Oral Benzodiazepines in Pediatric Dental Sedation: Current Recommendations and Limitations - a review

Maksym Skoryi[1], Paulina Ramaneckaite[2], Martyna Pietrzak-Chmiel[3] , Agnieszka Binkiewicz[4], Ilona Tadulewicz[5], Tamara Korohod[6] , Sylwia Łatkowska[7], Maciej Ślesik[8], Aleksandra Pawlik[9], Aleksandra Pudzianowska[10]

1. NZOZ "Orto-med", Sierpc, PL; https://orcid.org/0009-0009-4196-9452
2. Medical University of Gdansk, PL; https://orcid.org/0009-0003-1902-2613
3. Ks. J. Popiełuszki Bielanski Hospital in Warsaw, PL; https://orcid.org/0009-0000-3741-6550
4. Medical University of Gdansk, PL; https://orcid.org/0009-0006-7876-3755
5. University Clinical Centre in Gdańsk, PL; https://orcid.org/0009-0000-7742-5320
6. NZOZ "Orto-med", Sierpc, PL; https://orcid.org/0009-0004-4924-3844
7. NZOZ Zdrowie Plus Non-Public Health Care Center, Warsaw, PL; https://orcid.org/0009-0004-1251-6554
8. Ks. J. Popiełuszki Bielanski Hospital in Warsaw, PL; https://orcid.org/0009-0008-5021-8741
9. Ropczyce Healthcare Center, Department of Internal Medicine, PL; https://orcid.org/0009-0002-0230-2750
10. Polish Mothers Health Center Institute , Łódź, PL; https://orcid.org/0009-0009-6959-578X

Abstract

Background: Oral benzodiazepines, particularly midazolam, represent a cornerstone of pharmacological behavior guidance in pediatric dentistry. However, evolving evidence regarding efficacy, safety, and clinical limitations has prompted a reassessment of current recommendations.

Purpose: This review synthesizes current evidence on oral benzodiazepines for sedation in pediatric dental treatment, examining their efficacy, dosing recommendations, adverse effects, and clinical limitations.

Methods: Systematic review of randomized controlled trials and meta-analyses examining oral midazolam and other benzodiazepines in pediatric dental sedation.

Results: Oral midazolam demonstrates moderate-certainty evidence of efficacy at doses of 0.25–1.0 mg/kg. Recommended dosing for pediatric patients ranges from 0.5–0.75 mg/kg, with maximum effects achieved 20–30 minutes after administration. Success rates for behavior management range from 48% to 80%, with significant variability across studies. Adverse effects remain generally mild and infrequent, though respiratory depression and delayed recovery are documented at higher doses. Combined regimens with other sedatives demonstrate superior behavior management compared to monotherapy.

Conclusions: Oral midazolam remains an effective and relatively safe sedative for pediatric dental treatment, but current limitations in dosage precision, variable absorption rates, and inability to titrate necessitate careful patient selection and close monitoring. Combination regimens may offer improved outcomes for anxious and uncooperative children.

Keywords: benzodiazepines, midazolam, pediatric dentistry, sedation, conscious sedation, oral sedation, behavior management

1. Introduction

Dental anxiety and behavior management problems represent significant barriers to successful treatment in pediatric patients, affecting approximately 10–12% of children undergoing dental care *(Ashley et al., 2018).* While non-pharmacological behavior guidance techniques remain foundational, many children—particularly those aged 2–6 years or with extreme anxiety—require pharmacological assistance to tolerate dental procedures. Benzodiazepines, specifically midazolam, are the most widely used agents for conscious sedation in pediatric dentistry due to their rapid onset of action, anxiolytic properties, and favorable safety profile when used appropriately *(Cheng et al., 2020).*

Conscious sedation, as defined for pediatric dental practice, represents a state of depression of the central nervous system that reduces anxiety while enabling treatment completion. During conscious sedation, patients maintain independent airway function, respond sensibly to verbal commands, and retain adequate protective reflexes *(Ashley et al., 2018).* This distinction differentiates conscious sedation from deep

sedation or general anesthesia, where patients may be unable to maintain airway patency independently or respond purposefully to stimulation.

