Nitrous oxide versus midazolam for paediatrics

Précis

This review shows little to separate midazolam and nitrous oxide as single-agent sedatives for conscious sedation for healthy children. This supports the careful use of nitrous oxide or midazolam as a means of giving options to children to receive appropriate dental care in Ireland, by suitably trained and skilled conscious sedation teams in certain circumstances.

Abstract

Statement of the problem: There is often a need for pharmacological behaviour support among children requiring dental care. Midazolam sedation is rarely considered for the paediatric population in Ireland, in line with Dental Council guidelines. However, the evidence base for this guidance is unclear.

Purpose of the review: The aim of this systematic review is to summarise the strongest available evidence relating to comparison of the safety and effectiveness of nitrous oxide and midazolam in conscious sedation for healthy young dental patients.

Materials and methods: Using a systematic review methodology, according to a predefined protocol, searches of PubMed and Google Scholar were conducted. Citation chaining was undertaken and seven key journals were hand searched. Titles and abstracts were screened by two authors and full texts read. Included studies were randomised controlled trials comparing the use of nitrous oxide and midazolam, as single-sedative agents, in children ≤16 years of age. Information regarding methods, participants, interventions, outcome measures and results were extracted. Each trial was assessed for risk of bias. Grading of recommendations, assessment, development and evaluations (GRADE) standards were then applied to measure the strength of evidence.

Results: Six randomised controlled trials were included. All trials were at high risk of bias. Trials were grouped into those comparing nitrous oxide with oral midazolam, intravenous midazolam or transmucosal midazolam. There is weak evidence that both nitrous oxide and midazolam are safe and effective sedative agents for use in the healthy paediatric population.

Conclusions: This review considers the strongest level of evidence available regarding comparison of the safety and effectiveness of nitrous oxide and midazolam as single-drug sedatives. It shows little to separate both techniques, at least when compared as single-drug techniques. The evidence, limited as it is, supports nitrous oxide as a preferred sedative and the judicious use of midazolam as a means of giving options to children to receive appropriate dental care.

KEY WORDS: nitrous oxide; midazolam; dental; conscious sedation; systematic review; Ireland

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Introduction

There is extensive dental disease among Irish children.[1,2] This means that they are likely to need a lot of dental treatment. However, children often find dentistry difficult because it is anxiety evoking.[3] This is associated with a number of negative outcomes including increased oral disease, avoidance of care, and behavioural challenges in the dental surgery.[4-6] With most cases of dental anxiety originating in childhood and adolescence,[7] the repercussions of this anxiety can be life long.[8,9] Therefore, the acceptable application of proportionate behaviour support for children attending Irish dentists is essential. A range of options is available to do so, which can be broadly considered as non-pharmacological or pharmacological behaviour supports.[10] Pharmacological support generally includes general anaesthesia and sedation with either nitrous oxide and oxygen inhalation sedation, or benzodiazepine, mainly midazolam-based, intravenous, transmucosal or oral sedation (see **Table 1** for a comparison of nitrous oxide and midazolam). The Dental Council of Ireland recommends avoidance of intravenous sedation for children, particularly under the age of 10 years, meaning that children generally only receive general anaesthesia or nitrous oxide sedation.[11] This has effectively ruled out the use of intravenous and, more generally, midazolam-based sedation for many children in Ireland. As a result, children are offered inhalation sedation or general anaesthesia as pharmacological behaviour support but not midazolam. This is limiting because general anaesthesia should be avoided where possible, due to the rare risk of morbidity, potential mortality and the emotional impact on the child.[12-15]

Recent changes to the availability of general anaesthetic services in the public dental service have challenged capacity to meet need by these traditional means. Meanwhile, a number of evidence-based developments from the UK and Scotland have suggested that benzodiazepines are now an acceptable alternative to nitrous oxide for use in children and young people in specific circumstances.[16-18] It is worth noting that, in these guidelines, a child is defined as a person under the age of 12 years and a young person is between the ages of 12 and 16 years. In view of the limited availability[19,20] and associated high costs[21] of securing timely access to both commonly applied methods of pharmacological support in Ireland, and with the imminent updating of Dental Council guidelines, it is time to ask whether it is reasonable to limit our patients' options by effectively excluding midazolam-based conscious sedation for children?

Within this context, this review aims to systematically review the evidence to answer this question: is midazolam-based sedation as safe and effective as nitrous oxide sedation for use with children undergoing dental care?

