Cochrane Library

Cochrane Database of Systematic Reviews

Sedation of children undergoing dental treatment (Review)

Ashley PF, Chaudhary M, Lourenço-Matharu L

Ashley PF, Chaudhary M, Lourenço-Matharu L.
Sedation of children undergoing dental treatment.
Cochrane Database of Systematic Reviews 2018, Issue 12. Art. No.: CD003877.
DOI: 10.1002/14651858.CD003877.pub5.

www.cochranelibrary.com

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Review]

Sedation of children undergoing dental treatment

Paul F Ashley[1], Mohsin Chaudhary[2], Liege Lourenço-Matharu[3]

[1]Unit of Paediatric Dentistry, Department of Craniofacial Growth and Development, UCL Eastman Dental Institute, London, UK. [2]Paediatrics, University College London Hospital, London, UK. [3]London, UK

Contact: Paul F Ashley, Unit of Paediatric Dentistry, Department of Craniofacial Growth and Development, UCL Eastman Dental Institute, 256 Grays Inn Road, London, WC1X 8LD, UK. p.ashley@ucl.ac.uk.

Editorial group: Cochrane Oral Health Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 12, 2018.

Citation: Ashley PF, Chaudhary M, Lourenço-Matharu L. Sedation of children undergoing dental treatment. *Cochrane Database of Systematic Reviews* 2018, Issue 12. Art. No.: CD003877. DOI: 10.1002/14651858.CD003877.pub5.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Children's fear about dental treatment may lead to behaviour management problems for the dentist, which can be a barrier to the successful dental treatment of children. Sedation can be used to relieve anxiety and manage behaviour in children undergoing dental treatment. There is a need to determine from published research which agents, dosages and regimens are effective. This is the second update of the Cochrane Review first published in 2005 and previously updated in 2012.

Objectives

To evaluate the efficacy and relative efficacy of conscious sedation agents and dosages for behaviour management in paediatric dentistry.

Search methods

Cochrane Oral Health's Information Specialist searched the following databases: Cochrane Oral Health's Trials Register (to 22 February 2018); the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 1) in the Cochrane Library (searched 22 February 2018); MEDLINE Ovid (1946 to 22 February 2018); and Embase Ovid (1980 to 22 February 2018). The US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform were searched for ongoing trials. No restrictions were placed on the language or date of publication when searching the electronic databases.

Selection criteria

Studies were selected if they met the following criteria: randomised controlled trials of conscious sedation comparing two or more drugs/techniques/placebo undertaken by the dentist or one of the dental team in children up to 16 years of age. We excluded cross-over trials.

Data collection and analysis

Two review authors independently extracted, in duplicate, information regarding methods, participants, interventions, outcome measures and results. Where information in trial reports was unclear or incomplete authors of trials were contacted. Trials were assessed for risk of bias. Cochrane statistical guidelines were followed.

Main results

We included 50 studies with a total of 3704 participants. Forty studies (81%) were at high risk of bias, nine (18%) were at unclear risk of bias, with just one assessed as at low risk of bias. There were 34 different sedatives used with or without inhalational nitrous oxide. Dosages, mode of administration and time of administration varied widely. Studies were grouped into placebo-controlled, dosage and head-to-head comparisons. Meta-analysis of the available data for the primary outcome (behaviour) was possible for studies investigating oral midazolam versus placebo only. There is moderate-certainty evidence from six small clinically heterogeneous studies at high or unclear risk of bias, that the use of oral midazolam in doses between 0.25 mg/kg to 1 mg/kg is associated with more co-operative behaviour compared

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

to placebo; standardized mean difference (SMD) favoured midazolam (SMD 1.96, 95% confidence interval (CI) 1.59 to 2.33, P < 0.0001, I^2 = 90%; 6 studies; 202 participants). It was not possible to draw conclusions regarding the secondary outcomes due to inconsistent or inadequate reporting or both.

Authors' conclusions

There is some moderate-certainty evidence that oral midazolam is an effective sedative agent for children undergoing dental treatment. There is a need for further well-designed and well-reported clinical trials to evaluate other potential sedation agents. Further recommendations for future research are described and it is suggested that future trials evaluate experimental regimens in comparison with oral midazolam or inhaled nitrous oxide.

PLAIN LANGUAGE SUMMARY

Sedation of children undergoing dental treatment

Review question

The aim of this Cochrane Review was to find out which drugs used to sedate children during dental treatment were the most effective.

Background

Fear of the dentist may be expressed as unco-operative behaviour in children requiring dental treatment. Behaviour management problems can result in a child's tooth decay going untreated. While behavioural techniques play an important role in managing children, some children still find it difficult to co-operate with dental treatment and may require sedation. This review examined the effects of drugs to sedate a child whilst keeping them conscious.

Study characteristics

Authors from Cochrane Oral Health carried out this review and the evidence is up to date to 22 February 2018. A total of 50 randomised controlled trials were included with a total of 3704 participants. Within these studies 34 different sedatives were used, often with inhalational nitrous oxide as well. Dosages and delivery of these drugs varied widely. We grouped studies into those where drugs were compared to a placebo, where drugs were compared to other drugs or where different dosages of drugs were compared. Because all the studies were so different we could only carry out a meta-analysis for studies comparing oral midazolam to a placebo. The review showed that use of oral midazolam made patients more co-operative for dental treatment than a placebo drug. Where reported, adverse effects were few and minor.

Key results

Oral midazolam probably improves behaviour of children during dental treatment. We evaluated other sedatives but there is insufficient evidence to draw any conclusions.

Certainty of the evidence

There is some moderate-certainty evidence that midazolam administered in a drink of juice is effective.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Sedative compared to placebo for children needing dental care

Sedative compared to placebo for children needing dental care					
Patient or population: children needing dental care **Setting:** hospital **Intervention:** sedative **Comparison:** placebo					
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with placebo	**Risk with sedative**				
Houpt/other behavioural score - Midazolam (oral) **SD units:** investigators measure behaviour using different scales - Higher values mean better behaviour	The Houpt/other behavioural score in the **midazolam (oral)** group was on average **1.96 SDs higher** (1.59 higher to 2.33 higher) than the placebo group		-	202 (6 RCTs)	⊕⊕⊕⊖ MODERATE[1]	As a rule of thumb 0.2 SD represents a small difference, 0.5 a moderate difference, and 0.8 a large difference Adverse events: vomiting/hiccupping reported in 1 study. Amnesia reported in 1 study Oral midazolam probably improves behaviour
Houpt/other behavioural score - Midazolam (intravenous) **SD units:** investigators measure behaviour using different scales - Higher values mean better behaviour	The Houpt/other behavioural score in the **midazolam (intravenous)** group was on average **1.21 SDs higher** (0.24 higher to 2.18 higher) than the placebo group		-	20 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1, 2]	As a rule of thumb 0.2 SD represents a small difference, 0.5 a moderate difference, and 0.8 a large difference No adverse events reported Uncertain whether intravenous midazolam improves behaviour
Houpt/other behavioural score - Nitrous oxide **SD units:** investigators measure behaviour using different scales - Higher values mean better behaviour	The Houpt/other behavioural score in the **nitrous oxide** group was on average **0.69 SDs higher** (0.13 higher to 1.26 higher) than the placebo group		-	52 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1, 3]	As a rule of thumb 0.2 SD represents a small difference, 0.5 a moderate difference, and 0.8 a large difference No adverse events reported Uncertain whether nitrous oxide improves behaviour

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.
Cochrane Database of Systematic Reviews

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Houpt/other behavioural score - Diazepam (oral) **SD units:** investigators measure behaviour using different scales - Higher values mean better behaviour	The Houpt/other behavioural score in the **diazepam (oral)** group was on average **0.62 SDs higher** (0.28 lower to 1.53 higher) than the placebo group	-	20 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1, 2]	As a rule of thumb 0.2 SD represents a small difference, 0.5 a moderate difference, and 0.8 a large difference No adverse events reported Uncertain whether oral diazepam improves behaviour
Good or better behaviour - Chloral hydrate	**Study population** 533 per 1000 — 709 per 1000 (427 to 1000)	RR 1.33 (0.80 to 2.22)	60 (1 RCT)	⊕⊖⊖⊖ VERY LOW[3, 4]	Adverse events: associated with airway problems Uncertain whether chloral hydrate improves behaviour
Good or better behaviour - Meperidine	**Study population** 133 per 1000 — 711 per 1000 (193 to 1000)	RR 5.33 (1.45 to 19.64)	60 (1 RCT)	⊕⊕⊖⊖ LOW[5]	Adverse events: nausea, vomiting and unmanageable behaviour were associated with meperidine use Meperidine may improve behaviour

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio; **SD:** standard deviation; **SMD:** standardized mean difference.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded for risk of bias (lack of blinding and randomisation processes unclear).
[2]Downgraded for imprecision (large confidence interval and small numbers).
[3]Downgraded for imprecision (large confidence interval).
[4]Downgraded for risk of bias (randomisation unclear and incomplete outcome assessment).
[5]Downgraded for risk of bias (randomisation unclear) and imprecision.

Summary of findings 2. Sedative compared with different dosage of the same sedative for children needing dental care

Sedative compared with different dosage of the same sedative for children needing dental care
Patient or population: children needing dental care **Setting:** hospital

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.
Cochrane Database of Systematic Reviews

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Intervention: sedative
Comparison: different dosage of the same sedative

Outcomes	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
Any behavioural score - Midazolam (any mode of delivery)	394 (10)	⊕⊖⊖⊖ VERY LOW[1]	There is insufficient evidence to determine whether any specific dose of intranasal midazolam is effective There is weak evidence from two trials that oral midazolam at a dose of 0.5 mg/kg to 0.75 mg/kg is an effective sedative for children. However, one trial administered both nitrous oxide and midazolam so it is difficult to attribute benefit to midazolam alone
Any behavioural score - Hydroxyzine	30 (1)	⊕⊖⊖⊖ VERY LOW[1]	There is insufficient evidence to determine whether any specific dose of hydroxyzine is effective

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded for risk of bias, inconsistency and/or imprecision.

Summary of findings 3. Sedative compared with a different sedative for children needing dental care

Sedative compared with a different sedative for children needing dental care

Patient or population: children needing dental care
Setting: hospital
Intervention: sedative
Comparison: different sedative

Outcomes	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
Any behavioural score - Chloral hydrate/hydroxyzine versus	235 (6)	⊕⊖⊖⊖ VERY LOW[1]	No two studies evaluating the same intervention and comparison found the same effect. There is insuf-
Any behavioural score -	24 (1)	⊕⊖⊖⊖	

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.
Cochrane Database of Systematic Reviews

Chloral hydrate/promethazine versus		VERY LOW[1]	ficient evidence to draw any conclusions
Any behavioural score - Dexmedetomidine versus	120 (2)	⊕⊖⊖⊖ VERY LOW[1]	
Any behavioural score - Ketamine versus	494 (8)	⊕⊖⊖⊖ VERY LOW[1]	
Any behavioural score - Ketamine/midazolam versus	27 (1)	⊕⊖⊖⊖ VERY LOW[1]	
Any behavioural score - Midazolam (oral) versus	654 (7)	⊕⊖⊖⊖ VERY LOW[1]	
Any behavioural score - Midazolam (intravenous) versus	70 (2)	⊕⊖⊖⊖ VERY LOW[1]	
Any behavioural score - Midazolam (rectal) versus	90 (1)	⊕⊖⊖⊖ VERY LOW[1]	
Any behavioural score - Sevoflurane versus	1140 (3)	⊕⊖⊖⊖ VERY LOW[1]	

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded for risk of bias, inconsistency and/or imprecision.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

BACKGROUND

Description of the condition

Dental decay is one of the most common human diseases and affects almost 100% of adults and 60% to 90% of school children across the world (WHO 2012). This decay in children is often untreated. In 2015, 25% of 5-year olds in England had teeth affected by dental decay with each of these children having on average three teeth damaged. Only 12% of these damaged teeth were filled (NDEP 2015). This represents a significant problem, if dentine caries is left it will usually lead to pain and sepsis which can often only be managed by extraction or extensive restoration of the affected teeth. Historically this has been managed in children by use of general anaesthetic. Whilst a proportion of children will always require this process, it is now recognised that it should be avoided wherever possible due to the associated rare risk of death. General anaesthesia is also very costly, it requires the use of specialist facilities and staff such as anaesthetists and specialist nurses.

The obvious alternative is to provide treatment under local anaesthesia, however some children will not be able to accept to this. Barriers to treatment may be dental fear or behaviour management problems (BMP). Estimates of the prevalence of dental fear and BMP are hard to find, however one Swedish study reported a value of 10.5% of children with BMP out of a population of 4 to 11-year olds (Klingberg 1994). Dental fear and BMP are closely related phenomena. Dental fear or anxiety is associated with increased levels of caries and BMP, however not all children who are dentally anxious will present with BMP, one study reported that only 60% of children with dental fear presented with BMP (Klingberg 1995). In turn, children exhibiting BMP may also be dentally anxious, though in the same study only 25% of those children with BMP were dentally anxious.

Methods of managing anxiety and behaviour are therefore required to meet this need. Whilst behavioural techniques that do not involve the use of drugs can play an important part in a child's management, many children will still find it difficult to tolerate dental treatment. In these cases sedation could be considered as a method for reducing anxiety and facilitating the provision of dental treatment.

Description of the intervention

Views of what constitutes sedation differ between clinicians, however any definition should seek to differentiate sedation from general anaesthetic. Unfortunately many sedative agents can also act as general anaesthetics and the difference in dose required to move from a sedated patient to an anaesthetised patient can be very small and extremely variable between patients. The ideal sedative agent would reduce anxiety and improve behaviour thus facilitating the completion of dental treatment and providing a positive experience for the patient. It could be carried out safely in the primary care sector and have a wide margin of safety. For the purposes of this review, therefore, a widely used definition of sedation will be followed which clearly states the level of consciousness beyond which a patient could be considered to be anaesthetised (AAP 1992):
"a state of depression of the central nervous system which reduces anxiety thus enabling treatment to be carried out satisfactorily. During sedation the patient will be able to independently maintain an open mouth, and respond sensibly to verbal commands. In addition, the patient will retain adequate function of protective reflexes such as the laryngeal reflex. The drugs used should carry a margin of safety sufficient to render unintended loss of consciousness extremely unlikely."

This type of sedation will be referred to as conscious sedation or moderate sedation.

This review will not consider agents used to induce so-called 'deep sedation' for the above mentioned reasons. Deep sedation can be defined as (AAP 1992):
"a medically controlled state of depression consciousness or unconsciousness from which the patient is not easily aroused. Deep sedation may be accompanied by a partial or complete loss of protective reflexes, including the inability to maintain an airway independently and to respond purposefully to physical stimulation or to verbal command. The state and risks of deep sedation may be indistinguishable from those of general anaesthesia."

Why it is important to do this review

Commonly used agents for sedation include the benzodiazepines, nitrous oxide or other agents. Unfortunately these agents are delivered by a large variety of methods (such as oral, rectal and nasal), in a bewildering variety of combinations and in varying doses. They may also be used in conjunction with forms of physical restraint (such as a papoose board). A preliminary search of the literature suggests that very few of these drugs have been assessed against a negative or placebo control to test their efficacy. In addition many of the agents or combinations of agents may induce deep sedation rather than conscious sedation. Finally, outcome variables in the majority of studies assessing the different sedative agents appear to focus predominantly on its effect on behaviour rather than anxiety.

The aim of this review was to determine which sedative agents are effective for behaviour management in children who are receiving dental care in order to allow completion of dental treatment. This is the second update of the Cochrane Review first published in 2005 and previously updated in 2012 (Matharu 2005; Matharu 2012).

OBJECTIVES

To evaluate the efficacy and relative efficacy of conscious sedation agents and dosages for behaviour management in paediatric dentistry.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (including cluster-randomised). Quasi-randomised trials were excluded. We also excluded cross-over trials from this review, as they are not an appropriate study design when the intervention can have a long lasting effect (Higgins 2011). The relationship between pain and anxiety is well established, it is clear that the child's experience of any procedure will have an impact on any subsequent one (Shashikiran 2006).

Types of participants

Both the following criteria had to be met for a study to be included in this review.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

- Children and adolescents aged 0 to 16 years of age (including children with specific medical or behavioural problems).
- Children having simple restorative treatment with local anaesthesia (e.g. fillings, stainless steel crowns), simple extractions or management of dental trauma (e.g. repositioning of tooth, splinting, removal of nerve from tooth).

Studies where children were having complex surgical procedures were not included in this review. We included studies regardless of whether a measure of anxiety was reported at baseline.

Types of interventions

Test group

Any sedative agent via any route of admission that can be administered by a dentist, anaesthetist, sedationist or dental auxiliary in an outpatient setting or dental office. Studies that reported induction of deep sedation were excluded.

Control group

Placebo (including no intervention) or alternative sedation agent or different dosage of the same agent.

Types of outcome measures

Primary outcomes

- Behaviour.

This was measured by a range of different indices; where possible these were combined to allow meta-analysis to be carried out. Behaviour for the procedure overall would be recorded; if this information was not available then behaviour at the time of injection was used.

Secondary outcomes

- Completion of treatment (yes/no).
- Postoperative anxiety.
- Adverse events.

Search methods for identification of studies

Electronic searches

Cochrane Oral Health's Information Specialist conducted systematic searches in the following databases for randomised controlled trials and controlled clinical trials without language or publication status restrictions:

- Cochrane Oral Health's Trials Register (searched 22 February 2018) (Appendix 1);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 1) in the Cochrane Library (searched 22 February 2018) (Appendix 2);
- MEDLINE Ovid (1946 to 22 February 2018) (Appendix 3);
- Embase Ovid (1980 to 22 February 2018) (Appendix 4).

Subject strategies were modelled on the search strategy designed for MEDLINE Ovid. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 6 (Lefebvre 2011).

Searching other resources

The following trial registries were searched for ongoing studies:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 22 February 2018) (Appendix 5);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 22 February 2018) (Appendix 6).

The reference lists of all eligible trials were checked for additional studies.

Specialists in the field known to review authors were contacted for any unpublished data.

Titles and abstracts were assessed by review authors for inclusion in the review.

We did not perform a separate search for adverse effects of interventions used, we considered adverse effects described in included studies only.

Data collection and analysis

Selection of studies

Following the electronic search, two review authors independently screened the titles and abstracts to exclude all articles clearly not meeting the inclusion criteria. The search was designed to be sensitive and include controlled clinical trials, these were filtered out early in the selection process if they were not randomised. Of all the remaining articles, full texts were obtained and assessed independently by two review authors and only articles fully meeting the inclusion criteria were considered. Any disagreements were resolved by discussion.

Data extraction and management

Data extraction was carried out on a specially designed form independently by two review authors who were blinded to each other's data. Results were compared to check for inconsistencies and disagreements resolved by discussion. Review authors were not blinded to the journal of publication or the author's names on the papers.

Descriptive data collected (where available) in addition to that already outlined included:

- year study started, if not available, year it was published,
- country where study was carried out,
- use of supplemental nitrous oxide gas (N_2O),
- use of restraints during the procedure,
- previous dental treatments of patients,
- anxiety prior to treatment,
- baseline behaviour,
- sample size calculation,
- dental treatment procedure,
- fasting before the procedure,
- level of consciousness throughout the procedure,
- adverse effects,
- monitoring used,

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

- procedure and recovery time,
- assessment of examiner variability,
- patient satisfaction/acceptance.

The characteristics of the trial participants, interventions and outcomes for the included trials are presented in Characteristics of included studies table. Where information in the published report was incomplete or unclear, we contacted the trial authors for clarification or for further information.

Assessment of risk of bias in included studies

We assessed risk of bias in included studies using Cochrane's risk of bias tool and the methodology set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We analysed data using Review Manager software (Review Manager 2014). We completed a 'Risk of bias' table for each included study. Each study was assessed on the following domains:

- sequence generation (selection bias),
- allocation concealment (selection bias),
- blinding - of participant and operator/sedationist (performance bias), and outcome assessor (detection bias). If the authors stated that a study was double-blinded then it was assumed that at least the patient and outcome assessor were blinded,
- incomplete outcome data (attrition bias),
- free of selective outcome reporting (reporting bias),
- free of other bias.

For each domain the risk of bias was judged either low, unclear or high.

We categorised the overall risk of bias of individual studies. Studies were categorised as being at low, high, or unclear risk of bias according to the following criteria:

- low risk of bias (plausible bias unlikely to seriously alter the results) if all domains were at low risk of bias;
- high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more domains were at high risk of bias; or
- unclear risk of bias (plausible bias that raises some doubt about the results) if one or more domains were at unclear risk of bias.

We also presented the 'Risk of bias' summary graphically.

Measures of treatment effect

Dichotomous outcomes such as treatment completion were compared by calculating risk ratios along with 95% confidence intervals. Continuous outcomes (e.g. Frankl behaviour scale) were reported as mean and standard deviations in each group.

In this review outcome measures were reported either using scales where a higher score is associated with desired behaviour, or scales where a higher score indicates greater anxiety (i.e. undesirable outcome). In order for outcomes to be comparable between studies, anxiety scores (as measured on the Venham scale) were transformed by subtracting the mean score per group from the maximum possible score of five (see *Cochrane Handbook for Systematic Reviews of Interventions* Section 9.2.3.2 (Higgins 2011)).

Unit of analysis issues

The participant was the unit of analysis. Cross-over trials were excluded because the level of baseline anxiety/behaviour in the second treatment phase is highly dependent on the success or otherwise of the first treatment period.

Dealing with missing data

Only available data were analysed. We attempted to contact the author(s) of all included studies, where feasible, for clarification, and missing data.

Assessment of heterogeneity

Heterogeneity in the results of the trials was assessed where appropriate by inspection of a graphical display of the results and by formal tests of heterogeneity (Higgins 2011).

Assessment of reporting biases

If sufficient number of studies were included in a meta-analysis, we would have assessed publication bias according to the recommendations on testing for funnel plot asymmetry (Egger 1997), as described in Section 10.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If asymmetry were identified, we would have examined possible causes.

Data synthesis

Where either dichotomous outcome variables or continuous outcome variables with means and standard deviations were available, these data were recorded.

- Completion of treatment (yes/no).
- Difference in behaviour between test and control groups.
- Difference in postoperative anxiety between test and control groups.
- Adverse events.

Because the trials included in this review presented complex data with a range of different interventions being compared and different outcome measures, we separated studies into three groups:

- those comparing active treatment with a placebo;
- those comparing different doses of the same agent (or different routes of administration of the same agent);
- those which compare different agents head to head.

Results of individual studies are presented in a narrative format and differences between interventions are reported as statistically significant if the trial reported $P < 0.05$. Data from these three groups were summarised in Additional Table 1; Table 2; and Table 3 respectively. There were few opportunities to combine data from similar trials for meta-analysis, but where this was possible the data are presented in forest plots in Analyses 1 to 5 in the Data and analyses section. Data from trials evaluating active interventions compared to placebo, or the following four commonly used agents: chloral hydrate, ketamine, midazolam or nitrous oxide were presented. It was not possible nor did we attempt to combine these data by meta-analysis. However, we decided that presenting data within forest plots would help the reader to understand the data. The following rules were used when compiling this information.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

- Where data were only presented in their raw format this was used to calculate the appropriate mean and standard deviations.
- Data were treated as continuous even though Houpt (and other scales) were commonly used as outcome measure (ranked scores).
- Houpt was taken as the standard when ranking behaviour i.e. higher values equal better behaviour. Where scales ran in the reverse order, values were transformed so that higher values equalled better behaviour e.g. anxiety scores as measured on the Venham scale have been transformed by subtracting the mean score per group from the maximum possible score (see Higgins 2011 Section 9.2.3.2).
- Where dosage studies were analysed, the lowest dosage was compared to the highest dosage. Results from the lowest dosage were listed first.

'Summary of findings' tables were produced for data from placebo studies only as in the other groups the large number of different combinations tested made this type of summary difficult to understand.

Subgroup analysis and investigation of heterogeneity

We proposed conducting subgroup analyses for the following groups provided sufficient data existed.

- Age.

This would be subdivided into three groups, 0 to 5, 6 to 11, 12 to 17 (as recommended by the British National Formulary (BNF) when prescribing drugs to children).

- Dental procedure.

Sensitivity analysis

Sensitivity analysis was planned a priori to compare the study results for risk of bias. Both fixed and random-effects model meta-analyses were undertaken to assess the robustness of the results.

Summary of findings

The certainty of the evidence was assessed using GRADE methodology. We produced 'Summary of findings' tables for the main comparisons of the review and the following outcomes: mean Houpt/other behavioral score and good or better behaviour, and adverse events. We used GRADE methods (GRADE 2004), and the GRADEpro online tool for developing the 'Summary of findings' tables (www.guidelinedevelopment.org). We assessed the certainty of the body of evidence for each comparison and outcome by considering the overall risk of bias of the included studies, the directness of the evidence, the inconsistency of the results, the precision of the estimates, and the risk of publication bias. We categorised the certainty of each body of evidence as high, moderate, low, or very low.

