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Review Paper: An Overview of Pharmacological Considerations in Management of Dental Anxiety in General Dentistry Procedures

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ABSTRACT

Dental anxiety is a frequently encountered problem in dental offices which result in avoidance of dental care for most patients. Providing acceptable evidence based therapies for such patients is essential. Generally, dental anxiety can be managed by psychological interventions, behavioural techniques and pharmacological treatments, or a combination of them, depending on the level of dental anxiety, patient characteristics, clinical situations, type and duration of dental treatment. Pharmacological approaches can help to manage the patients using either level of sedation from mild sedation to general anesthesia. Pharmacological agents are usually sedative in action and do not eliminate anxiety but merely enhance patient acceptance. The agents used are varied and diverse and include nitrous oxide, benzodiazepines and narcotics, and they can be administered via different routes. This paper aims to review some pharmacological points in administration of sedative drugs in the management of dental anxiety.

Keywords:
Dental Anxiety,
Anesthesia,
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Introduction

Dental anxiety is a common problem in dentistry resulting in an unpleasant experience for both the patient and the dentist. Despite the advances in different dentistry techniques, dental anxiety has not diminished over the past 50 years with a prevalence of 40-75% in different countries and populations. The severity of dental anxiety ranges widely from mild anxiety to severe phobia and affects both children and adults (1, 2).

Patients dealing with dental anxiety, fear, or phobia usually avoid dental treatments leading to bad oral health, with more missing teeth, decayed teeth, and poor periodontal status. They usually receive dental treatments only in acute emergency situations with complicated and traumatic treatment procedures that more intensifies their fear, and if they are not managed appropriately may lead to complete avoidance of dental care in future (3, 4).

Dental anxiety and fear evoke physical, cognitive, emotional, and behavioral responses in an individual. However, there is a close relationship between fear and pain. Pain is basically caused by a physiological process but it has a strong cognitive component, as well. Patients with dental anxiety may experience increased pain perception having more pain that lasts longer; while they also exaggerate their memory of pain (5-7). Treating such anxious patients is also stressful for the dentist. It will result in reduced cooperation and requires more time and resources for treatment (8). It has been reported that severe anxiety may result in misdiagnosis during vitality testing for endodontic therapy (9).

Some general approaches such as appropriate treatment environment and chairside manners including proper communications with the patient, basic behavioral modifications, distraction, and some relaxing techniques can help in controlling dental anxiety to a great extent (10). However, anxious patients often require special interventions to allow conduction of dental procedures. Different pharmacologic and non-pharmacologic approaches have been developed to manage anxiety in patients. The behavioral or psychological techniques are the first choice and are necessary as a long-term solution. In cases where non-pharmacological considerations will not work, or in patients with mild or moderate anxiety that need acute treatments, pharmacologic approaches are recommended (10, 11). This paper summarizes the pharmacologic approaches for management of anxiety in dental patients and highlights the pharmacologic and pharmaceutical considerations in this regard.

Discussion

Indications of pharmacological interventions for management of dental anxiety

The primary indication for pharmacologic management of anxious patients in dentistry is the presence of anxiety, fear, or phobia in a way that interrupts the process of dental care. The dentists should be able to identify and manage anxious or phobic individuals. They should evaluate patient's cognitive and emotional needs and personality and consider the extent of patient's dental needs and severity of anxiety. Finally, they are supposed to select appropriate evidence-based approach according to the level of dental anxiety and urgency of dental care, considering cost of the procedure. Pharmacological interventions usually enable comfortable delivery of urgent dental treatment but they are only minimally effective in helping the individual overcome their dental fear (12, 13).

When anxiety is coupled with some traumatic or acute dental procedures like when there is a need to immobilize the patient, or it is impossible to render the patient pain-free with local anesthesia, pharmacologic interventions may be necessary. Moreover, Patients with special needs (i. e. mental retardation, autism, mental illness, traumatic brain injury) and some clinical situations can also necessitate pharmacological management. Some examples include:

- Patients with some grades of motor dysfunction like cerebral palsy or Parkinson disease, whose tremor or uncoordinated movements may be increased by dental anxiety.

- Patients that cannot physiologically tolerate the stress that even a minimal amount of

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anxiety like patients with ischemic heart disease, hypertension, or stress-induced asthma.

- Presence of cognitive impairment, such as in mentally challenged patients or patients with Alzheimer dementia that are unable to cooperate sufficiently for treatment or even an adequate oral examination.

- Children who may not understand the treatment and act normal as a child (14-16).

The American Society of Anesthesiologists (ASA), patients are classified regarding their ability to tolerate the stress of a planned procedure (Table 1).