Methods

Study selection

Adhering to a predefined protocol, and following standardised methods, a systematic review was undertaken.[22] The following search string was entered into PubMed on 04/09/2017: "((((“paediatric” OR “pediatric” OR “child” OR “adolescent”)) AND (“dentistry” OR “dental” OR “oral” OR “orofacial”)) AND (“nitrous oxide sedation” OR “inhalation sedation” OR “inhalational sedation” OR “relative analgesia” OR “laughing gas” OR “gas and air”)) AND (“midazolam” AND “sedation”)". An advanced search of Google Scholar was carried out. Hand searching was undertaken of key journals including: the *International Journal of Paediatric Dentistry; Journal of Dentistry for Children; British Dental Journal; Journal of the Irish Dental Association; Anaesthesia; Journal of Disability and Oral Health*; and, *SAAD Digest*. Citation chaining was

Table 1: Properties of nitrous oxide and midazolam.

Sedative agent	Nitrous oxide	Midazolam
Properties	Colourless gas, with pleasant sweet smell	Water-soluble, short-acting, high-potency benzodiazepine
Clinical effects of sedation	▸ Anxiolysis ▸ Analgesia	▸ Acute detachment for 20-30mins then a period of relaxation for approximately one hour ▸ Anterograde amnesia ▸ Anticonvulsant action ▸ Muscle relaxant
Advantages	▸ Non-invasive technique ▸ Rapid onset and recovery due to low solubility ▸ Ability to titrate according to patient's response	▸ Ability to titrate when used intravenously ▸ Level of sedation achieved pharmacologically rather than psychologically ▸ Recovery within a reasonable period; patient discharged usually less than two hours following treatment ▸ Ability to reverse with flumazenil
Disadvantages	▸ Level of patient acceptance required ▸ Level of sedation relies heavily on psychological reassurance ▸ Potential hazard to staff if effective scavenging and ventilation systems not in place	▸ Need for venepuncture ▸ No clinically useful analgesia

Table 2: Inclusion and exclusion criteria.

PICOS parameter	Inclusion	Exclusion
Population	Children ≤16 years of age ASA I/II/III Undergoing dental treatment or oral surgery	>16 years of age ≤16 years with ASA >III Undergoing dental treatment or oral surgery
Intervention	Inhalation sedation with N_2O	Multi-drug techniques
Comparison	Midazolam All routes of administration	Multi-drug techniques
Outcome	Any behavioural, physiological outcomes Adverse effects Completion of treatment	
Study design	Randomised controlled trials comparing nitrous oxide and midazolam	All other designs

Table 3: Characteristics of included studies.

Author	Source	Year	Study design	Drug	Route	Dosage	Sample size	Age	ASA	Treatment	Measure
Luhmann *et al.*	*Annals of Emergency Medicine*	2001	Prospective randomised clinical trial	Nitrous oxide Midazolam	Inhalation Oral	Continuous flow 50% 0.5mg/kg	103	2-6 years (mean 4.1)	I and II	Facial laceration repair	Observational Scale of Behavioural Distress – Revised (OSBD-R). Visual analogue scale.
Wilson *et al.*	*Anaesthesia*	2002	Prospective randomised controlled crossover trial	Nitrous oxide Midazolam	Inhalation Oral	Maximum dose – 30% N_2O 0.5mg/kg	46	10-16 years (mean 12.5)	I	Orthodontic extraction of at least four teeth	1) Brietkopf and Buttner Classification of emotional status. 2) Frankl Behaviour Rating Scale. 3) Houpt Behaviour Rating Scale. 4) Spielberger's State Anxiety Inventory. 5) Children's Fear Survey Schedule, dental subscale.
Wilson *et al.*	*British Dental Journal*	2002	Prospective randomised controlled crossover trial	Nitrous oxide Midazolam	Inhalation Oral	Maximum dose – 30% N_2O 0.5mg/kg	26	10-16 years (mean 12.5)	I	Orthodontic extraction of at least four teeth	1) Brietkopf and Buttner Classification of emotional status. 2) Frankl Behaviour Rating Scale. 3) Houpt Behaviour Rating Scale.
Wilson *et al.*	*British Journal of Anaesthesia*	2003	Prospective randomised controlled crossover trial	Nitrous oxide Midazolam	Inhalation Intravenous	Maximum dose – 30% N_2O Mean dose 2.8mg (range 1mg-5mg) Max. 5mg.	42	12-16 years (mean 13.2)	I and II	Orthodontic extraction of at least four teeth	1) Brietkopf and Buttner Classification of emotional status. 2) Frankl Behaviour Rating Scale. 3) Houpt Behaviour Rating Scale. 4) Spielberger's State Anxiety Inventory. 5) Children's Fear Survey Schedule, dental subscale.
Wilson *et al.*	*Anaesthesia*	2006	Prospective randomised controlled crossover trial	Nitrous oxide Midazolam	Inhalation Oral	Max. dose - 30% N_2O 0.3mg/kg	42	5-10 years (mean 7.4)	I and II	Extraction of four primary teeth, one in each quadrant of the mouth	1) Brietkopf and Buttner Classification of emotional status. 2) Houpt Behaviour Rating Scale.
Wilson *et al.*	*Acta Anaesthesia Scand*	2007	Prospective randomised controlled crossover trial	Nitrous oxide Midazolam	Inhalation Transmucosal	30% N_2O 0.2mg/kg	45	10-16 years (mean 12.9)	I and II	Orthodontic extractions of four premolar teeth	1) Brietkopf and Buttner Classification of emotional status. 2) Houpt Behaviour Rating Scale. 3) Spielberger's State Anxiety Inventory. 4) Children's Fear Survey Schedule, dental subscale.