RESULTS

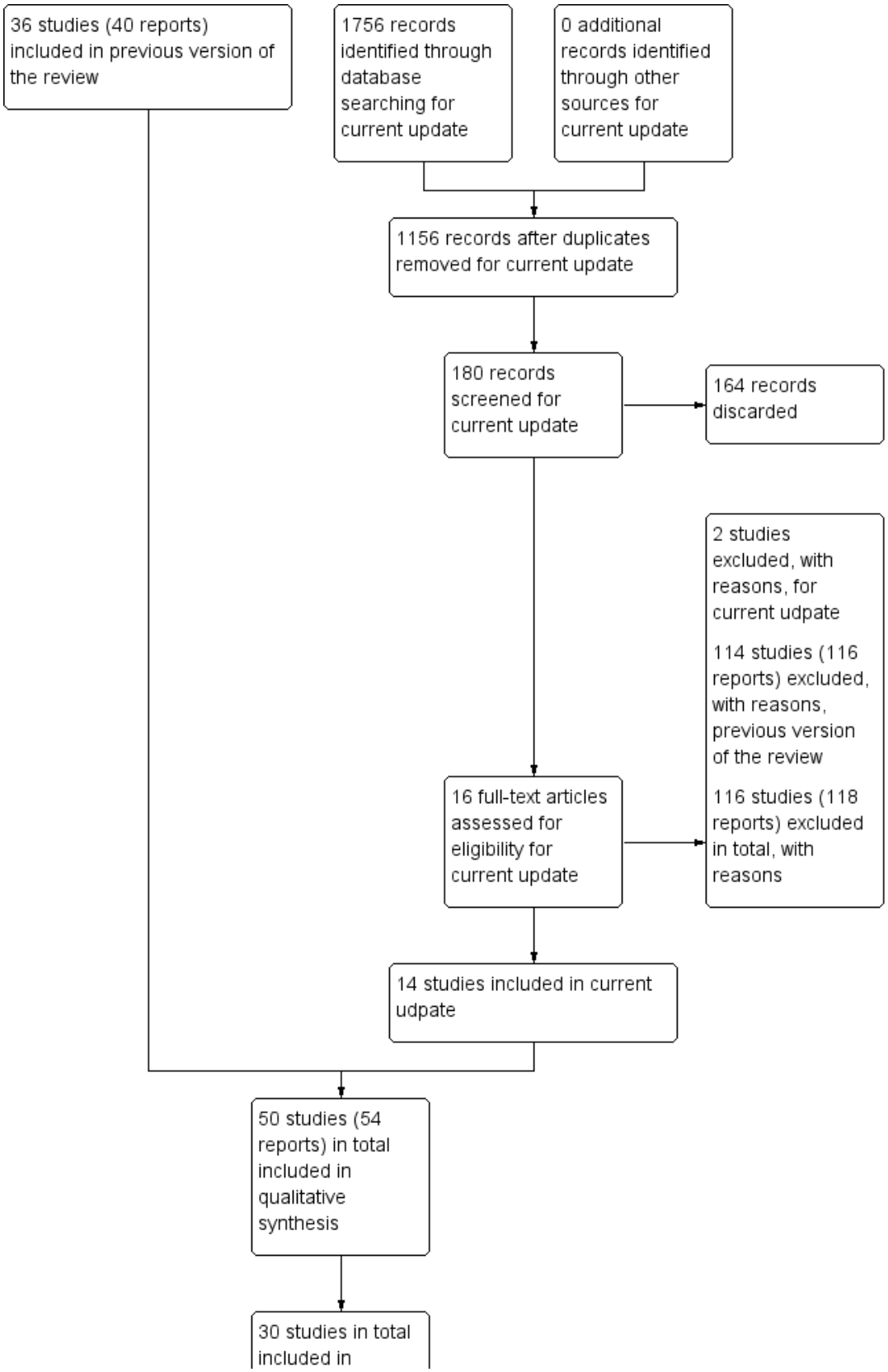
Description of studies

Results of the search

As this is the first version of this review to incorporate a PRISMA flow diagram (Figure 1), only information about searches for the current update are presented, the previous version of the review serves as one particular source of studies. One thousand one hundred and fifty-six records were identified in this update as possibly meeting the inclusion criteria. We screened the title and abstracts of 180 records and assessed 16 full-text articles for eligibility. Of these, two studies were excluded, with reasons, bringing the total number of excluded studies (including the 114 from the previous version of this review) to 116. Fourteen studies were found to fulfil the inclusion criteria of the review bringing the total number of included studies (including the 36 from the previous version of this review) to 50. Summary details are given in the Characteristics of included studies and Characteristics of excluded studies tables.

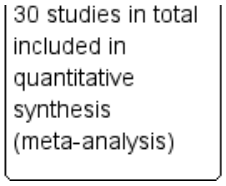
Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 1. Study flow diagram.



Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 1. (Continued)



Included studies

Characteristics of the studies

Dates of publication ranged from 1966 to 2017.

Studies were undertaken in 16 different countries with the greatest proportion of studies (n = 12, 24%) from the USA (see Characteristics of included studies table for details).

Six studies reported a sample size calculation (Baygin 2010; Gomes 2017; Isik 2008a; Moreira 2013; Shanmugaavel 2016a; Shanmugaavel 2016b). Averley et al conducted a pilot study (Averley 2004a) which refers to the collection of information to enable a sample size calculation to be done, and this pilot was then followed by a full trial (Averley 2004b). However, a sample size calculation was not reported in the published papers for either of these studies.

Characteristics of the participants

Age of participants included in the trials ranged from 1 year to 16 years. Mean age (approximation) for all studies was 4.8 years. The mean number of participants was 74.08 (standard deviation (SD) = 109) with a total of 3704 subjects randomised in the 50 included trials.

In the majority of studies (n = 39, 78%) subjects were reported as being unco-operative or anxious at the beginning of the study with the Frankl behavioural rating scale often used to measure baseline behaviour. Sixteen of the included studies reported the use of restrain such as papoose boards or pediwrap to support or restrain children during the dental procedure. Papoose boards were used in seven of the studies conducted in the USA (Alfonzo-Echeverri 1993; Bui 2002; Lam 2005; Lee-Kim 2004; Meyer 1990; Reeves 1996; Sams 1993a), and also in Brazil (Moreira 2013), China (Wan 2006), Mexico (Avalos-Arenas 1998) and Saudi Arabia (Al-Rakaf 2001), and the trials by Faytrouny 2007 and Özen 2012 used a pediwrap.

Characteristics of interventions

A wide variety of drugs (n = 34) either singly or in combination were used (Additional Table 4) and delivered orally, intranasally, intravenously, rectally, intramuscularly, submucosally, transmucosally or by inhalation depending on the type of drug and experimental aims. Inhalation sedation required a bulky machine and scavenging system. Intranasal sedation was administered by a metered-dose atomizer. Rectal sedation was usually given with a rectal applicator applied to a syringe inserted 3 to 4 centimetres into the rectum and the buttocks opposed tightly for 1 minute. In some studies, enemas were given to parents to apply 1 hour before each appointment to avoid variations in rectal absorption.

In 14 of the studies (28%) all participants were administered supplemental nitrous oxide/oxygen (Alfonzo-Echeverri 1993; Baygin 2010; Bui 2002; Faytrouny 2007; Isik 2008a; Isik 2008b; Lam 2005; Lee-Kim 2004; Meyer 1990; Moody 1986; Moore 1984; Özen 2012; Park 2006; Sams 1993a). The proportion of studies looking at either comparison with a placebo, comparison of the same drug with different dosages, or comparison of different drugs are summarised in Additional Table 1, Table 2, and Table 3. Some of the studies appear in more than one group as they included a combination of these types.

Dental treatment was poorly described on the whole, all subjects appeared to have some sort of restoration under rubber dam or extraction with local anaesthetic, but little information was given on type of restoration, number of teeth involved, type of local anaesthetic or if any attempt was made to ensure similar treatment was provided in control and experimental groups.

In the following section summary data are presented first, followed by a more detailed breakdown into three classifications. This is intended to help the reader in meaningful interpretation of the data. The three classifications are as follows.

1. Studies where test drug(s) were compared to a placebo.
2. Studies where differing dosages of the same drug(s) were compared.
3. Studies comparing different drugs, or combinations of drugs.

Within each of the three classifications, studies have been grouped where possible by the chief agent used (e.g. chloral hydrate, nitrous oxide, etc.). This was difficult when collating data for studies comparing different drugs or combinations of drugs, therefore some of the grouping decisions made for this table may appear arbitrary. Nevertheless we feel that this grouping helps the reader to understand these data. Drug groupings are in alphabetical order. Where a study compares different drugs with each other and also with a placebo, it has been filed in the placebo section under a different heading for each drug. It has also been filed in the drug comparison section. Where different routes of administration of the same drug have been compared, this has been filed in the dosage section.

Characteristics of outcome measures

Of the outcome measures proposed for this review (completion of treatment, difference in behaviour, difference in postoperative anxiety, and adverse events), meaningful data could only be extracted on behaviour. Postoperative anxiety was rarely mentioned and in most of the studies almost all the participants completed treatment. Adverse events were recorded but this was not done in a uniform manner between studies.

Outcome variables reported in the studies were predominantly ordinal (e.g. five-point scale for increasing movement) or dichotomous in nature (e.g. success/failure). Methods used for statistical analysis in the trials included both non-parametric (Chi^2

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

test, Wilcoxon matched pairs, Kruskal-Wallis, Mann-Whitney U test, Fishers Exact test, non-parametric two-factor ANOVA, McNemar test, sign test) and parametric tests (t-test, ANOVA, Tukey's range test, Friedman two-way analysis, method of least squares).

Measures of behaviour or level of sedation scales were commonly used (Houpt or modified versions of Houpt used most frequently (n = 19, 40%). Nineteen different types of measurement scales for behaviour or sedation were used and these are summarised in Additional Table 5 and Table 6.

1. Placebo-controlled studies

There were 12 placebo studies included which investigated oral chloral hydrate (Moore 1984), intranasal dexmedetomidine (Malhotra 2016), oral diazepam (Tyagi 2012), melatonin (Isik 2008a), intramuscular meperidine (McKee 1990), oral midazolam (Gallardo 1994; Isik 2008a; Kapur 2004; Moreira 2013; Mortazavi 2009; Tyagi 2012; Wan 2006), intravenous midazolam (Tyagi 2012), midazolam/ketamine (Malhotra 2016; Moreira 2013), and nitrous oxide (Nathan 1988; Veerkamp 1993) (Additional Table 1).

Where the general medical status of the children was reported they were usually healthy or had mild systemic disease (American Society of Anesthesiologists (ASA) physical status classification system: ASA I and ASA II). Six papers did not report on the gender balance, seven did not report the weight of the children.

Times for withholding food prior to the sedation (NPO - nil per os: nothing by mouth) were given in four papers (Isik 2008a; Kapur 2004; Mortazavi 2009; Wan 2006). Monitoring of the children during the sedation included blood pressure, heart rate, oxygen saturation, body temperature, and respiratory rate. There was no specified involvement with an anaesthetist during sedation though in some studies patients were assessed by an anaesthetist before treatment.

Papoose board or pediwrap was used in one study (Wan 2006). Nitrous oxide was used in conjunction with the main sedative agents under test in two studies (Isik 2008a; Moore 1984). A range of outcome variables were used and these are summarised in Additional Table 1. One study reported recovery times (Nathan 1988) and three gave the total treatment time (Isik 2008a; Kapur 2004; Veerkamp 1993). Three studies used video cameras to record sedation during dental treatment (Nathan 1988; Veerkamp 1993; Wan 2006).

Data from the different drug types are listed below.

Oral midazolam

Seven trials compared oral midazolam with placebo (Gallardo 1994; Isik 2008a; Kapur 2004; Moreira 2013 Mortazavi 2009; Tyagi 2012; Wan 2006).

Gallardo 1994 randomised children aged 4 to 10 years to either 7.5 mg of midazolam or placebo (the range of weight of the children included in the trial is not reported but the stated average weight of 21.65 kg would result in a dose equivalent to 0.35 mg/kg). The actual dose in mg/kg would be expected to vary considerably. The authors used means and standard errors to summarise ranked data in each group with only three categories which was thought to be inappropriate. However, subsequent analysis using Wilcoxon's rank test was appropriate. Midazolam was reported to be significantly better than placebo.

Isik 2008a used a dose of 0.75 mg/kg and noted vomiting and hiccupping in the midazolam group.

Kapur 2004 described midazolam delivery in their study as being a mixture of oral and transmucosal with a dose of 0.5 mg/kg.

Moreira 2013 used the highest dose in this group of trials, of 1 mg/kg. Co-operation as recorded by the sum of the Ohio State University Behavior Rating Scale (OSUBRS) score at each measurement point was not significantly different than the placebo (P = 0.55).

Mortazavi 2009 used the lowest dose of the five trials in this group (0.25 mg/kg).

Tyagi 2012 used a dose of 0.5 mg/kg.

Wan 2006 used a dose of 0.5 mg/kg and noted amnesia associated with midazolam use.

Nitrous oxide/oxygen

Two studies (Nathan 1988; Veerkamp 1993) evaluated nitrous oxide/oxygen sedation compared to placebo and both were assessed as being at high risk of bias. In Nathan 1988 children received 20% to 50% nitrous oxide in oxygen and in Veerkamp 1993 participants received up to 40% nitrous oxide in oxygen. No adverse effects were mentioned.

Chloral hydrate

In Moore 1984 children were randomly allocated to either 20 mg/kg, 40 mg/kg or 60 mg/kg of chloral hydrate or a placebo and then all children received up to 40% nitrous oxide in oxygen as well. This trial was assessed as being at high risk of bias.

Meperidine

Intramuscular meperidine (0.55 mg/kg to 2.2 mg/kg - calculated from mg/lb given in text) was evaluated in a single study (McKee 1990) which was assessed at unclear risk of bias.

Intravenous midazolam

0.06 mg/kg body weight was used in one study, Tyagi 2012, assessed as at high risk of bias.

Oral diazepam

0.5 mg/kg body weight was used in one study, Tyagi 2012, assessed as at high risk of bias.

Midazolam/ketamine

Moreira 2013 used a dose of 0.5 mg/kg midazolam with 3 mg/kg ketamine.

2. Dose comparison studies

There were 10 studies which compared different dosages or routes of admission of sedative agents: one used hydroxyzine (Faytrouny 2007), the remaining nine varied dosage or method of midazolam with six primarily using intranasal midazolam (Al-Rakaf 2001; Lam 2005; Lee-Kim 2004; Shashikiran 2006; Shanmugaavel 2016a;

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Shanmugaavel 2016b) and three oral midazolam (Aydintug 2004; Isik 2008b; Somri 2012) (Additional Table 2).

All children were assessed as healthy or having mild systemic disease (ASA I and ASA II). Eight studies described the gender balance. Seven recorded the mean weight. Two studies measured baseline anxiety and compared this to anxiety at the end (Shanmugaavel 2016a; Shanmugaavel 2016b).

All studies described NPO times which ranged from either a light breakfast (but no milk) up to nothing from midnight. Monitoring was reported in all studies, using a precordial stethoscope, blood pressure unit and electrocardiograph as well as clinical observations. Five studies mentioned the involvement of anaesthetists (Al-Rakaf 2001; Lam 2005; Shanmugaavel 2016a; Shanmugaavel 2016b; Somri 2012).

Use of papoose board (or equivalent) was mentioned in four studies (Al-Rakaf 2001; Lam 2005; Lee-Kim 2004; Shanmugaavel 2016a), one study mentioned manual restraint (Somri 2012). In four studies nitrous oxide was used in conjunction with the main sedative agent (Faytrouny 2007; Isik 2008b; Lam 2005; Lee-Kim 2004). A range of outcome variables were used and these are summarised in Additional Table 2. Three studies recorded recovery times (Al-Rakaf 2001; Isik 2008b; Shashikiran 2006) and two gave the total dental treatment time (Shashikiran 2006; Somri 2012). Four studies used video cameras to record dental treatment during sedation (Lam 2005; Lee-Kim 2004; Shanmugaavel 2016a; Shanmugaavel 2016b).

In addition to looking at behaviour ratings and sedation, Al-Rakaf 2001 also assessed the effects of fasting on behaviour.

Data from the different drug types are listed below.

Hydroxyzine

One study (Faytrouny 2007) looked at the effect of a dose of hydroxyzine given 24 hours preoperatively (20 mg) at home followed by a second dose at the appointment (3.7 mg/kg) versus hydroxyzine given at the appointment only (3.7 mg/kg). The study was at high risk of bias. All children also received 50% nitrous oxide. Faytrouny 2007 reported the dose as 20 mg/kg hydroxyzine in the main text but 20 mg in the abstract.

Midazolam (intranasal)

Six studies looked primarily at intranasal midazolam (Al-Rakaf 2001; Lam 2005; Lee-Kim 2004; Shanmugaavel 2016a; Shanmugaavel 2016b; Shashikiran 2006). The participants in the Lam 2005 and Lee-Kim 2004 trials all received nitrous oxide inhalation as well at 50% or 45% respectively. All studies were at high risk of bias.

Al-Rakaf 2001 compared 0.5 mg intranasal midazolam to either 0.3 mg/kg or 0.4 mg/kg.

Lee-Kim 2004 compared intranasal midazolam (0.3 mg/kg) to oral midazolam (0.7 mg/kg).

Lam 2005 and Shashikiran 2006 compared 0.2 mg/kg intranasal midazolam versus 0.2 mg/kg intramuscular midazolam. Lam 2005 used the midazolam as a premedication for an unspecified intravenous sedative.

Shanmugaavel 2016a and Shanmugaavel 2016b compared 0.2 mg/kg intranasal midazolam to 0.2 mg/kg sublingual midazolam.

Midazolam (oral)

Three studies (Aydintug 2004; Isik 2008b; Somri 2012) evaluated oral midazolam, with participants in Isik 2008b also receiving nitrous oxide inhalation. Aydintug 2004 was assessed as being at high risk of bias and in Isik 2008b; Somri 2012 risk of bias was unclear.

Aydintug 2004 compared 0.5 mg/kg oral midazolam versus 0.35 mg/kg rectal midazolam.

Isik 2008b randomised children to oral doses of either 0.2 mg/kg, 0.5 mg/kg, 0.75 mg/kg or 1 mg/kg after fasting for 3 to 5 hours. All children also received 40% nitrous oxide in oxygen (Additional Table 2).

Somri 2012 compared oral doses of 0.5 mg/kg, 0.75 mg/kg and 1 mg/kg.

3. Head-to-head drug comparison studies

There were 31 studies comparing different drugs and delivery methods which are summarised in Additional Table 3.

All studies reported children's medical status at baseline. In 14 studies gender was not specified and in 22 papers the mean weight of participants was not described. The age of children in these studies ranged from 1 year to 14 years of age.

NPO was not mentioned in 12 of the studies (Abrams 1993; Averley 2004a; Averley 2004b; Bhatnagar 2012; Koirala 2006; Lahoud 2002; Özen 2012; Roelofse 1996a; Roelofse 1996b; Singh 2002; Tyagi 2012; Torres-Perez 2007). Of those studies reporting NPO, times ranged from midnight to 2 hours before sedation or appointment. Monitoring was well reported in most of the studies and included verbal contact, pulse oximeter, precordial stethoscope, automatic blood pressure, capnograph, nasal respiration monitor, end-tidal carbon dioxide tension. Fourteen studies mentioned the involvement of anaesthetists (Abrams 1993; Alfonzo-Echeverri 1993; Averley 2004a; Averley 2004b; Bhatnagar 2012; Eshghi 2016; Gomes 2017; Kaviani 2015; Lahoud 2002; Malhotra 2016; Moreira 2013; Singh 2014; Surendar 2014; Tyagi 2012).

The use of a papoose board was mentioned in nine of the studies (Alfonzo-Echeverri 1993; Avalos-Arenas 1998; Bui 2002; Meyer 1990; Moreira 2013; Özen 2012; Park 2006; Reeves 1996; Sams 1993a), and in seven nitrous oxide/oxygen inhalation was used in conjunction with sedation (Alfonzo-Echeverri 1993; Baygin 2010; Bui 2002; Meyer 1990; Moody 1986; Özen 2012; Sams 1993a). A range of outcome variables were used and these are summarised in Additional Table 3. Two papers reported dentist and parents preferences after sedation (Averley 2004a; Averley 2004b). Recovery times were given in 13 papers (Abrams 1993; Alfonzo-Echeverri 1993; Averley 2004a; Averley 2004b; Eshghi 2016; Kaviani 2015; Lahoud 2002; Meyer 1990; Roelofse 1996a; Roelofse 1996b; Singh 2002; Singh 2014; Surendar 2014), and nine gave the total dental treatment time (Alfonzo-Echeverri 1993; Avalos-Arenas 1998; Baygin 2010; Bui 2002; Lahoud 2002; Reeves 1996; Roelofse 1996a; Roelofse 1998; Torres-Perez 2007). Four studies used video cameras to record sedation during dental treatment (Gomes 2017; Meyer 1990; Park 2006; Surendar 2014).

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Data from drug types is summarised below.

Chloral hydrate/hydroxyzine

Six studies investigated chloral hydrate/hydroxyzine and compared it to other agents (Avalos-Arenas 1998; Meyer 1990; Moody 1986; Park 2006; Reeves 1996; Torres-Perez 2007). In Meyer 1990; Moody 1986 and Park 2006 all participants also received nitrous oxide inhalation. All studies in this group were assessed at high risk of bias.

Avalos-Arenas 1998 compared chloral hydrate (70 mg/kg)/hydroxyzine (2 mg/kg) with chloral hydrate (70 mg/kg) alone.

Meyer 1990 compared oral chloral hydrate (40 mg/kg) plus hydroxyzine (25 mg) with oral triazolam (0.02 mg/kg) in children who also received inhalation of 40% nitrous oxide.

In the trial by Moody 1986 rectal chloral hydrate (50 mg/kg) was compared with either oral chloral hydrate (50 mg/kg) or oral chloral hydrate (30 mg/kg) plus hydroxyzine (25 mg) in children who all received 30% to 50% inhalational nitrous oxide as well.

Park 2006 compared chloral hydrate (60 mg/kg) plus hydroxyzine (1 mg/kg) to chloral hydrate (60 mg/kg oral) plus hydroxyzine (1 mg/kg oral) plus midazolam (0.1 mg/kg submucosal) in children who all received 50% inhalational nitrous oxide as well. Outcome measures were Houpt and whether or not restraint was required.

Chloral hydrate (50 mg/kg) plus hydroxyzine (25 mg) was compared to oral midazolam (0.5 mg/kg) plus acetaminophen (10 mg/kg) (M/A) in Reeves 1996.

In a trial by Torres-Perez 2007 children were randomised to sedation with chloral hydrate (50 mg/kg)/hydroxyzine (1.5 mg/kg) or midazolam (0.5 mg/kg)/hydroxyzine (1.5 mg/kg) or hydroxyzine (2 mg/kg plus further 1 mg/kg).

Chloral hydrate/promethazine

Sams 1993a compared chloral hydrate (50 mg/kg)/promethazine (1 mg/kg) with meperidine (1 mg/kg)/promethazine (1 mg/kg), in children planned to receive inhalational nitrous oxide as well.

Dexmedetomidine

Surendar 2014 randomised patients into four groups for intranasal intervention: dexmedetomidine (1 µg/ kg), dexmedetomidine (1.5 µg/kg), midazolam (0.2 mg/kg), and ketamine (5 mg/kg).

Ketamine

Eight studies evaluated ketamine (Abrams 1993; Alfonzo-Echeverri 1993; Bui 2002; Rai 2007; Roelofse 1996a; Roelofse 1996b; Roelofse 1998; Singh 2014). In two of these trials (Alfonzo-Echeverri 1993; Bui 2002) nitrous oxide inhalation was also used at a concentration of 30% to 50% or 35% to 50% respectively. One of the eight trials in this group (Singh 2014) was assessed at low risk of bias, one (Bui 2002) at unclear risk of bias, and the remainder at high risk of bias.

Abrams 1993 compared 3 mg/kg ketamine with either 0.4 mg/kg midazolam or 1.0 µg/kg or 1.5 µg/kg sufentanil all administered intranasally.

Anaesthetists in the trial by Rai 2007 administered a premedication of 0.5 mg/kg midazolam to all the children followed by a bolus dose plus infusion of either midazolam (0.1 mg/kg followed by 0.004 mg/kg/min), propofol (1 mg/kg followed by 0.06 mg/kg/min) or ketamine (0.5 mg/kg followed by 0.01 mg/kg/min).

Roelofse 1996a compared rectal ketamine (5 mg/kg)/midazolam (0.35 mg/kg) to rectal midazolam (1 mg/kg) alone.

In a second study (Roelofse 1996b) children were randomised to either an oral dose of 12.5 mg/kg ketamine or 0.5 ml/kg of standard oral premedication (comprising trimeprazine (6 mg/ml)/physeptone (methadone) (0.4 mg/ml)) to which was added droperidol (0.1 mg/ml).

The third trial by this group (Roelofse 1998) compared oral ketamine (5 mg/kg) plus midazolam (0.35 mg/kg) with a combination of oral trimeprazine (3 mg/kg) and methadone (0.2 mg/kg) administered 30 minutes prior to dental treatment.

Two trials evaluated ketamine in combination with inhalation of nitrous oxide (Alfonzo-Echeverri 1993; Bui 2002).

Alfonzo-Echeverri 1993 compared oral ketamine (6 mg/kg) with oral meperidine (2 mg/kg) plus promethazine (0.5 mg/kg) in children who had NPO for 6 hours. Nitrous oxide (30% to 50%) was administered to all the children prior to the local anaesthetic.

In the trial by Bui 2002, oral ketamine (10 mg/kg) was compared with oral ketamine (10 mg/kg) plus promethazine (1.1 mg/kg) in a trial where all the participants also received 50% nitrous oxide inhalation.

