

Oral Sedation in Pediatric Dentistry

Riya Ojha^{1,*}, Sonal Gupta², Mahima Panwar³, and Neha¹

ABSTRACT

Anxiety, dental phobia, parental expectations, and challenging patient behavior highlight the need for sedation in paediatric dentistry. Various pharmacological drugs are present within the oral sedation which helps in achieving a calm, relaxed patient who can guard their own airway, sustain their own respiration, and respond to vocal commands. An in-depth overview of oral sedation in pediatric dentistry is what this review's main goal is to deliver. It will provide knowledge for practitioners who wish to administer oral sedative medications to their pediatric patients. The pharmacodynamics and pharmacology of frequently used oral sedative drugs will be discussed, along with pre-operative concerns, monitoring equipment requirements, and physiological considerations of the paediatric patient.

Keywords: Anxiety, Children, Oral Sedation, Pediatric Dentistry.

Submitted: May 18, 2023

Published: January 06, 2024

 10.24018/ejdent.2024.5.1.276

¹Second Year Postgraduate Student, Department of Pediatric and Preventive Dentistry, K. D. Dental College and Hospital, India.

²Professor and Head, Department of Pediatric and Preventive Dentistry, K. D. Dental College and Hospital, India.

³Third Year Postgraduate Student, Department of Pediatric and Preventive Dentistry, K. D. Dental College and Hospital, India.

*Corresponding Author:

e-mail: riyaojha18@gmail.com

1. INTRODUCTION

It can be quite difficult to manage child patients for different dental procedures in a dental clinic. Children under the age of six are more likely to experience behavioral issues as a result of a variety of factors, including under-developed reasoning, limited coping mechanisms, and anxiety/fear-inducing factors [1]. Many of the behavioral problems are tackled by non-pharmacological methods like tell show and do, euphemism, active communication, modelling, etc., however, a sizable portion of these patients are resistant to cooperating with regular dental procedures. Therefore, the requirement for more sophisticated methods of behavior management, such as pharmaceutical interventions, comes into play [2].

Unpleasant dental experiences can have a negative psychological impact. Unrestored caries may contribute to pain, disturbed sleep, trouble learning, and poor growth in children. The fear of going to the dentist and past painful dental experiences cause the majority of dental anxiety to start in childhood. If the proper measures are not performed, the child may become overwhelmed during dental treatment, leading to dental phobia and avoidance. 10%–20% of the general population avoids getting the necessary dental treatment because of these anxieties, which last into adulthood. Such issues are minimized by oral sedation, which also establishes trust in the family and the child [3].

The pharmacological alternatives include oral sedatives, combinations of oral sedatives and/or inhalation agents, and general anesthesia [4]. Oral sedation is a medical practice that involves giving sedative medications orally. It is typically used to expedite dental procedures and lessen patient anxiety. It is widely accepted, simple, handy, painless, and affordable. It involves the delivery of pharmacological agents to achieve a calm, relaxed patient who can protect their own airway, support their own ventilation, and respond to verbal commands [5].

2. OBJECTIVES FOR SEDATION IN PEDIATRIC DENTISTRY

Dental fear and anxiety are most commonly seen in children which makes it difficult to provide complete dental treatment. Here oral sedation comes into play by reducing the stress and unpleasant emotions which in turn helps in preventing the burn out syndrome. This makes it easier for the child to cope up with the treatment as pain perception is also reduced. It is also advantageous for the dentist as the procedure is completed within time.

2.1. Indication

Following are the indications for oral sedation:

- Children with low coping skills
- Children having Behaviour management problems
- Dental fear and anxiety
- Children showing Mental retardation
- ASA Classes I & II



2.2. Contraindication

Following are the contraindications for oral sedation:

- Children smaller than 1 year.
- ASA Classes III & IV.
- Known allergy or adverse effects to sedative drugs [6].

2.3. Levels of Sedation

There is a range of sedative levels for both adults and children. These have been described by the American Society of Anesthesiologists [7] (Table I).

2.4. Health of the Patient–ASA Physical Status (American Society of Anesthesiologists)

Certainly, dentists ought to restrict the use of sedation in dental offices to those with ASA 1 or well-controlled ASA 2 conditions [8] (Table II).

3. EVALUATION AND PREPARATION OF THE CHILD FOR SEDATION

3.1. Age

Frequently, children under the age of three cannot fully comprehend the procedure. To get the intended results, the child is likely to need deeper degrees of sedation. A patient who receives both pharmacological and non-pharmacologic behavior control approaches is likely to be more cooperative [9].