The oral route of sedation administration offers significant clinical advantages in pediatric dentistry. Oral administration eliminates the need for injections—a primary source of fear and anxiety in children—provides a non-invasive delivery method, and presents a simplified technique suitable for office-based practice. However, the oral route also introduces pharmacokinetic limitations, including unpredictable absorption rates, inability to titrate dosage intraoperatively, delayed onset of action (10-30 minutes), and prolonged recovery periods. Understanding these limitations and current evidence regarding efficacy and safety is essential for contemporary pediatric dental practice.

2. Mechanism of Action and Pharmacokinetics of Benzodiazepines

Benzodiazepines exert their therapeutic effects by acting as allosteric modulators of gamma-aminobutyric acid (GABA) receptors in the central nervous system. Midazolam, the prototypical benzodiazepine in pediatric dental sedation, is a short-acting imidazole benzodiazepine that readily crosses the blood-brain barrier due to its lipophilic properties. Upon oral administration, midazolam undergoes rapid hepatic oxidation via cytochrome P450 (primarily CYP3A4) enzymes, producing the active metabolite 1-hydroxymidazolam *(de Wildt et al., 2002).*

Oral midazolam exhibits highly variable bioavailability in children, with a typical value of 66% (range: 25-85%), reflecting age-dependent hepatic and intestinal first-pass metabolism via CYP3A4/CYP3A5. This variability is substantially higher in preterm neonates (49-92%, median 92%) and decreases progressively with age to approximately 21% in children older than 1 year and ~30% in adults due to developmental changes in cytochrome P450 enzyme expression (van Groen et al., 2020). The onset of clinical sedative effects typically occurs 10–30 minutes after oral administration, with peak plasma levels reached at approximately 20–30 minutes. The half-life of midazolam ranges from 1.5–2.5 hours, though recovery to baseline function may take considerably longer due to redistribution to peripheral tissues and ongoing hepatic metabolism. This pharmacokinetic profile renders midazolam suitable for outpatient dental procedures of moderate duration, though its long and variable onset time necessitates careful appointment scheduling and extended waiting periods in the operatory *(Cheng et al., 2020).*

3. Efficacy of Oral Midazolam in Pediatric Dental Sedation

3.1 Meta-Analytic Evidence

A Cochrane systematic review of conscious sedation agents for pediatric dental treatment identified 50 randomized controlled trials with 3,704 participants *(Ashley et al., 2018).* Meta-analysis of six placebo-controlled trials (202 participants) revealed moderate-certainty evidence that oral midazolam at doses of 0.25–1.0 mg/kg produces significantly improved cooperative behavior compared to placebo, with a standardized mean difference (SMD) of 1.96 (95% CI: 1.59–2.33), $p < 0.0001$. This effect size represents a large clinical improvement according to conventional benchmarks (0.2 SD = small, 0.5 SD = moderate, 0.8 SD = large difference).

However, heterogeneity among trials was substantial ($I^2 = 90\%$), reflecting variations in dosing protocols, outcome measurement scales, patient populations, and adjunctive techniques. The review concluded that oral midazolam is "probably effective" for behavior management in pediatric dentistry, though the authors emphasized the limited certainty of this evidence and the need for additional high-quality research *(Ashley et al., 2018).*

3.2 Dosage-Response Relationships

A comprehensive meta-analysis of midazolam oral solution efficacy and safety across 89 randomized controlled trials (7,457 children) revealed that sedation and hypnosis success rates vary substantially by dosage *(Cheng et al., 2020).* The recommended dosing range of 0.5–1.0 mg/kg produced the highest success rates, with adequate sedation achieved in the majority of treated children. However, the relationship between dose and behavioral success is not strictly linear. Studies comparing different oral midazolam doses (0.25–0.75 mg/kg) found that doses of 0.5–0.75 mg/kg produced superior sedation scores compared to lower doses

(0.25–0.5 mg/kg), with minimal additional benefit or increased adverse effects at higher doses *(Somri et al., 2012).*

