared.
   (c) Shy children will beg to communicate.
   (d) Children avoiding eye contact will start looking towards dentists during verbal interaction.
2. Body movement and position
   (a) Body movements may reduce.
   (b) Tense and taut appearance of body may reduce.
   (c) Tingling in extremities and warmth in body are experienced by the child.
   (d) A child holding an object in his/her hand may drop the object.
   (e) Hands may fall down from the side of dental chair (Fig. 3.11).
   (f) Shoulders may relax and drop down.

(g) A child may be more comfortable with legs in uncrossed position (Fig. 3.12). However, children in younger age group may cross their legs indicating that they are in relaxed position.

3. Eyes response
   (a) Eye ball movements will reduce.
   (b) Slight drooping of upper eye lid may be evident (Fig. 3.13).
   (c) Blink rate may reduce.
   (d) Few children may have watery eyes due to nitrous oxide as leaking towards the eyes.
   (e) Child may have a dazed or staring look when oversedated.

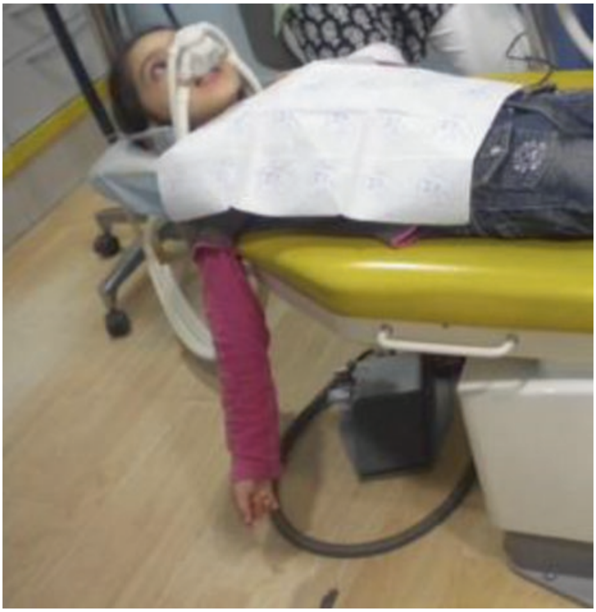

Fig. 3.11 Hands drop down on side on dental chair

Fig. 3.12 Children place their legs in uncrossed position with feet in abduction

Fig. 3.13 Pictures show eye response during nitrous oxide sedation and after sedation is over

Fig. 3.14 Tense appearance of face before starting the sedation and relaxed appearance of face during sedation

4. Expressions on face
   (a) Face appears less tense and relaxed (Fig. 3.14).
   (b) Tonicity of facial muscles reduces.
   (c) Frowning may reduce.
   (d) Forehead creases during stress may appear to be reduced.
   (e) Child may begin to giggle or may have a smile on face.
   (f) Voice changes can also be appreciated.
5. Knowledge about surroundings
   (a) Child will be fully aware about surroundings.
   (b) Few children may begin to cry and look for their parents.

Table 3.6 Clinical tips to evaluate level of N_2O inhalation sedation

Clinical sign	Inference
Reduced activity of the eyes	Desirable level of sedation
Increased activity of the eyes	Sedation is too light
Fixed, hard stare of the eyes	Sedation is too deep, N_2O% needs to be decreased
Arms and legs crossed	The patient is not relaxed yet, increase N_2O%
Patient talks too much	Sedation is too light due to mouth breathing. (Do not increase; try to get patient to stop talking, use of a rubber dam.)
Patient answers rapidly	Sedation is too light
Patient answers slowly and deliberately	Good sedation
Patient does not answer	May be tired and asleep. (If used in combination with another sedative agent, stimulate patient and check verbally.)
Paraesthesia of extremities	Reassure patient that this is normal and will disappear after treatment
Paraesthesia of lips, tongue, or oral tissues	Profound depth; time for injection of local anesthetic

6. Cognitive ability [90]
   (a) Nitrous oxide can lead to slowing of response in children though not clinically significant.
   (b) It also causes increase in reaction time.
   (c) It may even have characteristics of CNS stimulant.

A guide which helps in determining the correct level of sedation desired using nitrous oxide is described in Table 3.6.

For some patients, the feeling of “losing control” may be troubling. Others may be claustrophobic and unable to tolerate the nasal hood, finding it confining and unpleasant [91]. A patient’s experience after nitrous oxide is believed to be similar to a post-hypnotic state. During N_2O, there is an enhancement of suggestibility and imaginative ability that may be utilized while managing the child’s behavior and dental experience. This can be advantageous.

Individual biovariability accounts for different reactions to various concentrations of N_2O. Some individuals experience several symptoms; others only a few. Symptoms are intense for some and insignificant for others. Sometimes, signs are obvious; at other times, they are subtle. Titration allows for the biovariability of any patient that may be associated with the administration of the substance.

> Titrating nitrous oxide–oxygen and careful observation of child’s responses are keys to successful administration.

Table 3.7 Table showing activities which are stimulated or depressed by nitrous oxide

Right side of brain—stimulated by N_2O Introspective side	Left side of brain—depressed by N_2O Extrospective side
Nonverbal communication	Verbal communication
Logical and analytical thinking	Emotional thinking
Intuitive and holistic	Tends to focus
Simultaneous	Sequential
Fantasy (strong in children)	Objective literal
Factual-holistic dimensional	Linear perceptive

Source: Nitrous Oxide Monitoring Certificate for Dental Hygienists and Dental Assistants. Available from: http://icourses.uthscsa.edu/courses/nitrous2/planes

If patients become irritated or they can no longer cooperate and their mouth tends to close, plane three is being approached. This is an indication that the nitrous oxide level is too high. Also, changes in physical symptoms, such as dilation of pupils or nausea, would be an indication of too much nitrous oxide. At this point, the clinician should reduce the level of nitrous oxide (or turn it off depending upon severity of the side effect or reaction) and increase the level of oxygen.

Nitrous oxide is believed to stimulate the right side of brain and depress the left side of the brain. Left side of the brain is considered to be the extrospective side, and right side is considered as introspective side. The activities stimulated or depressed are described in Table 3.7.

3.3 Conclusion

Nitrous oxide is useful in dentistry because of its three main properties that is analgesia, euphoria, and anxiolysis. There is evidence that the relaxation and relief from anxiety during inhalation of N_2O is a specific anxiolytic effect that is independent of the analgesic action of N_2O. The mechanisms involved are not yet completely understood. However, there is sufficient evidence to suggest that nitrous oxide's analgesic and anxiolytic actions are parallel to those of opioids and benzodiazepines, respectively [2]. Also, it is essential to make a clear distinction between the high anesthetic concentrations of nitrous oxide producing unconsciousness and the much lower doses that are associated with consciousness, analgesia, and anxiolysis.

Clinicians must know what signs and symptoms to look for when administering N_2O and deciphering the level of sedation. Keeping a constant vigil is imperative because pleasant sensations may quickly change and become unpleasant. Knowledge of the appropriate technique and associated physical, physiologic, and psychological changes minimizes negative patient experiences.

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Technical Considerations for the Use of Nitrous Oxide in Pediatric Dentistry

4

Justin Lee and Kunal Gupta

Contents

Learning Objectives

1. To understand in detail about various components of the nitrous oxide delivery system.
2. Know differences between the portable and centralized system of nitrous oxide delivery.
3. Be well versed with the maintenance schedules and checks.
4. Have in-depth knowledge about scavenging and its role in a dental office.

The equipment used to deliver nitrous oxide along with oxygen in pediatric dental offices will vary depending on the setup of dental office. Some offices use portable machines to deliver the gas, whereas offices which use nitrous oxide more frequently, often use a centralized supply of gases. Whichever system is used, it is important for the operator to understand the role of different components and the way they work, in order to ensure a safe and most efficient delivery of gases to the child patient.

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In this chapter, we will look at different types of setups, their components, and most importantly the safety features built into these machines. We will also mention the importance of regular checks and maintenance of the various parts so that we can make delivery and use of nitrous oxide safe not only for patients but also for our team members.

4.1 Equipment

Main components of nitrous oxide delivery system are breathing circuit, flowmeter assembly, regulators, pressure gauges, and cylinders. Broadly it can be of two types—centralized system or a portable system (Table 4.1).

4.1.1 Flowmeter Assembly-Flowmeter, Breathing Circuit, Nasal Hood

Flowmeter assembly comprises of flowmeters tubes, fail safe, emergency air inlet, oxygen flush, on–off switch, reservoir bag, concentration control knob, flow control knob, breathing circuit, and nasal hood.

Flowmeter Assembly

This is the main part of the nitrous oxide delivery system which helps in regulating the flow and concentration of gases being delivered to the child (Fig. 4.1a, b). Various components of this assembly are described below.

1. Flowmeter tubes: It provides visual readings on the flow rate of gases. It consists of color-coded glass tubes for O_2 and N_2O with ball floats for flow rate indication.
2. Fail safe: It prevents delivery of nitrous oxide in the absence of oxygen.
3. Flow adjustment knob: This knob helps in adjusting the flow rate of gases, without altering the N_2O or O_2 concentration.

Table 4.1 Broad categorization of nitrous oxide delivery system

Nitrous oxide delivery system	
Portable	Centralized
• Flowmeter—digital/analog (mounted on trolley) • Cylinders mounted on yoke with pressure gauges and regulators • Breathing circuit • Scavenging pump/passive scavenging	• Cylinders • Manifold with pressure gauges and regulators • Gas outlets • Flowmeter assembly—digital or analog (trolley/cupboard/wall mounted) • Breathing circuit • Scavenging pump/passive scavenging (**A certified Medical Gas Plumber *must* be contracted for installation of a centralized Gas "Copper Piping" system**)

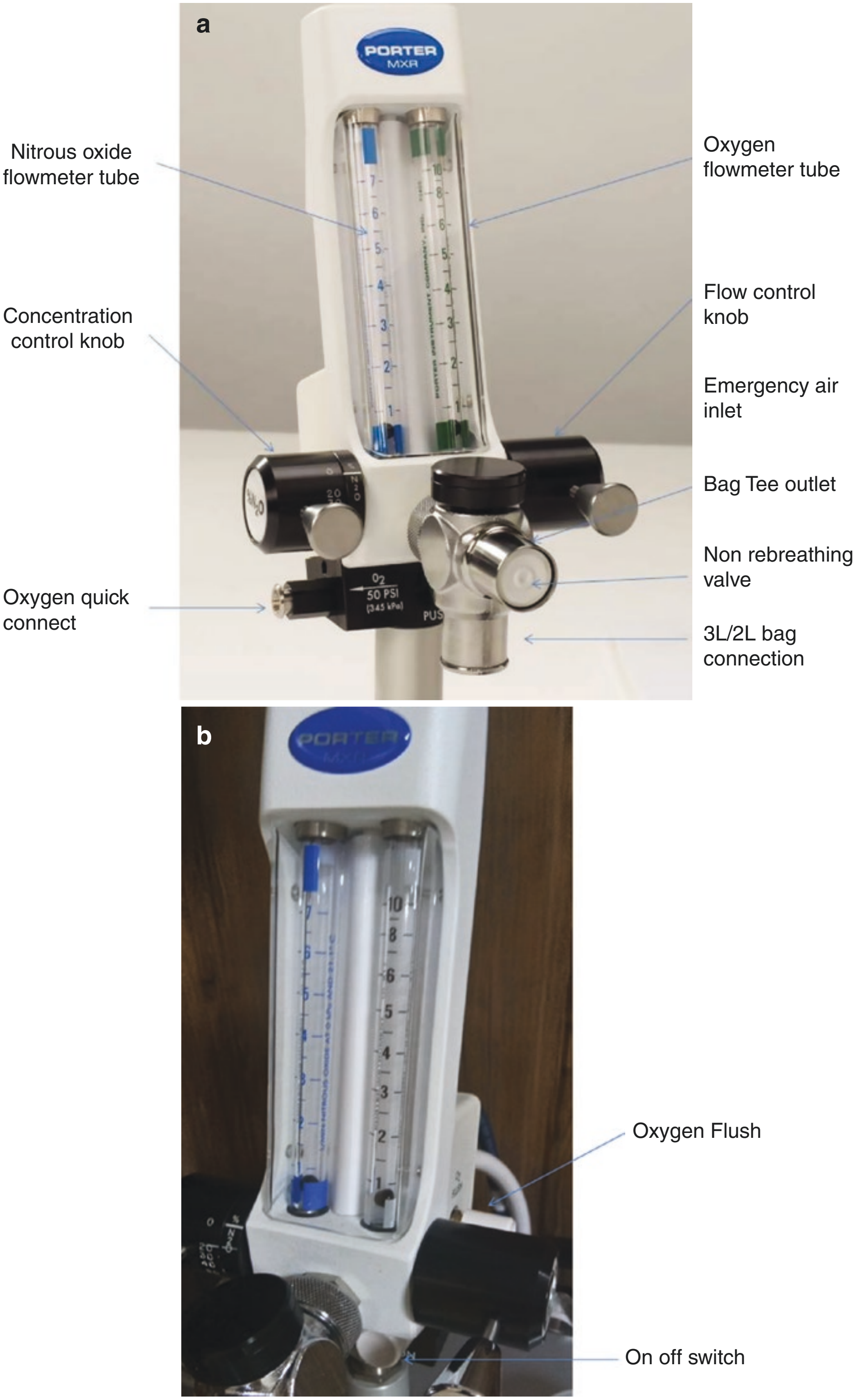

Fig. 4.1 (**a**) Parts of flowmeter assembly. (**b**) Parts of flowmeter assembly

4. Concentration control valve: This knob regulates the desired titration concentration of one of the gases (N_2O for the Porter MXR model as shown in Fig. 4.1a, b).
5. Emergency air valve: Allows patient to inhale ambient air in case the flow of gases is interrupted.
6. Non-rebreathing check valve: It prevents inhaling of used gases.
7. Oxygen flush button: It provides extra delivery of oxygen. It helps to deliver 100% oxygen overriding all other gas flows.
8. On–off switch: It prevents accidental delivery of gases.
9. Bag tee assembly: This part in front of flowmeter helps to connect flowmeter to reservoir bag and the corrugated hose and circuit. Emergency air inlet and non-rebreathing check valve are also a part of the bag tee assembly.
10. Reservoir bag: This helps to maintain a reservoir of gases from which a child patient can inhale. It is however, not required with modern circuits like the Silhouette Mask.
11. Oxygen inlet: It comprises of the male component of DISS system (CGA-1240).
12. Nitrous oxide inlet: It comprises of the male component of DISS system (CGA-1040).

Flowmeter Accessories

1. *Positive pressure resuscitation / oxygen demand valve*

   Porter flowmeter can be equipped with a “Resuscitator Quick Connect” which delivers 100% oxygen with positive pressure on pressing a trigger button with the index finger (Fig. 4.2). It consists of a universal mask which can fit an adult as well a child. It provides 100% oxygen to a non-breathing patient in a fast and effective manner. There is also an alarm which indicates airway blockage and a valve which prevents overinflation [1, 2].

   For a breathing patient (patient with respiratory distress), demand valve function allows to deliver 100% oxygen with minimal respiratory effort [1, 2]. This helps to prevent hypoxia and apnea.

Fig. 4.2 Porter O-Two positive pressure resuscitator. (Source: https://www.porterinstrument.com/product/dental/Porter-O-Two)

Porter O-Two device helps to provide an effective way to manage a situation with respiratory distress [2] (Table 4.2). The practitioner and the staff should be trained in first-aid or resuscitation, and an Ambu-bag should always be kept and used for resuscitation purposes.

2. In-line vacuum control kit
   It helps in removing the exhaled air from scavenging circuit [3]. The vacuum control kit is attached to the vacuum hose. It should be adjusted in such a manner that the ball lies above the green area which indicates that the vacuum rate is 45 L/min. If the vacuum rate is less than this, greater exposure to the dentist and the dental staff can occur. However, if the vacuum pressure is higher, then it implies more gases are removed from the breathing circuit, thereby causing wastage of gases (Fig. 4.3).
3. Automatic vacuum switch
   This device gets activated as soon as the gases begin to flow from the flowmeter [4]. The vacuum for scavenging doesn't have to be turned on separately, thereby making scavenging a part of the nitrous oxide delivery to the patient (Fig. 4.4).
   Two main manufacturers of flowmeters are Parker (Matrx, Porter) and Accutron.

Types of Flowmeters

1. ***Analog***
   Analog type of flowmeters contain two glass tubes with ball floats to indicate the flow rate of nitrous oxide and oxygen gases (Fig. 4.1a). It may either be a trolley mount (Fig. 4.5) or a cabinet mount type (Fig. 4.6). The trolley mount makes the flowmeter portable whereas the cabinet mount offers low profile design which is sleek and occupies less space [5].

   Porter Company has two types of nitrous oxide mixers which have analog flowmeters. First type is the MDM analog mixer (Fig. 4.5), which is the only pneumatic mixer with auto-compensation to maintain the flow rate when gas mixture concentration is changed. It also maintains the concentration when the flow rate is changed. It is available in portable (stand) mount, wall mount, and under-counter mount configurations (*Refer Sect.* 4.1.6).

Table 4.2 Comparison between methods for positive pressure resuscitation

	Porter O-Two	Porter bag valve mask	Flowmeter with reservoir bag
Positive pressure and demand valve functions	✓	✓	×
Delivers 100% O_2 during resuscitation	✓	✓	×
Delivers 100% O_2 on demand	✓	✓	✓
Universal child and adult mask	✓	✓	×
Alarm system for pressure relief	✓	×	×

Source: http://www.porterinstrument.com/dentalcontent/files/datasheets/Porter-Emergency-Oxygen-Brochure-FM-956.pdf

Fig. 4.3 In-line vacuum control kit. (Source: https://www.porterinstrument.com/product/dental/Porter-In-Line-Vacuum-Control)

Fig. 4.4 Automatic vacuum switch. (Source: https://www.porterinstrument.com/product/dental/Porter-Automatic-Vacuum-Switch)

Fig. 4.5 Figure showing trolley-mounted flowmeter. (*Courtesy: Porter Inc.*)

The other type is the Porter MXR-1 (Fig. 4.6), the operator can adjust the "total flow" of O_2 and N_2O, by not effecting the desired concentration of N_2O. When increasing the concentration of N_2O, the flow rate is also increased.

2. ***Digital***

The digital type of flowmeter will have color-coded digital and electronic type of display to differentiate both O_2 and N_2O gases. The flow rate can be set by an up and down arrow key. Similarly, concentration of a gas can also be set using an up and down arrow key which changes concentration by 5%. It also has a separate key for on/off and oxygen flush (Fig. 4.7a, b).

Like the Matrx MDM analog, the Digital MDM is the only electronic mixer technology that maintains the flow when the gas mixture concentration is changed. It also maintains the concentration when the flow rate is changed.

Fig. 4.6 Porter MXRWall mount/cupboard mount analog type flowmeter. (Source: https://www.porterinstrument.com/product/dental/Porter-MXR-1-Cabinet-Mounted-Flowmeter)

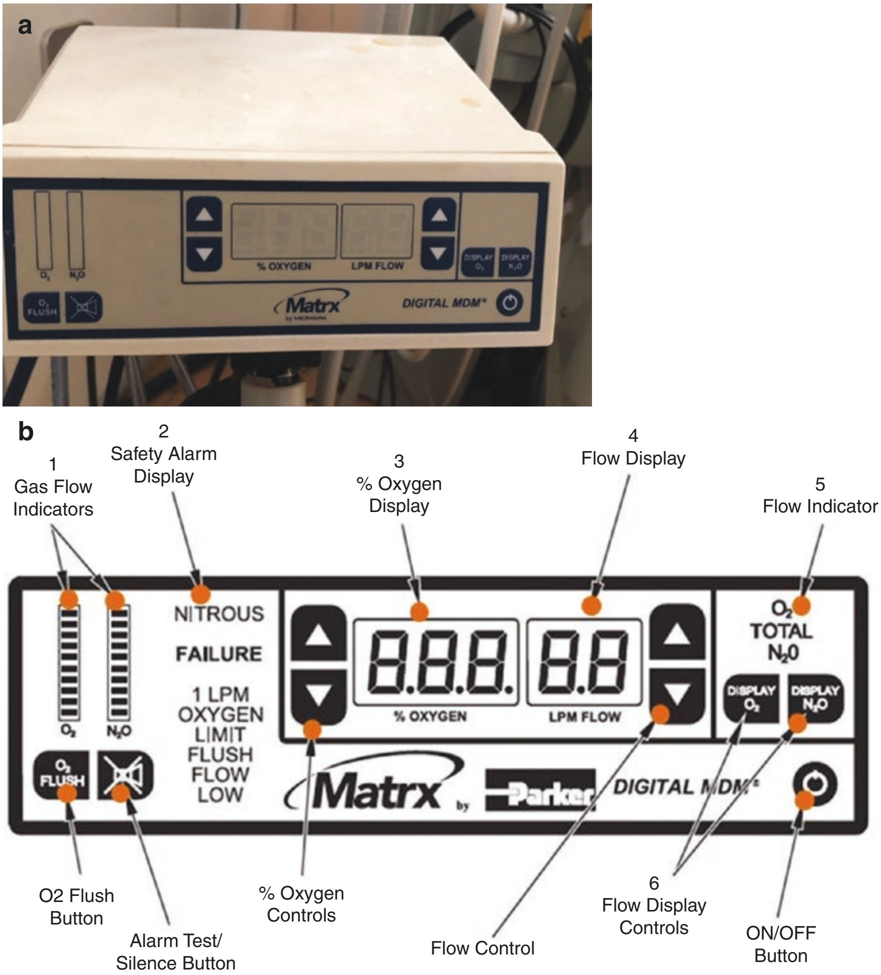

Fig. 4.7 (**a**) Digital Flowmeter. (**b**) Parts of Digital Flowmeter. (*Courtesy: Porter Inc.*)

It also has four (4) audio/visual alarms for

- **OXYGEN FAILURE**: This alarm indicates that the oxygen (O_2) flow cannot be delivered. Oxygen supply should be checked. During an *oxygen failure* alarm, the nitrous oxide delivery is automatically shut off. The LPM (liters per minute) flow and *% oxygen* displays are off.
- **NITROUS FAILURE**: This alarm indicates that the set nitrous oxide (N_2O) flow cannot be delivered. Nitrous oxide supply should be checked. During a *nitrous failure* alarm, the LPM (liters per minute) flow display indicates oxygen flow and the *% oxygen* display is off.
- **1 LPM OXYGEN LIMIT**: This message is displayed when the oxygen flow rate reaches a value of 1 LPM (liter per minute); the unit will not allow the oxygen flow rate to go below this value. If the user attempts to lower the *% oxygen* while this message is displayed, the unit compensates by increasing the total flowrate.
- **FLUSH FLOW LOW**: This message indicates that the oxygen flush flow rate is less than 10 LPM.

The oxygen supply pressure should be checked.

Both the *oxygen failure* and *nitrous failure* are self-canceling alarms. When the gas is restored, the unit returns to the flow rate and mixture ratio which were in effect before the alarm condition.

Breathing Circuit

Breathing circuit involves rubber tubings which deliver gases from the flowmeter to the patient and removes the exhaled gases (Fig. 4.8).

1. 22 mm right angle connector: This connects the bag tee assembly to the corrugated hose.
2. Corrugated hose: This is connected with a Y connector to the coaxial tubing.
3. Coaxial tubing: These are a set of two tubes which run parallel to each other. One tube carries only inhaled air and other tube carries only exhaled air so that there is no mixing of the inhaled and exhaled air.
4. Hood assembly: It consists of a nasal hood with inner liners or a nasal hood with exhalation flap valve.

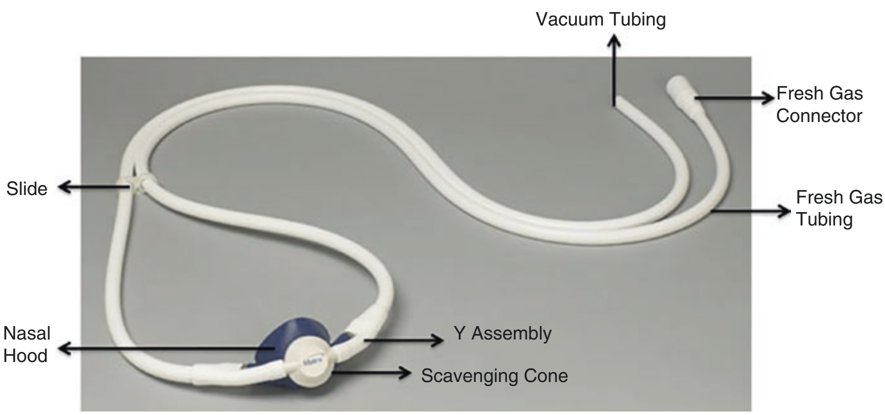

Fig. 4.8 Parts of breathing circuit

Nasal Hoods

Nasal hoods can be of various types.

- Single use: This avoids any cross-contamination and saves time of dental auxiliaries (Fig. 4.9).
- Scented or unscented: These can be used based on the personal likings of children.
- Low profile: It provides easier access and better visibility (Fig. 4.10).
- Contoured design: It will have an outer rigid mask with an inner soft disposable liner. This kind of mask is very effective for scavenging purposes, thereby reducing the ambient air concentration of nitrous oxide (Fig. 4.11).
- Nasal hoods are available in different sizes such as small, medium, and large (Fig. 4.12).

Fig. 4.9 Figure showing scented masks

Fig. 4.10 Low profile "Sizer masks". (Intended use is only to size the correct Silhouette Disposable Circuit, *NOT* intended for delivery of N_2O to the patient)

Fig. 4.11 Contoured masks

Fig. 4.12 Masks of varying sizes

4.1.2 Portable

Portable system of nitrous oxide delivery consists of a breathing circuit and flowmeter assembly, mounted on a yoke with cylinders, gauges, and regulators (Fig. 4.13).

E-Block

The E-block installed on the mobile trolley is used to attach the O_2 and N_2O cylinders. This is also referred to as the Yoke. Initial setup cost of the portable type is lower than the centralized one. However, portable type occupies more space in the operatory, and visibility of cylinders may induce anxiety in child patients. Also due to the smaller size of cylinders, their frequent changing may be required especially when used regularly (Fig. 4.14a, b).

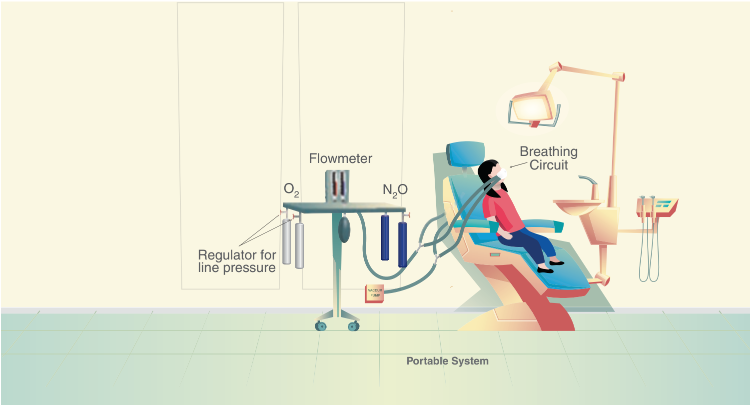

Fig. 4.13 Portable nitrous oxide delivery system

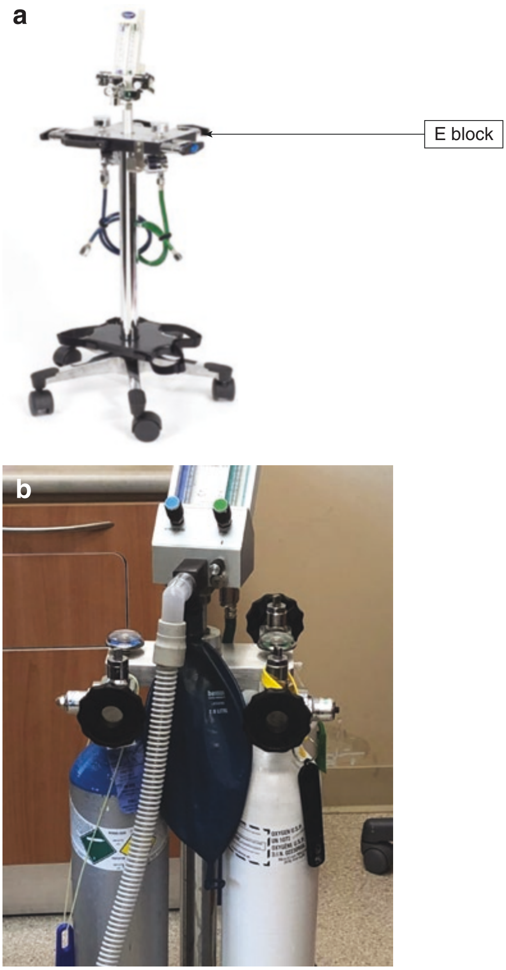

Fig. 4.14 (**a**) E-block and flowmeter mounted on a portable vertical stand. (**b**) Cylinders attached to the yoke

E-block will also have pressure gauges and regulators attached to it (Fig. 4.15a, b). Pressure gauges indicate the pressure of gases in the cylinders, and the regulators help in reducing the pressure of gases in cylinders, to that desired in the hoses delivering gases to the flowmeter (for oxygen from 2000 psi to 50 psi and for nitrous oxide from 750 psi to 50 psi).

4.1.3 Centralized System

Centralized system consists of cylinders, pressure gauges, manifold, regulators, copper tubings, outlet station, flowmeter, and breathing circuit (Fig. 4.16).

Manifold

Manifold is a group of large cylinders which supply gases through separate pipelines and gas outlets to which flowmeters are attached. Manifold can either be a conventional type which requires manual changing of cylinders or a digital type (Fig. 4.17a). Cylinder pressure gauges, indicating pressure of cylinders, are attached to the manifold (Fig. 4.17b). Porter Inc. has manifold which has inbuilt regulators and cylinder pressure gauges [6] (Fig. 4.17c). Digital manifold (Fig. 4.18a, b) allows automatic switching of cylinders to take place using auto switchover option.

Parts of digital manifold are as follows:

Fig. 4.15 (**a**) Figure showing regulators for nitrous oxide (blue) and oxygen (green) attached to the yoke; (**b**) pressure gauges for nitrous oxide and oxygen attached to yoke

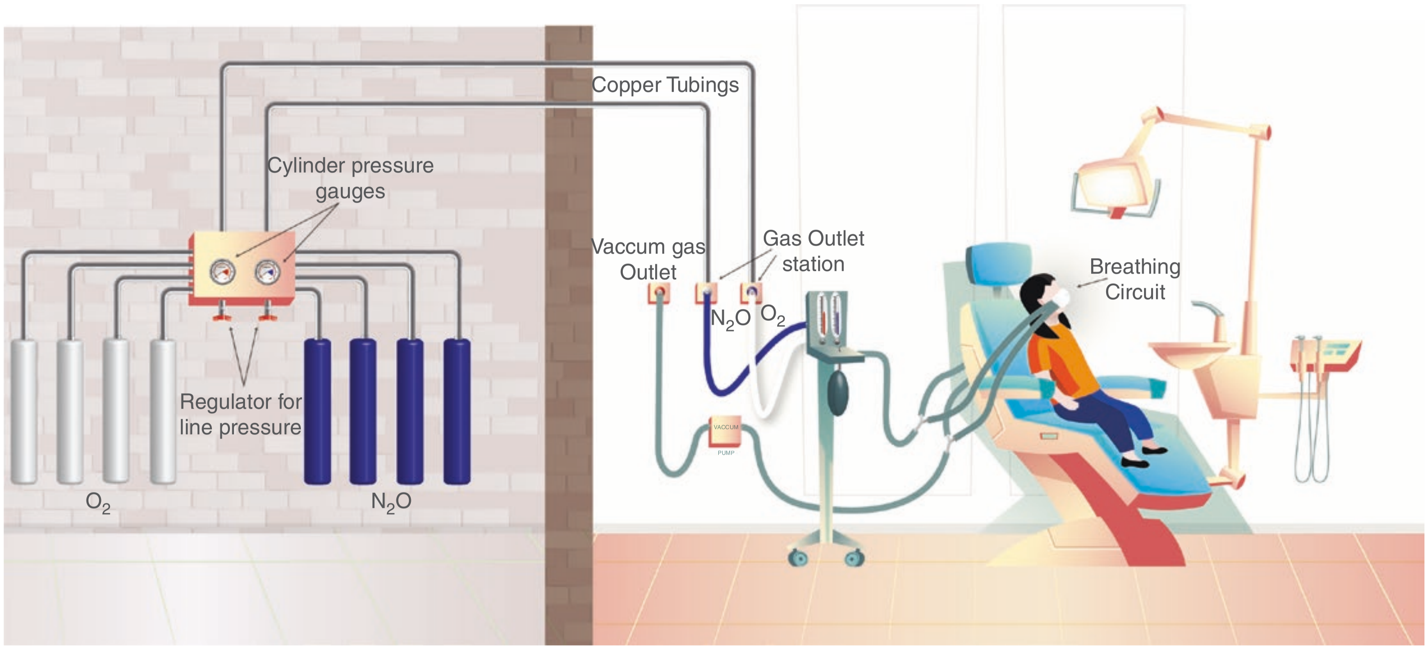

Fig. 4.16 Parts of centralized system of nitrous oxide delivery. (**A certified Medical Gas Plumber** ***must*** **be contracted for installation of a centralized Gas "Copper Piping" system**)

Fig. 4.17 (**a**) Conventional type of manifold attaching two cylinders of each gas with a separate cylinder pressure gauge for each gas. (**b**) Figure showing nitrous oxide manifold with pressure gauge and regulator. (**c**) Manifold by Porter Inc. showing in-built line pressure gauges and indicators for two cylinders each of nitrous oxide and oxygen. (Source: *Porter Vanguard Manifold.* https://www.porterinstrument.com/product/dental/Porter-Vanguard-Manifold)

Digital Indicators

Digital manifold has LED numeric line pressure readings, which are clear and precise. It has regulators, which will maintain the line pressure at 50 psi, and in the event of variation in line pressure, alarm system will provide visual and audio alerts.

It has a manifold status reading which shows on/off.

Gas cylinder status is also clearly notified as inline/reserve/empty.

Microprocessor

Microprocessor causes 1-min delay when the system is turned on. This delay is to prevent any false alarms arising from fluctuations in gas flow.

Power Interruption

In Accutron Digiflow automatic manifold system, if the power supply is interrupted, gases will continue to flow without any alarms or switching. If the power supply is

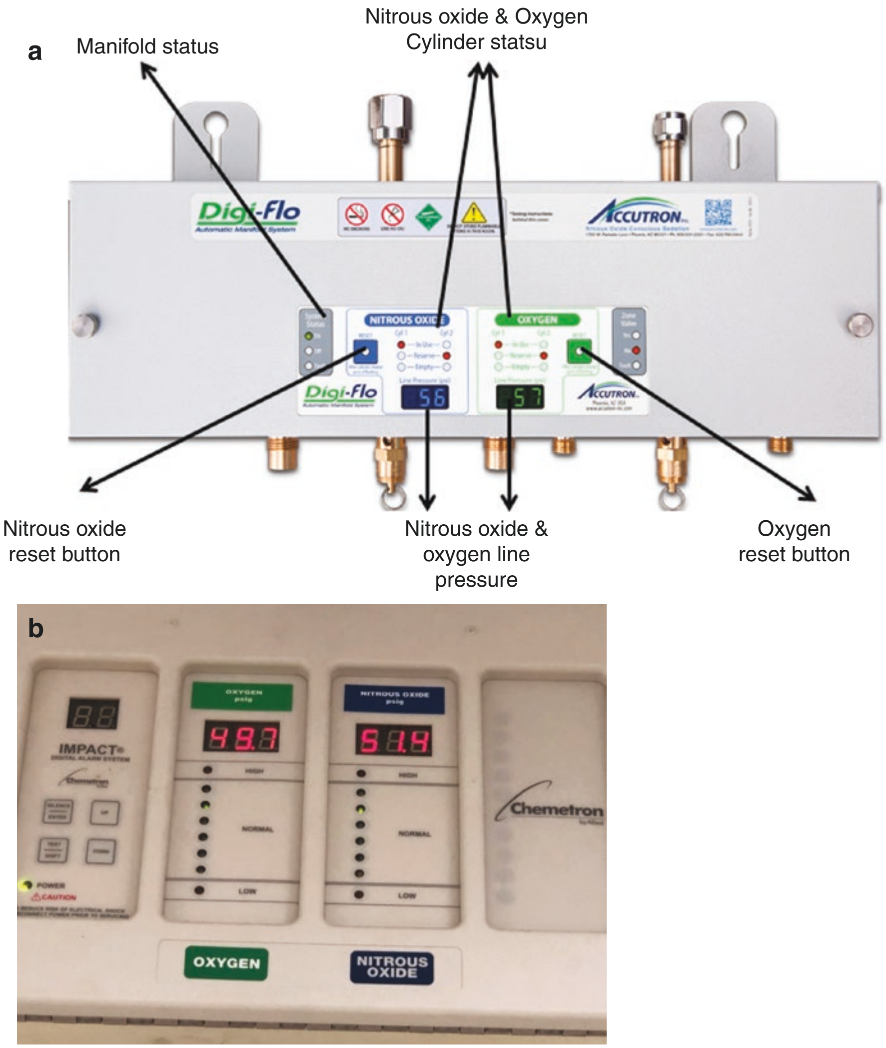

Fig. 4.18 (**a**) Digital Manifold. (Source: Equipment brochure. Accutron Inc. [7]). (**b**) Digital Manifold showing line pressure of oxygen and nitrous oxide

interrupted for less than 4 s, the manifold will start in the same mode as before. However, if the power supply is interrupted for more than 10 s, then the manifold should be restarted.

Office Alarm Panel System

Office alarm panel can either be wall mounted or desk mounted. The alarm panel system consists of an electrical circuit with a microprocessor. It indicates when the system is turned on, when the cylinder changes, and when the pressure in cylinder drops.

Zone Valves

As the name indicates, this component helps to demarcate or isolate two zones using a manual valve. It is usually located in a corridor, which is easily accessed by staff. It consists of two valves, one for nitrous oxide and another for oxygen, which can be closed in case of any emergency, to isolate gas cylinder areas from the operatories.

Oxygen Fail Safe

It is an automatic safety feature of the manifold which prevents the supply of nitrous oxide alone in case both the oxygen cylinders connected to manifold become empty.

Pressure Regulator

This is attached to oxygen and nitrous oxide cylinders separately and functions to reduce the pressure present in the cylinders to the desired level of 50 psi line pressure. Regulators where the PSI can be adjusted should not be purchased.

Gas Outlet Panels

Gas outlet panels are DISS (diameter indexed safety system—different gases have gas outlet port of different sizes and shapes which fit with the male counterpart of respective gases only to avoid cross connection) enabled panels which have outlets for oxygen and nitrous oxide or oxygen, nitrous oxide, and vacuum (Fig. 4.19).

Mount

Different types of mounting options are available for the flowmeters (digital or analog) in the centralized system. In the portable system, flowmeter is always mounted on a trolley.

Fig. 4.19 Figure showing gas outlet panel of oxygen, nitrous oxide, and vacuum using DISS system

Chair Mount Pedestal

The nitrous oxide mixer and equipment are permanently mounted on the dental chair which provides easy access to the operator and also prevents entanglements of hoses.

Cupboard Mount Pedestal [8]

Here the mixer and equipment are mounted inside a cupboard. The advantages are that the mixer does not occupy the working space of the operatory and is not visible. However, it requires enough space inside the cupboard (Fig. 4.20).

Wall Mount Slide Assembly [8]

The mixer and the equipment are mounted on a wall, and the mount allows for slight flexibility due to its sliding movement (Fig. 4.21).

Fig. 4.20 Cupboard mounted flowmeter. (Source: http://www.porterinstrument.com/dentalcontent/files/datasheets/Porter-Full-Products-and-Accessories-Catalog-FM-1423.pdf)

Fig. 4.21 Wall mount slide assembly for flowmeter

Fig. 4.22 Chair mount remote flow system. (Source: http://www.accutron-inc.com/product/rfstm-chairmount-kits1)

Chair Mount Remote Flow System [9]
This system manufactured by Accutron Inc. combines gas delivery, reservoir bag for patient monitoring, and vacuum control to form a single unit. This central unit replaces the conventional bag tee and vacuum control valve. It creates an uncluttered appearance in the operatory due to the absence of long hoses (Fig. 4.22).

4.1.4 Safety Features

The operator must be well familiar with the safety features of the equipment, and these must be checked on a regular basis to ensure the absolute safety of our patients and people administering it [10] (Table 4.3). More importantly, the operator should be able to act swiftly in case of an emergency arising as a result of the use of nitrous oxide. If operator is in the middle of a procedure, then the first and most important step is to remove the nasal hood from the nose so that the child can begin to breathe ambient air which would be containing 21% oxygen [11].

Table 4.3 Table showing various safety features of a nitrous oxide equipment

Safety feature	Description
Alarms	The alarm system cautions about the reduction in the pressure of oxygen or nitrous oxide
Color coding	Color coding helps to easily identify the gas in the cylinders and hoses
Diameter Index safety system	This system, based on difference in diameter, prevents any cross-connection of tubings with the gas cylinders
Pin Index safety system	This system on the gas tank yoke has different geometric configurations for oxygen and nitrous oxide to be connected to the correct gas tank and avoid connection of non-oxygen tank to the oxygen portal
Emergency air inlet	This feature allows the patient to breathe ambient air through the inlet when the oxygen fail safe system shuts supply of gases or when higher minute volume causes the reservoir bag to collapse
Locks	This features prevents inappropriate use of nitrous oxide by the dental staff
Oxygen fail safe system	This feature prevents inhalation of nitrous oxide gas alone by the patient. Nitrous oxide supply is cut off when the oxygen supply is exhausted
Oxygen flush button	This allows for 100% oxygen to be administered through a reservoir bag
Quick connect for positive pressure	This feature allows positive pressure oxygen to be delivered to a patient in an emergency situation
Reservoir bag	It is a bag in which gases from the nitrous oxide mixer are gradually filled. It allows a check on the flow of gases in the circuit

Fig. 4.23 Figure showing color coding of tubes—blue for nitrous oxide and white for oxygen

Color Coding

Gas cylinders are color coded along with the non-conductive tubes which connect the cylinders to the mixer. The color of the non-conductive tubings is same as the color of cylinders (Fig. 4.23). Nitrous oxide cylinders are blue in color worldwide, but the color of oxygen cylinders vary in different countries (e.g., it is green in the USA and white in India). Even the background of the flowmeter is color coded.

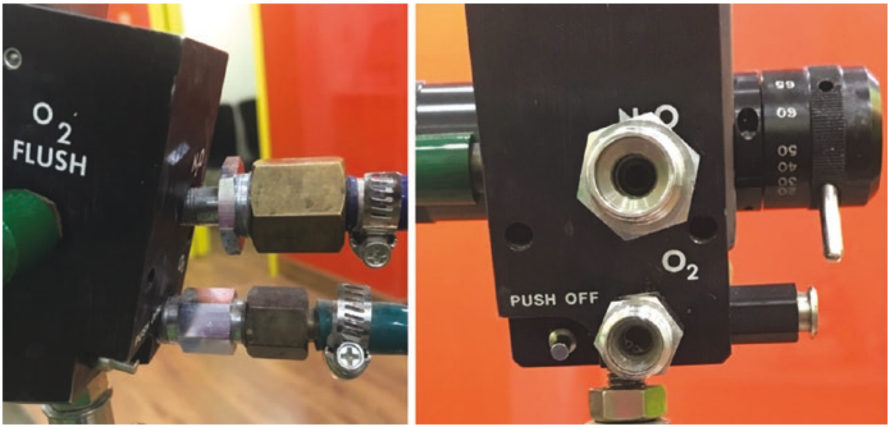

Fig. 4.24 DISS on flowmeter assembly showing nitrous oxide with larger diameter (above) and oxygen with a smaller diameter (below)

Diameter Index Safety System (DISS)

DISS was developed by the Compressed Gas Association (Chantily, USA). According to this system, a non-interchangeable, removable connection can be made for different gases based on the diameter of the adapters. Each type of gas has a DISS number which is unique for it. For example, oxygen has DISS number 1240 and it has 9/16 in., 18 thread connection. Nitrous oxide has DISS number 1040 and has 3/4 in., 16 thread connection. Hence, the diameter of the connection component of oxygen is smaller than the nitrous oxide (Fig. 4.24).

The diameter of the connection components acts in a key-like manner to fit the components of the respective gases. The parts of the system are adapter, nipple, and nut. DISS system makes it nearly impossible for cross-connections to be made unless the adapter on the tube is changed.

Pin Index Safety System

This system is based on the geometric figures rather than the diameter alone. For the portable system, it ensures proper connection of the gas cylinders to the yoke. The pins protruding from the yoke have a unique configuration so that cylinders through their valves are attached at the correct positions in the yoke (Fig. 4.25).

Emergency Air Inlet

This remains closed under normal circumstances when the gases are being administered to the patient. If the supply of gases is turned off due to failure of fail safe system, emergency air inlet allows ambient air containing 21% oxygen to be delivered to the child enabling him/her to breathe through the nasal hood or face mask (Fig. 4.26).

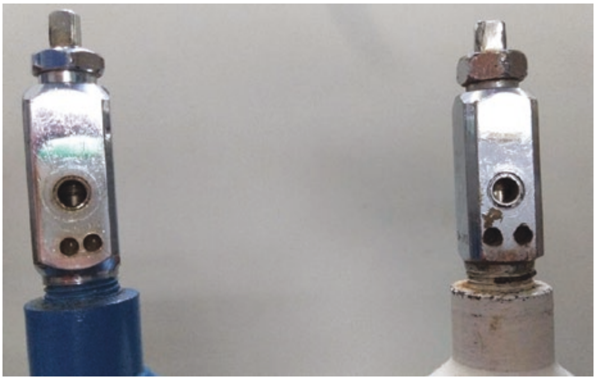

Fig. 4.25 Figure showing pin index system with nitrous oxide having two holes placed close to each other and oxygen having holes slightly apart

Fig. 4.26 Figure showing deflated reservoir bag. In this situation, emergency air inlet allows inhalation of ambient air

Minimum Oxygen Liter Flow

Nitrous oxide–oxygen delivery systems are designed to provide a minimum oxygen flow of 2.5–3.0 L/min. This safety feature ensures that the child has access to 100% oxygen as soon as the machine is turned on (Fig. 4.27).

