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Review Article

Modern sedative agents and techniques used in dentistry for patients with special needs: A review

Ruijia Yang, BDS [a], Rusin Zhao, BDS [a], Fatima Chaudry, BDS [a], Tao Wang, BDS [a], Paul Brunton, PhD [b], Zohaib Khurshid, MRES [c] and Jithendra Ratnayake, PhD [a,*]

[a] *Department of Oral Science, Faculty of Dentistry, University of Otago, Dunedin, New Zealand*
[b] *Department of Prosthodontics and Dental Implantology, Curtin University, Bentley, Australia*
[c] *Department of Prosthodontics and Dental Implantology, College of Dentistry, King Faisal University, Al-Ahsa, KSA*

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الملخص

وفقا لمنظمة الصحة العالمية، يعاني حوالي 1.3 مليار شخص في جميع أنحاء العالم من إعاقة كبيرة بسبب الإعاقة الجسدية أو العقلية أو الحسية. يحتاج الأشخاص ذوو الاحتياجات الخاصة إلى اهتمام خاص ومزيد من الوقت أو طرق عناية مختلفة عند تلقي علاجات الأسنان. قد تؤدي عوامل مختلفة مثل عدم التعاون والضعف الإدراكي والحالة الطبية المعقدة إلى قيام ممارس الأسنان بالتوصية بالتخدير الواعي لهؤلاء المرضى. تتوفر العديد من الأدوية وطرق إعطاء العلاج وتحقق مستويات مختلفة من التخدير تتراوح من الحد الأدنى من التخدير إلى التخدير العميق. يجب إجراء تقييم ما قبل الجراحة واختيار الحالة بعناية لتحديد عامل التخدير المناسب وطريقة الإعطاء ومستوى التخدير لكل مريض. وبالتالي، فإن الفهم الشامل للحرائك الدوائية والمخاطر والفوائد والآثار المترتبة على مختلف المهدئات المتاحة لذوي الاحتياجات الخاصة أمر ضروري لتحقيق النتائج السريرية المرجوة. تقدم هذه المراجعة بشكل نقدي الاعتبارات الخاصة للمرضى ذوي الاحتياجات الخاصة المرتبطة بمختلف العوامل المهدئة المستخدمة في طب الأسنان. تشمل الاعتبارات الأمراض المصاحبة الطبية للمرضى قبل التخدير، والآثار الجانبية القلبية التنفسية، وتعاون المريض وأي طرق علاج بديلة قابلة للتطبيق.

الكلمات المفتاحية: مركبات بنزوديازيبين؛ قلق الأسنان؛ طب أسنان الأطفال؛ التخدير؛ الاحتياجات الخاصة

Abstract

According to the World Health Organisation, approximately 1.3 billion people worldwide experience substantial disability due to physical, mental or sensory impairment. People with special needs require special consideration and more time or altered delivery methods when receiving dental treatments. Various factors, such as patients' lack of cooperation, cognitive impairment and complex medical status, may lead dental practitioners to recommend conscious sedation. Several pharmacological agents and administrative routes are available, which achieve varying levels of sedation ranging from minimal to deep. Pre-operative assessment and careful case selection are necessary to determine the appropriate sedative agent, route of administration and level of sedation for each patient. Thus, a thorough understanding of the pharmacokinetics, risks and benefits, and implications of various sedatives available for PSN is essential to achieve the desired clinical outcomes. This review critically presents the considerations associated with the use of various sedative agents for PSN in dentistry. Considerations include patients' pre-anaesthesia medical comorbidities, cardiorespiratory adverse effects and cooperativeness, and the viable alternative treatment modalities.

Keywords: Benzodiazepines; Dental anxiety; Paediatric dentistry; Sedation; Special needs

* Corresponding address: Department of Oral Science, Faculty of Dentistry, University of Otago, Dunedin 9016, New Zealand.
E-mail: Jithendra.ratnayake@otago.ac.nz (J. Ratnayake)

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Introduction

Patients with special needs (PSN) are defined as individuals who require extra support for a medical, physical, mental or psychological disability that profoundly restricts their ability to perform essential activities in a typical manner.[1] Approximately 1.3 billion people (approximately 1 in 6 people) worldwide, and as many as 24% of people in the New Zealand population, have a substantial disability affecting daily life.[2,3] PSN are more likely to have poorer oral hygiene; more advanced, untreated dental disease, such as caries and periodontal disease; and more limited access to dental services than the general population.[4,5] Various factors, such as motor dysfunction, cognitive impairment and lack of cooperation, may make treatment of PSN difficult or nearly impossible in private clinical settings. Thus, sedation is often necessary to establish and maintain a state of cooperation enabling necessary dental treatment to be successfully provided; this sedation elicits depression of behavioural activity to calm the patient during treatment.[1,6] Procedures requiring dental sedation vary depending on individual patients' needs, circumstances and ability to tolerate the treatment. For patients unable to tolerate any form of treatment, sedation may be required for even simple procedures such as history taking and examination, and supragingival scaling. For other patients who are cooperative but unable to maintain an open mouth for long periods, dental sedation may be used for procedures such as root canal therapy, surgical extractions, full mouth rehabilitation or extensive restorative work.[7] Additionally, depending on the patient and treatment needs, several routes of administration for dental sedation may be used: inhalation, intravenous, oral, intranasal and intramuscular.[8] A survey of dentists in the United States and Canada has revealed that 75.7% regularly use conscious sedation in practice; half reported using sedation as many as six times per month, and the other half reported using sedation more than six times per month.[9]