Table 1. The American Society of Anesthesiologists (ASA) physical status classification system

Class	Description
ASA I	Normal healthy patient
ASA II	Patient with mild systemic disease
ASA III	Patient with severe systemic disease
ASA IV	Patient with severe systemic disease that is a constant threat to life
ASA V	Moribund patient who is not expected to survive without the operation
ASA VI	Patient declared brain-dead whose organs are being removed for donor purposes
E	Emergency operation of any variety (used to modify one of the aforementioned classifcations, ie, ASA III–E)

According to these categories, ASA I and II patients are usually suitable candidates for sedation or general anesthesia in the outpatient setting.

Various levels of sedation

Sedation is defined as the use of drugs to depress the Central Nervous System (CNS) and reduce patient awareness of their surroundings. Depending on the degree of CNS suppression, the sedation may be conscious, deep, or general. However, it should be noted that sedation does not control the pain, and consequently does not eliminate the need for the use of local anesthetics (17).

The indicator of sedation need (IOSN) tool can be utilized in defining the need for sedation to helps dentists in their clinical decision-making. It evaluates and scores the levels of anxiety, medical and behavioral states, and treatment complexity and the total scores define need of patient for level of sedation: minimal, moderate need, high, and very high need or even use of general anesthesia (18).

Sedation levels range from minimal to deep sedation in a dose–response manner. The characteristics and definition of each level is described below:

Minimal sedation

The consciousness level is depressed minimally but the patient's ability to maintain an airway independently and continuously remains and the patient responds normally to tactile stimulation and verbal command. Although cognitive function and coordination may be modestly impaired, ventilatory and cardiovascular functions are unaffected. Minimal sedation is used for managing patients with mild-to-moderate anxiety.

Moderate/conscious sedation

Depression of consciousness is achieved in a way that patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained. Conscious sedation is used for management of moderate-to-severe anxiety.

Deep sedation

is a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully after repeated or painful stimulation. The ability to maintain ventilatory function independently may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

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General anesthesia

is a drug-induced loss of consciousness during which patients are unarousable, even by painful stimulation. The ability to maintain ventilatory function independently is often impaired. Patients often require assistance in maintain ing 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.

Deep sedation or general anesthesia may be indicated when lighter forms of CNS depression are insufficient like patients with severe learning difficulties, severe anxiety and phobias, severe psychiatric disorders, physical disability and congenital disorders in whom sedation may not be safe. However, this level requires a formal and increased level of education and training, patient monitoring, and physical resources (e.g., anesthetic equipment and supplies). These levels of sedation (deep sedation or general anesthesia) can be induced by many of the same drugs that induce moderate sedation, depending on patient susceptibility, age, medical status, degree of anxiety, and the administered dose. Consequently, if minimal or moderate sedation is targeted and the patient remains uncooperative, administration of excessive doses of a sedative must be avoided because it may lead to a deepening of sedation in which airway patency and protective reflexes may be lost (19).

Routes of administration

Various routes of administration, including inhalation, oral, intravenous, intramuscular, sublingual, rectal, and intranasal route, can be applied to achieve each level of sedation in dentistry. The appropriate route of administration for each patient is selected considering the following points:

- Which level of sedation is required?
- Which route of administration is proper for the patient? (Some routes of administration are more acceptable for the patient depending on their age and cooperation level)
- What are the available formulations on the market?
- Does the drug reach the therapeutic level through the intended route of administration according to evidence-based studies?

The drugs are effective only when they enter the systemic blood circulation. This may be achieved through direct administration into blood vessels (intravenous administration) or absorption from site of administration (i. e. Oral, intramuscular, inhalation, sublingual, rectal, and intranasal). It should be noted that the route of administration is not synonymous with the depth of sedation. Any route has the potential to induce any degree of sedation or anesthesia. Management of an anxious patient can be discussed according to route of administration, however, because the inhalation and oral techniques are most commonly used for minimal and moderate sedation and are normally the first to be considered. The intravenous route is more likely to be selected to induce a greater depth of effect. Possible routes of administration for sedation in dentistry are described in the following sections.

Oral Sedation

Oral administration is one of the most frequently used route of administration to obtain minimal or moderate sedation in dentistry. It is convenient, noninvasive and economical and most patients easily accept oral medications. However, young children, the mentally challenged, and those with dementia may refuse to swallow drugs, particularly in tablet or capsule form. Efforts have been made to mask the bitter taste of oral medications but children may spit or regurgitate them. Problems such as overdose, idiosyncratic reactions, allergy, and other adverse events are less likely to arise when drugs are given orally, and if they do develop, they are often less intense.