Minimum Oxygen Percentage

This is one safety feature which enables this device to deliver at least 30% oxygen at any given time which is more than the ambient air oxygen of 21%. This happens

Fig. 4.27 Figure showing minimum oxygen liter flow

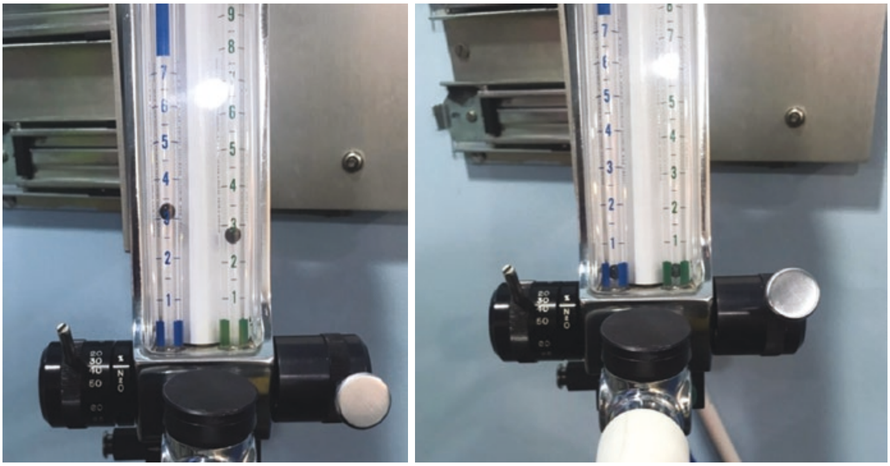

Fig. 4.28 Figure showing oxygen fail safe mechanism. Nitrous oxide flow stops if oxygen flow is interrupted (right)

when the nitrous oxide concentration is 70% (maximum for nitrous oxide–oxygen delivery system). Usually the concentration of nitrous oxide being delivered is 35–50% which means oxygen concentration being inhaled by a child is 50–65%.

Oxygen Fail Safe System

This safety feature ensures that under no circumstances, a child can inhale 100% nitrous oxide. If the oxygen supply is interrupted due to the depletion of gas in cylinder, even the nitrous oxide supply is stopped. On the other hand, if nitrous oxide supply is interrupted, oxygen supply would continue as such. Fail system can fail due to rupture of the internal diaphragm in poorly manufactured non-standardized mixers. The fail safe is the most important component of the analog and digital mixers (Fig. 4.28).

Oxygen Flush Button

This feature allows for 100% oxygen to be delivered through the reservoir bag. Oxygen is delivered straight from the pipeline at 45–50 psi when the oxygen flush button is pressed. The flow rate is 35–75 L/ min. If the oxygen flush button gets defective, over dilution of the nitrous oxide gas can happen.

Reservoir Bag

It is a rubber inflatable breathing bag in which the gases fill from the circuit and are removed by inhalation. It gives a visual cue on the inhalation pattern of the child and whether the child is breathing through the nose (not required with modern circuits like the Porter Silhouette Low Profile mask).

Locks

To prevent abuse of nitrous oxide by the dental staff, few manufacturers provide additional locks at the mixer level. This intercepts unwarranted access to the nitrous oxide gas.

Alarms

Few nitrous oxide oxygen delivery systems are equipped with alarms to signal any deviation from normal such reduction in oxygen line pressure indicating depletion of gases (Fig. 4.29a, b).

4.1.5 Maintenance and Calibration

Maintenance schedules should be followed strictly. It helps to ensure that the equipment is functioning smoothly and flawlessly.

Daily Checks

- All the connections are securely attached and functioning properly.
- Inspect the tubings and other rubber parts for any visible cracks or tears.
- Check for cleanliness around the cylinders.
- Check the functioning of fail safe device.
- With the concentration knob and flow control knob both in working position, close the flow control knob to zero. This should reduce the flow rate of both the gases to zero, although the concentration knob is not turned off.
- Another method is to move the concentration control knob to 50%, without turning on the flow control knob. On doing this, the flowmeter readings will not rise from zero.

Monthly Checks

- Check for leakage on all the joints using soapy water solution.
- Check line pressure gauges and cylinder pressure gauges.
- *Check functioning of the concentration control knob valve or calibration.*
- Concentration control knob valve should be set to 50% and flow control knob set to 3–4 L/min. After doing this, the ball indicators in the flowmeter should almost be at the same level.

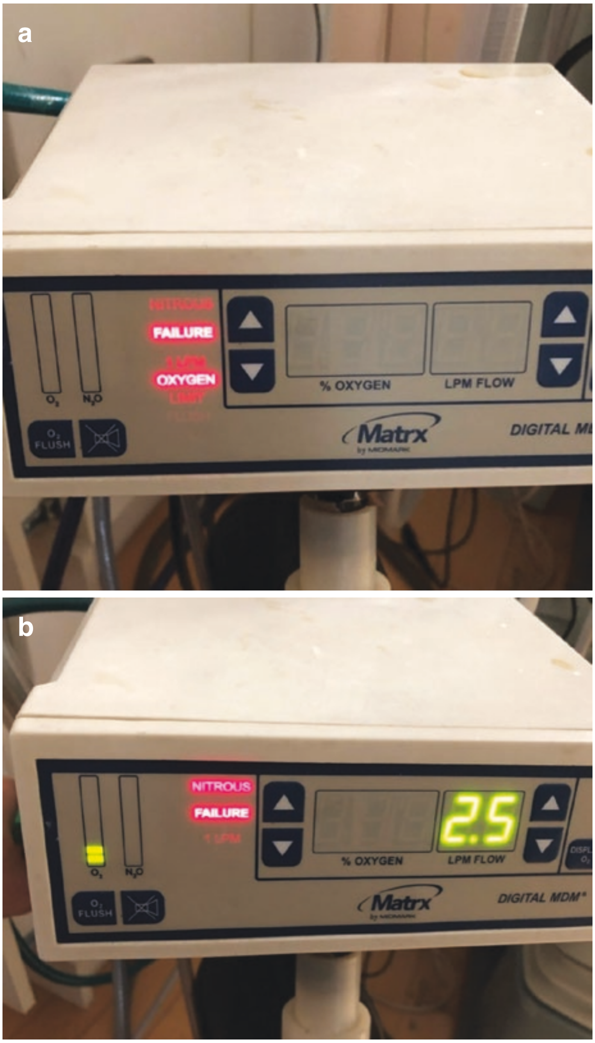

Fig. 4.29 (**a**) Figure showing reduction in line pressure of oxygen as *failure oxygen* which stops flow of nitrous oxide gas also due to fail safe mechanism. (**b**) Figure showing reduction in line pressure of nitrous oxide as *nitrous failure*. In this situation, oxygen flow continues as shown in this figure

- After doing this, the concentration control knob should be turned to zero and this should immediately reduce nitrous oxide concentration to zero. This part is usually done after every patient when the child is administered 100% oxygen for 5 min (Fig. 4.30a, b).
- *Oxygen flush*
- For doing this check, corrugated tube should be removed from the bag tee assembly. After blocking the flow of gas from the front of bag tee using the palm of a hand, the oxygen flush button should be pressed. This should fill the reservoir bag within 5 s (Fig. 4.31).
- *Non-rebreathing valve*
- With the control knobs turned off, the corrugated tube should be separated from the coaxial tubings. The operator should breathe into the corrugated tube. On doing this, the reservoir bag should not be filled from the operator's exhaled air.

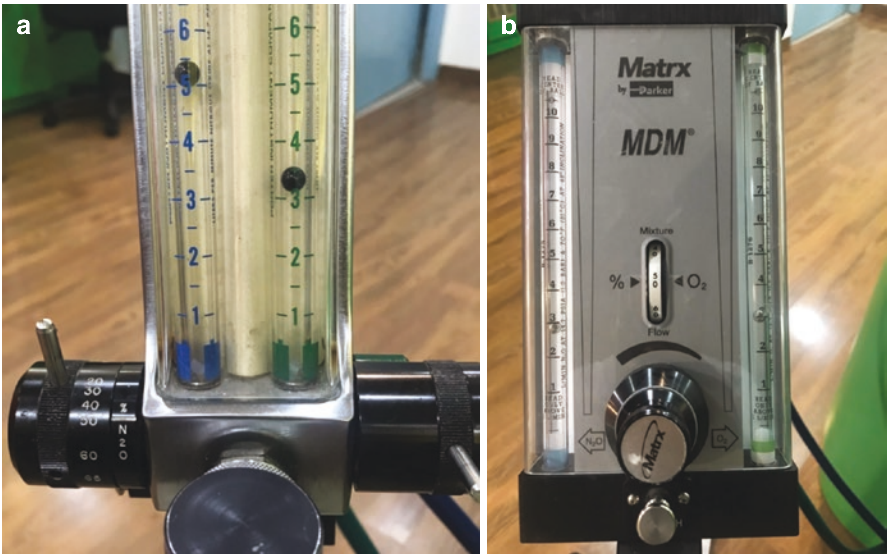

Fig. 4.30 (**a**) Figure showing failure of calibration check. (**b**) Figure showing properly calibrated flowmeter

Fig. 4.31 Figure showing maintenance check for oxygen flush

However, if the reservoir bag inflates, it indicates that the non-rebreathing valve is not functioning properly (Fig. 4.32).

- *Emergency air inlet*
- With the control knobs turned off, the corrugated tube should be separated from the coaxial tubings. Reservoir bag should be completely deflated. The operator should inhale from the corrugated tube. This should allow ambient air to be

Fig. 4.32 Figure showing check for non-rebreathing valve. Reservoir bag does not inflate on blowing air into corrugated tube

drawn from the emergency air inlet which makes a different sound than the normal gas flow.

- *Flowmeter system working pressure leaks*

With all the hose connections tightened and flow control knob turned to zero position, cylinder valves should be opened and line pressure checked to be 50 psi. If the ball floats in the flowmeter do not move, it indicates that there is no leakage from the flowmeter. The on/off switch should then be closed and the line pressure be maintained for overnight. After over night time period, if the line pressure does not reduce from 50 psi, it indicates that there is no leakage from the lines.

4.1.6 Disinfection

Disinfection of flowmeter, breathing circuit, reservoir bag, and vacuum control unit cannot be ignored considering that most of them are rubber goods.

Flowmeters, Vacuum Control

Flowmeters should only be wiped with surface disinfectants. However, care should be taken to avoid excessive moisture coming in contact with the flowmeter directly. To prevent this from happening, never spray disinfectant directly on the flowmeter. Instead, spray on a cloth and wipe with it. Bag/sleeves is preferable for cross-contamination.

Reservoir Bag

The outer surface of the reservoir bag should be wiped with a cloth moistened with disinfectant (non-alcoholic). The inner surface of the reservoir bag is prevented from infection due to the use of non-rebreathing valve.

Breathing Circuit

Breathing circuit should be disinfected as per the manufacturer's instructions.

1. Porter Brown system: The circuits should be disassembled and all the parts cleaned in an ultrasonic cleaner containing enzymatic cleaner. Following this, autoclaving should be done at 121 °C.

2. Matrx autoclavable nitrous scavenger system: All the parts of the circuit should be separated from each other, washed in mild detergent, and then autoclaved at 121 °C. Single-use white nasal hood and scavenger control valve should not be autoclaved.
3. Accutron: All the reusable parts should be thoroughly cleaned before use, and the spiral vacuum tubing containing vacuum flow gauge is not autoclavable and should not be immersed in liquid solutions.

4.1.7 Trouble Shooting

During the use of nitrous oxide delivery system, certain problems may arise. Clinician should be well aware of the reasons behind these deviations and be capable of addressing these issues (Table 4.4).

Table 4.4 Table showing various roadblocks of nitrous oxide delivery system and their solutions

Problem	Reason	Solution
No oxygen or nitrous oxide gas	Gas supply is interrupted due to leakage Cylinders are empty Cylinder valves are not open	Check the line for any leakage sounds Check for cylinder contents on cylinder pressure gauges Open the cylinder valves
Gas leakage	Leakage from cylinder valve Leakage from outlet port Leakage from ON/OFF switch Around pin wheel threads	Check for the valve seal Replace the O ring Stop using the device and send for repair Check if threads are worn out and replace if required Teflon tape may be wrapped on the thread to achieve a tight seal
Nitrous oxide flow meter working but the oxygen flowmeter not working	Malfunctioning of the fail safe device	Stop using the equipment and send for repair
Both nitrous oxide and oxygen levels are falling on flowmeter	Oxygen cylinder is empty	Replace the oxygen cylinder
Reservoir bag getting overinflated	Child is not breathing through nose Kink in the breathing circuit Flow rate of gases is much higher than the respiratory volume of the child	Encourage the child to breathe through nose Check for kinks or physical obstructions in breathing circuit Reduce the total flow rate of gases
Reservoir bag become flat during the procedure	Respiratory volume of the child is more than the flow of gases being delivered to the child	Increase the flow rate of gases
With concentration of nitrous oxide set, flow rate of both gases keeps fluctuating, although flow control knob is not being moved	Oxygen regulator is varying pipeline pressure	Check oxygen regulator. Ensure that oxygen line pressure is 50 psi

4.2 Scavenging

Nitrous oxide gas can leak through various sources in a dental operatory and contaminate the surrounding air which a dentist and other dental staff breathe. The process of scavenging is very important and is required to keep nitrous oxide levels in a dental operatory to minimum.

4.2.1 Definition

Scavenging is the process of collecting and removing the exhaled and excess gases to prevent them from contaminating the operating room.

4.2.2 Why Is Scavenging Required?

Nitrous oxide concentration in a dentist's breathing zone has been found to vary between 409 ppm in scavenged offices and 24,000 ppm in unscavenged ones [12–15]. Scavenging is required to reduce occupational exposure of nitrous oxide to dentists and other dental staff as excessive exposure to nitrous oxide has been found to be hazardous depending on various factors and situations.

4.2.3 Parts of Scavenging System

Main parts of a scavenging system are as follows:

1. Scavenging circuit
2. Scavenging mask
3. Scavenging unit/vacuum pump

Scavenger breathing systems are manufactured by two companies:

- Parker Hannifin/Porter Instruments
- Accutron

4.2.4 Types of Scavenging

1 **Passive:** There is no vacuum pump attached to the exhaust tube. As the child exhales, the exhalation valve in the scavenging cone system permits passage of air into the expiratory hose through the tubing and the expired air is forced out by normal expiratory effort (Fig. 4.33a, b). The expiratory hose should be carried on the level of the floor and its opening should be placed outside the building. It should not be sloped upwards, as there will be "back flooding" of nitrous oxide

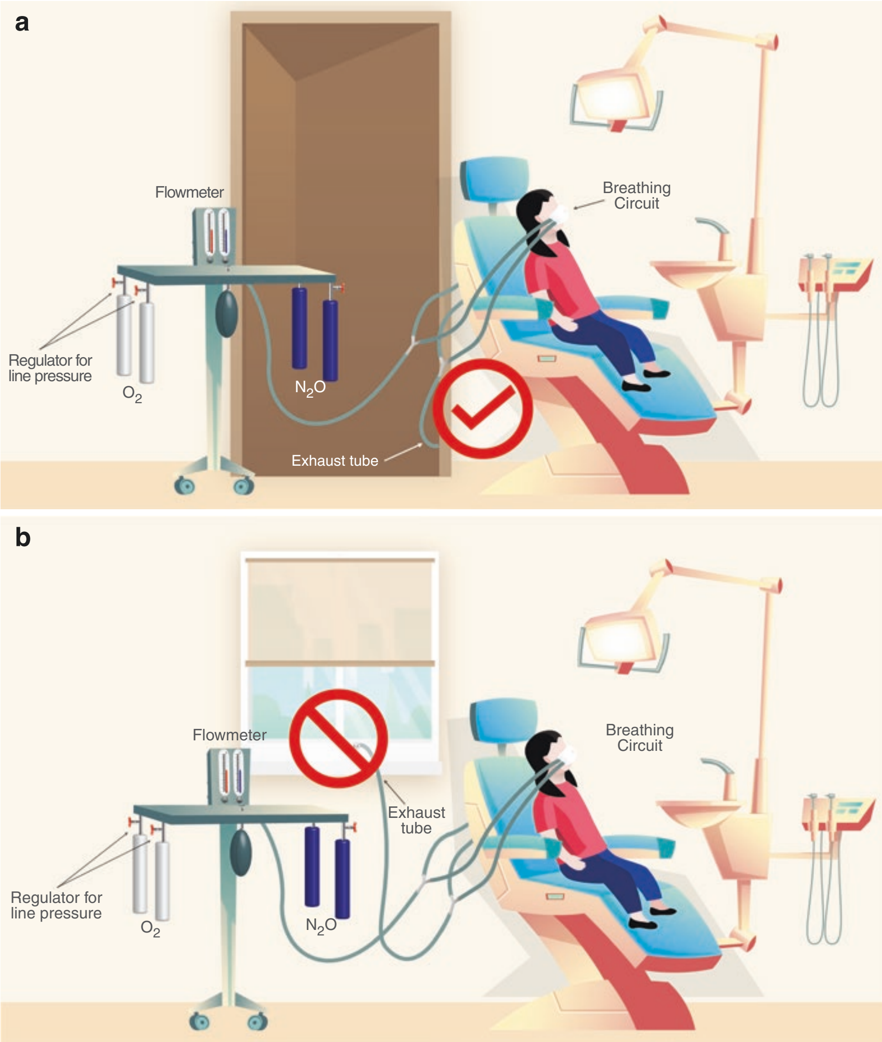

Fig. 4.33 (**a**) Passive scavenging—exhaust tube exiting through door at the level of floor. (**b**) Incorrect passive scavenging—exhaust tube should not be raised higher than the floor level to be placed outside a window

air, since it is heavier than air. This back flooding would lead to "ambient pollution."

2 **Active**: The exhaust tube is connected to a device which actively removes exhaled air at a rate of 40–45 L/min. This can be done by using three kinds of devices
   (a) Connected to dental vacuum in high volume evacuation tube (Fig. 4.34).
   (b) Use of centralized scavenging system where the exhaust tube is connected to the wall outlet.

Fig. 4.34 In-line vacuum control kit attached to high volume suction of dental unit

(c) Miniscav unit: A smaller unit contained in a box which works as a part of an active breathing circuit. It requires a 15-mm external vent and a power supply (Fig. 4.35).

Active scavenging can reduce the ambient air pollution by 90% or more [16–18].

4.2.5 Various Scavenging Systems

Matrx

This was originally manufactured by Matrx. In this system, fresh air passes through tubings of 22 mm diameter to the nasal hood. The nasal hood is attached to a scavenging cone system. It consists of an outer cone, exhalation valve and the exhalation

Fig. 4.35 Miniscav unit. (Source: https://ramedical.com/wp-content/uploads/2017/10/Miniscav-UK-Manual-MK1-2017.pdf)

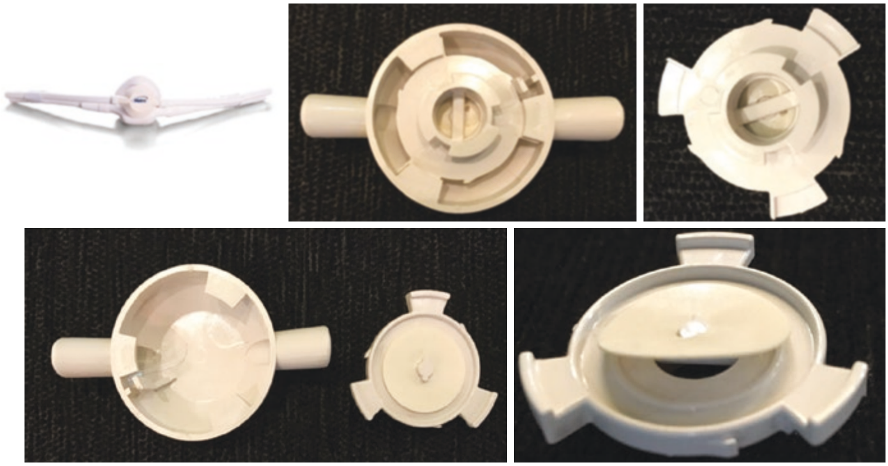

Fig. 4.36 Matrx scavenging circuit containing exhalation cage and exhalation valve raised as in exhalation. (Source: https://www.porterinstrument.com/product/dental/Dynomite-Universal-Conversion-Kit)

valve cage. As the child exhales, the exhalation valve rises and the exhaled air passes through the exhalation cage into the coaxial tubes. This kind of mask is inefficient as far as scavenging is concerned, and there is leakage around the nose (Fig. 4.36).

Porter Brown Scavenging System

It uses a double mask consisting of a soft flexible inner disposable liner and an outer nasal hood (Fig. 4.37). Fresh air passes through the corrugated tube, coaxial tubes into the inner liner. When the patient exhales, the flapper valve in the inner liner

Fig. 4.37 Porter Brown scavenging circuit consisting of coaxial tube and a double mask having soft flexible inner liner and exhalation flap valve. (Source:https://www.porterinstrument.com/product/dental/Porter-Double-Mask-Autoclavable-Hood-Kit-With-Liners)

opens and the gas passes to the outer hood. The gases then pass through the second set of coaxial tubes into the exhaust air vacuum hose (Fig. 4.38).

This mask is proven to be efficient [19–23]. The advantage of Porter Brown mask is that a tight fit is not critical. Due to the gap between the inner liner and the outer hood, waste gases produced by leakage around the mask, mouth breathing, or speaking are sucked into the coaxial tube meant for exhaled air and then into the vacuum hose.

Also, in Porter Brown mask, the outer mask covers the inner mask completely. However, in the Matrx mask, the scavenging cap is small in size and occupies a small portion on top of the mask, thereby having an added area from where leakage could take place. Also, the inner mask of the Porter mask was found to be very soft and pliable making adaptation to the nose and face much better.

It has been reported that Porter Brown scavenger removed 71–91% of nitrous oxide compared to Matrx and Accutron. It was also found that Porter Brown mask maintained ambient N_2O levels below 50 ppm [14].

Porter Silhouette Scavenging System

This kind of mask is anatomic, low profile, and lightweight and fits snugly over the nose. It also provides better vision to the operator. It does not require the use of a reservoir bag. It is disposable and hence infection control is optimal (Fig. 4.39a, b).

It is potentially an efficient mask due to its snugly fitting ability. However, its efficiency is unproven. This is because the gas flow is continuous in this compared to the masks with reservoir bag where the gas flow is demand based.

Advantages of Silhouette mask/circuit are as follows:

1. The circuit is light weighted.
2. The circuit and mask does not pose a problem for disinfection as the entire circuit is disposable.

3. Nasal hoods are not bulky and do not restrict access to the oral cavity.
4. Silhouette nasal masks make a seal around the nose using an adhesive strip which helps to minimize any leakage around the mask.
5. There is accurate delivery of N_2O via nasal cannulae to the nasal meatus.
6. The tubes do not need to be clamped behind the chair; instead, it can be passed behind the ear lobe of the patient, allowing the dentist to maneuver the patients head when required.

In January 2009, Porter Instruments purchased the Matrx nitrous oxide division from Midmark. Later that year, Porter Instruments discontinued the passive breathing system.

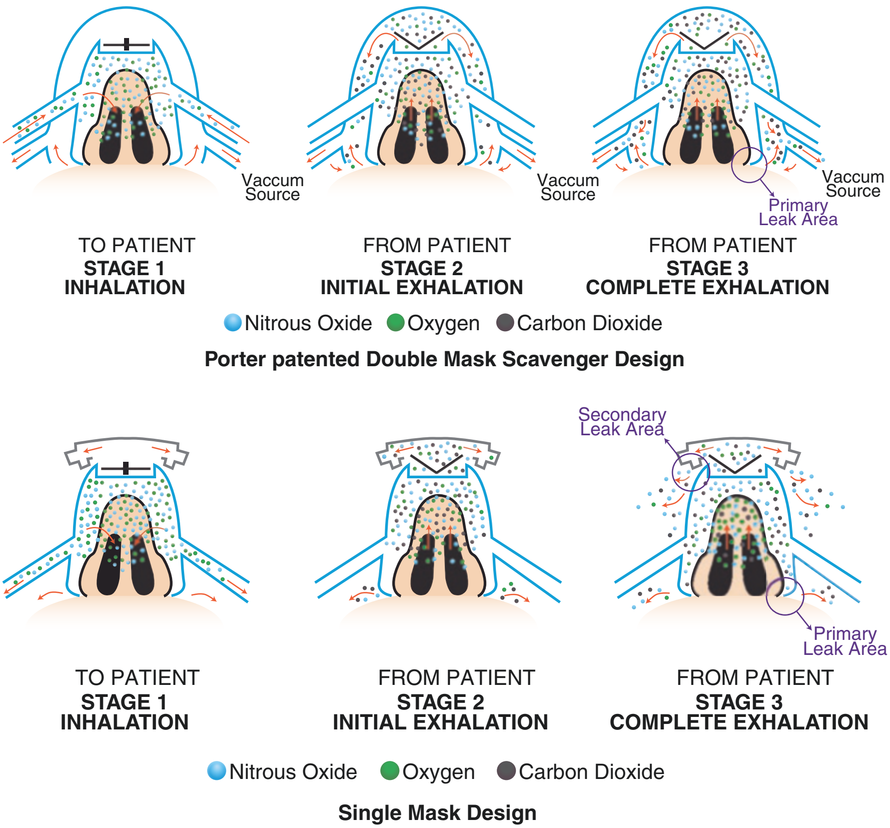

Fig. 4.38 Figure showing better efficiency of double mask than single mask. (*Courtesy: Porter Inc.*)

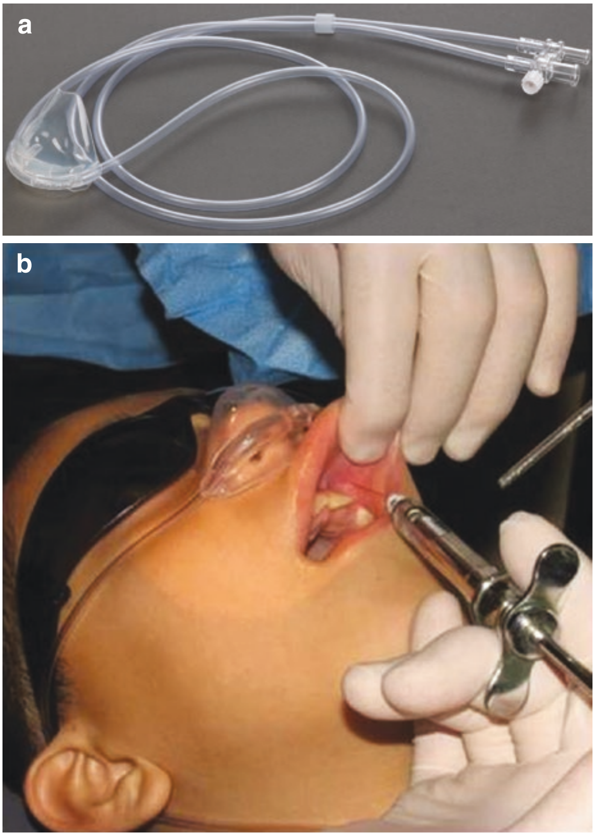

Fig. 4.39 (**a**) Silhouette scavenging circuit. (**b**) Silhouette mask. (*Courtesy: Porter Inc.*)

Accutron Scavenging System

The fresh air passes gray or white corrugate tubes and white coaxial tubes into the nasal hood. It has an outer clear collecting cap. The inner hood is either gray which is autoclavable or scented single-use one (Fig. 4.40).

Axess Scavenging System (Fig. 4.41)

The differences from Silhouette scavenging system are as follows:

- There is no nasal cannula for accurate delivery of N_2O to the meatus.
- There is no adhesive strip to limit leakage of N_2O.
- There are only three (3) sizes of masks and no "sizers" for accurate selection of mask size.
- Only the mask is disposable not the delivery tubing, exposing the remainder tubing to contamination and poor infection control.

Fig. 4.40 Accutron scavenging system with outer collecting cap attached to the nasal hood. (Source: https://www.accutron-inc.com/product/piptm-scavenging-circuits-multi-use-nasal-masks/)

Fig. 4.41 Axess scavenging system

Advantages of Axess Scavenging Circuit

1. It does not obstruct the vision of the operator as it is less bulky.
2. It is also more comfortable for the patient as it fits snugly on the nose.
3. The tubes do not need to be clamped behind the chair; instead, it can be passed behind the ear lobe of the patient. The tubes are also more slender.

Differences between Porter Silhouette/Axess scavenging circuit with the other scavenging circuits are mentioned in Table 4.5.

Table 4.5 Comparison of Silhouette/Axess mask with other nitrous oxide nasal masks

	Silhouette/Axess mask	Other masks
Reservoir bag	Not included	Included in breathing circuit
Usage of gas	Not efficiently	Efficiently

4.2.6 Effect of Scavenging

In the 1970s, when the dental offices were not scavenged, the reports cited nitrous oxide concentrations in the range 3800–5000 ppm [24, 25]. Later in 1977, NIOSH recommended that the dental operatories should have ambient nitrous oxide <50 ppm. In 1980, American Dental Association recommended the use of scavenging devices in order to reduce the nitrous oxide levels in dental operatories.

Numerous studies indicated that typically in dental operatories, N_2O levels were much higher than the levels recommended by NIOSH [21, 24, 26–31].

Factors which govern ambient N_2O recorded in the dentists' breathing zone.

(a) *Sampling probe's distance from patient and operator*
The probe should be attached to the lapel of the operator that is at a distance of 21–25 cm from the operator's nose [21, 26, 27, 32]. However, later it was suggested that this distance should be 45 cm [20, 30, 31] to avoid interference from exhaled carbon dioxide and water vapor at a distance more closer to the operator's nose.

(b) *Room size and its ventilation*
Ambient N_2O levels were found to be higher in non-ventilated rooms whether scavenged [27] or non-scavenged [27, 33]. The ventilation (air change per hour and the degree of mixture with fresh air) helps in reducing the ambient N_2O level of a dental operatory. It is recommended that a dental operatory should have 6–7 air changes per hour [34].
In large-sized operatories, which are unscavenged, the N_2O levels reduce at a more rapid rate than in small-sized ones after cessation of the use of nitrous oxide. Large-sized operatories with better ventilation will have lesser ambient nitrous oxide levels. Also, scavenged operatories reduce ambient N_2O levels to baseline level more rapidly when compared to non-scavenged ones.

(c) *Type of nasal hood and its fit*
Porter Brown mask is considered to be most efficient for scavenging compared to other masks. The N_2O level in dentist's breathing zone was found to be in the range of 33–80 ppm in scavenged operatories and 375–1000 ppm in non-scavenged operatories. The fit of the mask does not matter if the scavenging efficiency of the mask is high like in Porter Brown. In masks where the

Fig. 4.42 Silhouette has the best fit due to its anatomic shape and softness. (*Courtesy: Porter Inc.*)

scavenging efficiency is not high such as the Matrx, poor fit of the masks will add to an increase in ambient N_2O concentrations. Silhouette mask has the best fit, thereby reducing leakage around the mask (Fig. 4.42).

Different facial characteristics such as the height of bridge of the nose and facial contours will affect the fit of the mask.

(d) Flow rate of gases and concentration of nitrous oxide used
If the flow rate of gases is more than desired (tidal volume of the child) as indicated by overinflated reservoir bag, then the gases are bound to leak from the periphery of the nasal hood. In such a situation, the ambient N_2O levels are higher [14, 35]. A higher level of ambient nitrous oxide is also found when a higher concentration of nitrous oxide is used.

(e) L*eakage from equipment*
Leakage from the equipment, mainly from the tubings or cracks in reservoir bag, contributes to a higher level of ambient N_2O.

(f) *Operator's technique such as use of rubber dam and high-speed evacuation*
Use of rubber dam can help in minimizing the mouth breathing, thereby reducing the ambient level of nitrous oxide (Fig. 4.43). Almquist and Young have found a reduction of ambient nitrous oxide by 30% when the rubber dam is used [36]. During the period of rubber dam placement, there was a rise in the ambient nitrous oxide levels probably due to open mouth during this time [14]. Also use of high speed evacuation during the operative procedures can help in removing the nitrous oxide gas around the patient's mouth. However, the effects of these variables in reducing ambient N_2O levels remain inconclusive.

In a study, it was found that nitrous oxide levels in surrounding air decreased from 192 to 109 ppm following rubber dam placement [21]. The decrease was not much because McGlothin demonstrated using infrared imaging that rubber dam placement simply redirected the nitrous oxide flow to the sides of the rubber dam [37]. This effect could be reduced by using high volume evacuation.

Fig. 4.43 Use of rubber dam can help in minimizing the mouth breathing

(g) *Patient's breathing pattern (mouth breathing)*
Mouth breathing during the operative procedure or incessant crying does contribute to increasing ambient nitrous oxide levels.

(h) *Procedure*
The exposure of a dentist may increase when the procedure is difficult due to longer duration of administration, a higher concentration of gas, or a child who starts to cry in the middle of the procedure.

4.2.7 Role of Ventilation

The ventilation of room is governed by the following [38]:

(a) Rate of air exchange: This is a major factor which governs the rate at which nitrous oxide gas is expelled from the operatory. In a dental operatory, this should be at least 6–7 air changes per hour. Rate of air exchange and ambient nitrous oxide concentration have an inverse relationship.

(b) Air conditioning: When compared to an office which relies on just doors and windows, air conditioning may contribute more actively to expulsion of nitrous oxide. However, Witcher et al. felt that air conditioning system plays a small role in influencing the amount of nitrous oxide inhaled by the dental personnel [39].

(c) Use of windows and fans: These usually contribute in increasing the air exchanges. The exhaust fans must be vented out of the building. The exhaust fans should be kept at a low level as nitrous oxide gas is heavier than air.
(d) Laminar flow of air: This is usually used in general anaesthetic operatories and not in dental operatories.

Good ventilation should be carried out during the nitrous oxide procedure and also 1 h after the completion of the procedure so that nitrous oxide can be cleared from the ambient air of the operatory.

Even the dental staff may act as "biological reservoir" after the usage of nitrous oxide is stopped as they may exhale nitrous oxide and may prevent a sudden decrease in the nitrous oxide level of a dental office. However, if they leave soon after the completion of the procedure, the ambient nitrous oxide levels tend to decrease rapidly [28].

Although some authors have suggested the use of exhausts close to the patient's mouth, placement of such an exhaust poses challenge for the dentist, as it reduces the working space. It will be even more difficult in pediatric dentistry because the procedures need to be performed quickly without any interferences, hindrances, and lack of maneuverability.

4.3 Conclusion

The main idea behind going into detail in much of the equipment in this chapter was to give some background information to the clinician on their normal functioning and more importantly to make him/her aware of the fact that despite all the fail safe mechanisms built into these machines, things can go wrong sometimes. If you are well aware of the normal function of something, then you are more likely to cognizant when things are not working as they should. In our offices, the whole team can be made aware of different components of the nitrous oxide machine and the common mistakes which can happen so that there is more than one layer of defense to prevent accidents from happening.

Also, scavenging and the fail safe are the important part of nitrous oxide delivery mixers to child patients and can be "tested" easily before every patient. All possible precautions should be taken to ensure minimum leakage of nitrous oxide inside operatory.

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Clinical Application of Nitrous Oxide in Pediatric Dentistry

5

Kunal Gupta and Priyanshi Ritwik

Contents

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Learning Objectives
1. To get acquainted with the process of introducing nitrous oxide to parents and children.
2. To realize the importance of basic behavior management techniques as an adjunct to the use of nitrous oxide.
3. To understand various aspects of using nitrous oxide in child patients.
4. To have a thorough knowledge about the need for monitoring, technique of monitoring, and operators response during the administration of nitrous oxide in child patients.
5. To be aware about the adverse events related to the use of nitrous oxide in pediatric population.
6. To be well versed with the documentation of nitrous oxide sedation in children.
7. To know about the importance of having a team for administration of nitrous oxide.

5.1 Technique of Administration

Proper technique of administration is critical for the success of nitrous oxide inhalation sedation, especially in pediatric patients. Since most of children are unable to communicate what they are experiencing during the course of inhalation sedation, the proper administration of nitrous oxide becomes extremely important.

5.1.1 First Nitrous Visit

First nitrous visit implies the visit when nitrous oxide is introduced to the child for the first time.

It is as important as the first dental visit. If the introduction of nitrous oxide, especially the mask, is done appropriately, then its successful administration in subsequent visits is very likely.

Objectives of the First Nitrous Visit
1. To familiarize the child with the technique of nitrous oxide, using euphemisms
2. To inform, demonstrate, and let the child experience (IDE—Inform, demonstrate, and experience) the nasal hood
3. To understand the cooperative ability of the child and decide if the child will be a good candidate for use of this technique

4. To explain the benefits of using nitrous oxide to the parents
5. To inform parents of possible minimal side effects
6. To examine the child properly, take records, radiographs
7. NOT to start the dental treatment on the first nitrous visit

Importance of Communication and Basic Behavior Management Skills

Careful use of the conventional behavior management/modification techniques, such as tell-show-do, modeling, and distraction along with tender, love and care, when introducing nitrous oxide inhalation sedation to children, will ensure the success of the first nitrous visit, which in turn is important for carrying out the treatment under nitrous oxide.

> Dentist's gestures, facial expressions, general behavior with the correct choice of words and tone of voice play an important role for acceptance of nitrous oxide by a child.

Steps of First Nitrous Visit

Introduction to nitrous oxide begins with an effective communication with the parents and understanding the temperament of the child.

Effective communication is the key to gain confidence of the parents through well-expressed explanation of the technique, expectations, and outcomes. A dentist should be able to speak with assurance to the parents for them to gain trust in this technique.

Child's behavior on the first dental visit is governed by various factors [1]. The prominent factors are child's developmental age and corresponding level of cognition. Recognition of the behavior is the stepping stone to successful first nitrous visit in children. Dentist's proficiency in gauging the child's willingness to cooperate is a major determining factor in introducing nitrous oxide effectively to facilitate a positive dental experience [2].

> Dentist's thorough explanation with conviction, of using nitrous oxide in children, plays a pivotal role in acceptance by parents.

1. Introduce the technique of nitrous oxide to the parents by explaining the benefits and purpose of using nitrous oxide inhalation sedation in their child (Fig. 5.1). However, a successful outcome using nitrous oxide for a highly anxious child should not be promised to the parents.

2. Explain that nitrous oxide is used because it helps in reducing anxiety in their child, relaxes the child, and also decreases pain to some extent during the procedure.
3. Following this, tell them that the child will have to breathe through the nasal hood throughout the procedure.
4. Inform them that nitrous oxide is very safe and has minimal side effects such as nausea/vomiting during the administration or slight dizziness/headache after the treatment.
5. Give preoperative instructions to the parents such as fasting for 2 h prior to appointment and that the child should not be having nasal congestion on the day of the procedure.
6. Following this, inform the child about using the technique using euphemisms such as let's do some exercise of deep breathing through the nose, let's see how big a balloon can you blow from your nose, and let's check how strong you are by the size of balloon you will blow.
7. Demonstrate the nasal hood to the child and how it has to be kept on the nose (Fig. 5.2). Sometimes modeling can be carried out on parents for children to understand the process in a better way (Fig. 5.3).
8. Let them experience the process of nasal breathing through the nasal hood. Let the child practice nasal breathing by keeping the mouth open. This enables the child to understand that he/she should not be breathing from the mouth during the procedure.
9. Gradually increase the concentration of nitrous oxide and let them experience the clinical effects of nitrous oxide.
10. Motivate the child that he/she did a good job and carry out positive reinforcement for subsequent visits.

Fig. 5.1 Introduction of nitrous oxide technique to parents

Fig. 5.2 Tell-show-do for nitrous oxide technique on a child patient

Fig. 5.3 Modeling of nitrous oxide technique on parent

Introduction of Nitrous Oxide Based on Different Behaviors

1. *Definitely positive child (a child who smiles, greets, and communicates with the dentist)*
   Introduction of nitrous oxide is simple, easy, and predictable for such children. It can be done in the manner outlined above (Fig. 5.4).
   Dental examination records, and radiographs can be done before introducing nitrous oxide to these children.

2. *Positive child (a child who does not smile or interact with the dentist in a carefree manner)*
   Establishment of good personal rapport is important for such children before the introduction of nitrous oxide to such children. Sometimes, modeling is the key to remove the initial inhibition of the child. Also use of situation appropriate euphemisms is beneficial for such children (Figs. 5.5 and 5.6a, b).

Ability to establish communication with the child is crucial for the acceptance of nitrous oxide nasal hood by him/her.

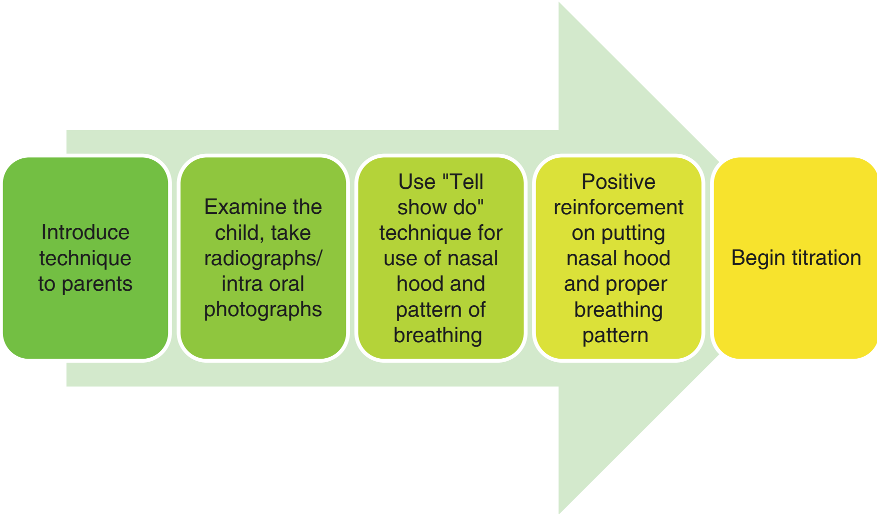

Fig. 5.4 Sequence of "first nitrous visit" for a child with definitely positive behavior

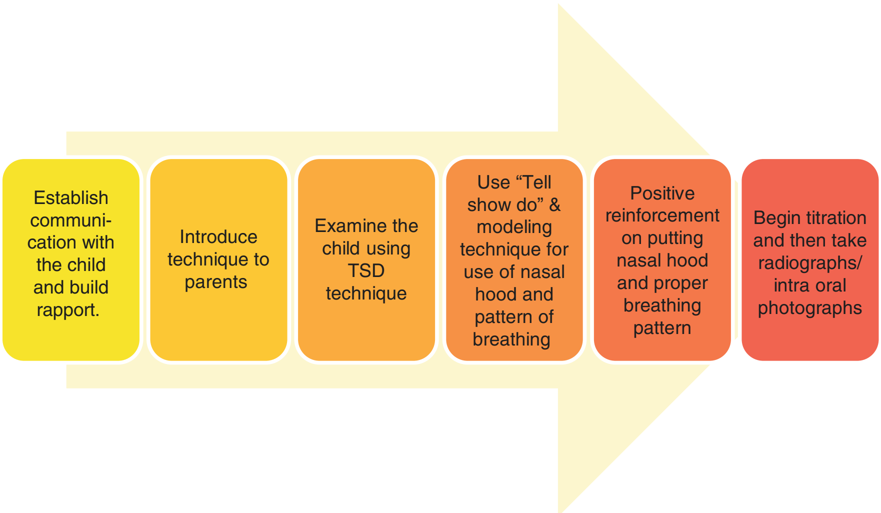

Fig. 5.5 Sequence of "first nitrous visit" for a child with positive behavior

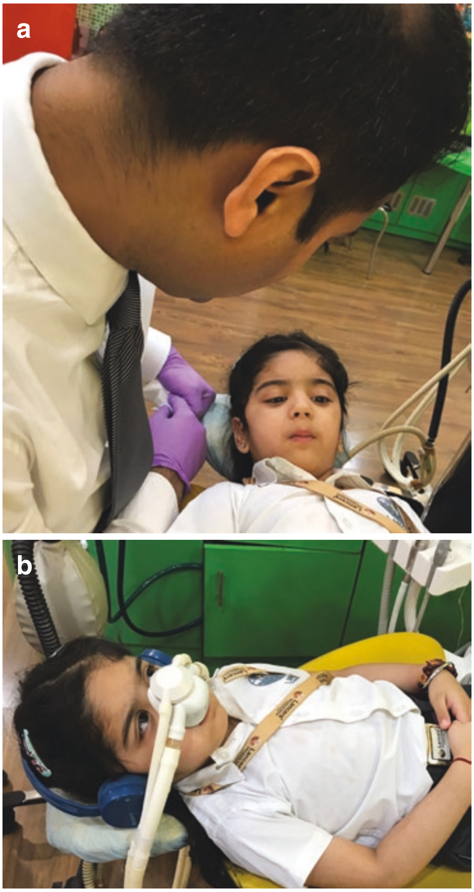

Fig. 5.6 (**a**) A child who does not want to make eye contact and talk to the dentist. (**b**) Child after using nitrous oxide looks relaxed

Dental examination, can be done before introducing nitrous oxide to these children, following which the child is explained and demonstrated about using nitrous oxide. Subsequent to this, records and radiographs are taken under the effect of nitrous oxide.

3. *Negative child (a child who hides behind parent, does not want to interact with the dentist, and asks the parents to take him/her away from the clinic/had a previous negative dental experience)*

Such children may already be anxious or fearful and hence will need more time to introduce nitrous oxide. Understanding the anxiety of the child by effective communication will guide the introduction of nitrous oxide. Nitrous oxide must be proposed to them using the following sequence. Firstly, explain to them about the new technique using euphemisms. Then, do modeling on self or parents or older siblings and let them see the movement of the reservoir bag which may encourage them to try the technique. Following this, let them experience that in their comfortable position which may be in standing position away from the dental unit (when the child is quite anxious probably due to previous negative dental experience) or sitting on parents lap on the dental chair. Audiovisual distraction can also be used for such children during the introduction of the nasal hood.

Sometimes, rapid titration (*Refer Sect. 5.1.5*) can be used to reduce the anxiety in a child quickly. Also, rapid titration can be used with a higher flow of nitrous oxide for children who do not want the mask to be placed very close to them or have a feeling of claustrophobia or may complain that they don't like the smell of the mask. The child should be placed in a supine position as this would cause heavier nitrous oxide gas to settle down around the nose [3, 4] (Fig. 5.7a, b). Once the child has inhaled some amount of nitrous oxide, then the mask may be placed closer to the child with a reduction in flow rate as well as the concentration of nitrous oxide. **This method**

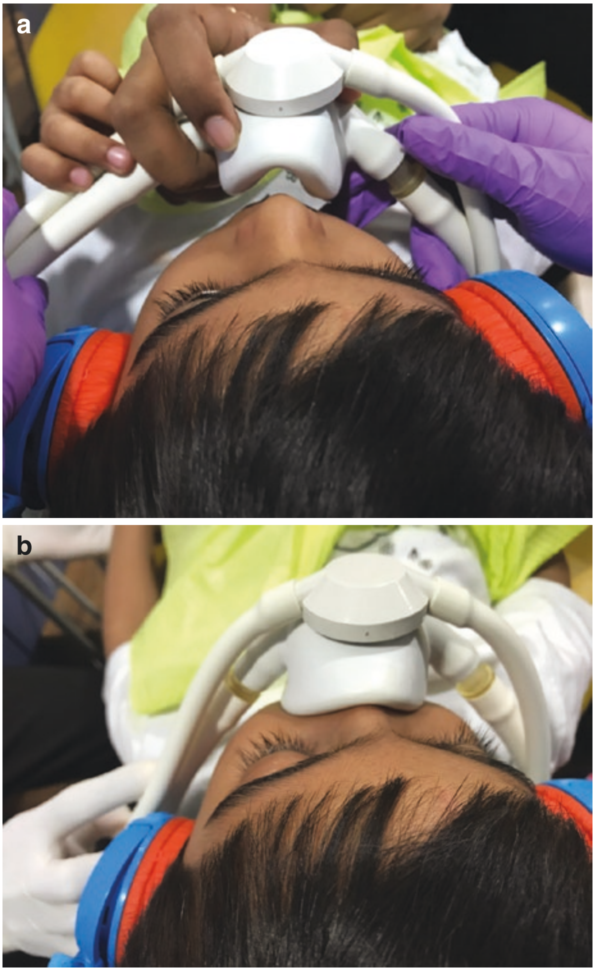

Fig. 5.7 (**a**) Nasal mask placed slightly away from the nose with the child in a supine position. (**b**) Nasal mask resting on the nose after the child's anxiety is reduced during rapid titration

should be seldom practiced as nitrous oxide gas would leak into the operatory from the nasal mask.