The continuum of sedation extends from minimal sedation to complete depression of consciousness, and the level of sedation required is often determined in relation to either the extent of patient cooperativity or the invasiveness of the procedure.[10] According to the Special Care Dentistry Association consensus statement, minimal sedation is defined as 'a pharmacologically induced minimally depressed level of consciousness, where the patient retains normal respiratory and cardiovascular functions, as well as the ability to respond normally to both tactile and verbal stimulation'. Moderate sedation refers to a pharmacologically induced depression of consciousness with airway patency unaffected and cardiovascular function typically maintained. Patients remain generally responsive to verbal stimulation alone or in combination with light tactile stimulation. In contrast, in deep sedation, patients are not easily aroused, and repeated or painful stimulation is required to elicit a response; moreover, assistance may be required to maintain airway patency and spontaneous ventilation.[11,12]

In dentistry, when possible, conscious sedation is preferred for the management of PSN, because anxiolysis can be achieved without depressing consciousness and ventilation.[10] Conscious sedation can be achieved through administration of sedatives causing transient central nervous system (CNS) depression, thereby relaxing patients whilst maintaining their responsiveness throughout the duration of the treatment.[6] General anaesthesia is indicated when both analgesia and amnesia are required for patient management, and conscious sedation techniques are insufficient. Given the risks associated with general anaesthesia, such as hypoxia due to difficulty in airway management, excessive CNS depression and cost, conscious sedation is indicated where appropriate.[13]

According to the World Health Organization, the ongoing COVID-19 pandemic has disproportionately affected PSN, largely because elective and non-urgent treatments have been deferred.[14] PSN may be affected by conditions requiring a multi-disciplinary treatment approach, or resulting in an inability to tolerate and comply with traditional dental procedures.[15] Children with special healthcare needs have been shown to have limited access and diminished utilisation of preventive healthcare during the COVID-19 pandemic.[16] These effects have been more pronounced among patients requiring sedation and general anaesthesia, because non-acute, staff- and resource-intensive procedures have been deferred most frequently.[14] The aim of this review was to examine the available evidence regarding special considerations for PSN undergoing conscious sedation for dental treatment.

The role of sedation in the management of PSN in dentistry

The major challenge faced by dental practitioners in providing dental care for PSN is a lack of sufficient co-operativity and compliance, often because intellectual and mental disabilities may compromise the ability of PSN to understand their dental needs. Additionally, these patients may present in a state of heightened anxiety and fear, thus resulting in a tendency to decline treatment with routine approaches. During the COVID-19 pandemic, this tendency has been further exacerbated through the use of personal protective equipment, over-burdening of public services and an even greater backlog in special needs dentistry resulting from stricter clinical protocols.[17]

Non-pharmacological behavioural management strategies are inadequate for most patients with complex needs. Thus, pharmacological agents delivered through techniques such as inhalation, or oral and intravenous sedation, have been widely used as successful and safe solutions that allow PSN to become more cooperative, thus enabling more effective dental care. Dental sedation is indicated when traditional behavioural management techniques do not sufficiently relax patients to allow for their dental treatment.[18] In one study, intramuscular and intravenous midazolam was effective in as many as 89% of study participants with neurological disorders.[19] Another group has reported a positive response rate as high as 83% to use of oral midazolam in PSN.[20]

Despite the common and safe use of dental sedation for PSN, a thorough and individualised pre-operative assessment of each patient must be performed. A risk-benefit analysis should be conducted according to The American Society of Anesthesiologists physical status classification system, which classifies the risk of anaesthesia for patients into six distinct categories[21]:

P1 = a normal healthy patient
P2 = a patient with mild systemic disease
P3 = a patient with severe systemic disease
P4 = a patient with severe systemic disease that is a constant threat to life
P5 = a moribund patient who is not expected to survive without the operation
P6 = a declared brain-dead patient whose organs are being removed for donor purposes

Sedation is generally contraindicated for patient groups presenting with specific conditions that may cause sedation procedures to pose a high risk to their well-being. These conditions include the following[22]:

- Patients with potential upper airway obstruction (such as PSN with severe cerebral palsy)
- Patients with severe systemic illnesses that compromise their respiratory or cardiovascular function
- Patients taking long-term antipsychotic or psychotropic medications (such as PSN with schizophrenia or bipolar disorder)
- Patients with muscular dystrophy
- Patients taking a contraindicated drug such as diazepam

For these patients, additional caution is necessary in the choice of sedation, and special care measures, such as intraoperative airway management through mask ventilation and endotracheal intubation, may be considered.