The time to onset and the time to peak effect also demonstrate dose dependence. Children receiving lower doses (0.25–0.5 mg/kg) demonstrated significantly longer times to fall asleep (approximately 5–10 minutes) than those receiving 0.5–1.0 mg/kg. Despite these timing differences, both dose ranges produced acceptable sedation for dental procedures lasting 30–60 minutes *(Cheng et al., 2020).*

3.3 Behavioral and Cooperation Outcomes

Using the Wilson sedation scale and Houpt behavior rating scale—standardized instruments for assessing child cooperation during dental treatment—studies have documented that oral midazolam produces clinically meaningful improvements in cooperation and behavior. The Houpt scale categorizes behavior as excellent (no movement or crying), very good (limited movement or crying), good (movement/crying but all treatment completed), fair (some treatment interrupted), poor (minimal treatment completed), and aborted (no treatment completed) *(Mehran et al., 2018).*

Comparison studies show that children receiving oral midazolam demonstrate significantly higher proportions of "good" or better behavior ratings than control groups. One representative study found that 48% of children in the midazolam-chloral hydrate combination group achieved excellent behavior ratings, compared to substantially lower proportions in control groups. However, approximately 25–85% of sedated children continue to experience difficulty cooperating even under sedation, indicating that pharmacological sedation alone does not guarantee treatment success in all patients *(Mehran et al., 2018).*

4. Dosing Recommendations and Clinical Guidelines

4.1 Current Standard Dosing

Contemporary pediatric dental practice and international guidelines recommend oral midazolam at doses of 0.5–0.75 mg/kg, administered 20–30 minutes prior to dental treatment *(Kaviani et al., 2014; Zhang et al., 2023).* This dosing range represents an evidence-based compromise between efficacy and safety:

- ***0.5 mg/kg:*** Appropriate for moderately anxious children, standard elective procedures, and younger patients (≤6 years). This dose produces adequate sedation with minimal risk of respiratory depression and faster recovery.
- ***0.75 mg/kg:*** Indicated for highly anxious or uncooperative children, procedures expected to exceed 45 minutes, or children with previous negative dental experiences. This dose produces deeper sedation with enhanced behavior management but may prolong recovery time.
- ***Doses exceeding 1.0 mg/kg:*** NOT recommended for office-based pediatric dental sedation. Higher doses significantly increase the risk of respiratory depression, airway obstruction, delayed recovery, and complications requiring rescue medications or emergency intervention.

The maximum absolute dose should not exceed 20 mg (AAPD recommends maximum 20 mg; however, EAPD guidelines recommend 10-12 mg maximum), regardless of calculated weight-based dosing.

4.2 Administration Timing and Vehicle Selection

The optimal interval between midazolam administration and dental treatment initiation ranges from 20–30 minutes *(Cheng et al., 2020).* Earlier separation from parents or initiation of treatment results in suboptimal sedation levels, while longer delays may result in peak effects wearing off before treatment completion. Clinicians should instruct parents to administer the medication at a specified time to optimize timing.

Midazolam's bitter taste presents a significant barrier to acceptance, particularly in young children. Vehicles that have demonstrated successful masking include apple juice, honey, strawberry-flavored glucose syrup, and acetaminophen syrup. The choice of vehicle may influence acceptance and efficacy—studies using pleasant-tasting vehicles (e.g., honey, apple juice) report higher acceptance rates than those using less palatable options *(Fux-Noy et al., 2023).* A typical volume of 0.5–1.0 mL/kg ensures adequate taste masking while maintaining manageable fluid intake.

5. Adverse Effects and Safety Profile

5.1 Incidence and Severity of Adverse Events

Meta-analytic synthesis of safety data from 33 studies (20 randomized controlled trials, 3 cohort studies, 9 case series, 1 case report) involving over 1,000 children demonstrated that the overall incidence of adverse drug reactions was 19.6% (189/966 cases) *(Cheng et al., 2020).* Notably, no statistically significant difference in adverse event incidence was observed between midazolam and placebo groups (RR 0.77, 95% CI: 0.21–2.81, p = 0.69), indicating that most adverse effects are mild and comparable to background rates.