Rapid titration with a large-sized mask using high concentration and flow rate without resting on the nose may be used to reduce the initial anxiety in a child with negative behavior. However, this method carries the risk of contamination of ambient air in the operatory with nitrous oxide.

Dental examination is done under the effect of nitrous oxide following which records and radiographs are also taken under its effect (Figs. 5.8, 5.9a–c, and 5.10a–d).

4. *Definitely negative child (a child who cries without any provocation, pulls the parents outside the clinic, or does not want to enter the clinic)*

In children with this kind of behavior, it is important to let the child be only in formed about the technique. Experiencing the technique can be carried out on the subsequent visit. This is because in very anxious children, just the introduction of a new concept is a surprise. They have to be "sensitized" towards the technique for them to accept it. Parents should be informed that they can reinforce at home about the use of nasal hood before visiting the dental clinic for the subsequent appointment.

For a child with definitely negative behavior, the introduction of nitrous oxide may have to be postponed to the next visit.

If the parents are willing for slight physical restraint, then rapid titration along with physical restraint can be used till the child calms down. Use a large-sized mask, so that it covers both nose and mouth (ensure a proper seal is maintained around the nose and mouth to present any leakage of nitrous oxide into ambient air). Even if the child is crying initially, use of large-sized mask will ensure that the child is breathing in nitrous oxide (if a small-sized mask is used, child will not breathe in nitrous oxide if he/she is crying). Once the child calms down, large-sized mask should be quickly changed to an appropriately sized one.

This technique of restraint should be used in special circumstances such as when an emergency treatment has to be performed for a definitely negative child or the child does not require multiple visits and may be requiring just an extraction. Voice control or parents separation may also be used in these special circumstances (Figs. 5.11 and 5.12a–e).

Dental examination is also postponed for the "desensitization" visit. On the second visit, the child may be considered as one with "negative behavior," and dental examination, records, and radiographs carried out under the effect of nitrous oxide.

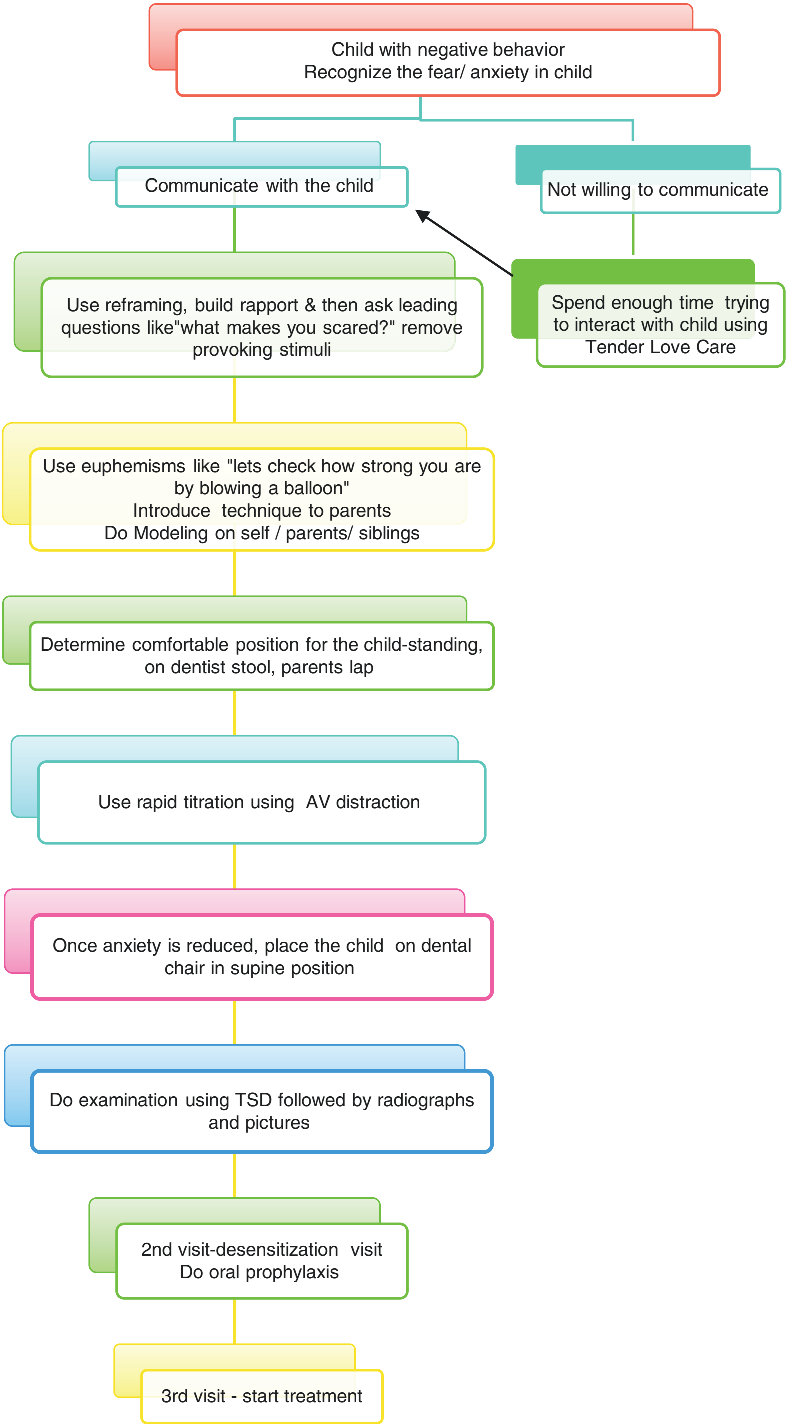

Fig. 5.8 Flowchart depicting sequence of first nitrous visit for a child with negative behavior

Fig. 5.9 (**a**) Negative child willing to communicate and ready to put mask in standing position. (**b**) After rapid titration, child agrees to sit on the parents lap on a dentist stool. (**c**) Child showing cooperation on parents lap in the dentist chair

Fig. 5.10 (**a**) Child with negative behavior. (**b**) Child not willing to communicate. (**c**) Child begins to communicate after tender love and care by the dentist. (**d**) Child willing for treatment on parent's lap

Desensitization Visit

This is an extra visit planned for children with negative or definitely negative behavior. During this visit, the child is allowed to inhale nitrous oxide for a while. When the child relaxes down, a proper dental examination is carried out along with records and radiographs using the tell-show-do technique.

After this, the child is also introduced to the compressed air from three way syringe, water spray from three way syringe, and also to the suction tube.

If the child is not accepting the mask or not ready for examination under the effect of nitrous oxide or not comfortable with suction and air, then the child should be considered for other modes of sedation such as oral/IV/IM or general anesthesia.

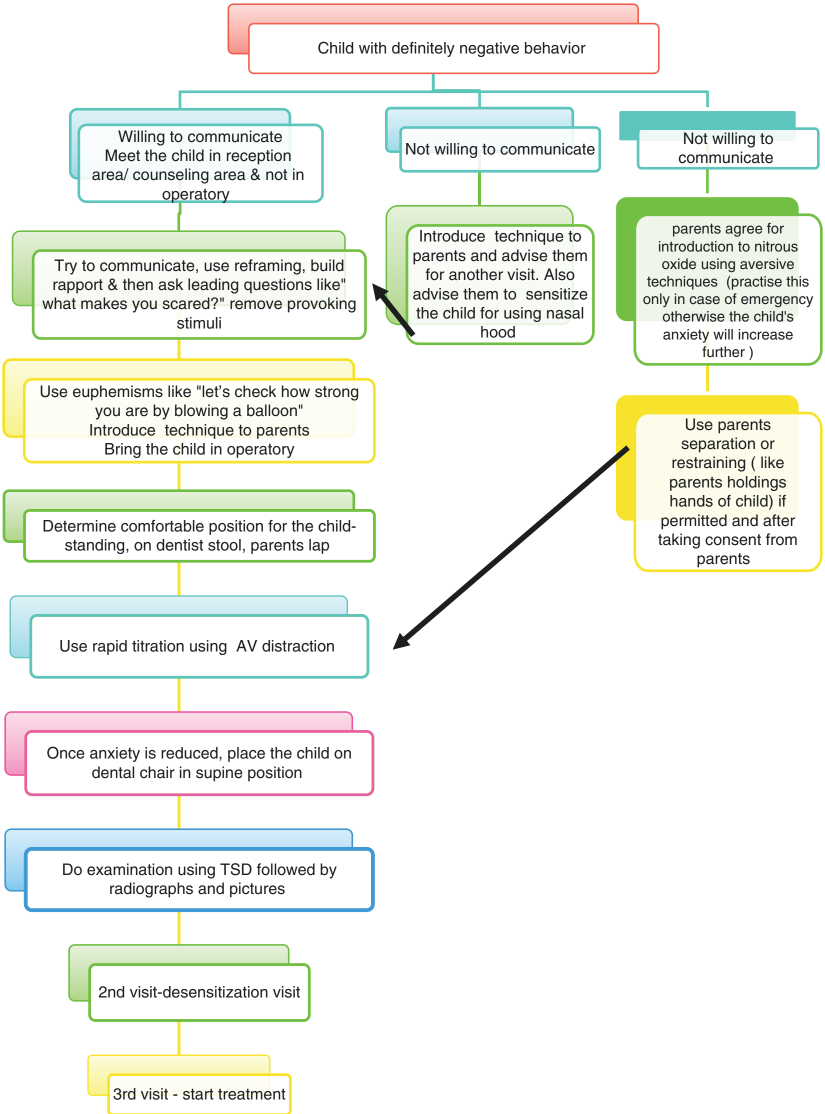

Fig. 5.11 Flowchart showing sequence of first nitrous visit for a child with definitely negative behavior

5.1.2 Pre-sedation Instructions

A certain set of instructions must be given to the parents for the day of the procedure, in order to perform sedation procedure effectively and to minimize the chances of possible adverse events.

Fig. 5.12 (**a**) Child with definitely negative behavior. (**b**) After much persuasion, child willing to observe nitrous oxide being demonstrated on parent. (**c**) Child agrees to accept nasal mask on parents lap. (**d**) Child cooperates for examination. (**e**) Child cooperates well for records

1. Child should not be having running nose on the day of the procedure.
2. Avoid eating 2 h prior to the treatment.
3. Light meal may be consumed up to 2 h before the procedure. Avoid fatty food (fried food) or milk/milk products (like pastries) up to 2 h before the procedure [5]. This is more important for children who have motion sickness (feel sick during traveling in car or aeroplane).
4. Child can consume water until just before the procedure.
5. Child should not be having stomach pain before the procedure.
6. Don't let the child wear contact lenses as the eyes may feel dry and sore [5]. (This is important for adolescents, as young children do not use contact lenses.)
7. Tight clothing should be avoided.

"Restrictions are for safety reasons since the reflexes are not reduced. However, there is no literature in support of this" [6]. Also, there is no consensus on this.

Readers can refer to Appendix VIII for the summary of four contemporary guidelines for pre-Inhalation Sedation instructions [7]. In view of this, we advise our readers to follow above mentioned instructions as a precautionary measure.

Pre-sedation fasting instructions vary in different guidelines, there being no consensus on the same.

5.1.3 Pre-administration Assessment

It is important to review the medical history (Table 5.1) and carry out a physical assessment before administering nitrous oxide sedation to a child [8].

Day of Treatment

Before starting the administration of nitrous oxide, recheck all the pre-sedation instructions given to the parents. Although these instructions do not require postponement of the treatment, nitrous oxide administration may be carried out with more vigilance. Advise the parents to make child visit restroom and void if necessary.

Recheck the medical status using following questions:

1. Does your child have asthma? If yes, when was the last attack?
2. Did your child have any recent URI?
3. Did your child have recent ear infections or surgeries?
4. Does your child have severe drug-related dependencies or emotional disturbances?
5. Is your child undergoing any treatment using bleomycin sulphate?
6. Does your child have MTHFR gene mutation?
7. Does your child have vitamin B_{12} deficiency?

If a child has nasal congestion, advise parents to postpone the appointment.

Table 5.1 Pre-sedation assessment of medical history and physical assessment

Medical history	Physical assessment
• Allergies or previous allergic/adverse drug reactions • Current medications including dose, time, route, and site of administration • Diseases, disorders, or physical abnormalities • Details of previous hospital admissions	• Respiratory system • Airway patency (nasal) • Breath sounds on inspiration and expiration

Fig. 5.13 Nitrous oxide unit kept behind the child to avoid developing anxiety

Positioning the Child Patient

Position the child in a semi-recline or supine position based on the comfort of the child. Some children may get anxious in supine position. For such children, it is better to place the child in semi-recline position, and as the anxiety level reduces on using nitrous oxide gas, the child may be placed in supine position.

In case, a portable unit of nitrous oxide is being used, it should be kept out of sight of child (behind the child patient), lest it may induce anxiety (Fig. 5.13).

5.1.4 Preparation of the Equipment

Before starting to administer nitrous oxide/oxygen to a child, a quick check of equipment should be done for proper function, flow, calibration, and fail safe mechanism (Refer Sects. 4.1.4 and 4.1.5). This should be done before the child is seated on the dental chair, otherwise it may lead to anxiety in a child. The gas cylinders should be opened and pressure gauges checked for the adequacy of gases in cylinders (in case of centralized supply, this is done once in the morning); exhaust tubing should be connected to high vacuum suction and checked for the optimal level of suction. Choose an appropriately sized nasal hood and attach it to the breathing circuit. Turn the machine on.

5.1.5 Titration

Nitrous oxide is always administered using the titration technique. This implies that there is no standard dosage for children based on the weight or age of a child, whereas the dosage/concentration is completely dependent on the clinical symptoms achieved.

> Titration of a drug is the process of determining the medication dose that reduces symptoms to the greatest possible degree while avoiding possible side effects.

The technique of nitrous oxide administration can be divided into two types:

1. Slow titration or the standard titration
2. Rapid titration

Standard Titration Method

In this technique, nitrous oxide concentration is gradually increased by 10% every 2–3 minutes.

Standard titration method is divided into the following steps (Fig. 5.14a–d):

1. Introduction phase
2. Induction phase
3. Injection phase
4. Maintenance phase
5. Withdrawal phase

Introduction Phase

*P*ress oxygen flush to fill the reservoir bag to two-thirds of its capacity and then place the nasal hood on the child's nose. Ensure that the mask fits comfortably on the child's nose. Nasal hood can be secured in place using the tubing clamp.

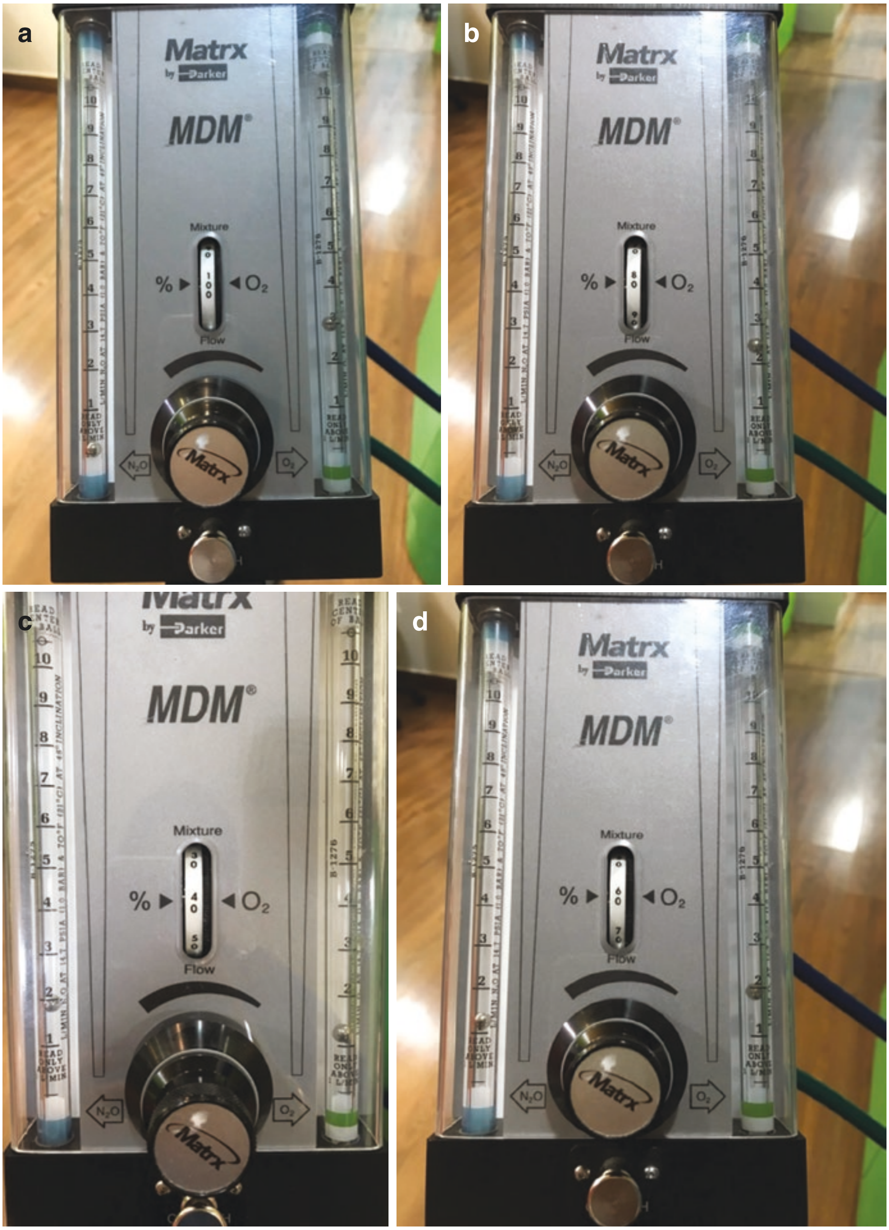

Fig. 5.14 (**a**) Introduction phase with 100% O_2 and flow rate of 3 L/min. (**b**) Induction phase with N_2O 20%, O_2 80% and flow rate maintained at 3 L/min. (**c**) Injection phase with N_2O 60%, O_2 40% and flow rate maintained at 3 L/min. (**d**) Maintenance phase with 40% N_2O and 60% O_2, flow rate at 3 L/min

In this phase, oxygen is administered for a period of 2–3 min in a concentration of 100% at a flow rate of 3–5 L/min (depending on the tidal volume of the child) (Table 5.2). Ask the child to take slow deep breaths.

Appropriate flow rate for the child should be determined at this stage. The flow rate is determined by ensuring that the reservoir bag is two-third filled. For example, if oxygen is being delivered at 3 L/min and the reservoir bag appears deflated, then increase flow rate of oxygen to 5 L/min. If the reservoir bag remains two-third filled at this stage, then the appropriate flow rate for this child is 5 L/min. However, if at 5 L/min, reservoir bag appears overinflated, then reduce flow rate of oxygen to 4 L/min to ensure that reservoir bag is now two-third filled and the appropriate flow rate for this child will be 4 L/min (Table 5.3).

Induction Phase

In this phase, the nitrous oxide concentration is gradually increased by 10% every 2–3 mins till the desirable clinical symptoms are achieved. The point at which the child begins to experience the desired clinical signs is known as the "Critical Point." This is usually manifested as hand/wrist drop, dropping off a toy or ball in child's palm, relaxed appearance on the face, and reduced eye ball movements. This is usually in the range of 35–50%. Reassure the child, motivate the child during this process, and inform the child about the expected feelings. Adjust the flow rate based on flowmeter based on the respiratory volume of the child.

As the nitrous flow rate is introduced, then the total flow rate of gases would increase (total of oxygen flow rate and nitrous oxide flow rate). To maintain the same flow rate as deciphered during the introduction phase, oxygen flow rate should be reduced slightly to ensure the total flow rate remains the same (this has to be

Table 5.3 Table showing steps for determining the adequate flow rate for a child

	Oxygen (L/min)	Nitrous oxide	Reservoir bag	Total flow rate (L/min)
Start	3	–	Deflated	3
Few seconds later	4	–	Less than two-third	4
Few seconds later	5	–	Over inflated	5
Few seconds later	4 1/2	–	Two-third fill (appropriate flow rate)	4 1/2
After 2 min	3 1/2	1 L/min	Two-third fill	4 1/2
After 2 min	2 1/2	2 L/min	Two-third fill (critical point)	4 1/2

Table 5.2 Table showing tidal volume and respiratory rate at different ages

	Tidal volume (mL)	Rate	Total (mL/min)
Infant	75–125	30/min	2250–3750
Child	200–250	20–24/min	4000–6000
Adult	400–450	12–18/min	4800–8100

done in analog flowmeter Porter MXR; however, in analog flowmeter Matrx MDM, this is not required as there is a provision for auto adjustment of flow rate).

Injection Phase

When some painful procedure has to be performed such as the injection of local anesthesia or extraction of an abscessed tooth, the concentration of nitrous oxide should be increased to 50–60%, 2–3 min prior to the painful stimulus. Slow injection and verbal distraction may be done during while injecting or during extraction.

> Injection phase of nitrous oxide uses a higher concentration of nitrous oxide to produce better analgesia.

Maintenance Phase

Once the injection has been given, the nitrous oxide concentration is again brought about to the level at which the desired clinical symptoms were achieved. Keep reminding child, intermittently, to breathe through the nose.

Withdrawal Phase

After the dental procedure has been carried out, the nitrous oxide concentration is reduced to zero, thereby increasing oxygen concentration to 100%. The child is administered oxygen at this concentration for a period of 5 min.

Discharge or Seeing Off the Child

The child should be asked the following after he/she gets up from the dental chair

1. Are you feeling fine?
2. Are you feeling dizzy?
3. Are you experiencing any headache?
4. Do you have nausea? or are you feeling sick?

Inform the parents that the child is absolutely fine and may resume normal activities soon after exiting from the dental clinic.

Rapid Titration Method

> In this method, titration begins from a higher concentration of nitrous oxide and is gradually brought down to the maintenance level.

Rapid titration method is divided into the following steps (Fig. 5.15a–d):

1. Explosion phase
2. Maintenance phase
3. Withdrawal phase

Fig. 5.15 (**a**) Rapid titration with 60% N_2O and 40% O_2 and higher flow rate of 6 L/min. (**b**) Nasal mask covering nose and mouth to ensure that the child is inhaling most of nitrous oxide delivered to him. (**c**) N_2O reduced to 50% after child stops crying with flow rate maintained at a higher level. (**d**) N_2O reduced to maintenance level like 40% and flow rate reduced to 3 L/min

Explosion Phase

During this phase, nitrous oxide is administered at a high concentration (in the range of 55–65%) for the first few minutes, till the child begins to calm down.

Maintenance Phase

The nitrous oxide concentration is brought down to the level at which the desired clinical symptoms can be maintained or below which the desired clinical symptoms cannot be achieved.

Withdrawal Phase

After the procedure is carried out, the child is administered only oxygen at a concentration of 100% for a period of 3–5 min or little longer till the child appears normal as before.

Indications for Rapid Titration

1. Negative or definitely negative child.
2. Emergency treatment to be carried out for a child.
3. Introduction of nitrous oxide to a special child

5.1.6 Duration of Administration

Using nitrous oxide inhalation sedation, it is always advisable to practice quadrant dentistry for which 15–60 min may be required depending on the extent of decay and the type of procedure required. Duration of administration is also governed by the clinical signs of sedation. In a few children, as the time passes by, the child may start showing signs of increasing level of sedation, that is moderate sedation. At this juncture, it is prudent to reduce the concentration of nitrous oxide being administered to the child by 5–10%.

Also children who receive nitrous oxide for more than 30 min need more time for recovery (should be administered 100% oxygen for at least 5–7 min).

> There is no fixed limit on the duration of administration of nitrous oxide to a child. It is dependent on the time required by an operator to complete the procedures and also on clinical signs of sedation in a child.

5.1.7 Size of the Nasal Mask

Size of the nasal mask to be used is dependent on the length of the nose and the size of nostrils. Usually, a small-sized mask can be used for children less than 5 years old and medium-sized mask used for children 5–12 years.

If a smaller nasal mask is used, it may cause a feeling of claustrophobia. If a large-sized mask is used than desired, then it may cover the upper lip and may interfere with the intra-oral procedures. It may also cause leakage from the upper border

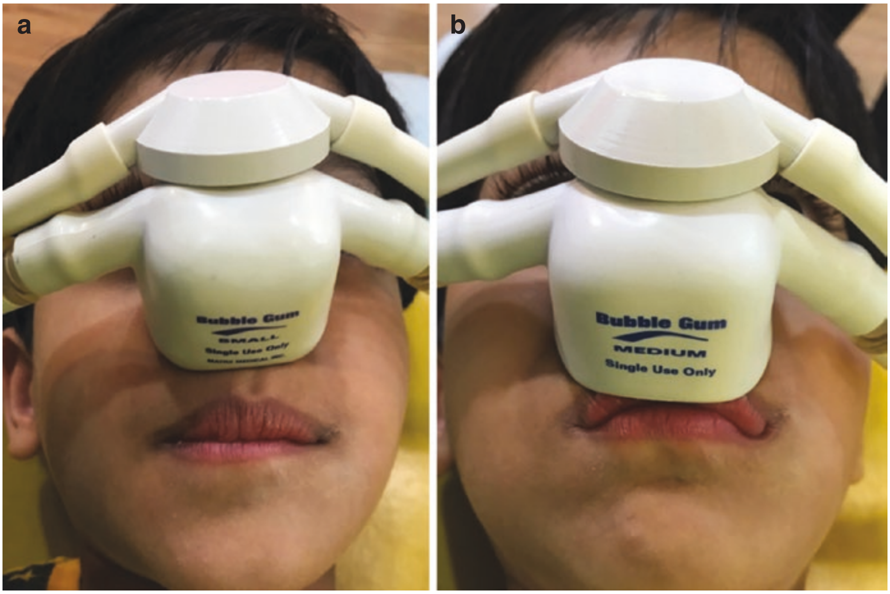

Fig. 5.16 (**a**) Figure showing correct placement of nasal mask. (**b**) Figure showing incorrect placement of nasal mask

leading to watering of eyes. The correct positioning is that the lower border of the mask should rest on the philtrum and not on the upper lip (Fig. 5.16a, b).

5.1.8 Concentration of Nitrous Oxide

Nitrous oxide sedation is an individual response, and it is inappropriate to recommend a specific or even mean concentration of nitrous oxide that would be an analgesic dose [9].

Most desirable concentration of nitrous oxide varies from child to child. Also the concentration may vary in the same child on different days. A child who is tired after school may require a lesser concentration of nitrous oxide.

Concentration for Procedures

Certain procedures require higher concentration (50–60%) as higher concentration provides better analgesia. These procedures include extraction, administration of local anesthesia, and gingival abscess drainage. Also a child who is rebellious or showing temper tantrums would need a higher nitrous oxide concentration till the child's anxiety is reduced.

> Invasive procedures like the administration of local anesthesia, extraction, and drainage of an abscess may require a higher concentration of nitrous oxide.

Other procedures like fluoride application and sealant application require lower concentration (30–35%) of nitrous oxide because the requirement for analgesia is negligible. However, this is again dependent on the pain threshold of the child. Few children may require slightly higher concentration for these procedures as well.

Actual Concentration Inhaled by a Child

Actual concentration inhaled by the child varies considerably (much lower) than what is being delivered by the flowmeter. This is because of the leakage which might be taking place at various levels, such as the area around the nasal hood and from the mouth (due to intermittent mouth breathing in many children and also due to talking) (Fig. 5.17).

Other factors which reduce the effective nitrous oxide concentration to the child are as follows [10]:

1. Incorrectly calibrated flowmeters.
2. Improperly adjusted scavenging rates.
3. Ill-fitting nasal mask which causes mixing of nitrous oxide with ambient air [11]
4. Sudden movement of the head in an uncooperative child, which dislodges nasal mask from the nose, and again causes mixing of nitrous oxide gas with ambient air.

> Nitrous oxide concentration in nasopharynx is much lower than the concentration being delivered by the flowmeter due to leakage at various sources.

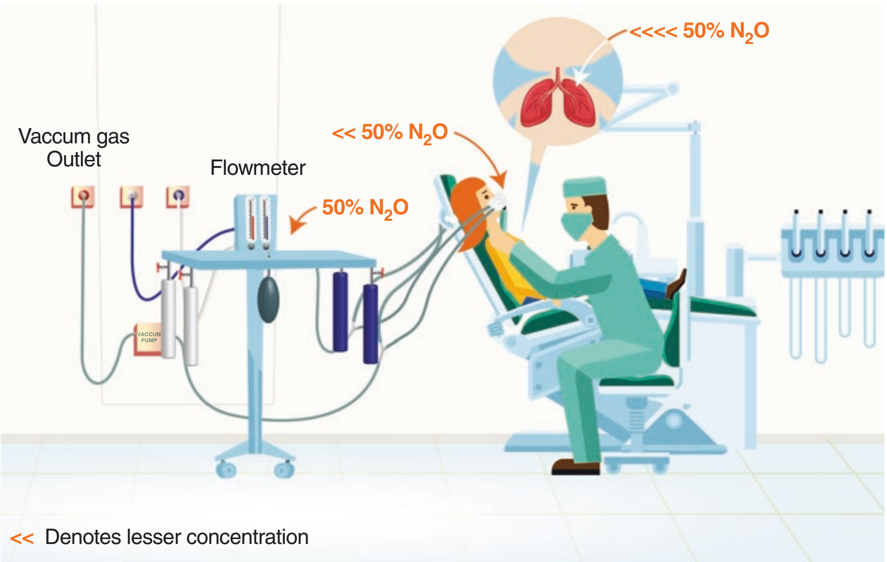

Fig. 5.17 Figure showing reduction of nitrous oxide concentration at various levels with actual concentration reaching nasopharynx being much lower than the concentration set at the flowmeter

A study reported in 2004 (Klein, Bucklin) [10] stated that there is a decrease by 31% of nitrous oxide delivered from the flowmeter to the nasal mask and by another 19% from nasal mask to nasopharynx. Thus, nitrous oxide concentration in nasopharynx was found to be lower by 50% of concentration set at flowmeter. ***However, this study was carried out in adults and authors also concluded that results could not be applied to children directly due to anatomical differences between the children and adults.*** Few other interesting findings of this study which could have clinical implications are as follows:

1. Nitrous oxide could be measured in the nasopharynx only when the flowmeter setting is greater than 20%. This implies that nitrous oxide flowmeter setting should start with 20% when the administration of nitrous oxide commences.
2. There were considerable inter-individual differences in nasopharyngeal N_2O concentrations, with identical flowmeter settings. This implies that every individual will have different nasopharyngeal nitrous oxide concentration irrespective of similar flowmeter settings. Hence, even the clinical response will be different for individuals.
3. During the period of increasing nitrous oxide concentrations, expired nasopharyngeal N_2O concentration was 22% lower than the inspired concentration, and it took 2 min for both the concentrations to become equal. This implies that the concentration of nitrous oxide should be gradually increased in increments of 10% every 2 min.

In another study (Klein, Robinson, Allshouse, 2011) [12] conducted on children (6–9 year old), it was found that an expired concentration was 63% less than that dispensed by the flowmeter. However, authors concluded that patient movement did not affect the gas delivery. They also inferred that on an average 90 s are required to reach the maximum N_2O saturation after rapid induction with 50% N_2O.

Increasing the Efficacy and Potency

The efficacy of the inhaled nitrous oxide can be maximized by the following:

1. Child should not be having any nasal congestion so that the child does nasal breathing completely. Instruct the child to breathe into and out of the mask.
2. Child should be discouraged from talking. Avoid unnecessary conversation.
3. Child should not be breathing from mouth.
4. Use snugly fitting nasal hood.
5. Use rubber dam to ensure a good seal around the mouth which prevents mixing with atmospheric air. The upper border of the rubber dam should be placed over the nasal hood and not below the nasal hood.

If the above mentioned factors are taken into consideration, then the concentration of nitrous oxide required by a child can be minimized and the potency of the gas can be maximized.

> Efficacy and potency of nitrous oxide being administered to a child can be maximized by preventing leakage at various sources.

Table 5.4 Table showing effect of altitude on nitrous oxide concentration to be used

	Sea level	Altitude 2000 m
Barometric pressure	760 mm	600 mm
pCO_2	40	40
Water vapor pressure	47	47
Pressure exerted by gases delivered by flowmeter	760 − 40 − 47 = 673	600 – 40 − 47 = 513
Nitrous oxide pressure at 35%	35% of 673 = 235	35% of 513 = 180 45% of 513 = 231

Sensitization

The level of nitrous oxide can be titrated down at subsequent visits due to its placebo effect.

Effect of Altitude

Higher concentration of nitrous oxide is required at a higher altitude (Table 5.4).

Thirty-five percent of nitrous oxide at sea level will have same sedative effect as 45% of nitrous oxide being administered at an altitude of 2000 m above sea level.

5.1.9 Continuous Flow Technique

The technique described so far is known as the continuous flow technique, where a continuous flow of the gases is maintained irrespective of the respiratory volume of a child. Therefore, it is beneficial for children who may not follow instructions properly or may have shallower respiration. Demand flow technique, which is obsolete now, required an inspiratory effort to activate the gas flow, which was impractical and unachievable in children.

> Continuous flow technique has improved the ease of administration of nitrous oxide to children.

5.1.10 Special Considerations during the Administration of Nitrous Oxide in Children

- ***Upper respiratory tract infection***
  Upper respiratory tract infection makes it difficult for a child to breathe through the nose, thereby reducing the efficacy of nitrous oxide sedation in children. Also, on nitrous oxide inhalation, air in the middle ear chamber gets replaced with nitrous oxide. In chronic nasal congestion, the eustachian tube also gets congested, thereby limiting the ability of air pressure to equilibrate between the middle ear and the oropharynx. This may produce bulging, fullness, tingling of the tympanic membrane, or earache. An appropriate dose of anti-histamines or nasal sprays or decongestants can be used prior to the appointment.

- **Mouth breathing**
  Child who has no obstructive cause to mouth breathing should be trained by a constant verbal reminder to breathe through the nose. A modified hand over mouth or wet towel over mouth method can be carried to ensure nasal breathing. If mouth breathing is related to anxiety, after initial euphoria and relaxation caused by nitrous oxide, nasal breathing would take over mouth breathing.
  For children with an obstructive cause, nitrous oxide is administered using a technique known as "Insufflation." [3, 4] In this technique, after the placement of rubber dam, one end of nitrous oxide tubing can pass under the rubber dam, filling oropharynx with nitrous oxide. The other tube is clamped off.
- **Obese child**
  An obese patient may feel uncomfortable breathing through the nose when positioned in a supine position, as abdominal contents press on the diaphragm. In such a scenario, the child should be positioned in an upright position and the dentist would have to compromise on his/her preferred working position [3, 4].
- **Claustrophobic patient**
  Use of nasal cannula with continuous flow system should be considered.

5.1.11 Success of Nitrous Oxide Sedation in Children

Nitrous oxide inhalation sedation should not be considered as a magical wand for behavior management of children. The children may accept nitrous oxide sedation well but may not be willing to accept the dental treatment completely. For example, the child may be putting the nasal hood or may like using the nasal hood, but when the child is asked to keep the mouth open, the child may not agree. At the same time, the child would like to continue using the mask or show unhappiness if the mask is removed.

Clinical success of nitrous oxide sedation has been reported to be in the range of 85–95% by various authors [2, 14–17]. It is dependent on previous anxiety, fear level of a child, any previous traumatic dental experience, and the ability to communicate and cooperate [18, 19].

> A major determining factor for the success of inhalation sedation in pediatric dentistry is dependent on the dentist's ability to judge the cooperative ability of a child and child's willingness to support the dentist in the dental treatment [20].

Factors such as age, sex, complexity of the dental procedure, and the type of dental procedure, do not govern the success of nitrous oxide inhalation sedation in children [13]. A wide variety of individual attributes govern the success of nitrous oxide inhalation sedation in children. Various authors have stated that the children with difficult temperament usually result with unsuccessful inhalation sedation [21–24].

Role of the dentist is also important to govern the success of inhalation sedation in pediatric dentistry. Children who may fail to be treated using nitrous oxide inhalation sedation should be considered for oral sedation or general anesthesia rather than letting them develop negative dental experience.

A dentist should be able to determine the fear or anxiety in a child's mind, handle them with tender love and care, and also apply basic behavior management skills, which helps in handling children with difficult temperament.

Factors used to assess that nitrous oxide may be unsuccessful in a child
Child does not want to enter the clinic
Child is constantly crying
Child is less than 40 months old
Child does not communicate with the dentist
Child with special health care needs

Reasons for Failure with Nitrous Oxide

- Ineffective communication
- Ignoring or failure in recognizing anxiety in a child
- Incorrect evaluation of child's compliance
- Poor behavior management
- Excessive interference from parents
- Failure in managing pain
- Using pharmacological pain measures after the occurrence of pain
- Not practicing fragmented treatment for children with attention and cooperation deficits

5.2 Monitoring

Monitoring during nitrous oxide inhalation sedation is the key to safe and efficacious sedation appointment. The entire monitoring process of inhalation sedation in children is focused around maintaining the minimal level of sedation and preventing it from going to a moderate-deep level of sedation.

Monitoring is defined as the continuous observation of response from specific organ systems to evaluate the status of physiologic function [25].

5.2.1 Purpose of Monitoring

1. Clinically determine the level of sedation
2. To promptly recognize deviation from normal
3. To determine the level of consciousness
4. Establish verbal communication with the child at regular intervals
5. Clinically determine oversedation, if present
6. Monitor respiration

Respiratory system is considered to be the most important system for monitoring of pediatric patient sedation other than cardiovascular and central nervous system.

5.2.2 Types of Monitoring

1. Clinical observation
2. Electronic devices

Electronic devices used for monitoring should ideally be continuous or "real time," accurate, dependable, convenient, affordable, rapidly responsive, and noninvasive.

> Proper monitoring helps to maintain the child in a minimal level of sedation.

Clinical Observation

(a) *Establishing communication with the child* (Fig. 5.18)
- Purposeful response is a clear indicator of minimal sedation
- There should be minimal time lag between the operator's questions and the child's response.
- In pediatric dentistry, the operator cannot allow the child to talk while carrying out dental procedures. Therefore, the operator should ask questions which just need a nod. For example, "are you ok?"; "are you doing fine?"; "can you raise your left hand?

(b) *Observing facial and eye response* (Fig. 5.19)
- Repeated mouth closing is a sign that the child is going towards moderate sedation. This sign can be missed if a mouth gag is being used. The jaw appears more rigid because of muscular contractions.
- The eye response is not very definite in children. Usually in adolescents, a slight drooping of upper eye lid may be seen. In younger children, this may not be very evident.

Fig. 5.18 Establishing communication with the child by asking the child to raise left hand

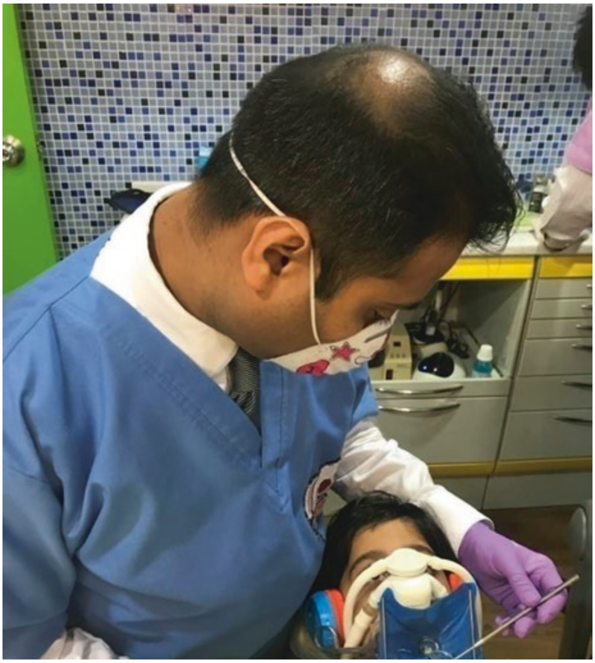

Fig. 5.19 Operator checking the child's facial expressions during the procedure

- Eye ball movements are reduced in minimal sedation. Fixed eye balls or a stare-like appearance or dazed look is an indication of moderate level of sedation.
- Closing eye lids is also an indication for moderate sedation
- Flushing on face is an indication of oversedation
- Sweating on forehead, neck creases, or scalp is also a sign of oversedation

(c) *Observing movement of reservoir bag* (Fig. 5.20)
- It is best to have an assistant who has been assigned to observe the movement of reservoir bag intermittently, while carrying out his/her work. Movement of reservoir bag monitors the respiration of a child.
- Reservoir bag should always be two-thirds fill so as to visualize its movements clearly.
- If the movement of reservoir bag is not appreciated well, it is best to verify by checking the placement of nasal mask, pressing the nasal mask gently over the nose to reduce any leakage. This will usually make movement of reservoir bag more noticeable.

Fig. 5.20 Dental assistant intermittently checks for movement of reservoir bag, during the procedure

(d) *Observing thoracic or abdominal movement* (Fig. 5.21)
- In case, the movement of the reservoir bag is not noticeable due to shallow respiration, then the abdominal movement or chest raises help in confirming the respiratory movements.
- Visual observation of respiratory excursions needs continuous and close attention, which is not practical for the operator. Also, shallow respirations in children are sometimes difficult to be appreciated because of clothing or drapes.
- Sudden and exaggerated movement of thorax or abdomen is usually a sign of adverse event—vomiting. This is usually seen before a child has regurgitation or vomiting.

Establishing communication with the child at regular intervals is the key to a successful monitoring.

Fig. 5.21 Operator looking for chest raises during the procedure by movement of the patient drape

Signs of Oversedation

To summarize signs of over sedation are as follows:

1. Fixed eyes—no eye ball movement is seen or is minimal (Fig. 5.22).
2. Flushing of face—face appears stern and red in color.
3. Sweating on scalp, neck, back, and palm (Fig. 5.23).
4. Abnormal breathing pattern or abnormal breath sounds.

Electronic Devices

One of the simplest and useful monitoring tools is pulse oximetry. It is a non-invasive instrument whose probe is attached to the child's finger/big toe or ear (Fig. 5.24a, b). This device helps to determine the oxygen saturation and the cardiac rhythm during the procedure.

Fig. 5.22 Fixed eyes with no eye ball movement

Fig. 5.23 Sweating on forehead is a sign of oversedation

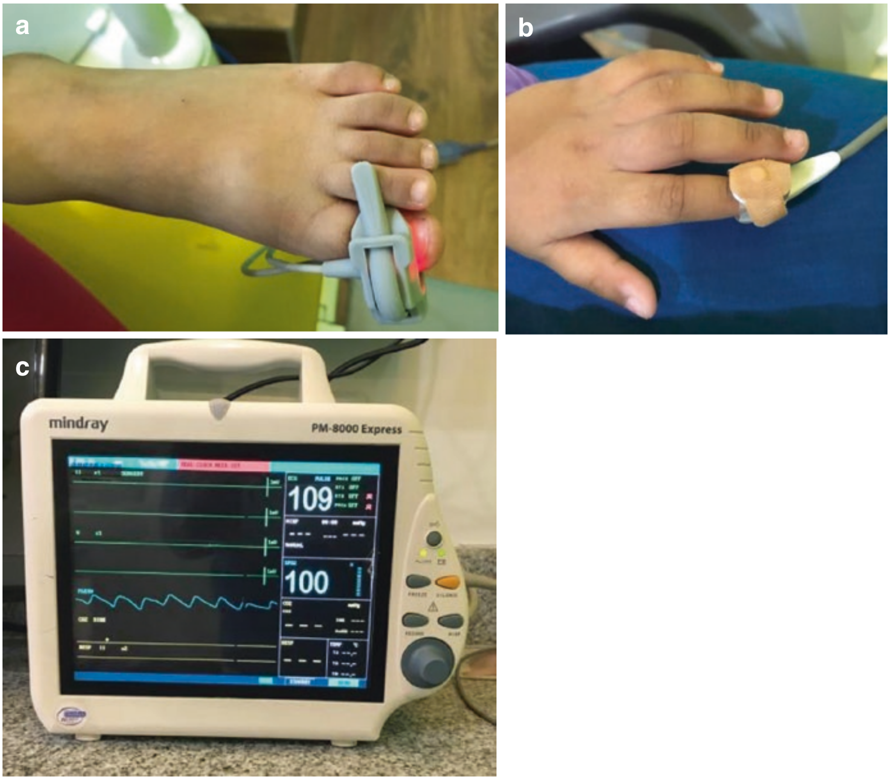

Fig. 5.24 (**a**) Pulse oximeter sensor attached to big toe. (**b**) Pulse oximeter Nellcor sensor attached to index finger. (**c**) Multiparameter monitor showing oxygen saturation in numerical and graphic form

Pulse oximeter is a valuable monitor because it is very accurate and rapidly responsive. It requires no calibration, warm up time, or tissue preparation. It can detect hypoxemia much before the clinical signs and symptoms of it are manifested.

Oxygen desaturation rarely occurs during inhalation sedation with nitrous oxide. In fact, there is always a good concentration of oxygen being received by the child (usually 65–50% if the child is receiving 35–50% nitrous oxide). It has been stated that the maximum concentration of nitrous oxide recommended for dental operations is 55% in which there is no chance of hypoxemia [26–28].

It is very sensitive in detecting hypoxemia than visual assessment. Oxygen desaturation can only occur in cases of airway obstruction, which is rare during minimal sedation. Even a slight decrease in oxygen saturation based on pulse oximeter needs attention and prompt action. This is more important in children due to their high basal oxygen consumption and less oxygen reserve, owing to their small size. As a result, desaturations occur more rapidly in children. Saturation levels above 95% are preferable for a child and anything below 90 should be a cause of definite concern.

In a study carried out in adults, it was found that 96.88% of patients did not experience arterial blood oxygen desaturation [29].