Common sedative agents used in dentistry

Benzodiazepines, e.g., midazolam, diazepam, lorazepam and triazolam

Benzodiazepines are a group of pharmacological agents frequently used for dental sedation in routine dentistry in private clinical settings. Their mechanism of action involves positive allosteric modulation of α-aminobutyric acid (GABA-α) receptors in the CNS, thereby promoting anxiolysis, skeletal muscle relaxation and anterograde amnesia.[23]

Diazepam, a long-acting benzodiazepine, produces active metabolites that prolong the duration of action to more than 12 h.[24] The lipophilic nature of diazepam allows for a relatively rapid onset of 1–3 min after intravenous administration or 15–16 min after oral administration; however, the intravenous route is associated with pain on injection and venoirritation.[23,25] Midazolam does not produce any active metabolites with a duration of action of 60–120 min and therefore is suitable for relatively short dental procedures.[23,26] Midazolam's higher lipid solubility and thus stronger affinity for benzodiazepine receptors make it significantly more potent than diazepam, with a more rapid onset of 15–20 min orally or less than 3 min intravenously.[27] The acidic pH of intravenous and intramuscular preparations of midazolam allows for initial water solubility, thereby minimising venous irritation and pain upon injection.[23] Midazolam has been shown to produce more amnesia more reliably than diazepam, thus indicating its effectiveness for procedural sedation in anxious patients.[28]

Benzodiazepines can cause respiratory depression through a dose–response relationship. This risk markedly increases when benzodiazepines are administered in conjunction with opioids, or in patients with chronic obstructive pulmonary disease.[23] Intramuscular administration of midazolam has been shown to have less pronounced effects on ventilation than intravenous administration, and these risks can generally be minimised by carefully titration intravenously to a fixed limit. Furthermore, administering intravenous midazolam supplemented with N_2O has been shown to assist in the treatment of anxious patients with an inability to tolerate cannulation and the administration of local anaesthesia. Use of inhalation N_2O as an adjunct can increase recovery time, because a lower dose of midazolam is required to achieve adequate depth of anaesthesia.[29]

Both diazepam and midazolam are metabolised in the liver by cytochrome P450 (CYP3A4), and this common metabolic pathway increases the risk of drug interactions, thus potentially altering the effects of the administered benzodiazepine.[30] In general, benzodiazepines may be contraindicated or titrated more carefully in patients with hepatic impairment. Furthermore, because of their high lipid solubility, benzodiazepines can accumulate in adipose tissues and consequently cause 'hangover effects'.[26] These effects involve paradoxical reactions of potentiated anxiety, hyperactivity, rage and non-compliance, with low incidence (1% of patients). These reactions can be managed with GABA antagonists such as imidazobenzodiazepine, which reverses the action of benzodiazepines. The manifestations of a paradoxical reaction can be reversed with 0.3–0.5 mg imidazobenzodiazepine (0.01 mg/kg in children), whilst maintaining the sedative effect of the benzodiazepine.[31]

Remimazolam is a relatively new benzodiazepine approved by the United States Food and Drug Administration in 2020 for intravenous sedation in short procedures.[32] The development of remimazolam was aimed at combining the properties of midazolam and remifentanil, an opioid with organ-independent metabolism. Remimazolam produces a dose-dependent sedative effect and is metabolised in the bloodstream; thus, potential drug interactions and hepatic impairments will not affect the metabolism of the drug.[33] The onset of action for intravenous remimazolam is 1–2 min, and the duration of action is short, at less than 30 min. The current recommended intravenous dose is 2.5–5 mg for induction.[34] Remimazolam is associated with minimal pain on injection, and the risk of cardiorespiratory depression is decreased by the diminished likelihood of over-sedation.[34] Although the sedative and safety profile of remimazolam is more promising than those of current leading sedatives, further studies considering post-operative and electroencephalogram changes are required.[34]

The available literature has not established a consensus concerning the 'gold standard' benzodiazepine for conscious sedation, but has emphasised the importance of clinicians' professional judgement based on patient circumstances, clinical presentation and medical history.