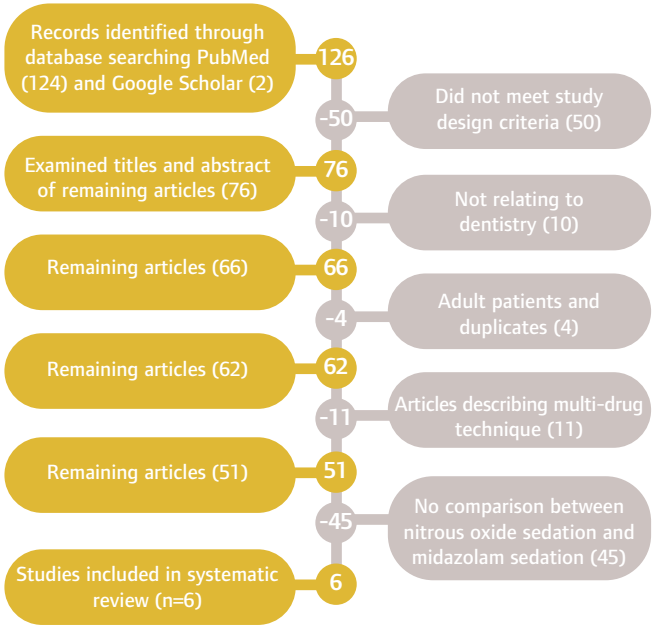

FIGURE 1: Modified PRISMA diagram of studies included in the systematic review.

undertaken for included studies and the corresponding author of a number of included trials was contacted. Title and abstract screening was undertaken by two authors independently and differences discussed. Full texts were retrieved for articles meeting the selection criteria (**Table 2**). Data were extracted and tabulated by one author.

Quality assessment and synthesis

All studies meeting selection criteria were included in this review. Included trials were quality assessed regarding sequence generation; allocation concealment; blinding (this was assessed in three groups: patient, operator/sedationist and outcome assessor); incomplete outcome assessment; freedom from selective reporting; and, other bias.[23] Within each study, a summary assessment of low risk of bias was made when there is a low risk of bias for all key domains, unclear risk of bias when there is an unclear risk of bias for one or more key domains, and high risk of bias when there is a high risk of bias for one or more key domains.

A narrative synthesis was structured according to the interventions compared: trials comparing oral midazolam and nitrous oxide; trials comparing intravenous midazolam and nitrous oxide; and, trials comparing transmucosal midazolam and nitrous oxide. Quality assessment was undertaken to assess level of evidence from all reviewed articles according to grading of recommendations, assessment, development and evaluations (GRADE) methods.[24]

Table 4: Summary of interventions and outcomes.