Oral medications are subject to first-pass metabolism in the gut and liver before reaching the systemic circulation. This cause lesser amounts of drug being available in blood circulation, and there is a lag time between administration and

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action. Furthermore, the amount of medication actually absorbed varies between individuals, and food and other medications can interact to increase or decrease the drug's availability for systemic circulation, hence the results may be unpredictable (20, 21).

The major disadvantage of oral sedation is the inability to titrate reliably, so the dentist cannot adjust for individual patient response (22). Titration is defined as the incremental administration of small amounts of a drug until a desired clinical effect is observed. After a drug is taken orally, it is often impractical to provide an additional dose because of the delay in absorption and onset of action. There can also be a delay in drug equilibration between the plasma and effect site concentrations, which can lead to overdose if additional doses are administered on the basis of patient anxiety. A predetermined dose is best administered while recognizing, on one hand, the risk of an excessive dose leading to prolonged action or inadvertent deep sedation and, on the other hand, the risk of an insufficient dose, in which case the patient would be inadequately sedated to allow dental treatment.

Inhalation sedation

Inhalation sedation is a technique of choice for dental procedures that require

minimal sedation. It is based on absorption of the gases into the vasculature of the respiratory system. First-pass metabolism is avoided, and onset is rapid which allows for titration to effect. As gases are not usually metabolized, the cessation of action occurs by redistribution of the gases out of the blood and into the lungs for exhalation. Consequently, the inhalation route is the only route in which the actions of a drug can be quickly adjusted in either direction and recovery is usually rapid. When delivered by nasal hood or facemask, the administration of gases by inhalation can be diluted if the equipment is poorly fitting or the patient will not tolerate it. As any mechanical devices can fail, careful technique and continuous observation of the patient are more effective in preventing accidents than simple reliance on mechanical safeguards (22, 23).

Parenteral (Intravenous) sedation

The intravenous route is also a common pathway to achieve moderate sedation, as well as deep sedation for drug administration. Parenteral administration will insert the medication directly into blood circulation and no first-pass metabolism occurs. Drug action is rapid and the effects are easier to predict due to very short latent period, which provides the ability to titrate the drug. In clinical practice, the operator requires 2 to 15 minutes to titrate a drug to a desired clinical end point. However, it is an invasive route of drug administration, is painful, and requires extra training for injection. Intravenous sedation is often undesirable for patients and sometimes impossible for children (22).

Intramuscular route

The intramuscular route is frequently used in sedation and general anesthesia. It provides an onset and uptake intermediate between that of oral and intravenous routes. The drug is absorbed into the vasculature in a fairly predictable and uniform manner. Onset of action is less rapid than intravenous injection, and the absorption is spread out, so the duration of action tends to be longer. There is a limited ability to titrate with this route, but it can be particularly advantageous for patients who are incapable of cooperating, such as cognitively impaired patients. It requires less technical skill than intravenous cannulation. This route can be painful and locally irritating, and only a certain volume of medication can be injected at each site, depending on the size of the muscle (usually thigh or deltoid muscles) (21).

Intranasal route

Intranasal sedation involves the topical application of drug in nasal mucosa in form of nasal drops or aerosols. It provides rapid absorption, quick onset of action and a relatively quick recovery. It has been used as an alternative to intramuscular injection for uncooperative children

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although there is usually a need for restraint to achieve administration.

Intranasal administration has been proven to be a safe and effective for short procedures. Another possible advantage of intranasal sedation is that a strict adherence to fasting requirements may not be essential and there is less risk of nausea, vomiting, and respiratory complications. However, Nasal mucosal secretions can also affect intranasal drug absorption. Although intranasal administration is usually simple, relatively painless, and requires less patient cooperation, it has been associated with mucosal irritation. This may lead to coughing, sneezing, crying and the expulsion of part of the dose especially in administration of large volume of medication (24).

Buccal and sublingual route

Sublingual and buccal administration are alternative routes for delivery of sedative agents. The drug is directly absorbed through oral mucosa into the systemic circulation resulting in avoidance of hepatic first pass metabolism, increased bioavailability, and faster onset compared to oral sedation. The difference in recommended dosages can be large when comparing oral versus sublingual/buccal absorption depending on the extent of first-pass metabolism in the intestine and liver. The buccal mucosa has a rich blood supply and is relatively permeable, being an alternative to the intranasal route. However, there is a possibility of experiencing the bitter taste specially with aerosol formulations (24).