3.2. Medical History

The child's medical history must be thoroughly reviewed with the parents [9]. Respiratory issues, such as asthma, and upper respiratory tract infections should be reviewed.

An increased risk of hypoxia, laryngospasm, and coughing is evident in pediatric patients with these illnesses. For mild upper respiratory infections, a patient can be treated with sedation without any risk. Any cardiovascular issues need to be dealt with beforehand. If a child suffers from sleep apnea or other breathing issues while asleep, the

parent or guardian should always be questioned about it [8]. History of epilepsy and diabetes should be considered. The frequency and types of seizures must be noted [10].

3.3. Fasting

Regardless of the level of sedation, it's vital to fast before the session since stomach contents can be re-aspirated or vomited, which might cause pneumonia or pneumonitis [9].

For elective procedures using oral sedation, the 2–4–6 fasting rule is applied: 2 hours for clear fluid, 4 hours for breast milk, 6 hours for solids [9] (Table III).

3.4. Consent

A written and informed consent form should be carefully completed by parents and caregivers in the forms as well as verbally. The risks and benefits of oral sedation is explained to the parents [9].

3.5. Preoperative and Postoperative Instructions

Parents of children who will be sedated must receive written instructions. The type of anesthesia the child will receive during surgery, as well as the need to fast before the procedure, should be covered in the preoperative instructions. Following the appointment, fluids should be consumed along with advice to relax for the remainder of the day. Soft, easily digestible foods can be provided to the child after the visit if there is no postoperative nausea and vomiting.

If local anesthesia was used, the parents should be warned about tongue, lip, and cheek biting. For any questions or concerns, a telephone number that can be reached at any time should be given [9].

3.6. Training and Monitoring

Dentists must hold qualifications in Pediatric Advanced Life Support (PALS) and/or Advanced Cardiac Life Support (ACLS). This assists the dentist in managing patients who are experiencing respiratory distress, heart failure,

TABLE I: LEVELS OF SEDATION [7]

	Minimal or light sedation (Anxiolysis)	Moderate sedation or analgesia (Conscious sedation)	Deep sedation or analgesia	General anesthesia
Responsiveness	Normal response to verbal stimuli	Purposeful response to verbal or tactile stimuli	Purposeful response following repeated or painful stimuli	Unarousable even with repeated or painful stimuli
Airway	Unaffected	No intervention required	Intervention may be required	Intervention is often required
Spontaneous ventilation	Unaffected	Adequate	Maybe inadequate or compromised	Frequently inadequate and is compromised
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	Maybe impaired

TABLE II: ASA PHYSICAL STATUS CLASSIFICATION [8]

ASA physical status 1	A normal healthy patient
ASA physical status 2	A patient with mild systemic illness
ASA physical status 3	A patient with severe systemic disease
ASA physical status 4	A patient with severe systemic disease that is a constant threat to life
ASA physical status 5	A moribund patient who is not expected to survive without the operation
ASA physical status 6	A declared brain-dead patient whose organs are being removed for donor purposes

TABLE III: SUMMARY OF FASTING GUIDELINES [10]

Food	Time prior to appointment (hours)
Clear fluids	2–3
Breast milk	4
Formula, non-human milk	6
Solids	6–8

or unintentional deeper sedation until emergency care is available [9].

Throughout the procedure, it is important to continuously check the patient's blood pressure, oxygen saturation, heart rate, and breathing rate [10].

4. DISCHARGE CRITERIA

Patient is allowed to be discharged if following conditions are noted:

- Reflexes are present (swallowing, coughing, gagging).
- Minimal dizziness.
- Eyes are open and able to keep his/her head up.
- Activity is consistent with respect to age or development.
- At least 2 hours have elapsed since the last administration of reversal agents if any were administered.
- Given written discharge instructions regarding post-operative diet, pain medications, precautions, and a telephone number to use in case of emergency.
- Parents should be given a post-op phone call in the evening to see how the patient is doing [6].