Studies	Time to maximum sedation (mins)	Level of sedation	Behaviour	Vital signs	Adverse events	Total appointment time (mins)	Patient preference
Luhmann (2001)	Not recorded	Not recorded	Significantly lower levels of anxiety in N_2O group	No cardio-respiratory adverse events at any time	Increased incidence in midazolam group	Only recovery time noted, N_2O: 21 Midazolam: 30	N/A
Wilson (2002)	N_2O: 5 Midazolam: 20	Higher for midazolam	Overall behaviour score similar for both groups	Within safe limits for both groups	Incidence low for both groups	N_2O: 35 Midazolam: 100	54% preferred midazolam 44% preferred N_2O 2% no preference
Wilson (2002) *BDJ*	N_2O: 5.2 Midazolam: 26.8	Higher for midazolam Difference highly significant	No difference in overall behaviour scores	Within safe limits for both groups	Self-limiting Not serious	N_2O: 32.8 Midazolam: 93.6	65% preferred midazolam 35% preferred N_2O
Wilson (2003)	N_2O: 6 Midazolam: 8	Difference between two groups not significant	No significant difference between both groups	Stayed within normal limits for both groups	Not serious None required emergency attention	N_2O: 34.8 Midazolam: 69.2	51% preferred midazolam 38% preferredN_2O 11% no preference
Wilson (2006)	N_2O: 6.8 Midazolam: 15.9	Higher for midazolam Difference found to be significant	No statistically significant difference between the two groups	Within safe limits for both groups	Self-limiting No treatment required	N_2O: 33.2 Midazolam: 74.8	No difference found between the two groups regarding preference
Wilson (2007)	N_2O: 7.1 Midazolam: 14.4	Similar for both groups	No significant difference in overall behaviour was noted	Within safe limits for both groups	No significant difference between groups. Symptoms minimal	N_2O: 34.1 Midazolam: 64.7	57.1% preferred N_2O 28.6% preferred midazolam 14.3% no preference

Results

Eligible studies

The PubMed and Google Scholar database search yielded 126 articles (**Figure 1**). Hand searching seven journals, citation chaining, scanning reference lists of relevant articles and contacting lead authors did not identify any new article that met the inclusion criteria. Six trials met the inclusion criteria. See **Table 3** for a summary of included trials.

Trial characteristics: design, setting and participants

Five of the studies adopted randomised, controlled, crossover trial design,[25-29] and one was a randomised clinical trial.[30] Dates of publication ranged from 2001 to 2007. Five were undertaken in the United Kingdom[25-29] and one in the USA.[30] All studies were hospital based. The number of paediatric patients analysed in the six trials ranged from 26 to 103 (304 in total). Participant age ranged from two to 16 years. Two trials included American Society of Anesthesiology (ASA) Classification ASA I patients only,[25,26] while four included both ASA I and ASA II.[27-30] Three trials recorded participants' baseline anxiety levels prior to commencing treatment.[25,27,29] Two of these used Spielberger's State Anxiety Inventory, to assess general anxiety, and the Children's Fear Survey Schedule, dental subscale to score dental anxiety.[25,29] The Observational Scale of Behavioural Distress – Revised (OSBD-R) was used in the third trial to assess distress at baseline.[30]

Characteristics of interventions

All articles compared nitrous oxide and midazolam as the sole sedative agent used. One trial included four treatment groups, one of which received both nitrous oxide and midazolam in combination, and this was compared with a treatment group that received standard care alone, one that used nitrous oxide only and one that used midazolam only.[30] The former two groups were not considered in the synthesis as they did not meet the inclusion criteria.

Regarding nitrous oxide, most trials (n=5) used a Quantiflex MDM relative analgesia machine to administer nitrous oxide via a nasal mask, in increments of 10%, to a final and maximum level of 30%.[25-29] One trial used continuous delivery of 50% nitrous oxide.[30]

Midazolam was delivered orally in four studies,[25,26,28,30] intravenously in one[27] and transmucosally in one.[29] Oral doses were defined as 0.5mg/kg, 20-45 minutes prior to treatment, in three trials,[25,26,30] and at 0.3mg/kg 20-30 minutes before commencing treatment in the fourth trial.[28] The study comparing intravenous midazolam delivered titrated midazolam via a 24-gauge venous cannula at a rate of 0.5mg/min to a maximum of 5mg, following application of EMLA.[27] The trial using the transmucosal route applied EPISTAT, for buccal administration[29] at a dose of 0.2mg/kg, placed in the buccal sulci, for a minimum of 10 minutes.