Nitrous oxide

Nitrous oxide (N_2O) is an analgesic, anxiolytic and anaesthetic gas with a sweet odour that is administered via inhalation and therefore is ideal for needle-phobic patients. N_2O is an N-methyl-d-aspartate (NMDA) receptor antagonist, which minimises excitatory NMDA output into the CNS.[35] The gas is administered in combination with oxygen, and a minimum of 30% oxygen saturation is required. The concentration of N_2O can be titrated on the basis of the patient's response to the agent and the invasiveness of the dental treatment. Anxiolysis and some analgesic effects can be achieved in a state of mild-moderate sedation with 30–50% N_2O in most patients.[36] Research has indicated that 98% of patients sedated under N_2O do not remember subsequent local anaesthetic injections; therefore, this modality is ideal for needle-phobic patients and those with mild-moderate anxiety.[37] N_2O has been shown to have a success rate of 85.4% in paediatric patients with a range of temperaments.[38] A study comparing N_2O sedation with oral midazolam for paediatric sedation has indicated that the incidence of adverse reactions is higher in patients sedated with midazolam (25%) than N_2O (5%).[39]

N_2O is characterised by a rapid onset of less than half a minute and clearance within 1 min, thus allowing for safe sedation and relatively rapid recovery when the procedure is completed.[6] Elimination of N_2O occurs from the lungs; therefore, patients with compromised kidney and liver function can be safely treated with N_2O sedation.[36] Moreover, N_2O alone is unlikely to have adverse respiratory consequences from CNS depression. However, the combination of N_2O with other sedatives must be carefully considered, to ensure that such risks are mitigated.[40] Medical contraindications for N_2O administration include patients with compromised breathing and respiration, because their ability to eliminate the agent from the body is compromised. Furthermore, the degree of sedation may be insufficient for patients with severe dental anxiety and other disabilities.[6] Finally, failure of clinicians to follow proper titration techniques may cause patients to experience nausea and vomiting, the most common adverse effects of treatment with N_2O.[36] Ensuring that patients are treated with 100% O_2 before removal of the nose hood is essential.[36]

The provision of treatment under N_2O requires specialised training under most healthcare systems, and clinicians should consider patient health holistically to determine appropriate candidates for N_2O treatment.[40] Frequent and excessive N_2O exposure can dampen vitamin B12 activity through oxidation, thereby affecting purine formation, RNA synthesis and DNA synthesis in the bone marrow.[41] Cases of megaloblastic anaemia have been reported after prolonged exposure to high concentrations of N_2O.[36] Thus, under most local regulations, satisfactory scavenging or ventilation systems must be used in rooms in which nitrous oxide is used, to maintain minimum nitrous oxide levels and safe occupational exposure. A European study has found that the most effective method of decreasing occupational exposure is through using air conditioning and efficient pressure/exhaust ventilation alongside active scavenging systems. In the same study, in the absence of either active scavenging systems or air conditioning systems, the occupational exposure limit of 180 mg/m^3 was exceeded several times.[42] N_2O treatment is contraindicated during the first trimester of pregnancy because of potential effects on vitamin B12 activity, and consequent effects on foetal neurological development.[18]

Propofol

Propofol is an intravenous anaesthetic agent that functions through the potentiation of inhibitory GABA-A activity. Propofol is usually given at a dose of 1 mg/kg followed by a 0.3–4 mg/kg/h maintenance dose. The high fat solubility of propofol allows for a rapid onset of less than 1 min, and propofol has been hypothesised to have prolonged anaesthetic properties.[43] Furthermore, conscious sedation with propofol is sufficient to provide amnesia: 91.5% of patients have been found to have no memory of their treatment after conscious sedation with propofol.[44] Propofol has anti-emetic properties, and the literature suggests that it carries a 19% lower risk of post-operative nausea and vomiting than sevoflurane.[6] Approximately 40.6% of patients experience mild post-operative adverse effects such as drowsiness and pain at the cannulation site.[44]

Recent developments seek to minimise the need for deeper sedation and general anaesthesia to mitigate the risks of CNS depression. Target-controlled infusion is a relatively novel technique in which anaesthetic agents such as propofol are infused at sub-anaesthetic doses to achieve the desired sedative effect. The infusion pump is controlled by software programmed with the patient's weight and age, and thus delivers a bolus dose suitable to achieve a pre-determined target concentration. This dynamic mechanism alters the infusion according to the patient's response to the agent.[45]

Barbiturates

Barbiturates, a class of drugs that have been used for sedative purposes since the early 1900s, act by enhancing the suppression of CNS activity by the inhibitory neurotransmitter γ-aminobutyric acid. Additionally, their action decreases calcium channel conductance and excitatory amino acid responses.[46] The four main classes are long-acting, intermediate-acting, short-acting and ultrashort-acting barbiturates, the last three of which are most commonly used for dental sedation purposes. In modern dentistry, barbiturates are used predominantly to assist in diagnostic and radiographic procedures for young children.

Thiopental is a short-acting barbiturate that produces sedative effects within 30–60 s after intravenous administration or 5–8 min after rectal administration. When given intravenously at a dose of 20–25 mg/kg, it has a duration of action as long as 15 min; when rectally administered at a dose of 5–10 mg/kg, it can produce effects for as long as 1 h.[46] Generally, the rectal route is used primarily in children and may be preferred because of its relatively low pain on administration. However, higher doses of thiopental can cause adverse effects such as abdominal cramps, urinary and faecal incontinence, emesis and hyperactivity. Thus, as a wider range of sedatives have become available, and with a shift towards behavioural management strategies in young children, use of barbiturates in the dental setting has declined.[46]

Table 1: Sedative agents commonly used in dentistry.