Singh 2014 in their trial compared oral ketamine 8 mg/kg^{-1} to oral dexmedetomidine in doses of 3 $\mu g/kg^{-1}$, 4 $\mu g/kg^{-1}$ and 5 $\mu g/kg^{-1}$.

Midazolam (oral)

Eight studies evaluated oral midazolam compared to other sedatives (Baygin 2010; Bhatnagar 2012; Koirala 2006; Malhotra 2016; Moreira 2013; Özen 2012; Singh 2002; Tyagi 2012). In two of these trials (Baygin 2010; Özen 2012) participants also received nitrous oxide by inhalation. The studies were assessed as being at high risk of bias.

Baygin 2010 randomised participants to either oral administration of hydroxyzine (1 mg/kg), oral midazolam (0.7 mg/kg), oral administration of ketamine (3 mg/kg) plus midazolam (0.25 mg/kg) or no oral premedication (nitrous oxide alone). All patients in the trial received 40% nitrous oxide.

Bhatnagar 2012 compared oral administration of midazolam 0.5 mg/kg, tramadol 2 mg/kg, triclofos 70 mg/kg and zolpidem 0.4 mg/kg.

Koirala 2006 randomised participants to six different oral interventions: midazolam (0.5 mg/kg), ketamine (5 mg/kg), zolpidem (0.4 mg/kg), midazolam (0.4mg/kg) plus ketamine (3 mg/kg), midazolam (0.5 mg/kg) plus tramadol (2 mg/kg) and zolpidem (0.4 mg/kg) plus tramadol (2 mg/kg).

Malhotra 2016 compared oral midazolam (0.5 mg/kg) plus oral ketamine (5 mg/kg) plus intranasal placebo, with intranasal dexmedetomidine (1 µ/kg) plus oral placebo and a third group of oral and intranasal placebo.

Moreira 2013 randomised participants into two oral intervention groups: midazolam (0.5 mg/kg) plus ketamine (3 mg/kg),

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

midazolam 1 mg/kg and compared it to a no sedation group. The study used protective stabilisation.

Özen 2012 compared four interventions: 0.20 mg/kg midazolam (40 mg/ml) intranasally plus inhalation sedation 50%–50% nitrous oxide/oxygen, 0.75 mg/kg midazolam (15 mg/ 3 ml) orally plus inhalation sedation 50%–50% nitrous oxide/oxygen, 0.50 mg/kg midazolam (15 mg/3 ml) orally plus inhalation sedation 50%–50% nitrous oxide/oxygen, and inhalation sedation 50%–50% nitrous oxide/oxygen. Restraint was used. A modified scale was used to classify behaviour/response to treatment/sedation.

Singh 2002 compared midazolam (0.5 mg/kg) to either triclofos (70 mg/kg) or promethazine (1.3 mg/kg), all administered in fruit juice prior to treatment. Sedation scores were reported on an eight-point scale in which a high score indicated poor sedation.

Tyagi 2012 randomised participants into four groups: oral midazolam 0.5 mg/kg, oral diazepam 0.5 mg/kg, intravenous midazolam 0.06 mg/kg, and placebo.

Midazolam (intravenous)

Two studies, both at high risk of bias, compared intravenous midazolam to other sedatives (Eshghi 2016; Kaviani 2015).

Eshghi 2016 randomised participants into two groups for intravenous sedation administration: remifentanil (0.1 µg/kg/min) plus midazolam (0.01 mg/kg) plus propofol (0.5 mg/kg), and ketamine (0.5 mg/kg) plus midazolam (0.1 mg/kg) plus propofol (0.5 mg/kg).

Kaviani 2015 compared intravenous midazolam (0.05 mg/kg) plus ketamine (0.5 mg/kg) with midazolam (0.05 mg/kg) plus fentanyl (0.5 µg/kg). Additional midazolam (0.25 mg) was administered to both groups if needed.

Midazolam (rectal)

Rectal sedation was evaluated by Jensen 1999 who compared diazepam (0.7 mg/kg) with midazolam (0.3 mg/kg).

Sevoflurane

Three trials evaluated sevoflurane (Averley 2004a; Averley 2004b; Lahoud 2002), but used different outcome measures. Two were assessed at high and one at unclear (Lahoud 2002) risk of bias.

Lahoud 2002 compared sevoflurane (0.1% to 0.3%)/nitrous oxide (40%) with nitrous oxide (40%) alone.

Averley 2004a was a pilot study which randomised children to either intravenous midazolam (0.5 mg/min) titrated to induce adequate sedation, or 40% nitrous oxide inhalation plus intravenous midazolam (0.5 mg/min) titrated to induce adequate sedation, or inhalation of 0.3% sevoflurane plus 40% nitrous oxide plus intravenous midazolam (0.5 mg/min) titrated to induce adequate sedation.

In the subsequent trial (Averley 2004b) the same interventions were used.

Excluded studies

Reasons for trial exclusion are summarised in Characteristics of excluded studies table. Reasons included description of the study as using deep sedation, the sedative agent being used as a pre-medication prior to an anaesthetic, no comparative groups or evaluating outcomes not relevant to this review. We continued to exclude cross-over trials.

Risk of bias in included studies

Allocation

Eleven studies were assessed as low risk of bias with regard to method of sequence generation (Averley 2004a; Averley 2004b; Eshghi 2016; Gomes 2017; Malhotra 2016; Moreira 2013; Shanmugaavel 2016a; Shanmugaavel 2016b; Singh 2014; Somri 2012; Surendar 2014). Barring four of these (Shanmugaavel 2016a; Shanmugaavel 2016b; Somri 2012; Surendar 2014) all of the others reported adequate allocation concealment. Two other studies were reported as having adequate allocation concealment, but the method of sequence generation in these studies was not described (Jensen 1999; Lahoud 2002). Bui 2002 used an independent person to select patients, make the random allocation and administer the intervention, this was assessed as unclear risk. Eshghi 2016 used an anaesthetist to divide the sample into two groups based on odd and even codes, this was considered to be at unclear risk of bias for allocation concealment. Lee-Kim 2004, the principal investigator conducted the subject selection and random allocation, this was assessed to be at high risk of selection bias. In the remaining trials neither the method of sequence generation, nor any concealment of allocation was described, and these studies were assessed as being at unclear risk of selection bias.

Blinding

For avoiding performance and detection bias the ideal situation is when the operator, outcome assessor and patient are all blinded to the intervention. However, we acknowledge that in trials of sedative agents in children, blinding of dental operators is difficult in part due to the nature of the equipment and drugs involved, and the need to ensure patient safety during the procedure. Blinding of children participating in these studies is usually possible, especially with young children. Some of the trials incorporated video recordings and one of more outcome assessors, blinded to the allocated treatment, evaluated the outcomes from these recordings.

In many trials the outcome was assessed by the operative dentist carrying out the procedure. In some trials the sedatives were administered by a nurse or researcher and the operator, who was blinded to the intervention, undertook the assessment. In other trials the procedures were videotaped and outcomes were assessed from the recordings, but bias is possible if an unblinded operator interacts with the patients in different ways depending on expectations about the effect of a specific sedative.

Where studies were described as double-blinded, this was interpreted to mean participant and outcome assessor were blinded to the allocated treatment. Where the participant and outcome assessor at least were blinded to the treatment, the risk of performance and detection biases were deemed to be low. The outcome assessor and operator could be separate individuals or the same person.

Twenty-three studies were assessed as being at low risk of performance and detection biases (Alfonzo-Echeverri 1993; Al-Rakaf 2001; Avalos-Arenas 1998; Averley 2004a; Averley 2004b;

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Bui 2002; Gallardo 1994; Gomes 2017; Isik 2008a; Jensen 1999; Kapur 2004; Koirala 2006; McKee 1990; Moore 1984; Mortazavi 2009; Reeves 1996; Roelofse 1996a; Roelofse 1996b; Sams 1993; Singh 2002; Singh 2014; Surendar 2014; Wan 2006).

In eight trials only the assessor was blinded to the intervention (Lam 2005; Lee-Kim 2004; Meyer 1990; Nathan 1988; Park 2006; Shanmugaavel 2016b; Torres-Perez 2007; Veerkamp 1993).

In five trials the operator and the outcome assessor was blinded (Baygin 2010; Kaviani 2015; Malhotra 2016; Roelofse 1998; Shashikiran 2006).

In three studies only the operator was blinded (Faytrouny 2007; Shanmugaavel 2016a; Somri 2012).

In four trials there was no blinding (Aydintug 2004; Moody 1986; Moreira 2013; Tyagi 2012). The mother of the patient was aware of the treatment in Moreira 2013. In Tyagi 2012 the intravenous midazolam group was not blinded.

There was no placebo used in Baygin 2010, therefore participants would have been aware that this was the control group.

Incomplete outcome data

The number of trial participants included in the outcome evaluations was poorly reported in many trials, and it was sometimes difficult to determine whether or not dropouts had occurred. Twenty-one studies were at low risk of attrition bias. In three studies the risk of attrition bias was assessed as unclear (Bhatnagar 2012; Malhotra 2016; Nathan 1988) and in the remainder, where incomplete treatment/sedation failure was not recorded or reported on at all, trials were assessed as being at high risk of attrition bias.

Selective reporting

All but four of the included trials reported the outcomes described in the methods sections of the reports, and were deemed to be at low risk of reporting bias. Averley 2004a and Averley 2004b reported the primary outcome, treatment completion, on all the trial participants who received the allocated intervention, but reported secondary outcomes only on those who were deemed to have undergone successful sedation (69% and 78% respectively) of those who received sedation, and 69% and 65% of those randomised. Bhatnagar 2012 did not report on the recovery times in the results.

Other potential sources of bias

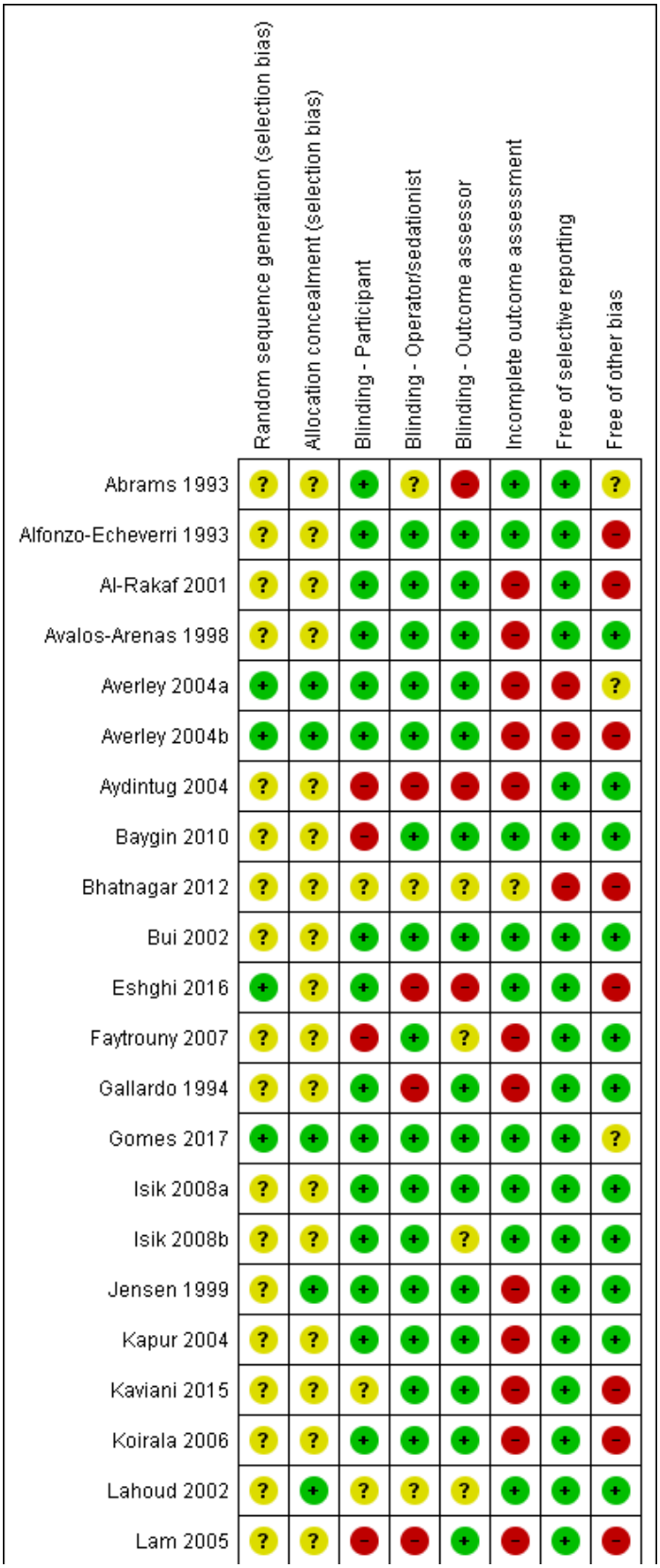
There were no baseline demographic data reported on the participants in nine trials (Alfonzo-Echeverri 1993; Al-Rakaf 2001; Bhatnagar 2012; Kaviani 2015; Koirala 2006; Lam 2005; Nathan 1988; Shanmugaavel 2016a; Tyagi 2012), and little or unclear baseline demographic data in a further seven trials (Averley 2004a; Malhotra 2016; Mortazavi 2009; Özen 2012; Rai 2007; Singh 2002; Veerkamp 1993). There were inconsistencies in two trials (Eshghi 2016; Gomes 2017). In the trial by Averley 2004b baseline demographic data were only provided for 65% of those randomised. The randomisation code in Abrams 1993 was broken early due to significant desaturations in the study and there was a subsequent change to the protocol reducing the high dose sufentanil 1.5 µg/kg to 1.0 µg/kg. In Moreira 2013 it was not clear if the no sedation group had a placebo intervention or no intervention at all. The remainder of studies was assessed as at low risk of other bias.

Overall risk of bias

See Figure 2. Of the 50 trials included in this review, only one was assessed as being at low risk of bias overall (Singh 2014). Nine trials (18%) were assessed as being at unclear risk of bias (Bui 2002; Gomes 2017; Isik 2008a; Isik 2008b; Lahoud 2002; McKee 1990; Mortazavi 2009; Somri 2012; Wan 2006) and in the remaining 40 trials (81%) at least one domain was assessed as being at high risk of bias.

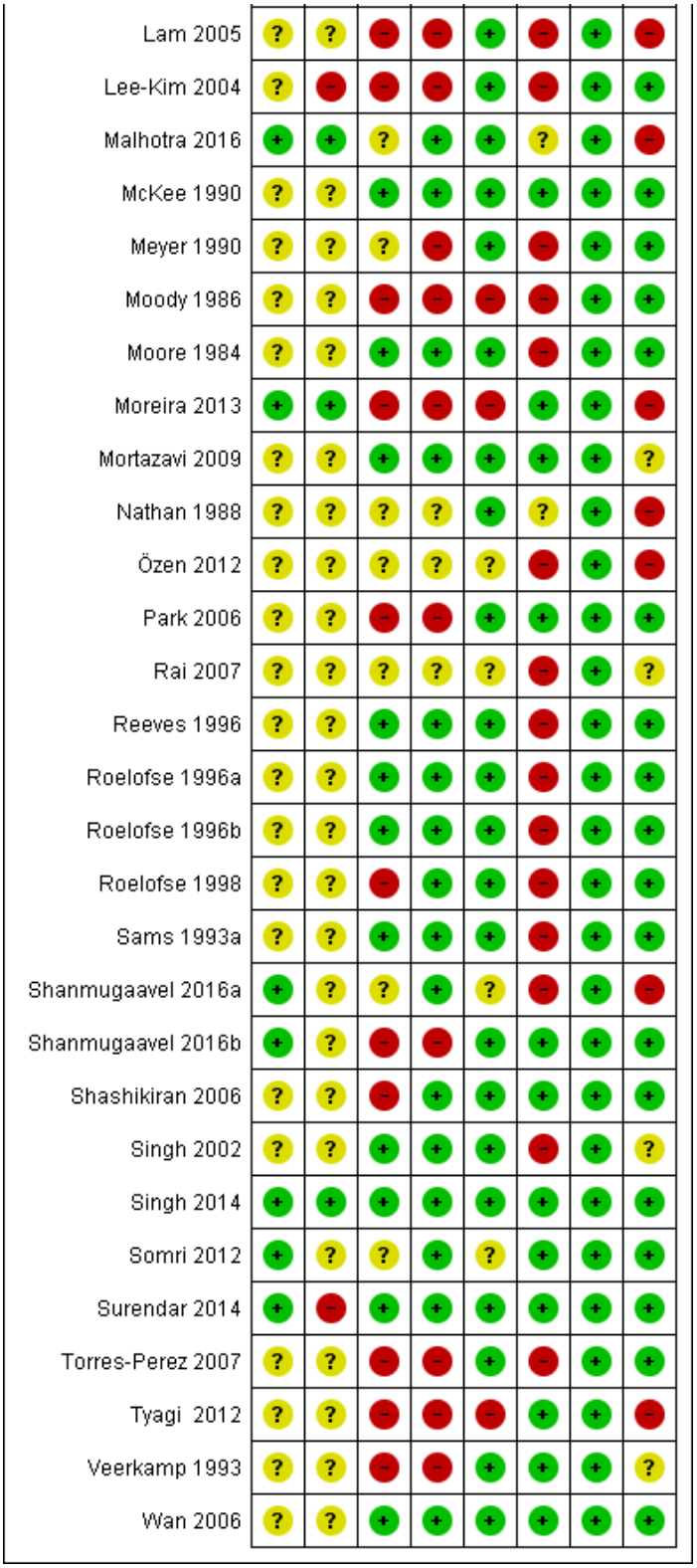
Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 2. (Continued)



In common with many other Cochrane Reviews the overall quality of studies was found to be disappointing. Poor reporting was an obvious problem with these studies and this may have masked other defects in design or conduct of these trials.

Effects of interventions

See: **Summary of findings for the main comparison** Sedative compared to placebo for children needing dental care; **Summary of findings 2** Sedative compared with different dosage of the same

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

sedative for children needing dental care; **Summary of findings 3** Sedative compared with a different sedative for children needing dental care

1. Placebo-controlled studies

See Additional Table 1 We included 12 placebo studies in the review.

Oral midazolam

Where possible studies were included in the meta-analysis using overall behaviour as measured by Houpt (or a scale in the same direction) as an outcome measure. Gallardo 1994 and Isik 2008a did not record Houpt but did use a similar scale (three-point as opposed to six-point). Raw data were supplied by Isik 2008a and Tyagi 2012 so these were used to calculate mean and standard deviation (satisfactory scored as 3, unsatisfactory as 1 in Isik 2008a). Gallardo 1994 reported standard error so this was converted to standard deviation. Kapur 2004 used a reversed scale so these data were transformed. Wan 2006 appeared to have a reporting error whereby test and control results were transposed. Close examination of the paper shows that values for all measures of behaviour reported in Table 2 are the opposite as described in the text i.e. they suggest the intervention worsens behaviour whereas in the text it states that patient behaviour improved. The same is not true for the physiological measures (Table 2 again), subjects in the intervention group had a significantly lower heart rate. We were unable to contact the authors therefore we have decided this most likely represents an error in reporting and have therefore transposed values for the control and intervention groups. Moreira 2013 did not report overall behaviour, instead behaviour was recorded at discrete intervals throughout the visit. In addition, behaviour was recorded using OSUBRS as opposed to a scale like Houpt (or similar). OSUBRS runs in the reverse direction to Houpt. We therefore decided not to include this study in the meta-analysis.

The results can be seen in Analysis 1.1. A fixed-effect model and standardized mean difference (SMD) was used as the scales were not completely alike. Use of oral midazolam produced a significant improvement in behaviour in all of these trials (SMD 1.96, 95% confidence interval (CI) 1.59 to 2.33; P < 0.0001; 6 studies; 202 participants). The considerable heterogeneity (I^2 = 90%, P < 0.00001) in this estimate is likely due to the different tools used to measure the outcome in each trial and the range of doses of oral midazolam used from 0.25 mg/kg to 0.75 mg/kg (see Additional Table 1). We assessed the certainty of the evidence as moderate (according to GRADE recommendations). The risk of bias was high or unclear in most studies. The remaining measures were scored as low. We could not assess the risk of publication bias. Oral midazolam probably improves behaviour (moderate-certainty evidence).

Nitrous oxide/oxygen

Two trials (Nathan 1988; Veerkamp 1993) reported changes in favour of nitrous oxide in either behaviour or anxiety, but no data were available from the Nathan trial. Data from Veerkamp 1993 was added to the meta-analysis. In this study they reported anxiety on the Venham scale which is in the opposite direction to Houpt, so scores were transformed for forest plots (Analysis 1.1). No adverse effects were mentioned. We assessed the certainty of evidence as very low (according to GRADE recommendations) due to the risk of bias and imprecision. We are uncertain whether nitrous oxide/oxygen improves behaviour (very low-certainty evidence).

Chloral hydrate (CH)

There was no statistically significant increase in positive behaviour between placebo and any of the oral chloral hydrate groups, and all participants completed treatment regardless of group (Moore 1984). There was no statistically significant difference between placebo and the three active chloral hydrate groups combined for the outcome of positive behaviour during the operatory (Analysis 1.2), possibly due to a strong response to the placebo. However, after nitrous oxide/oxygen was administered, there were airway issues with four children (27%) in the 60 mg/kg chloral hydrate group not responding to obstruction. We are uncertain whether chloral hydrate improves behaviour as the certainty of the evidence has been assessed as very low due to the risk of bias, incomplete outcome assessment and imprecision. We could not assess the risk of publication bias.

Meperidine

Meperidine was statistically significantly more effective (P < 0.05) than placebo for the outcome of good or better behaviour (good, very good or excellent behaviour) (71% in meperidine groups compared to 13% in placebo) (Analysis 1.2.). However, two patients in the meperidine groups (13%) had unmanageable behaviour and treatment had to be aborted and rescheduled. Nausea and vomiting were more frequent in the meperidine groups (38% versus 7%) and rates showed a dose response (McKee 1990). Meperidine may improve behaviour (low-certainty evidence due to unclear risk of bias and imprecission).

Intravenous midazolam

Overall behaviour was significantly better in this group when compared to placebo (P = 0.01) (Analysis 1.1) (Tyagi 2012). However, we are uncertain whether intravenous midazolam improves behaviour as the certainty of the evidence has been assessed as very low due to high risk of bias and imprecision. We could not assess the risk of publication bias.

Oral diazepam

Overall behaviour was not significantly better in this group when compared to placebo (P = 0.18) (Analysis 1.1, Tyagi 2012). No adverse effects were reported. We are uncertain whether oral diazepam improves behaviour (very low-quality/certainty evidence).

Midazolam/ketamine

0.5 mg/kg midazolam with 3 mg/kg ketamine produced significantly better behaviour (as measured by the sum of the OSUBRS score at each measurement point) than the placebo and oral midazolam (P = 0.03) (Moreira 2013). Because of the way these data were presented, we were unable to include them in the meta-analysis.

2. Dose comparison studies

See Additional Table 2. Ten studies compared different dosages or routes of admission of sedative agents.

Hydroxyzine

Faytrouny 2007 reported no differences between groups at any of the time points measured. No adverse effects were reported.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Midazolam (intranasal)

Al-Rakaf 2001 found that behaviour improved in the group receiving 0.5 mg intranasal midazolam compared to either 0.3 mg/kg or 0.4 mg/kg (Analysis 4.1), but there was no statistically significant improvement in behaviour between 0.4 mg group and 0.3 mg group. The number of patients completing treatment increased also (79%, 96% and 100% in groups 1, 2 and 3 respectively - data from fasting children were used). Authors also reported that fasting made no difference to overall behaviour (P = 0.8286).

Lee-Kim 2004 found no differences between groups in mean Houpt behaviour score at any of the times measured - data not available (P = 0.749). As expected, mean time to onset of sedation was much shorter in the intranasal group, but mean duration of sedation (working time) was statistically significantly longer in the group who received oral midazolam (Additional Table 2).

Lam 2005 reported that there was improved behaviour at time of delivery of local anaesthetic and venepuncture in the intramuscular group, and good or excellent sedation was achieved in all of the intramuscular group compared to only 6/11 (54%) of the intranasal group (Analysis 4.1).

Shashikiran 2006 reported no difference with regard to behaviour between the intramuscular and intranasal groups, which both showed improvement from baseline. Induction of sedation, treatment and recovery however was faster in the intranasal group (Analysis 4.1). Despite receiving a light snack prior to treatment, none of the children vomited.

Shanmugaavel 2016a reported a decrease in the anxiety after 20 minutes of the sedatives administration in both groups. Although the intranasal group showed more statistically significant decrease in anxiety at various set points during treatment compared to the sublingual group. They could not show a link between measuring salivary cortisol levels and detection of anxiety.

Adverse effects were reported by Al-Rakaf 2001 and Shashikiran 2006 and included sneezing, coughing, diplopia and hiccups.

Midazolam (oral)

Aydintug 2004 found oral and rectal midazolam to be equally effective with no differences in behaviour between the groups (Additional Table 2). However, acceptance of rectal administration by the children was much poorer when compared to oral administration.