4.1. Documentation and Records

It is recommended that the documentation include:

- Medical history including prescribed medication.
- Previous dental history.
- Pre-sedation assessment.
- Written instructions are provided pre- and post-operatively.
- Presence of an accompanying responsible adult.
- Arrangements for suitable post-operative transportation and supervision.
- Compliance with pre-treatment instructions.
- The course of the treatment;
 - Monitoring;
 - Dose, and route of administration of sedative drugs
 - Dental treatment performed
 - Sedation evaluation (sedation scale).
 - Accept of sedation and treatment (behavioral scale).
 - Complications.

5. DRUGS USED FOR ORAL SEDATION IN PEDIATRIC DENTISTRY

5.1. Midazolam

Midazolam is a water-soluble benzodiazepine which is used for anesthesia and procedural sedation. It is available

as a clear, colourless midazolam hydrochloride solution with a 2–5 mg/ml concentration. When given orally as a premixed syrup or after being diluted with a pleasant, pH-balanced drink (such as apple juice), midazolam is quickly absorbed. It has an oral bioavailability of 35% to 44%. Midazolam has a short duration of action due to its high lipophilicity, high metabolic clearance, and rapid rate of excretion. Midazolam's principal effects include hypnosis, drowsiness, anxiolytics, anterograde amnesia, anticonvulsant properties, and muscle relaxation. Its metabolism occurs via hepatic oxidation and glucuronidation. Drugs including physostigmine, glycopyrronium, and flumazenil can be used to reverse the medication's clinical effects [11].

Onset: 15–20 min, working time: 30–45 min, half-life: 1.5–2.5 hours.

Dosage:

- Oral - 0.25 to 1.0 mg/kg to a maximum single dose of 20 mg.
- Supplied - oral tablets 0.3–0.6 mg/kg.
- Syrup - 2 mg/ml.

Side effects: respiratory depression with higher doses, paradoxical reaction and in case of rapid administration-apnea, hypotension, etc.

5.2. Ketamine

Ketamine is an N-methyl D-aspartate (NMDA) dissociative anaesthetic that induces a catalepsy-like condition that provides drowsiness, pain relief, and amnesia [12]. The main effects of ketamine are its amnestic and analgesic properties, its relatively stable cardiovascular system, and its minimal effects on respiratory mechanics. It comes in the form of a white, crystalline powder (a phencyclidine derivative), which must be diluted in water before use to produce a colourless solution containing 10–50–100 mg/ml racemic ketamine hydrochloride. It has an oral bioavailability of 20% [13]. NDE methylation and hydroxylation of the cyclohexylamine ring in the liver turn ketamine into usable forms. The conjugated metabolites are excreted in the urine. Activated charcoal is administered in a dose of 1 g/kg to treat ketamine toxicity, with a maximum oral dose of 50 g/ng [14].

Onset: 20 min, working time: 20–120 min, half-life: 11 min.

Dosage: 3 mg–6 mg/kg.

Side effects: a dissociative state that makes it difficult to communicate with the patient, increased salivation, unpleasant emerging phenomena (such as nightmares), and vomiting as undesirable side effects.

5.3. Choral Hydrate

Chloral hydrate is a geminal diol with weak analgesic and psycho-sedative properties. It is available in several different preparations including capsules (250, 500 mg), syrup (250 and 500 mg/5 mL), and suppositories (325, 500, and 650 mg) [15]. The active metabolite trichloroethanol is thought to be the primary cause of chloral hydrate's CNS depressing effects [16]. It is metabolized by the liver and erythrocytes to form trichloroethanol, an active metabolite, and excreted in the urine. There is no specific antidote

for chloral hydrate, but there has been a case report of reversal with flumazenil [14].

In small dosage it acts as mild sedation and in intermediate dosage it works as natural sleep.

Onset: 30 min, working time: 60 min, half-life: 8–12 hours in children, but may be prolonged up to 24–36 hours in neonates and infants.

Dosage: 25 to 50 mg/kg to a maximum of 1 g.

Supplies: oral capsule - 500 mg, oral solution - 250 mg/5 ml.

Side effects: depressed blood pressure and respiratory rate, gastric irritation, nausea, vomiting, myocardial depression, and arrhythmia.

Contraindications: heart disease, renal problems, hepatic impairment.

5.4. Diazepam

Diazepam is a medicine of the benzodiazepine family that acts as an anxiolytic. Being available for more than 42 years and still being widely used, it is frequently referred to be the “grandfather” of the medication class. It has 100% oral bioavailability. Due to its high lipophilicity, it has a rapid beginning of action (often within 20–40 min) and peaks in plasma levels 1–2 hours after oral intake [17].