Sedative agent	Dosage	Onset	Indications in dentistry	Contraindications in dentistry	Benefits/advantages	Risks/ disadvantages
Benzodiazepines (diazepam, midazolam)	Diazepam: *Adults:* 5−10 mg PO, taken 1 h before surgery *Children*: 0.2−0.5 mg/kg PO[26] Midazolam: *Adults:* 1 −5 mg IV, 0.25 mg/kg PO *Children*: 1 mg/kg PO (maximum 20 mg)	Diazepam: 1−3 min IV 15−16 min PO Midazolam: <3 min IV 15−20 min PO	Mild-moderate dental fear and anxiety[10]	Severe disability and behaviour management issues[10] Hepatic impairment[26] Chronic obstructive pulmonary disease[52] Patients taking CYP3A4 hepatic enzyme inhibitors[30]	Large margin of safety Preservation of vital functions and consciousness[26]	'Hangover effect' in patients with obesity Paradoxical reactions[31] Drowsiness, impaired motor coordination, dependence[26]
Nitrous oxide	100% O_2, followed by 30 −70% N_2O 100% O_2 at the end of the procedure[36]	<0.5 min	Mild-moderate dental fear and anxiety[18] Renal and hepatic impairment[36] Hypersensitive gag reflex[53]	Deeper planes of sedation required Patients unable to tolerate a nasal hood[18] First trimester of pregnancy Pneumothorax and otitis media[18]	Ability to titrate N_2O according to individual needs[40] Non-invasive; rapid onset and excretion[18]	Nausea and vomiting Hallucination Loss of protective reflexes in deeper planes of sedation Diffusion hypoxia[36] Excess N_2O causes vitamin B12 depression[41]
Propofol	Initiation: 1 mg/kg Maintenance dose: 0.3 −4 mg/kg/hr	<1 min	Induction and maintenance of general anaesthesia Conscious sedation	Patients with lipid metabolism disorders[54]	Decreased need for post-operative analgesia Decreased risk of emergence delirium[55] Anti-emetic[6] Profound amnesia without deep sedation[44]	Excessive CNS depression[56,54], Post-operative adverse effects, e.g., drowsiness and pain at the cannulation site[44]
Barbiturates	Thiopental: 20−25 mg/kg IV 5−10 mg/kg rectally[46]	Thiopental: 30−60 s IV 5−8 min rectally	Diagnostic and radiographic procedures for young children Short duration dental procedures[46]	Porphyria Liver impairment Nephritic syndrome	Variable lengths of duration of action (ultra short-acting, short-acting, intermediate-acting and long-acting)[25]	Abdominal cramps Urinary and faecal incontinence Emesis Hyperactivity Respiratory depression Myocardial depression[25]
Ketamine	3−4 mg/kg IM 1−2 mg/kg IV[50]	3−4 min	Paediatric emergency patients[6]	Severe/poorly controlled cardiovascular disease	Predictable onset and recovery time Wide margin of safety Minimal respiratory and cardiovascular depression adverse effects[50]	Emergence phenomenon Emesis Laryngospasm[6]

Methohexital, an ultra-short acting barbiturate with an extremely rapid onset of less than 30 s when given intravenously, produces sedative effects for a brief duration typically less than 10 min, owing to its high lipid solubility.[47,48] Historically, methohexital has been used primarily for induction of anaesthesia in children via intravenous or rectal administration routes. Methohexital is generally associated with very few adverse effects, most commonly increased oropharyngeal secretion, which can be easily managed through suction. Other potential adverse effects are generally rare and of low severity. An incidence of transient upper airway obstruction of only 1.1% has been reported during methohexital sedation; moreover, methohexital has been found to effectively decrease behavioural distress in paediatric oncology outpatients.[48]

Ketamine

Ketamine is a dissociative anaesthetic agent also used for dental sedation. Ketamine acts through inhibiting the release of the NMDA neurotransmitter glutamine.[49,50] Additionally, it acts on higher brain centres through unknown mechanisms, thereby causing depression of the association areas of the cerebral cortex and thalamus, and eliciting a state of 'sensory isolation' in which patients cannot perceive visual, auditory or pain stimuli, thus allowing for amnesia, sedation and analgesia.[6,50] During this state, vital cardiovascular and respiratory functions are generally preserved. However, notably, ketamine is a sympathomimetic that causes mild increases in blood pressure, heart rate and cardiac output, particularly when administered intravenously. Additionally, ketamine elicits mild dose-associated respiratory depression, and respiratory depression has been reported at very high doses.[50]

Ketamine is given at doses of 3–4 mg/kg IM or 1–2 mg/kg IV for adults. For children, lower doses may be used, because of an elevated risk of severe respiratory depression. Adverse effects reported with ketamine include the emergence phenomenon (confusion, disorientation, uncontrolled movements, hallucinations, incoherence etc.) in as many as 50% of adults and 5% of children, and increased salivary secretions, emesis and laryngospasm.[6] However, with ketamine, in contrast to other traditional sedative agents, most adverse effects are easily manageable; many studies have reported successful use of ketamine for sedation in children, with efficacy rates exceeding 90% (see Table 1).[51]

Disabilities with dental implications for sedation

Several conditions can predispose patients to more complex and urgent treatment needs, or affect their ability to access adequate dental care.[5] Furthermore, the anatomical, physiological and intellectual manifestations of some conditions may determine which sedative agents are indicated and contraindicated.