Limitations of using pulse oximeter in children

- A child tends to move his/her finger or toe which may displace the sensor thereby giving false reading.
- A child, at times, may not allow the operator to put the sensor on finger or toe.
- It may increase anxiety in a child or even parents.

Some dentists consider the use of pulse oximeter as absolute necessary during inhalation sedation using nitrous oxide [28]; others do not find it necessary but only prefer to use it [30] while some dentists do not prefer to use it at all because of its limitations mentioned above [31]. **However, according to the guidelines by the American Academy of Pediatric Dentistry, use of pulse oximetry is not required when nitrous oxide is used alone for sedation in pediatric patients. Authors would recommend, recording of baseline oxygen saturation levels in case of children with prexisting systemic diseases such as congenital heart disease, obstructive pulmonary diseases, sickle cell disease etc. In cases where nitrous oxide inhalation sedation is being used for children in ASA III or IV, pulse oximeter may be used during the procedure.**

Bispectral Index System

This monitoring technique is best suited for non-anesthesiologists. It is used to measure the level of sedation following the use of anesthetic or sedative agent. It is electroencephalogram-based cerebral activity measurement, which is computer processed. The score ranges from 0 to 100, with 0 representing the state of no brain activity and 100 representing an awake state (Fig. 5.25).

40–60 general anesthesia
61–70 deep sedation
71–90 moderate sedation
>90 awake

It represents a noninvasive and continuous method for assessment of the level of sedation [32]. It also increases clinicians comfort and improves safety. It may allow a clinician to objectively determine deepening of sedation and take appropriate steps to reverse that.

Use of Bispectral index is not of significance when the nitrous oxide is used alone as it is meant to bring about minimal sedation. It will be of importance when nitrous oxide is combined with other drugs such as midazolam to produce moderate sedation.

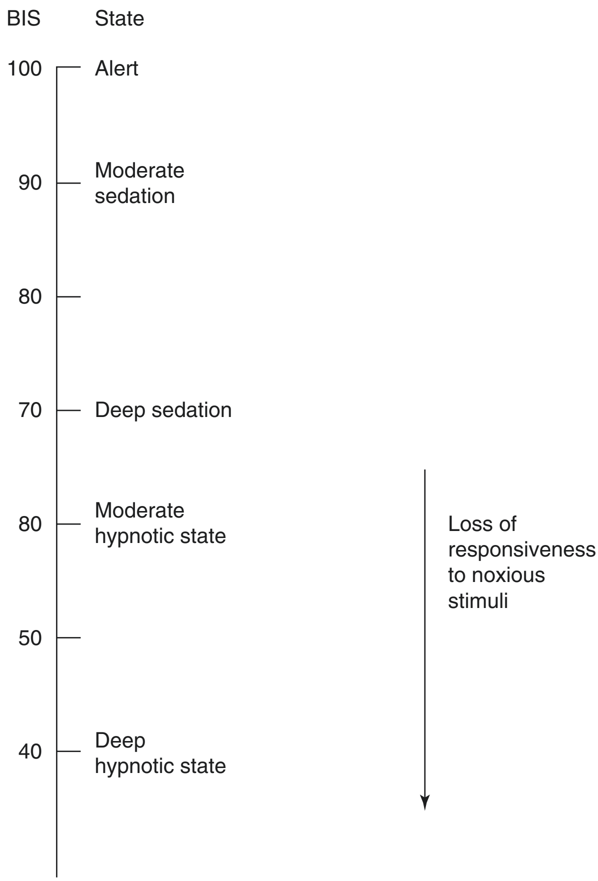

Fig. 5.25 Bispectral index

It has been found that BIS did not change with inspired nitrous oxide concentrations up to 50% [33]. Two researches showed that no change in BIS value was seen even up to 70% nitrous oxide concentration even though the patients lost consciousness clinically [33].

Also, in children, it is difficult to perform bispectral index system.

> Electronic monitoring may not be very accurate in children.

Capnography

Capnography is the measurement of carbon dioxide in the patient's exhaled air over time. It measures end-tidal carbon dioxide which is the amount of carbon dioxide released at the end of expiration. This is essential for assessing proper oxygenation and metabolism in the body. High $eTCO_2$ is indicative of hypoventilation and increased metabolic activity. On the other hand, low $eTCO_2$ is indicative of hyperventilation and decreased metabolic activity. Hence, purpose of capnography is to detect the presence or absence of ventilation and the depth of respiration.

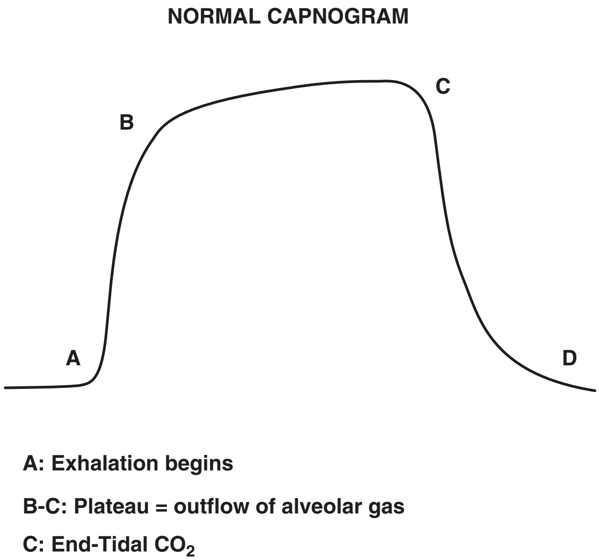

Fig. 5.26 Normal capnograph

Capnography has a role to play during moderate sedation and therefore is not of significance when nitrous oxide is used alone [34] (Fig. 5.26).

Sedation Scales

Sedation scales are quantitative and subjective indication of the level of sedation. The most popular one for pediatric patients is the Houpt Sedation scale (Appendix IX). It measures different parameters such as sleep, movement, crying, and behavior.

Another one is the Observer's Assessment of Alertness and Sedation scale (OAA/S) (Appendix X). It measures the level of alertness in sedated subjects based on the assessment of four categories: responsiveness, speech, facial expression, and ocular appearance.

Ramsay Sedation scale (RSS) is a well-established tool for the evaluation of sedation which is easy and inexpensive to perform (Appendix XI). However, sedation scales are not objective methods.

5.2.3 Operator's Response to Monitoring

During the process of monitoring, if the operator feels that the child is proceeding towards a moderate level of sedation, then he/she should reduce the concentration of nitrous oxide by 5–10% and observe for a decrease in signs of oversedation. If not then, the nitrous oxide concentration should be decreased further by 5–10% (Fig. 5.27). This process of gradual reduction in the concentration of nitrous oxide should be carried on till the desirable clinical signs are achieved.

> If the child goes into a moderate level of sedation, then the nitrous oxide concentration should be reduced by 5–10% till the child is in level of minimal sedation.

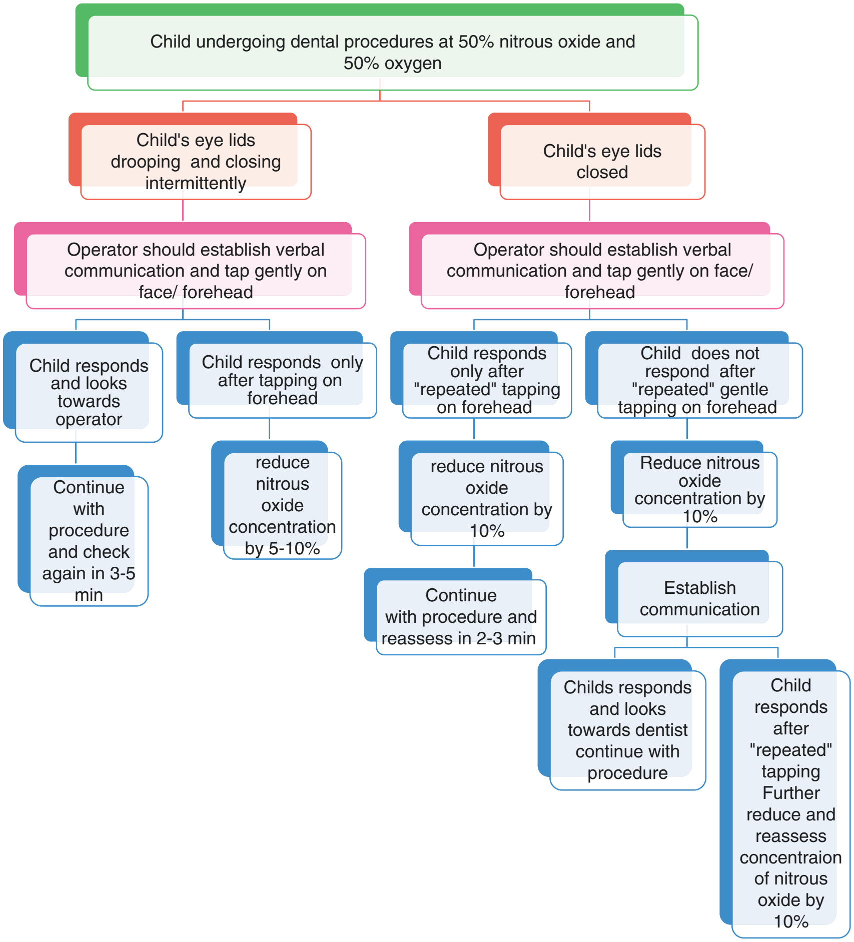

Fig. 5.27 Operator's response during monitoring

5.3 Adverse Events

Nitrous oxide is a commonly used agent for minimal sedation in pediatric dentistry. Nitrous oxide is easy to administer and produces predictable and desirable clinical effects, namely anxiolysis, analgesia, and amnesia. Its effects are completely reversed prior to discharging the patient by flushing with 100% oxygen for 5 min. Due to its high safety profile, ease of use, and acceptance, nitrous oxide remains an important adjunct to behavior guidance for pediatric patients. However, no procedure is free of side effects or complications. There are risks and adverse events that necessitate practitioner's vigilance when considering the use of nitrous oxide.

An adverse event can be defined as any untoward medical occurrence in a patient which does not have a causal relationship with the drug being used.

The adverse events related to the use of nitrous oxide are not serious or life threatening if treated promptly [35]. Most common "intra-administration" adverse events can be hallucinations, dreams, or development of nausea and vomiting.

Broadly, adverse events related to nitrous oxide sedation may be categorized as minor and major adverse events. The classic minor adverse events discussed in literature include dizziness, headache, perioperative/postoperative nausea and vomiting, diffusion hypoxia, and expansion of gas-filled spaces (causing flatulence, stomach ache, or earache). However, current literature reports elucidate major adverse events such as laryngospasm, cardiovascular morbidity and mortality, impaired wound healing, and acute and chronic pain [13]. It is important to keep in mind that most major adverse events associated with nitrous oxide have been reported when nitrous oxide is used at high concentrations for the administration of general anesthesia or during pediatric medical sedation in an emergency room, and not at low concentrations for anxiolysis used in a dental office.

An observational study on 1- to 17-year-old children reported 8.3% minor and self-resolving adverse events in children inhaling 50% nitrous oxide in oxygen and found no significant difference in adverse events between nitrous oxide of 50 and 70% [36, 37]. However, adverse events are higher in children <3 years old when a higher concentration of nitrous oxide is used.

Another report in children between 33 days and 18 years with a median age of 5.0 years reported minor adverse events including nausea (1.2–1.6%), vomiting (2.2%), and diaphoresis (0.4%). A total of 0.14% reported serious adverse events including oxygen desaturation and generalized seizures which were resolved promptly with an increase in oxygen [38, 39].

A systematic review on use of nitrous oxide in minor pediatric medical procedures reported minor adverse events of 4–8% and major adverse events of less than 0.5% in children aged 0–19 years.

> American Academy of Pediatric Dentistry has recommended 50% as maximum concentration of nitrous oxide to minimize adverse events.

Reasons for Precipitation of Side Effects

- Side effects observed during nitrous oxide administration are relatively uncommon. Their incidence can be further minimized by certain precautions during its administration. These are as follows:

  (a) Restricting administration of nitrous oxide/oxygen to 30–45 min.
  (b) Avoiding fluctuations in nitrous oxide concentrations.
  (c) Using nitrous oxide at a concentration >50% for a longer duration.
  (d) Mechanical or equipment failure (though rare).

5.3.1 Diffusion Hypoxia

When nitrous oxide is administered to a child, there is a rapid uptake of the gas into the blood stream through the alveoli, due to the concentration gradient and low solubility of nitrous oxide in blood. Nitrous oxide is transported in blood as free gas. It does not combine with hemoglobin and does not undergo biotransformation. When the administration of nitrous oxide is discontinued, the gas is eliminated by expiration in precisely the reverse manner. Again, due to low solubility, nitrous oxide is eliminated rapidly.

However, when the administration of nitrous oxide is discontinued, a high concentration of the gas rapidly builds up in the alveoli. This dilutes the partial pressure of oxygen in the alveoli and leads to hypoxia. This phenomenon is called diffusion hypoxia. The hypoxia is transient, yet should not be taken lightly.

If a child gets up from a dental chair, soon after cessation of nitrous oxide administration, he/she may fall down due to the imbalance caused by diffusion hypoxia. The clinical sequelae related to diffusion hypoxia are headache, disorientation and nausea/vomiting, and lethargy after the treatment. Some children may sleep in the car while returning from the clinic or at home, after the treatment, which may result in parents getting worried. Prior information to parents or reassurance will be helpful in reducing parents distress, if any.

Maximum excretion of nitrous oxide gas takes place in the first 3–5 min after discontinuing its administration. A clinical study has mentioned that 99% of nitrous oxide is excreted during the first 5 min [40], and diffusion hypoxia occurs during the first 4 min in the majority of cases [41, 42]. Hence, it is the standard of care and conventional practice to provide 100% oxygen to a pediatric patient for at least 5 min after the administration of nitrous oxide in a dental practice [43]. In pediatric patients, the lingering effects of nitrous oxide should be assessed and further oxygenation should be provided if the child has had a long dental appointment under nitrous oxide [44]. Oxygenating the patient in this manner reduces diffusion hypoxia and related clinical manifestations. It provides an opportunity for a waning placebo effect. It also enables expiration of nitrous oxide into the scavenging system and, hence, minimizes the escape of nitrous oxide into the clinical environment [43].

> Diffusion hypoxia is not of much clinical significance in healthy child patients. Significance increases in medically compromised children, children suffering from bronchitis, or when a high concentration of nitrous oxide has been used for a long time.

Certain studies have questioned the clinical significance of diffusion hypoxia [45]. It has been reported that diffusion hypoxia is not clinically significant in healthy pediatric dental patients [40]. This is because arterial oxygen pressure remains higher than usual during the administration of nitrous oxide [46] (e.g., even if a child is inhaling nitrous oxide at a concentration of 50%, he/she is also inhaling 50% oxygen which is much higher than the oxygen available in the atmospheric air). A child patient allowed to breathe atmospheric air (having 21% oxygen) under careful observation on a dental chair for 5 min will not develop diffusion hypoxia [40, 47]. It has been reported in a clinical study that only 2–3% drop in alveolar oxygen tension occurs during washout period in spontaneously breathing patients who had inhaled 50% N_2O and 5 L/min flow rate [48].

The clinical significance gains magnitude when the respiratory ventilation gets compromised (like in bronchitis) [40, 49] or a higher concentration of nitrous oxide (meaning lesser concentration of oxygen has been used for a longer time). Also, in children who are medically compromised it becomes essential to administer 100% for 5 min after the cessation of nitrous oxide.

5.3.2 Nausea and Vomiting

Nausea and vomiting are the most common adverse events associated with the use of nitrous oxide [50]. There are different mechanisms for nausea and vomiting associated with the inhalation of nitrous oxide. These include

(a) Action on central opioid and dopaminergic receptors.
(b) Diffusion of nitrous oxide into the middle ear cavity which may cause barometric changes within middle ear, thereby stimulating vomiting center [51, 52].
(c) Bowel distension [53, 54].
(d) Children who suffer from motion sickness are more likely to develop nausea.
(e) Pre-existing gastrointestinal disease.

Clinical signs which may suggest that nausea is precipitating are perspiration on scalp or neck/palm creases, excessive swallowing, change in thoracic and abdominal movement, sudden movement of a child who was otherwise calm and still, coughing, and a child trying to remove the nasal mask. Adolescents may express verbally by saying that “I feel sick” or “I don’t want to use this mask anymore.”

The emetogenic effect of nitrous oxide is significantly related to the duration of administration and a higher concentration of nitrous oxide [50, 53]. A report mentions increased chances of nausea and vomiting when nitrous oxide is administered at a concentration of 50% for more than 2 h [55]. It is also related to the titration method. If nitrous oxide is titrated very quickly, then it can cause nausea (e.g., in rapid titration method, instead of increasing nitrous oxide concentration by 10% every 2–3 minutes, it is increased by 10% every 30 s). Also, younger age group has been reported to have an increased incidence of vomiting [56]. An inexperienced operator can alter the concentrations of nitrous oxide very frequently. This causes a “Roller Coaster effect” precipitating nausea.

Nausea and vomiting are distressing perioperative events for the child, parents, as well as for the practitioner. If vomiting occurs, primary action should be to prevent aspiration of vomitus. Further, a supine child on a dental chair may aspirate gastric contents if emesis occurs, which increases the risk of aspiration pneumonia.

Hence, it is prudent to institute a 2-h fasting period prior to the administration of nitrous oxide to minimize emesis and aspiration [50]. It was found that chances of vomiting increased when fasting was less than 2 h [57]. However, a prospective case series on 220 children concluded that there was no association between pre-procedural fasting and emesis [58].

> Nausea and vomiting can be minimized by administering a minimum effective concentration of nitrous oxide for the shortest duration required.

Efficacy of Laryngeal Reflex

It has been found that the laryngeal reflex is not depressed during nitrous oxide inhalation sedation, if nitrous oxide concentration is kept less than 50% [59]. An experimental clinical study conducted on 50 anxious and fearful children found no aspiration into larynx or chest [59].

A contradictory report mentioned aspiration in 20% of adult patients on using a fixed concentration of 50% nitrous oxide in oxygen [60].

Handling Situation with Vomiting

If a child vomits, immediately use high vacuum suction and keep telling the child to spit out. Check for the alertness of the child and then administer 100% oxygen. Lift the chin upwards to maintain the airway.

In the event of any emergency, follow certain steps to assess proper functioning of the above mentioned systems.

1 Maintain patency of airway why head-tilt/chin-lift maneuver.
2 Scan the child's chest for rise and fall for no more than 10 s to assess breathing.
   (a) If there is normal breathing and pulse, activate emergency response system.
3 Palpate the pulse (carotid and femoral pulse in a child). Signs of poor perfusion are cool extremities, decline in responsiveness, weak pulse, and pale mottled skin which may turn to cyanosis.
   (a) If there is no normal breathing but presence of pulse, then provide rescue breathing (1 breathe every 3–5 s or 12–20 breaths/min).

If there is no breathing and only gasping or no pulse, then activate CPR (cycle of 30 compressions and 2 breaths for single rescuer or 15 compressions and 2 breaths for 2 rescuers).

5.3.3 Pain in Ears

Seldom, children may complain of pain in the ears due to the pressure changes in middle ear. This may progress to rare (mostly seen during use of nitrous oxide as a general anesthetic, meaning use of nitrous oxide gas at a higher concentration for a longer duration) but more serious events such as tympanic membrane rupture or blood in ear [52, 61]. This is due to an increased pressure in the middle ear. Mechanism of increased middle ear pressure is because of the blood gas partition coefficient being 30 times greater than nitrogen (gas predominantly present in air). As a result of this, nitrous oxide fills in air-filled cavity more rapidly than nitrogen is removed from those cavities, thereby increasing middle ear pressure. This gets reduced by passive venting of nitrogen gas from the eustachian tube [52].

Also, after the discontinuation of nitrous oxide, development of negative pressure may occur in the middle ear. This can be explained by rapid outward movement of nitrous oxide from the middle ear at a rate much higher than the movement of nitrogen gas replacing it. Consequently, flexible walls of the eustachian tube tend to collapse inwards which prevents equilibration of sub-atmospheric pressure. This may lead to earache or in rare instances, rupture of the tympanic membrane [52].

Pain in ears and stomach is due to the difference in the rate of entry of nitrous oxide into closed air spaces and the rate of exit of nitrogen gas from these spaces.

This is a common occurrence in children following the use of nitrous oxide as a general anesthetic agent [52] though not so common with its use for inhalation sedation in a dental setting. Its clinical significance increases in children with respiratory tract infection or history of ear problems such as eustachian tube dysfunction. Also, in children with anatomic variations in the ear such as in Crouzon's syndrome (acoustic nerve compression from skull base and cartilage anomalies causes narrowing in internal acoustic meatus), increased middle ear pressure following the use of nitrous oxide can cause postoperative hearing loss [62].

5.3.4 Sexual Phenomenon

Although this phenomenon may not be an adverse event in true sense, it may present an embarrassing moment for the parents and the dentist. This phenomenon is of greater significance in adolescents and dental staff of both the sexes should be present in the dental operatory, while treating adolescents.

During this phenomenon, children may move their hands towards their genitals (Fig. 5.28). Some children may even touch dentist's face with affection.

This phenomenon usually occurs because of transition into a state of light sleep or dreamy state which may become erotic or sexual in nature [63]. It may also be because of a hypnotic state which may occur spontaneously or unintentionally [64].

5.3.5 Laryngospasm

Laryngospasm has been reported in a child during procedural sedation in medical emergency and analgesia using nitrous oxide alone at a high concentration (70%

Fig. 5.28 Child putting hands near genitals during nitrous oxide sedation

induced deep sedation, close to GA) [65]. High concentrations of nitrous oxide may cause laryngospasm due to variability in patient responses [50]. The oral cavity provides access to the airway, and dental treatment may produce aerosols or pooling of saliva, which in conjunction with sedation can predispose to a laryngospasm [50]. Careful monitoring of the patient and use of saliva ejectors and rubber dam isolation can help minimize the likelihood of this serious adverse event. Also, laryngospasm cannot occur in minimal or moderate sedation.

5.3.6 Malignant Hyperthermia

This is a very rare adverse event (one in 15,000 anesthetic procedures) [66] and can occur in patients who are sensitive to general anesthetics and depolarizing muscle relaxants because of an autosomal recessive trait. This can result in muscle contracture, acidosis, hyperkalemia, and hyperthermia. Occurrence of this adverse event in a dental setting has not been reported ever. The child must get unconscious before malignant hyperthermia due to nitrous oxide can occur [46], and hence it cannot happen in a dental setting. However, it is mentioned here for knowledge of readers.

5.3.7 Head Trauma and Nitrous Oxide

Nitrous oxide can increase cerebral blood flow and intracranial pressure. In animal models, this increase in oxygen consumption seems to exacerbate ischemic neurologic injuries. In light of this information, intracranial injuries and head concussion should be ruled out in children who have sustained dental trauma before administration of inhalational nitrous oxide.

5.3.8 Fire

Nitrous oxide is capable of supporting combustion. A report mentioned fire in the mouth of a 54-year-old patient undergoing removal of leukoplakia patches from posterior part of tongue using electrocautery. It was believed that combination of electrocautery, dry gauze, and nitrous oxide caused combustion [46].

5.3.9 Accidents with Nitrous Oxide

Nitrous oxide in dentistry has a safety record of more than 150 years. There have been sporadic incidents of nitrous oxide-mediated complications due to technical problems. In these incidents, cross-connections of central nitrous oxide and oxygen lines during construction lead to nitrous oxide asphyxiation-related deaths [67]. Another reason was failure of mechanical interlocking between oxygen and nitrous oxide flowmeter controls. This leads to severe hypoxia due to inhalation of 100% nitrous oxide [67].

A complication due to wrong gas tank connection was reported in 1977 [68]. The event occurred during the recovery period after nitrous oxide sedation in a US dental school oral surgery clinic. Pins were dislodged from the machine, compromising the pin index system, which lead to wrong connection of the gas tank. As a result, during the recovery period, patient inhaled 100% nitrous oxide instead of 100% oxygen resulting in cyanosis and loss of consciousness.

5.3.10 Asphyxiation Related to Impurities in Nitrous Oxide Cylinder

This adverse event is not of significance now but is being mentioned here for knowledge of readers. Before 1970s, there were higher chances of contamination of nitrous oxide cylinders with nitrogen in concentration of 0.5–2.0%. Inhalation of contaminated nitrous oxide has potential of triggering a rapid methemoglobinemia, chemical pneumonitis, and acidosis causing intense cyanosis, respiratory distress, and loss of consciousness [69] which is incapable of being managed by administering 100% oxygen. In scientific literature, two fatalities have been reported as a consequence of nitrogen contamination [49].

5.4 Documentation

5.4.1 Medical History

Prior to using nitrous oxide–oxygen minimal sedation, it is essential to review the patient's medical history and make a note of any changes to the medical status of the patient, any medications being taken by the child (including dose, time, route, and site of administration), and allergies. It is important to also have a record of any previous hospitalizations or surgeries and any complications during the same (Fig. 5.29).

Parents must be instructed to update the office if the child had any recent illness, a cold or congestion, for instance, which may compromise the airway. In case of any such changes to medical history, the procedure may need to be rescheduled.

5.4.2 Informed Consent

A written informed consent must be obtained from the parent or the legal guardian of the child and documented in the dental record prior to the use of nitrous oxide (Fig. 5.30). The informed consent should explain the indication and rationale for the use of inhalational nitrous oxide, all the risks and benefits associated with its use, and alternatives, if applicable. Prior to the procedure, all questions from the parents/legal guardians should be encouraged and answered by the dentist.

Documentation of using nitrous oxide in child patients involves recording of the medical history, taking informed consent from parents, providing preoperative and postoperative instructions, and recording per-operative notes including any adverse events.

MEDICAL HISTORY

☐ Yes ☐ No Is Your child in good health? Date of last medical exam ____________

☐ Yes ☐ No Has your child ever had a health problem ____________

☐ Yes ☐ No Is your child allergic to anything? ____________

☐ Yes ☐ No Is your child currently taking any medications? If yes, please provide medication, Dose and reason: ____________

☐ Yes ☐ No Are your child's immunizations current? ____________

☐ Yes ☐ No Have you ever been told that your child needs to take antibiotics before dental treatment?

☐ Yes ☐ No Has your child ever been hospitalized, had general anesthesia, or emergency room visits?

☐ Yes ☐ No Were there any difficulties at birth or pre-mature? ____________

Please check if your child has been treated for any of the following

☐ Heart disease	☐ Heart murmur	☐ Bleeding/transfusions	☐ Asthma/breathing
☐ Anemia	☐ Blood disorders	☐ Tonsil/abenoid problems	☐ Tuberculosis
☐ Liver Disease	☐ Sickle cell disease/trait	☐ Diabetes	☐ AIDS
☐ Kidney disease	☐ Rheumatic fever	☐ Hepatitis	☐ Mental delays
☐ Speach/hearing	☐ Seizures	☐ Cleft lip/palate	☐ Physical delays
☐ Eyesight	☐ Congenital birth defects	☐ Gastric disease/reflux	☐ Cancer/tumors
☐ Recurrent headaches	☐ Frequent infections	☐ Adverse drug reactions	☐ Cerebral/tumors
☐ Significant injuries	☐ Endocrine/growth	☐ Autism	☐ Arthritis
☐ ADHD	☐ Spina bifida	☐ Snoring	☐ Abuse

Other: ____________

Fig. 5.29 Medical history form

5.4.3 Preoperative Instructions

The dentist should provide the parents/legal guardians written preoperative instructions on how to prepare the child for the dental appointment with nitrous oxide–oxygen inhalation sedation. Pretreatment dietary precautions should be discussed with the parent. The parent should be instructed to keep the child NPO for 2 h prior to the scheduled dental appointment. The parent should be advised on ensuring that the child arrives in a loose, comfortable clothing on the day of the appointment (Fig. 5.31).

The anticipated effects of nitrous oxide should be explained well to the parents, with an emphasis that the desired effect is anxiolysis only. The parent should be informed that their child will maintain all protective reflexes and will be awake during the procedure. Parents should ensure that reliable transportation is available after the completion of the procedure to transport the child home on completion of the procedure.

NITROUS OXIDE INFORMED CONSENT

I hereby authorize **Dr**.____
to give nitrous oxide/oxygen (laughing gas) for my child/ward:

____

1. I accept and understand that Nitrous Oxide is commonly called laughing gas and provides relaxation. I understand that my child will be awake, conscious, aware of what is happening, and able to respond to questions and instructions.

2. I have provided to the doctor and the dental clinic staff:

   a. a complete medical history for my child
   b. list of all prescription and over-the-counter medications he/ she is taking
   c. known food and drug allergies
   d. history of emergency room visits
   e. history of past surgeries
   f. history of anycomplications with anesthesia for my child or in the immediate family
   g. any known genetic mutations in my child or in the immediate family, including MTHFR gene mutation

3. I will let the doctor and the staff know if my child falls ill or develops a cold, runny nose, respiratory infection, ear infection, asthma, or difficulty breathing.This will make it difficult for my child to breath in the nitrous oxide gasor have complications.

4. Nitrous oxide sedation has been recommended for my child to help him/ her feel more relaxed during the dental treatment. Local anesthesia in the form of an injection inside the mouth may also be required to numb the teeth and/or gums for the dental treatment.

5. The doctor has discussed with me the possible complications associated with Nitrous Oxide. They include, but are not limited to:

   a) Nausea and vomiting: This is the most frequent of the side effects of breathing nitrous oxide. In order to avoid this, your child must not have eaten or drank anything for the 2 hours prior to the appointment time.

   b) Temporary tingling in the fingers, toes, cheeks, lips, tongue and head or neck area

   c) Temporary warm feeling throughout the body with accompanying flushing/ blushing

   d) Temporary detachment or “out of body” sensation

   e) Temporary “floaty” feeling

   f) Temporary sluggishness in motion and/or speech

   g) Shivering –usually at the end of the procedure

Fig. 5.30 Informed consent for nitrous oxide sedation in children

5.4.4 Dental Chart Notations

The child’s dental chart should provide the indications for utilization of nitrous oxide/oxygen inhalation. This may entail a description of the child’s behavior, anxiety, and/or past dental experiences as well as the extent of dental treatment needs. Scales used to assess fear, anxiety, or phobia of children have been described in Appendix XII and XIII.

6. Nitrous oxide sedation iseffective for most children if they breathe it. However,some children may not like the feeling it produces, or it may produce increased activity in some children. If the dentist notices these effects, nitrous oxide will be discontinued for my child, and my child will receive 100% oxygen for at least 5 minutes.

7. Some children may not calm down enough with only nitrous oxide. If this happens, the dentist may stop the procedure at a safe stopping point and discuss other options such as moderate sedation or general anesthesia to safely complete the treatment for my child.

I hereby certify that I understand this authorization and the reasons for the above named sedative procedure and its associated risks. I am aware that the practice of dentistry is not an exact science. I acknowledge that every effort will be made for my child to have a positive outcome, but no guarantees have been made as to the result of the procedure authorized above.

________________ ________________________________

Date Parent or Guardian's Signature

________________ ________________________________

Date Dentist's Signature

Parent Instructions for Children having Dental Treatment with Inhalational Nitrous Oxide

It is essential to follow these instructions for the safety of your child. Failure to follow instructions may lead to cancellation of your child's dental appointment.

Before your child's appointment:

1. Your child should not eat or drink in the two hours before the appointment.

2. Before the two-hour fasting period your child may have a light meal. Examples include toast, small fruit, small sandwich, crackers, water. Avoid greasy or fried foods.

3. Please do not bring any other children or individuals who need supervision to the dental appointment. This will allow the dental team to focus on your child who is going to receive dental treatment with nitrous oxide.

4. If your child takes any daily medication(s), the dentist would have advised you about whether your child should or should not take them. Please follow the dentist's recommendation for medication(s).

5. If your child develops anyillness, such as fever, runny nose, respiratory infection,asthma,ear infectionor stomach illness, you should let us know immediately as we may have to reschedule your child's appointment.

6. Have your child wear loose, comfortable clothes for the appointment.

7. If your child has finger nail polishor false nails, please remove them before the appointment.

After your child's appointment:

1. You should make arrangements to travel home by car rather than by public transport.

2. Observe your child, and if he/ she shows any behavior that is unusual for him/ her, please call the dental office.

3. After the effects of the local anesthetic (numbness medicine) wears off, your child can eat. Give your child something light to eat at first. Make sure that he/ she does not feel nauseated before giving more food.

The effects of inhalational nitrous oxide generally wear off within minutes of the treatment being completed. It is still important to follow the instructions above.

Your child's care will be provided by: **Dr.** ______________________________

Clinic telephone number: ______________________________________

Fig. 5.31 Preoperative instructions for nitrous oxide sedation in children

No. 8, First Floor, MGF Megacity Mall, MG Road, Gurgaon - 122002

SEDATION RECORD SHEET

Name of the child: Age/ Gender :

Last meal : Last meal time:

Any significant medical history: Cold/ cough/ runny nose:

ASA Classification: I / II / III / IV Consent form Signed : Yes/ No

Pre operative levels (for ASA II /III): SpO_2: Blood pressure: Pulse rate:

Primary assessment of anxiety: Crying aloud/ Struggling/ Quiet/ Shy or withdrawn/ Talkative or friendly

Method of Titration : Slow/Rapid

	Nitrous Oxide Concentration	Oxygen concentration	Flow rate	Time
Oxygenation phase				
Induction phase				
Injection phase				
Maintenance phase				
Recovery phase				
Total Time				
Procedures performed				

Intra operative behavior: Quiet throughout/ Mostly quiet but responded to few procedures/ Cried/ Procedure aborted

Sedation outcome: Minimal sedation throughout/ minimal sedation with periods moderate sedation

Adverse events

Perioperative: Nausea/vomiting
Post operative: Nausea/ Vomiting/ Headache/ Dizziness/ Sleepy/Drowsy

Name of operator: Signature of operator:
Date :

Fig. 5.32 Sedation record sheet

Evaluate the child's airway prior to the procedure and document the clearance. Preoperative blood pressure and pulse must be recorded on the chart as well (for ASA II/III).

Other records for the sedation procedure must include the following (Fig. 5.32):

- Outcome of sedation may be described based on "Sedation outcome assessment scale" (Appendix XIV).
- Total flow rate of nitrous oxide and oxygen
- Percentage and duration of administration of nitrous oxide
- Duration of administration of 100% oxygen at the end of the sedation procedure
- Notation regarding the patient's tolerance of the sedation procedure (any use of additional behavior guidance techniques to augment should be mentioned).
- The occurrence of any minor or major adverse events (with complete details of management done)
- Recovery status at the end of procedure (stable vital signs, orientation, ambulation)

Dentist should make a note of the parental presence (or lack of it) within the dental operatory during the procedure. Mentioning the presence of dental team members and parents is particularly important if nitrous oxide is being administered to adolescent patients.

It is a good idea to mention the effect of nitrous oxide/oxygen administration on the behavior of the child as a part of the clinical note too. The patient should be discharged only when the preoperative level of ambulation and cognition are achieved.

5.5 Personnel and Team Building

Nitrous oxide sedation in a child patient requires concomitant efforts by the dentist and dental assistants. Effective teamwork ensures a successful nitrous oxide sedation. Effective teamwork has certain components such as well-designated roles and effective communication.

5.5.1 Components of a Team

Three key members of nitrous oxide sedation team are regulator, facilitator, and surveillant. In nitrous oxide sedation team, the dentist is a regulator, dental chair side assistant is a facilitator, and another dental assistant is a surveillant (Fig. 5.33).

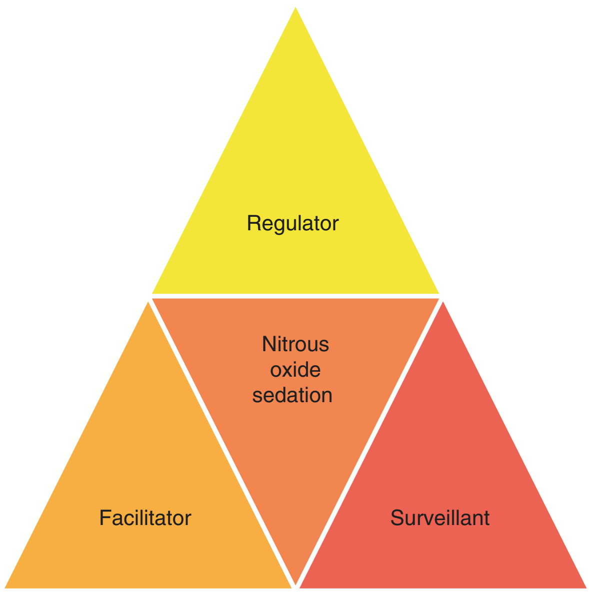

Fig. 5.33 Team members for nitrous oxide sedation in children

Well-Designated Roles

Understanding roles and responsibilities will help in the clear demarcation of actions, adequate monitoring during sedation, prevention of adverse events, and successful seeing off/discharge of patient.

Roles of a Regulator

1. Regulator/dentist serves as a team leader.
2. Regulator organizes the team, provides education/training to team members.
3. Regulator sets expectations for facilitator and surveillant.
4. Gives clear instructions to facilitator regarding the size of nasal mask to be used, titration technique to be followed (standard or rapid), adjustments in concentration of nitrous oxide, and cessation of use of nitrous oxide.
5. Regulator observes for any sudden thoracic or abdominal movement.
6. Maintains verbal contact with the child intermittently during the procedure.
7. Regulator records the details of sedation procedure in the sedation record sheet.
8. Regulator should not leave the dental operatory while nitrous oxide is being administered. This is based on the regulations of a country or state.

> Success of using nitrous oxide in child patients is dependent on a well-coordinated team with each member having clear designated roles and the ability to communicate effectively with each other.

Roles of a Facilitator

1. *Facilitator, if required, should be able to introduce the use of nitrous oxide to parents with assurance and sincerity.*
2. Facilitator/dental chair side assistant facilitates the use of nitrous oxide in a child based on clear instructions given by a regulator.
3. Facilitator changes the nasal mask after every patient.
4. Facilitator checks with the parents regarding pre-appointment, fasting, or upper respiratory tract infection.
5. Facilitator introduces nitrous oxide mask to a child.
6. Facilitator adjusts the nasal mask on a child's nose.
7. Facilitator titrates nitrous oxide gas and keeps reminding the child to take deep slow breaths from the nose and not to breathe from the mouth.
8. Facilitator verbally repeats the concentration of nitrous oxide after the regulator advises for any adjustment (e.g., regulator says increase nitrous oxide concentration to 50%, facilitator says nitrous 50).
9. Facilitator ensures that 100% oxygen is delivered to a child after the procedure is over.
10. Facilitator checks for signs of diffusion hypoxia or other minor adverse symptoms before seeing off or discharging the child from the dental operatory.

Roles of a Surveillant

1. Surveillant serves as a monitor during the nitrous oxide sedation.
2. Surveillant checks for any leakages from cylinders or cuts in tubings.
3. Surveillant checks for adequate pressure in cylinders and also checks for depleting oxygen flow rate on flowmeter during procedure indicating emptying of cylinders.
4. Surveillant ensures nasal breathing pattern by observing the movement of reservoir bag.
5. Surveillant looks for any signs of adverse events such as sweating on the scalp and sudden movement in thorax or abdomen
6. Surveillant also observes the eye responses and informs the regulator in case the eye lids are closing indicating deepening of the level of sedation.
7. Surveillant checks for any kinks in the tubing.
8. Surveillant changes the oxygen and nitrous oxide cylinders.

Each team member must be proficient in performing their roles. They should be having adequate knowledge about their roles and know how to act in a particular situation. Each member should be observant and concentrate on their roles to ensure the success of nitrous oxide sedation in a child.

When the roles are unclear, the efficiency of nitrous oxide sedation decreases (due to improper placement of mask or lack of adequate nasal breathing). It may also lead to an increase in the number of adverse events.

If each member of the team follows their roles to the best of their abilities, then the dentist can concentrate on the procedure with minimum distraction from a clinical procedure. This not only improves their efficiency but also reduces any stress on their mind (some dentists may be stressed during the use of nitrous oxide sedation).

5.5.2 Communication

Each team member should be well aware and cautious about what to communicate, how to communicate, when to communicate, and whom to communicate.

Incorrect communications may create stressful environment and also convey wrong message to the parents present in the operatory (Table 5.5).

Table 5.5 Examples of the correct way of communicating amongst team members

Communicating team member	Incorrect	Correct
Surveillant	Child is not breathing	Child is not breathing well through his/her nose
Surveillant	Reduce the oxygen	Decrease flow rate of oxygen
Surveillant	Child is getting oversedated	Nitrous oxide concentration can be reduced now
Regulator	Child will vomit	Can you please keep a vomiting bag handy

Good Communication Skills

Messages should be communicated in a calm and direct manner. Yelling or shouting should be avoided. Communications which are not loud and clear can be missed by the recipient and cause unwanted events during the sedation procedure.

Mutual Respect

Regulator, facilitator, and surveillant should have respect for each other and not criticize any mistake committed by a team member during the process of sedation. Regulator should play a key role in rectifying any faults on part of the facilitator and surveillant (e.g., facilitator increases the concentration of nitrous oxide too rapidly).

Any wrong action taken by the facilitator or surveillant should be pointed out by regulator in a respectful and tactful manner (e.g., instead of saying "why did you increase the concentration of nitrous oxide so rapidly," a better manner of communicating is "for this patient it is better if you increase the concentration of nitrous oxide at a rate of 10% every 2 min).

Another example is "why aren't you observing the movement of reservoir bag properly to ensure that the child is breathing through the nose" is an incorrect and authoritative way of communicating. A more polite way would be "I need your help in carefully observing the movement of reservoir bag so that we ensure that the child is not breathing through his/her mouth."

Using Closed End Commands

Regulator should deliver messages which are short, concise, clear, and loud to ensure that it is well received by the facilitator. For example, during the administration of local anesthesia, if the regulator wants to increase the concentration of nitrous oxide to 60%, then it can be communicated as "nitrous 60%." The recipient team member should perform the task and confirm that the action has been taken. For example, after increasing the concentration to 60%, the facilitator says "nitrous 60%." Regulator can then say "Thanks."

Analyzing the Sedation Procedure

It is important that the regulator conducts a short debriefing session, if required, after the sedation procedure to discuss any mistakes committed by the facilitator or the surveillant. This will help in understanding the mistakes and its implications. It will also help in preventing such mistakes in future. It will also help in reinforcing the team spirit and strengthening the bond as well as the respect amongst team members. Such debriefing sessions also act as short education sessions for the team members.

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Risks of Nitrous Oxide

6

Kunal Gupta and Amit Sethi

Contents

Learning Objectives

1. Understanding the hazard and toxicity related to nitrous oxide
2. Gaining knowledge about techniques to minimize the hazard potential of nitrous oxide gas in the dental operatory
3. Methods of monitoring nitrous oxide concentrations in ambient air of dental operatories
4. Comprehending biochemical basis of occupational hazards of nitrous oxide
5. Have complete information about hazard potential of nitrous oxide on organ systems of human body

Nitrous oxide has been used in clinical anesthesia practice for more than 150 years. Its administration is safe and efficient method for managing pain and anxiety in dentistry. The dentist, the allied staff, and the patient all benefit from reduced stress and increased patient comfort. However, its use has had its share of controversies, and most of these have centered around the adverse effects of chronic long-term

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exposure to nitrous oxide. Even though in pediatric dentistry, the duration of exposure to nitrous oxide is shorter and the risk of adverse effects is low, but there could be a subgroup of patients, who could be put to risk even by short duration of exposure to nitrous oxide.

6.1 Background of Hazards Related to Nitrous Oxide

6.1.1 Health Hazard of Nitrous Oxide

Health concerns related to nitrous oxide was first raised by a publication in Russian literature which described an unusual number of miscarriages in anesthesiologists [1, 2]. In 1980, a large-scale epidemiological study reported in the Journal of American Dental Association recognized that use of nitrous oxide in dental offices could be a health hazard for the dentist and their ancillary staff [1]. In this study also, of all the findings, spontaneous abortion in female chair side assistants was the most significant finding. This study was limited by its design since it was a questionnaire study and recall was used as the sole source of collecting evidence of adverse events and also it failed to exclude dentists and chair side assistants who abused nitrous oxide [1]. However, few years later, two studies in Sweden and Finland could find no link between the working in an operating room with anesthetic gases and miscarriages [3, 4].

Health hazard potential of nitrous oxide is based on the duration of exposure and concentration of exposure in ppm.

Hazard potential of nitrous oxide is based on two parameters:

1. *Concentration of exposure to nitrous oxide in ppm*
   The concentration of exposure is maximum within the vicinity of the patient. Therefore, the dentist and the dental assistant will have the maximum exposure as expressed in ppm as compared to the other staff who are away from the patient such as the circulating dental assistant. The concentration is measured in the breathing space of the dentist and dental assistant.
2. *Duration of exposure to nitrous oxide*
   This implies the time duration for which the dentist and the dental assistant are exposed to nitrous oxide.

$$\text{Total dose of exposure} = \text{Concentration} \times \text{duration of exposure to nitrous oxide}$$

Factors Governing the Concentration of Ambient Air Nitrous Oxide

1. Duration of exposure—It was stated in a study that as long as the duration of exposure is less than 2.5 h, then usually the risk of adverse effects is low.

However, if the time of exposure is more than 12 h, then there can be adverse consequences to the health of the dentist and team members.

2. Presence of scavenging—Presence of active and effective scavenging keeps the concentration of nitrous oxide in safe limits.
3. Flow rate of nitrous oxide gas—In operatories where nitrous oxide gas is used at a higher flow rate, the concentration of nitrous oxide is more due to greater leakage of gas from the peripheries of nasal mask.
4. Concentration of nitrous oxide gas being used—Procedures which are carried out using a higher concentration of nitrous oxide will expose the operator and his team to higher concentrations in their immediate surroundings.
5. Frequency of use—Operatories, where nitrous oxide is used more frequently, have a higher concentration of nitrous oxide. This is often the case with pediatric dentistry and oral surgery offices.
6. Room dimensions of operatory—Smaller operatories have higher ambient nitrous oxide concentration than larger operatories.
7. Ventilation—Well-ventilated offices will have lesser ambient nitrous oxide levels than poorly ventilated ones. This is usually measured as “dilution ventilation rate” or “air changes per hour.”
8. Distance of operator from the working zone: Cleaton Jonset et al. [5] described maximum nitrous oxide level at zero meters from the working zone (nasal hood and mouth of child). Mustafa described that distance and nitrous oxide level follow the inverse square law. There is a greater fall in nitrous oxide levels when the distance from the working zone increases. Therefore, child’s attendants are at a much lesser risk of exposure to nitrous oxide in a well-scavenged dental office. Operator closest to the breathing zone of the patient will have more exposure than the other staff who may be away from the breathing zone of the patient (Fig. 6.1).

Gender and the type of dental procedure have no impact on the nitrous oxide levels in ambient air. However, if the child cries, for example, during the administration of local anesthesia, then the ambient air concentration may increase.