It acts as an Anxiolytic, sedative, anticonvulsant and muscle relaxant. Mode of action are thought to result from a facilitation of the action of gamma amino butyric acid (GABA), an inhibitory neurotransmitter in the central nervous system. Diazepam undergoes hepatic metabolism by oxidative reduction [18]. The antidote for an overdose of diazepam (or any other benzodiazepine) is flumazenil (Anexate) [19].

Onset: 20–40 min, working time: 1–2 hours, half-life: 20–80 hours.

Dosage: Oral or rectal - 0.2 to 0.5 mg/kg to a maximum single dose of 10 mg. It is available as tablets (2, 5, 10 mg), as a solution (1 mg/1 ml).

Side effects: anterograde amnesia, tolerance, dependency, withdrawal syndrome, etc.

5.5. Diphenhydramine (Benadryl)

Diphenhydramine is an antihistamine of the ethanolamine class. It is a mild sedative that targets H₁ receptors and is frequently prescribed for that purpose [20]. The FDA initially authorised it as a prescription-only medication in 1946, but later altered its status to nonprescription, over-the-counter (OTC) [21]. Diphenhydramine acts as an inverse agonist at the H₁ receptor, thereby reversing the effects of histamine on capillaries, reducing allergic reaction symptoms [22]. Due to its ability to induce drowsiness, it is also promoted as an OTC hypnotic (Sominex) [21]. The liver metabolizes diphenhydramine via CYP450 and is excreted in the urine. In case of diphenhydramine overdose activated charcoal is administered followed by physostigmine.

Onset: 15 to 30 min, working time: 2 to 4 hours, half-life: 3.4 to 9.2 hours.

Dosage: Oral - 1.0 to 1.5 mg/kg; maximum single dose is 50 mg.

Side effects: paradoxical excitement, hypotension, tachycardia, and urinary retention.

5.6. Hydroxyzine

Hydroxyzine is a first-generation histamine H₁-receptor antagonist of the diphenylmethane and piperazine classes that exhibits sedative, anxiolytic, and antiemetic properties [23], [24]. It is the only antihistamine that has been authorized for use in pediatric dental sedation.

No cardiovascular or respiratory effect was seen. Its mode of action is as a potent and selective histamine H₁ receptor inverse agonist.

Onset: 15–30 min, working time: 4–6 hours, half-life: 7.1 hours.

Dosage:

- Oral - 0.6–1.5 mg/kg or 25 mg delivered as a bolus. It is available as a 10, 25 and 50 mg capsule and a 2 mg/ml syrup.
- Commercially - Hydroxyzine hydrochloride (Atarax) which contains alcohol and Hydroxyzine pamoate (Vistaril).

Side effects: chest pain, discomfort or tightness, difficulty with swallowing, increased heart rate, puffiness or swelling of the eyelids or around the eyes, face, lips, or tongue.

5.7. Promethazine (Phenergan)

It is a first-generation antihistamine- phenothiazine which has anticholinergic, sedative, antiemetic, and some local anaesthetic properties. It acts primarily as a strong antagonist of the H₁ receptor. It works as an antagonist of histamine H₁, post-synaptic mesolimbic dopamine, alpha adrenergic, muscarinic, and NMDA receptors [25]–[27]. The liver breaks down promethazine into a number of different substances; the sulfoxides of promethazine and N-demethylpromethazine are the main metabolites seen in urine [28]. First reported use in dentistry as a cocktail with Demerol and Thorazine to serve as an antiemetic to control the nausea and vomiting [29].

Onset: 20 min, working time: 1 to 2 hours.

Dosage:

- Oral/intramuscular - 0.5 to 1.1 mg/kg.
- Subcutaneous not recommended.
- Maximum recommended single dose - 25 mg.

Side effects: drowsiness, dizziness, anxiety, blurred vision, dry mouth, stuffy nose.

5.8. Meperidine

As a synthetic opioid in the hydrochloride salt form, meperidine belongs to the same class as phenylpiperidine. It is employed to alleviate pain ranging from moderate to severe. It can be administered intramuscularly, subcutaneously, intravenously, as syrup, or as tablets. It is the most commonly used opioid in dentistry with strong analgesic properties. It provides a euphoric like state. Metabolized in the liver and excreted by the kidney [30].

Onset: 30–44 min, working time: 30–45 min.