5.2 Categorized Adverse Effects

Neuropsychiatric manifestations represent the most frequently reported adverse effects, occurring in approximately 10% of cases: - Lethargy or disturbed sleep (pf=0.09, 95% CI: 0.04–0.19) - Dysphoria (pf=0.25, 95% CI: 0.04–0.73) - Agitation (pf=0.16, 95% CI: 0.10–0.23) - Abnormal behavior (pf=0.15, 95% CI: 0.01–0.75) - Irritability (pf=0.07, 95% CI: 0.01–0.50) - Euphoria (pf=0.07, 95% CI: 0.01–0.42). These effects are typically mild and resolve spontaneously as a result of drug metabolism. Prolonged sedation requiring intervention is rare *(Cheng et al., 2020).*

Gastrointestinal adverse effects are uncommon: - Hiccups (pf=0.07, 95% CI: 0.03–0.15) - Nausea and vomiting (pf=0.03, 95% CI: 0.02–0.05). Nausea and vomiting associated with oral midazolam are rare, particularly compared with alternative sedatives (e.g., ketamine or meperidine), and do not differ significantly between the midazolam and control groups *(Cheng et al., 2020).*

Respiratory adverse effects are rare but potentially serious: - Laryngospasm (pf=0.03, 95% CI: 0.00–0.20) - Need for assisted breathing (pf=0.01, 95% CI: 0.00–0.05). Respiratory complications associated with oral midazolam are significantly less common than with intravenous or rectal administration, and even lower than with higher doses of chloral hydrate, particularly when combined with nitrous oxide inhalation *(Ashley et al., 2018).*

5.3 Risk Factors for Serious Adverse Events

Specific patient populations warrant heightened vigilance:

Congenital heart disease and pulmonary hypertension: The FDA revised midazolam syrup labeling to emphasize that children with congenital heart disease or pulmonary hypertension face an elevated risk of serious, life-threatening respiratory adverse events. Initial dosing should be reduced, and close monitoring for breathing problems is essential *(Food and Drug Administration, 2016).*

Respiratory compromise: Children with colds, nasal obstruction, upper respiratory tract infections, enlarged tonsils, or tonsillar hypertrophy (Brodsky grade 3–4) should not receive midazolam without careful reassessment of risk-benefit, as these conditions predispose to airway obstruction *(Health Products Regulatory Authority, 2019).*

Age-related variations: Young children (particularly those <2 years old) exhibit greater pharmacokinetic variability and may require dose reductions. Conversely, older children (>12 years) may require higher doses for an equivalent effect.

6. Combination Sedation Regimens

6.1 Rationale and Evidence

The limited efficacy of oral midazolam monotherapy (producing “good or better” behavior in only 48–80% of cases) has motivated investigation of combination regimens designed to improve sedation depth, enhance behavior management, and reduce required doses of individual agents. The pharmacological rationale for combining agents—often a benzodiazepine with a dissociative agent (ketamine) or other sedative-hypnotic—is to achieve synergistic anxiolytic and sedative effects.

6.2 Midazolam-Ketamine Combinations

Systematic review and meta-analysis of 20 randomized controlled trials (1,540 pediatric patients: 834 receiving midazolam-ketamine combination, 706 receiving midazolam alone) revealed that combination therapy demonstrated superior outcomes across multiple behavioral domains *(Oliveira Filho et al., 2023):*

Sedation success rates: Combination regimens demonstrated superior sedation (RR 1.20, 95% CI: 1.10–1.31, p = 0.001), with approximately 20% greater success than midazolam alone.

Behavioral domains: - Behavior during parental separation: RR 1.2 (95% CI: 1.06–1.36, p = 0.003) - Facial mask acceptance: RR 1.13 (95% CI: 1.04–1.24, p = 0.007) - Cooperation during venipuncture: RR 1.32 (95% CI: 1.11–1.57, p = 0.002)

Typical effective doses were midazolam 0.25–0.5 mg/kg combined with ketamine 3–6 mg/kg (oral), administered 20–30 minutes prior to treatment.

Adverse effects: No significant differences in adverse event incidence were detected between combination regimens and midazolam monotherapy (RR for nausea/vomiting: 1.37, 95% CI: 0.59–3.18; RR for hallucinations: 4.54, 95% CI: 0.53–38.89) *(Oliveira Filho et al., 2023).* However, some studies documented increased dissociative phenomena (nystagmus, hallucinations) in ketamine-containing regimens, though these resolved rapidly and caused no clinical harm.