Table 5: Risk of bias summary: review author's judgements about each risk of bias item for each included trial.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding – patient	Blinding – operator/ sedationist	Blinding – outcome assessor	Incomplete outcome assessment	Free of selected reporting	Free of other bias
Luhmann (2001)	+	+	-	-	+	+	+	+
Wilson (2002) (*Anaesthesia*)	+	+	-	-	-	+	+	-
Wilson (2002) (*BDJ*)	?	+	-	-	-	+	+	-
Wilson (2003)	+	+	-	-	-	+	+	-
Wilson (2006)	+	+	-	-	?	+	+	+
Wilson (2007)	+	+	-	-	?	+	+	+

+ Low risk of bias - High risk of bias ? Unclear risk of bias

Characteristics of outcome measures

Outcomes related to behaviour and physiological parameters, and number of patients completing treatment in all trials. Most trials reported adverse events. Behaviour during treatment was measured using the Frankl Behaviour Rating Scale[27-29] and the Houpt Behaviour Rating Scale.[25,26] Overall behaviour and outcome of treatment was measured using the Houpt Behaviour Rating Scale.[25-29] Levels of general anxiety and dental anxiety were measured using Spielberger's State Anxiety Inventory and the Children's Fear Survey Schedule, dental subscale, respectively.[25,27,29] The level of sedation observed was measured using Brietkopf and Buttner's classification of emotional status in five trials.[25-29] The OSBD-R was used in one trial to assess distress throughout treatment.[30] These and additional outcomes are summarised in **Table 4**. A summary of quality assessment for these trials is presented in **Table 5**.

Synthesis

1. Trials where oral midazolam and nitrous oxide are compared (n=4)

Four trials compared nitrous oxide sedation to oral midazolam in samples ranging from two years to 16 years.[25,26,28,30] A total of 209 children participated in these four studies, with 205 of them completing treatment. Twelve patients withdrew for reasons including inability to tolerate the taste of oral midazolam or the nasal mask, lack of co-operation, failure to attend second visit, and requesting inhalation sedation for any further treatment. Behaviour during treatment and overall behaviour was measured using the Houpt Behaviour Rating Scale and Frankl Behaviour Rating Scale, respectively, in three trials.[25,26,28] No significant difference in behaviour was noted between the two groups. A significant reduction in anxiety levels was noted in both groups when pre- and postoperative levels were measured using Spielberger's State Anxiety Inventory and the Children's Fear Survey Schedule, dental subscale.[25] A significant difference in maximum level of sedation was noted in three trials, with midazolam producing higher levels of sedation.[25,26,28] Luhmann *et al.* (2001), using the visual analogue scale (VAS) for anxiety, recorded the deepest level of consciousness in each included group. This trial also reported a significantly lower mean OSBD-R score for the group that received nitrous oxide sedation compared to midazolam. All four trials state that the physiological parameters of patients remained within acceptable clinical limits for both groups. Two trials found that while the difference in arterial oxygen saturation for the nitrous oxide group and the midazolam group was statistically significant, the values for the midazolam group remained within safe limits for conscious sedation (91%-100%).[25,26] The incidence of side effects was low across all four trials for both nitrous oxide and midazolam sedation. Luhmann *et al.* (2001) reported that children who received midazolam were more likely to experience adverse events up to 24 hours after the procedure including ataxia, dizziness and difficulty walking.[30] The total appointment time was significantly greater for the midazolam group in all four trials. This major disparity can be attributed to the difference in time spent in the recovery area.

Table 6: GRADE: summary of findings.

Nitrous oxide compared with midazolam to sedate an anxious paediatric patient.

Patients or population: Healthy children undergoing dental treatment
Setting: Dental hospitals, emergency departments
Intervention: Nitrous oxide
Comparison: Midazolam

Outcomes	No. of participants (trials)	Quality of the evidence (GRADE)[24]	Comments
Behaviour	N_2O 304 Midazolam 304 (six trials)	Low ⨁⨁◯◯	Five trials found no significant difference. Increased behaviour with N_2O in one trial.
Physiological parameters	N_2O 304 Midazolam 304 (six trials)	Low ⨁⨁◯◯	Remained within safe clinical limits.
Adverse events	N_2O 304 Midazolam 304 (six trials)	Low ⨁⨁◯◯	Incidence low. Self-limiting. Not serious.

Five studies were downgraded due to lack of blinding of participants and four were downgraded due to unclear blinding of assessors.