Isik 2008b reported that children receiving 0.75 mg/kg or 1 mg had a statistically significantly greater sedation score compared to those receiving 0.2 mg/kg or 0.5 mg/kg (P < 0.05) (Analysis 4.1). Sedation was considered inadequate in 86%, 38%, 23% and 38% of children in groups 1 to 4 respectively. Three children in group 4 (1 mg/kg) had delayed recovery time and in one patient a desaturation. Hypoxaemia, vomiting and nausea were reported as adverse effects. Authors recommended the 0.75 mg/kg dose as providing adequate sedation with good recovery time and few adverse effects.

Somri 2012 reported significant difference in sedation scores with 0.75 mg/kg and 1 mg/kg having higher scores compared to 0.5 mg/kg. No statistically significant difference was found in the sedation score of 0.75 mg/kg and 1 mg/kg groups. Behavioural co-operation was better in the 1 mg/kg group followed by 0.75 mg/kg and 0.5 mg/kg groups. There was no difference in the duration of treatment between the groups although completion of treatment scores were better in the 1 mg/kg group. Discharge times were the shortest in the 0.5 mg/kg group followed by the 0.75 mg/kg group and the longest in the 1 mg/kg group. Adverse effects of respiratory events and nausea and drowsiness were noted more as the dose of midazolam increased. Authors recommended the 0.75 mg/kg as the optimal dose for effectiveness, acceptability and safety.

3. Head-to-head drug comparison studies

See Additional Table 3. Thirty-one included studies compared different drugs and delivery methods.

Chloral hydrate/hydroxyzine

Avalos-Arenas 1998 found significantly decreased crying and movement, but higher rates of oxygen desaturations and deep sedation in the chloral hydrate/hydroxyzine group. Overall there was no statistically significant difference between the groups at the time of giving the local anaesthetic injection (Analysis 2.1 and Additional Table 3). All participants completed treatment in both groups.

Meyer 1990 reported that both regimens resulted in similar sedation (Additional Table 3) and one child in the chloral hydrate/hydroxyzine group experienced vomiting.

In the trial by Moody 1986 good or excellent sedation was achieved by 70% of children in both the rectal chloral hydrate and oral chloral hydrate/hydroxyzine groups suggesting that these two regimens have equivalent sedative effects compared to oral chloral hydrate alone which resulted in good/excellent sedation in 40% of children, but the difference was not statistically significant (Analysis 2.2 and Additional Table 3).

In Park 2006 subjects in the chloral hydrate/midazolam group showed better overall behaviour as measured by Houpt (P = 0.004) and less restraint was required in the chloral hydrate/midazolam group (P < 0.05).

Reeves 1996 reported no difference in the mean overall behaviour score in each group (Analysis 2.1), though the authors noted that children in the chloral hydrate/hydroxyzine group were in a significantly deeper sleep (P = 0.0015). Treatment was aborted for one participant in the chloral hydrate/hydroxyzine group, and 60% of children in the chloral hydrate/hydroxyzine group compared with 55% of children in the midazolam/acetaminophen group had an overall evaluation of good or better sedation, a difference which was not statistically significant. This suggests that the regimens were similar in terms of effective sedation, but approximately 40% of procedures were still difficult.

In the trial by Torres-Perez 2007 chloral hydrate/hydroxyzine resulted in "quieter" sedation as measured by OHSBRS and mean cardiac rate in each group. Authors did not provide any estimates of statistical significance but comment that although hydroxyzine alone was "not controllable", the addition of either choral hydrate or midazolam resulted in similarly enhanced sedative effects (Additional Table 3).

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Chloral hydrate/promethazine

In Sams 1993a three patients did not actually receive nitrous oxide because of their behaviour (one in the chloral hydrate/promethazine group displayed excellent behaviour and nitrous oxide was not required, and two children in the meperidine/promethazine group exhibited extreme head body movements such that the hood could not be used). The authors describe that over all 10 time points there was a statistically significantly greater likelihood that children were drowsy or asleep rather than awake and alert in the choral hydrate/promethazine group, but at the time the local anaesthetic injection was administered there was no difference between the two groups (Analysis 2.1). Differences between the groups in movement, crying and overall scores statistically significantly favoured the choral hydrate/promethazine group at 40% of the time points measured and in the remainder there was no difference (Sams 1993a). Both groups completed all planned treatment and there was no difference in mean duration of treatment (Additional Table 3). No adverse effects were reported.

Dexmedetomidine

Surendar 2014 reported no significant difference in overall behaviour, overall success rate of treatment and distribution of sedation levels between the groups. Midazolam had statistically significant higher intra and post-operative analgesia scores compared to the other groups. Significant difference in onset time, recovery time, pulse rate and systolic blood pressure of the two dexmedetomidine groups compared to the midazolam and ketamine groups was observed. The authors concluded that all the interventions can be used safely and effectively.

Ketamine

Abrams 1993 reported that both ketamine and midazolam induced the same mean sedation score of 4 (where 5 is ideal) and both had short recovery times (7 ± 7 and 3 ± 2 minutes respectively). Use of sufentanil resulted in heavily sedated children and oxygen desaturations; desaturations were of such concern that the operators broke the code during the study to determine which drug was the cause (1.5 µg/kg sufentanil in all four cases). Authors concluded that both intranasal ketamine (3 mg/kg) and midazolam (0.4 mg/kg) resulted in acceptable sedation in children.

Rai 2007 found that ketamine showed higher mean overall behaviour scores when compared to either midazolam or propofol (Additional Table 3, Analysis 3.1).

When rectal ketamine (5 mg/kg)/midazolam (0.35 mg/kg) was compared to rectal midazolam (1 mg/kg) alone (Roelofse 1996a), both regimens were well accepted by 78% and 70% of children, and only one child in the combination group experienced nausea. The combined regimen resulted in a statistically significant improvement in behaviour. Excessive salivation was reported in 26% and 14% and hallucinations in 14% and 42% of children in the midazolam only and ketamine/midazolam groups respectively (Roelofse 1996a). In this study treatment was aborted in one patient (2%) in the ketamine/midazolam group (Additional Table 3).

In a second study (Roelofse 1996b) very good or excellent sedation was achieved in 80% of the SOP (trimeprazine/physeptone/droperidol) group and 93% of the ketamine group (Analysis 3.2) but this difference was not statistically significant. Overall evaluation, which was more subjective, was good/very good in 67% of the SOP group and 90% of the ketamine group, a difference that was statistically significant (Additional Table 3). There were more adverse effects in the ketamine group (Additional Table 3) but all participants in both groups completed treatment.

The third trial by this group (Roelofse 1998) compared oral ketamine (5 mg/kg) plus midazolam (0.35 mg/kg) with a combination of oral trimeprazine (3 mg/kg) and methadone (0.2 mg/kg) administered 30 minutes prior to dental treatment. In the group receiving the ketamine/midazolam combination, 46% of children were "oriented and calm" at the start of dental treatment compared to 84% in the other group (Analysis 3.2). However, the more subjective outcome of overall sedation was rated as good or very good in 94% of children in the ketamine/midazolam group compared to 78% in the trimeprazine/methadone group, a statistically significant difference favouring ketamine. However, adverse outcomes of vomiting (4%) and hallucinations (20%) were only observed in the ketamine/midazolam group in this trial.

Alfonzo-Echeverri 1993 found no statistically significant difference in the distribution of sedation outcomes between the groups (Additional Table 3; Analysis 3.1), however four children (20%) had treatment aborted in the meperidine/promethazine group compared to none in the ketamine group. Eight children (40%) in the ketamine vomited, half of them during treatment and the remainder during recovery.

In the trial by Bui 2002 there was a statistically significant difference in mean Houpt behaviour score favouring ketamine (Analysis 3.1) compared to ketamine/promethazine. In one child, planned treatment was aborted (ketamine/promethazine group) but vomiting was only observed in the ketamine group (n = 3, 27%).

Singh 2014 showed that oral dexmedetomidine at 5 $\mu g/kg^{-1}$ had the most "adequate" depth of sedation and "satisfactory" completion of treatment, but had no statistically significant difference compared to the other groups. Ketamine 8 $mg/kg^{-1}$and dexmedetomidine at 5 $\mu g/kg^{-1}$ had a quicker onset time, prolonged recovery time, and better intra and post-operative pain score compared to the other groups. Ketamine resulted in more profound retrograde amnesia. 25% (n = 7) sessions with ketamine resulted in adverse effects of vomiting and hallucinations, whereas one patient on dexmedetomidine at 5 $\mu g/kg^{-1}$ reported vomiting.

Midazolam (oral)

Baygin 2010 reported that all premedication agents produced better behaviour than just nitrous oxide at all time points (Analysis 4.1). Ramsay sedation scores were statistically significantly greater in midazolam plus nitrous oxide group compared to nitrous oxide alone ($P < 0.05$) (Analysis 4.1). There was no statistically significant difference found between midazolam plus nitrous oxide and either hydroxyzine (Analysis 4.1) or midazolam/ketamine (Analysis 4.1). A wide variety of adverse effects were recorded including nausea/vomiting, cough, hiccup, enuresis, bronchospasm, hypersalivation, otalgia, hallucination and epistaxis (Additional Table 3).

Bhatnagar 2012 noted better depth of sedation and ease of treatment in the midazolam and tramadol groups compared to the other interventions. Ease of treatment scores between midazolam, tramadol and triclofos were not significantly different. The authors

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

concluded that midazolam followed by tramadol is best to produce sufficient levels of sedation.

Koirala 2006 reported the most favourable sedation scores in the group receiving midazolam plus ketamine followed by the group receiving midazolam plus tramadol (data only presented graphically in paper) (Additional Table 3). No adverse effects were reported.

Malhotra 2016 found significant difference in improvement of behaviour during treatment compared to baseline in the two groups. Significant difference in the level of sedation in group 1 and group 2 when a comparison is made at specific time stages (treatment-baseline and end of treatment-baseline) (e.g. for group 1 treatment-baseline comparison shows significant difference (P = 0.002) in the level of sedation). No significant difference in sedative efficacy or anxiolysis potential. The authors concluded that success of sedation and ease of treatment was higher in the midazolam/ketamine group compared to the dexmedetomidine group.

Moreira 2013 noticed significant differences in behaviour with the midazolam/ketamine group having better behaviour compared to the midazolam group and the no sedation group. All groups showed the same behavioural pattern at the end of the treatment session. Adverse reactions of agitation and vomiting were reported in the midazolam/ketamine group.

Özen 2012 found the highest scores for behaviour for the intranasal midazolam/nitrous oxide followed by oral midazolam 0.75 mg/kg and nitrous oxide, oral midazolam 0.50 mg/kg and nitrous oxide and lastly the inhalation sedation nitrous oxide group. Overall success of operative treatment was significantly better in the intranasal midazolam/nitrous oxide group compared to oral midazolam 0.50 mg/kg and nitrous oxide. Between the intranasal midazolam/nitrous oxide and oral midazolam 0.75 mg/kg and nitrous oxide group no significant difference was reported. This was similar to the two oral midazolam groups where no significant difference was reported. Inhalation sedation with nitrous oxide group showed the least success rate compared to all other groups. Depth of sedation was measured using bispectral index (BIS) values. Oral midazolam 0.75 mg/kg and nitrous oxide group was most sedated except for at 30 minutes after initiation of sedation. From 15 minutes after initiation of sedation to the end of treatment in all groups had BIS values were above 90 and therefore the patients were awake. Recovery time in minutes was shorter for intranasal midazolam compared to oral midazolam groups. Adverse effect reported in the oral midazolam group was of vomiting. In the intranasal group nose bleeding, along with transient burning and discomfort was reported. After discharge irritability, crying, sleepiness and nausea were recorded. The authors concluded that both oral and intranasal midazolam in conjugation with nitrous oxide can be used to achieve moderate sedation.

Singh 2002 sedation scores were reported on an eight-point scale in which a high score indicated poor sedation. In order to use these data in meta-analysis (Analysis 4.1) scores were transformed and standard deviations were calculated (Additional Table 3). No adverse effects were reported.

Tyagi 2012 reported that the overall behaviour rating was significantly better in the intravenous midazolam group compared to other groups. Positive behaviour postsedation was significantly approved in the intravenous midazolam group compared to the other groups, no significant difference was reported between the oral midazolam and the oral diazepam. This study did not report standard deviations for the overall behaviour. However, as raw data were reported, these could be calculated.

Midazolam (intravenous)

In Eshghi 2016 bispectral index system values noted for the ketamine/midazolam/propofol group were all in the range of general anaesthesia, whereas for the remifentanil/midazolam/propofol group at 15 minutes postadministration of the sedation the values were in the range of general anaesthesia. The ketamine/midazolam/propofol group were more deeply sedated compared to the remifentanil/midazolam/propofol group, the difference was statistically significant. Dental Sedation Teachers Group scale (DSTG) in both groups was noted as 5 (eyes closed, no response to mild physical stimulus) during the treatment. Heart rate and respiratory rate showed no significant difference between the two groups. Remifentanil/midazolam/propofol group showed quicker recovery. Adverse effects of severe nausea and vomiting was reported in the remifentanil group. The authors concluded that the remifentanil/midazolam/propofol group produced effective and safe sedation with a shorter recovery time.

Kaviani 2015 noted no significant difference in the sedation score or score of operative conditions at specific time intervals. The authors concluded that there was no difference between the two interventions

Midazolam (rectal)

Jensen 1999 at 10 minutes found no significant difference in sedation level between the groups. After 1 hour there was a statistically significant difference favouring diazepam. More children were agitated with diazepam at 1 hour when comparing rectal midazolam to rectal diazepam (data only presented graphically in paper) (Additional Table 3).

Sevoflurane

Lahoud 2002 compared sevoflurane (0.1% to 0.3%)/nitrous oxide (40%) with nitrous oxide (40%) alone. There was a statistically significant difference in rate of effective sedation favouring the sevoflurane/nitrous oxide group (P < 0.001) (Additional Table 3).

Averley 2004a was a pilot study which randomised children to either intravenous midazolam (0.5 mg/min) titrated to induce adequate sedation, or 40% nitrous oxide inhalation plus intravenous midazolam (0.5 mg/min) titrated to induce adequate sedation, or inhalation of 0.3% sevoflurane plus 40% nitrous oxide plus intravenous midazolam (0.5 mg/min) titrated to induce adequate sedation. Treatment was successfully completed in 50%, 73% and 83% of children in each group respectively and researchers noted that nine of the 16 children in groups 1 or 2 who failed were subsequently successfully treated with the addition of sevoflurane and nitrous oxide (Additional Table 3).

In the subsequent trial (Averley 2004b) the same interventions were used as in the pilot study and treatment completion rates were 54%, 80% and 94% for groups 1 to 3 respectively. Vomiting only occurred in group 3, but incidence was low (n = 6, 2%) (Additional Table 3).

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

DISCUSSION

Summary of main results

See Summary of findings for the main comparison; Summary of findings 2; and Summary of findings 3.

In common with the findings from many other systematic reviews, the design and reporting of studies included in this review was mostly poor. In general, the risk of bias for most studies was at best a mix of low and unclear (18% of included trials) and likely to have at least one domain that was high (82% of included trials). Combining data from included studies to facilitate a meta-analysis was difficult. The enormous range of sedative agents used both in combination and singly, along with the wide range of outcome measures, precluded meta-analysis of homogenous groups of interventions.

Placebo-controlled studies

It was possible to carry out a meta-analysis for studies comparing oral midazolam with placebo (Analysis 1.1). There is consistent evidence from six heterogeneous trials, that following administration of oral midazolam the behaviour of children was improved relative to placebo, with variations in the size of the benefit according to the dosage used. Where reported, adverse effects were few and minor. This effect was considered to be moderately sized and of moderate certainty according to the GRADE recommendations.

Dose comparison studies

Intranasal midazolam was evaluated in four studies, but the comparators and dosages were different and results conflicting. There is insufficient evidence to determine whether any specific dose of intranasal midazolam is effective.

There is weak evidence from two trials that oral midazolam at a dose of 0.5 mg/kg to 0.75 mg/kg is an effective sedative for children. However, one trial administered both nitrous oxide and midazolam so it is difficult to attribute benefit to midazolam alone.

Head-to-head drug comparison studies

In this group no two studies evaluating the same intervention and comparison found the same effect. There is insufficient evidence to draw any conclusions from these trials.

Adverse effects

There is insufficient evidence from trials in this review to support the effectiveness of either chloral hydrate or ketamine. However, it should be noted that chloral hydrate was associated with significant adverse effects, specifically airway issues especially when high doses (> 50 mg/kg) were combined with the use of inhalational nitrous oxide. Ketamine was also associated with significant adverse effects.

Overall completeness and applicability of evidence

It was apparent whilst carrying out this review that there were significant differences in techniques and drugs used between countries and regions. Studies can be loosely grouped into two types, those based on a 'North American' model of sedation and those based on a more 'European' model. The North American model was typified by use of multiple agents (including adjunctive nitrous oxide) at any age, the use of restraint and intent to induce a deeper level of sedation. The European model was typified by use of single agents (typically nitrous oxide or midazolam) with intent to induce lighter levels of sedation. This is most likely due to cultural and legal differences and needs to be considered when making recommendations for the most effective methods of conscious sedation.

Interpretation of outcome data related to behaviour was difficult. Over half of the studies used the Houpt or a modified Houpt scoring system to record behaviour, however the remaining studies used a wide variety of methodologies. Even within studies using modified versions of the Houpt scale, there was a large variation in how Houpt was modified. Behaviour was recorded in some studies for the whole episode and in others at a series of discrete points such as application of local anaesthetic or venepuncture. Furthermore, many of the outcome measures used relied on observations of movement, yet in a large proportion of studies patients were restrained in a papoose board. It is difficult to determine how this might have influenced recorded values of behaviour. Interestingly participants often completed treatment regardless of which group they were assigned to. This might reflect a lack of baseline anxiety in all participants which then begs the question as to why they were included in the study. Alternatively given the use of papoose boards and supplemental nitrous oxide oxygen perhaps it is not surprising.

The efficacy of a particular agent will be influenced by the baseline anxiety of the child involved. Ideally this should always be recorded and then compared to levels of anxiety after sedation. Baseline values of anxiety were not uniformly reported and very few studies recorded anxiety at the end.

The majority of studies involved sedation in children less than 6 years of age, probably because this age range belongs to a 'pre-co-operative' group. Treatment needs and management of children will vary as they grow and develop. Techniques that are appropriate in a 3-year old may not be appropriate in a 12-year old and vice versa.

In most papers the medical status of the children was healthy or having mild systemic disease (American Society of Anesthesiologists (ASA) physical status classification system: ASA I and ASA II). Some of the techniques described may be useful in the management of medically compromised patients, but at present there are no studies carried out in these groups.

Little information was provided on restorative treatment carried out in many of the studies, although several articles mentioned the use of local anaesthesia, mouth prop and rubber dam. Obviously the treatment provided may well influence the behaviour and anxiety of the participant.

Quality of the evidence

In general reporting of the trials was poor with data such as method of sequence generation and allocation concealment frequently not reported. Participants were poorly described with important information such as gender or weight often missing. Sample size calculations were either not carried out or not reported, and it is likely that many of the trials lacked statistical power to detect a difference between intervention and control. This would then result in significant imprecision. Statistical methods used varied widely between studies even though outcome measures were sometimes

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

similar. In some instances these tests were arguably inappropriate for the types of data usually produced by these studies.

Potential biases in the review process

In a previous update (Matharu 2012) the decision was made to exclude cross-over trials. Cross-over trials were excluded as they are not an appropriate study design when the intervention can have a lasting effect (*Cochrane Handbook for Systematic Reviews of Interventions* Section 16.4.2, Higgins 2011). It is well recognised that previous treatment episodes influence the anxiety associated with dental treatment, especially in children. Evidence to support this can be found in Veerkamp 1995. In this study, anxiety in children who received a treatment phase under nitrous oxide was compared with children who received treatment without nitrous oxide approximately 72 weeks after the first phase. They found that overall and peak scores for anxiety were significantly reduced ($P < 0.05$) in the nitrous oxide group at the start of the second treatment phase when compared to the control group. This decision resulted in a significant proportion of included studies from earlier versions becoming excluded. We felt this approach was justified.

Agreements and disagreements with other studies or reviews

A related review was published by the National Institute for Health and Care Excellence (NICE) on sedation in children and young people (NICE 2010). It was different from this Cochrane Review in that it considered sedation for any medical or dental therapeutic procedure, and it also was restricted to procedures that could be used within the regulatory framework of England and Wales. Randomised controlled trials with less than 20 subjects were excluded, cross-over studies were included. NICE 2010 recommended for dentistry that only midazolam or nitrous oxide be used. In common with this review they found "surprisingly few high-quality published reports and clinical trials."

AUTHORS' CONCLUSIONS

Implications for practice

There is moderate-certainty evidence from six trials that oral midazolam is an effective agent for sedation of children. Although other sedatives have been evaluated, the range of sedatives, regimens, doses, modes of administration and comparisons included makes it impossible to produce a clear statement of implications for practice regarding other agents.

Implications for research

This is the second update of the Cochrane Review first published in 2005 and previously updated in 2012. It is unfortunate that there has been little improvement in the design, statistical power and reporting of studies carried out since then.

The shortfalls of studies reported in this review are many. The principles that researchers should adhere to when designing, carrying out and reporting clinical trials in the future are the CONSORT guidelines (Moher 2001). There also needs to be a improvement in reporting of variables like gender, weight, time starved, time of onset of sedation, dropouts, reason for patient failing to complete treatment, etc.

More specific recommendations for studies assessing sedative agents are as follows.

Blinding

Ideally the operator, participant and assessor should all be blinded to the sedation agent used, however blinding of the operator is problematic. When comparing drugs with different modes of delivery e.g. oral midazolam versus nitrous oxide/oxygen, it would not be possible to blind the operator as techniques of administration are totally different. If this is the case then it is important that the assessor is blinded to the allocation. In the aforementioned example this could be achieved by using an inhalation mask to deliver air in the midazolam group and the patient videotaped, to enable blinded outcome assessment.

Sample

Obviously calculating and reporting sample sizes should be carried out before starting any clinical trial, something that has not been done well to date in trials of sedation agents in children requiring dental treatment. More consideration also needs to be given to the children included in trials, in particular their age. Consideration should be given to dividing age into three broad groups (as recommended by the British National Formulary (BNF) when prescribing drugs to children). These groups are: from 1 to 6 years, from 6 to 12 years and over 12 years of age. There is a need to establish which sedation is more effective for a given age group.

Consideration should also be given to the reasons for sedation which may well vary widely between groups. In pre-co-operative children (under 6) the intention is often to get treatment done. In older children (e.g. over 12) the intention might be to provide a pleasant experience for the patient thus reducing anxiety for further visits. It would also be helpful for research to investigate suitable sedative regimens for dental treatment in medically compromised children of various ages, those with learning difficulties or other behavioural problems such Attention Deficit Hyperactivity Disorder (ADHD).

Design

Only studies of a parallel design should be carried out. Cross-over trials are not appropriate because the level of baseline anxiety/ behaviour in the second treatment phase is highly dependent on the success or otherwise of the first treatment period.

Baseline and outcome variables

Behaviour is the most commonly used outcome measured in a range of ways. Anxiety is sometimes measured before the study commences but rarely afterwards. Treatment completion is not always reported and very rarely statistically tested between groups. Outcome variables are very clinician centred - what was the quality of the sedation? How immobile was the child? etc. These approaches need to change.

Outcome variables need to be more patient-centred. This might include satisfaction, reduction in anxiety or other measures relating the patient's perception.

A wider debate needs to be had on the purpose of sedation. The majority of studies to date, focus on the use of sedation as a tool to facilitate the delivery of dental treatment in children. This is important; but sedation could (and should) have a larger

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

role. It could be used to facilitate the introduction of treatment to anxious children with a view to reducing or removing sedation in subsequent visits (an approach taken by Veerkamp 1993). Outcome variables should be chosen to reflect this.

Where behaviour-type outcome measures are used, thought must be given to the appropriateness of movement-based measures for children who are restrained e.g. by a papoose board.

Considering the above comments the review authors would suggest that reviews have the following 'key' or 'core' variables in common to allow comparison between studies in future.

1. Some measurement of baseline anxiety.
2. Completion of treatment as the primary outcome variable.
3. Patient satisfaction or preference.

Deep versus conscious sedation

It was originally intended to exclude any papers that dealt with deep sedation for reasons outlined in the introduction. This proved to be impossible because many papers did not state explicitly whether they were practicing conscious or deep sedation, sleeping was also poorly reported. We believe that in some of these papers deep sedation was undertaken, as participants were reported as falling asleep and mouth props were used. This highlights the importance of reaching a consensus definition of conscious sedation, or at the very least using the definitions already available. Without this information it is impossible for researchers or clinicians in countries where the existing regulatory framework does not permit deep sedation to make appropriate use of published data. Alternatively the definition of deep sedation could be abandoned, as it is not used.

Agents/regimens under test

There are 32 sedative drugs or drug combinations tested for conscious sedation in this review, given either orally, by inhalation, intramuscular injections, intranasally and/or rectally and at varying dosages. The majority were not compared against a placebo or even a drug of known efficacy. Future trials should consider the use of either oral midazolam or nitrous oxide sedation as a comparator.

As mentioned, not all agents are available in all countries and the choice of sedation will depend on cultural acceptance and also laws and availability. It would seem appropriate to identify agents of particular interest and co-ordinate research on these internationally. Furthermore, it would seem appropriate for different countries to investigate those drugs and modes of delivery that are most appropriate for them.