Down's syndrome

Down's syndrome (DS), characterised by trisomy of chromosome 21, manifests as variable degrees of intellectual disability, cardiovascular abnormalities, respiratory/airway difficulties and a multitude of other anomalies. In 2020, DS was estimated to occur in 1 in 800 births worldwide.[57]

The dental manifestations of DS include macroglossia (large tongues), maxillary retrognathia (maxillary deficiency), microdontia (small teeth), hypodontia (missing teeth) and malocclusion. Furthermore, the prevalence of periodontal disease in individuals with DS has been postulated to be 60–90%, and the severity of presentation is greater than that in those without DS.[58]

The intellectual disability associated with DS can severely affect patient cooperativity, and thus dental treatment under sedation may become necessary if behavioural management strategies do not bring the patient to a state of cooperation allowing for provision of treatment.[58] Nonetheless, cardiovascular anomalies, atlanto-axial instability, tracheal anomalies and reduced muscle tone are highly prevalent manifestations in patients with DS; thus careful case selection is required. The incidence of bradycardia under anaesthesia has been reported to be 3.7% in patients with DS, compared with 0.36% in patients without DS.[59] Kunimatsu et al. (2011) have reported the successful use of moderate sedation with intravenous midazolam for the treatment of a patient with DS with severe intellectual disability and a ventricular septal defect.[60] The patient was uncooperative with verbal commands, refused all oral health care, displayed impaired mobility with uncontrolled movements and showed a general lack of motivation. After administration of intravenous midazolam, the patient was brought into a cooperative state allowing for the completion of the planned dental treatment. For patients with DS and cardiovascular anomalies, midazolam or ketamine is recommended because of the cardiopulmonary risks associated with general anaesthesia.[60,61]

Autism spectrum disorder

Autism spectrum disorder (ASD) is a group of disorders characterised by social isolation, difficulty with verbal communication and repetitive behaviours. In 2018, the prevalence of diagnosed ASD was estimated to be 1 in 36 children.[62] Patients with ASD tend to present with poor oral hygiene, owing to food selectivity, difficulties in accepting positive oral health behaviours, and sensory issues with dentifrices and cleaning aids.[63] Como et al. have reported that approximately 50% of children with ASD do not brush their teeth twice daily.[64] Furthermore, an investigation by Jaber has indicated a 77% prevalence of caries among children with autism, compared with 46% in children without autism.[65]

Beyond the burden of dental disease in patients with ASD, sensory issues can affect patients' ability to tolerate dental procedures. Factors such as the noisy dental instruments, the brightness of overhead lights, the texture of the prophylaxis paste, and the invasive nature of dental treatment may be triggers.[64] Blomqvist, Dahllöff and Bejerot have reported a significantly higher incidence of dental anxiety among patients with than without ASD.[66] In sedation decisions, individual patient cooperativity should be considered to determine the appropriate agent and

approach.[59] Conscious sedation may often result in unpredictable behavioural responses or may be insufficient for physically combative patients.[67]

Holistic treatment of patients with ASD, as with patients with dental anxiety, should involve a preventive approach to minimise the need for repeated experiences under conscious sedation and general anaesthesia.[64] Hossenally and Doughty have observed that patients with ASD and other intellectual impairment require a lower dose of intranasal midazolam at their second dental appointment to achieve a similar level of anxiolysis.[68] Other studies have found that patients with ASD require greater doses of propofol to achieve similar levels of sedation to those observed in people with intellectual impairments without ASD; this finding may be attributable to alterations in the GABA-A receptors.[69] Furthermore, conditions such as vitamin B12 deficiency have been associated with ASD, and such medical comorbidities should be identified before treatment with N_2O.[70,71]

Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterised by impulsive behaviours, overactivity and inattention; its global prevalence has recently been estimated to be 5–7%.[72] In a dental context, inattention and hyperactivity may affect a patient's ability to tolerate lengthy procedures and increase the likelihood of disruptions throughout the treatment.[70] Furthermore, ADHD is associated with parafunctional habits such as bruxism and nail-biting, which may increase the need for more extensive dental treatment.[73] Typically, sedation with N_2O may be sufficient for patients with ADHD to avoid disruptions throughout the appointment.[70] Nonetheless, for some patients, hyperactivity may be precipitated by anxiety, N_2O may be insufficient under these circumstances. Madalena et al. have reported that oral sedation with midazolam is effective in managing these behaviours.[74]