Rectal route

Rectal administration (enema or suppository) is not often used in dentistry, but would be an option for pediatrics, vomiting, or uncooperative patients. Rectal route has some limitations including inability to titrate, inconsistencies in absorption, poor patient acceptance, and possibility of interruption of absorption by defecation. Rectal administration avoids drug inactivation by stomach acid and digestive enzymes and about 30-50% of that absorbed bypasses the first-pass effect. In some circumstances, it may be advantageous to administer a drug rectally, for example if a patient is unconscious in some way, but generally, it is considered an unpleasant method (25, 26).

Common and recent pharmacological agents

Selection of medications is a critical step in sedation plan. The dentist should select a proper medication considering duration of appointment and some points including medical history, use of concurrent medication, and history of the patient's response to mood-altering drugs such as alcohol. Patients who take large amounts of alcohol, opioids, or other mood-altering drugs may require an increased dose of sedative because of tolerance. However, when possible, consideration should be given to sedatives with available reversal agents. In the event of over sedation, benzodiazepine and narcotic medications may be preferred over drugs without known reversal agents, such as chloral hydrate.

There are different category of drugs used for sedation in dentistry, which are summarized in the following sections.

Nitrous oxide inhalation

Nitrous oxide inhalation is a technique of choice for dental procedures that require minimal sedation. The technique employs subanesthetic concentrations of N_2O delivered along with oxygen from dedicated machinery through a nasal mask. It is an anxiolytic/analgesic agent that causes CNS depression and varying degree of muscle relaxation with hardly any effect on the respiratory system. Analgesic effects of N_2O is initiated by the neuronal release of endogenous opioid peptides with activation GABAA and inhibition of N methyl D aspartate (NMDA) glutamate receptors. One major advantage of the agent is the lack of prolonged effects after the

treatment session. Its other advantages includes its wide range of safety for the patient, rapid onset of action and rapid elimination. N_2O

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does not significantly impair higher cognitive tasks and thus patients who have had treatment with nitrous oxide sedation are able to resume normal activities in the immediate postoperative period. The use of N_2O is contraindicated in patients with common cold, porphyria, and COPD.

Benzodiazepines

Benzodiazepines are drugs of choice for oral and intravenous sedation and have a wide margin of safety compared with other antianxiety and sedative drugs. These drugs are also delivered via rectal, intranasal and buccal administration. They are well absorbed, and most have a rapid onset of action. Benzodiazepines with short duration of action are ideally suited to dentistry, allowing for rapid recovery, which is important for outpatient procedures. Relative contraindications to the use of benzodiazepines include myasthenia gravis, obstructive sleep apnea, and acute angle-closure glaucoma. The most frequently used benzodiazepines for minimal or moderate sedation in dentistry are summarized below.

Triazolam, (available in 0.125 mg or 0.25 mg tablets) is an effective anxiolytic agent with a rapid onset of action and a short elimination half-life which allows rapid recovery being suitable for outpatient dental procedures. Possible interaction can occur with drugs that inhibit CYP3A4, including erythromycin, clarithromycin, ketoconazole, fluconazole, itraconazole, cimetidine. These drugs inhibit metabolic breakdown of triazolame leading to increased and prolonged plasma concentrations, and may potentiate the magnitude and duration of triazolam's sedative effect.

Diazepam is the most popular benzodiazepine that has a long history of use in dentistry. It has a lipid soluble nature and is available in tablets (2, 5, and 10 mg), syrup (5 mg/5 ml and 25 mg/5 ml) and injectable solution (5 mg/ml). Given intramuscularly, its absorption is slow, erratic and incomplete and it should therefore only be administered orally, rectally or by the intravascular route. Diazepam is effective within 30–45 min of oral administration and has a duration of action of at least 4–6 h. However, when administered in the dental clinic prior to treatment, it may take up to 60 min before sedation is effected and with low doses, fear and tension may not be abated. Diazepam induces sedation within 1–2 min after bolus intravenous administration but it has a long elimination half-life (20–90 h). This results partly from enterohepatic recirculation. In addition, one of its metabolites, N-desmethyl diazepam is pharmacologically active and has a long half-life. It thus takes a long while for full alertness to be recovered following drug administration (15).

Midazolam, is a water soluble derivative that has almost replaced diazepam as an intravascular sedative. It is available as 2 mL ampoules containing 5 mg/mL and 5 mL ampoules containing 2 mg/mL. It has a slightly more rapid onset of action than diazepam after intravenous injection because it is lipid solubile at physiological pH and can cross the blood–brain-barrier. It also has a stable sedative effect and minimal residual effects. It has a short duration of action, with an elimination half-life of 1.5–2.5 h because its metabolites are inactive.