Dosage:

- Oral - 1.0 to 2.2 mg/kg, not to exceed 100 mg when given alone or 50 mg when in combination with other CNS depressants.
- Supplied - Oral tablets - 50 and 100 mg.

- Oral syrup-50 mg/5 ml.

Side effects: When administered submucosally, drugs can have a hyperemic impact that frequently causes a wheal and itching all over the face. Potential interaction between local anesthetics. Used with extreme caution in patients with hepatic or renal disease, or history of seizures.

5.9. Melatonin

The pineal gland produces melatonin, also known as 5-methoxy-N-acetyltryptamine, which is primarily responsible for controlling the body's natural circadian rhythm. This hormone has antioxidant and immunomodulatory activities [31]. It has several functions, including hypnotic, anxiolytic, sedative, and anti-inflammatory actions [32].

Dosage:

- Preschool - age (3 to 5 years): 1 to 2 mg.
- School - age (6 to 12 years): 2 to 3 mg.
- Adolescents (13 to 18 years): 5 mg.

Side effects of Melatonin in children: agitation, dizziness, drowsiness, fatigue, increased bedwetting, mood swings.

6. ADVANTAGES AND DISADVANTAGES OF ORAL SEDATION

6.1. Advantages

Oral sedation is very easy to administer. Since, no needles are involved it is better accepted by the pediatric patients. It has an added advantage of amnesic effects. It is more cost effective when compared to other modes of sedation.

Most common advantages are:

- Ease of administration
- No needles involved
- High patient acceptance
- Amnesic effect
- Lower cost versus intravenous sedation

6.2. Disadvantages

Oral sedation has few drawbacks like it has a delayed acting time. It gives inflexible sedation which cannot be altered by the doctor and therefore it cannot be titrated. It has a long latent period i.e., over 30–60 minutes. Sometimes it shows unreliable drug absorption by GI tract.

Most common disadvantages are:

- Delayed acting time
- Inflexible sedation level
- Long latent period (30–60 min)
- Unreliable drug absorption in GI tract
- Inability to titrate effect

7. CONCLUSION

Pediatric dentistry is increasingly employing oral sedation. Use of oral sedatives with caution, knowledge of the dangers and advantages of their use, and the capacity to recognize anxious and frightened patients and treat

them effectively in accordance with their needs can foster a positive attitude toward dental care. Proper evaluation, medication administration, monitoring, and discharge of each patient must be done properly.

CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

REFERENCES

- [1] Henry RJ, Jerrell RG. Ambient nitrous oxide levels during pediatric sedations. *Pediatr Dent*. 1990 Apr 1;12(2):87–91.
- [2] Wilson S. Pharmacological management of the pediatric dental patient. *Pediatr Dent*. 2004 Mar 1;26(2):131–6.
- [3] Nelson TM, Xu Z. Pediatric dental sedation: challenges and opportunities. *Clin Cosmet Investig Dent*. 2015 Aug 26;7:97–106.
- [4] Wilson S editor. *Oral Sedation for Dental Procedures in Children*. Springer; 2015 Jul 21.
- [5] Donaldson M, Gizzarelli G, Chanpong B. Oral sedation: a primer on anxiolysis for the adult patient. *Anesth Prog*. 2007;54(3):118–29.
- [6] Coté CJ, Wilson S. American academy of pediatrics, American academy of pediatric dentistry. Guidelines for monitoring and management of pediatric patients before, during, and after sedation for diagnostic and therapeutic procedures. *Pediatr*. 2019 Jun 1;143(6):2587–602.
- [7] Mayhew D, Mendonca V, Murthy BV. A review of ASA physical status-historical perspectives and modern developments. *Anaesthesia*. 2019 Mar;74(3):373–9.
- [8] American Society of Anesthesiologists. New classification of physical status. *Anesthesiol*. 1963;24:111.
- [9] Rothman DL. Sedation of the pediatric patient. *J Calif Dent Assoc*. 2013 Aug;41(8):603–11, PMID: 24073499.
- [10] Eslaamizaad S, Toopch S. Sedation in pediatric dentistry. *Acta Scienti Dent Sci*. 2019;3(2):40–6.
- [11] Sasada MP, Smith SP. *Drugs in Anesthesia and Intensive Care*. Oxford: Oxford University Press; 1997.
- [12] Rodriguez E, Jordan R. Contemporary trends in pediatric sedation and analgesia. *Emerg Med Clin*. 2002 Feb 1;20(1):199–222.
- [13] Karapinar V, Yilmaz D, Demirag K, Kantar M. Sedation with intravenous ketamine and midazolam for painful procedures in children. *Pediatr Int*. 2006;48:146–51.
- [14] Morgenstern J. *Chloral Hydrate Toxicity*. First10EM; April 3, 2017.
- [15] National Center for Biotechnology Information. *PubChem Compound Summary for CID 2707*. Chloral Hydrate; 2023.
- [16] Lu J, Greco MA. Sleep circuitry and the hypnotic mechanism of GABAA drugs. *J Clin Sleep Med*. 2006;2(2):S19–26.
- [17] Donaldson M, Gizzarelli G, Chanpong B. Oral sedation: a primer on anxiolysis for the adult patient. *Anesth Prog*. 2007 Fall;54(3):118–28. doi: 10.2344/0003-3006(2007)54[118:OSAP OA]2.0.CO;2.
- [18] Jacobi J, Fraser GL, Coursin DB, Riker RR, Dorrie Fontaine, Wittbrodt ET, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med*. 2002;30(1):119–41.
- [19] Möhler H. *Benzodiazepines*. e LS. 2001 May 30.
- [20] Rickels K, Morris RJ, Newman H, Rosenfeld H, Schiller H, Weinstock R. Diphenhydramine in insomniac family practice patients: a double-blind study. *J Clin Pharmacol*. 1983;23:234–42.
- [21] Physicians' Desk Reference, 61st ed. Montvale, NJ: Thompson Co; 2006, pp. 1868.
- [22] Sicari V, Zabbo CP. *Diphenhydramine*. [Updated 2023 Jul 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK526010/>.
- [23] Altamura AC, Moliterno D, Paletta S, Maffini M, Mauri MC, Bareggi S. Understanding the pharmacokinetics of anxiolytic drugs. *Expert Opin Drug Metab Toxicol*. 2013 Apr;9(4):423–40. doi: 10.1517/17425255.2013.759209. Epub 2013 Jan 21.
- [24] Sawantdesai NS, Kale PP, Savai J. Evaluation of anxiolytic effects of aripiprazole and hydroxyzine as a combination in mice. *J Basic Clin Pharm*. 2016 Sep;7(4):97–104. doi: 10.4103/0976-0105.189429. PMID: 27999468; PMCID: PMC5153890.
- [25] Southard BT, Al Khalili Y. *Promethazine*. 2022 Jul 21. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. PMID: 31335081. (PubMed ID 31335081).

- [26] Smith HS, Cox LR, Smith BR. Dopamine receptor antagonists. *Ann Palliat Med*. 2012 Jul;1(2):137–42. doi: 10.3978/j.issn.2224-5820.2012.07.09. PMID: 25841474.
- [27] Adolph O, Koster S, Georgieff M, Georgieff EM, Moulig W, Fohr KJ. Promethazine inhibits NMDA-induced currents—new pharmacological aspects of an old drug. *Neuropharmacol*. 2012 Aug;63(2):280–91. Epub 2012 Apr 7.
- [28] Scherl ER, Wilson JF. Comparison of dihydroergotamine with metoclopramide versus meperidine with promethazine in the treatment of acute migraine. *Headache*. 1995;35(5):256–9.
- [29] Cantisani C, Ricci S, Grieco T, Paolino G, Faina V, Silvestri E, et al. Topical promethazine side effects: our experience and review of the literature. *Biomed Res Int*. 2013;2013:151509. doi: 10.1155/2013/151509. Epub 2013 Nov 19. PMID: 24350243; PMCID: PMC3852816.
- [30] Yasaei R, Rosani A, Saadabadi A. Meperidine. [Updated 2023 Jul 10]. In *StatPearls*. [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from <https://www.ncbi.nlm.nih.gov/books/NBK470362/>.
- [31] Simonneaux V, Ribelayga C. Generation of the melatonin endocrine message in mammals: a review of the complex regulation of melatonin synthesis by norepinephrine, peptides, and other pineal transmitters. *Pharmacol Rev*. 2003;55:325–95.
- [32] Peuhkuri K, Sihvola N, Korpela R. Dietary factors and fluctuating levels of melatonin. *Food Nutr Res*. 2012;56. doi: 10.3402/fnr.v56i0.17252. Epub 2012 Jul 20. PMID: 22826693; PMCID: PMC3402070.