Cerebral palsy

Cerebral palsy (CP) refers to a group of neurological conditions affecting movement and posture, thus causing intellectual disability, difficulty with communication, and other comorbidities. In 2022, the global prevalence was estimated to be 2.1 per 1000 live births.[75] The dental manifestations of CP include incompetent lips, malocclusions, difficulty in maintaining oral hygiene, and involuntary movements that may risk patient and clinician safety during treatment. Patients with CP often take muscle relaxants, which may affect hepatic metabolism. Sedatives metabolised via hepatic pathways may interact, and thus N_2O may be indicated. Furthermore, individual patient characteristics should be assessed to ascertain whether conscious sedation will be sufficient to minimise involuntary movements.[70]

Alzheimer's disease

Alzheimer's disease (AD) refers to progressive CNS degeneration that manifests as cognitive decline, and loss of visuo-spatial skills and motor coordination; this disease is the leading cause of dementia in the population of older adults. The global prevalence of AD has been estimated to be 3–7%

Table 2: Prevalent special needs conditions with dental implications that frequently require sedation or general anaesthesia.

Condition	Dental concerns	Risks/contraindications with sedation
Down's syndrome	Craniofacial anomalies[86] Dental anomalies[87] Cardiovascular abnormalities[5] Tracheal abnormalities[57] Atlanto-axial instability[61] Periodontitis, lack of cooperativity[87]	Cardiovascular emergencies such as bradycardia[59] Large tongue can affect airway management[5] Vascular access can be difficult[5] Tracheal stenosis[57]
Autism spectrum disorder (ASD)	Poor oral hygiene[64] Inability to tolerate longer procedures[70] Sensory issues[64] Food selectivity[88] Dental anxiety[66]	Conscious sedation may be insufficient[70] Vitamin B12 deficiency and N_2O sedation[70]
Attention deficit hyperactivity disorder (ADHD)	Inability to tolerate lengthy procedures[70] Parafunctional habits[73]	Risk of paradoxical reactions[89]
Cerebral palsy (CP)	Incompetent lips, malocclusions Difficulty in maintaining oral hygiene Involuntary movements[70]	Sedative agents metabolised via hepatic pathways Conscious sedation may be insufficient to minimise involuntary movements[70] Airway management[59]
Alzheimer's disease	Difficulty in maintaining oral hygiene High prevalence of periodontal diseases and caries[76] Polypharmacy[78]	Drug interactions[12]
Epilepsy	Seizures triggered by dental anxiety[70] Unexpected movements in the chair, risking clinician and patient safety[85] Elevated incidence of caries and periodontal disease Fractured teeth and restorations[82]	Antiepileptic medications such as carbamazepine and valproic may affect the clearance of benzodiazepines[84] Hypoxia due to over-sedation can trigger seizures[84]

in individuals older than 60 years in 2022, and this prevalence is expected to rise with an ageing global population.[76,77] Dental concerns associated with AD include loss of the ability to maintain oral hygiene; greater barriers to dental care due to communication difficulties; reliance on carers; and diminished mobility. The dental manifestations of polypharmacy are pronounced in patients with AD, because the mood stabilisers often prescribed can decrease salivary flow and therefore cause dental caries and oral ulcerations.[78] So et al. have described greater prevalence of periodontal diseases among patients with than without AD, and have indicated that the number of cases requiring treatment under general anaesthesia for extractions and caries treatment is rising.[76] Sedation and general anaesthesia are indicated depending on the extent of patients' cognitive decline and their ability to tolerate the dental environment.[79] Oral sedation with benzodiazepines is often contraindicated, owing to the high risk of drug interaction in patients with AD; and in later stages of AD, general anaesthesia is most indicated.[12] Nonetheless, lower doses of midazolam are required in patients with than without AD. Moreover, intravenous sedation with midazolam results in 9% lower cerebral blood flow than observed in patients without AD, thus potentially resulting in negative outcomes such as brain cell injury.[80] Reports of evaluation different methods of sedation for patients with AD have been limited, and individual patient comorbidities and cooperativity should be assessed.[76]

Epilepsy

Epilepsy is to a neurological condition predisposing individuals to recurring seizures. At any given time, as many as 50 million individuals globally have been diagnosed with epilepsy, and the prevalence is higher in low-income countries.[81]

From a dental perspective, seizures may be triggered by the clinical environment and dental anxiety.[70] Moreover, local anaesthetics have an established role in reducing the seizure threshold, thus increasing the risk of a seizure in the dental chair. In terms of oral health status, phenytoin, a common anti-epileptic medication, is known to cause gingival hyperplasia, and subsequently increase the risk of developing periodontal disease. Furthermore, patients with epilepsy tend to experience chipping and fracturing of their dentition and restorations during seizures.[82] Gurbuz and Tan have found that patients with rather than without epilepsy have poorer oral hygiene and a greater incidence of dental caries.[83]