6.1.2 Measurement of Nitrous Oxide in Ambient Air

1. **Real-Time Sampling**
   A portable infrared gas analyzer is used to provide direct, immediate, and continuous readout of nitrous oxide concentration in air at a particular point of time. (eg: VIASENSOR G200 Analyzer manufactured by QED Environmental Systems, Inc). The advantage of this method is that it can instantaneously give a feedback on nitrous oxide leakage as well as on the effectiveness of control measures (Fig. 6.2).

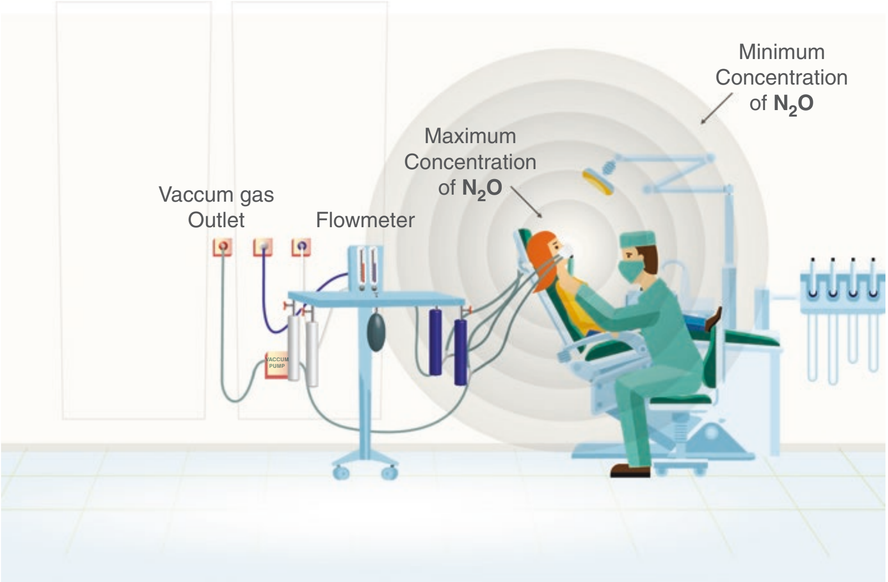


Fig. 6.1 Figure showing zones of varying nitrous oxide concentration with respect to leakage from a child's mouth

2. **Time-Integrated Sampling**
   In this method, nitrous oxide concentration obtained is an "average value" for a sampling period.
   (a) ***Bag Sampling***
   An integrated air sample is collected in a plastic bag using a portable battery powered pump. The plastic bag is impervious to nitrous oxide. Analysis of the gas sample is done using a long path length portable infrared spectrophotometer.
   (b) ***Diffusive Sampling***
   Time integrated samples are taken using diffusive sampler called a Landauer passive dosimeter badge. These badge samplers measure the exposure of dental workers and are attached to their lapel. Accurate sampling time has to be recorded and communicated to the lab analyzing the badges sampler. "Sampling start time" is when the cap of the sampler is removed, and the "sampling end time" is when the cap is replaced. This method is very simple and easy to use (Fig. 6.3).

At a fixed point of time, individual dosimeter can be considered to be a more accurate measure of an "individual's exposure" to ambient N_2O than the infrared spectrophotometry method.

Fig. 6.2 Hand held infrared monitor for analyzing nitrous oxide gas in ambient air. (Source: https://afcintl.com/gas-detection-instruments/gas-detectors/single-gas-detectors/product/Nitrous-Oxide-Monitor/)

Fig. 6.3 Diffusive sampling badge

Steps of Using Diffusive Sampling Monitors

1. Remove the monitor from the sealed pouch and record the monitor ID and sample ID.
2. Open sampler cap to reveal sampling holes (Fig. 6.4).
3. Attach the monitor to the lapel using a clip. Avoid attaching to front pocket as the monitor should be as close as possible to the breathing zone of the personnel (Figs. 6.5 and 6.6).

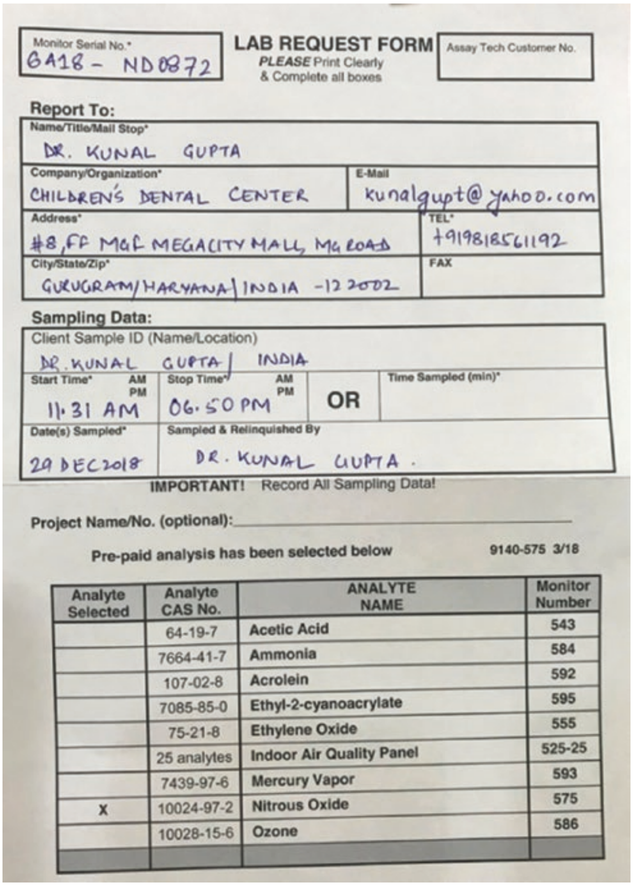
Fig. 6.4 Sampling holes in monitor badge

Fig. 6.5 Proper way of attaching the monitor badge

4. Record sampling date and start time.
5. At the end of the sampling, remove monitor, record end time.
6. Place it in the container to be transported to the lab for analysis (Fig. 6.7).
7. Attach the lab request form with all the particulars filled in properly (Fig. 6.8).
8. Receive report from the lab (Fig. 6.9).

Fig. 6.6 Improper way of attaching the monitor as it is away from the breathing zone of the dentist

Fig. 6.7 Placing monitor in the air tight container after use, to be transported to the lab for analysis



LAB REQUEST FORM
PLEASE Print Clearly
& Complete all boxes

Monitor Serial No.*: 6A18 – ND0872

Assay Tech Customer No.:

Report To:

Name/Title/Mail Stop*: DR. KUNAL GUPTA

Company/Organization*: CHILDREN'S DENTAL CENTER

E-Mail: kunalgupt@yahoo.com

Address*: #8, FF MGF MEGACITY MALL, MG ROAD

TEL*: +919818561192

City/State/Zip*: GURUGRAM/HARYANA/INDIA -122002

FAX:

Sampling Data:

Client Sample ID (Name/Location): DR. KUNAL GUPTA / INDIA

Start Time* AM PM: 11.31 AM

Stop Time* AM PM: 06.50 PM

OR

Time Sampled (min)*:

Date(s) Sampled*: 29 DEC 2018

Sampled & Relinquished By: DR. KUNAL GUPTA.

IMPORTANT! Record All Sampling Data!

Project Name/No. (optional):

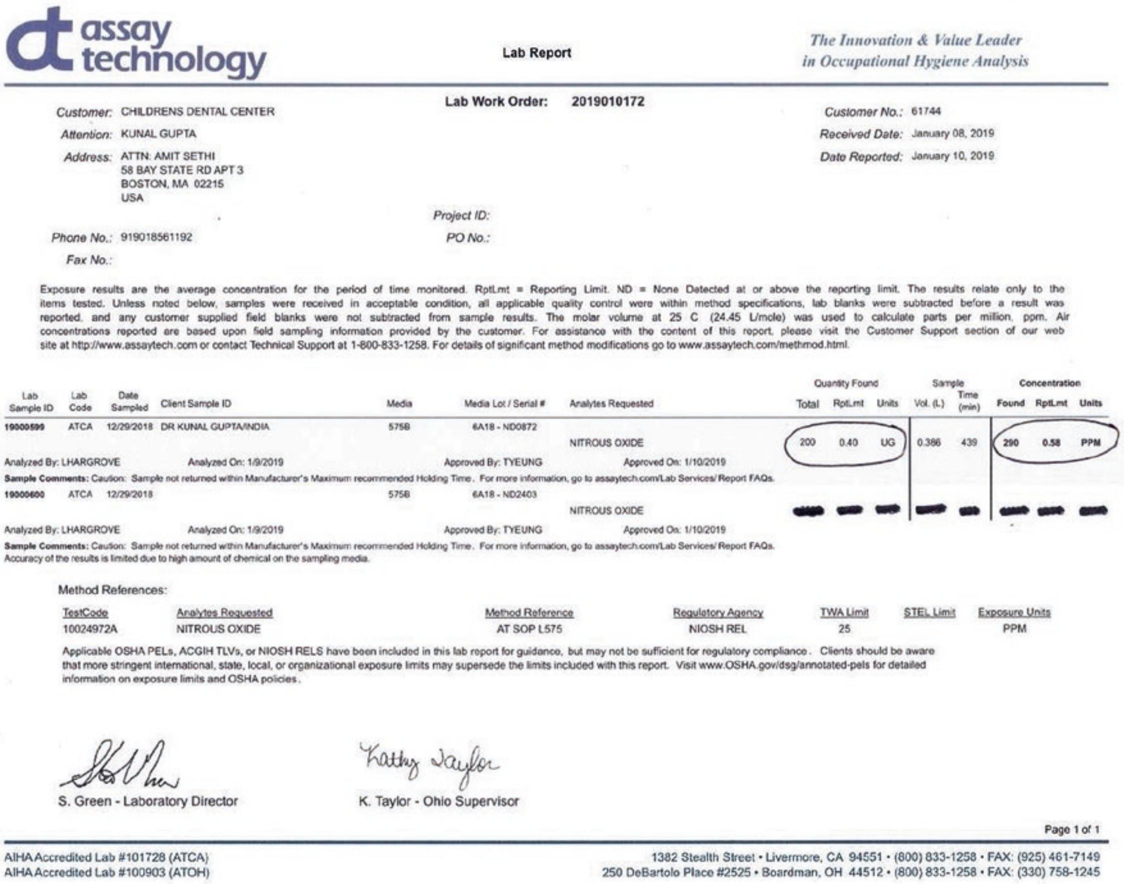
Pre-paid analysis has been selected below 9140-575 3/18

Analyte Selected	Analyte CAS No.	ANALYTE NAME	Monitor Number
	64-19-7	Acetic Acid	543
	7664-41-7	Ammonia	584
	107-02-8	Acrolein	592
	7085-85-0	Ethyl-2-cyanoacrylate	595
	75-21-8	Ethylene Oxide	555
	25 analytes	Indoor Air Quality Panel	525-25
	7439-97-6	Mercury Vapor	593
X	10024-97-2	Nitrous Oxide	575
	10028-15-6	Ozone	586

Fig. 6.8 Lab request form with all the details filled in

Exposure can be denoted numerically in two ways:

1. *Total exposure:* This is calculated by multiplying the concentration of nitrous oxide in a particular space with the number of hours of exposure. This measurement is better for determining the exposure of staff who are not in close proximity to the patient but are exposed to almost constant levels of nitrous oxide in the ambient air of dental clinic, example a front office staff. This is usually determined using real-time sampling.
2. *Time-weighted average (TWA):* It is defined as the average of the airborne concentrations of a chemical agent determined from air samples to which a worker is exposed in a workday or work week [6]. This is calculated by dividing the sum of total exposures at different time intervals by the sum of number of hours of exposure. Eight-hour time-weighted average is calculated when the exposure is calculated over a period of 8 h.



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Attention: KUNAL GUPTA
Address: ATTN: AMIT SETHI
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BOSTON, MA 02215
USA

Phone No.: 919018561192
Fax No.:

Lab Work Order: 2019010172
Project ID:
PO No.:

Customer No.: 61744
Received Date: January 08, 2019
Date Reported: January 10, 2019

Exposure results are the average concentration for the period of time monitored. RptLmt = Reporting Limit. ND = None Detected at or above the reporting limit. The results relate only to the items tested. Unless noted below, samples were received in acceptable condition, all applicable quality control were within method specifications, lab blanks were subtracted before a result was reported, and any customer supplied field blanks were not subtracted from sample results. The molar volume at 25 C (24.45 L/mole) was used to calculate parts per million, ppm. Air concentrations reported are based upon field sampling information provided by the customer. For assistance with the content of this report, please visit the Customer Support section of our web site at http://www.assaytech.com or contact Technical Support at 1-800-833-1258. For details of significant method modifications go to www.assaytech.com/methmod.html.

Lab Sample ID	Lab Code	Date Sampled	Client Sample ID	Media	Media Lot / Serial #	Analytes Requested	Quantity Found Total	Quantity Found RptLmt	Quantity Found Units	Sample Vol. (L)	Sample Time (min)	Concentration Found	Concentration RptLmt	Concentration Units
19000599	ATCA	12/29/2018	DR KUNAL GUPTA/INDIA	575B	6A18 - ND0872	NITROUS OXIDE	200	0.40	UG	0.386	439	290	0.58	PPM
19000600	ATCA	12/29/2018		575B	6A18 - ND2403	NITROUS OXIDE	[redacted]							

Analyzed By: LHARGROVE Analyzed On: 1/9/2019 Approved By: TYEUNG Approved On: 1/10/2019
Sample Comments: Caution: Sample not returned within Manufacturer's Maximum recommended Holding Time. For more information, go to assaytech.com/Lab Services/Report FAQs.

Analyzed By: LHARGROVE Analyzed On: 1/9/2019 Approved By: TYEUNG Approved On: 1/10/2019
Sample Comments: Caution: Sample not returned within Manufacturer's Maximum recommended Holding Time. For more information, go to assaytech.com/Lab Services/Report FAQs. Accuracy of the results is limited due to high amount of chemical on the sampling media.

Method References:

TestCode	Analytes Requested	Method Reference	Regulatory Agency	TWA Limit	STEL Limit	Exposure Units
10024972A	NITROUS OXIDE	AT SOP L575	NIOSH REL	25		PPM

Applicable OSHA PELs, ACGIH TLVs, or NIOSH RELS have been included in this lab report for guidance, but may not be sufficient for regulatory compliance. Clients should be aware that more stringent international, state, local, or organizational exposure limits may supersede the limits included with this report. Visit www.OSHA.gov/dsg/annotated-pels for detailed information on exposure limits and OSHA policies.

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K. Taylor - Ohio Supervisor

Page 1 of 1

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Fig. 6.9 Monitoring report

Time-weighted average (TWA) is a better tool for measuring the cumulative exposure for an individual working in proximity to the patient who may be exposed to varying concentrations throughout the day.

$$\text{TWA} = \frac{t_1c_1 + t_2c_2 + \ldots + t_nc_n}{t_1 + t_2 + \ldots + t_n}$$

where t denotes the time duration in hours and c denotes the concentration of nitrous oxide.

$$8\text{hTWA} = \frac{t_1c_1 + t_2c_2 + \ldots + t_nc_n}{8}$$

For example,

	Concentration of nitrous oxide (ppm)		Duration of exposure
c_1	500	t_1	0.5
c_2	20	t_2	2.0
c_3	450	t_3	1.0
c_4	10	t_4	1.5

Note: For other time period during the 8 hour working day, the dentist was not working on a patient

$$\begin{aligned}\text{TWA} &= \frac{500 \times 0.5 + 20 \times 2.0 + 450 \times 1.0 + 10 \times 1.5}{0.5 + 2.0 + 1.0 + 1.5} \\ &= \frac{250 + 40 + 450 + 15}{5} \\ &= \frac{755}{5} \\ &= 151.0\text{ppm}\end{aligned}$$

$$8\text{hTWA} = \frac{755}{8} = 94.4\text{ppm}$$

This example shows that although the dentist was exposed to higher concentrations of nitrous oxide gas (500 ppm and 450 ppm) during the day, but the 8 hour average was much lower (94.4 ppm).

Urine and breath samples could be convenient, reliable, and inexpensive biomonitoring techniques for checking the exposure of nitrous oxide concentrations to dental personnel [7].

6.1.3 Levels of Nitrous Oxide Recommended in Dental Environment

Occupational exposure limit has been defined as the maximum average concentration of an airborne chemical agent to which a worker or clinical staff member can be exposed daily, based on an 8 h working day and a 40 h week. It is assumed that no other exposure to nitrous oxide occurs for the remainder of the day.

It also means the maximum limit to which all workers may be repeatedly exposed on day to day basis without adverse health effects.

The best practice for occupational hygiene implies that the workers should be exposed to 50% of the maximum limit to ensure a safety margin which would prevent exceeding the occupational exposure limit by chance [8].

Occupational exposure limit to nitrous oxide gas in a dental operatory varies from 25 to 100 ppm in different countries based on an exposure period of 8 h per day or 40 h per week.

1. National Institute of Occupational Safety and Health have recommended level of **25 ppm or 45 mg/m³** in dental operatories while administering nitrous oxide [9] (Table 6.1). This recommended level has been found to be too low practically [10]. Air samples should be taken from two locations: the breathing zone around the workers (placing a dosimeter on the uniform top). The second sample should be from the room air, and this can be done by using an infrared spectrophotometer.
2. In UK, it has been recommended that exposure should not exceed **100 ppm** over an 8-h time-weighted average (8-h TWA) reference period [11] (Table 6.1). Time-weighted average has been described as average air concentration during a given period.
3. American Dental Association has not proposed a maximum permissible limit for nitrous oxide due to lack of consensus among the scientific community [12].
4. ACGIH (Association Conference of Governmental Industrial Hygienists) mentions 50 ppm or 90 mg/m³ as the maximum exposure limit for an 8-h TWA (time-weighted average) for a workday or a 40 h week (Table 6.1).
5. Sweden has the limit of continuous TWA of 100 ppm for an 8 h day (Table 6.1).

Table 6.1 Recommended levels of exposure to nitrous oxide by various organizations/countries

Country	TWA/ppm
Australia	25
Austria	100
Canada	25–100
Denmark	50
United Kingdom	100
Estonia	100
Finland	100
Germany	100
The Netherlands	80
Norway	50
New Zealand	25
Spain	50 (daily exposure)
Sweden	100
Switzerland	100
South Africa	100
USA	25(NIOSH)-50 (ACIH)

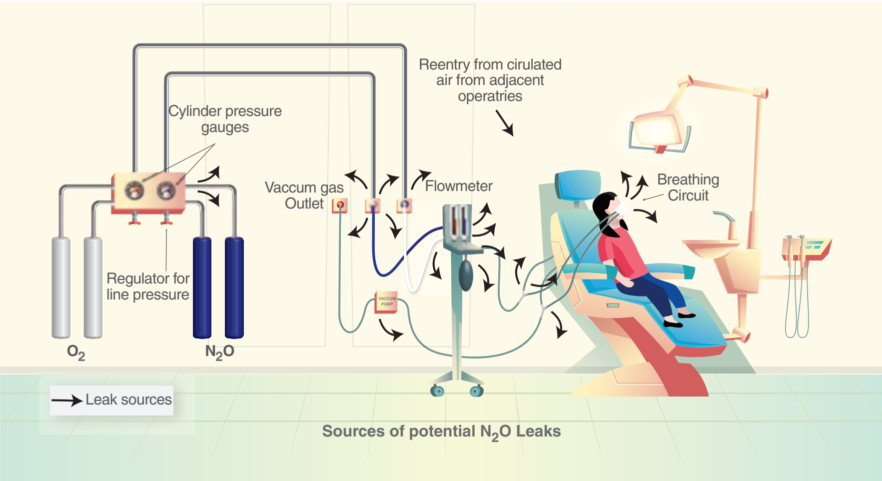

Fig. 6.10 Sources of leakage of nitrous oxide gas in the operatory

6.1.4 Sources of Nitrous Oxide Leakage in Dental Office

Leakage from various sources can increase the concentration of nitrous oxide in ambient air, thereby increasing the risk of health hazards on long-term exposure. Various sources of nitrous oxide leakage are discussed here, and conscious effort must be made to check leakage from these sources (Fig. 6.10).

1. ***Inadequate ventilation and scavenging systems***: Most dental offices use scavenging systems to remove excess gas but still some amount of nitrous oxide will escape into the immediate surroundings. This unscavenged gas is one of the most common sources of increasing levels of nitrous oxide in the air of operatory. National Institute of Occupational and Safety Health (NIOSH) has recommended an optimum scavenging rate of 45 L/min [9]. However, scavenging at this rate has been shown to reduce the level of sedation achieved [10].

   Dental offices which are well scavenged are able to reduce the concentration of nitrous oxide by 70% [11, 12]. In a very well-scavenged office where all the measures are followed strictly, ambient nitrous oxide can be reduced to 50 ppm [1].

   Higher levels of contamination have been reported in the dental offices in the order of 5000 ppm due to higher flow rate of the gases and poor ventilation [13].

   Data collected by NIOSH has shown nitrous oxide levels of more than 1000 ppm in scavenged dental offices compared to 300 ppm in hospital operating theaters [14]. The difference in these levels is attributed to the fact that in dental operatories, use of nasal hood allows leakage of gas from the mouth, whereas in operating rooms, there is a seal made around the nose and mouth.

Pediatric dental offices have a higher concentration of nitrous oxide in ambient air of operatory than general dental offices.

Fig. 6.11 Cracks and hole in reservoir bag

2. ***Equipment malfunction***: Equipment leaks from the pipes, the reservoir bag (cracks, worn out signs in old reservoir bag) (Figs. 6.11 and 6.12), tanks left improperly closed, improperly attached tubings in manifold, or leakage from the outlet port (in centralized supply) can contribute to increased concentration of nitrous oxide in ambient air of dental operatory.
3. ***Poor technique***: The following examples illustrate the link between faulty technique and increased levels of nitrous oxide in operatories.
   (a) Poorly fitting masks may cause nitrous oxide gas to leak in the surrounding air (Fig. 6.13). Silhouette masks have been recommended to reduce the leakage of nitrous oxide gas from the edges of the mask.
   (b) Starting the flow of nitrous oxide gas before the mask is placed on the child's nose.
   (c) Using a nitrous oxide mask which does not have an effective scavenging design will also add to ambient nitrous oxide concentrations.
   (d) Overinflated reservoir bag will usually cause gas leaking into the environment. This is because it implies the delivery of gases at a higher rate than required to be inhaled by a child. The extra gases thence leak from the nasal hood.
   (e) Not administering oxygen after the flow of nitrous oxide gas has been stopped.

Fig. 6.12 Worn out reservoir bag with probable cracks causing leakage

Fig. 6.13 Poorly fitting nasal mask

Fig. 6.14 Child crying during rapid titration will contribute to leakage of nitrous oxide gas in operatory

4. ***Uncooperative child and younger age group***: A child who may keep crying or may keep pulling off mask from the nose may contribute towards increasing nitrous oxide concentration in the ambient air of dental operatory. The younger age group of children contributes more to nitrous oxide levels in dental clinic as compared to the older age group due to laughing, crying, talking, and movement of mask (Fig. 6.14). As age of patients decreases the levels of nitrous oxide have been known to worsen [15]. Henry et al. stated that the patient behavior can result in significant increase in nitrous oxide levels of the ambient air. In pediatric dental offices, child patients who are talking may exhale more nitrous oxide thus adversely affecting the ambient air quality [15]. The effectiveness of rubber dam in reducing leakage from the mouth has been disputed, but its use is part of the policy statement by American Association of Pediatric Dentistry in minimizing occupational health hazards associated with nitrous oxide [16] (Fig. 6.15).

Use of rubber dam prevents inadvertent mouth breathing during the procedure, thereby minimizing leakage of nitrous oxide gas into the ambient air of operatory.

Fig. 6.15 Use of rubber dam minimizes leakage from mouth

Fig. 6.16 O rings used for adequate seal in gas station outlets in the centralized supply of gases

6.1.5 Minimizing Exposure of Nitrous Oxide

After understanding various sources of leakage of nitrous oxide, certain precautions can be taken at three different levels to avoid any unnecessary exposure to ambient nitrous oxide [16]. These are at the level of equipment (engineering controls), operator (work practice controls), and practice management (administrative controls).

Engineering Controls

(a) Use of nasal scavenging mask.
(b) O rings at the high pressure connections should be replaced at regular intervals (Fig. 6.16). O rings are the neoprene washers in gas station outlets which makes the outlet assembly leak proof.

Fig. 6.17 Well-ventilated operatory

(c) Adequate room ventilation should be present. Outside air inflow into the room should be increased so that mixing of clinic air with outside air leads to dilution of nitrous oxide levels within the clinic (Figs. 6.17, 6.18, and 6.19).
(d) Use of supplemental local ventilation/exhaust system should be used. The placement of this is crucial and should be placed close to the patient where the leakage is maximum.

Supplemental exhaust system should be located at the floor level because nitrous oxide gas being heavier than air settles at the floor level of the operatory.

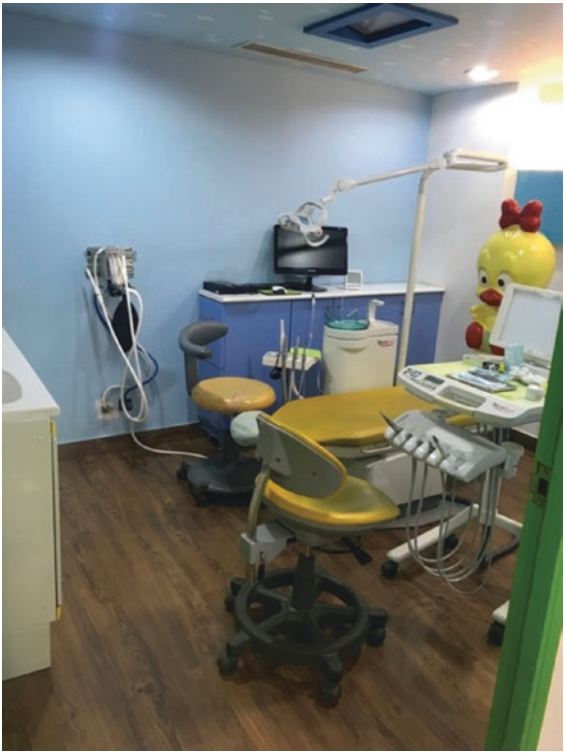

Fig. 6.18 A small-sized operatory with no windows can have higher concentrations of nitrous oxide in ambient air

Children's Dental Center

NITROUS OXIDE MAINTENANCE CHECK LIST

MM/YYYY......01/2019...

DATE	No leakage found on opening Cylinders	Pressure gauges working	No Leakage heard from Gas station outlets	Tubings Checked	No Leakage sound on turning on of flow meters	No Cracks seen on reservoir bag	Scavenging Pump working adequately	Checked by
1	—	H O	L I	D A Y	—	—	—	[illegible]
2	✓	✓	✓	✓	✓	✓	✓	[illegible]
3	✓	✓	✓	✓	✓	✓	✓	[illegible]
4	✓	✓	✓	✓	✓	✓	✓	[illegible]
5	✓	✓	✓	✓	✓	✓	✓	[illegible]
6	—	H	O L	I D	A Y	—	—	[illegible]
7	✓	✓	✓	✓	✓	✓	✓	[illegible]
8	✓	✓	✓	✓	✓	✓	✓	[illegible]
9	✓	✓	✓	✓	✓	✓	✓	[illegible]
10	X	✓	✓	✓	✓	✓	✓	[illegible]
11	✓	✓	✓	✓	✓	✓	✓	[illegible]
12	✓	✓	✓	✓	✓	✓	✓	[illegible]
13	—	H	O L	I D	A Y	—	—	[illegible]
14	✓	✓	✓	✓	✓	✓	✓	[illegible]
15	✓	✓	✓	✓	✓	✓	✓	[illegible]
16	✓	✓	✓	✓	✓	X	✓	[illegible]
17	✓	✓	✓	✓	✓	✓	✓	[illegible]
18	✓	✓	✓	✓	✓	✓	✓	[illegible]
19	✓	✓	✓	✓	✓	✓	✓	[illegible]
20	—	—	H O	L I	D A Y	—	—	[illegible]
21	✓	✓	✓		✓	✓	✓	[illegible]
22	✓	✓	✓	✓	✓	✓	✓	[illegible]

Fig. 6.19 Maintenance check list to inspect leakage of nitrous oxide in dental operatory

Work Practice Controls

(a) Check for leaks in the morning before starting work.
High pressure leaks—This can occur between the cylinder and the flowmeter such as at the cylinder valve or the copper pipeline in centralized line or at the regulator in the portable equipment.
Low pressure leaks—This can occur between the flowmeter and the scavenging mask such as the rubber hoses, tubings, and breathing bags.
(b) Nitrous flow should be started after ensuring that the scavenging vacuum device is switched on or is connected to the exhaust tube.
(c) Scavenging system exhaust flow rate should be 45 L/min. If it is less than this, then there is leakage around the mask.
(d) Use oxygen flush to fill the reservoir bag.
(e) Start using nitrous only after the mask is securely placed on the nose.
(f) Prevent overinflation of reservoir bag indicating higher flow rate than desired as this contributes to leakage of gas around the mask.
(g) Use high concentrations only for stressful procedures such as the administration of local anaesthesia or extractions.
(h) Discourage the child from talking while he/she has the mask on.
(i) At the end of the procedure, 100% oxygen should be administered for 3–5 min. This ensures that the residual nitrous oxide in the child's body is exhaled into the scavenging system and not into the clinic's environment.

Using nitrous oxide gas at appropriate concentration, flow with adequate scavenging aids in curtailing nitrous oxide concentration in ambient air of operatory.

Administrative Controls

(a) Proper education and training of the staff should be carried out to make them aware of the work practice controls and hazard potential.
(b) Training of staff regarding immediate step in case of high pressure leakage.
(c) Maintain a check list for regular inspection of all possible sites of leakage (Fig. 6.19).
(d) Check the ambient air nitrous oxide levels and operators/assistant's breathing zone nitrous oxide levels at regular intervals.
(e) Written monitoring and maintenance plan should be in place.
(f) Staff rotation should be carried out so that a particular team member is not continuously exposed to nitrous oxide.

Well-trained and vigilant staff play a key role in preventing unnecessary leakage of nitrous oxide gas into the operatory.

6.2 Toxicity

Toxicity of nitrous oxide is due to chronic and long-term exposure to nitrous oxide gas. It is of higher significance to dentists and their staff rather than the child patients in whom the exposure is only for a short duration. Most of the toxic effects of nitrous oxide are related to vitamin B_{12} metabolism.

6.2.1 Types of Toxicity

1. **Acute toxicity**
   Acute exposure may be due to accidental leakage from cylinders or hoses. Acute exposure may cause dizziness, difficult breathing, cough, shortness of breath, headache, nausea, fatigue, and irritability. Acute exposure to nitrous oxide concentration of 400,000 to 800,000 ppm may cause loss of consciousness [17].
2. **Chronic toxicity**
   Chronic exposure may cause hematological abnormalities, neurological deficits (like tingling, numbness, lack of concentration, interference with gait), and reproductive effects.

6.2.2 Effects of Toxicity

Main issues related to exposure to trace amounts of nitrous oxide are as follows:

1. **Psychomotor performance**
   Bruce et al. reported that inhaling nitrous oxide at 500 ppm for 4 h could delay perceptual, cognitive, and motor skills of health care workers [18].

   Bruce and Bach found that 50 ppm inhaled for over 2 h caused impairment in audiovisual tasks [19]. However, later Cook et al. could not detect any performance deficit with nitrous oxide concentration to which a dentist is exposed in a clinical practice [20].
2. **Biochemical disturbances**
   Excessive amounts of nitrous oxide can cause interference with the normal biochemical processes in the human body which forms the basis for clinical signs.

Biochemical Basis for Hazards or Toxicity Related to Nitrous Oxide

Most of the hazards related to nitrous oxide are due to inactivation of vitamin B_{12}. Sweeney et al. provided the first direct evidence that altered vitamin B_{12} metabolism, and impaired synthesis of DNA is related to occupational exposure to nitrous oxide in dentists [21]. This inactivation is due to oxidation of monovalent cobalt ion in vitamin B_{12} to trivalent state (Fig. 6.20). As a result of this inactivation, biochemical pathways in which vitamin B_{12} serve as coenzymes also get affected.

Around 20–60% of vitamin B_{12} in plasma, blood cells, and liver is destroyed after exposure to nitrous oxide in anesthetic concentrations [22].

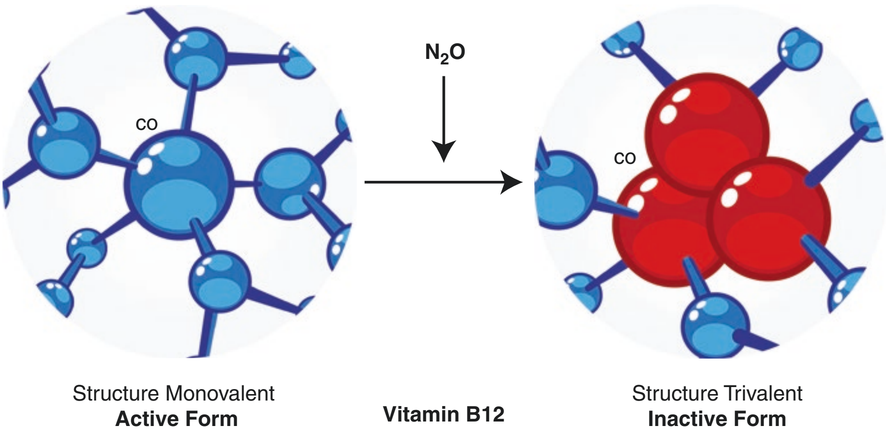

Fig. 6.20 Inactivation of vitamin B_{12} by nitrous oxide by changing monovalent cobalt atom to trivalent

Inactivation of vitamin B_{12} is the biochemical basis for health hazards related to nitrous oxide.

Few such pathways of inactivation are as follows:

1. Enzymatic conversion of homocysteine to methionine using enzyme methionine synthase and coenzyme vitamin B_{12}. Vitamin B_{12} inactivation leads to increased levels of homocysteine and decreased levels of methionine and subsequently S adenosyl methionine which causes reduction in myelin production (due to reduced methylation of myelin sheath phospholipids) (Fig. 6.21).

   Methionine is present in diet and can also be produced by the betaine pathway. Therefore, with short-term exposure to nitrous oxide, resulting inactivation of methionine synthase will not be of much clinical significance.
2. Conversion of 5-methyltetrahydrofolate to tetrahydrofolate which affects the DNA synthesis (Fig. 6.22).
3. Conversion of methylmalonyl CoA to succinyl CoA which increases the levels of methylmalonyl CoA (Fig. 6.23). This affects the fatty acid synthesis as accumulation of methylmalonate provides abnormal substrate for fatty acid synthesis. This leads to abnormal fatty acids which are incorporated into the myelin sheath. This further leads to subacute combined degeneration of spinal cord (dorsal posterior and lateral spinal columns). The result is neuropathy which is symmetrical affecting legs more than arms.

Inactivation of vitamin B_{12} leads to reduction in myelin production, DNA synthesis, and abnormal fatty acid production.

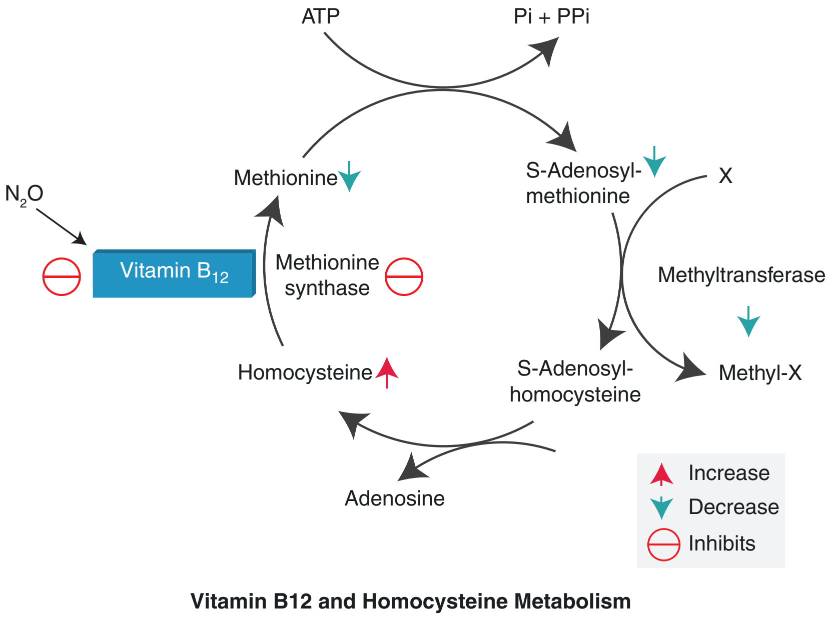

Fig. 6.21 Inhibition of homocysteine metabolism due to nitrous oxide

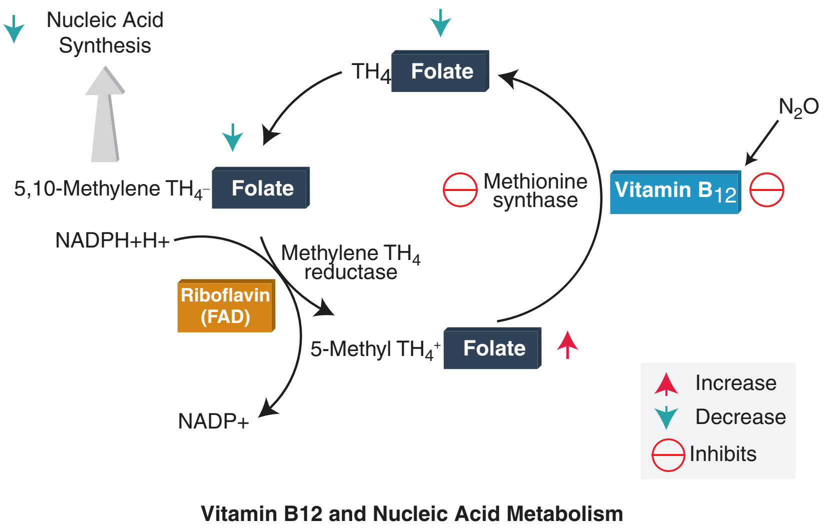

Fig. 6.22 Inhibition of folate metabolism due to nitrous oxide

Various biochemical changes, their relevance, based on the duration of exposures and in individuals with varying conditions are highlighted in Table 6.2.

Vitamin B_{12} is mainly found in food of animal origin. Vitamin B_{12} intrinsic factor complex is absorbed in the terminal ileum. The free enzyme enters the portal

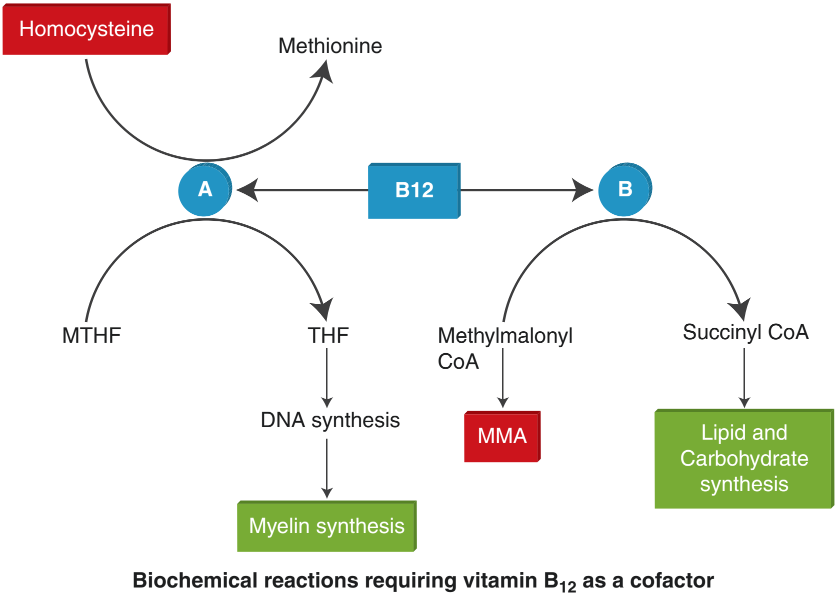

Fig. 6.23 Various biochemical pathways affected by vitamin B_{12}

Table 6.2 Biochemical changes based on different durations of exposure and in individuals with varying conditions

Duration of administration	Relevance	Biochemical changes	Prevention
More than 24 h	Not relevant in dental practice	• Gross interference with DNA synthesis • Production of granulocytes seriously impaired • >3 days of exposure leukopenia and agranulocytosis develop • Clinical changes depend on marrow stores of granulocytes	Protection from megaloblastic changes can be obtained with folinic acid 30 mg twice daily
24 h	Not relevant in dental practice	• Megaloblastic marrow changes • Abnormal dU suppression test • Leukopenic changes usually not seen	Protection from megaloblastic changes can be obtained with folinic acid 30 mg twice daily
Less than 24 h	Dentists/dental assistants	• No changes in methionine synthase in exposure of less than 30 min • Variable response to exposure of 30 min to 2 h • >2 h cause interference with hepatic methionine synthase with abnormal dU suppression test	Protection from megaloblastic changes can be obtained with folinic acid 30 mg twice daily

(continued)

Table 6.2 (continued)

Duration of administration	Relevance	Biochemical changes	Prevention
Repeat exposures to nitrous oxide	Child patients/ dentists/dental assistants	• Inhibition of methionine synthase is rapid and recovery is slow [23] • If repeat exposure occurs before fourth day of first exposure, cumulative effect of methionine synthase inhibition is seen • However, clinical outcome more favorable • Leukocytes counts may remain unchanged [25]	Folinic acid 30 mg twice daily may be administered as preventive therapy
Sick patient	Child patients with systemic diseases	• "Possibility" of marrow changes and abnormal dU suppression test though no specific data on relation to duration of exposure	Avoid treatment using nitrous oxide for longer durations in children with systemic diseases
Wound healing and infection	Dentist	• Only if the biochemical changes affect the DNA synthesis (which can happen after few days of exposure), then the wound healing may get affected • Evidence lacking on the correlation	
Pregnancy	Dentists/dental assistants	• No effect on short duration of exposure [25] during cesarean section • Organogenesis may be affected for exposure for many hours during first 4 weeks of pregnancy [25]	Folinic acid may be administered during early pregnancy [25]
Exposure to trace concentrations	Dentists/dental assistants	Abnormal dU suppression test may be seen in poorly scavenged offices though evidence in support of this is very poor	
Abuse	Dentists/dental assistants	Signs and symptoms of subacute degeneration of spinal cord	Complete avoidance of nitrous oxide and vitamin B_{12} supplementation
Patients with subclinical B_{12} deficiency	Child patients/ dentists/dental assistants who are strict vegetarians or vegans	• Methionine synthase may get inactivated • Evidence lacking	
Methotrexate therapy	Child patients	• May cause pulmonary toxicity	

Table 6.3 Table showing the recommended dietary allowance of vitamin B_{12} for different age groups

Age (years)	Recommended dietary allowance of vitamin B_{12} (μg)
1–3	0.9
4–8	1.2
9–13	1.8
14+	2.4

circulation, is stored in liver, secreted by bile, and then reabsorbed from ileum, thereby conserving B_{12} in children with normal absorption. Therefore, the recommended dietary allowance is quite low (Table 6.3). The vitamin B_{12} stored in an adult is 2500 μg.

Vitamin B_{12} deficiency can be seen in older individuals, individuals with pernicious anemia, gastric malabsorption, and individuals who have had recent gastrointestinal surgery. It is also seen in vegetarians because main dietary source of vitamin B_{12} is through animal products like meat, fish, poultry, milk, milk products, and eggs.

6.2.3 Relationship of Animal Studies to Response in Humans

There is a difference in the rate of methionine synthase inactivation between rats and humans. In rats, more than 50% of enzyme activity is inhibited on exposure to concentration of less than 30% [23, 24]. However, in humans, inhibition averaged 50% after about 2 h of exposure to a mean concentration of 60% [24]. Therefore, a high concentration of nitrous oxide for a long duration is required for inactivation of enzyme and its related clinical effects in humans. Also, in humans there is individual variation based on individual residual methionine synthase activity after various periods of exposure [25].

Factors affecting clinical effects of nitrous oxide-related hazards are as follows [1]:

1. The intensity, duration, and pattern of exposure to nitrous oxide (under the control of the clinician)
2. Degree of inactivation of methionine synthase and the time course of recovery
3. Extent to which body reserves and dietary intake can compensate for methionine synthase inactivation (has the potential to be modified)
4. Sensitivity of methionine synthase-related biochemical pathways to decrease in substrate
5. Sensitivity of tissues to changes by affected biochemical pathways

> The findings of various animal studies cannot be extrapolated to humans due to the difference in species.

6.2.4 Difference in Nitrous Oxide-Related Toxicity in Patients and Dentists

The main difference in the risk of use of nitrous oxide in child patients compared to the dentists is that the patients are exposed only for a short duration (30–90 min), whereas the dentists are exposed for prolonged duration and on multiple instances. Soon after the exposure to nitrous oxide ends, the biochemical recovery initiates. Various studies have mentioned that 4 days are required for a full recovery of methionine synthase activity [1]. Also, the child patients continue having normal diet which aids in relaxing some of the lost essential metabolites.

Repeated administration within a span of 3–4 days will have a potential to cause leukopenia and megaloblastic changes in a child with preexisting hematological disturbances.

Chronic toxicity of nitrous oxide due to prolonged exposure is of significance to dentists and their staff rather than patients.

6.2.5 Occupational Hazards (Chronic Toxicity)

Exposure of nitrous oxide gas alone to dental personnel is two to three times greater than the medical personnel who work in operating theaters and use nitrous oxide along with other anesthetic gases [26]. This is because in the dental operatories nasal hood is used rather than the full mask which allows larger amounts of nitrous oxide being leaked into the ambient air from an open mouth. Only one survey has been completed to study the adverse health effects of nitrous oxide on dental personnel [27]. Most of the studies regarding occupational exposures to inhaled anesthetics predate modern scavenging and operating room ventilation and often considered exposure to all anesthetic gases instead of just nitrous oxide. Hence, relevance of many of these studies to current practice is questionable [28].

Reproductive Effects and Genotoxicity

The inhibition of methionine synthase by nitrous oxide which in turn affects the synthesis of DNA and RNA is known to cause genetic and protein aberrations thus causing adverse effects related to reproductivity, fertility, as well as genotoxicity. These effects are severe enough to affect male fertility, sperm motility, and normal female ovulation [29].

A retrospective study done by Cohen found a 2.3-fold increase in the rate of spontaneous abortion among female chair side dental assistants who were exposed to nitrous oxide. The same study also found increased rates of spontaneous abortions among wives of male dentists who were chronically exposed to nitrous oxide [26]. A retrospective study by Rowland and colleagues found that exposure to high levels of unscavenged nitrous oxide (>100 ppm) for 5 or more hours per week adversely affected the fertility of female dental assistants [30]. The conclusions of both studies have been challenged because of the nature (retrospective) of the studies as well as lack of measured data on trace gases involved in the environments reported [31].