A further problem is the use of supplemental nitrous oxide/oxygen. This is often used in studies (particularly from North America) and would be expected to increase the overall level of sedation. Whilst there is nothing wrong in using supplemental nitrous oxide/oxygen it needs to be made clear from the outset that this is the case in clinical trials. Unfortunately it is often not mentioned initially when agents under test are described. For example the drug under investigation should be given as chloral hydrate and nitrous oxide/oxygen rather than just chloral hydrate with a subsequent note buried in the text describing the use of supplemental nitrous oxide oxygen.

Finally the use of papoose boards needs to be clarified. What is the impact of physical restraint on sedative effectiveness? Or anxiety reduction? Further work needs to be done on the role of physical restraints in sedation of children. However, it is important that use of papoose board in a clinical trial of sedation should also be specified clearly from the outset.

ACKNOWLEDGEMENTS

The review authors would like to thank the two translators, Pati Pungchanchaikul and Jens Poppen. We also acknowledge the help and assistance of Cochrane Oral Health and the contribution of Susan Furness to all aspects of the 2012 update of this review, in particular data extraction, analysis and interpretation of data and entering data into Review Manager. We would like to thank Professor MT Hosey, King's College London, and Professor Richard Welbury, University of Central Lancashire, for their peer review comments.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

REFERENCES

References to studies included in this review

Abrams 1993 *{published data only}*

Abrams R, Morrison JE, Villasenor A, Hencmann D, Da Fonseca M, Mueller W. Safety and effectiveness of intranasal administration of sedative medications (ketamine, midazolam, or sufentanil) for urgent brief pediatric dental procedures. *Anesthesia Progress* 1993;**40**(3):63-6.

Alfonzo-Echeverri 1993 *{published data only}*

Alfonzo-Echeverri EC, Berg JH, Wild TW, Glass NL. Oral ketamine for pediatric outpatient dental surgery sedation. *Pediatric Dentistry* 1993;**15**(3):182-5.

Al-Rakaf 2001 *{published data only}*

Al-Rakaf H, Bello LL, Turkustani A, Adenubi JO. Intra-nasal midazolam in conscious sedation of young paediatric dental patients. *International Journal of Paediatric Dentistry* 2001;**11**(1):33-40.

Avalos-Arenas 1998 *{published data only}*

Avalos-Arenas V, Moyao-Garcia D, Nava-Ocampo AA, Zayas-Carranza RE, Fragoso-Rios R. Is chloral hydrate/hydroxyzine a good option for paediatric dental outpatient sedation?. *Current Medical Research and Opinion* 1998;**14**(4):219-26.

Averley 2004a *{published data only}*

Averley PA, Lane I, Sykes J, Girdler NM, Steen N, Bond S. An RCT pilot study to test the effects of intravenous midazolam as a conscious sedation technique for anxious children requiring dental treatment - an alternative to general anaesthesia. *British Dental Journal* 2004;**197**(9):553-8.

Averley 2004b *{published data only}*

Averley PA, Girdler NM, Bond S, Steen N, Steele J. A randomised controlled trial of paediatric conscious sedation for dental treatment using intravenous midazolam combined with inhaled nitrous oxide or nitrous oxide/sevoflurane. *Anaesthesia* 2004;**59**(9):844-52.

Aydintug 2004 *{published data only}*

Aydintug YS, Okcu KM, Guner Y, Gunaydin Y, Sencimen M. Evaluation of oral or rectal midazolam as conscious sedation for pediatric patients in oral surgery. *Military Medicine* 2004;**169**(4):270-3.

Baygin 2010 *{published data only}*

Baygin O, Bodur H, Isik B. Effectiveness of premedication agents administered prior to nitrous oxide/oxygen. *European Journal of Anaesthesiology* 2010;**27**(4):341-6.

Bhatnagar 2012 *{published data only}*

Bhatnagar S, Das UM, Bhatnagar G. Comparison of oral midazolam with oral tramadol, triclofos and zolpidem in the sedation of pediatric dental patients: an in vivo study. *Journal of the Indian Society of Pedodontics and Preventive Dentistry* 2012;**30**(2):109-14.

Bui 2002 *{published data only}*

Bui T, Redden RJ, Murphy S. A comparison study between ketamine and ketamine-promethazine combination for oral sedation in pediatric dental patients. *Anesthesia Progress* 2002;**49**(1):14-8.

Eshghi 2016 *{published data only}*

Eshghi A, Mohammadpour M, Kaviani N, Tahririan D, Akhlaghi N. Comparative evaluation of bispectral index system after sedation with midazolam and propofol combined with remifentanil versus ketamine in uncooperative during dental procedures. *Dental Research Journal* 2016;**13**(1):1-6.

Faytrouny 2007 *{published data only}*

Faytrouny M, Okte Z, Kucukyavuz Z. Comparison of two different dosages of hydroxyzine for sedation in the paediatric dental patient. *International Journal of Paediatric Dentistry* 2007;**17**(5):378-82.

Gallardo 1994 *{published data only}*

Auil B, Cornejo G, Gallardo F. Flunitrazepam and diazepam compared as sedatives in children. *ASDC Journal of Dentistry for Children* 1983;**50**(6):442-4.

* Gallardo F, Cornejo G, Borie R. Oral midazolam as premedication for the apprehensive child before dental treatment. *Journal of Clinical Pediatric Dentistry* 1994;**18**(2):123-7.

Gomes 2017 *{published data only}*

Gomes HS, Gomes HS, Sado-Filho J, Costa LR, Costa PS. Does sevoflurane add to outpatient procedural sedation in children? A randomised clinical trial. *BMC Pediatrics* 2017;**17**(1):86.

Isik 2008a *{published data only}*

Isik B, Baygin O, Bodur H. Premedication with melatonin vs midazolam in anxious children. *Pediatric Anesthesia* 2008;**18**(7):635-41.

Isik 2008b *{published data only}*

Isik B, Baygin O, Bodur H. Oral midazolam premedication in anxious children: effectiveness of different doses. *Anestezi Dergisi* 2008;**16**(1):34-40.

Jensen 1999 *{published data only}*

Jensen B, Schroder U, Mansson U. Rectal sedation with diazepam or midazolam during extractions of traumatized primary incisors: a prospective, randomized, double-blind trial in Swedish children aged 1.5-3.5 years. *Acta Odontologica Scandinavica* 1999;**57**(4):190-4.

Kapur 2004 *{published data only}*

Kapur A, Chawla HS, Goyal A, Gauba K, Bhardwaj N. Efficacy and acceptability of oral-transmucosal midazolam as a conscious sedation agent in pre-school children. *Journal of the Indian Society of Pedodontics and Preventive Dentistry* 2004;**22**(3):109-13.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Kaviani 2015 *{published data only}*

Kaviani N, Ashrafi S, Jabbarifar SE, Ghaffari E. The efficacy of two intravenous sedative drugs in management of uncooperative children for dental treatments. *Journal of Dentistry* 2015;**16**(1 Suppl):29-34.

Koirala 2006 *{published data only}*

Koirala B, Pandey RK, Saksen AK, Kumar R, Sharma S. A comparative evaluation of newer sedatives in conscious sedation. *Journal of Clinical Pediatric Dentistry* 2006;**30**(4):273-6.

Lahoud 2002 *{published data only}*

Lahoud GY, Averley PA. Comparison of sevoflurane and nitrous oxide mixture with nitrous oxide alone for inhalation conscious sedation in children having dental treatment: a randomised controlled trial. *Anaesthesia* 2002;**57**(5):446-50.

Lam 2005 *{published data only}*

Lam C, Udin RD, Malamed SF, Good DL, Forrest JL. Midazolam premedication in children: a pilot study comparing intramuscular and intranasal administration. *Anesthesia Progress* 2005;**52**(2):56-61.

Lee-Kim 2004 *{published data only}*

Lee-Kim SJ, Fadavi S, Punwani I, Koerber A. Nasal versus oral midazolam sedation for pediatric dental patients. *Journal of Dentistry for Children* 2004;**71**(2):126-30.

Malhotra 2016 *{published data only}*

Malhotra PU, Thakur S, Singhal P, Chauhan D, Jayam C, Sood R, et al. Comparative evaluation of dexmedetomidine and midazolam-ketamine combination as sedative agents in pediatric dentistry: a double-blinded randomized controlled trial. *Contemporary Clinical Dentistry* 2016;**7**(2):186-92.

McKee 1990 *{published data only}*

McKee K, Nazif MM, Jackson DL, Barnhart DC, Close J, Moore PA. Dose-responsive characteristics of meperidine sedation in preschool children. *Pediatric Dentistry* 1990;**12**(4):222-7.

Meyer 1990 *{published data only}*

Meyer M, Mourino AP, Farrington FH. Comparison of triazolam to a chloral hydrate/hydroxyzine combination in the sedation of pediatric dental patients. *Pediatric Dentistry* 1990;**12**(5):283-7.

Moody 1986 *{published data only}*

Moody EH Jr, Mourino AP, Campbell RL. The therapeutic effectiveness of nitrous oxide and chloral hydrate administered orally, rectally, and combined with hydroxyzine for pediatric dentistry. *ASDC Journal of Dentistry for Children* 1986;**53**(6):425-9.

Moore 1984 *{published data only}*

Moore PA, Mickey EA, Hargreaves JA, Needleman HL. Sedation in pediatric dentistry: a practical assessment procedure. *Journal of the American Dental Association* 1984;**109**(4):564-9.

Moreira 2013 *{published data only}*

Moreira TA, Costa PS, Costa LR, Jesus-França CM, Antunes DE, Gomes HS, et al. Combined oral midazolam-ketamine better than midazolam alone for sedation of young children: a randomized controlled trial. *International Journal of Paediatric Dentistry* 2013;**23**(3):207-15.

Mortazavi 2009 *{published data only}*

Mortazavi M, Pourhashemi SJ, Khosravi MB, Ashtari S, Ghaderi F. Assessment of a low dose of IV midazolam used orally for conscious sedation in pediatric dentistry. *Daru* 2009;**17**(2):79-82.

Nathan 1988 *{published data only}*

Nathan JE, Venham LL, West MS, Werboff J. The effects of nitrous oxide on anxious young pediatric patients across sequential visits: a double-blind study. *ASDC Journal of Dentistry for Children* 1988;**55**(3):220-30.

Özen 2012 *{published data only}*

Özen B, Malamed SF, Cetiner S, Özalp N, Özer L, Altun C. Outcomes of moderate sedation in paediatric dental patients. *Australian Dental Journal* 2012;**57**(2):144-50.

Park 2006 *{published data only}*

Park M, Kim Y, Jung S, Beak K. Safety and efficacy of submucosal midazolam when combined with oral chloral hydrate, hydroxyzine and nitrous oxide sedation by using Houpt's scale. *Journal of the Korean Dental Society of Anesthesiology* 2006;**6**:103-12.

Rai 2007 *{published data only}*

Rai K, Hegde M, Goel K. Sedation in uncooperative children undergoing dental procedures: a comparative evaluation of midazolam, propofol and ketamine. *Journal of Clinical Pediatric Dentistry* 2007;**32**(1):1-4.

Reeves 1996 *{published data only}*

Reeves ST, Wiedenfeld KR, Wrobleski J, Hardin CL, Pinosky ML. A randomized double-blind trial of chloral hydrate/hydroxyzine versus midazolam/acetaminophen in the sedation of pediatric dental outpatients. *ASDC Journal of Dentistry for Children* 1996;**63**(2):95-100.

Roelofse 1996a *{published data only}*

Roelofse JA, Joubert JJ, Roelofse PG. A double-blind randomized comparison of midazolam alone and midazolam combined with ketamine for sedation of pediatric dental patients. *Journal of Oral and Maxillofacial Surgery* 1996;**54**(7):838-44.

Roelofse 1996b *{published data only}*

Roelofse JA, Joubert JJ, Swart LC, Stander I, Roelofse PG. An evaluation of the effect of oral ketamine and standard oral premedication in the sedation of paediatric dental patients. *Journal of the Dental Association of South Africa* 1996;**51**(4):197-201.

Roelofse 1998 *{published data only}*

Roelofse JA, Louw LR, Roelofse PG. A double-blind randomized comparison of oral trimeprazine-methadone and ketamine-midazolam for sedation of pediatric dental patients for oral surgical procedures. *Anesthesia Progress* 1998;**45**(1):3-11.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Sams 1993a *{published data only}*

Sams DR, Cook EW, Jackson JG, Roebuck BL. Behavioral assessments of two drug combinations for oral sedation. *Pediatric Dentistry* 1993;**15**(3):186-90.

Shanmugaavel 2016a *{published data only}*

Shanmugaavel AK, Asokan S, Baby JJ, Priya G, Gnana Devi J. Comparison of behavior and dental anxiety during intranasal and sublingual midazolam sedation - A randomized controlled trial. *Journal of Clinical Pediatric Dentistry* 2016;**40**(1):81-7.

Shanmugaavel 2016b *{published data only}*

Shanmugaavel AK, Asokan S, John JB, Priya PR, Raaja MT. Comparison of drug acceptance and anxiety between intranasal and sublingual midazolam sedation. *Pediatric Dentistry* 2016;**38**(2):106-11.

Shashikiran 2006 *{published data only}*

Shashikiran ND, Reddy SV, Yavagal CM. Conscious sedation - an artist's science! An Indian experience with midazolam. *Journal of the Indian Society of Pedodontics and Preventive Dentistry* 2006;**24**(1):7-14.

Singh 2002 *{published data only}*

Singh N, Pandey RK, Saksena AK, Jaiswal JN. A comparative evaluation of oral midazolam with other sedatives as premedication in pediatric dentistry. *Journal of Clinical Pediatric Dentistry* 2002;**26**(2):161-4.

Singh 2014 *{published data only}*

Singh C, Pandey RK, Saksena AK, Chandra G. A comparative evaluation of analgo-sedative effects of oral dexmedetomidine and ketamine: a triple-blind, randomized study. *Pediatric Anesthesia* 2014;**24**(12):1252-9.

Somri 2012 *{published data only}*

Somri M, Parisinos CA, Kharouba J, Cherni N, Smidt A, Abu Ras Z, et al. Optimising the dose of oral midazolam sedation for dental procedures in children: a prospective, randomised, and controlled study. *International Journal of Paediatric Dentistry* 2012;**22**(4):271-9.

Surendar 2014 *{published data only}*

Surendar MN, Pandey RK, Saksena AK, Kumar R, Chandra G. A comparative evaluation of intranasal dexmedetomidine, midazolam and ketamine for their sedative and analgesic properties: a triple blind randomized study. *Journal of Clinical Paediatric Dentistry* 2014;**38**(3):255-61.

Torres-Perez 2007 *{published data only}*

Torres-Perez J, Tapia-Garcia I, Rosales-Berber MA, Hernandez-Sierra JF, Pozos-Guillen AJ. Comparison of three conscious sedation regimens for pediatric dental patients. *Journal of Paediatric Dentistry* 2007;**31**(2):183-6.

Tyagi 2012 *{published data only}*

Tyagi P, Dixit U, Tyagi S, Jain A. Sedative effects of oral midazolam, intravenous midazolam and oral diazepam. *Journal of Clinical Pediatric Dentistry* 2012;**36**(4):383-8.

Veerkamp 1993 *{published data only}*

Veerkamp JS, Gruythuysen RJ, Hoogstraten J, van Amerongen WE. Dental treatment of fearful children using nitrous oxide. Part 4: Anxiety after two years. *ASDC Journal of Dentistry for Children* 1993;**60**(4):372-6.

Veerkamp JS, Gruythuysen RJ, van Amerongen WE, Hoogstraten J. Dental treatment of fearful children using nitrous oxide. Part 2: The parents' point of view. *ASDC Journal of Dentistry for Children* 1992;**59**(2):115-9.

* Veerkamp JS, Gruythuysen RJ, van Amerongen WE, Hoogstraten J. Dental treatment of fearful children using nitrous oxide. Part 3: Anxiety during sequential visits. *ASDC Journal of Dentistry for Children* 1993;**60**(3):175-82.

Veerkamp JS, van Amerongen WE, Hoogstraten J, Groen HJ. Dental treatment of fearful children, using nitrous oxide. Part I: Treatment times. *ASDC Journal of Dentistry for Children* 1991;**58**(6):453-7.

Wan 2006 *{published data only}*

Wan K, Jing Q, Zhao JZ. Evaluation of oral midazolam as conscious sedation for pediatric patients in oral restoration. *Chinese Medical Sciences Journal* 2006;**21**(3):163-6.

References to studies excluded from this review

Al-Zahrani 2009 *{published data only}*

Al-Zahrani AM, Wyne AH, Sheta SA. Comparison of oral midazolam with a combination of oral midazolam and nitrous oxide-oxygen inhalation in the effectiveness of dental sedation for young children. *Journal of the Indian Society of Pedodontics and Preventive Dentistry* 2009;**27**(1):9-16.

Arya 2002 *{published data only}*

Arya VS, Damle SG. Comparative evaluation of midazolam and propofol as intravenous sedative agents in the management of unco-operative children. *Journal of the Indian Society of Pedodontics and Preventive Dentistry* 2002;**20**(1):6-8.

Badalaty 1990 *{published data only}*

Badalaty MM, Houpt MI, Koenigsberg SR, Maxwell KC, Desjardins PJ. A comparison of chloral hydrate and diazepam sedation in young children. *Pediatric Dentistry* 1990;**12**(1):33-7.

Baldinelli 1989 *{published data only}*

Baldinelli L, Melloti R. Outpatient intravenous sedation. *Anesthesia Progress* 1989;**36**(4-5):157-8.

Berge 1999 *{published data only}*

Berge TI. Acceptance and side effects of nitrous oxide oxygen sedation for oral surgical procedures. *Acta Odontologica Scandinavica* 1999;**57**(4):201-6.

Blake 1999 *{published and unpublished data}*

Blake K. A comparison of midazolam and propofol for dental sedation. National Research Register Document 1999.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Campbell 1998 *{published data only}*

Campbell RL, Ross GA, Campbell JR, Mourino AP. Comparison of oral chloral hydrate with intramuscular ketamine, meperidine, and promethazine for pediatric sedation-preliminary report. *Anesthesia Progress* 1998;**45**(2):46-50.

Canpolat 2017 *{published data only}*

Canpolat DG, Yildirim MD, Kutuk N, Dogruel F, Ocak H, Aksu R, et al. Comparison of ketamine-propofol and ketamine-dexmedetomidine combinations in children for sedation during tooth extraction. *Journal of the Pakistan Medical Association* 2017;**67**(5):693-7.

Cathers 2005 *{published data only}*

Cathers JW, Wilson CF, Webb MD, Alvarez ME, Schiffman T, Taylor S. A comparison of two meperidine/hydroxyzine sedation regimens for the uncooperative pediatric dental patient. *Pediatric Dentistry* 2005;**27**(5):395-400.

Chaushu 2002 *{published data only}*

Chaushu S, Gozal D, Becker A. Intravenous sedation: an adjunct to enable orthodontic treatment for children with disabilities. *European Journal of Orthodontics* 2002;**24**(1):81-9.

Coldwell 1999 *{published data only}*

Coldwell SE, Awamura KA, Milgrom P, Depner KS, Kaufman E, Preston KL, et al. Side effects of triazolam in children. *Pediatric Dentistry* 1999;**21**(1):18-25.

da Costa 2007 *{published data only}*

da Costa LR, da Costa PS, Lima AR. A randomized double-blinded trial of chloral hydrate with or without hydroxyzine versus placebo for pediatric dental sedation. *Brazilian Dental Journal* 2007;**18**(4):334-40.

Dallman 2001 *{published data only}*

Dallman JA, Ignelzi MA Jr, Briskie DM. Comparing the safety, efficacy and recovery of intranasal midazolam vs oral chloral hydrate and promethazine. *Pediatric Dentistry* 2001;**23**(5):424-30.

Davila 1990 *{published data only}*

Davila JM. Restraint and sedation of the dental patient with developmental disabilities. *Special Care Dentist* 1990;**10**(6):210-2.

Doring 1985 *{published data only}*

Doring KR. Evaluation of an alphaprodine-hydroxyzine combination as a sedative agent in the treatment of the pediatric dental patient. *Journal of the American Dental Association* 1985;**111**(4):567-76.

Downs 1997 *{published data only}*

Downs AT, Dembo J, Ferretti G, Lyons TD, Pelphery A. A comparative study of midazolam to meperidine/promethazine as an IM sedative technique for the pediatric dental patient. *ASDC Journal of Dentistry for Children* 1997;**64**(3):197-200.

Duncan 1984 *{published data only}*

Duncan GH, Moore P. Nitrous oxide and the dental patient: a review of adverse reactions. *Journal of the American Dental Association* 1984;**108**(2):213-9.

Duncan 1994 *{published data only}*

Duncan WK, De Ball S, Perkins TM. Chloral hydrate sedation: a simple technique. *Compendium* 1994;**15**(7):884-7.

Dunn-Russell 1993 *{published data only}*

Dunn-Russell T, Adair SM, Sams DR, Russell CM, Barenie JT. Oxygen saturation and diffusion hypoxia in children following nitrous oxide sedation. *Pediatric Dentistry* 1993;**15**(2):88-92.

el Magboul 1995 *{published data only}*

el Magboul KM, O'Sullivan EA, Curzon ME. A clinical trial comparing two doses of oral temazepam for sedation of paediatric dental patients. *International Journal of Paediatric Dentistry* 1995;**5**(2):97-102.

Erlandsson 2001 *{published data only}*

Erlandsson AL, Backman B, Stenstrom A, Stecksen-Blicks C. Conscious sedation by oral administration of midazolam in paediatric dental treatment. *Swedish Dental Journal* 2001;**25**(3):97-104.

Evans 1966 *{published data only}*

Evans WO, Tannenbaum K, Turek B, Ailing EF. A method for evaluating the use of premedicating agents in difficult pedodontic patients. *ASDC Journal of Dentistry for Children* 1966;**33**:317-23.

Flaitz 1985 *{published data only}*

Flaitz CM, Novak AJ. Evaluation of the sedative effect of rectally administered diazepam for the young dental patient. *Pediatric Dentistry* 1985;**7**(4):292-6.

Flaitz CM, Nowak AJ, Hicks MJ. Double-blind comparison of rectally administered diazepam to placebo for pediatric sedation: the cardiovascular response. *Anesthesia Progress* 1985;**32**(6):232-6.

Fuks 1994 *{published data only}*

Fuks AB, Kaufman E, Ram D, Hovav S, Shapira J. Assessment of two doses of intranasal midazolam for sedation of young pediatric dental patients. *Pediatric Dentistry* 1994;**16**(4):301-5.

Fukuta 1993 *{published data only}*

Fukuta O, Braham RL, Yanase H, Atsumi N, Kurosu K. The sedative effect of intranasal midazolam administration in the dental treatment of patients with mental disabilities. Part 1: the effect of a 0.2 mg/kg dose. *Journal of Clinical Pediatric Dentistry* 1993;**17**(4):231-7.

Fukuta 1994 *{published data only}*

Fukuta O, Braham RL, Yanase H, Kurosu K. The sedative effects of intranasal midazolam administration in the dental treatment of patients with mental disabilities. Part 2: optimal concentration of intranasal midazolam. *Journal of Clinical Pediatric Dentistry* 1994;**18**(4):259-65.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Gallardo 1984 *{published data only}*

Gallardo F, Cornejo G, Auil B. Premedication with flunitrazepam, diazepam and placebo in the apprehensive child. *ASDC Journal of Dentistry for Children* 1984;**51**(3):208-10.

Gamonal Aravena 1989 *{published data only}*

Gamonal Aravena J. Effectiveness of chlormezanone and flunitrazepam in treatment of difficult children. *Revista Dental de Chile* 1989;**80**(2):64-9.

Garton 1970 *{published data only}*

Garton J. Intravenous sedation in dental practice. *Dental Student* 1970;**48**(9):66-7.

Haas 1996 *{published data only}*

Haas DA, Nenninger SA, Yacobi R, Magathan JG, Grad HA, Copp PE, et al. A pilot study of the efficacy of oral midazolam for sedation in pediatric dental patients. *Anesthesia Progress* 1996;**43**(1):1-8.

Hall 2006 *{published data only}*

Hall DL, Tatakis DN, Walters JD, Rezvan E. Oral clonidine pre-treatment and diazepam/meperidine sedation. *Journal of Dental Research* 2006;**85**(9):854-8.

Hartgraves 1994 *{published data only}*

Hartgraves PM, Primosch RE. An evaluation of oral and nasal midazolam for pediatric dental sedation. *ASDC Journal of Dentistry for Children* 1994;**61**(3):175-81.

Hasty 1991 *{published data only}*

Hasty MF, Vann WF Jr, Dilley DC, Anderson JA. Conscious sedation of pediatric dental patients: an investigation of chloral hydrate, hydroxyzine pamoate, and meperidine vs chloral hydrate and hydroxyzine pamoate. *Pediatric Dentistry* 1991;**13**(1):10-9.

Heard 2010 *{published data only}*

Heard C, Smith J, Creighton P, Joshi P, Feldman D, Lerman J. A comparison of four sedation techniques for pediatric dental surgery. *Pediatric Anesthesia* 2010;**20**(10):924-30.

Henry 1990 *{published data only}*

Henry RJ, Jerrell RG. Ambient nitrous oxide levels during pediatric sedations. *Pediatric Dentistry* 1990;**12**(20):87-91.

Houpt 1985a *{published data only}*

Houpt MI, Weiss NJ, Koenigsberg SR, Desjardins PJ. Comparison of chloral hydrate with and without promethazine in the sedation of young children. *Pediatric Dentistry* 1985;**7**(1):41-6.