2. Trials where intravenous midazolam and nitrous oxide are compared (n=1)

Wilson *et al.* (2003)[27] compared the effectiveness of intravenous midazolam sedation in paediatric dental patients with nitrous oxide sedation, for the orthodontic extraction of at least four teeth in 12-16 year olds. Some 42 patients were recruited for inclusion. A total of 13 other patients (24%) were unwilling to take part, citing concern over cannulation. Two participants withdrew as they were not happy to have intravenous sedation. Some 40 patients completed the trial. No significant difference in Houpt Behaviour Rating Scale and Frankl Behaviour Rating Scale was seen between the two groups. Favourable results were indicated for outcome of treatment in both groups, recorded by section four of the Houpt Behaviour Rating Scale. Brietkopf and Buttner's classification of emotional status noted greater levels of sedation for the midazolam group, with level of sedation remaining higher during recovery for this group. The difference was not statistically significant. Physiological variables remained within normal limits for both study groups. On returning home, side effects, including nausea, drowsiness and headache, were reported by 14 patients in the midazolam group compared to 11 in the nitrous oxide group. The total appointment time was greater for the intravenous sedation group. This outcome can be attributed mainly to the increased recovery time associated with midazolam sedation.

3. Trials where transmucosal midazolam and nitrous oxide are compared (n=1)

Wilson *et al.* (2007)[29] evaluated the effectiveness, safety and patient acceptability of buccal midazolam, 0.2mg/kg, in comparison with nitrous oxide sedation, for orthodontic extractions in 10- to 16-year-old patients. Some 36 patients completed the trial. The reasons for withdrawal included inability to tolerate the taste of midazolam and patients becoming unco-operative. Using the Houpt Behaviour Rating Scale, no child demonstrated disruptive behaviour in either group, with no significant difference in overall behaviour noted. Pre- and postoperative levels of general and dental anxiety were assessed using Spielberger's State Anxiety Inventory and the Children's Fear Survey Schedule, dental subscale, respectively. A significant reduction in anxiety levels was noted. The maximum sedation scores recorded using Brietkopf and Buttner's classification of emotional status were similar for both groups. All vital signs remained within acceptable clinical limits for both forms of sedation. Side effects were reported by 16 patients in the midazolam group, compared to 14 patients in the nitrous oxide group. These included sleepiness, headache and slight nausea. The duration of visit for the buccal midazolam group was 64.7 minutes (60-90 minutes) compared with 34.1 minutes (28-44 minutes) for the nitrous oxide group.

Quality assessment

According to Higgins and Altman,[23] all studies reviewed were at high risk of bias due to the lack of blinding of participants and operators (see **Table 5**). Applying the GRADE[24] approach to assess the quality of evidence included in this systematic review, the quality of evidence was low due mainly to the lack of blinding across all trials (see **Table 6**).

Discussion

Summary of main results

This review found that nitrous oxide and midazolam are equally safe and effective sedative agents for use with healthy children and young people in hospital settings. No patient suffered significant respiratory depression in any of the included trials, with a low incidence of excitatory behaviour observed for both nitrous oxide and midazolam. The safety of both these techniques is further highlighted, as any desaturation recorded remained within safe clinical limits in all trials. While one trial concluded that nitrous oxide is more effective for relieving anxiety and has fewer adverse effects than oral midazolam,[30] their overall effectiveness, in relation to behaviour scores, level of sedation and treatment completion, was largely equal. However, treatment with midazolam took longer than with nitrous oxide.

Limitations of included studies and systematic review

These results are largely in agreement with similar reviews, which found weak to very weak evidence for midazolam and nitrous oxide as sedative agents for children undergoing dental treatment.[12] The results of this systematic review need to be considered in view of the limitations of both the studies included and the actual review process. The overall risk of bias across included trials was high, mainly due to a lack of operator, outcome assessor and participant blinding. This may have influenced how interventions were delivered, experienced and measured. Suggestions to reduce associated detection and performance biases have been made since.[12] Another possible bias arises because the effectiveness of nitrous oxide is largely dependent on operator

communication skills.[31] Therefore, the same operator should deliver sedation to all participants in research of this kind to remove this potential confound. This was not carried out in most included trials. We can conclude that the evidence supporting our findings is at risk of bias, but still useful.