In absence of any prospective studies which measured exposures in nitrous oxide group vs a control group, it is difficult to substantiate the risks about reproductive toxicity especially in a modern day dental office which has "adequate scavenging."

It has also been stated that the nitrous oxide associated decrease in fertility may be related to the physiological disturbances such as the decreased release of luteinizing hormone-releasing hormone which is caused due to interaction of nitrous oxide with the endogenous opioid system [32].

Fetotoxicity of nitrous oxide was believed to be due to the reduction of folates, but this could be compensated by the use of folinic acid during pregnancy [33]. Also the betaine pathway of methionine synthesis may get induced in the first few days of exposure to nitrous oxide [34], thereby compensating for reduction of folates.

The findings of various animal studies cannot be extrapolated to humans due to difference in species. Also a large number of epidemiological studies have reported no increase in fetal malformations following exposure to nitrous oxide in anesthetic concentrations [25, 35–38].

Neurological Effects

A questionnaire study of 60,000 dentists and their assistants showed that high exposure (>6 h a week for 10 years) was associated with neurological symptoms such as tingling, numbness, and weakness [39]. However, as with the previous studies the lack of scavenging and the retrospective nature of study with no adequate measurement of effective nitrous oxide levels do not substantiate the adverse neurological effects of nitrous oxide [28]. The neurological effects are attributed to inactivation of methionine synthase by nitrous oxide which in turn affects metabolism of vitamin B_{12}. These effects are more pronounced with the recreational use of nitrous oxide in which a large amount of gas is inhaled in a single or multiple exposures [40].

Chances of neurological effects as an occupational hazard in dentists and dental staff are quite remote, in a modern day operatories having adequate scavenging system.

Symptoms of Severe B_{12} Deficiency

Although severe B_{12} deficiency in dentists is rare, the signs of neurological effects are highlighted here because neurological signs appear before the hematological signs [28].

Symptoms of subacute combined degeneration of spinal cord are related to ischemic neuropathy and demyelination [41]. Symptoms are generally symmetrical, affecting legs more than hands.

The symptoms are paresthesia with associated loss of vibration and sense of position. This progresses to severe weakness, spasticity, clonus, paraplegia, and even fecal or urinary incontinence. It can further progress to irritability, memory loss, and dementia [42].

Lhermitte's syndrome, which is a shock-like sensation that radiates to feet during neck flexion, may also be present [43, 44].

Diagnosis

Diagnosis can be made by checking the serum vitamin B_{12} levels. In case the vitamin B_{12} levels are normal but neurological symptoms are present, then diagnosis should be based on "functional" vitamin B_{12} levels which are done by measuring the substrates (methylmalonic acid and homocysteine) of reactions catalyzed by vitamin B_{12} [41].

Treatment

Complete avoidance of nitrous oxide along with proper dosage of vitamin B_{12} should be considered. Parenteral vitamin B_{12} (1000 μg IM) is administered for a week, followed by weekly administration for a total of 4 weeks [45]. Neurological symptoms should improve at the end of a month, but treatment should be carried on for 6 months to achieve complete recovery [45, 46].

Hematological Effects

The effects of nitrous oxide are dose dependent and duration dependent. The hematological picture in cases of very high exposure to nitrous oxide (>1800 ppm) is consistent with deficiency of vitamin B_{12} [12]. In male dentists who have been exposed to more than 1800 ppm of nitrous oxide, bone marrow toxicity has been demonstrated [21].

> Hematological effects do not occur at levels seen in occupational exposures and should not be a risk for dentists and dental staff, with routine use of nitrous oxide in dental operatories.

Shorter procedures would not result in clinically significant changes [47–49]. Nitrous oxide with related hematological changes is seen after prolonged exposure [50] or after multiple short exposures [51]. Megaloblastic changes are seen when exposure is greater than 24 h at anesthetic concentrations [52, 53]. For exposure which are less than 24 h, stores of mature polymorphs are sufficient enough to prevent reduction in granulocytes in the peripheral blood [25]. It has been stated that the short-term exposure for less than 6 h has no potential of affecting the white cell counts [54]. Some studies have shown that the duration of exposure of nitrous oxide in excess of 6 h is required to provoke hematological changes and that these are preventable by folic acid supplementation prior to the start of procedure [55].

The effects of nitrous oxide-related vitamin B_{12} deficiency can cause the following:

1. Depression of bone marrow activity. This was first reported by Larsen et al. in 1956 [56].
2. Granulocytopenia.
3. Megaloblastic anemia.
4. Thrombocytopenia.
5. Leukopenia and decreased chemotactic effect of leukocytes [54].
6. Decreased phagocytic ability of lymphocytes for tumor cells.

If a patient suffers from latent vitamin B_{12}, folic acid deficiency (although thought to be rare earlier, but found to be more common recently) [57], or from bone marrow depression, then even a short exposure to nitrous oxide (<1 h) can cause development of clinical symptoms within a few days or weeks [58].

Among the pediatric population, we have to be careful with patients who have MTHFR (methylene tetrahydro folate reductase) deficiency. It is a rare autosomal recessive disorder characterized by progressive hypotonia, convulsions, and psychomotor retardation. A case has been reported in the literature in which a child (MTHFR deficient) who having been exposed to nitrous oxide twice during the course of receiving general anesthesia presented postoperatively with seizures and breathing distress. He unfortunately died a few days later as a result of respiratory arrest [59].

Most sensitive red cell markers of vitamin B_{12} deficiency were found to be within normal limits in pediatric patients who had received a large dose of nitrous oxide (received nitrous oxide as an anesthetic agent for major spinal surgery), indicating that regular erythropoiesis is not always affected by nitrous oxide [60].

Plasma Methionine Concentrations

In anesthetic concentrations, plasma methionine concentrations are 30% of preanesthesia level after 8 h of exposure and 20% after 24 h for exposure [53]. The level was found to be unchanged after 3 h of exposure.

Deoxythymidine Synthesis

Another sensitive indicator of disturbance in the synthesis of DNA induced by nitrous oxide is the deoxyuridine suppression test which is related to the disturbance in thymidylate metabolism [61]. There is a considerable individual variation which may be dependent on the previous reserves and general health of the patient (medically compromised patients may be more sensitive to nitrous oxide).

Immune Effects

Nitrous oxide has been associated with decreased proliferation of human peripheral blood mononuclear cells and with decreased as well as increased chemotaxis.

This has led to a concern that nitrous oxide may affect immune system [39]. The effect of nitrous oxide in the synthesis of WBCs is so distinctive that in early 1990s studies were published when nitrous oxide was used to potentiate the effects of chemotherapy in patients with acute myeloid leukemia and chronic myeloid leukemia. However, this practice was soon stopped because of the significant increase in side effects such as stomatitis, pneumonia, and sepsis in patients who had undergone mastectomy under nitrous oxide anesthesia followed by methotrexate/5-flourouracil therapy [7].

> Evidence is lacking for immune effects in dentists and their staff on occupational exposure.

Enigma Trial and Nitrous Oxide

No mention of the toxic effects of nitrous oxide is complete without mentioning the ENIGMA trial. ENIGMA trial compared the use of intraoperative oxygen (80%) in nitrogen (20%) versus nitrous oxide (70%) in oxygen (30%) in 2050 patients undergoing major surgery in multiple centers. This trial found an increased incidence of infection, pneumonia, and atelectasis in the nitrous oxide group when compared to the nitrous oxide free group [40].

However, the results of this study have to be considered keeping in mind a few caveats. The study design was designed to compare two groups, first, 80% oxygen–20% nitrogen and second group 70% nitrous oxide and 30% oxygen. Both oxygen concentration and balance gases vary. With two variables changing, we cannot know which is a critical factor, is it the higher concentration of oxygen in the first group, or is it the missing nitrous oxide which makes a difference. Also, the biochemical and hematological monitoring of patients was not standardized despite well known effects of nitrous oxide on methionine synthase. The study was also not blinded because those individuals diagnosing wound infection and deciding on discharge from hospital were aware of the treatment group since anesthetic records were available in the notes [39]. In the absence of a well-designed study, the interpretation of results of ENIGMA trial cannot be taken as a mandate on adverse effects of nitrous oxide. As of now, there is no evidence to suggest that nitrous oxide induces more immunosuppression than other anesthetics [39].

Renal and Liver Diseases

Correlation between chronic nitrous oxide exposure and renal/liver disease is not frequently found in literature [26, 62].

Hallucinations

Nitrous oxide has been reported to increase episodes of erotic hallucinations in patients [63–65]. Therefore, when treating adolescent patients in a pediatric dental practice, the dentists must ensure to have a parent or any other accompanying person to prevent any accusations of molestation.

Abuse of Nitrous Oxide

There are a few reports of abuse of nitrous oxide by dentists, but its incidence is lower when compared to other agents which have much higher abuse potential. Abuse related to nitrous oxide shall be discussed in the last chapter of this book.

Prevention of Clinical Effects Due to Exposure in Dentists and Dental Assistants

1. **Methionine**—Methionine may be taken by oral route to cover for shortfall due to inactivation of methionine synthase. Dietary items rich in methionine are nuts, beef, cheese, turkey, eggs, dairy, and beans.
2. **Folinic Acid**—There is a strong evidence that 30 mg of folinic acid may be administered twice daily when exposed to prolonged duration of nitrous oxide to prevent development of abnormal deoxyuridine suppression and megaloblastic marrow changes. Since this involves prolonged exposure to nitrous oxide, this may be of importance to dentists and dental assistants.

6.3 Conclusion

Nitrous oxide is a safe and effective method for allaying fear and anxiety and cannot be abandoned because of its potential hazards. Moreover, with proper scavenging in the operatories, chances of adverse effects are minimized. Reports of biological effects have been found only in instances of abuse or in dental offices where no scavenging is done. Prospective clinical studies on toxic effects of nitrous oxide which measure both concentration and duration of exposure in a dental operatory are lacking. Also, results of animal studies cannot be extrapolated to humans due to difference in species. Further, most of the research studying toxicity of nitrous oxide has been done using anesthetic concentrations of nitrous oxide. Nonetheless, every effort should be made by the dentist to reduce the exposure of office staff as well as the patients to excessive levels of nitrous oxide. The adverse effects due to long-term exposure to nitrous oxide are of higher significance to dental staff rather than the child patients.

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Sedation Using Nitrous Oxide in Children with Special Health Care Needs

7

Priyanshi Ritwik

Contents

Learning Objectives

1. Understanding the potential of nitrous oxide sedation for children with special needs.
2. Gaining knowledge on various technical considerations when using nitrous oxide for children with special needs.

Providing optimal dental treatment to this special group of our patients can be most satisfying yet the most challenging task for dentists. Various reasons such as difficulty in establishing communication, delayed neurodevelopment, absence of typical motor coordination and altered physiological parameters contribute to the

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challenges. These get compounded by increased fear and anxiety in patients and families towards accepting dental treatment. Using nitrous oxide in children with special health care needs not only reduces fear and anxiety but also decreases the number of pediatric patients having to undergo general anesthesia in order to receive optimum dental care. This chapter will address a few important conditions which a dentist usually encounters, and special considerations which can be taken to render adequate dental treatment to these children.

7.1 Asthma

Asthma is a chronic lung disorder characterized by inflammation of the airways and copious mucus secretion [1]. The airway gets narrow due to bronchoconstriction [1]. This results in associated symptoms, which can include coughing, wheezing, chest tightness, and shortness of breath [1]. Asthma classification is based on severity and frequency of symptoms, as shown in Table 7.1 [2]. Children with intermittent and mild persistent asthma can receive nitrous oxide safely for dental treatment.

7.1.1 Preoperative Assessment

Obtaining a thorough medical history in pediatric patients with asthma is important to determine the feasibility of using inhalational nitrous oxide in order to achieve anxiolysis before and during dental treatment. Frequency and severity of symptoms, functional limitations, night-time episodes, number of medications, compliance with medical care, and level of control are important factors to discuss with the parents of children with asthma. Only children with well-controlled intermittent and mild persistent asthma without a recent or active episode should be considered for dental treatment with nitrous oxide. A consultation with the pediatric pulmonologist may be necessary if the parents are unable to provide accurate information.

Table 7.1 Classification of asthma (Modified from NAEPP guidelines) [2]

	Intermittent asthma	Mild persistent asthma	Moderate persistent asthma	Severe persistent asthma
Symptoms	Cough, wheeze, tightness of chest, difficulty breathing	Cough, wheeze, tightness of chest, difficulty breathing	Cough, wheeze, tightness of chest, difficulty breathing	Cough, wheeze, tightness of chest, difficulty breathing
Frequency	<twice/week	3–6/week	Daily	Continual
In-between flare-ups	Brief	Effect activity	Effect activity	
Night-time episodes	<2/month	3–4/month	>5/month	Frequent

7.1.2 Technical Considerations

Nitrous oxide is not irritating to the tracheobronchial tree [3]. Inhalational nitrous oxide leads to anxiolysis, and since emotional stress can be a trigger for asthma [3], using nitrous oxide may actually reduce the likelihood of activating a known trigger or precipitating an acute asthma episode.

Use of nitrous oxide is not contraindicated in asthmatic children. It helps in reducing the probability of precipitating stress-induced asthma by reducing anxiety and stress during dental treatment.

The parent and child should be asked to bring the child's albuterol inhaler to the dental appointment, as this is the medical dose titrated to be most effective for the child. The dental office should always have an albuterol inhaler in the emergency medication kit as a backup. A dental practice which treats young children should also have a spacer to facilitate uptake of rescue albuterol. A pediatric spacer is shown in Fig. 7.1. The technique for administration of nitrous

Fig. 7.1 Spacer and albuterol for young children with asthma

Fig. 7.2 Restorative dental care provided with inhalational nitrous oxide and rubber dam isolation

oxide for children with asthma is the same as it is with healthy children. It is imperative to start with pre-oxygenation with 100% inhalational oxygen and to end the appointment with at least 5 min of 100% oxygen to minimize any adverse events. The dentist should utilize high volume suction and rubber dam isolation to prevent secretions and aerosols from triggering an acute asthma episode. Figure 7.2 shows the utilization of nitrous oxide with rubber dam isolation.

With accurate medical history review and proper administration technique, inhalational nitrous oxide is a safe and effective anxiolytic agent for children with asthma who exhibit dental fear and anxiety.

7.2 Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is a neurobiological behavioral disorder characterized by inattention, impulsivity, and hyperactivity [4]. It has its origin in early childhood and may persist into adulthood. It affects an individual's ability to focus on day-to-day tasks as well as interferes with their ability to regulate their activities consistent with their developmental age.

7.2.1 Technical Considerations

Children with ADHD are unable to stay still and/or quiet for a dental appointment [5]. They may experience a difficult dental appointment not due to dental fear and anxiety but rather due to the restlessness and/or talkativeness, which are inherent to ADHD [5].

First appointment should be restricted to building personal rapport and tell-show-do on various aspects of dental treatment. Use of nitrous oxide should be done using modelling. Rapid titration technique should be used to introduce nitrous oxide so that the child calms down and relaxes soon. Second visit should be used for desensitization to allow the child to understand the process of nitrous oxide and dental treatment in a better way.

Administration of inhalational nitrous oxide helps these children tolerate longer dental appointments with fewer disruptive behaviors. The timing of the dental appointment should be in close proximity temporally to the intake of medication(s). Most children with ADHD take medications in the morning, and therefore, their dental appointments should be scheduled in the mornings. Administration of nitrous oxide does not interfere with any systemic medications that a child may be taking for management of ADHD.

Short clear instructions should be given to the children and only one instruction should be given at a time. Signalling system and counting out should be used for every procedure. Counting can be gradually increased depending on the cooperation of the child. For example:

1. Let's count till three.
2. Very well done! Now, let's count backward from three.
3. Let's count five now. Take child's consent for this and proceed.
4. Gradually keep increasing the number depending on child's acceptance and comfort. Positive reinforcement is an important part of this process.

> Along with basic behavior guidance techniques, such as short morning appointments, positive reinforcement, and short scheduled breaks, nitrous oxide provides a safe and effective method to deliver dental care for children with ADHD.

7.3 Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a developmental disorder that affects communication and behavior. It is considered a developmental disorder because symptoms generally appear in the first 2 years of life. Autism is designated as a spectrum disorder because there is a wide variation in the type and severity of symptoms experienced by children with the condition [6].

The salient features of autism spectrum disorder per the DSM-V classification [7] are as follows:

A. **Persistent deficits in social communication and social interaction across multiple contexts.**
   1. Deficits in social-emotional reciprocity
   2. Deficits in nonverbal communicative behaviors used for social interaction
   3. Deficits in developing, maintaining, and understanding relationships
B. **Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history.**
   1. Stereotyped or repetitive motor movements, use of objects, or speech
   2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal–nonverbal behavior
   3. Highly restricted, fixated interests that are abnormal in intensity or focus
   4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment
C. **Symptoms must be present in the early developmental period.**
D. **Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.**
E. **These disturbances are not better explained by intellectual disability** (intellectual developmental disorder) or global developmental delay. Inadequate social communication is a good index to look at before arriving at conclusion that a child has both intellectual disability and autism spectrum disorder.

7.3.1 Preoperative Assessment

High caries prevalence, poor oral hygiene, and need for complex dental treatment present challenges for the dental team as a whole. These patients also have difficulty accepting dental treatment [8, 9]. There is a lack of an objective scale on the severity of autism in the medical literature. A modified adaptation of the severity of autism based on function and communication is presented in Table 7.2 [10]. This will enable dentists assess which patients with autism may be better candidates for attempting dental treatment in the office with nitrous oxide.

Based on this classification of severity of autism, a child with level 1 severity would be a good candidate for dental treatment with inhalational nitrous oxide. Depending on the presenting behavior and skill sets of the patient, dentists may also utilize nitrous oxide to facilitate dental care for children with level 2 severity. Anxiolysis with inhalational nitrous oxide can be utilized for these patients if they accept and keep the nitrous oxide delivery hood on their nose.

Table 7.2 Severity levels for autism spectrum disorder (Adapted from www.autismspeaks.org and DSM-5) [10]

Characteristics	Level 3	Level 2	Level 1
Support needed	Very substantial	Substantial	Needed
Verbal and nonverbal communication	Severe deficits	Marked deficits	Deficits
Coping with change	Extremely difficult	Difficult	Difficulty in changing activities
Repetitive behaviors	Marked and in all spheres	Frequent and observable to casual observer	Not an impediment
Example	A person with few words of intelligible speech, rarely initiates interaction and, when he or she does, makes unusual approaches to meet needs only. The person responds to only very direct social approaches	A person who speaks simple sentences, whose interaction is limited to narrow special interests, and who has markedly odd nonverbal communication	A person who is able to speak in full sentences and engages in communication but whose to-and-fro conversation with others fails, and whose attempts to make friends are odd and typically unsuccessful

Parents should be asked about biochemical abnormalities related to folic acid metabolism, vitamin B_{12} deficiency, and MTHFR deficiency in children with ASD. Use of nitrous oxide may be avoided in case of presence of any of these conditions.

7.3.2 Technical Considerations

If use of nitrous oxide is being considered for a child with ASD, the child should be given the time and opportunity to familiarize themselves with the equipment and dental operatory to be utilized. The child should be shown the room where treatment with inhalational nitrous oxide will be performed. The child should be allowed to touch, hold, and smell the nasal hood. An advantage of disposable hoods is that the child can be allowed to take the hood home and practice using it at home. It is important to help children with ASD to become familiar and comfortable with the operatory and equipment because routine, familiarity, and repetition improve behavioral outcomes in children with ASD. Rapid titration technique may be utilized by positioning the nasal hood slightly away from the nose in a standing or sitting position. Once the child relaxes, the child should be seated in the dental chair in the desired position.

A child with ASD should be allowed to explore the operatory devoid of anxiety-provoking environment such as presence of more dental staff, noise of dental drills or suction. Nitrous oxide can be introduced after building personal rapport.

Weighted blankets are often recommended by allied health professionals for young patients with ASD to assist with calming and relaxation [11]. Weighted blankets have a calming effect based on sensory integration. It is hypothesized that the deep pressure and consistent sensory input provided by weighted items reduces physiologic level of arousal and stress in children with autism. Thus, weighted blankets offer a relatively inexpensive and nonpharmacologic intervention. The weighted blanket can be used in conjunction with inhalational nitrous oxide to facilitate a successful dental appointment in children with ASD.

A non-communicative child may be a poor candidate for nitrous oxide sedation.

7.4 Cerebral Palsy

Cerebral palsy (CP) is a group of neurological disorders that appear in early childhood and affect gait, posture, balance, movement, muscle control, and muscular coordination. It may be caused by damage or abnormalities in the developing brain [12]. The range of physical limitations and behavioral complexities in children with CP varies greatly with each individual child.

Children with cerebral palsy are usually on long-term medication, and use of a sedative agent which may affect hepatic metabolism. Since nitrous oxide is an inorganic gaseous agent, it does not have any affect on hepatic metabolism, thereby making its use safe for these children.

Children with cerebral palsy may often have an autonomic imbalance characterized by the predominance of sympathetic action, which is marginally taken care by nitrous oxide, due to its ability to reduce heart rate within physiological parameters [13].

7.4.1 Technical Considerations

It may be difficult to deliver dental care to children with CP who have uncontrolled movements and/or behavioral challenges. In addition to basic behavior guidance techniques, dental treatment for children with CP can be facilitated with administration of inhalational nitrous oxide. Nitrous oxide has been shown to decrease stress in these patients, improve behavior, and facilitate better patient care in children with nitrous oxide. Inhalational nitrous oxide reduces untoward, uncontrolled movement in children with cerebral palsy [13]. Administration of nitrous oxide also decreases the orofacial muscle tonus while delivering dental care for children with cerebral palsy [14]. All of these factors make nitrous oxide an important adjunct to behavior guidance for children with cerebral palsy to help them receive dental care.

> Rolled towels and cushions may be used for comfortable positioning of children with cerebral palsy.

The child should be positioned in the dental chair in the posture which is most comfortable to the child without moving or forcefully repositioning any extremity or part of the body which has unique posture(s) due to hypertonic muscles. If the dental appointment is expected to be lengthy, all bony prominences, such as ankles, knees, and elbows, should be cushioned. The child should be introduced to the nitrous oxide delivery hood, and then the hood should be placed over the child's nose accommodating the natural head position of the child. If the child's head is tilted in any specific direction due to muscular tone and/or skeletal adaptations, the head should not be forcefully redirected for the dentist's convenience. Usually, after administration of nitrous oxide begins, the muscle tonus relaxes and the child may naturally reposition their head to a better alignment in the dental chair.

The technique for administration of nitrous oxide for children with CP remains the same as for healthy children with emphasis on pre- and post-oxygenation to prevent hypoxia. High volume suction should be used through the dental appointment to clear oral secretions, which can be copious in children with CP.

7.5 Epilepsy

Children with epilepsy have repeated seizures due to abnormal electrical activity in the brain [15]. The seizures may be managed with medications, diet, and/or device (such as vagal nerve stimulator). Children with epilepsy have dental treatment needs and anxiety, just as their healthy counterparts.

7.5.1 Technical Considerations

Only children with controlled seizures should be considered for elective dental care in an out-patient dental clinic. Inhalational nitrous oxide is an important adjunct to managing dental fear and anxiety in children with medically controlled epilepsy. Administration of nitrous oxide does not produce any changes in electroencephalograms of patients with epilepsy [16]. Increased stress, anxiety, dental pain, and/or dental infection increase the risk for seizures [15]. Hence, it is important to treat dental disease as well as allay fear and anxiety using nitrous oxide in children with epilepsy.

> Nitrous oxide is not epileptogenic and does not increase the risk for precipitating a seizure.

After a thorough review of medical history, type of epilepsy, frequency of seizures, assessment of triggers, and compliance with medications, the dentist may consider the use of nitrous oxide to reduce dental anxiety in a child with epilepsy. Occasionally, children with acute head injury may have seizures, and nitrous oxide should not be administered to children with acute head trauma. Nitrous oxide should be administered in children with epilepsy with caution to prevent hypoxia, as hypoxia may trigger the onset of a seizure. It is imperative to pre-oxygenate with 100% oxygen inhalation and administer 100% oxygen for at least 5 min after the completion of the dental procedure to prevent hypoxia.

7.6 Sickle Cell Disorder

Sickle cell disease (SCD) is a group of inherited red blood cell disorders caused by abnormal hemoglobin, causing the red blood cells to distort to sickle-shaped cells upon exposure to hypoxia, stress, or dehydration [17]. It is the most prevalent genetic blood disorder worldwide [17]. The two key characteristics are chronic hemolytic anemia and intermittent vasoocclusion. Vasoocclusion occurs from aggregation of sickled red blood cells and leads to sickle cell crises manifesting as episodes of acute and severe pain.

7.6.1 Preoperative Assessment

Prior to performing dental treatment for the pediatric patient with SCD, it is important to consult their hematologist/pediatrician to determine if dental treatment should be carried out in the dental office or if the child needs to be treated in a hospital setting. Often this answer can be obtained by taking a thorough medical history with emphasis on the following [18]:

1. Severity of their SCD and the frequency of sickle cell crisis.
2. Medications (including the use of antibiotics, folic acid, and nonsteroidal anti-inflammatory drugs).
3. Complications secondary to sickle cell disease (jaundice, splenectomy, bleeding disorders, renal issues, or growth impairment).
4. Treatment for SCD.

7.6.2 Technical Considerations

Elective dental appointments should be deferred during sickle cell crisis. Stress should be minimized during a dental appointment to prevent precipitating a sickle cell crisis [18]. Nitrous oxide can be an important adjunct to minimize stress involved in dental treatment [18]. Pre-oxygenation with 100% oxygen should precede delivery of nitrous oxide. During inhalational nitrous oxide, the child should receive at least 50% oxygen and must receive 100% oxygen for at least 5 min at the end of treatment to avoid diffusion hypoxia.

Pretreatment oxygenation with 100% oxygen and use of pulse oximeter during use of nitrous oxide in children with sickle cell disease must be considered.

While monitoring oxygen saturation is not routinely needed during the delivery of nitrous oxide, it is prudent to utilize pulse oximetry while delivering nitrous oxide to a child with SCD to ensure that a minimum of 95% oxygen saturation is maintained [19]. Figure 7.3 shows the use of pulse oximetry to monitor oxygen saturation.

It is imperative to maintain hydration in children with SCD as dehydration can precipitate a sickle cell crisis [19]. Hence, out of abundance of caution, it is also

Fig. 7.3 Use of pulse oximetry in children with sickle cell disease or cardiac conditions

prudent to encourage the child to drink water or balanced electrolyte solution after completion of dental care under nitrous oxide.

By reducing dental fear and anxiety with inhalational nitrous oxide, the dentist can provide much needed dental care for these children and reduce the likelihood of a sickle cell crisis by reducing stress related to the dental appointment.

7.7 Diabetes Mellitus

Children with a medical diagnosis of type I or type 2 diabetes mellitus can be successfully treated with inhalational nitrous oxide. Dentists should be prepared to treat children with diabetes in their practices due to increasing number of children being diagnosed with type 2 diabetes [20].

Diabetes mellitus does not represent a contraindication to use of nitrous oxide. As with any chronic systemic disease, the dentist needs to obtain a thorough medical history, medications, average and current blood glucose levels, compliance with care, and consultation with endocrinologist. Provided the child has adequate glycemic control and compliance with medical care, nitrous oxide can be administered to facilitate dental treatment.

> Prevention of hypoglycemia should be kept in mind while timing the appointment in children suffering with diabetes mellitus.

7.7.1 Technical Considerations

The dentist should schedule the appointment such that the 2-h fasting recommendation does not interfere with the child's mealtime or timing of diabetes medication(s). The most suitable dental appointment time for these patients is usually mid-morning since these children usually take their medications after breakfast. A 2-h fasting and an average 1-h dental appointment will ensure that the patient is in time for the lunch time and the next dose of their medication. The dentist should consult the child's endocrinologist if the fasting periods may interfere with scheduled medications or meals [19].

7.8 Intellectual Disability

Children with intellectual disability or cognitive impairment may exhibit uncooperative dental behaviors as well as oro-motor sensitivity and gagging [21]. These children often have difficulty with dental evaluations and treatment. Nitrous oxide is an important armamentarium for dentists who treat this patient population, as it can help avert dental treatment under general anesthesia and the associated risks.

Nitrous oxide has been shown to increase the success rate of delivering dental treatment in children with intellectual disability [22]. It is an important adjunct to behavior guidance for these children, provided they can tolerate the nitrous hood on their nose and face for the delivery of the gaseous mixture [23].

A sincere and genuine effort should be made by using nitrous oxide before deciding to use general anesthesia in children with intellectual disability.

Many children have oro-motor sensitivity and gagging, either in association with intellectual disability or as an isolated finding. Inhalation nitrous oxide has proven to be highly effective in eliminating or at least minimizing severe gagging [24]. Impressions, radiographs, or other procedures may be made little easier by using nitrous oxide to reduce the gag reflex associated with these procedures.

Facial expressions, gestures, physical contact, models, videos, and demonstrations can play a major role for children with intellectual disability. The dentist should not realy entirely on verbal instructions to elicit cooperation from a child with cognitive delays.

In summary, when children with varying disabilities need dental treatment, outpatient treatment with nitrous oxide should be attempted, and dental treatment under general anesthesia be considered only if inhalational sedation is ineffective.

7.9 Congenital and Acquired Heart Disease

Children may present with congenital or acquired cardiac conditions [25]. Irrespective of the underlying cardiac diagnosis, it is important to provide preventive and restorative dental care for these children to maintain oral health and function. Oral disease increases morbidity and mortality in children with cardiac disease by different mechanisms [26]. The mouth is a portal of entry for microbial infection [26]. Bacteremia may cause injury by directly damaging the epithelium and indirectly by generating an inflammatory response [26]. In more severe cases, oral disease may also compromise nutrition, which in turn may have a deleterious effect on the course of the underlying cardiac condition and growth of the child.

Stress and pain secondary to the dental appointment may generate catecholamine release enough to compromise hemodynamic stability. In an attempt to limit stress and pain in this vulnerable population, the dentist should consider all behavior guidance strategies to allay dental fear and anxiety for these children.

7.9.1 Technical Considerations

After a thorough medical history and consultation with pediatric cardiologist, the dentist can administer inhalational nitrous oxide for anxiolysis to facilitate dental care. It is imperative to start the appointment with pre-oxygenation with 100% oxygen, deliver at least 50% oxygen while administering nitrous oxide, and administer 100% oxygen for at least 5 min at the end of the appointment. In this patient population, it is prudent to monitor oxygen saturation with pulse oximetry, with the goal to maintain oxygen saturation at or above 95% for acyanotic children.

Continuous monitoring using pulse oximeter should be done in children with cyanotic heart disease, undergoing dental treatment using nitrous oxide.

If the child is cyanotic at rest and/or baseline, the safety of performing dental treatment in a non-hospital setting should be discussed with the pediatric cardiologist. It is usually best to treat these children within the safety net of a pediatric hospital.

When considering nitrous oxide inhalation for children with cardiac conditions, all other precautions such as need for prevention of bacterial endocarditis and coagulopathies should be implemented in addition to the nitrous oxide protocol.

7.10 Other Conditions

7.10.1 Down Syndrome

Children diagnosed with Down syndrome have hypoplastic maxilla predisposing them to persistent nasal congestion.

7.10.2 Cleft Palate

Children with cleft palate have oro-nasal communication, and mixture of gases can dilute the inhaled concentration of nitrous oxide. To prevent this, an acrylic obturator should be worn by the patient or 2″ × 2″ gauze tied with 18″ long floss may be placed superficially within the cleft [27, 28].

7.10.3 Spinal Deformities

Mechanical deformations or postural changes may cause alterations in the normal breathing and chest movements in children with spinal deformities. A dentist should be able to identify such changes which may be normal for that child. Children having kyphosis or scoliosis generally have altered ventilations and limited flexibility of thier chest [27, 28].

7.10.4 Chest Deformities

Children with chest deformities such as pectus excavatum, spastic contractures (as in cerebral palsy), or neuromuscular disorders involving muscles of respiration such as in Werdnig-Hoffman, myotonic dystrophy, and muscular dystrophy have extreme ventilatory aberrations [27, 28]. Dental treatment with the use of nitrous oxide should be considered only after consultations with the trating pediatric pulmonologist.

7.11 Conclusion

Nitrous oxide, with its analgesic and anxiolytic properties, is a useful agent for special children who are likely to have high degree of dental anxiety [28]. Also, being relatively safe makes it a preferable agent for use in these children. Rapid titration, adequate oxygenation, and desensitization are important considerations for using nitrous oxide successfully in children with special health care needs.

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Past, Current, and Future of Nitrous Oxide Usage in Pediatric Dentistry

8

Amit Sethi and Jyotsna Gupta

Contents

Learning Objectives

1. Understand how nitrous oxide evolved into a useful sedative and anesthetic agent
2. Get an insight on the pitfalls in history of nitrous oxide and reasons behind it
3. Gaining knowledge on the abuse potential of nitrous oxide
4. Take cognizance of effects on the environment due to nitrous oxide gas

The journey of nitrous oxide from its discovery has witnessed a path similar to that of a roller coaster with bouts of its widespread use to spells of rejection. Initially, it had a widespread use as a recreational agent because of its euphoric properties. After gaining much popularity, it was embarked on a platform from where its association with dentistry became unbreakable due to its analgesic properties.

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Today, on one hand, the "future of nitrous oxide" in anesthesiology is being questioned and its use in operating rooms has decreased; on the other hand, its use for "recreational purposes" has increased manifold. It was almost as if the clock is turning back 200 years to where it all began! Adolescent age is a period during which children like to have new experiences and may get enthusiastic about using nitrous oxide for hysteria and euphoria.

Nitrous oxide has facilitated the care of many patients in our offices who otherwise would have had no option except to go under general anesthesia for delivery of dental care which in turn would mean a huge implication in terms of resources involved. In this chapter, we will look at some of the issues surrounding nitrous oxide and then try to see if the advantages still are enough to carry it into the future!

8.1 History of Nitrous Oxide

The story of the discovery of nitrous oxide is actually the mirror through which we can see the development of anesthesia and pain control as we know it today. We will appreciate the development of anesthesia more if we realize that there was a time, not too long ago, when surgeries were being done without any form of pain control let alone general anesthesia. The history of nitrous oxide and its evolution can be divided into different time periods depending on its development, usage, and acceptance.

8.1.1 Era of Discovery

The earliest reference to nitrous oxide can be found in lecture notes made by a student named Thomas Cochrane who was studying at University of Edinburgh under Scottish physician and chemist Joseph Black. In his notes made in the years 1776–1778, he recorded that "Ammon Nitros (Ammonium Nitrate): is the most fusible of common salts; when heat is increased (it) is copiously converted into vapour." Many historians believe that this is a reference to the common method of preparing nitrous oxide by heating ammonium nitrate (which is still used today). However, in the absence of any published work on nitrous oxide by Joseph Black, the credit for isolating nitrous oxide is given to Joseph Priestly (Fig. 8.1) who is believed to have isolated the gas in 1772 [1].

Joseph Priestley is credited with the isolation of nitrous oxide gas and Sir Humphry Davy with highlighting its euphoric and analgesic properties.

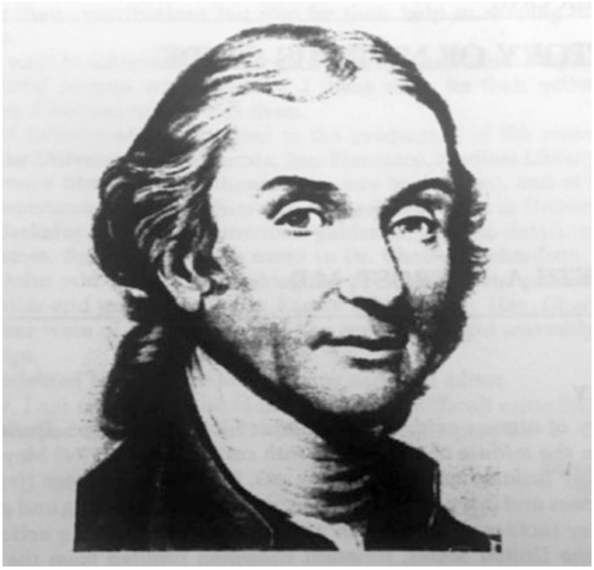
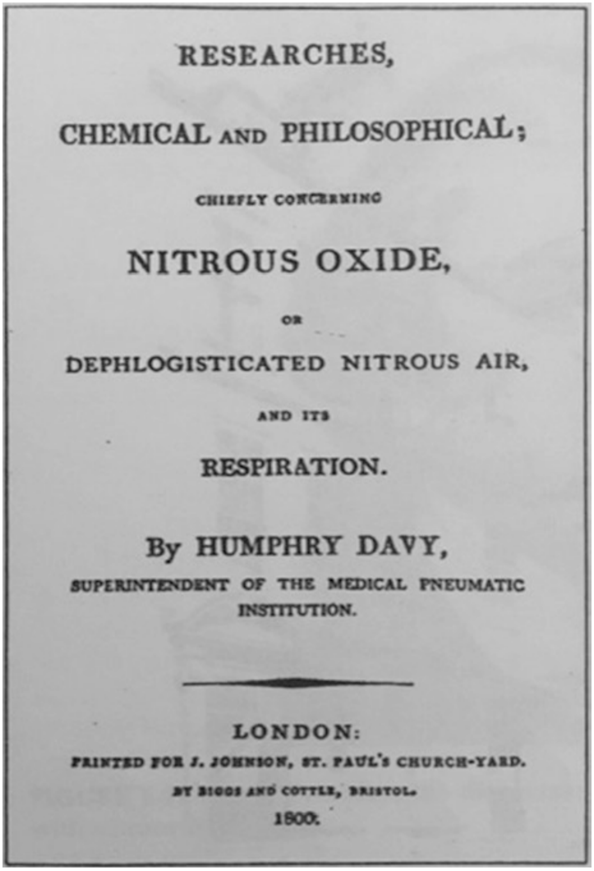


Fig. 8.1 Joseph Priestly who also discovered oxygen is credited with isolating nitrous oxide. (Source: Nitrous Oxide—Edmond I. Eger II)

Among the many new branches of science being developed at that time, there was one which dealt with the study and use of vapors and gases. This branch of medicine was called "pneumatic medicine" and for its advancement "Pneumatic Institute" was established in Bristol, England. It was here that Sir Humphry Davy began experimenting with nitrous oxide and also published a book titled "Researches, Chemical and Philosophical; chiefly concerning nitrous oxide" (Fig. 8.2). He also took an interest in the effects of inhalation of nitrous oxide, and on one such occasion after self-administering the gas to relieve himself of toothache and gingival inflammation, he noted that "pain always diminished after first four or five inspirations….as nitrous oxide in its extensive operation appears capable of destroying physical pain, it may probably be used with advantage during surgical operations in which no great effusion of blood takes place" [2].

8.1.2 Laughing Gas Exhibitions and Parties

Despite having realized the possible value of nitrous oxide as an analgesic, it did not attain the popularity it should have, partly because around this time, the gas because of its "euphoric and dizzying effects" was being used for entertainment and enjoyment among young people as a part of "laughing gas demonstrations" (Fig. 8.3). These demonstrations which used to be carried out as a part of exhibitions and shows that travelled around smaller towns and cities involved



RESEARCHES,

CHEMICAL AND PHILOSOPHICAL;

CHIEFLY CONCERNING

NITROUS OXIDE,

OR

DEPHLOGISTICATED NITROUS AIR,

AND ITS

RESPIRATION.

By HUMPHRY DAVY,

SUPERINTENDENT OF THE MEDICAL PNEUMATIC INSTITUTION.

LONDON:

PRINTED FOR J. JOHNSON, ST. PAUL'S CHURCH-YARD.

BY BIGGS AND COTTLE, BRISTOL.

1800.

Fig. 8.2 The first book written on nitrous oxide by Sir Humphry Davy. (Source: Nitrous Oxide—Edmond I. Eger II)

men inhaling the gas by the means of rubber balloons which were filled with nitrous oxide [1, 3]. The idea was to cause euphoric effects in people in a social setting so that they could feel euphoric and “laugh, sing, dance, speak, or fight.”

> Nitrous oxide was termed as laughing gas because of its ability to bring about a feeling of euphoria.

The idea that a gas which was being used for enjoyment could also be used to diminish pain, did not gain acceptance and for many more years, people would continue to have surgical procedures done with no means of analgesia or anesthesia [4].

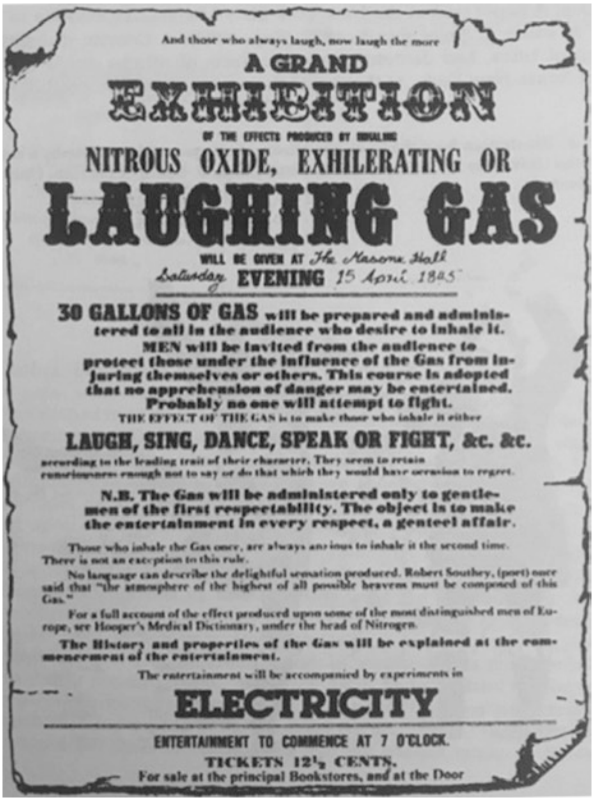


Fig. 8.3 Bills such as these advertised the "euphoric effects of nitrous oxide." (Source: Nitrous Oxide—Edmond I. Eger II)

8.1.3 The "Demonstration" and a Tragedy

This was the time when nitrous oxide gained little more popularity, thanks in part to the effort of Colton and Horace Wells. Horace Wells (Fig. 8.4) is credited with the introduction of anesthesia in the United States. Apart from Wells who is well known, there was one more man who has had very little recognition and reward. His name was Gardner Quincy Colton (Fig. 8.5), and the statement "Had there been no Colton, there would have been no Wells" rightly sums up his contribution [5].

Colton who has also been called the "pioneer of nitrous oxide anesthesia" entered the Crosby Street College of Physicians and Surgeons in New York and probably learnt the effects of nitrous oxide during his medical studies, as medical students often experimented with this gas during that time. He left medical school without taking a degree and began lecturing on different scientific topics including nitrous oxide [6]. During these lectures, several "volunteers" were invited to experience the

Fig. 8.4 Horace Wells. (Source: Picture courtesy—Smith W.D.A. A history of Nitrous oxide and oxygen anesthesia. Part V: The crucial experiment, its eclipse, and its revival. British Journal of Anesthesia 1966; 38: 143–156)

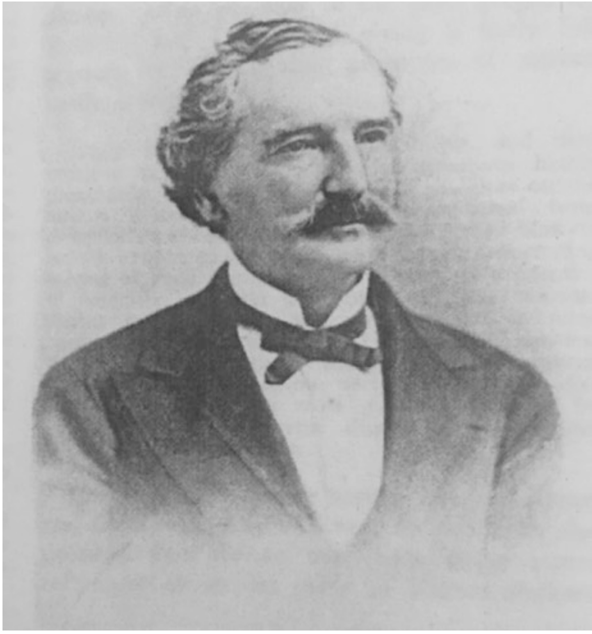


Fig. 8.5 Gardner Quincy Colton. (Source: Smith W.D.A. A history of Nitrous oxide and oxygen anesthesia. Part V: The crucial experiment, its eclipse, and its revival. British Journal of Anesthesia 1966; 38: 143–156)

effects of the gas. Dr. Horace Wells, who was practicing as a dentist, was in the audience for one of the lectures and happened to notice that a man named Cooley after having inhaled 100% nitrous oxide became intoxicated and injured himself while running around the stage. Despite the injury and bleeding, he was neither uncomfortable nor aware of the injury.

Dr. Horace Wells was the first to establish the use of nitrous oxide in dentistry.

This observation convinced Dr. Wells that nitrous oxide does alleviate pain and in order to be sure he requested Dr. Colton to serve as an anesthesiologist for extraction of his own tooth by a dentist called Dr. John Riggs. Wells would later testify that he was totally unaware of the procedure and that he had been no pain. Colton would go on to teach the process of manufacturing of nitrous oxide to Wells who began using it routinely with great success [3].

In December 1844, in order to gain acceptance and find "takers" for his discovery, Wells decided to demonstrate the usefulness of gas to faculty and students of the Harvard Medical School. Wells administered nitrous oxide to a medical student who volunteered to have his tooth extracted after inhaling the gas. After giving the gas for some time, the inhaler had to be removed in order to do the extraction. It was at this point when extraction was attempted that the patient cried out (Fig. 8.6). The people who had gathered to see the demonstration got the impression that the procedure had been a failure and labeled Wells as an imposter.

Dr. Horace Wells experiment at Harvard Medical School was not a failure of nitrous oxide gas but had undesired result due to an error in technique.

Fig. 8.6 Crying patient during demonstration by Horace Wells at the Harvard Medical School. (Source: George S. Bause; Horace Wells' "Humbug Affair" Occurred at Massachusetts General Hospital? Humbug!. *Anesthesiology* 2013;119(5):1009–1010)

Wells (1847) himself describes the whole episode in these lines "I was then invited to extract a tooth for a patient in the presence of the medical class, where operation was performed, but not entirely successful, because the bag was removed too soon; and as the man said he experienced some pain, the whole demonstration was denounced as an imposition, and no-one was inclined to assist me in further experiments" [7].

The patient on awakening said that he had no recollection of crying out loud or of the attempted extraction. These certainly appear two different perspectives and the audience's perception of failure can be attributed to the fact that when the mask was removed to do the extraction, the patient who started breathing room air started to regain consciousness and hence the sudden cry [6]. The whole exercise could have been a success if Wells had the company of an assistant who would ensure that the mask was on all the time.