It can be administered via the oral, intramuscular, intravenous, nasal, sublingual or rectal routes. However, because of its rapid hepatic clearance, the nasal, intramuscular and intravenous routes of administrations ensure higher systemic availability than the other routes. Nasal route has been suggested as the administration route of choice because the sedative effect appears within 5–10 min, with a stable level attained by 10 min compared to the 30 min which occurs with the oral, rectal or intra-muscular routes.

Similar to triazolam, oral midazolam is contraindicated in patients taking erythromycin or other strong CYP3A4 inhibitors. Midazolam's high first-pass effect leads to large differences in the parenteral and oral dosing (15).

Lorazepam is another benzodiazepine that has been commonly used. Although it can elicit satisfactory sedation for dental procedures, it has long duration of action and peak effects

may occur 1 to 6 hours after administration, making appropriate scheduling difficult. It may be considered for longer dental appointments (e.g., over 3 hours) and is not recommended in pediatric patients (27).

Alprazolam may be given for longer procedures as an alternative to lorazepam. Alprazolam is subject to the same CYP3A4 interactions as triazolam.

Temazepam or oxazepam can be considered as an alternative for minimal or moderate sedation if triazolam is unavailable. There is not as much documented for use in dental anxiety.

Zolpidem and zaleplon are sedative-hypnotics related pharmacologically to benzodiazepines because they interact with a subtype of benzodiazepine receptors. They are similar to triazolam (also classified as a sedative-hypnotic) in providing anxiolysis, sedation, and a rapid onset of action, with peak effects occurring in 20 minutes. Prolonged sedation is not a problem because of their short metabolic half-lives and conversion to inactive derivatives. Possible disadvantages are their relative lack of anticonvulsant and muscle relaxant properties. Zolpidem is characterized as a category B drug with regard to pregnancy and may be considered an oral sedative of choice for pregnant women (25).

Antihistamines

Promethazine is a phenothiazine derivative with antihistaminic properties that has been used for sedation, particularly in pediatric patients.

Hydroxyzine, the only antihistamine approved specifically as an antianxiety drug, is similar to promethazine in that it is an antihistamine and induces sedation and has anticholinergic and antiemetic effects (27).

Opioids

These drugs primarily act centrally to decease pain, fear and anxiety and are not used alone for sedation. They are commonly given to supplement benzodiazepines or other sedatives either to facilitate moderate sedation or, with increasing doses, to induce deep sedation or general anesthesia. The duration of action varies with the drug. Administration of an opioid should be timed so that the peak effect coincides with the most painful part of the procedure.

Specific concerns with intravenous opioids include respiratory depression and chest wall rigidity. Opioids commonly used for moderate sedation include fentanyl, meperidine, pentazocine, and nalbuphine.

Fentanyl is appropriate for procedures of short duration around 30 to 60 minutes. Advantages of fentanyl over other opioids include cardiovascular stability, a relatively short duration of action, and lack of histamine release.

Meperidine has a duration of action of 1 to 2 hours. In addition to its expected effects of analgesia and sedation, meperidine is noted for its potential to induce tachycardia. It should be used cautiously, or not at all, in patients with asthma because of the potential for histamine release. A more recent concern is its potential to interact with other drugs—serotonin-selective reuptake inhibitors and various other antidepressants—that can increase the activity of endogenous 5-hydroxytryptamine (serotonin).

Pentazocine is a mixed agonist-antagonist, which results in a ceiling effect regarding analgesia and respiratory depression. Adverse reactions include a potential for psychotomimetic effects, such as disorientation, confusion, depression, hallucinations, dysphoria, diaphoresis, and dizziness. Pentazocin can be expected to have a duration of action of 1 to 2 hours. Nalbuphine is also a mixed agonist-antagonist used for sedation (28).

Other drugs

Propofol is an intravenous general anesthetic that can be used for moderate sedation or deep sedation in low doses. It has a good sedative effect together with additional antiemetic properties and a short recovery time of approximately 15 min.

Dexmedetomidine is a centrally acting α2-adrenoceptor agonist similar in properties

to clonidine. Originally indicated for sedation of intubated patients in the intensive care unit, the drug has been approved for moderate sedation, although not yet widely used. Xerostomia, hypotension, and bradycardia are the most common side effects. An initial evaluation of dexmedetomidine given as a loading dose of 0.1µg/kg/min for 5 minutes and followed by a continuous infusion of 0.2µg/kg/hr seemed to be safe and effective for dental patients.

There are a number of agents that have been used in the past for oral sedation that are no longer recommended, as their risk/ benefit balance is inferior to the benzodiazepines and antihistamines. For those trained only in minimal or moderate sedation techniques, agents such as chloral hydrate, opioids, ketamine, and barbiturates are not recommended as oral sedatives (25).

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