Other limitations involve external validity. In the studies reviewed, baseline anxiety and behaviour levels were not always clearly recorded. Given that treatment was very often completed, and that some populations, such as patients requiring orthodontic extractions, were unlikely to represent highly anxious groups or those with behavioural issues, the effectiveness of these sedative agents may vary when applied to patients who most readily benefit from conscious sedation in practice. One must also remember that these studies were undertaken on hospital sites under research conditions by appropriately trained and supported sedationists. There is an obvious need for future research in community and practice settings.

Regarding the methods applied here, the search strategy was limited to two electronic databases and hand searching of key journals. It is worth noting that the randomised controlled trial conducted by Luhmann *et al.*[30] studied children attending an emergency department for facial laceration repair. As the search strategy aimed to include similar orofacial procedures, the decision was made to include it in this review. The five other trials were conducted by the same team of authors. Five trials included here adopted crossover designs, which introduce a possibility of a carryover effect influencing the direct treatment effect.[22] For these reasons, the latest Cochrane review on paediatric sedation excluded crossover trials,[12] whereas they were included in NICE guidance.[18] While techniques involving multi-drug sedation were excluded in this study, largely because the Dental Council of Ireland does not permit multi-drug sedation in Ireland, there is a broader literature suggesting that combined nitrous oxide and midazolam is an attractive alternative.[32-34]

Implications for practice in Ireland

There are many factors that influence the sedative agent chosen for a patient, including complexity of treatment, medical and behavioural complexity, and level of anxiety.[35] Given this complexity, neither nitrous oxide nor midazolam will serve the needs of every child who requires pharmacological support. Guidance from the UK and Scotland[16,17] recognises the need for a range of sedative options for children. This considers nitrous oxide as a first choice, basic or standard technique. It also acknowledges that midazlolam is a valid[18] advanced technique, for those under the age of 12 years, when the clinical needs of the patient are not suited to sedation using nitrous oxide. Out of interest, midazolam is considered a basic technique for young people over the age of 12 years, unless the patient has complex needs. This designation as an advanced technique stipulates that dentists who sedate children under 12 years of age, using midazolam, must be skilled in paediatric immediate life support, at a level equivalent to a consultant anaesthetist, competent in sedation for dentistry.[16,17] The evidence reviewed here, albeit of low quality, suggests that clinicians in Ireland should have the limited option of both nitrous oxide and midazolam, in line with these UK recommendations. As stipulated by the Dental Council of Ireland, and highlighted in each trial reviewed, any dentist practising conscious sedation must have postgraduate training in the technique they are using.

Nevertheless, this review demonstrates the safety of both sedative agents when applied according to the regimens described. This is an important finding, given that the safety profile and efficacy of midazolam is not as well established as nitrous oxide for this cohort of patients.[36] The incidence of adverse effects was low, with no significant difference between groups. Where they did occur, they were considered not serious, self-limiting and not requiring emergency attention.

While not statistically significant, there were some potentially clinically significant differences noted. In one study reviewed here, up to 23% of participants taking midazolam demonstrated disruptive crying or movement, compared to no disruptive behaviour in the nitrous oxide group.[28] Relative to literature-based comparisons, disinhibition or paradoxical reactions are said to occur in 1% of children undergoing midazolam sedation.[36-38] This review also suggests that midazolam required more time than nitrous oxide. The authors claimed that these times were within acceptable limits for both groups, with time spent in recovery being the main reason for such a discrepancy.

Conclusion

This review has highlighted that both midazolam and nitrous oxide can safely support paediatric populations to achieve dental care. Research comparing the effectiveness of nitrous oxide and midazolam as single sedative agents in the paediatric population is sparse, offering weak evidence that nitrous oxide and midazolam are both safe and effective in this age group. There is a need for future research in this area, including well-designed, randomised controlled trials conducted in a community setting with suitably blinded controls. Clinicians have two potentially safe and effective agents that could be applied by an appropriately trained and skilled sedationist with appropriate support for carefully selected patients, if the Dental Council of Ireland Code of Practice supports this.

Conflict of interest

Since authoring this paper, Dr Caoimhin Mac Giolla Phadraig has been co-opted onto the Dental Council of Ireland Review Group to produce guidelines relating to general anaesthesia, conscious sedation and resuscitation/medical emergencies in dentistry. This has not affected his impartiality in following the evidence reviewed or commitments undertaken as part of this group. The authors declare no other conflicts.

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