This failure shook him up and Wells ended up committing suicide a few years later by cutting the femoral artery in his left thigh, after having used chloroform to produce analgesia [8]. In 1864, 16 years after his death, Wells was credited with being the person responsible for the introduction of anesthesia [3].

8.1.4 Revival of Nitrous Oxide

The popularity of nitrous oxide which had waned after the death of Wells was revived by Colton who began using it extensively in dental extractions. He opened institutes all over America which specialized in extracting teeth with nitrous oxide anesthesia. They used 100% nitrous oxide as an inhalation gas (Fig. 8.7) to facilitate extractions in more than 120,000 patients [8].

The rationale of not using oxygen laid in the false belief that the oxygen attached to the nitrogen part of nitrous oxide would be sufficient to provide oxygen to the tissues. Fortunately, despite being based on an incorrect belief, Colton did not lose a single patient to nitrous oxide anesthesia.

It was around 1868 that Andrews proposed adding 20% oxygen to nitrous oxide and claimed that this was "the safest and most pleasant than any anesthetic mixture known then" [9]. Who knew that what Andrew proposed would still hold true 150 years later! Andrews also suggested that the anesthetic use of ether and chloroform would be safer by combining these with 70% nitrous oxide and oxygen. This made it safer to do longer operations and the foundations of balanced anesthesia were laid. In 1872, liquid nitrous oxide became available for the first time to the dentists and physicians in England. This was a big change as they did not have to make their own gas which often had impurities [3].

It was only after 1868 that nitrous oxide began to be used in combination with oxygen. Before that, it was used as 100% nitrous oxide.

Fig. 8.7 Early method of administering nitrous oxide during extractions was simple but crude. (Source: Nitrous Oxide—Edmond I. Eger II)

As changes were being made with regard to the proportion of nitrous oxide administered to patients, there were also developments in terms of hardware used to administer gases. In 1887, Fredrick Hewitt made a machine (Fig. 8.8) which had two separate rubber bags to deliver nitrous oxide and oxygen. This period was also the time when nitrous oxide began to be used by Klikovitsch in Russia to alleviate pain during child birth [10].

8.1.5 Nitrous Oxide as an Anxiolytic

During the first half of the twentieth century, the analgesic properties of nitrous oxide remained the primary focus, and in most dental offices it was being used to control pain during extractions (Fig. 8.9).

Though most dentists at this time were using nitrous oxide and oxygen in the ratio of 80:20, there were still practitioners who were using 100% nitrous oxide. This technique of administering pure nitrous oxide was called "blue gassing" and continued to be used even after the second world war. Seldin called this method as "straight nitrous oxide." Since this technique caused asphyxia, the duration of the procedure was limited to 2–3 min which meant that the dentist/surgeon had to work extremely fast and with "little regard for the oral tissues" [11].

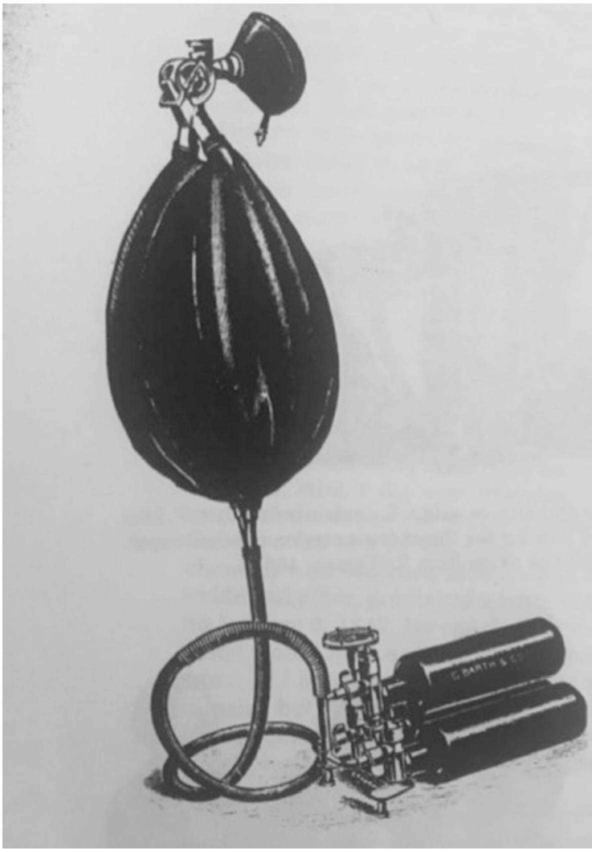


Fig. 8.8 Sir Fredrick Hewitt's apparatus to give nitrous oxide and oxygen. (Source: Nitrous oxide—Edmond I. Eger II)

In 1939, Courville published a book detailing the harmful effects of hypoxia with nitrous oxide even when used with 20% oxygen [12]. This and the fact that the duration of procedures with previous technique had to be extremely short led to the development of new techniques in which lower concentrations of nitrous oxide began to be used. Dr. Harry Langa, who is often credited with reviving the use of nitrous oxide in a dental office, recommended using it alongside 20–30% oxygen and as a substitute for local anesthetic. His technique was later modified by lowering the amount of nitrous oxide and came to be known as nitrous oxide–oxygen conscious sedation or what is currently known as nitrous oxide–oxygen minimal sedation [13].

Increasing oxygen concentration in nitrous oxide oxygen sedation widened its use for anxiolysis rather than just for analgesia.

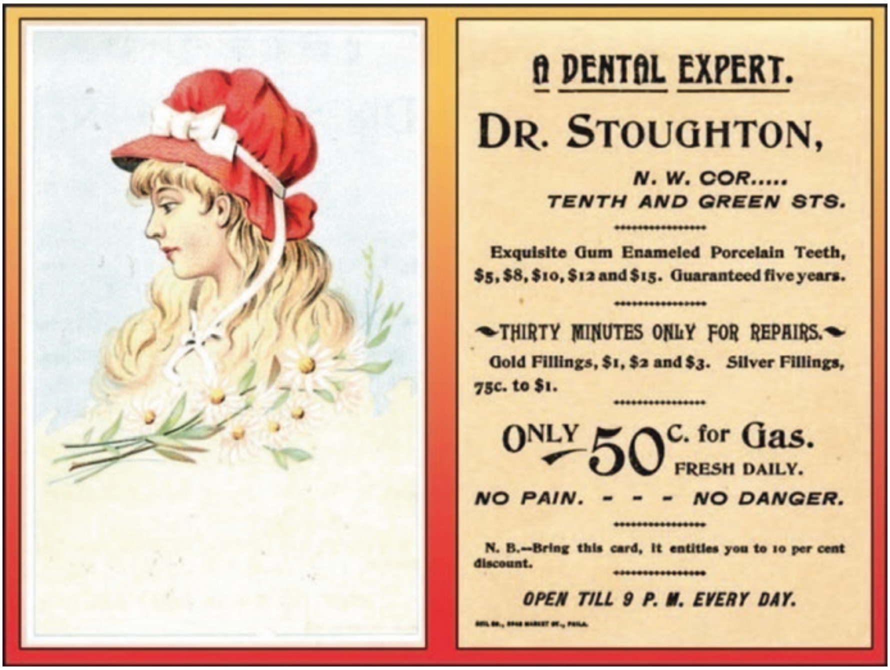


Fig. 8.9 A pamphlet advertising the "availability of gas" which is prepared fresh daily for dental treatment and also proclaims "no pain-no danger"

The introduction of local anesthetic in the form of lidocaine in 1945 caused a paradigm shift in the management of pain. This also altered the main role of nitrous oxide in the dental office. Nitrous oxide instead of being used as an analgesic, now began to be used as an anxiolytic and to help patients relax before and during the dental treatment [14].

8.1.6 Using Nitrous Oxide Sedation in Children

Earlier it was felt that children were not suitable patients to receive nitrous oxide but in 1925, a physician, John S. Lundy, specifically described its use as an induction agent to prepare children for extractions. A dentist named Leonard Ray (1929) advocated inducing patients with 90% nitrous and 10% oxygen for 30 seconds, thus quickly moving them towards surgical anesthesia and then lowering the oxygen even further to 7% for the remaining duration of procedure. He felt that this would ensure that dentistry could be performed unhindered. He was also a great advocate for behavior management techniques such as suggestion, demonstration, and encouragement especially in order to introduce the nasal mask [15].

In 1972, Amian shared his 15 years of experience of having used nitrous oxide during cavity preparation in children. He favored using nitrous oxide–oxygen in a ratio of 60:40 and found it to be safe in more than 50,000 applications. He noted that both analgesic and euphoric effects of nitrous oxide were beneficial to the child patients [16]. In 1973, Roth and Sorenson emphasized the value of using inhalation sedation with nitrous oxide–oxygen in order to reduce the children's fear of injections [17]. They laid stress on making use of its anxiolytic or euphoric properties, when used with nitrous oxide concentration being less than 40%, rather than using it as an analgesic, with nitrous oxide concentration of more than 40%.

Nitrous oxide–oxygen finds its use in pediatric dentistry because of its euphoric, anxiolytic, and analgesic properties.

8.1.7 The Era of "Formal Training" and the Widespread Use of Nitrous Oxide

In 1953, the American Dental Society of Anesthesiology (ADSA) was formed in order to "encourage study of anesthesiology; to encourage specialization in anesthesiology; to foster higher standards of education in dental schools" [14]. Dr. Langa who began using nitrous oxide in 1936 presented his first course in 1949 and by 1976 had trained more than 6000 dentists [3]. This period marked the introduction of inhalation sedation as a course in some dental schools, and this provided the first platform for organized teaching for that generation of dentists.

In 1985, a Consensus Development Conference on Anesthesia and Sedation in Dental office sponsored by NIDR, FDA, and NIH was the first to issue guidelines for the administration of anesthesia and sedation in dental office [15]. Plans to make dental anesthesiology a separate specialty were not well received by the American Association of Oral and Maxillofacial Surgeons who considered this as a possible encroachment on their exclusive ability to provide anesthesia for patients.

At present, nitrous oxide is a part of curriculum in almost all the dental schools in North America. The belief and knowledge that "pain and anxiety control is essential to the delivery of dental care" has been shared by patients and their providers and is more than adequately presented by the story of development and evolution of nitrous oxide.

8.2 Abuse of Nitrous Oxide

As we learnt in the previous section in beginning, nitrous oxide was mainly used for "entertainment" purposes. It was later that its anesthetic and analgesic properties were realized, and it was then used as such for a long time. But today in the presence of newer agents, its use as an anesthetic agent is becoming less popular. However its use as a "recreational agent" has become more common in recent years. Low cost and easy availability have helped it to gain traction with people who wish to use it as such. In this section, we will learn more about the "abuse" of nitrous oxide and its adverse consequences.

8.2.1 What Makes Nitrous Oxide an Ideal Agent for Recreational Use?

The properties which make it a favorable anesthetic drug also account for its popularity as a recreational agent. It has a very rapid onset of action and effects like "euphoria, excitement, heightened consciousness and disinhibition begin within seconds of inhaling the gas" and peak at 1 min after inhaling the gas. Similarly, the "recovery" is also swift and the effects disappear after 2 min [18, 19]. With no hangover effect, the user can resume his activities almost immediately [18].

> Quick onset of excitement, disinhibition following inhalation of nitrous oxide made it popular as a recreational agent.

8.2.2 Regulation Surrounding Nitrous Oxide

Since nitrous oxide is not a regulated substance in the UK, its use is subject to "Misuse of Drugs Act" of 1971 [19]. In the UK, the sale of nitrous oxide in large cylinders as an anesthetic agent or as a medicinal product is regulated by Medicines and Health care products Regulatory Agency (MHRA), and there are restrictions on who can supply the gas or who can administer it. However, nitrous oxide sold in small canisters is not subject to Human Medicines Regulations [19].

In the United States also, nitrous oxide is not a controlled substance so while it is illegal to possess heroin it is not illegal to have nitrous oxide as long as it is for a legitimate purpose. Its use in the United States is regulated by Food and Drug Administration and not by Drug Enforcement Agency (DEA). However, possession of nitrous oxide with intent to inhale it is considered a misdemeanor in most states in the United States [18].

8.2.3 Epidemiology of Abuse of Nitrous Oxide

The use of nitrous oxide as a recreational agent has been increasing in the UK and parts of Europe. According to a survey done in the UK, nitrous oxide was the second most common recreational drug used by young people (age 16–24) which suggests its ease of availability among the youth [19]. Nitrous oxide is used in food industry as a mixing and foaming agent in the production of whipped cream (Fig. 8.10). It is also used in automobile industry as a fuel booster to increase the speed of racing cars.

- One study in 2009 [20] involved conducting a survey in adolescents between the ages of 13 and 17, Missouri Division of Youth Services, USA (DYS) who were committed to one of 27 facilities through juvenile court; there were 723 interviewed as a part of the study. Of those:
  - 15.8% had ever abused nitrous oxide in any form
  - 57% of those who abused nitrous oxide did so via whippets (whipped cream chargers)
  - 38.6% abused nitrous oxide directly from whipped cream cans
  - 39.5% inhaled the gas through another form, like a balloon
  - Multiple methods of abuse were reported by those who abused nitrous on several occasions
  - 77.2% of the lifetime nitrous oxide users reported abusing the substance in the year prior to entering the facility

Nitrous oxide can easily be obtained from any of these sources. In the UK, it is also available from street vendors, catering companies, and through home delivery [18]. It is used in settings like clubs, parks, and festivals where it is commonly sold in small metal canisters containing the gas. These 10 cc canisters contain 8 g of nitrous oxide and can produce about 8 L of nitrous oxide at standard temperature

Fig. 8.10 Nitrous oxide is a component of bottles of whipped cream, also shown are the whippets (silver color), crackers (gold)

and pressure. The gas is transferred into balloons for inhalation using a puncturing device called "charger" or a cracker [18]. These canisters can also be obtained online where they are sold under the category of "whipped cream propellant" or "whippets" [19]. "Nagging or nanging" is a common term used to describe the act of inhaling nitrous oxide from the bulbs. The balloons are then rapidly deflated into the user's mouth, therefore, also called by the name "ballooning." Abusers acquire large amounts of food additive aerosol cans and empty their contents while trying to keep the cartridges intact. Cartridges are then punctured and inhaled through the nose which is commonly nicknamed as "canister." Nitrous oxide is also a part of culture called "hippy crack" which is prevalent in some clubs and music festivals and which involves "inhaling the nitrous oxide." There have been 17 fatalities related to the use of laughing gas in the UK between 2006 and 2012 [18].

Despite the increasing episodes of abuse in recent years, many dentists and physicians are not aware of this and may not recognize the effects of abuse even if they were to see a patient with it. Next part of the chapter will look at some manifestations of acute and chronic abuse of nitrous oxide.

What is acute and what classifies as chronic is not universally defined. Just to give a perspective to our readers on this, one publication discussing the same topic has classified acute as being a period of less than 2 weeks, whereas chronic is anything more than 3 months with subacute falling in between these two categories [21]. We are somewhat in consensus with this but also want to stress that acute is something that happens sooner than later after using a substance. So we have tried to classify them by mentioning the effects which are seen almost immediately as acute whereas those that are seen after some weeks or months as chronic.

8.2.4 Acute Effects of Recreational Use of Nitrous Oxide

There have been multiple case reports in literature which have shown that if nitrous oxide is inhaled in an enclosed space (such as by using a bag over the head, as is done by people to get "more high" or those trying to commit suicide), then it can lead to hypoxia and subsequent death [22]. In these cases, the source of nitrous oxide was found to be either nitrous oxide cylinders or the "whippets." Even a small "whippet" can decrease the percentage of oxygen available from 21 to 9%. If the person using nitrous oxide is in an enclosed space or has his head covered, then hypoxia and asphyxia can occur rather quickly. Nitrous oxide also has the potential to blunt the normal physiological response to hypoxia, thereby further increasing the risk of the worst possible outcome [22].

> People abusing nitrous oxide in large quantities may experience disorientation and have weak motor control and reflexes, thus being a risk for themselves and others especially if they drive or operate heavy machinery soon after abusing it.

This is the reason why many centers/clinics make it mandatory for patients receiving nitrous oxide to be accompanied by an attendant while going home. Another acute effect reported in literature includes pneumomediastinum which occurs due to "rupture of alveolar walls secondary to high intra-alveolar pressure caused by inhaling pressurized nitrous oxide from a whippet" [23]. Frost bite of face and hand has been reported both as an occupational hazard in anesthetists and other team members handling nitrous oxide cylinders as well as in people trying to use nitrous oxide for "recreation." The gas is stored in cylinders as a colorless liquid. When the valve is opened, some of the liquid turns into gas and escapes through the valve. The temperature of the gas coming out near the outlet is "as low as −55 °C, and this can cause frostbite injuries to the part of skin coming in contact with the gas [24]. Less than serious consequences are seen in people using nitrous oxide in low concentrations (20–30%) and may range from impaired memory and recall, learning difficulties, reduced psychomotor performance, and confusion. But these effects gradually subside within 5 min post-inhalation.

8.2.5 Long-Term Effects of Nitrous Oxide Abuse

The two main effects seen in people who use nitrous oxide regularly over a period of several weeks and months are related to the effects of nitrous oxide on the metabolism of vitamin B_{12}. This aspect has been covered in detail in Chap. 6.

8.2.6 Nitrous Oxide Dependency

There is no concrete evidence to show that nitrous oxide causes psychological dependence and cases of isolated nitrous oxide addiction have not been reported by addiction centers. In some parts of the world, especially in the UK and Europe, its use has increased but in comparison to other agents its use is relatively safe.

8.3 Nitrous Oxide: "Not as Inert as We Thought"?

In recent years, the voices which are urging the scientific community and medical profession to look beyond nitrous oxide have certainly become more prominent. One of the reasons behind it is the environmental concerns associated with its usage. In this section, we will look at some of those concerns.

8.3.1 Climate Change: Why Are We Worried?

The World Health Organization has recently called climate change as the "defining issue for health systems" in this century, but ironically, the health industry itself is the leading emitter of carbon dioxide and accounts for more than eight percent of

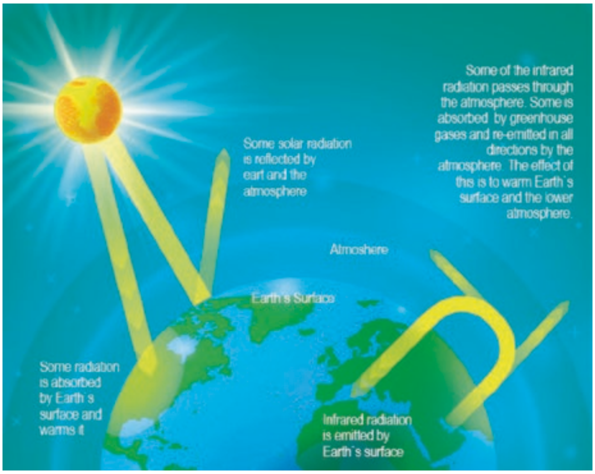


Fig. 8.11 The greenhouse effect

carbon dioxide emissions in the United States alone [25]. WHO believes that the climate change accounts for about 0.3% of all deaths and this number is expected to increase in the coming years [26]. With increasingly poor quality of air, it could be due to higher incidence of chest diseases, asthma, and cardiovascular diseases. Increasing temperatures may mean a faster spread of infectious diseases, melting glaciers, and rising level of our oceans, thus challenging our future and survival. It therefore makes sense for us to minimize our negative impact on the environment.

8.3.2 Role of Nitrous Oxide in Depleting Ozone Layer

In the past, many papers have stressed that nitrous oxide is a major contributor to green house effect. In a paper published in Science in 1976, the authors looked at green house effect (Fig. 8.11) caused by trace gases and looked at the role of nitrous oxide along with methane and ammonia in detail [27]. In that paper, the authors emphasized that decay of organic matter and fertilizers was the main source of nitrous oxide in the atmosphere. About 70% of atmospheric emissions of nitrous oxide are natural, mostly from breakdown of nitrogen by bacteria in the soil and ocean. Human activities including agriculture, use of fertilizers, and the production of nitrogen fixing crops are responsible for the remaining 30% of nitrous oxide emissions.

However, the world changed significantly between 1976 to now and the scope and amount of activities we did to contribute nitrous oxide to atmosphere increased manifold and what was thought to be trace substance in 1976 [27] became dominant and in year 2009, in the same journal *Science*, a paper was published which was called **Nitrous Oxide: The Dominant Ozone-Depleting Substance Emitted in the 21st Century** [28]. This paper and many others published since then have emphasized the increasing role of nitrous oxide in having a negative environmental impact.

Fig. 8.12 Chemical reaction which forms the basis of "destruction of ozone" by nitrogen oxides. (Source: Science (326) 2009: 123–125)

$$NO + O_3 \longrightarrow NO_3 + O_2$$
$$O + NO_2 \longrightarrow NO + O_2$$
$$O + O_3 \longrightarrow 2O_2$$

In the past, a lot of attention was given to chlorofluorocarbons and their role in depleting ozone layer. These were given a special name "Ozone Depleting Substance" (**ODS**), and their effect was quantified by "Ozone Depleting Potential" (**ODP**). An ODP is the "relative amount of stratospheric ozone destroyed by the release of a unit mass of a chemical at earth's surface to the amount destroyed by the release of a unit mass of chloroflourocarbon CFC-11 ($CFCl_3$). Nitrous oxide is similar to chloroflourocarbons in being stable in the troposphere where it is released and the ability to travel to stratosphere where they release active chemicals which destroy ozone by chlorine or nitrogen oxide-catalyzed process [28] (Fig. 8.12).

The ozone-depleting potential of nitrous oxide was found to be 0.017 which is about one-sixth of CFCs.

Large amount of man-made emissions of nitrous oxide make it the most important ozone-depleting substance today [28]. But unlike CFCs which are being phased out nitrous oxide production continues to be unregulated.

8.3.3 Role of Nitrous Oxide in Causing Global Warming

The role of nitrous oxide as an operating room pollutant and its harmful effects on personnel have been studied in detail, but there are a few guidelines on limiting the discharge of anesthetic gases including nitrous oxide into the atmosphere [29]. The current inhaled anesthetic gases undergo very little metabolism in the body and are exhaled and scavenged by the anesthetic machine with almost no degradation, from which they are vented out. These remain in atmosphere for a long time and act as green house gases.

The green house effect is measured by "global warming potential" or GWP, and it is a "measure of how much a given mass of gas contributes to global warming over a specified time period." It is a relative scale that compares the contribution of a gas to the same mass of carbon dioxide which is given a GWP of 1 [30]. Most anesthetics will cause their impact in a time frame of about 20 years, and this is corroborated as being twice as long as the lifetime of longest potent inhaled anesthetic agent (approximately 10 years for desflurane). Hence, when reporting their effect, the short form used is GWP_{20}. In contrast, nitrous oxide has a longer atmospheric lifetime and is reported using both GWP_{20} and GWP_{100}.

Nitrous oxide as a green house gas becomes more significant in the operating room rather than at a dental office, because of its role as a carrier gas when delivering more potent anesthetic gases such as sevoflurane and desflurane [30]. As a carrier gas with "high MAC percentage, low potency, and GWP_{100} of 310 times that of carbon dioxide," nitrous oxide becomes a major contributor to green house gases [29].

Nitrous oxide, when combined with desflurane, has an even bigger impact because of high heat trapping effect of desflurane combined with large amount of nitrous oxide which gets released in large quantities and stays for a longer period of time in the atmosphere [29].

> Although nitrous oxide gas is a green house gas and has global warming potential, 70% of atmospheric emissions are natural. Contribution from its medical and dental use is negligible.

Thus, nitrous oxide not only depletes ozone layer but also increases the risk of global warming. All these facts presented above suggest the need for anesthesiologist and us as dentists to look at ways of reducing the amount of nitrous oxide we are using and discharging into the atmosphere.

Some recommendations include

1. High fresh gas flow should be avoided when not required.
2. Desflurane and nitrous oxide as combination to be used only in those cases where they may reduce mortality and morbidity.

In the absence of any policy on the discharge of waste anesthetic gases into the atmosphere, new technologies have been developed which may purify/destroy anesthetic gases. These include photochemical air purification which can "theoretically destroy all waste anesthetic gases" [31] and "Deltasorb" which uses a canister that gets attached to an existing scavenging circuit and then adsorbs volatile anesthetic gases. These canisters are then returned to the vendor who extracts, liquifies, and purifies the captured anesthetics into medical grade anesthetics [29]. Technologies like these when fully developed and adopted will help to minimize the adverse effect of discharge of anesthetic gases into the atmosphere.

8.4 Conclusion

Nitrous oxide has made it possible to deliver care for numerous patients including children who in the absence of this valuable adjunct would have either discontinued their dental care or would have had no option but to go "under general anesthesia" each time they wanted to receive even routine dental treatment. History of nitrous oxide teaches us that its analgesic and anxiolytic potential are immense and it will remain an integral part of dentistry. As of now, there has been no substitute found to replace the use of nitrous oxide in dental offices. Its safety index remains high, and the quick onset and recovery means that there is no break in the continuity or "down-time" in our schedules. It remains a valuable adjunct in ensuring adequate delivery of dental care to our most vulnerable patient groups—the fearful, stressful, and anxious child patients, many of whom are seeing us for the first time! Ease of availability, low cost, and fast onset and recovery have all contributed to increased popularity of nitrous oxide for recreational purposes. Its usage among youth who are exposed to it at parties, youth festivals, night clubs etc. is definitely a cause for concern.

As far as environment is concerned, total emission of nitrous oxide from medicinal use is estimated to contribute to <0.05% of total green house emission, which in opinion of some authors, is an "ethical dilemma." However, considering its benefits in pediatric dentistry and the fact that it is only a negligible contributor of total green house emission, its use cannot be discarded.

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Appendix I: Children's Fears at Different Ages

Age	Fear
0–6 months	Loss of support, loud noises, sudden movement
7–12 months	Strangers, sudden appearance of large objects, loud noises
1 year	Separation from parent, strangers, injury, toilet
2 years	Large animals, dark rooms, large objects and machines, loud noises
3 years	Dark rooms, masks, large animals, snakes, separation from parent
4 years	Dark rooms, noises at night, large animals, snakes, separation from parent
5 years	Wild animals, bodily injury, dark, bad people, separation from parent
6 years	Ghosts, monsters, witches, dark, being alone, thunder and lightening
7 years	Dark, monsters, storms, being lost, kidnapping, being alone
8 years	Dark, people (kidnapper, robber, mugger), guns or weapons, being alone, animals
9 years	Dark, being lost, bad dreams, bodily harm or accident, being alone
10 years	Dark, people, bad dreams, punishment, strangers
11 years	Dark, being alone, bad dream, being hurt by someone, being sick, tests, grades
12 years	Dark, punishment (being in trouble, bad grades), being alone, being hurt or taken away, tests, grades
13 years	Crime, being hurt or kidnapped, being alone, war and nuclear war, bad grades, tests, punishment
14+ years	Failure at school, personal relations, war, tests, sex issues (pregnancy, AIDS), being alone, family concerns

Source: Robinson III, E., & Rotter, J. (1991). Children's fears: Toward a preventive model. *School Counselor*, 38(3), 187

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Appendix II: ASA Classification

Grade	ASA classification	Grade	Revised classification
1	Class 1	1a	Normal healthy patient
		1b	Patient with mild systemic disease
			Normal healthy patient, with operative or anesthetic risk(s)
2	Class 2	2a	Patient with moderate systemic disease
			Patient with mild systemic disease, with operative or anesthetic risk(s)
		2b	Patient with moderate to severe systemic disease that does not limit activity
			Patient with mild systemic disease, with operative or anesthetic risk
			Patient with moderate systemic disease, with operative or anesthetic risk(s)
3	Class 3	3	Patient with severe systemic disease that limits activity but is not incapacitating
			Patient with moderate systemic disease that does not limit activity, with operative or anesthetic risk(s)
			Patient with moderate to severe systemic disease, that does not limit activity, with operative or anesthetic risk
4	Class 4	4	Patient with an incapacitating systemic disease that is a constant threat to life
			Patient with severe systemic disease that limits activity, incapacitated
5	Class 5	5	Moribund patient not expected to survive 24 h with or without operation

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Appendix III: Safety Data Sheet - Nitrous Oxide and Oxygen

PRAXAIR
Making our planet more productive

Nitrous oxide, compressed

Safety Data Sheet P-4636

This SDS conforms to U.S. Code of Federal Regulations 29 CFR 1910.1200, Hazard Communication.

Date of issue: 01/01/1979 Revision date: 10/28/2016 Supersedes: 12/29/2014

SECTION: 1. Product and company identification

1.1. Product identifier

Product form	:	Substance
Name	:	Nitrous oxide, compressed
CAS No	:	10024-97-2
Formula	:	N2O
Other means of identification	:	Nitrous oxide

1.2. Relevant identified uses of the substance or mixture and uses advised against

Use of the substance/mixture : Industrial use. Use as directed.

1.3. Details of the supplier of the safety data sheet

Praxair, Inc.
10 Riverview Drive
Danbury, CT 06810-6268 - USA
T 1-800-772-9247 (1-800-PRAXAIR) - F 1-716-879-2146
www.praxair.com

1.4. Emergency telephone number

Emergency number : Onsite Emergency: 1-800-645-4633

CHEMTREC, 24hr/day 7days/week
— Within USA: 1-800-424-9300, Outside USA: 001-703-527-3887
(collect calls accepted, Contract 17729)

SECTION 2: Hazard identification

2.1. Classification of the substance or mixture

GHS-US classification

Ox. Gas 1	H270
Liquefied gas	H280
STOT SE 3	H336

2.2. Label elements

GHS-US labeling

Hazard pictograms (GHS-US) :

Signal word (GHS-US) : DANGER

Hazard statements (GHS-US) :
H270 - MAY CAUSE OR INTENSIFY FIRE; OXIDIZER
H280 - CONTAINS GAS UNDER PRESSURE; MAY EXPLODE IF HEATED
H336 - MAY CAUSE DROWSINESS OR DIZZINESS
OSHA-H01 - MAY DISPLACE OXYGEN AND CAUSE RAPID SUFFOCATION
CGA-HG01 - MAY CAUSE FROSTBITE

Precautionary statements (GHS-US) :
P202 - Do not handle until all safety precautions have been read and understood
P220 - Keep/Store away from combustible materials, clothing
P244 - Keep reduction valves/valves and fittings free from oil and grease
P261 - Avoid breathing gas
P262 - Do not get in eyes, on skin, or on clothing
P271+P403 - Use and store only outdoors or in a well-ventilated place
P370+P376 - In case of fire: Stop leak if safe to do so
CGA-PG05 - Use a back flow preventive device in the piping
CGA-PG20+CGA-PG10 - Use only with equipment of compatible materials of construction and

EN (English US) SDS ID: P-4636 1/10

K. Gupta et al. (eds.), *Nitrous Oxide in Pediatric Dentistry*,
https://doi.org/10.1007/978-3-030-29618-6

rated for cylinder pressure
CGA-PG22 - Use only with equipment cleaned for oxygen service
CGA-PG21 - Open valve slowly
CGA-PG06 - Close valve after each use and when empty
CGA-PG02 - Protect from sunlight when ambient temperature exceeds 52°C (125°F)

2.3. Other hazards

Other hazards not contributing to the classification : Asphyxiant in high concentrations

Contact with liquid may cause cold burns/frostbite.

2.4. Unknown acute toxicity (GHS US)

No data available

SECTION 3: Composition/Information on ingredients

3.1. Substance

Name : Nitrous oxide, compressed

CAS No : 10024-97-2

Name	Product identifier	%
Nitrous oxide	(CAS No) 10024-97-2	99.5 - 100

3.2. Mixture

Not applicable

SECTION 4: First aid measures

4.1. Description of first aid measures

First-aid measures after inhalation : Remove person to fresh air and keep comfortable for breathing. . If breathing is difficult, trained personnel should give oxygen. . If not breathing, give artificial respiration. Call a POISON CENTER or doctor/physician if you feel unwell.

First-aid measures after skin contact : The liquid may cause frostbite. For exposure to liquid, immediately warm frostbite area with warm water not to exceed 105°F (41°C). Water temperature should be tolerable to normal skin. Maintain skin warming for at least 15 minutes or until normal coloring and sensation have returned to the affected area. In case of massive exposure, remove clothing while showering with warm water. Seek medical evaluation and treatment as soon as possible.

First-aid measures after eye contact : Immediately flush eyes thoroughly with water for at least 15 minutes. Hold the eyelids open and away from the eyeballs to ensure that all surfaces are flushed thoroughly. Contact an ophthalmologist immediately.. Consult an eye specialist immediately.

First-aid measures after ingestion : Ingestion is not considered a potential route of exposure.

4.2. Most important symptoms and effects, both acute and delayed

No additional information available

4.3. Indication of any immediate medical attention and special treatment needed

None.

SECTION 5: Firefighting measures

5.1. Extinguishing media

Suitable extinguishing media : Use extinguishing media appropriate for surrounding fire.

5.2. Special hazards arising from the substance or mixture

Fire hazard : Oxidizing agent; vigorously accelerates combustion. Contact with flammable materials may cause fire or explosion.

Explosion hazard : If venting or leaking gas catches fire, do not extinguish flames. Vapors may spread from leak, creating an explosive reignition hazard. Vapors can be ignited by pilot lights, other flames, smoking, sparks, heaters, electrical equipment, static discharge, or other ignition sources at locations distant from product handling point. Contact with combustible materials such as oil, grease, and other hydrocarbon products, especially in the presence of ignition sources such as pilot lights, other flames, smoking, sparks, heaters, electrical equipment, and static discharges may cause fire or explosion. Explosive atmospheres may linger. Before entering an area, especially a confined area, check the atmosphere with an appropriate device.

Reactivity : No reactivity hazard other than the effects described in sub-sections below.

5.3. Advice for firefighters

Firefighting instructions : Evacuate all personnel from the danger area. Use self-contained breathing apparatus (SCBA) and protective clothing. Immediately cool containers with water from maximum distance. Stop flow of gas if safe to do so, while continuing cooling water spray. Remove ignition sources if safe to do so. Remove containers from area of fire if safe to do so. On-site fire brigades must comply with OSHA 29 CFR 1910.156 and applicable standards under 29 CFR 1910 Subpart L—Fire Protection.

Special protective equipment for fire fighters : Wear gas tight chemically protective clothing in combination with self contained breathing apparatus. Standard protective clothing and equipment (Self Contained Breathing Apparatus) for fire fighters.

Specific methods : Use fire control measures appropriate for the surrounding fire. Exposure to fire and heat radiation may cause gas containers to rupture. Cool endangered containers with water spray jet from a protected position. Prevent water used in emergency cases from entering sewers and drainage systems

Stop flow of product if safe to do so

Use water spray or fog to knock down fire fumes if possible.

Other information : Containers are equipped with a pressure relief device. (Exceptions may exist where authorized by DOT.)

Oxidizing agent; vigorously accelerates combustion. Contact with flammable materials may cause fire or explosion

Smoking, flames, and electric sparks are potential explosion hazards.

SECTION 6: Accidental release measures

6.1. Personal precautions, protective equipment and emergency procedures

General measures : **DANGER: High-pressure, oxidizing gas.** Evacuate personnel to a safe area. Appropriate self-contained breathing apparatus may be required. Approach suspected leak area with caution. Remove all sources of ignition. Vapor can spread from spill. Contact with flammable materials may cause fire or explosion. Ventilate area or move container to a well-ventilated area. Before entering the area, especially a confined area, check the atmosphere with an appropriate device.

6.1.1. For non-emergency personnel

No additional information available

6.1.2. For emergency responders

No additional information available

6.2. Environmental precautions

Prevent waste from contaminating the surrounding environment. Prevent soil and water pollution. Dispose of contents/container in accordance with local/regional/national/international regulations. Contact supplier for any special requirements.

6.3. Methods and material for containment and cleaning up

No additional information available

6.4. Reference to other sections

See also sections 8 and 13.

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Nitrous oxide, compressed

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SECTION 7: Handling and storage

7.1. Precautions for safe handling

Precautions for safe handling : Wear leather safety gloves and safety shoes when handling cylinders. Protect cylinders from physical damage; do not drag, roll, slide or drop. While moving cylinder, always keep in place removable valve cover. Never attempt to lift a cylinder by its cap; the cap is intended solely to protect the valve. When moving cylinders, even for short distances, use a cart (trolley, hand truck, etc.) designed to transport cylinders. Never insert an object (e.g, wrench, screwdriver, pry bar) into cap openings; doing so may damage the valve and cause a leak. Use an adjustable strap wrench to remove over-tight or rusted caps. Slowly open the valve. If the valve is hard to open, discontinue use and contact your supplier. Close the container valve after each use; keep closed even when empty. Never apply flame or localized heat directly to any part of the container. High temperatures may damage the container and could cause the pressure relief device to fail prematurely, venting the container contents. For other precautions in using this product, see section 16.

7.2. Conditions for safe storage, including any incompatibilities

Storage conditions : Store only where temperature will not exceed 125°F (52°C). Post "No Smoking/No Open Flames" signs in storage and use areas. There must be no sources of ignition. Separate packages and protect against potential fire and/or explosion damage following appropriate codes and requirements (e.g, NFPA 30, NFPA 55, NFPA 70, and/or NFPA 221 in the U.S.) or according to requirements determined by the Authority Having Jurisdiction (AHJ). Always secure containers upright to keep them from falling or being knocked over. Install valve protection cap, if provided, firmly in place by hand when the container is not in use. Store full and empty containers separately. Use a first-in, first-out inventory system to prevent storing full containers for long periods. For other precautions in using this product, see section 16

OTHER PRECAUTIONS FOR HANDLING, STORAGE, AND USE: When handling product under pressure, use piping and equipment adequately designed to withstand the pressures to be encountered. Never work on a pressurized system. Use a back flow preventive device in the piping. Gases can cause rapid suffocation because of oxygen deficiency; store and use with adequate ventilation. If a leak occurs, close the container valve and blow down the system in a safe and environmentally correct manner in compliance with all international, federal/national, state/provincial, and local laws; then repair the leak. Never place a container where it may become part of an electrical circuit.

7.3. Specific end use(s)

None.

SECTION 8: Exposure controls/personal protection

8.1. Control parameters

Nitrous oxide, compressed (10024-97-2)		
ACGIH	ACGIH TLV-TWA (ppm)	50 ppm
USA OSHA	Not established	
Nitrous oxide (10024-97-2)		
ACGIH	ACGIH TLV-TWA (ppm)	50 ppm

8.2. Exposure controls

Appropriate engineering controls : Use a local exhaust system, if necessary, to prevent oxygen deficiency and to keep hazardous fumes and gases below all applicable limits in the worker's breathing zone. MECHANICAL ENGINEERING CONTROLS: Not recommended as a primary ventilation system to control worker's exposure. USE ONLY IN A CLOSED SYSTEM. An explosion-proof, corrosion-resistant, forced-draft fume hood is preferred.

Hand protection : Wear working gloves when handling gas containers.

Eye protection : Wear safety glasses with side shields. Wear safety glasses with side shields or goggles when transfilling or breaking transfer connections. Wear goggles and a face shield when transfilling or breaking transfer connections.

Respiratory protection	: When workplace conditions warrant respirator use, follow a respiratory protection program that meets OSHA 29 CFR 1910.134, ANSI Z88.2, or MSHA 30 CFR 72.710 (where applicable). Use an air-supplied or air-purifying cartridge if the action level is exceeded. Ensure that the respirator has the appropriate protection factor for the exposure level. If cartridge type respirators are used, the cartridge must be appropriate for the chemical exposure. For emergencies or instances with unknown exposure levels, use a self-contained breathing apparatus (SCBA).
Thermal hazard protection	: Wear cold insulating gloves when transfilling or breaking transfer connections.
Environmental exposure controls	: Refer to local regulations for restriction of emissions to the atmosphere. See section 13 for specific methods for waste gas treatment.
Other information	: Consider the use of flame resistant safety clothing. Wear safety shoes while handling containers.

SECTION 9: Physical and chemical properties

9.1. Information on basic physical and chemical properties

Physical state	: Gas
Appearance	: Colorless, non-flammable gas.
Molecular mass	: 44 g/mol
Color	: Colorless.
Odor	: Sweetish.
Odor threshold	: Odor threshold is subjective and inadequate to warn for overexposure.
pH	: Not applicable.
Relative evaporation rate (butyl acetate=1)	: No data available
Relative evaporation rate (ether=1)	: Not applicable.
Melting point	: -90.81 °C
Freezing point	: No data available
Boiling point	: -88.5 °C
Flash point	: Not applicable.
Critical temperature	: 36.4 °C
Auto-ignition temperature	: Not applicable.
Decomposition temperature	: 650 °C
Flammability (solid, gas)	: No data available
Vapor pressure	: 5080 kPa
Critical pressure	: 7255 kPa
Relative vapor density at 20 °C	: No data available
Relative density	: 1.2
Density	: 0.785 g/cm³ (at 20 °C)
Relative gas density	: 1.5
Solubility	: Water: 2.2 mg/l
Log Pow	: Not applicable.
Log Kow	: Not applicable.
Viscosity, kinematic	: Not applicable.
Viscosity, dynamic	: Not applicable.
Explosive properties	: Not applicable.
Oxidizing properties	: Oxidizer.
Explosion limits	: Non flammable.

9.2. Other information

Gas group	: Liquefied gas
Additional information	: Gas/vapor heavier than air. May accumulate in confined spaces, particularly at or below ground level

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SECTION 10: Stability and reactivity

10.1. Reactivity

No reactivity hazard other than the effects described in sub-sections below.

10.2. Chemical stability

Stable under normal conditions. In the presence of catalysts (e.g. halogen products, mercury, nickel, platinum) the rate of decomposition increases and decomposition can occur at even lower temperatures. At temperatures over 575°C and at atmospheric pressure, nitrous oxide decomposes into nitrogen and oxygen. Pressurized nitrous oxide can also decompose at temperatures equal or greater than 300°C. Nitrous oxide dissociation is irreversible and exothermic, leading to a considerable rise in pressure.

10.3. Possibility of hazardous reactions

Violently oxidizes organic material.

10.4. Conditions to avoid

Heat.

10.5. Incompatible materials

Flammable materials, Hydrocarbons, Avoid oil, grease and all other combustible materials, Asphalt, Ethers, Alcohols, Acids, and Aldehydes. Alkali metals, Boron (B), tungsten carbide, and powdered aluminum.

10.6. Hazardous decomposition products

Nitrous oxide decomposes explosively at 1202°F (650°C) into two parts Nitrogen and one part oxygen. In the presence of catalytic surfaces such as Silver, Platinum (Pt), Cobalt (Co), and Copper or nickel oxide, this reaction occurs at lower temperatures.

SECTION 11: Toxicological information

11.1. Information on toxicological effects

Acute toxicity : Not classified

Nitrous oxide, compressed (\f)10024-97-2	
LC50 inhalation rat (ppm)	> 250 ppm/4h
Nitrous oxide (10024-97-2)	
LC50 inhalation rat (ppm)	> 250 ppm/4h

Skin corrosion/irritation : Not classified
pH: Not applicable.

Serious eye damage/irritation : Not classified
pH: Not applicable.

Respiratory or skin sensitization : Not classified

Germ cell mutagenicity : Not classified

Carcinogenicity : Not classified

Reproductive toxicity : Not classified

Specific target organ toxicity (single exposure) : MAY CAUSE DROWSINESS OR DIZZINESS.

Specific target organ toxicity (repeated exposure) : Not classified

Aspiration hazard : Not classified

SECTION 12: Ecological information

12.1. Toxicity

Ecology - general : No data available. No ecological damage caused by this product.

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12.2. Persistence and degradability

Nitrous oxide, compressed (10024-97-2)	
Persistence and degradability	Not applicable for inorganic gases.
Nitrous oxide (10024-97-2)	
Persistence and degradability	Not applicable for inorganic gases.

12.3. Bioaccumulative potential

Nitrous oxide, compressed (10024-97-2)	
Log Pow	Not applicable.
Log Kow	Not applicable.
Bioaccumulative potential	No data available.
Nitrous oxide (10024-97-2)	
Log Pow	Not applicable for inorganic gases.
Bioaccumulative potential	No data available.

12.4. Mobility in soil

Nitrous oxide, compressed (10024-97-2)	
Mobility in soil	No data available.
Ecology - soil	Because of its high volatility, the product is unlikely to cause ground or water pollution.
Nitrous oxide (10024-97-2)	
Ecology - soil	Because of its high volatility, the product is unlikely to cause ground or water pollution.

12.5. Other adverse effects

Effect on ozone layer : None

Global warming potential [CO2=1] : 298

Effect on the global warming : When discharged in large quantities may contribute to the greenhouse effect

SECTION 13: Disposal considerations

13.1. Waste treatment methods

Waste treatment methods : Do not discharge into any place where its accumulation could be dangerous. Contact supplier if guidance is required.

Waste disposal recommendations : Do not attempt to dispose of residual or unused quantities. Return container to supplier.

SECTION 14: Transport information

In accordance with DOT

Transport document description : UN1070 Nitrous oxide, 2.2

UN-No.(DOT) : UN1070

Proper Shipping Name (DOT) : Nitrous oxide

Class (DOT) : 2.2 - Class 2.2 - Non-flammable compressed gas 49 CFR 173.115

Hazard labels (DOT) : 2.2 - Non-flammable gas
5.1 - Oxidizer

DOT Special Provisions (49 CFR 172.102) : A14 - This material is not authorized to be transported as a limited quantity or consumer commodity in accordance with 173.306 of this subchapter when transported aboard an aircraft

Additional information

Emergency Response Guide (ERG) Number : 122 (UN1070)

Other information : No supplementary information available.

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Special transport precautions	: Avoid transport on vehicles where the load space is not separated from the driver's compartment. Ensure vehicle driver is aware of the potential hazards of the load and knows what to do in the event of an accident or an emergency. Before transporting product containers: - Ensure there is adequate ventilation. - Ensure that containers are firmly secured. - Ensure cylinder valve is closed and not leaking. - Ensure valve outlet cap nut or plug (where provided) is correctly fitted. - Ensure valve protection device (where provided) is correctly fitted.

Transport by sea

UN-No. (IMDG)	: 1070
Proper Shipping Name (IMDG)	: NITROUS OXIDE
Class (IMDG)	: 2 - Gases
MFAG-No	: 122

Air transport

UN-No. (IATA)	: 1070
Proper Shipping Name (IATA)	: Nitrous oxide
Class (IATA)	: 2
Civil Aeronautics Law	: Gases under pressure/Gases nonflammable nontoxic under pressure

SECTION 15: Regulatory information

15.1. US Federal regulations

Nitrous oxide, compressed (10024-97-2)	
Listed on the United States TSCA (Toxic Substances Control Act) inventory	
SARA Section 311/312 Hazard Classes	Delayed (chronic) health hazard Fire hazard Immediate (acute) health hazard Sudden release of pressure hazard

All components of this product are listed on the Toxic Substances Control Act (TSCA) inventory.