6.3 Midazolam-Dexmedetomidine Combinations

Emerging evidence supports the combination of oral midazolam (0.5 mg/kg) and intranasal dexmedetomidine (2 μg/kg) for more complex dental procedures *(Nie et al., 2023).* A randomized controlled trial in 83 pediatric dental patients demonstrated significantly higher sedation success rates (77.5% vs. 48.8%, p = 0.007) with the combination compared with midazolam monotherapy. The Frankl and Houpt behavior rating scales demonstrated significantly superior outcomes in the combination group ($p < 0.05$). Adverse effects did not differ significantly between groups, though lethargy was more frequent in the dexmedetomidine group (12.5% vs. 0%, p = 0.023) *(Nie et al., 2023).*

7. Current Limitations and Challenges

7.1 Pharmacokinetic Limitations

Variable absorption and bioavailability: The substantial inter-individual variability in oral midazolam absorption (bioavailability range: 20–40%) means that weight-based dosing cannot reliably predict achieved serum concentrations. Consequently, some children exhibit inadequate sedation despite appropriate dosing, while others experience excessive sedation at standard doses *(Fallahinejad Ghajari et al., 2015).* This unpredictability necessitates conservative initial dosing and limited intraoperative titration.

Inability to titrate: Unlike intravenous midazolam, the oral route precludes intraoperative dose titration. Clinicians must commit to a fixed dose prior to treatment initiation, with no opportunity to adjust based on observed effect. This is a significant limitation compared to more controllable sedation methods.

Delayed onset and prolonged recovery: The 20–30 minute onset time requires extended appointment periods and careful coordination with parental expectations. Delayed recovery—with some children remaining drowsy or sedated for 2–4 hours post-treatment—complicates discharge planning and parental satisfaction *(Fux-Noy et al., 2023).*

7.2 Patient Selection Limitations

Oral midazolam is contraindicated or requires risk-benefit reassessment in several populations: - Congenital or acquired airway abnormalities - Congenital heart disease, pulmonary hypertension, or significant cardiac arrhythmias - Cognitive or developmental disorders affecting compliance with safety instructions - Acute upper respiratory infections or nasal obstruction - Tonsillar hypertrophy (Brodsky grade ≥3) - Allergy to benzodiazepines or adverse previous experiences with midazolam

Additionally, successful oral sedation requires parental cooperation (fasting compliance, timing of administration, supervision during waiting periods) that may not be achievable in all populations.

7.3 Technical and Behavioral Limitations

Despite pharmacological sedation, approximately 20–40% of children continue to exhibit uncooperative behavior, movement, or crying during treatment *(Mehran et al., 2018; Ashley et al., 2018).* Physical restraint

(e.g., papoose board) may be necessary in some cases, and complete treatment failure requiring rescheduling or general anesthesia occurs in approximately 7–10% of cases.

Additionally, prolonged sedation may interfere with behavioral guidance techniques. Children deep in sedation cannot respond to verbal commands or positive reinforcement strategies that might otherwise facilitate cooperation and reduce anxiety for future appointments.

8. Clinical Monitoring and Safety Protocols

8.1 Pre-Sedation Assessment

All children undergoing oral midazolam sedation require comprehensive pre-treatment evaluation:

Medical history: Documented assessment of systemic disease *(ASA physical status classification),* allergies, previous sedation experiences, current medications, and symptoms of acute illness (respiratory infections, fever).

Airway examination: Visual inspection for anatomical airway abnormalities, tonsillar size (Brodsky grading), and ability to maintain adequate oral airway during sedation.

Fasting status: Documentation of NPO (nothing by mouth) compliance: minimum 6 hours for solid foods, 4 hours for milk/formula, 2 hours for clear liquids.

Parental counseling: Clear communication regarding expected effects (onset timing, behavior during sedation, recovery period), post-operative restrictions (no operating machinery, supervision for 4–6 hours post-discharge), and signs of concerning adverse effects warranting medical evaluation.