Houpt 1985b *{published data only}*

Houpt MI, Sheskin RB, Koenigsberg SR, Desjardins PJ, Shey Z. Assessing chloral hydrate dosage for young children. *ASDC Journal of Dentistry for Children* 1985;**52**(5):364-9.

Houpt 1989 *{published data only}*

Houpt M, Manetas C, Joshi A, Desjardins P. Effects of chloral hydrate on nitrous oxide sedation of children. *Pediatric Dentistry* 1989;**11**(1):26-9.

Houpt 1996 *{published data only}*

Houpt MI, Kupietzky A, Tofsky NS, Koenigsberg SR. Effects of nitrous oxide on diazepam sedation of young children. *Pediatric Dentistry* 1996;**18**(3):236-41.

Hulland 2002 *{published data only}*

Hulland SA, Freilich MM, Sandor GK. Nitrous oxide-oxygen or oral midazolam for pediatric outpatient sedation. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* 2002;**93**(6):643-6.

Isik 2008 *{published data only}*

Isik B, Baygin O, Bodur H. Effect of drinks that are added as flavouring in oral midazolam premedication on sedation success. *Pediatric Anesthesia* 2008;**18**(6):494-500.

Jensen 1998 *{published data only}*

Jensen B, Schroder U. Acceptance of dental care following early extractions under rectal sedation with diazepam in preschool children. *Acta Odontologica Scandinavica* 1998;**56**(4):229-32.

Kantovitz 2007 *{published data only}*

Kantovitz KR, Puppin-Rontani RM, Gaviao MB. Sedative effect of oral diazepam and chloral hydrate in the dental treatment of children. *Journal of the Indian Society of Pedodontics and Preventive Dentistry* 2007;**25**(2):69-75.

Kayalibay 1987 *{published data only}*

Kayalibay H. The use of chloral hydrate for enteral sedation in adaptation of patients in pedodontics. *Dent, Contemporary Dentistry* 1987;**2**(1):20-5.

Kerins 2007 *{published data only}*

Kerins CA, McWhorter AG, Seale NS. Pharmacologic behavior management of pediatric dental patients diagnosed with attention deficit disorder/attention deficit hyperactivity disorder. *Pediatric Dentistry* 2007;**29**(6):507-13.

Kopel 1971 *{published data only}*

Kopel HM. Hydroxyzine as a pre-operative sedative: a double-blind study with apprehensive children. *Anesthesia Progress* 1971;**18**(6):127-33.

Koroluk 2000 *{published data only}*

Koroluk LD. Dental anxiety in adolescents with a history of childhood dental sedation. *ASDC Journal of Dentistry for Children* 2000;**67**(3):200-5.

Kramer 1991a *{published data only}*

Kramer N, Krafft T, Kunzelmann KH, Hickel R. Individually controlled sedation using midazolam. *Deutsche Zahnarzthiche Zeitschrift* 1991;**46**(2):142-4.

Kramer 1991b *{published data only}*

Kramer N, Krafft T, Hunzelmann KH, Hickel R. Sedation under rectal application of midazolam. *Deutsche Zahnarzthiche Zeitschrift* 1991;**46**(9):609-11.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Kupietzky 1996 *{published data only}*

Kupietzky A, Holan G, Shapira J. Intranasal midazolam better at effecting amnesia after sedation than oral hydroxyzine: a pilot study. *Pediatric Dentistry* 1996;**18**(1):32-4.

Lahoud 2001 *{published data only}*

Lahoud GY, Averley PA, Hanlon MR. Sevoflurane inhalation conscious sedation for children having dental treatment. *Anaesthesia* 2001;**56**(5):476-80.

Leelataweedwud 2001 *{published data only}*

Leelataweedwud P, Vann WF Jr. Adverse events and outcomes of conscious sedation for pediatric patients: study of an oral sedation regimen. *Journal of the American Dental Association* 2001;**132**(11):1531-9.

Leelataweewud 2000 *{published data only}*

Leelataweewud P, Vann WF Jr, Dilley DC, Lucas WJ. The physiological effects of supplemental oxygen versus nitrous oxide/oxygen during conscious sedation of pediatric dental patients. *Pediatric Dentistry* 2000;**22**(2):125-33.

Lima 2003 *{published data only}*

Lima AR, da Costa LR, da Costa PS. A randomized, controlled, cross-over trial of oral midazolam and hydroxyzine for pediatric dental sedation. *Pesquisa Odontologica Brasileira* 2003;**17**(3):206-11.

Lindh-Stromberg 2001 *{published data only}*

Lindh-Stromberg U. Rectal administration of midazolam for conscious sedation of uncooperative children in need of dental treatment. *Swedish Dental Journal* 2001;**25**(3):105-11.

Lindsay 1980 *{published data only}*

Lindsay SJ, Roberts GJ. Methods for behaviour research on dentally anxious children. The example of relative analgesia. *British Dental Journal* 1980;**149**(6):175-9.

Lindsay 1985 *{published data only}*

Lindsay SJ, Yates JA. The effectiveness of oral diazepam in anxious child dental patients. *British Dental Journal* 1985;**159**(5):149-53.

Litman 1997 *{published data only}*

Litman RS, Kottra JA, Berkowitz RJ, Ward DS. Breathing patterns and levels of consciousness in children during administration of nitrous oxide or after midazolam premedication. *Journal of Oral and Maxillofacial Surgery* 1997;**55**(12):1372-7.

Litman 1998 *{published data only}*

Litman RS, Kottra JA, Verga KA, Berkowitz RJ, Ward DS. Chloral hydrate sedation: the additive sedative and respiratory depressant effects of nitrous oxide. *Anesthesia and Analgesia* 1998;**86**(4):724-8.

Lökken 1994 *{published data only}*

Lökken P, Bakstad OJ, Fonnelop E, Skogedal N, Hellsten K, Bjerkelund CE, et al. Conscious sedation by rectal administration of midazolam or midazolam plus ketamine as alternatives to general anesthesia for dental treatment of uncooperative children. *Scandinavian Journal of Dental Research* 1994;**102**(5):274-80.

Machen 1977 *{published data only}*

Machen JB, Ayer WA, Mueller BH. Psychomotor effects of nitrous oxide-oxygen sedation on children. *ASDC Journal of Dentistry for Children* 1977;**44**(3):219-21.

Malamed 1989 *{published data only}*

Malamed SF, Quinn CL, Hatch HG. Pediatric sedation with intramuscular and intravenous midazolam. *Anesthesia Progress* 1989;**36**(4-5):155-7.

Marshall 1999 *{published data only}*

Marshall WR, Weaver BD, McCutcheon P. A study of the effectiveness of oral midazolam as a dental pre-operative sedative and hypnotic. *Special Care in Dentistry* 1999;**19**(6):259-66.

Martinez 2006 *{published data only}*

Martinez D, Wilson S. Children sedated for dental care: a pilot study of the 24-hour postsedation period. *Pediatric Dentistry* 2006;**28**(3):260-4.

McCann 1996 *{published data only}*

McCann W, Wilson S, Larsen P, Stehle B. The effects of nitrous oxide on behavior and physiological parameters during conscious sedation with a moderate dose of chloral hydrate and hydroxyzine. *Pediatric Dentistry* 1996;**18**(1):35-41.

Milnes 2000 *{published data only}*

Milnes AR, Maupome G, Cannon J. Intravenous sedation in pediatric dentistry using midazolam, nalbuphine and droperidol. *Pediatric Dentistry* 2000;**22**(2):113-9.

Moore 1997 *{published data only}*

Moore PA, Finder RL, Jackson DL. Multidrug intravenous sedation: determinants of the sedative dose of midazolam. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* 1997;**84**(1):5-10.

Musial 2003 *{published data only}*

Musial KM, Wilson S, Preisch J, Weaver J. Comparison of the efficacy of oral midazolam alone versus midazolam and meperidine in the pediatric dental patient. *Pediatric Dentistry* 2003;**25**(5):468-74.

Myers 1977 *{published data only}*

Myers M, Shoaf HK. The intramuscular use of a combination of meperidine, promethazine and chlorpromazine for sedation of the child dental patient. *ASDC Journal of Dentistry for Children* 1977;**44**(6):453-6.

Myers 2004 *{published data only}*

Myers GR, Maestrello CL, Mourino AP, Best AM. Effect of submucosal midazolam on behaviour and physiologic response when combined with oral chloral hydrate and nitrous oxide sedation. *Pediatric Dentistry* 2004;**26**(1):37-43.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Nathan 1987 *{published data only}*

Nathan JE, West MS. Comparison of chloral hydrate-hydroxyzine with and without meperidine for management of the difficult pediatric patient. *ASDC Journal of Dentistry for Children* 1987;**54**(6):437-44.

Oei-Lim 1991 *{published data only}*

Oei-Lim LB, Vermeulen-Cranch DM, Bouvy-Berends EC. Conscious sedation with propofol in dentistry. *British Dental Journal* 1991;**170**(9):340-2.

Pandey 2010 *{published data only}*

Pandey RK, Padmanabhan MY, Saksena AK, Chandra G. Midazolam-fentanyl analgo-sedation in pediatric dental patients - a pilot study. *Journal of Clinical Pediatric Dentistry* 2010;**35**(1):105-10.

Pisalchaiyong 2005 *{published data only}*

Pisalchaiyong T, Trairatvorakul C, Jirakijja J, Yuktarnonda W. Comparison of the effectiveness of oral diazepam and midazolam for the sedation of autistic patients during dental treatment. *Pediatric Dentistry* 2005;**27**(3):198-206.

Poorman 1990 *{published data only}*

Poorman TL, Farrington FH, Mourino AP. Comparison of a chloral hydrate/hydroxyzine combination with and without meperidine in the sedation of pediatric dental patients. *Pediatric Dentistry* 1990;**12**(5):288-91.

Primosch 1999 *{published data only}*

* Primosch RE, Buzzi IM, Jerrell G. Effect of nitrous oxide-oxygen inhalation with scavenging on behavioral and physiological parameters during routine pediatric dental treatment. *Pediatric Dentistry* 1999;**21**(7):417-20.

Primosch RE, Buzzi IM, Jerrell G. Monitoring pediatric dental patients with nasal mask capnography. *Pediatric Dentistry* 2000;**22**(2):120-4.

Primosch 2001 *{published data only}*

Primosch RE, Bender F. Factors associated with administration route when using midazolam for pediatric conscious sedation. *ASDC Journal of Dentistry for Children* 2001;**68**(4):233-8.

Quarnstrom 1992 *{published data only}*

Quarnstrom FC, Milgrom P, Moore PA. Experience with triazolam in preschool children. *Anesthesia and Pain Control in Dentistry* 1992;**1**(3):157-9.

Ram 1999 *{published data only}*

Ram D, Mamber E, Chosack A, Fuks AB. The effect of metoclopramide and hydroxyzine in sedation of infants undergoing dental treatment. *ASDC Journal of Dentistry for Children* 1999;**66**(1):49-52.

Reinemer 1996 *{published data only}*

Reinemer HC, Wilson CF, Webb M. A comparison of two oral ketamine-diazepam regimens for sedating anxious pediatric dental patients. *Pediatric Dentistry* 1996;**18**(4):294-300.

Robbins 1967 *{published data only}*

Robbins MB. Chloral hydrate and promethazine as premedicants for the apprehensive child. *Journal of Dentistry for Children* 1967;**34**(5):327-31.

Roberts 1979 *{published data only}*

Roberts GJ, Gibson A, Porter J, de Zoysa S. Relative analgesia. An evaluation of the efficacy and safety. *British Dental Journal* 1979;**146**(6):177-82.

Roberts 1982 *{published data only}*

Roberts GJ, Wignall BK. Efficacy of the laryngeal reflex during oxygen-nitrous oxide sedation (relative analgesia). *British Journal of Anaesthesia* 1982;**54**(12):1277-81.

Roberts 1992 *{published data only}*

Roberts SM, Wilson CF, Seale NS, McWhorter AG. Evaluation of morphine as compared to meperidine when administered to the moderately anxious pediatric dental patient. *Pediatric Dentistry* 1992;**14**(5):306-13.

Robertson 1998 *{published data only}*

Robertson HG. A Comparison Between Nitrous Oxide and Oral Midazolam for Sedation in Paediatric Dentistry [Diploma in Conscious Sedation]. Newcastle upon Tyne (UK): University of Newcastle upon Tyne 1998.

Roelofse 1990 *{published data only}*

Roelofse JA, van der Bijl P, Stegmann DH, Hartshorne JE. Preanesthetic medication with rectal midazolam in children undergoing dental extractions. *Journal of Oral and Maxillofacial Surgery* 1990;**48**(8):791-6.

Roelofse 1993 *{published data only}*

Roelofse JA, van der Bijl P. Comparison of rectal midazolam and diazepam for premedication in pediatric dental patients. *Journal of Oral and Maxillofacial Surgery* 1993;**51**(5):525-9.

Rohlfing 1998 *{published data only}*

Rohlfing GK, Dilley DC, Lucas WJ, Vann WF Jr. The effect of supplemental oxygen on apnea and oxygen saturation during pediatric conscious sedation. *Pediatric Dentistry* 1998;**20**(8):8-16.

Sams 1992 *{published data only}*

Sams DR, Thornton JB, Wright JT. The assessment of two oral sedation drug regimens in pediatric dental patients. *ASDC Journal of Dentistry for Children* 1992;**59**(4):306-12.

Sams 1993b *{published data only}*

Sams DR, Russell CM. Physiologic response and adverse reactions in pediatric dental patients sedated with promethazine and chloral hydrate or meperidine. *Pediatric Dentistry* 1993;**15**(6):422-4.

Sanders 1997 *{published data only}*

Sanders BJ, Avery DR. The effect of sleep on conscious sedation: a follow-up study. *Journal of Clinical Pediatric Dentistry* 1997;**21**(2):131-4.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Shapira 1992 *{published data only}*

Shapira J, Holan G, Guelmann M, Cahan S. Evaluation of the effect of nitrous oxide and hydroxyzine in controlling the behavior of the pediatric dental patient. *Pediatric Dentistry* 1992;**14**(3):167-70.

Shapira 1996 *{published data only}*

Shapira J, Holan G, Botzer E, Kupietzky A, Tal E, Fuks AB. The effectiveness of midazolam and hydroxyzine as sedative agents for young pediatric dental patients. *ASDC Journal of Dentistry for Children* 1996;**63**(6):421-5.

Shapira 2004 *{published data only}*

Shapira J, Kupietzky A, Kadari A, Fuks AB, Holan G. Comparison of oral midazolam with and without hydroxyzine in the sedation of pediatric dental patients. *Pediatric Dentistry* 2004;**26**(6):492-6.

Sharma 1992 *{published data only}*

Sharma RK, Pinto RR, Mirchandani NN. Use of sedation analgesia for pediatric dentistry. *Journal of the Indian Society of Pedodontics and Preventive Dentistry* 1992;**10**(1):28-32.

Sheroan 2006 *{published data only}*

Sheroan MM, Dilley DC, Lucas WJ, Vann WF. A prospective study of 2 sedation regimens in children: chloral hydrate, meperidine, and hydroxyzine versus midazolam, meperidine, and hydroxyzine. *Anesthesia Progress* 2006;**53**(4):83-90.

Silver 1994 *{published data only}*

Silver T, Wilson C, Webb M. Evaluation of two dosages of oral midazolam as a conscious sedation for physically and neurologically compromised pediatric dental patients. *Pediatric Dentistry* 1994;**16**(5):350-9.

Songvasin 1990 *{published data only}*

Songvasin C, Pasavorakul A. A comparison of the child's behavior between two groups of oral sedative drugs. *Journal of the Dental Association of Thailand* 1990;**40**(6):237-45.

Subramaniam 2017 *{published data only}*

Subramaniam P, Girish Babu KL, Lakhotia D. Evaluation of nitrous oxide-oxygen and triclofos sodium as conscious sedative agents. *Journal of the Indian Society of Pedodontics and Preventive Dentistry* 2017;**35**(2):156-161.

Sullivan 2001 *{published data only}*

Sullivan DC, Wilson CF, Webb MD. A comparison of two oral ketamine-diazepam regimens for the sedation of anxious pediatric dental patients. *Pediatric Dentistry* 2001;**23**(3):223-31.

Tanaka 2000 *{published data only}*

Tanaka M, Sato M, Saito A, Nishikawa T. Reevaluation of rectal ketamine premedication in children: comparison with rectal midazolam. *Anaesthesiology* 2000;**93**(5):1217-24.

Tobias 1975 *{published data only}*

Tobias M, Lipschultz DH, Album MM. A study of three preoperative sedative combinations. *ASDC Journal of Dentistry for Children* 1975;**42**(6):453-9.

Tsinidou 1992 *{published data only}*

Tsinidou KG, Curzon ME, Sapsford DJ. A study to compare the effectiveness of temazepam and a chloral hydrate/hydroxyzine combination in sedating paediatric dental patients. *International Journal of Paediatric Dentistry* 1992;**2**(3):163-9.

van der Bijl 1991 *{published data only}*

van der Bijl P, Roelofse JA, Joubert JJ, van Zyl JF. Comparison of various physiologic and psychomotor parameters in patients sedated with intravenous lorazepam, diazepam, or midazolam during oral surgery. *Journal of Oral and Maxillofacial Surgery* 1991;**49**(7):672-8.

Varpio 1991 *{published data only}*

Varpio M, Wellfelt B. Some characteristics of children with dental behaviour problems. Five-year follow-up pedodontic treatment. *Swedish Dental Journal* 1991;**15**(2):83-93.

Veerkamp 1997 *{published data only}*

Veerkamp JSJ, Porcelijn T, Gruythuysen RJ. Intravenous sedation for outpatient treatment of child dental patients: an exploratory study. *ASDC Journal of Dentistry for Children* 1997;**64**(1):48-54.

Whitehead 1988 *{published data only}*

Whitehead BG, Durr DP, Adair SM, Proskin HM. Monitoring of sedated pediatric dental patients. *ASDC Journal of Dentistry for Children* 1988;**55**(5):329-33.

Wilson 1990 *{published data only}*

Wilson S. Conscious sedation and pulse oximetry: false alarms?. *Pediatric Dentistry* 1990;**12**(4):228-32.

Wilson 1992 *{published data only}*

Wilson S. Chloral hydrate and its effects on multiple physiological parameters in young children: a dose-response study. *Pediatric Dentistry* 1992;**14**(3):171-7.

Wilson 1993 *{published data only}*

Wilson S. Facial electromyography and chloral hydrate in the young dental patient. *Pediatric Dentistry* 1993;**15**(5):343-7.

Wilson 2000 *{published data only}*

Wilson S, Easton J, Lamb K, Orchardson R, Casamassimo P. A retrospective study of chloral hydrate, meperidine, hydroxyzine, and midazolam regimens used to sedate children for dental care. *Pediatric Dentistry* 2000;**22**(2):107-12.

Wilson 2002 *{published data only}*

* Wilson KE, Welbury RR, Girdler NM. A randomised, controlled, cross-over trial of oral midazolam and nitrous oxide for paediatric dental sedation. *Anaesthesia* 2002;**57**(9):860-7.

Wilson KE, Welbury RR, Girdler NM. A study of the effectiveness of oral midazolam sedation for orthodontic extraction of permanent teeth in children: a prospective, randomised, controlled, cross-over trial. *British Dental Journal* 2002;**192**(8):457-62.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Wilson 2003 *{published data only}*

Wilson KE, Girdler NM, Welbury RR. Randomized, controlled, cross-over clinical trial comparing intravenous midazolam sedation with nitrous oxide sedation in children undergoing dental extractions. *British Journal of Anaesthesia* 2003;**91**(6):850-6.

Wilson 2006 *{published data only}*

Wilson KE, Girdler NM, Welbury RR. A comparison of oral midazolam and nitrous oxide sedation for dental extractions in children. *Anaesthesia* 2006;**61**(12):1138-44.

Wilson 2007 *{published data only}*

Wilson KE, Welbury RR, Girdler NM. Comparison of transmucosal midazolam with inhalation sedation for dental extractions in children. A randomized, cross-over, clinical trial. *Acta Anaesthesiologica Scandinavica* 2007;**51**(8):1062-7.

Yanase 1996 *{published data only}*

Yanase H, Braham RL, Fukuta O, Kurosu K. A study of the sedative effect of home-administered oral diazepam for the dental treatment of children. *International Journal of Paediatric Dentistry* 1996;**6**(1):13-7.

Additional references

AAP 1992

American Academy of Pediatrics Committee on Drugs. American Academy of Pediatrics Committee on Drugs: Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. *Pediatrics* 1992;**89**(6 Pt 1):1110-5.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34.

GRADE 2004

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(7454):1490.

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Klingberg 1994

Klingberg G, Vannas Lofqvist L, Bjarnason S, Noren JG. Dental behaviour management problems in Swedish children. *Community Dentistry and Oral Epidemiology* 1994;**22**(3):201-5.

Klingberg 1995

Klingberg G, Berggren U, Carlsson SG, Noren JG. Child dental fear: cause-related factors and clinical effects. *European Journal of Oral Science* 1995;**103**(6):405-12.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Moher 2001

Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;**357**(9263):1191-4.

NDEP 2015

Public Health England, National Dental Epidemiology Programme for England. National Dental Epidemiology Programme for England: oral health survey of five-year-old children 2015. A report on the prevalence and severity of dental decay. www.nwph.net/dentalhealth/14_15_5yearold/14_15_16/DPHEP%20for%20England%20OH%20Survey%205yr%202015%20Report%20FINAL%20Gateway%20approved.pdf (accessed 15 May 2016).

NICE 2010

National Institute for Health and Care Excellence (NICE). Sedation for diagnostic and therapeutic procedures in children and young people. Clinical Guideline CG112. Available from www.nice.org.uk/guidance/cg112 2010.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Veerkamp 1995

Veerkamp JS, Gruythuysen RJM, Hoogstraten J, van Amerongen WE. Anxiety reduction with nitrous oxide: a permanent solution. *Journal of Dentistry for Children* 1995;**62**(1):44-8.

WHO 2012

World Health Organization (WHO). Oral Health Factsheet 3018, April 2012. www.who.int/mediacentre/factsheets/fs318/en/index.htm (accessed 20 March 2016).