This product or mixture does not contain a toxic chemical or chemicals in excess of the applicable de minimis concentration as specified in 40 CFR §372.38(a) subject to the reporting requirements of section 313 of Title III of the Superfund Amendments and Reauthorization Act of 1986 and 40 CFR Part 372.

15.2. International regulations

CANADA

Nitrous oxide, compressed (10024-97-2)
Listed on the Canadian DSL (Domestic Substances List)
Nitrous oxide (10024-97-2)
Listed on the Canadian DSL (Domestic Substances List)

EU-Regulations

Nitrous oxide, compressed (10024-97-2)
Listed on the EEC inventory EINECS (European Inventory of Existing Commercial Chemical Substances)

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15.2.2. National regulations

Nitrous oxide, compressed (10024-97-2)
Listed on the AICS (Australian Inventory of Chemical Substances) Listed on IECSC (Inventory of Existing Chemical Substances Produced or Imported in China) Listed on the Japanese ENCS (Existing & New Chemical Substances) inventory Listed on the Korean ECL (Existing Chemicals List) Listed on NZIoC (New Zealand Inventory of Chemicals) Listed on PICCS (Philippines Inventory of Chemicals and Chemical Substances) Listed on the Canadian IDL (Ingredient Disclosure List) Listed on INSQ (Mexican National Inventory of Chemical Substances)

15.3. US State regulations

Nitrous oxide, compressed(10024-97-2)	
U.S. - California - Proposition 65 - Carcinogens List	No
U.S. - California - Proposition 65 - Developmental Toxicity	Yes
U.S. - California - Proposition 65 - Reproductive Toxicity - Female	Yes
U.S. - California - Proposition 65 - Reproductive Toxicity - Male	No
State or local regulations	U.S. - Massachusetts - Right To Know List U.S. - New Jersey - Right to Know Hazardous Substance List U.S. - Pennsylvania - RTK (Right to Know) List

California Proposition 65 - This product contains, or may contain, trace quantities of a substance(s) known to the state of California to cause cancer, developmental and/or reproductive harm

Nitrous oxide (10024-97-2)				
U.S. - California - Proposition 65 - Carcinogens List	U.S. - California - Proposition 65 - Developmental Toxicity	U.S. - California - Proposition 65 - Reproductive Toxicity - Female	U.S. - California - Proposition 65 - Reproductive Toxicity - Male	Non-significant risk level (NSRL)
No	Yes	Yes	No	

Nitrous oxide (10024-97-2)
U.S. - Massachusetts - Right To Know List U.S. - New Jersey - Right to Know Hazardous Substance List U.S. - Pennsylvania - RTK (Right to Know) List

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SECTION 16: Other information

Other information : When you mix two or more chemicals, you can create additional, unexpected hazards. Obtain and evaluate the safety information for each component before you produce the mixture. Consult an industrial hygienist or other trained person when you evaluate the end product. Before using any plastics, confirm their compatibility with this product

Praxair asks users of this product to study this SDS and become aware of the product hazards and safety information. To promote safe use of this product, a user should (1) notify employees, agents, and contractors of the information in this SDS and of any other known product hazards and safety information, (2) furnish this information to each purchaser of the product, and (3) ask each purchaser to notify its employees and customers of the product hazards and safety information

The opinions expressed herein are those of qualified experts within Praxair, Inc. We believe that the information contained herein is current as of the date of this Safety Data Sheet. Since the use of this information and the conditions of use are not within the control of Praxair, Inc, it is the user's obligation to determine the conditions of safe use of the product

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NFPA health hazard : 2 - Intense or continued exposure could cause temporary incapacitation or possible residual injury unless prompt medical attention is given.

NFPA fire hazard : 0 - Materials that will not burn.

NFPA reactivity : 0 - Normally stable, even under fire exposure conditions, and are not reactive with water.

NFPA specific hazard : OX - This denotes an oxidizer, a chemical which can greatly increase the rate of combustion/fire.

HMIS III Rating

Health : 1 Slight Hazard - Irritation or minor reversible injury possible

Flammability : 0 Minimal Hazard

Physical : 3 Serious Hazard

SDS US (GHS HazCom 2012) - Praxair

This information is based on our current knowledge and is intended to describe the product for the purposes of health, safety and environmental requirements only. It should not therefore be construed as guaranteeing any specific property of the product.

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Oxygen, compressed

Safety Data Sheet P-4638

This SDS conforms to U.S. Code of Federal Regulations 29 CFR 1910.1200, Hazard Communication.

Date of issue: 01/01/1979 Revision date: 10/21/2016 Supersedes: 06/23/2015

SECTION: 1. Product and company identification

1.1. Product identifier

Product form	: Substance
Name	: Oxygen, compressed
CAS No	: 7782-44-7
Formula	: O2
Other means of identification	: Oxygen, Compressed; MediPure Oxygen; Aviator's Breathing Oxygen; USP Oxygen; Oxygen - Diving Grade

1.2. Relevant identified uses of the substance or mixture and uses advised against

Use of the substance/mixture : Medical applications
Industrial use
Diving Gas (Underwater Breathing)

1.3. Details of the supplier of the safety data sheet

Praxair, Inc.
10 Riverview Drive
Danbury, CT 06810-6268 - USA
T 1-800-772-9247 (1-800-PRAXAIR) - F 1-716-879-2146
www.praxair.com

1.4. Emergency telephone number

Emergency number : Onsite Emergency: 1-800-645-4633

CHEMTREC, 24hr/day 7days/week
— Within USA: 1-800-424-9300, Outside USA: 001-703-527-3887
(collect calls accepted, Contract 17729)

SECTION 2: Hazard identification

2.1. Classification of the substance or mixture

GHS-US classification

Ox. Gas 1 H270
Compressed gas H280

2.2. Label elements

GHS-US labeling

Hazard pictograms (GHS-US) :

GHS03 GHS04

Signal word (GHS-US)	: DANGER
Hazard statements (GHS-US)	: H270 - MAY CAUSE OR INTENSIFY FIRE; OXIDIZER H280 - CONTAINS GAS UNDER PRESSURE; MAY EXPLODE IF HEATED
Precautionary statements (GHS-US)	: P202 - Do not handle until all safety precautions have been read and understood P220 - Keep/Store away from combustible materials, clothing P244 - Keep reduction valves/valves and fittings free from oil and grease P271+P403 - Use and store only outdoors or in a well-ventilated place P370+P376 - In case of fire: Stop leak if safe to do so CGA-PG05 - Use a back flow preventive device in the piping CGA-PG20+CGA-PG10 - Use only with equipment of compatible materials of construction and rated for cylinder pressure CGA-PG22 - Use only with equipment cleaned for oxygen service CGA-PG21 - Open valve slowly

CGA-PG06 - Close valve after each use and when empty
CGA-PG02 - Protect from sunlight when ambient temperature exceeds 52°C (125°F)

2.3. Other hazards

Other hazards not contributing to the classification : Breathing 80 percent or more oxygen at atmospheric pressure for more than a few hours may cause nasal stuffiness, cough, sore throat, chest pain, and breathing difficulty. Breathing oxygen at higher pressure increases the likelihood of adverse effects within a shorter time period. Breathing pure oxygen under pressure may cause lung damage and central nervous system (CNS) effects, resulting in dizziness, poor coordination, tingling sensation, visual and hearing disturbances, muscular twitching, unconsciousness, and convulsions. Breathing oxygen under pressure may cause prolongation of adaptation to darkness and reduced peripheral vision.

2.4. Unknown acute toxicity (GHS US)

No data available

SECTION 3: Composition/Information on ingredients

3.1. Substance

Name : Oxygen, compressed
CAS No : 7782-44-7

Name	Product identifier	%
Oxygen	(CAS No) 7782-44-7	99.5 - 100

3.2. Mixture

Not applicable

SECTION 4: First aid measures

4.1. Description of first aid measures

First-aid measures after inhalation : Move to fresh air. Get medical advice/attention.

First-aid measures after skin contact : Adverse effects not expected from this product.

First-aid measures after eye contact : Adverse effects not expected from this product. In case of eye irritation: Rinse immediately with plenty of water. Consult an ophthalmologist if irritation persists.

First-aid measures after ingestion : Ingestion is not considered a potential route of exposure.

4.2. Most important symptoms and effects, both acute and delayed

No additional information available

4.3. Indication of any immediate medical attention and special treatment needed

None.

SECTION 5: Firefighting measures

5.1. Extinguishing media

Suitable extinguishing media : Vigorously accelerates combustion. Use media appropriate for surrounding fire. Water (e.g. safety shower) is the preferred extinguishing media for clothing fires.

5.2. Special hazards arising from the substance or mixture

Fire hazard : Oxidizing agent; vigorously accelerates combustion. Contact with flammable materials may cause fire or explosion.

5.3. Advice for firefighters

Firefighting instructions : High-pressure, oxidizing gas

Evacuate all personnel from the danger area. Use self-contained breathing apparatus (SCBA) and protective clothing. Immediately cool containers with water from maximum distance. Stop flow of gas if safe to do so, while continuing cooling water spray. Remove ignition sources if safe to do so. Remove containers from area of fire if safe to do so. On-site fire brigades must comply with OSHA 29 CFR 1910.156 and applicable standards under 29 CFR 1910 Subpart L—Fire Protection.

Special protective equipment for fire fighters : Standard protective clothing and equipment (Self Contained Breathing Apparatus) for fire fighters.

Specific methods	: Use fire control measures appropriate for the surrounding fire. Exposure to fire and heat radiation may cause gas containers to rupture. Cool endangered containers with water spray jet from a protected position. Prevent water used in emergency cases from entering sewers and drainage systems Stop flow of product if safe to do so Use water spray or fog to knock down fire fumes if possible.
Other information	: Heat of fire can build pressure in container and cause it to rupture. Containers are equipped with a pressure relief device. (Exceptions may exist where authorized by DOT.) No part of the container should be subjected to a temperature higher than 125°F (52°C). Smoking, flames, and electric sparks in the presence of enriched oxygen atmospheres are potential explosion hazards.

SECTION 6: Accidental release measures

6.1. Personal precautions, protective equipment and emergency procedures

General measures : Prevent from entering sewers, basements and workpits, or any place where its accumulation can be dangerous. Ensure adequate air ventilation. Eliminate ignition sources. Evacuate area. Try to stop release. Monitor concentration of released product. Wear self-contained breathing apparatus when entering area unless atmosphere is proven to be safe. Stop leak if safe to do so.

6.1.1. For non-emergency personnel

No additional information available

6.1.2. For emergency responders

No additional information available

6.2. Environmental precautions

Try to stop release.

6.3. Methods and material for containment and cleaning up

No additional information available

6.4. Reference to other sections

See also sections 8 and 13.

SECTION 7: Handling and storage

7.1. Precautions for safe handling

Precautions for safe handling	: Wear leather safety gloves and safety shoes when handling cylinders. Protect cylinders from physical damage; do not drag, roll, slide or drop. While moving cylinder, always keep in place removable valve cover. Never attempt to lift a cylinder by its cap; the cap is intended solely to protect the valve. When moving cylinders, even for short distances, use a cart (trolley, hand truck, etc.) designed to transport cylinders. Never insert an object (e.g, wrench, screwdriver, pry bar) into cap openings; doing so may damage the valve and cause a leak. Use an adjustable strap wrench to remove over-tight or rusted caps. Slowly open the valve. If the valve is hard to open, discontinue use and contact your supplier. Close the container valve after each use; keep closed even when empty. Never apply flame or localized heat directly to any part of the container. High temperatures may damage the container and could cause the pressure relief device to fail prematurely, venting the container contents. For other precautions in using this product, see section 16.
Safe use of the product	: **The suitability of this product as a component in underwater breathing gas mixtures** is to be determined by or under the supervision of personnel experienced in the use of underwater breathing gas mixtures and familiar with the physiological effects, methods employed, frequency and duration of use, hazards, side effects, and precautions to be taken.

7.2. Conditions for safe storage, including any incompatibilities

Storage conditions : Store only where temperature will not exceed 125°F (52°C). Post "No Smoking/No Open Flames" signs in storage and use areas. There must be no sources of ignition. Separate packages and protect against potential fire and/or explosion damage following appropriate codes and requirements (e.g, NFPA 30, NFPA 55, NFPA 70, and/or NFPA 221 in the U.S.) or according to requirements determined by the Authority Having Jurisdiction (AHJ). Always secure containers upright to keep them from falling or being knocked over. Install valve protection cap, if provided, firmly in place by hand when the container is not in use. Store full and empty containers separately. Use a first-in, first-out inventory system to prevent storing full containers for long periods. For other precautions in using this product, see section 16

OTHER PRECAUTIONS FOR HANDLING, STORAGE, AND USE: When handling product under pressure, use piping and equipment adequately designed to withstand the pressures to be encountered. Never work on a pressurized system. Use a back flow preventive device in the piping. Store and use with adequate ventilation. If a leak occurs, close the container valve and blow down the system in a safe and environmentally correct manner in compliance with all international, federal/national, state/provincial, and local laws; then repair the leak. Never place a container where it may become part of an electrical circuit.

7.3. Specific end use(s)

None.

SECTION 8: Exposure controls/personal protection

8.1. Control parameters

Oxygen, compressed (7782-44-7)	
ACGIH	Not established
USA OSHA	Not established

Oxygen (7782-44-7)	
ACGIH	Not established
USA OSHA	Not established

8.2. Exposure controls

Appropriate engineering controls : Avoid oxygen rich (>23.5%) atmospheres. Use a local exhaust system with sufficient flow velocity to maintain an adequate supply of air in the worker's breathing zone. Mechanical (general): General exhaust ventilation may be acceptable if it can maintain an adequate supply of air.

Eye protection : Wear safety glasses with side shields.

Skin and body protection : Wear metatarsal shoes and work gloves for cylinder handling, and protective clothing where needed. Wear appropriate chemical gloves during cylinder changeout or wherever contact with product is possible. Select per OSHA 29 CFR 1910.132, 1910.136, and 1910.138. As needed for welding, wear hand, head, and body protection to help prevent injury from radiation and sparks. (See ANSI Z49.1.) At a minimum, this includes welder's gloves and protective goggles, and may include arm protectors, aprons, hats, and shoulder protection as well as substantial clothing.

Respiratory protection : When workplace conditions warrant respirator use, follow a respiratory protection program that meets OSHA 29 CFR 1910.134, ANSI Z88.2, or MSHA 30 CFR 72.710 (where applicable). Use an air-supplied or air-purifying cartridge if the action level is exceeded. Ensure that the respirator has the appropriate protection factor for the exposure level. If cartridge type respirators are used, the cartridge must be appropriate for the chemical exposure. For emergencies or instances with unknown exposure levels, use a self-contained breathing apparatus (SCBA).

SECTION 9: Physical and chemical properties

9.1. Information on basic physical and chemical properties

Physical state : Gas

Appearance : Colorless gas.

Molecular mass : 32 g/mol

Color : Colorless.

Odor : No odor warning properties.

Odor threshold	: No data available
pH	: Not applicable.
Relative evaporation rate (butyl acetate=1)	: No data available
Relative evaporation rate (ether=1)	: Not applicable.
Melting point	: -219 °C (-362°F)
Freezing point	: No data available
Boiling point	: -183 °C (-297°F)
Flash point	: Not applicable.
Critical temperature	: -118.6 °C (-181.48°F)
Auto-ignition temperature	: Not applicable.
Decomposition temperature	: No data available
Flammability (solid, gas)	: No data available
Vapor pressure	: Not applicable.
Critical pressure	: 50.4 bar (731.4 psia)
Relative vapor density at 20 °C	: 0.0827 lb/ft3 (1.325 kg/m3) absolute vapor density at 70°F/21.1°C, 1 atm
Relative density	: 1.1
Density	: 1.4289 kg/m³ (at 21.1 °C)
Relative gas density	: 1.1
Solubility	: Water: 39 mg/l
Log Pow	: Not applicable.
Log Kow	: Not applicable.
Viscosity, kinematic	: Not applicable.
Viscosity, dynamic	: Not applicable.
Explosive properties	: Not applicable.
Oxidizing properties	: Oxidizer.
Explosion limits	: No data available

9.2. Other information

Gas group	: Compressed gas
Additional information	: Gas/vapor heavier than air. May accumulate in confined spaces, particularly at or below ground level

SECTION 10: Stability and reactivity

10.1. Reactivity

No additional information available

10.2. Chemical stability

Stable under normal conditions.

10.3. Possibility of hazardous reactions

Violently oxidizes organic material.

10.4. Conditions to avoid

None under recommended storage and handling conditions (see section 7).

10.5. Incompatible materials

Keep equipment free from oil and grease. Consider the potential toxicity hazard due to the presence of chlorinated or fluorinated polymers in high pressure (> 30 bar) oxygen lines in case of combustion. May react violently with combustible materials. May react violently with reducing agents.

10.6. Hazardous decomposition products

None.

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Making our planet more productive

Oxygen, compressed

Safety Data Sheet P-4638

This SDS conforms to U.S. Code of Federal Regulations 29 CFR 1910.1200, Hazard Communication.

Date of issue: 01/01/1979 Revision date: 10/21/2016 Supersedes: 06/23/2015

SECTION 11: Toxicological information

11.1. Information on toxicological effects

Acute toxicity	: Not classified
Skin corrosion/irritation	: Not classified pH: Not applicable.
Serious eye damage/irritation	: Not classified pH: Not applicable.
Respiratory or skin sensitization	: Not classified
Germ cell mutagenicity	: Not classified
Carcinogenicity	: Not classified
Reproductive toxicity	: Not classified
Specific target organ toxicity (single exposure)	: Not classified
Specific target organ toxicity (repeated exposure)	: Not classified
Aspiration hazard	: Not classified

SECTION 12: Ecological information

12.1. Toxicity

Ecology - general : No ecological damage caused by this product.

12.2. Persistence and degradability

Oxygen, compressed (7782-44-7)	
Persistence and degradability	No ecological damage caused by this product.
Oxygen (7782-44-7)	
Persistence and degradability	No ecological damage caused by this product.

12.3. Bioaccumulative potential

Oxygen, compressed (7782-44-7)	
Log Pow	Not applicable.
Log Kow	Not applicable.
Bioaccumulative potential	No ecological damage caused by this product.
Oxygen (7782-44-7)	
Log Pow	Not applicable.
Log Kow	Not applicable.
Bioaccumulative potential	No ecological damage caused by this product.

12.4. Mobility in soil

Oxygen, compressed (7782-44-7)	
Mobility in soil	No data available.
Ecology - soil	No ecological damage caused by this product.
Oxygen (7782-44-7)	
Mobility in soil	No data available.
Ecology - soil	No ecological damage caused by this product.

12.5. Other adverse effects

Effect on ozone layer	: None
Effect on the global warming	: No known effects from this product

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SECTION 13: Disposal considerations

13.1. Waste treatment methods

Waste disposal recommendations : Dispose of contents/container in accordance with local/regional/national/international regulations. Contact supplier for any special requirements.

SECTION 14: Transport information

In accordance with DOT

Transport document description	: UN1072 Oxygen, compressed, 2.2
UN-No.(DOT)	: UN1072
Proper Shipping Name (DOT)	: Oxygen, compressed
Class (DOT)	: 2.2 - Class 2.2 - Non-flammable compressed gas 49 CFR 173.115
Hazard labels (DOT)	: 2.2 - Non-flammable gas 5.1 - Oxidizer

DOT Special Provisions (49 CFR 172.102)	: 110 - Fire extinguishers transported under UN1044 may include installed actuating cartridges (cartridges, power device of Division 1.4C or 1.4S), without changing the classification of Division 2.2, provided the aggregate quantity of deflagrating (propellant) explosives does not exceed 3.2 grams per extinguishing unit A14 - This material is not authorized to be transported as a limited quantity or consumer commodity in accordance with 173.306 of this subchapter when transported aboard an aircraft

Additional information

Emergency Response Guide (ERG) Number	: 122 (UN1072)
Other information	: No supplementary information available.
Special transport precautions	: Avoid transport on vehicles where the load space is not separated from the driver's compartment. Ensure vehicle driver is aware of the potential hazards of the load and knows what to do in the event of an accident or an emergency. Before transporting product containers: - Ensure there is adequate ventilation. - Ensure that containers are firmly secured. - Ensure cylinder valve is closed and not leaking. - Ensure valve outlet cap nut or plug (where provided) is correctly fitted. - Ensure valve protection device (where provided) is correctly fitted.

Transport by sea

UN-No. (IMDG)	: 1072
Proper Shipping Name (IMDG)	: OXYGEN, COMPRESSED
Class (IMDG)	: 2 - Gases
MFAG-No	: 122

Air transport

UN-No. (IATA)	: 1072
Proper Shipping Name (IATA)	: Oxygen, compressed
Class (IATA)	: 2
Civil Aeronautics Law	: Gases under pressure/Gases nonflammable nontoxic under pressure

SECTION 15: Regulatory information

15.1. US Federal regulations

Oxygen, compressed (7782-44-7)	
Listed on the United States TSCA (Toxic Substances Control Act) inventory	
SARA Section 311/312 Hazard Classes	Sudden release of pressure hazard Fire hazard

All components of this product are listed on the Toxic Substances Control Act (TSCA) inventory.

This product or mixture does not contain a toxic chemical or chemicals in excess of the applicable de minimis concentration as specified in 40 CFR §372.38(a) subject to the reporting requirements of section 313 of Title III of the Superfund Amendments and Reauthorization Act of 1986 and 40 CFR Part 372.

15.2. International regulations

CANADA

Oxygen, compressed (7782-44-7)
Listed on the Canadian DSL (Domestic Substances List)

Oxygen (7782-44-7)
Listed on the Canadian DSL (Domestic Substances List)

EU-Regulations

Oxygen, compressed (7782-44-7)
Listed on the EEC inventory EINECS (European Inventory of Existing Commercial Chemical Substances)

15.2.2. National regulations

Oxygen, compressed (7782-44-7)
Listed on the AICS (Australian Inventory of Chemical Substances) Listed on IECSC (Inventory of Existing Chemical Substances Produced or Imported in China) Listed on the Korean ECL (Existing Chemicals List) Listed on NZIoC (New Zealand Inventory of Chemicals) Listed on PICCS (Philippines Inventory of Chemicals and Chemical Substances) Listed on INSQ (Mexican National Inventory of Chemical Substances)

15.3. US State regulations

Oxygen, compressed(7782-44-7)	
U.S. - California - Proposition 65 - Carcinogens List	No
U.S. - California - Proposition 65 - Developmental Toxicity	No
U.S. - California - Proposition 65 - Reproductive Toxicity - Female	No
U.S. - California - Proposition 65 - Reproductive Toxicity - Male	No
State or local regulations	U.S. - Massachusetts - Right To Know List U.S. - New Jersey - Right to Know Hazardous Substance List U.S. - Pennsylvania - RTK (Right to Know) List

California Proposition 65 - This product does not contain any substances known to the state of California to cause cancer, developmental and/or reproductive harm

Oxygen (7782-44-7)				
U.S. - California - Proposition 65 - Carcinogens List	U.S. - California - Proposition 65 - Developmental Toxicity	U.S. - California - Proposition 65 - Reproductive Toxicity - Female	U.S. - California - Proposition 65 - Reproductive Toxicity - Male	Non-significant risk level (NSRL)
No	No	No	No	

Oxygen (7782-44-7)
U.S. - Massachusetts - Right To Know List U.S. - New Jersey - Right to Know Hazardous Substance List U.S. - Pennsylvania - RTK (Right to Know) List

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SECTION 16: Other information

Other information : When you mix two or more chemicals, you can create additional, unexpected hazards. Obtain and evaluate the safety information for each component before you produce the mixture. Consult an industrial hygienist or other trained person when you evaluate the end product. Before using any plastics, confirm their compatibility with this product

Praxair asks users of this product to study this SDS and become aware of the product hazards and safety information. To promote safe use of this product, a user should (1) notify employees, agents, and contractors of the information in this SDS and of any other known product hazards and safety information, (2) furnish this information to each purchaser of the product, and (3) ask each purchaser to notify its employees and customers of the product hazards and safety information

The opinions expressed herein are those of qualified experts within Praxair, Inc. We believe that the information contained herein is current as of the date of this Safety Data Sheet. Since the use of this information and the conditions of use are not within the control of Praxair, Inc, it is the user's obligation to determine the conditions of safe use of the product

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PRAXAIR and the Flowing Airstream design are trademarks or registered trademarks of Praxair Technology, Inc. in the United States and/or other countries.

NFPA health hazard : 0 - Exposure under fire conditions would offer no hazard beyond that of ordinary combustible materials.

NFPA fire hazard : 0 - Materials that will not burn.

NFPA reactivity : 0 - Normally stable, even under fire exposure conditions, and are not reactive with water.

NFPA specific hazard : OX - This denotes an oxidizer, a chemical which can greatly increase the rate of combustion/fire.

HMIS III Rating

Health : 0 Minimal Hazard - No significant risk to health

Flammability : 0 Minimal Hazard

Physical : 3 Serious Hazard

SDS US (GHS HazCom 2012) - Praxair

This information is based on our current knowledge and is intended to describe the product for the purposes of health, safety and environmental requirements only. It should not therefore be construed as guaranteeing any specific property of the product.

Appendix IV: Nitrous Oxide and Oxygen Cylinder Specifications in the UK

Nitrous oxide

Cylinder colour

Standard valve

Nitrous oxide

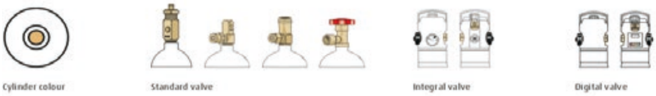
	AZ	D	E	F	G	J
Cylinder code	298122-AZ	141-D	141-E	141-F	141-G	141-J
Nominal content (litres)	450	900	1800	3600	9000	18000
Nominal pressure (bar)	44	44	44	44	44	44
Valve outlet connection	Pin-index	Pin-index	Pin-index	11/16"x 20 TPI (M)	11/16"x 20 TPI (M)	11/16"x 20 TPI (M)
Valve outlet specification	ISO 407	ISO 407	ISO 407	BS 341 No.13	BS 341 No.13	BS 341 No.13
Valve operation	Key	Key	Key	Handwheel	Handwheel	Handwheel
Dimensions LxD (mm)	290 x 106	535 x 102	865 x 102	930 x 140	1320 x 178	1520 x 229
Water capacity (litres)	1.2	2.3	4.7	9.4	23.6	47.2
Nominal full weight (kg)	3.0	5.0	9.0	22.0	52.0	105.0

Source: https://www.bochealthcare.co.uk/en/images/cylinder_data_med309965_2011_tcm409-54065.pdf

K. Gupta et al. (eds.), *Nitrous Oxide in Pediatric Dentistry*,
https://doi.org/10.1007/978-3-030-29618-6

Oxygen Cylinder Specifications in the UK

Oxygen



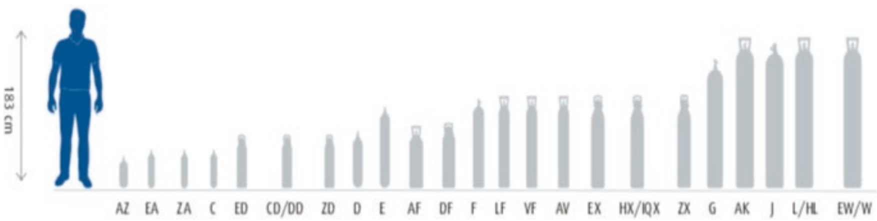
Oxygen

	ZA	AZ	CD	D	ZD	E	F	IQX	HX	ZX	G	J	W
Cylinder code	101-ZA	298121-AZ	101-CD	101-D	101-ZD	101-E	101-F	101-IQX	101-HX	101-ZX	101-G	101-J	101-W
Nominal content (litres)	300	170	460	340	600	680	1360	2000	2300	3040	3400	6800	11300
Nominal pressure (bar)	300	137	230	137	300	137	137	200	230	300	137	137	230
Nominal Outlet pressure (bar)	4	N/A	4	N/A	4	N/A	N/A	4	4	4	N/A	N/A	N/A
Valve type	Integral	Standard	Integral	Standard	Integral	Standard	Standard	Digital Integral	Integral	Integral	Standard	Standard	Standard
Valve outlet flow connection	6mm firtree	Pin-index ISO 407	6mm firtree	Pin-index ISO 407	6mm firtree	Pin-index ISO 407	5/8" BSP (F) BS 341 No. 3 Bullnose	6mm firtree	6mm firtree	6mm firtree	5/8" BSP (F) BS 341 No. 3 Bullnose	Pin-index ISO 407	ISO 5145 No. 5 (M)
Valve outlet pressure connection	N/A	N/A	Oxygen Schrader (BS 5682)	N/A	Oxygen Schrader (BS 5682)	N/A	N/A	Oxygen Schrader (BS 5682)	Oxygen Schrader (BS 5682)	Oxygen Schrader (BS 5682)	N/A	Side spindle	N/A
Valve operation	Handwheel	Key	Handwheel	Key	Handwheel	Key	Key	Handwheel	Handwheel	Handwheel	Key	Key	Key
Flow rate (litres/min)	0.1 – 15	N/A	Firtree: 1-15 Schrader: 40	N/A	Firtree: 1-15 Schrader: 40	N/A	N/A	Firtree: 0.5-15 Schrader: 40	Firtree: 1-15 Schrader: 40	Firtree: 1-15 Schrader: 40	N/A	N/A	N/A
Dimensions LxD (mm)	390 x 85	290 x 106	520 x 100	535 x 102	525 x 101	865 x 102	930 x 140	950 x 140	930 x 140	930 x 143	1320 x 178	1520 x 229	1540 x 230
Water capacity (litres)	1.0	1.2	2.0	2.3	2.0	4.7	9.4	10	10.0	10.0	23.6	47.2	46.6
Nominal full weight (kg)	1.6	2.5	3.5	3.9	4.1	6.5	17.0	18.0	19.0	14.0	39.0	78.0	85.0

Source: https://www.bochealthcare.co.uk/en/images/cylinder_data_med309965_2011_tcm409-54065.pdf

Cylinder Sizes in the UK

Cylinder types



Source: https://www.bochealthcare.co.uk/en/images/cylinder_data_med309965_2011_tcm409-54065.pdf

Appendix V: Nitrous Oxide and Oxygen Cylinder Specifications in Australia and New Zealand

BOC
A Member of The Linde Group

Medical Nitrous Oxide E.P.

Base anaesthetic and freezing agent

Nitrous Oxide is a non-flammable, colourless oxidising gas with a slightly sweetish taste and odour. It vigourously supports combustion of materials which will not normally burn in air. Nitrous Oxide is a Schedule 4 drug for Therapeutic use.

Uses
Nitrous Oxide is widely used as a base anaesthetic generally supplemented with either potent volatile or intravenous anaesthetic agents. These supplements are required in approximately half of their normal anaesthetising dose because of the anaesthetic effect of the Nitrous Oxide. It is used extensively for relative analgesia and as a freezing agent in cryosurgery.

Indications
Nitrous Oxide is indicated in adults and children for general anaesthesia (usually as an adjuvant to other volatile or intravenous anaesthetics) and analgesia (with Oxygen) e.g. dentistry and obstetrics.

Contraindications
- Should not be administered without the required level of Oxygen (at least 30%)
- Hypersensitivity to Nitrous Oxide or any other gas component is contraindicated
- Should not be used with any condition where air is entrapped within a body
- Nitrous Oxide should not be used on intoxicated or heavily sedated patients
- Where there is prolonged exposure, monitoring of peripheral blood for features of megaloblastic anaemia and leucopenia is recommended

Precautions
- Worksafe exposure standard TLV-TWA is 25 ppm as an 8 hour time weighted average
- For gas withdrawal use cylinder upright
- Liquid Nitrous Oxide presents a low temperature hazard and should not be allowed to contact the skin or clothing
- Nitrous Oxide is a simple asphyxiant in the absence of Oxygen. Classified as hazardous according to the criteria of Worksafe Australia
- Scavenging of waste Nitrous Oxide gas should be used to maintain levels to below the 25 ppm exposure limit

Dosage and Administration
Nitrous Oxide is inhaled through a face mask or tracheal tube by means of an anaesthetic apparatus. The gas is breathed in by the patient and absorbed through the lungs.
Nitrous Oxide should only be administered by medical personnel trained in the appropriate techniques.
Cylinder should only be used in conjunction with Medical Nitrous Oxide gas pressure regulators.

K. Gupta et al. (eds.), *Nitrous Oxide in Pediatric Dentistry*,
https://doi.org/10.1007/978-3-030-29618-6

→ Nitrous Oxide Base anaesthetic and freezing agent

Classifications

Compressed

1070 UN NUMBER — 114 AUST. MSDS

2.2, 5.1 CLASS — 109 N.Z. MSDS

Liquid

2201 UN NUMBER — 121 AUST. MSDS

2.2, 5.1 CLASS — 109 N.Z. MSDS

Medical Nitrous Oxide E.P. (*AUSTR 34466*)

AUST. Specifications

Component – (nominal) Compressed and Liquid	
Nitrous Oxide	> 98.0% (*gas*)

Impurities (max)	
Carbon Dioxide	< 300 ppm
Carbon Monoxide	< 5 ppm
N_2O/NO	< 2 ppm
Moisture	< 67 ppm

Liquid Supply

Cryogenic storage vessels of capacities from 130 m³ to 600 m³

Liquid Order Code

631

AUST. Order Codes

Cylinders	Contents (Litres)	Weight (kg)	Approximate Gauge Pressure kPa (g) at 15°C
610C	935	1.75	4,700
610D	3,520	6.6	4,700
610E	8,970	16.8	4,700
610G	18,690	35.0	4,700
610F8	124,400	233	4,700

Cylinder Outlets

AS 2473 Fig. 13 Pin Index

Medical Nitrous Oxide E.P. (*TT50-4008*)

N.Z. Specifications

Components – (nominal) Compressed and Liquid	
Nitrous Oxide	≥ 98%

Impurities (max)	
Carbon Dioxide	< 300 ppm
Carbon Monoxide	< 5 ppm
N_2O/NO	< 2 ppm
Moisture	< 67 ppm

N.Z. Order Codes

Cylinders	Weight (kg)
190A	1.99
190D	6.60
190G	33.9

Cylinder Outlets

AS 2473.3 Fig. 13 Pin Index

Equipment

Description	Inlet Fitting	Part Number AUST	Part Number NZ
Nitrous Oxide Regulator Series-0	Pin Index	518808	CW518808

Australia: BOC Limited ABN 95 000 029 729, BOC Healthcare 10 Julius Ave, North Ryde NSW 2113
T: 1300 363 109 F: 1300 363 438 E: hospital.care@boc.com
New Zealand: BOC Limited WN007748, BOC Healthcare NZ, 988 Great South Rd, Penrose Auckland,
T: 0800 656 334 F: 0800 275 275 E: HealthcareNZ@boc.com

HC00698 EQUA 0313

BOC
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Medical Oxygen E.P.

Life support, resuscitation, anaesthetic delivery

WARNING: OXYGEN AIDS AND INCREASES COMBUSTION

Oxygen strongly supports combustion (including some materials which do not normally burn in air). Smoking is prohibited when medical oxygen is in use, and no naked flame is allowed. There is a high risk of spontaneous combustion if oxygen comes into contact with oils, greases and tarry substances. Refer MSDS before use.

Oxygen is colourless, odourless and tasteless. Oxygen is pale blue in liquid form. It will vigorously support and accelerate combustion. It is supplied as a compressed gas in high pressure cylinders. Generally considered non-toxic at atmospheric pressure. Materials not normally considered combustible may be ignited by sparks in Oxygen-rich atmospheres. Advice should be sought from BOC before using any materials for Oxygen service which have not been supplied for use with Oxygen and marked accordingly.

Uses

- Essential for human respiration, Oxygen sustains life
- In anaesthesia, Oxygen functions as a carrier gas for the delivery of anaesthetic agents to the tissues of the body
- In respiratory therapy, Oxygen is administered to increase the amount of Oxygen and thus decrease the amount of other gases circulating in the blood
- Oxygen is also widely used in high altitude and underwater breathing, and hyperbaric chambers
- Oxygen is used as the basis for virtually all modern anaesthetic techniques as well as pre and post operative management
- To provide life support by restoring Oxygen levels in tissue for a range of conditions such as; cyanosis as a result of cardiopulmonary disease; surgical trauma, chest wounds and rib fractures; shock, severe haemorrhage and coronary occlusion; Carbon Monoxide poisoning; hyperpyrexia; major trauma e.g.: road traffic accidents and gunshot wounds
- In the management of sudden cardiac and respiratory arrest, whether drug induced or traumatic
- In the resuscitation of the critically ill when the circulation is impaired and in neo-natal resuscitation

White shoulder

Classifications 1072 UN NUMBER 2.2, 5.1 CLASS 115 AUST. MSDS 054 N.Z. MSDS

→ Oxygen Life support, resuscitation, anaesthetic delivery

Duration (hours)*

AUST. Cylinder

Cylinder Size	400 C	400 CD**	400 ND	400 NE	400 NG
Contents (Litres)	490	630	1,600	4,000	8,075
1 lpm	8:10	10:30	26:40	66:40	134:35
2 lpm	4:05	5:15	13:20	33:20	67:17
3 lpm	2:43	3:30	8:53	22:13	44:51
4 lpm	2:03	2:37	6:40	16:40	33:38
5 lpm	1:38	2:06	5:20	13:20	26:55
6 lpm	1:21	1:45	4:26	11:06	22:25
7 lpm	1:10	1:30	3:48	9:31	19:13
8 lpm	1:01	1:18	3:20	8:20	16:49
10 lpm	0:49	1:03	2:40	6:40	13:27
15 lpm	0:32	0:42	1:46	4:26	8:58

N.Z. Cylinder

Cylinder Size	180A	180D	180E	180F	180G
Contents (Litres)	440	1490	2350	3700	7290
1 lpm	7:20	24:50	39:10	61:40	121:30
2 lpm	3:40	12:25	19:35	30:50	60:45
3 lpm	2:25	8:17	13:03	20:33	40:30
4 lpm	1:50	6:12	9:48	15:25	30:23
5 lpm	1:28	4:58	7:50	12:20	24:18
6 lpm	1:13	4:08	6:32	10:17	20:15
7 lpm	1:03	3:33	5:36	8:49	17:21
8 lpm	0:55	3:06	4:54	7:42	15:11
10 lpm	0:44	2:29	3:55	6:10	12:09
15 lpm	0:29	1:39	3:37	4:07	8:06

* Times shown are approximations only.

** INHALO® (400CD) System incorporates valve, regulator and flowmeter.

Equipment

Description	Inlet Fitting	Part Number AUST	Part Number NZ
Carnét Oxygen Pressure Regulator – AS Outlet Fitting	Pin Index	819-0071	819-0071
Carnét Oxygen Pressure Regulator – BS Outlet Fitting	Pin Index	–	819-0080
Carnét Oxygen FireSafe Flowmeter – Single	AS Inlet Fitting	829-0901	829-0901
Carnét Oxygen FireSafe Flowmeter – Single	BS Inlet Fitting	–	829-0301
Carnét FireSafe Nozzle – PK 10	9-16" UNF (DISS)	827-0031	827-0031
Carnét Oxygen Dial-Flow Regulator 0-15LPM	Pin Index	818-0051	818-0051
Carnét Oxygen Dial-Flow Regulator 0-3LPM	Pin Index	818-0040	818-0040
Erie Oxygen Combined Regulator & Flowmeter 0-25LPM	Pin Index	–	ER473025
Erie Oxygen Combined Regulator & Flowmeter HP Port 0-25LPM	Pin Index	–	ER473025HP

Some parts are not available in Australia or New Zealand.

Appendix VI: Cylinder Specifications in India

	Oxygen Type D	Oxygen Type A	Nitrous oxide Type D	Nitrous oxide Type A
Water capacity	46.7 L	5 L	46.7 L	5 L
Capacity	7 m^3	0.71 m^3	17.2 m^3	1.85 m^3
Maximum working pressure	150 kgf/cm^2	150 kgf/cm^2		
Minimum weight of gas at supply			31 kg	3.3 kg
Cylinder color	Black and white	Black and white	Blue	Blue

K. Gupta et al. (eds.), *Nitrous Oxide in Pediatric Dentistry*,
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Appendix VII: Summary of Standards for Perioperative Assessment

Guideline	ANZCA (2014) Australian and New Zealand College of Anesthetists	AAP (2016) American Academy of Pediatric Dentistry	EAPD (2005) European Academy of Pediatric Dentistry	IACSD (2015)
Vital signs recorded	• Pulse oximeter • Records HR, O_2 saturation oxygen and nitrous dosage and BP Monitor depth of sedation respiratory and cardiac depression	Observation and intermittent assessment of level of sedation	Pulse oximeter not essential Clinical monitoring: • Physical and verbal response, breathing movement of thorax, passage of air stream, RR skin color • N_2O dosage • Treatment performed • Sedation evaluation (sedation scale) and behavior scale	Clinical monitoring: • Level of consciousness/ depth of sedation • Airway patency, respiration (rate and depth), skin color, capillary refill, HR, rhythm, and volume
Staff required	– A clinician credentialed in use of nitrous oxide and basic airway management – A clinician to perform the procedure	Not specified	Not specified	Not specified
Document pain/ distress	Yes	Unspecified	Yes (sedation scale and behavioral scale)	Unspecified
Document time Under sedation	Yes	Yes	Unspecified	Unspecified

K. Gupta et al. (eds.), *Nitrous Oxide in Pediatric Dentistry*,
https://doi.org/10.1007/978-3-030-29618-6

Guideline	ANZCA (2014) Australian and New Zealand College of Anesthetists	AAP (2016) American Academy of Pediatric Dentistry	EAPD (2005) European Academy of Pediatric Dentistry	IACSD (2015)
Patient selection and assessment	• ASA I and II	• ASA I and II	• ASA I and II	• ASA I and II
Pre- and post-op instructions	Verbal and written	Verbal and/ or written	Verbal and written	Verbal and written
Fasting	Two hours fasting required	Two hours fasting required	Two hours fasting required—rules vary between European countries	No fasting required

Appendix VIII: Houpt Sedation Scale

Rating scale	Definition	Score
Rating scale for sleep	Fully awake, alert	1
	Drowsy, disoriented	2
	Asleep	3
Rating scale for movement	Violent movement that interrupts treatment	1
	Continuous movement that makes treatment difficult	2
	Controllable movement that does not interfere with treatment	3
	No movement	4
Rating scale for crying	Hysterical crying that interrupts treatment	1
	Continuous, persistent crying that makes treatment difficult	2
	Intermittent, mild crying that does not interfere with treatment	3
	No crying	4
Rating scale for overall behavior	Aborted: No treatment	1
	Poor: Treatment interrupted, only partial treatment completed	2
	Fair: Treatment interrupted but eventually all completed	3
	Good: Difficult, but all treatment performed	4
	Very good: Some limited crying or movement, e.g., during anesthesia or mouth prop	5
	Excellent: No crying or movement	6

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Appendix IX: Observer's Assessment of Alertness/Sedation (OAA/S) Scale

Responsiveness	Speech	Facial expression	Eyes	Score
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (more than half the eye)	3
Responds only after mild prodding or shaking	Few recognizable words	–	–	2
Does not respond to mild prodding or shaking	–	–	–	1

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Appendix X: Ramsay Sedation Scale

Descriptions	Scores
Patient is anxious and agitated or restless, or both	1
Patient is cooperative, oriented, and tranquil	2
Patient responds to commands only	3
Patient exhibits brisk response to light glabellar tap or loud auditory stimulus	4
Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus	5
Patient exhibits no response	6

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Appendix XI: Summary of Different Fear and Anxiety Scales

CFSS-DS 15	1. Dentists 2. Doctors 3. Injections 4. Having somebody examine your mouth 5. Having to open your mouth 6. Having a stranger touch you 7. Having somebody look at you 8. The dentist drilling 9. The sight of the dentist drilling 10. The noise of the dentist drilling 11. Having somebody put instruments in your mouth 12. Choking 13. Having to go to the hospital 14. People in white uniform 15. Having the dentist clean your teeth
DFSS-SF 11	Three out of the 15 item of CFSS-DS were omitted (n. 3,7, and 14) and one is added: fear of dental treatment causing pain
DAS 4	If you had to go to the dentist tomorrow, how would you feel? When you are in the waiting room waiting for the dentist to call you, how do you feel? When you are in the dentist's chair waiting for the dentist to begin the local anesthesia procedures, how do you feel? You are in the dentist's chair, already anesthetized. While you are waiting for the dentist to get the instruments to begin the procedure, how do you feel?
MDAS 5	At four items of DAS, the following question has been added: "when you are in the dentist's chair waiting for dentist to begin the teeth scaling procedure, how do you feel?"
MCDAS 8	How do you feel about going to the dentist generally? How do you feel about having your teeth looked at? How do you feel about having your teeth scraped and polished? How do you feel about having an injection in the gum? How do you feel about having a filling? How do you feel about having a tooth taken out? How do you feel about having being put to sleep to have treatment? How do you feel about having a mixture of "gas and air" which will help you feel comfortable for treatment but cannot put you to sleep?

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MDFS 15	Making an appointment Approaching the dental office Sitting in the waiting room Being seated in the dental chair Smell of the dental office Seeing in the dentist walk in Having oral examination Seeing the injection needle Feeling the needle injection Seeing the drill Hearing the drill Feeling the drill 13 Having the teeth cleaned Feeling pain after oral anesthesia Overall fear of dental work
DFS 20	At 15 items of MDFS, the following 5 questions has been added: when having work done My muscles become tense My breathing rate increases I perspire I feel nauseated and sick to my stomach My heart beats faster

CFSS-DS Children's Fear Survey Schedule-Dental Subscale
DFSS-SF Dental Fear Schedule Subscale-Short Form
DAS Dental Anxiety Scale
MDAS Modified Corah Dental Anxiety Scale
MCDAS Modified Child Dental Anxiety Scale
MDFS Modified Dental Fear Scale—*DFS* Dental Fear Scale

Appendix XII: Seattle System of Diagnostic Criteria for Dental Phobia

Fear type	Diagnostic item	Classification of fear
Type 1	Fear of dental procedures	Simple conditioned phobia
Type 2	Fear of fainting, panic attack, heart attack	Fear of catastrophe
Type 3	Nervous person in general	Generalized anxiety
Type 4	Distrust of dentists	Fear of dentists
Subclass a		– High fear of dental procedures
Subclass b		– Generally anxious
Subclass c		– Fearful of dental catastrophes

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Appendix XIII: Sedation Outcome Assessment

Sedation outcome assessment		
0	Excellent	Treatment completed without difficulty, minimal crying, and patient quiet and/or asleep for most of case
1	Satisfactory	Treatment completed with minimum difficulty, but alternating periods of crying and struggling with period of quiet and/or sleep
2	Unsatisfactory	Treatment completed with difficulty due to crying and struggling throughout treatment
3	Aborted	Treatment not completed due to combative behavior that increased the risk of injury to the patient or dental team

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