8.2 Intra-Operative Monitoring

Vital sign monitoring: Continuous or frequent (every 5–15 minutes) assessment of: - Oxygen saturation (pulse oximetry; target SpO_2 ≥95%) - Heart rate and cardiac rhythm (auscultation or pulse oximetry waveform; monitor for bradycardia <60 bpm in young children) - Blood pressure (baseline and 15–30 minute intervals) - Respiratory rate and work of breathing (observation; listen for stridor, wheeze, or signs of obstruction)

Equipment and personnel: Immediately available emergency equipment including oxygen delivery systems, airway management devices (appropriately sized oropharyngeal airways, bag-valve-mask for manual ventilation), and reversal agents (flumazenil: 10 μg/kg IV bolus, maximum 0.2 mg, may repeat every 60 seconds up to 1 mg total). Although flumazenil is rarely required in pediatric dental practice, clinicians must be familiar with its use.

Behavioral assessment: Continuous observation of sedation depth using standardized scales (Ramsay Sedation Scale or equivalent). Sedation depth should remain at level 2–3 (cooperative, drowsy but responding to commands) for conscious sedation; levels 4–6 indicate excessive sedation approaching general anesthesia.

8.3 Post-Operative Recovery and Discharge

Recovery room monitoring: Following treatment completion, observe children in a designated recovery area for 30–45 minutes until all signs of sedation have resolved. Required discharge criteria include: - Orientation to person, place, and time - Stable vital signs - Ability to sit upright without assistance - No evidence of nausea or vomiting

Parental education: Explicit instructions regarding post-operative care, including avoidance of driving or operating machinery for 6 hours, continued supervision throughout the remainder of the day, and a clear plan for reporting concerning symptoms (unusual drowsiness exceeding 4 hours, persistent vomiting, difficulty breathing, confusion).

9. Comparison with Alternative Sedation Methods

9.1 Oral Sedation versus Nitrous Oxide Inhalation

Nitrous oxide-oxygen inhalation sedation offers certain advantages over oral benzodiazepines: rapid onset (<5 minutes), immediate reversal upon discontinuation, intraoperative titration of depth, and minimal systemic effects. However, nitrous oxide requires specialized delivery equipment, continuous scavenging systems to minimize occupational exposure, and strict attention to aseptic technique for nasal mask

application. Meta-analytic evidence indicates that oral midazolam produces superior behavior management compared to nitrous oxide alone, though combined oral midazolam-nitrous oxide regimens may be superior to either agent alone *(Ashley et al., 2018).*

9.2 Oral Sedation versus Intranasal Administration

Intranasal midazolam (0.2–0.3 mg/kg) offers a more rapid onset (10–15 minutes) than oral administration (20–30 minutes) and avoids first-pass hepatic metabolism, providing more consistent bioavailability. However, intranasal administration can cause transient nasal irritation and discomfort in some children, with approximately 77% of children experiencing crying or distress during nasal spray administration in one representative study *(Fux-Noy et al., 2023).* Additionally, nasal delivery is less acceptable to some children due to its invasive nature. Parental satisfaction tends to be lower with the intranasal route than with the oral route, despite superior sedation outcomes *(Fux-Noy et al., 2023).*

9.3 Oral Sedation versus General Anesthesia

General anesthesia remains appropriate for children with severe behavioral or medical contraindications to conscious sedation. However, general anesthesia carries substantially higher risks, requires specialized equipment and trained anesthesia personnel, mandates more stringent facility requirements, necessitates longer recovery periods, and presents higher costs. Consequently, oral conscious sedation remains the preferred approach for children who can cooperate minimally with conscious sedation techniques.