References to other published versions of this review

Matharu 2002

Matharu L, Ashley P. Sedation of anxious children undergoing dental treatment. *Cochrane Database of Systematic Reviews* 2002, Issue 3. [DOI: 10.1002/14651858.CD003877]

Matharu 2005

Matharu LM, Ashley PF. Sedation of anxious children undergoing dental treatment. *Cochrane Database of Systematic Reviews* 2005, Issue 2. [DOI: 10.1002/14651858.CD003877.pub2]

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Matharu 2006

Matharu L, Ashley PF. Sedation of anxious children undergoing dental treatment. *Cochrane Database of Systematic Reviews* 2006, Issue 1. [DOI: 10.1002/14651858.CD003877.pub3]

Matharu 2012

Lourenço-Matharu L, Ashley PF, Furness S. Sedation of children undergoing dental treatment. *Cochrane Database of Systematic Reviews* 2012, Issue 3. [DOI: 10.1002/14651858.CD003877.pub4]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abrams 1993

Methods	Parallel design, pilot study Funding: grant from Children's Hospital Research Institute Location: USA
Participants	Inclusion criteria: children whose "unruly or hysterical behavior precluded adequate examination or treatment" n = 30 (10 per group with sufentanil divided into 2 subgroups of 5 each) Age range = 17 to 62 months
Interventions	Group 1 (n = 10): ketamine (3 mg/kg) Group 2 (n = 10): midazolam (0.4 mg/kg) Group 3 (n = 5): sufentanil (1 µg/kg) Group 4 (n = 5): sufentanil (1.5 µg/kg) All intranasal, administered by paediatric anaesthesiologist or dentist
Outcomes	Sedation scoring criteria, recovery time
Notes	Sufentanil 1.5 µg/kg and ketamine caused significant desaturations as recorded by pulse oximeter

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Selected at random" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Low risk	Study described as double-blind
Blinding - Operator/sedationist	Unclear risk	It seems likely that operating dentist was blinded
Blinding - Outcome assessor	High risk	Study described as double-blind, but "significant desaturations observed early in the study resulted in breaking the code"
Incomplete outcome assessment	Low risk	All patients included in outcome evaluation
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Unclear risk	Following significant desaturations and prolonged recovery time the dose of sufentanil was reduced to 1.0 µg/kg during the trial

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Al-Rakaf 2001

Methods	Parallel design RCT Funded by College of Dentistry Research Centre, King Saud University, Riyadh Location: Saudi Arabia
Participants	Unco-operative ("Frankl behavior score 1 or 2") n = 38 children Mean age (SD) in years and gender: Group 1 (n = 12), 3.75 (0.75), 6 male, 6 female Group 2 (n = 13), 4.3 (0.65), 6 male, 7 female Group 3 (n = 13), 4 (0.71), 6 male, 7 female
Interventions	Group 1: midazolam (0.3 mg/kg) Group 2: midazolam (0.4 mg/kg) Group 3: midazolam (0.5 mg/kg) All intranasal
Outcomes	Houpt
Notes	Papoose board. Groups subdivided into fasting and non-fasting Error in Table 1 on page 36 where 49 was written instead of 4.9

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Low risk	Double-blind
Blinding - Operator/sedationist	Low risk	Double-blind
Blinding - Outcome assessor	Low risk	Quote: "Behaviour of the child during treatment was evaluated by a trained observer who was also blind to the drug regimen used"
Incomplete outcome assessment	High risk	Number of participants included in outcome evaluation unclear as only percentage given
Free of selective reporting	Low risk	Depth of sedation, time to onset of sedation and Houpt scores reported
Free of other bias	High risk	No characteristics of the groups at baseline are reported

Alfonzo-Echeverri 1993

Methods	Parallel design Funding: not stated

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Alfonzo-Echeverri 1993 *(Continued)*

	Location: USA
Participants	Inclusion criteria: "Unco-operative behaviour during initial screening evaluation e.g. refusing to separate from parent, sit in dental chair, open mouth" n = 40 Mean age (SD) in months: Group 1 (n = 20), 40.4 (10.2) Group 2 (n = 20), 37.5 (10.6)
Interventions	Group 1: ketamine (6 mg/kg) Group 2: meperidine (2.0 mg/kg) + promethazine (0.5 mg/kg) All oral, administered by paediatric anaesthesiologist
Outcomes	Modified Houpt
Notes	Papoose board (loose straps) 30-50:50 nitrous oxide/oxygen given to all participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomised" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Low risk	Both drugs masked using flavoured soft drink
Blinding - Operator/sedationist	Low risk	Quote: "operating dentist was not aware of which drug the child received"
Blinding - Outcome assessor	Low risk	Quote: "The quality of the sedation was assessed by the operating dentist who was blinded to the study drug"
Incomplete outcome assessment	Low risk	All patients included in outcome evaluation
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	High risk	Nitrous oxide/oxygen titrated to desired effect - this is a co-intervention. Levels of nitrous oxide not reported

Avalos-Arenas 1998

Methods	Parallel design RCT Funding: not stated Location: Mexico
Participants	Inclusion criteria: ASA I healthy children undergoing dental procedures n = 40 Mean age (SD) in months and gender: Group 1 (n = 20), 27.7 (2.9), 13 male, 7 female

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Avalos-Arenas 1998 *(Continued)*

	Group 2 (n = 20), 29.2 (3.6), 14 male, 6 female
Interventions	Group 1: chloral hydrate (70 mg/kg) + placebo Group 2: chloral hydrate (70 mg/kg) + hydroxyzine (2 mg/kg) All oral, administered by nurse
Outcomes	Houpt
Notes	Papoose board

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Low risk	Study described as double-blind
Blinding - Operator/sedationist	Low risk	Quote: "dental procedures were completed by one dentist who was ignorant of the patient location group"
Blinding - Outcome assessor	Low risk	Study described as double-blind, independent rater unaware of patient treatment
Incomplete outcome assessment	High risk	Numbers evaluated not stated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No other bias

Averley 2004a

Methods	Pilot study, parallel group Funding: NHS R&D Award Location: UK
Participants	Inclusion criteria: healthy children aged 6 to 14 years who are anxious (Wong & Baker scale), unco-operative (Venham scale) requiring 'invasive' dental procedures n = 65 randomised Mean age (SD) in years, gender, weight (SD) kg: Group 1 (n = 20), 9.3 (2.2), 13 males and 7 females, 33.6 (11.2) Group 2 (n = 22), 9.6 (2.3), 15 males and 5 females, 37.6 (14.6) Group 3 (n = 23), 9.9 (2.2), 4 males and 16 females, 36.1 (11.8)
Interventions	Group 1: midazolam (IV) (0.5 mg/min) + air (nasal inhalation) Group 2: midazolam (IV) (0.5 mg/min titrated) + nitrous oxide (40%) (nasal inhalation) Group 3: midazolam (IV) (0.5 mg/min titrated) + nitrous oxide (40%) (nasal inhalation) + sevoflurane (0.3%) (nasal inhalation)

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Averley 2004a *(Continued)*

	Administered by anaesthetist
Outcomes	Primary: completion of treatment Secondary: level of co-operation during treatment, recovery time, perception of anxiety and pain and parent's satisfaction
Notes	Secondary outcomes reported only for successful sedations Dr Averley was contacted to clarify blinding and to enquire about any unpublished literature on conscious sedation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised random number generation "used Newcastle Centre for Health Services Research web-based randomisation service"
Allocation concealment (selection bias)	Low risk	Envelope which had been placed in patient's record card opened by anaesthetist
Blinding - Participant	Low risk	Blinded
Blinding - Operator/sedationist	Low risk	Dentist blinded to sedation type. Anaesthetist not blinded
Blinding - Outcome assessor	Low risk	Outcomes assessed by dentist
Incomplete outcome assessment	High risk	ITT analysis done initially. However, secondary outcomes only reported on 'successful sedations' (69% of those randomised)
Free of selective reporting	High risk	All planned outcomes reported, but not for all participants
Free of other bias	Unclear risk	Some imbalance in the groups - gender and invasiveness of treatment

Averley 2004b

Methods	Parallel group RCT Funding: NHS R&D Award and sevoflurane provided by Abbott Laboratories Location: UK
Participants	Unco-operative children 848 children randomised, 697 children received intervention and evaluated Gender, mean age (SD) years, and weight (SD) kg: Group 1 (n = 222), 81 males, 9.1 (2.7), 36.3 (13.4) Group 2 (n = 306), 127 males, 9.5 (2.7), 37.8 (14.1) Group 3 (n = 320), 103 males, 9.6 (2.5), 37.7 (14)
Interventions	Group 1: midazolam (IV) (0.5 mg/min) + air (nasal inhalation) Group 2: midazolam (IV) (0.5 mg/min) + nitrous oxide (40%) (nasal inhalation) Group 3: midazolam (IV) (0.5 mg/min) + nitrous oxide (40%) (nasal inhalation) + sevoflurane (0.3%) (nasal inhalation)
Outcomes	Primary: completion of treatment

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Averley 2004b *(Continued)*

	Secondary: level of co-operation during treatment, recovery time, perception of anxiety and pain and parent's satisfaction
Notes	Secondary outcomes reported only for successful sedations Anaesthetist involvement Group 1 not included in the analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised random number generation
Allocation concealment (selection bias)	Low risk	Allocated by independent third person
Blinding - Participant	Low risk	Blinded
Blinding - Operator/sedationist	Low risk	Sedation administered by anaesthetist. Dentist unaware of allocated treatment
Blinding - Outcome assessor	Low risk	Dentist blinded to allocated treatment undertook outcome assessments
Incomplete outcome assessment	High risk	848 children randomised and 697 received intervention and were analysed. 22%, 16% and 17% of children randomised to groups 1, 2 and 3 did not receive allocated treatment. Paper states ITT performed but this appears to be only on those who received treatment (82% of those randomised)
Free of selective reporting	High risk	All planned outcomes reported, but secondary outcomes only reported for 'successful' sedations (65% of those initially randomised)
Free of other bias	High risk	Baseline data only reported for those who received treatment. Unbalanced for gender and anxiety. Interim analysis led to discontinuation of group 1 after 222 children randomised

Aydintug 2004

Methods	Parallel group RCT Location: Turkey Funding: not stated
Participants	Unco-operative (Frankl) n = 50 Gender, mean age (unclear, possibly SD) in years, mean weight (unclear, possibly SD) in kg: Group 1 (n = 25), 18 males, 7 females, 5.36 (1.7), 19.068 (3.43) Group 2 (n = 25), 12 males, 13 females, 4.96 (1.513), 17.804 (3.08)
Interventions	Group 1: midazolam (0.5 mg/kg) (orally)

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Aydintug 2004 *(Continued)*

	Group 2: midazolam (0.35 mg/kg) (rectal)
Outcomes	Ramsay Sedation Score, acceptance of local anaesthetic, acceptance of sedation, operating conditions
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly chosen" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	High risk	No blinding
Blinding - Operator/sedationist	High risk	No blinding
Blinding - Outcome assessor	High risk	No blinding
Incomplete outcome assessment	High risk	Numbers evaluated not stated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No apparent differences between groups at baseline

Baygin 2010

Methods	Parallel group RCT Location: Turkey Funding: not stated
Participants	Unco-operative (Frankl > 3) n = 60 (n = 15 per group) Gender, mean age (unclear, possibly SD) in years, mean weight (unclear, possibly SD) in kg: Group 1 (n = 15), 10 males, 5 females, 5.33 (0.62), 18.93 (2.31) Group 2 (n = 15), 11 males, 4 females, 5.27 (0.80), 19.07 (3.62) Group 3 (n = 15), 9 males, 6 females, 5.20 (0.41), 18.20 (2.34) Group 4 (n = 15), 6 males, 9 females, 5.53 (0.99), 20.01 (3.99)
Interventions	Group 1: hydroxyzine (1 mg/kg) (oral) + 40% nitrous oxide oxygen Group 2: midazolam (0.7 mg/kg) + 40% nitrous oxide oxygen Group 3: ketamine (3 mg/kg) + midazolam (0.25 mg/kg) + 40% nitrous oxide oxygen

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Baygin 2010 *(Continued)*

	Group 4: 40% nitrous oxide oxygen
Outcomes	Treatment completion, Ramsay Sedation Scale, Bispectral Index System, adverse effects
Notes	No placebo used 40% nitrous oxide all patients Sample size calculation given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Study drugs given by a trained nurse
Blinding - Participant	High risk	Study described as being double-blind, but no placebo used for group 4 who did not receive an oral medication
Blinding - Operator/sedationist	Low risk	Study drugs administered by nurse and described as double-blind
Blinding - Outcome assessor	Low risk	One of the researchers who was blinded to the premedication drug evaluated every patient
Incomplete outcome assessment	Low risk	All patients evaluated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No other risks identified

Bhatnagar 2012

Methods	Parallel design Funding: not stated Location: India
Participants	Inclusion criteria: patient who exhibited fearful or refractory behaviour at previous dental appointments, as documented by Frankl behaviour rating scale n = 60 Age range = 3 to 9 years
Interventions	Group 1: midazolam (0.5 mg/kg body weight) Group 2: tramadol (2 mg/kg body weight) Group 3: triclofos (70 mg/kg body weight) Group 4: zolpidem (0.4 mg/kg body weight) All orally

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Bhatnagar 2012 *(Continued)*

Outcomes	Sedation rating scale, ease of treatment completion, recovery time
Notes	No additional drug was administered if the children spat the drug or vomited. The number of children who spat the drug were not recorded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Unclear risk	Not described
Blinding - Operator/sedationist	Unclear risk	Not described
Blinding - Outcome assessor	Unclear risk	Not described
Incomplete outcome assessment	Unclear risk	Not described
Free of selective reporting	High risk	All planned outcomes not reported
Free of other bias	High risk	No information on the demographic characteristic at baseline

Bui 2002

Methods	Parallel group RCT Location: USA Funding: not stated
Participants	Unco-operative children n = 22 Mean age (SD) in months: Group 1 (n = 11), 34 (6.28) Group 2 (n = 11), 33 (6.65)
Interventions	Group 1: ketamine (10 mg/kg) + promethazine (1.1 mg/kg) Group 2: ketamine (10 mg/kg) All oral
Outcomes	Houpt, adverse effects
Notes	Papoose board 35:65 nitrous oxide/oxygen given to all participants

Risk of bias

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Bui 2002 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly selected" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Independent person randomly selected, allocated and administered
Blinding - Participant	Low risk	Study described as double-blind - operator, dentist/anaesthetist and patient did not know which regimen was selected
Blinding - Operator/sedationist	Low risk	Study described as double-blind - operator, dentist/anaesthetist and patient did not know which regimen was selected
Blinding - Outcome assessor	Low risk	Study described as double-blind - operator, dentist/anaesthetist and patient did not know which regimen was selected
Incomplete outcome assessment	Low risk	All randomised participants evaluated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No other bias

Eshghi 2016

Methods	Parallel design Funding: not stated Location: Iran
Participants	Inclusion criteria: unco-operative children (1 or 2 negatives based on Frankl behaviour management rating scale) n = 32 Age range = 3 to 7 years Group 1 (n = 16), 7 males and 9 females Group 2 (n =16), 8 males and 8 females
Interventions	Group 1: remifentanil (0.1 µg/kg/min) + midazolam (0.01 mg/kg) + propofol (0.5 mg/kg) Group 2: ketamine (0.5 mg/kg) + midazolam (0.1 mg/kg) + propofol (0.5 mg/kg) All IV
Outcomes	Bispectral Index System, DSTG scale
Notes	Results show BIS values for general anaesthesia or profound sedation. Patients with extraction or who needed dental work time more than 45 minutes were excluded

Risk of bias

Bias	Authors' judgement	Support for judgement

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Eshghi 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quotes: "On the day of the procedure each subject was given a code of which only the anethesiologist was aware" and "patients were randomly divided into 2 groups based on odd or even code"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Low risk	Study described as double-blinded
Blinding - Operator/sedationist	High risk	Study described as double-blinded and operator blinded but the sedationist (anaesthesiologist) not blinded
Blinding - Outcome assessor	High risk	The BIS score was recorded by the anaesthesiologist
Incomplete outcome assessment	Low risk	All randomised participants evaluated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	High risk	The number of the "few cases of severe nausea and vomiting" were not reported in the remifentanil group

Faytrouny 2007

Methods	Parallel group RCT Funding: not stated Location: Turkey
Participants	Inclusion criteria: unco-operative fearful healthy children, ASA I, requiring sedation due to Frankl score of definitely negative or negative n = 30, 14 females, 16 males Mean age (SD) months: Group 1 (n = 15), 61.9 (11.9) Group 2 (n = 15), 53.7 (12.8)
Interventions	Group 1: hydroxyzine (20 mg 24 hours before) + hydroxyzine (3.7 mg/kg at the appointment) Group 2: hydroxyzine (3.7 mg/kg at the appointment) All oral
Outcomes	Houpt
Notes	20 mg/kg as stated in the text a mistake as this appears to be high. 20 mg in the abstract, presumably this is the correct value 50:50 nitrous oxide/oxygen given to all participants Pediwrap used after sedation achieved

Risk of bias

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Faytrouny 2007 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Subjects were assigned randomly" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	High risk	Drugs given at home by parents or administered at clinic by the assistant
Blinding - Operator/sedationist	Low risk	Quote: "Blinded to subject group assignment"
Blinding - Outcome assessor	Unclear risk	Outcomes assessed by the "monitoring dentist." Unclear whether this person was blinded to treatment
Incomplete outcome assessment	High risk	Numbers evaluated not stated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No other bias

Gallardo 1994

Methods	Parallel group RCT Location: Chile Funding: not stated
Participants	Inclusion criteria: children referred to pedodontic clinic for treatment after treatment refusal following conventional psychological approach n = 32, age range = 4 to 10 years 17 male, 15 female
Interventions	Group 1: midazolam (7.5 mg) Group 2: placebo All oral, administered by dental assistant
Outcomes	Overall sedation, mental attitude, hypnotic effects, motor activity, ease of treatment
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Low risk	Study described as double-blind

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Gallardo 1994 *(Continued)*

Blinding - Operator/sedationist	High risk	Study described as double-blind but likely that sedative effects of active intervention were obvious to dentist
Blinding - Outcome assessor	Low risk	Study described as double-blind
Incomplete outcome assessment	High risk	Numbers evaluated not stated
Free of selective reporting	Low risk	All planned outcomes reported on
Free of other bias	Low risk	No other bias

Gomes 2017

Methods	Parallel RCT Funding: government Location: Brazil
Participants	Inclusion criteria: children requiring sedation for dental procedures Mean age (SD) in years, gender, mean weight (25% median to 75%) in kg: Group 1 (n = 13), 4.7 (0.6), 10 males, 3 females, 16.5 (15.7, 19.6) Group 2 (n = 14), 5.2 (0.8), 8 males, 6 females, 19.6 (16.7, 23.9)
Interventions	Group 1: midazolam (0.5 mg/kg) + ketamine (3 mg/kg) (oral) Group 2: midazolam (0.5 mg/kg) (oral) + ketamine (3 mg/kg) (oral) + sevoflurane (0.1% to 0.4%) (inhalation)
Outcomes	Houpt, adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "1 researcher that did not participate in the interventions and outcomes assessments created a computer-generated list through the website Randomization.com (www.randomization.com)"
Allocation concealment (selection bias)	Low risk	Quote: "Each child was assigned to a group at the day of the intervention according to the consecutively numbered code generated in the list. As only the physicians knew the codes, they assigned participants to interventions"
Blinding - Participant	Low risk	Study reported as triple-blind
Blinding - Operator/sedationist	Low risk	Study reported as triple-blind

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Gomes 2017 *(Continued)*

Blinding - Outcome assessor	Low risk	Study reported as triple-blind
Incomplete outcome assessment	Low risk	All patients evaluated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Unclear risk	More boys in Group 1 compared to Group 2. No significant differences in other demographic characteristics

Isik 2008a

Methods	Parallel Funding: not stated Location: Turkey
Participants	Inclusion criteria: children requiring sedation for dental procedures Mean age (SD) in years, gender, mean weight (SD) in kg: Group 1 (n = 15), 4.87 (0.99), 7 males, 8 females, 18.87 (2.5) Group 2 (n = 15), 4.93 (1.11), 7 males, 8 females, 17.87 (3.88) Group 3 (n = 15), 4.93 (1.10), 8 males, 7 females, 18.6 (3.31) Group 4 (n = 15), 5.01 (1.03), 9 males, 6 females, 19.73 (4.77)
Interventions	Group 1: melatonin (3 mg) (60 minutes prior to treatment) Group 2: melatonin (0.5 mg/kg) (60 minutes prior to treatment) Group 3: midazolam (0.75 mg/kg) (15 minutes prior to treatment) Group 4: placebo (half group 15 minutes prior to treatment and half 60 minutes prior to treatment) All oral, administered by nurse
Outcomes	Ramsay Sedation Score
Notes	40:60 nitrous oxide/oxygen given to all Sample size calculation given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Low risk	Study reported as double-blind

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Isik 2008a *(Continued)*

Blinding - Operator/sedationist	Low risk	Quote: "neither the researcher nor the parents were informed which drug was administered"
Blinding - Outcome assessor	Low risk	Study reported as double-blind
Incomplete outcome assessment	Low risk	All patients evaluated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No apparent differences between the groups at baseline

Isik 2008b

Methods	Parallel group RCT Location: Turkey Funding: not stated
Participants	Unco-operative, Frankl scores 3, 4 Mean age (SD) in years, gender, mean weight (SD) in kg: Group 1 (n = 14), 4.6 (1.2), 7 males, 7 females, 15.6 (2.8) Group 2 (n = 13), 4.4 (1.0), 8 males, 5 females, 16.2 (2.4) Group 3 (n = 13), 4.4 (0.9), 6 males, 7 females, 16.1 (2.4) Group 4 (n = 13), 4.3 (0.9), 5 males, 8 females, 15.8 (2.6)
Interventions	Group 1: midazolam (0.2 mg/kg) Group 2: midazolam (0.5 mg/kg) Group 3: midazolam (0.75 mg/kg) Group 4: midazolam (1 mg/kg) All orally
Outcomes	Ramsay Sedation Score
Notes	40:60 nitrous oxide/oxygen given to all Translated from Turkish

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomized" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Isik 2008b *(Continued)*

Blinding - Participant	Low risk	Subject blinded
Blinding - Operator/sedationist	Low risk	Dentist blinded
Blinding - Outcome assessor	Unclear risk	Separate outcome assessor, blinding unclear
Incomplete outcome assessment	Low risk	All patients evaluated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No other bias

Jensen 1999

Methods	Parallel group RCT Funding: grants from Swedish Dental Association Location: Sweden
Participants	n = 90 Median age (age range) in months and gender: Group 1 (n = 45), 32 (18 to 44), 23 male, 22 female Group 2 (n = 45), 29 (15 to 44), 23 male, 22 female
Interventions	Group 1: diazepam (0.7 mg/kg) Group 2: midazolam (0.3 mg/kg) All rectal, administered by dentist
Outcomes	Wilton's sedation scale, acceptance of treatment (Holst)
Notes	Dr Jensen was contacted to clarify blinding and to enquire about any unpublished literature on conscious sedation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly allocated" - method of sequence generation not described
Allocation concealment (selection bias)	Low risk	Coded bottles
Blinding - Participant	Low risk	Quote: "delivered by the pharmacy in coded bottles and neither the dentist nor the parents knew which agent was being used"
Blinding - Operator/sedationist	Low risk	Quote: "delivered by the pharmacy in coded bottles and neither the dentist nor the parents knew which agent was being used"
Blinding - Outcome assessor	Low risk	Dentist assessed outcomes

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Jensen 1999 *(Continued)*

Incomplete outcome assessment	High risk	Numbers evaluated not stated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No differences between groups at baseline

Kapur 2004

Methods	Parallel group RCT Location: India Funding: not stated
Participants	Potentially unco-operative (not measured), healthy children ASA I with > 1 carious deciduous mandibular molar requiring a class II amalgam restoration n = 40 Age: younger than 4 years old - no differences at baseline with regards to age, sex and body weight
Interventions	Group 1: midazolam (0.5 mg/kg) (oral/transmucosal) Group 2: placebo (same volume) Administered by chief investigator
Outcomes	Completion of treatment, sedation time, treatment time
Notes	Type of tooth or cavity matched for dental treatment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly divided" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Low risk	Study reported as double-blind
Blinding - Operator/sedationist	Low risk	"chief investigator blind to treatment allocation" - performed the restorative procedures
Blinding - Outcome assessor	Low risk	"chief investigator blind to treatment allocation" - recorded the various parameters
Incomplete outcome assessment	High risk	Numbers evaluated not stated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No differences at baseline with regards to age, sex and body weight

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Kaviani 2015

Methods	Parallel design Funding: not stated Location: Iran
Participants	Inclusion criteria: healthy children referred to dental operating room and needed treatment on "left upper teeth" n = 38 Age range = 4 to 9 years Gender, mean age in years: Group 1 midazolam-ketamine group (n = 18), 8 male, 10 female, 6.27 Group 2 midazolam-fentanyl group (n = 20), 12 male, 8 female, 6.75
Interventions	GROUP 1: midazolam (0.05 mg/kg) + ketamine (0.5 mg/kg) GROUP 2: midazolam (0.05 mg/kg) + fentanyl (0.5 µg/kg) All intravenous, administered by an anaesthesiologist
Outcomes	Dental sedation teacher groups system, Frankl behaviour rating scale
Notes	Additional midazolam (0.25 mg) was administered to both groups if needed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Unclear risk	Not described
Blinding - Operator/sedationist	Low risk	Operating dentist not aware of the group he was treating
Blinding - Outcome assessor	Low risk	Quote: "Neither the dentist nor the person who was collecting data had a clue about grouping method"
Incomplete outcome assessment	High risk	Dropouts and failed sedation difficult to examine, typo errors in tables
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	High risk	No information on the demographic characteristics at baseline

Koirala 2006

Methods	Parallel group RCT

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Koirala 2006 *(Continued)*

	Location: Nepal
	Funding: not stated
Participants	6 experimental groups, n = 120
	Age range 2 to 9 years
Interventions	Group 1 (n = 20): midazolam (0.5 mg/kg)
	Group 2 (n = 20): ketamine (5 mg/kg)
	Group 3 (n = 20): zolpidem (0.4 mg/kg)
	Group 4 (n = 20): midazolam (0.4 mg/kg) + ketamine (3 mg/kg)
	Group 5 (n = 20): midazolam (0.5 mg/kg) + tramadol (2 mg/kg)
	Group 6 (n = 20): zolpidem (0.4 mg/kg) + tramadol (2 mg/kg)
	All oral
Outcomes	Onset of action, level of sedation, ease of treatment completion, recovery time, anterograde amnesia
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Low risk	Study reported as double-blind
Blinding - Operator/sedationist	Low risk	No separate outcome assessor described. Assumed dentist was blinded
Blinding - Outcome assessor	Low risk	Study reported as double-blind
Incomplete outcome assessment	High risk	Numbers evaluated not reported
Free of selective reporting	Low risk	Planned outcomes reported
Free of other bias	High risk	No characteristics of the groups at baseline are reported

Lahoud 2002

Methods	Parallel group RCT
	Location: UK
	Funding: Abbot Laboratories provided the sevoflurane

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Lahoud 2002 *(Continued)*

Participants	Inclusion criteria: anxious children 3 to 10 years old able to sit in chair, tolerate dental exam, accept nasal hood, with unobstructed nasal airway n = 411 Mean age (SD) in years: Group 1 (n = 170), 6.2 (1.9) Group 2 (n = 241), 6 (1.7)
Interventions	Group 1: 40:60 nitrous oxide/oxygen Group 2: 40:60 nitrous oxide/oxygen + 0.1% to 0.3% sevoflurane All inhalation, administered by anaesthetist
Outcomes	Venham scale, level of sedation, treatment completion
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated" - method of sequence generation not described
Allocation concealment (selection bias)	Low risk	"allocated by means of sealed envelopes" - not stated whether these were numbered
Blinding - Participant	Unclear risk	Not described
Blinding - Operator/sedationist	Unclear risk	Not described
Blinding - Outcome assessor	Unclear risk	Not described
Incomplete outcome assessment	Low risk	All randomised participants included in outcome evaluation
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No reported differences between groups at baseline

Lam 2005

Methods	Parallel group RCT Location: USA Funding: not stated
Participants	Inclusion criteria: healthy ASA I children with severe caries involving 2 or more quadrants, very anxious, unlikely to tolerate treatment with or without N_2O, requiring IV sedation. Unco-operative (no index used) n = 23, 15 males, 7 females Mean age (range) in years: 5.13 (2-9)