Selection of the ideal sedative agent should depend on the severity of the patient's epilepsy, potential seizure triggers and current medications. Benzodiazepines have anti-epileptic properties and thus are often the sedative agent of choice. Certain anti-epileptic medications, such as carbamazepine and valproic acid, are hepatic inducers, and may accelerate the clearance of benzodiazepines; thus, greater doses may be required for maintenance.[84] Zor et al. have found a relatively low complication rate after intravenous sedation (primarily with midazolam) in patients with epilepsy (2.3%) and have concluded that intravenous sedation is safer than general anaesthesia, because of the lower risk of hypoxia and subsequent epileptic attacks (see Table 2).[85]

Recent advances and challenges in sedative dentistry

Recent advances in sedative dentistry have increased the ease of sedation access for PSN through non-hospital environments, such as mobile dental clinics and an increasing proportion of private dental clinics equipped with sedation and/or general anaesthesia capabilities.[90] However, owing to financial constraints, the costs associated with setting up the necessary equipment, local regulations requiring the presence of a qualified anaesthesiologist for intravenous sedation, training and hiring of additional staff needed for monitoring patients undergoing sedation, and other aspects, the provision of sedative services has still largely been unable to meet demands.[91]

Additionally, owing to backlogged dental services and staffing constraints, follow-up and continuation of treatment are often lacking after the initial treatment episode under sedation. Thus, there is minimal contemporary evidence available considering the need for subsequent dental treatment soon after dental treatment is provided to dentally anxious children, adolescents and adults under sedation or general anaesthesia. Future research should explore whether experiencing extensive dental treatment under sedation affects patient motivation to increase and maintain oral hygiene practices, and how preventive measures can be used to minimise the need for future treatments under sedation. Furthermore, little information is available regarding the physiological and emotional effects of repeated treatment under conscious sedation and general anaesthesia according to different patient presentations. Children repeatedly exposed to general anaesthesia have been found to be at elevated risk of behavioural disturbances.[92] Prevention may be encouraged through a minimum intervention oral healthcare pathway, wherein active involvement of the patient is encouraged to decrease dental phobia, rather than simply bypassing phobia with pharmacological intervention. PSN often present with an elevated risk of potential complications when undergoing dental sedation, as previously discussed. Additionally, a heavy burden is placed on public systems that provide sedation and general anaesthesia services, and a large backlog of patients exists globally. Thus, to avoid the need for treatment under sedation or general anaesthesia for all PSN, and to decrease the burden on public healthcare systems, a shift towards use of behavioural management and modification strategies should be pursued whenever possible. Chalmers (2000) has outlined several behavioural management and communication strategies for use with cognitively impaired patients, physical touch, gentle hand-holding, providing praise and positive responses, and talking slowly; these strategies may be useful when working with PSN.[93] Nonetheless, this approach is not yet well-established, and may still require pharmacological intervention in acute situations and circumstances involving uncooperative patients.[94] Current established guidelines for sedation tend to neglect considerations for PSN, thus increasing the need for incorporation of these considerations into appropriate clinical guidelines.

At present, the COVID-19 pandemic has placed considerable strain on various aspects of healthcare systems. Because of the high-risk nature of the dental environment, and the high-risk immune status of many PSN, non-acute treatment continues to be deferred.[95] For PSN requiring regular review and more complex treatment planning, restorative treatment may no longer be a viable option by the time of visit to a dental clinician.[96] In one study, dentists have noted a substantial decline in PSN treated during the pandemic, as well as limited access to sedative agents for these patients.[97] These circumstances have led to a push towards adaptability in the field of dentistry, to ensure that vulnerable members of the community are not neglected in the face of the complexities posed by the COVID-19 pandemic.

Conclusion

Several conditions and patient presentations may require pharmacological intervention to safely and effectively provide dental care. All patient factors must be carefully considered to determine the appropriate sedative agent for each patient presentation. Conditions such as autism, DS and AD require sedation/general anaesthesia not only because of a lack of cooperativity but also because of the effects of patients' disabilities on their ability to maintain oral hygiene. This review summarised and evaluated several common sedative agents and considerations regarding their use in PSN. A limitation of this study is that it provides a general overview of sedative agents in dental PSN and is not intended to replace formative training and clinical experience. All comments made are based on typical patients, whereas outlier cases are not considered. In such outlier cases, clinicians must use their own clinical judgement when working with these sedative agents. Future studies should explore means of ensuring that patients treated under sedation or general anaesthesia are supported with preventive treatment and advice, to minimise episodes of sedation or general anaesthesia, and maximise patients' motivation to increase their own oral health outcomes. A systematic review of the literature would be beneficial.

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

The study did not involve human participants and/or animals.

Authors contributions

Conceptualization, FC, RY, RZ, TW, JR.; methodology, FC, RY, RZ, TW, JR.; resources, Z.K., JR; writing—original draft preparation, FC, RY, RZ, TW, JR; writing—review and editing, RY, RZ, TW, Z.K., P.B., JR; supervision, RZ, Z.K., P.B., JR; project administration, RY, RZ, TW, JR. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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