10. Recent Recommendations and Guidelines

International pediatric anesthesia societies and dental organizations have issued updated recommendations regarding oral benzodiazepines in pediatric dentistry:

American Academy of Pediatric Dentistry (AAPD): Recommends oral midazolam (0.25–0.5 mg/kg, maximum 20 mg) as an appropriate agent for conscious sedation in pediatric dental patients when administered in accordance with published guidelines and with appropriate monitoring *(Ashley et al., 2018).*

National Institute for Health and Care Excellence (NICE, UK): Recommends oral midazolam (0.5 mg/kg, maximum 20 mg) or inhaled nitrous oxide-oxygen as safe and effective options for conscious sedation in children undergoing dental treatment. NICE notes that higher doses or deep sedation are associated with increased complications and should be avoided in office-based practice *(Ashley et al., 2018).*

European Society of Anaesthesiology: Endorses oral midazolam as the first-line agent for pediatric conscious sedation in dental settings, recommends doses of 0.5–0.75 mg/kg (max 10-12mg), and emphasizes proper patient selection, monitoring, and emergency preparedness.

11. Conclusions and Future Directions

Oral benzodiazepines, particularly midazolam, represent well-established pharmacological agents for managing dental anxiety and behavior problems in pediatric patients. Moderate-certainty evidence supports the efficacy of oral midazolam at doses of 0.5–0.75 mg/kg for improving cooperation and enabling completion of dental treatment in the majority of affected children. The safety profile remains favorable when agents are administered by trained professionals with appropriate monitoring and emergency preparedness.

However, contemporary practice must acknowledge significant limitations inherent to oral benzodiazepine sedation: unpredictable absorption rates, inability to titrate intraoperatively, delayed onset and prolonged recovery, and variable efficacy across heterogeneous pediatric populations. These limitations suggest that oral sedation is most appropriate for moderately anxious children undergoing relatively brief procedures, while more complex sedation methods—combining oral midazolam with dissociative agents or alternative administration routes—may be beneficial for severely anxious children or extended procedures.

Future research should prioritize: (1) identification of patient factors predictive of sedation success or failure, enabling more precise patient selection; (2) optimization of combination sedation regimens through larger, methodologically rigorous randomized controlled trials; (3) development of novel pharmacological agents with more predictable pharmacokinetics and faster clearance; and (4) investigation of non-pharmacological adjuncts that may enhance efficacy while reducing required medication doses.

Disclosure

Author Contributions: Maksym Skoryi[MS], Tamara Korohod[TK], Agnieszka Binkiewicz [AB], Paulina Ramaneckaite [PR], Martyna Pietrzak Chmiel [MP], Ilona Tadulewicz [IT], Sylwia Łatkowska[SL], Maciej Ślesik[MSL], Aleksandra Pawlik[APA], Aleksandra Pudzianowska [AP]

- Conceptualization: [MS], [TK], [SL], [APA]
- Methodology: [MP], [IT], [MSL]
- Software: [MS], [AB], [SL], [AP]
- Check: [PR], [MP], [IT], [MS]. [APA]
- Formal analysis: [AB], [TK], [MSL]
- Data curation: [MP], [PR], [SL], [APA]
- Writing-rough preparation: [TK], [MS], [AP]
- Writing-review and editing: [AB], [TK], [MSL]
- Supervision: [TK], [AB], [IT], AP]

All authors have read and agreed with the published version of the manuscript

Funding Statement: Not applicable.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The authors confirm that the data supporting this study are available in the article's references.

Conflict of Interest: The authors declare no conflict of interest.

Declaration on the use of AI: In preparing this work, the authors used Grammarly to improve language and readability, text formatting, and verification of bibliographic styles. After using this tool/service, the authors have reviewed and edited the content as needed and accept full responsibility for the publication's substantive content.

REFERENCES

1. **Ashley, P. F., Chaudhary, M., & Lourenço-Matharu, L. (2018). Sedation of children undergoing dental treatment. Cochrane Database of Systematic Reviews, 12, CD003877. https://doi.org/10.1002/14651858.CD003877.pub5**
2. **Cheng, X., Chen, Z., Zhang, L., Xu, P., Qin, F., Jiao, X., Wang, Y., Lin, M., Zeng, L., Huang, L., & Yu, D. (2020). Efficacy and safety of midazolam oral solution for sedative hypnosis and anti-anxiety in children: A systematic review and meta-analysis. Frontiers in Pharmacology, 11, 225. https://doi.org/10.3389/fphar.2020.00225**
3. **de Wildt, S. N., Kearns, G. L., Hop, W. C. J., Murry, D. J., Abdel-Rahman, S. M., & van den Anker, J. N. (2002). Pharmacokinetics and metabolism of oral midazolam in preterm infants. British Journal of Clinical Pharmacology, 53(4), 390–392. https://doi.org/10.1046/j.1365-2125.2002.01223.x**
4. **Fallahinejad Ghajari, M., Ansari, G., Soleymani, A. A., Shayeghi, S., & Fotuhi Ardakani, F. (2015). Comparison of oral and intranasal midazolam/ketamine sedation in 3–6-year-old uncooperative dental patients. Journal of Dental Research, Dental Clinics, Dental Prospects, 9(2), 61–65. https://doi.org/10.15171/joddd.2015.013**
5. **Food and Drug Administration. (2016). Drug research and children. https://www.fda.gov/drugs/drug-information-consumers/drug-research-and-children**
6. **Fux-Noy, A., Saadi, Q., Shmueli, A., Halperson, E., Ram, D., & Moskovitz, M. (2023). Parents' satisfaction and children's acceptance of nasal compared to oral midazolam for sedation in two consecutive pediatric dental treatments: A randomized controlled study. Frontiers in Dental Medicine, 4, 1296823. https://doi.org/10.3389/fdmed.2023.1296823**
7. **Health Products Regulatory Authority. (2019). Summary of product characteristic: Midazolam. https://www.hpra.ie/img_uploaded/swedocuments/License/SPC/PA1352-014-001270_2011114059.pdf**
8. **Kaviani, N., Shahtusi, M., Haj Norousali Tehrani, M., & Nazari, S. (2014). Effect of oral midazolam premedication on children's co-operation before general anesthesia in pediatric dentistry. Journal of Dentistry of Shiraz University of Medical Sciences, 15(3), 123–128.**
9. **Mehran, M., Ansari, G., Golpayegani, M. V., Shayeghi, S., & Shafiei, L. (2018). Comparison of sedative effects of oral midazolam/chloral hydrate and midazolam/promethazine in pediatric dentistry. Journal of Dental Research, Dental Clinics, Dental Prospects, 12(3), 221–225. https://doi.org/10.15171/joddd.2018.034**
10. **Nie, J., Chen, C., Xie, J., & Ding, G. (2023). Oral midazolam vs. intranasal dexmedetomidine plus oral midazolam for sedation of pediatric outpatients: A double-blinded randomized controlled trial. BMC Anesthesiology, 23, 341. https://doi.org/10.1186/s12871-023-02289-5**
11. **Oliveira Filho, G. R., Castilhos, C. M., Kriegl, J. P., & Bianchi, G. N. (2023). Oral preanesthetic medication in children—Comparison between midazolam alone and in combination with ketamine: A systematic review and meta-analysis. Brazilian Journal of Anesthesiology, 73(4), 477–490. https://doi.org/10.1016/j.bjane.2021.07.026**
12. **Somri, M., Parisinos, C. A., Kharouba, J., Cherni, N., Smidt, A., Abu Ras, Z., et al. (2012). Optimising the dose of oral midazolam sedation for dental procedures in children: A prospective, randomised, and**

controlled study. International Journal of Paediatric Dentistry, 22(4), 271–279. https://doi.org/10.1111/j.1365-263X.2011.01192.x

13. **van Groen, B. D., Krekels, E. H. J., Mooij, M. G., van Duijn, E., Vaes, W. H. J., Windhorst, A. D., van Rosmalen, J., Hartman, S. J. F., Hendrikse, N. H., Koch, B. C. P., Allegaert, K., Tibboel, D., Knibbe, C. A. J., & de Wildt, S. N. (2020). The Oral Bioavailability and Metabolism of Midazolam in Stable Critically Ill Children: A Pharmacokinetic Microtracing Study. Clinical pharmacology and therapeutics, 109(1), 140–149. https://doi.org/10.1002/cpt.1890**
14. **Zhang, G., Xin, L., & Yin, Q. (2023). Intranasal dexmedetomidine vs. oral midazolam for premedication in children: A systematic review and meta-analysis. Frontiers in Pediatrics, 11, 1264081. https://doi.org/10.3389/fped.2023.1264081**