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Lam 2005 *(Continued)*

	Mean weight (range) in kg: 21.74 (12-30)
Interventions	Group 1 (n = 12): midazolam (0.2 mg/kg) (intramuscular) Group 2 (n = 11): midazolam (0.2 mg/kg) (intranasal) All used as premedication for unspecified IV sedation drug. Drug administered by anaesthetist
Outcomes	Houpt
Notes	50% nitrous oxide all patients and papoose board

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	High risk	Not possible
Blinding - Operator/sedationist	High risk	Not blinded
Blinding - Outcome assessor	Low risk	Quote: "evaluators had no prior knowledge of which premedication route had been used"
Incomplete outcome assessment	High risk	Numbers evaluated unclear
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	High risk	No characteristics of the groups at baseline are reported

Lee-Kim 2004

Methods	Parallel group RCT Location: USA Funding: not stated
Participants	Inclusion criteria: healthy children ASA I requiring > 1 visits for comprehensive dental care, who demonstrated definitely or slightly negative behaviour on Frankl scale n = 40 Gender, mean age (unclear, possibly SD) in months, mean weight (unclear, possibly SD) in kg: Group 1 (n = 20), 11 males, 9 females, 40.8 (11), 17 (3.6) Group 2 (n = 20), 10 males, 10 females, 38.5 (9.8), 16.2 (4)
Interventions	Group 1: midazolam (0.7 mg/kg) (oral)

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Lee-Kim 2004 *(Continued)*

	Group 2: midazolam (0.3 mg/kg) (nasal) Administered by dental provider
Outcomes	Modified Houpt, time of onset, duration of sedation
Notes	45% nitrous oxide all patients and papoose board

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"subjects randomly received…" - method of sequence generation not described
Allocation concealment (selection bias)	High risk	Quote: "The principal investigator conducted subject selection and random assignment of PO or IN midazolam administration"
Blinding - Participant	High risk	Not possible
Blinding - Operator/sedationist	High risk	Not possible
Blinding - Outcome assessor	Low risk	Independent assessor using videotapes
Incomplete outcome assessment	High risk	Numbers evaluated not stated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No apparent differences between groups at baseline

Malhotra 2016

Methods	Parallel design RCT Funding: not stated Location: India
Participants	Inclusion criteria: ASA 1. Early childhood caries and negative behaviour according to Frankl behaviour rating scale in their first visit at outpatients n = 36 Age range = 3 to 9 years Mean age (SD) in years: 4.60 $\pm$ 1.99 Mean weight (SD) kg: 15.62 $\pm$ 4.21
Interventions	Group 1: intranasal normal saline, oral midazolam (0.5 mg/kg) + oral ketamine (5 mg/kg) in 30 ml of mango juice Group 2: intranasal dexmedetomidine (1 µ/kg), 30 ml of mango juice Group 3: intranasal normal saline, 30 ml of mango juice

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Malhotra 2016 *(Continued)*

Outcomes	Modified Observer Assessment of Alertness and Sedation (MOAAS), Houpt scale
Notes	Participants in the groups not evenly distributed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "allocated to 1 of 3 groups by envelope draw method"
Allocation concealment (selection bias)	Low risk	Quote:"3 different color codes were decided for each group and were printed and placed within envelope to eliminate any dissimilarity"
Blinding - Participant	Unclear risk	Not described
Blinding - Operator/sedationist	Low risk	Quote: "performed by a single experienced pediatric dentist, who was blinded to the study design"
Blinding - Outcome assessor	Low risk	Quote: "Evaluators and attending pedodontist were blinded to the study drug given"
Incomplete outcome assessment	Unclear risk	Material and methods mention "about 36" patients included in the study. Result table show count of 36 as sample size
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	High risk	Little information on demographics of participants in each group at baseline

McKee 1990

Methods	Parallel group RCT Location: USA Funding: not stated
Participants	Inclusion criteria: healthy children 2 to 5 years old, Frankl scale behaviour negative or definitely negative, failed non-pharma management, requiring restorative treatment with LA and rotary instrument n = 60 Mean age (SE) in months: Group 1 (n = 15), 36.5 (2.7) Group 2 (n = 15), 41.7 (3) Group 3 (n = 15), 35.9 (2.7) Group 4 (n = 15), 43 (2.7)
Interventions	Group 1: placebo Group 2: meperidine (0.25 mg/lb) (approximately 0.11 mg/kg) Group 3: meperidine (0.50 mg/lb) (approximately 0.22 mg/kg) Group 4: meperidine (1 mg/lb) (approximately 0.45 mg/kg) All intramuscular, administered by "third party"
Outcomes	Modified Houpt, dichotomous behaviour scale, 10-point behaviour scale, global rating scale, adverse effects

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

McKee 1990 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Low risk	Quote: "Dentist, patient and research observer were unaware of treatment allocation"
Blinding - Operator/sedationist	Low risk	Quote: "Dentist, patient and research observer were unaware of treatment allocation"
Blinding - Outcome assessor	Low risk	Quote: "Dentist, patient and research observer were unaware of treatment allocation"
Incomplete outcome assessment	Low risk	Dropouts/aborted patients reported
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No apparent differences between groups at baseline

Meyer 1990

Methods	Parallel group RCT Location: USA Funding: not stated
Participants	Inclusion criteria: children who were unco-operative at screening visit, ASA I needing dental treatment n = 40 Mean age (age range) in months: Group 1 (n = 20), 44 (21 to 74) Group 2 (n = 20), 42 (23 to 64)
Interventions	Group 1: triazolam (0.02 mg/kg) Group 2: chloral hydrate (40 mg/kg) + hydroxyzine (25 mg) All oral, administered by operating dentist
Outcomes	Houpt
Notes	Papoose board 50:50 nitrous oxide/oxygen given to all

Risk of bias

Bias	Authors' judgement	Support for judgement

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Meyer 1990 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Random administration" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Unclear risk	Not clear if the patient was blinded or not
Blinding - Operator/sedationist	High risk	Operating dentist not blinded to drug given
Blinding - Outcome assessor	Low risk	Quote: "Sedations were videotaped and evaluated by 2 paediatric dentists not involved in the study"
Incomplete outcome assessment	High risk	Numbers evaluated unclear
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No apparent differences between groups at baseline

Moody 1986

Methods	Parallel group RCT Location: USA Funding: not stated
Participants	Inclusion criteria: healthy children aged 27 to 74 months who were unco-operative at previous appointments and required dental restorations n = 30 Mean age in months: Group 1 (n = 10), 39.6 Group 2 (n = 10), 42 Group 3 (n = 10), 38.4
Interventions	Group 1: chloral hydrate (50 mg/kg) (oral) Group 2: chloral hydrate (50 mg/kg) (rectal) Group 3: chloral hydrate (30 mg/kg) + hydroxyzine (25 mg) (oral) All administered by operating dentist
Outcomes	Modified Barker, overall quality sedation
Notes	50:50 nitrous oxide/oxygen given to all, reduced to 30% to 40% after LA administered

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly placed" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Moody 1986 *(Continued)*

Blinding - Participant	High risk	Not possible
Blinding - Operator/sedationist	High risk	Operator administered sedation
Blinding - Outcome assessor	High risk	Operator administered sedation and assessed outcomes
Incomplete outcome assessment	High risk	Numbers evaluated unclear
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No significant differences between groups reported at baseline

Moore 1984

Methods	Parallel group RCT Location: USA/Canada Funding: PHS grant
Participants	Inclusion criteria: healthy children aged 2 to 5 years who were considered unco-operative and required treatment under local anaesthesia n = 60 Gender, mean age in years: Group 1 (n = 15), 11 male, 4 female, 3.6 Group 2 (n = 15), 7 male, 8 female, 3.3 Group 3 (n = 15), 9 male, 6 female, 3.8 Group 4 (n = 15), 7 male, 8 female, 3.9
Interventions	Group 1: placebo Group 2: chloral hydrate (20 mg/kg) Group 3: chloral hydrate (40 mg/kg) Group 4: chloral hydrate (60 mg/kg) All oral, administered by research assistant
Outcomes	Behaviour evaluations, completion of treatment
Notes	40:60 nitrous oxide/oxygen given to all

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Low risk	Quote: "double blind conditions"
Blinding - Operator/sedationist	Low risk	Quote: "double blind conditions"

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Moore 1984 *(Continued)*

Blinding - Outcome assessor	Low risk	Each child was monitored by a single research assistant, assumed to be blinded to allocated treatment
Incomplete outcome assessment	High risk	Numbers evaluated unclear
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No apparent differences between groups at baseline

Moreira 2013

Methods	Parallel design Funding: not stated Location: Brazil
Participants	Inclusion criteria: ASA 1 presenting with early childhood caries and definitely negative behaviour n = 44 Age range = below 36 months Mean age (SD) in months, gender: Group 1 (n = 11), 27.1 (8.3), 6 males, 5 females Group 2 (n = 18, parents refused treatment for 2), 27.7 (5.5), 9 males, 7 females Group 3 (n = 15, parents refused treatment for 1), 27.3 (6.4), 9 males, 5 females
Interventions	Group 1: midazolam (0.5 mg/kg) + ketamine (3 mg/kg) Group 2: midazolam (1 mg/kg) Group 3: no sedation Group 1 and 2 orally
Outcomes	Ohio State University Behavior Rating Scale (OSUBRS) reported at individual points or as a sum of all the measurements at individual points added together
Notes	Protective stabilization used. No placebo given

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomized using envelopes"
Allocation concealment (selection bias)	Low risk	Quotes: "48 opaque sealed envelopes divided equally among the 3 techniques", "shuffled the envelopes and had her pull 1 out. After opening the envelope, the mother reviewed the insert and the ascertained the child's treatment assignment"

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Moreira 2013 *(Continued)*

Blinding - Participant	High risk	Quote: "After opening the envelope, the mother reviewed the insert and ascertained the child's treatment assignment"
Blinding - Operator/sedationist	High risk	Blinding of the operator is unclear, all sedation was carried out by 1 anaesthesiologist and they appear to be unblinded
Blinding - Outcome assessor	High risk	Quote: "The behaviour of the children was assessed by 1 trained, unblinded observer throughout the dental exam"
Incomplete outcome assessment	Low risk	All patients and dropouts mentioned
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	High risk	Not clear if Group 3 had a placebo intervention or no intervention at all

Mortazavi 2009

Methods	Parallel group RCT Location: Iran Funding: university grant
Participants	Inclusion criteria: healthy children rate 1 or 2 on Frankl scale requiring dental treatment n = 40 Mean age (SD) in years: 3.99 (0.38)
Interventions	Group 1: placebo Group 2: midazolam (0.25 mg/kg) All oral, administered by dental nurse
Outcomes	Houpt
Notes	Lack of demographic data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly given" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Low risk	Study described as double-blind
Blinding - Operator/sedationist	Low risk	Quote: "operator blind to drug used"

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Mortazavi 2009 *(Continued)*

Blinding - Outcome assessor	Low risk	Study described as double-blind - outcomes assessed by "senior investigator"
Incomplete outcome assessment	Low risk	All randomised participants included in outcome assessment
Free of selective reporting	Low risk	Planned outcomes reported
Free of other bias	Unclear risk	Very little information on participant demographics at baseline

Nathan 1988

Methods	Parallel group RCT Location: USA Funding: university grant
Participants	Inclusion criteria: healthy children without previous dental experience requiring 4 restorative treatment visits, rated as anxious at screening visit n = 35 Age range = 48 to 72 months
Interventions	Group 1: no intervention Group 2: placebo inhalation (oxygen) Group 3: 20-50:50 nitrous oxide/oxygen Inhalation, all administered by anaesthetist
Outcomes	Venham scale, parental questionnaire, behavioural screening instrument
Notes	Dr Nathan was contacted to clarify the blinding in this trial and to enquire about any unpublished trials

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Unclear risk	Study described as double-blind. This only applies to Group 2 and Group 3
Blinding - Operator/sedationist	Unclear risk	Study described as double-blind. This only applies to Group 2 and Group 3
Blinding - Outcome assessor	Low risk	Ratings of unco-operative behaviour and anxiety were made by trained judges naive to experimental hypotheses and inhalant conditions
Incomplete outcome assessment	Unclear risk	Numbers included/dropouts unclear
Free of selective reporting	Low risk	All planned outcomes reported

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Nathan 1988 *(Continued)*

Free of other bias	High risk	No information on demographic characteristics at baseline

Park 2006

Methods	Parallel Location: South Korea Funding: not stated
Participants	Inclusion criteria: ASA I, under 6 years, 20 kg body weight, unco-operative requiring sedation for dental treatment Mean age in months (SD), gender, mean weight in kg (SD): Group 1 (n = 15), 44.5 (14.1), 6 males and 9 females, 15.6 (2.7) Group 2 (n = 16), 34.3 (9.3), 11 males and 5 females, 15.1 (2.6)
Interventions	Group 1: chloral hydrate (60 mg/kg) + hydroxyzine (1 mg/kg). Both oral Group 2: chloral hydrate (60 mg/kg) (oral) + hydroxyzine (1 mg/kg) (oral) + midazolam (0.1 mg/kg) (submucosal) Administered by dentist
Outcomes	Houpt, requirement for restraint
Notes	50% nitrous oxide/oxygen administered to all

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	High risk	Not blinded
Blinding - Operator/sedationist	High risk	Not blinded
Blinding - Outcome assessor	Low risk	Video used, assessor blinded
Incomplete outcome assessment	Low risk	All outcomes reported
Free of selective reporting	Low risk	Data from all subjects reported
Free of other bias	Low risk	No other bias detected

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Rai 2007

Methods	Parallel group RCT Location: India Funding: not stated
Participants	Inclusion criteria: healthy, unco-operative, anxious and apprehensive children requiring oral prophylaxis/fluoride gel/restorations/extractions/composite fillings/pulp therapies n = 30 (10 per group) Age range: 3 to 6 years
Interventions	Group 1: midazolam (0.1 mg/kg) (bolus) + 0.004 mg/kg/min infusion Group 2: propofol (1 mg/kg) (bolus) + 0.06 mg/kg/min infusion Group 3: ketamine (0.5 mg/kg) (bolus) + 0.01 mg/kg/min infusion All intravenous All children had premedication 1 hour before, comprising 0.5 mg/kg midazolam and atropine (0.6 mg), all drugs administered by anaesthetist
Outcomes	Houpt
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly divided" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Unclear risk	Not described
Blinding - Operator/sedationist	Unclear risk	Not described
Blinding - Outcome assessor	Unclear risk	Not described
Incomplete outcome assessment	High risk	Numbers evaluated not stated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Unclear risk	Very little information on participant demographics at baseline

Reeves 1996

Methods	Parallel group RCT

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Reeves 1996 *(Continued)*

	Location: USA Funding: not stated
Participants	Inclusion criteria: healthy children aged 27 to 73 months, definitely negative behaviour on Frankl scale n = 40 Gender, mean age (age range) in months: Group 1 (n = 20), 11 male, 9 female, 48 (32 to 73) Group 2 (n = 20), 10 male, 10 female, 42 (27 to 70)
Interventions	Group 1: chloral hydrate (50 mg/kg) + hydroxyzine (25 mg) Group 2: midazolam (0.5 mg/kg) + acetaminophen (10 mg/kg) All oral, administered by paediatric dentist not involved in study
Outcomes	Modified Houpt
Notes	Papoose board

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were assigned randomly" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Low risk	Study described as double-blind
Blinding - Operator/sedationist	Low risk	Study described as double-blind
Blinding - Outcome assessor	Low risk	Outcomes were evaluated by primary operator and 1 observer
Incomplete outcome assessment	High risk	Numbers evaluated not stated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No apparent differences between groups at baseline

Roelofse 1996a

Methods	Parallel group RCT Location: South Africa Funding: not stated
Participants	Inclusion criteria: unco-operative children n = 100 Gender, mean age (SD) in years: Group 1 (n = 50), 24 male, 26 female, 4.3 (1) Group 2 (n = 50), 22 male, 28 female, 4.3 (1.1)

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Roelofse 1996a *(Continued)*

Interventions	Group 1: ketamine (5 mg/kg) + midazolam (0.35 mg/kg) Group 2: midazolam (1 mg/kg) All rectal, administered by member of research team
Outcomes	Ramsay Sedation Score, movement, crying, overall sedation and behaviour
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Low risk	Study described as double-blind
Blinding - Operator/sedationist	Low risk	Study described as double-blind
Blinding - Outcome assessor	Low risk	Quote: "Anxiety was scored by an independent observer"
Incomplete outcome assessment	High risk	Numbers evaluated not stated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No apparent differences between groups at baseline

Roelofse 1996b

Methods	Parallel group RCT Location: South Africa Funding: not stated
Participants	Inclusion criteria: children ASA I aged 2 to 7 years old, requiring dental extraction under sedation n = 60 Gender, mean age (SD) in years: Group 1 (n = 30), 14 male, 16 female, 4.8 (1.3) Group 2 (n = 30), 16 male, 14 female, 4.9 (1.3)
Interventions	Group 1: 0.5 ml/kg of trimeprazine 6 mg/ml + physeptone (0.4 mg/ml) (SOP) Group 2: ketamine (12.5 mg/kg) All oral, administered by a member of the research team not the operator
Outcomes	Anxiety, level of sedation, movement, crying, overall behaviour
Notes	

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Roelofse 1996b *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Assigned randomly" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Low risk	Study described as double-blind
Blinding - Operator/sedationist	Low risk	Quote: "both operator and assessor blind to treatment received"
Blinding - Outcome assessor	Low risk	Quote: "both operator and assessor blind to treatment received"
Incomplete outcome assessment	High risk	Numbers evaluated not stated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No apparent differences between groups at baseline

Roelofse 1998

Methods	Parallel group RCT Location: South Africa Funding: not stated
Participants	Inclusion criteria: children ASA I aged 2 to 7 years, randomly selected from dental clinic n = 100 Gender, mean age (SD) in years: Group 1 (n = 50), 27 male, 23 female, 4.1 (1.3) Group 2 (n = 50), 29 male, 21 female, 4 (1.2)
Interventions	Group 1: ketamine (5 mg/kg) + midazolam (0.35 mg/kg) Group 2: trimeprazine (3 mg/kg) + methadone (0.2 mg/kg) All oral
Outcomes	Modified Houpt, Ramsay Sedation Score
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly selected" - method of sequence generation not described

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Roelofse 1998 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	High risk	Not reported as being blinded
Blinding - Operator/sedationist	Low risk	Operator blinded to the treatment regimen
Blinding - Outcome assessor	Low risk	Operator evaluated the sedation
Incomplete outcome assessment	High risk	Numbers evaluated not stated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No apparent differences between groups at baseline

Sams 1993a

Methods	Parallel group RCT Location:USA Funding: not stated
Participants	Inclusion criteria: children ASA I with no prior sedation experience, needing > 2 restorations, with Frankl score 1 (definitely negative behaviour) n = 24 Mean age (SD) in months: Group 1 (n = 13), 31.0 (8.6) Group 2 (n = 11), 35.8 (10.6)
Interventions	Group 1: chloral hydrate (50 mg/kg) + promethazine (1 mg/kg) Group 2: meperidine (1 mg/kg) + promethazine (1 mg/kg) All oral, sedation administered by principal investigator or attending faculty member
Outcomes	Modified Houpt
Notes	Papoose board Nitrous oxide/oxygen where indicated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Assigned randomly" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Low risk	Study described as double-blind

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Sams 1993a *(Continued)*

Blinding - Operator/sedationist	Low risk	Study described as double-blind
Blinding - Outcome assessor	Low risk	Operators, who were blinded to allocated treatment, assessed outcomes
Incomplete outcome assessment	High risk	Numbers evaluated not stated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No apparent differences between groups at baseline

Shanmugaavel 2016a

Methods	Parallel design RCT Funding: not stated Location: India
Participants	Inclusion criteria: ASA 1 and 2. Venham's clinical anxiety scale score ≥ 3 during first visit and required treatment under local anaesthesia n = 20 Age range = 4 to 7 years Group 1 (n = 10) Group 2 (n = 10)
Interventions	Group 1: midazolam (0.2 mg/kg) (intranasal) Group 2: midazolam (0.2 mg/kg) (sublingual)
Outcomes	Venham's clinical anxiety scale, salivary cortisol level
Notes	Procedure was videotaped, restraints were used

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomization pattern generated by computer software"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Unclear risk	Not described
Blinding - Operator/sedationist	Low risk	Quote: "single operator blinded to routes of drug administration"
Blinding - Outcome assessor	Unclear risk	Not described

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Shanmugaavel 2016a *(Continued)*

Incomplete outcome assessment	High risk	Number of sedation failure not recorded
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	High risk	Sample demographics not explained

Shanmugaavel 2016b

Methods	Parallel group RCT Location: India Funding: not stated
Participants	Inclusion criteria: ASA 1 and 2. Venham's clinical anxiety scale score ≥ 2 during first visit and required treatment under local anaesthesia n = 40 Mean age (SD) in years, gender, weight (SD) in kg: Group A: 5.1 (1.07), 12 males and 8 females, 17.5 (4.39) Group B: 5.2 (1.15), 12 males and 8 females, 17.4 (4.33)
Interventions	Group A: midazolam (0.2 mg/kg) (intranasal) Group B: midazolam (0.2 mg/kg) (sublingual)
Outcomes	Anxiety (Venham scale), acceptance
Notes	No apparent differences between groups at baseline

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Excel used
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	High risk	Not blinded (not possible)
Blinding - Operator/sedationist	High risk	Not blinded
Blinding - Outcome assessor	Low risk	Video used
Incomplete outcome assessment	Low risk	All outcomes assessed
Free of selective reporting	Low risk	Dropouts reported

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Shanmugaavel 2016b *(Continued)*

Free of other bias	Low risk	No other bias

Shashikiran 2006

Methods	Parallel group RCT Location: India Funding: not stated
Participants	n = 40 Group 1 (11 males, 9 females), mean age 3.4 years (SD = 0.6), mean weight 12.2 kg (SD = 1.2) Group 2 (8 males, 12 females), mean age 3.5 years (SD = 0.7), mean weight 12.6 kg (SD = 1.4)
Interventions	Group 1 (n = 20): midazolam (0.2 mg/kg) (intramuscular) Group 2 (n = 20): midazolam (0.2 mg/kg) (intranasal)
Outcomes	Houpt, Fukuta scales
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly allocated" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	High risk	Not blinded
Blinding - Operator/sedationist	Low risk	Operator blinded to route of administration
Blinding - Outcome assessor	Low risk	Outcomes assessed by operator
Incomplete outcome assessment	Low risk	All randomised participants included in outcome evaluation
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No apparent differences between groups at baseline

Singh 2002

Methods	Parallel group RCT Location: India

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Singh 2002 *(Continued)*

	Funding: not stated
Participants	Inclusion criteria: healthy children ASA I referred for short dental procedures n = 90 (30 per group) Age range: 3 to 9 years
Interventions	Group 1: midazolam (0.5 mg/kg) Group 2: triclofos (70 mg/kg) Group 3: promethazine (1.2 mg/kg) All orally
Outcomes	Sedation score, treatment completion
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomised" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Low risk	Study described as double-blind
Blinding - Operator/sedationist	Low risk	Study described as double-blind
Blinding - Outcome assessor	Low risk	Study described as double-blind
Incomplete outcome assessment	High risk	Numbers evaluated not stated
Free of selective reporting	Low risk	All selected variables reported
Free of other bias	Unclear risk	Little information on participants in each group at baseline

Singh 2014

Methods	Parallel design Funding: not stated Location: India
Participants	Inclusion criteria: ASA 1, basic non-phamacological behaviour guidance technique had not been successful, score 1 or 2 in behaviour/response to treatment rating scale n = 112 Age range = 1 to 10 years Mean age (SD) in years, gender and weight (SD) in kg:

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Singh 2014 *(Continued)*

	Group 1 (n = 28), 6.54 (1.79), 14 males and 14 females, 18.89 (4.33)
	Group 2 (n = 28), 6.93 (2.05), 13 males and 15 females, 17.04 (5.33)
	Group 3 (n = 28), 7.21 (1.98), 11 males and 17 females, 16.93 (4.22)
	Group 4 (n = 28), 6.82 (2.22), 14 males and 14 females, 16.61 (4.92)
Interventions	Group 1: ketamine (8 mg/kg^{-1})
	Group 2: dexmedetomidine (3 $\mu g/kg^{-1}$)
	Group 3: dexmedetomidine (4 $\mu g/kg^{-1}$)
	Group 4: dexmedetomidine (5 $\mu g/kg^{-1}$)
Outcomes	Onset time, recovery time, sedation rating scale modified from AAPD guidelines, Face, Legs, Activity, Cry and Consolability Pain Scale, anterograde amnesia, behaviour score
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized according to computer-generated random number list"
Allocation concealment (selection bias)	Low risk	Quote: "The professor of pharmacology was then informed about weight of the patient to enable him prepare the coded solutions of the drugs on the day of treatment"
Blinding - Participant	Low risk	Described as '"triple-blind"
Blinding - Operator/sedationist	Low risk	Quote: "the principal investigator (PI) obtained the drug solution having same volume (10 ml) and the same colour in a transparent disposable container for every patient, without knowing the drug ingredient in it"
Blinding - Outcome assessor	Low risk	PI was the outcome assessor and the operator sedationist. PI was not aware of the drug administered
Incomplete outcome assessment	Low risk	All participants included in the outcome evaluation
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No other bias

Somri 2012

Methods	Parallel design
	Funding: not stated
	Location: Israel
Participants	Inclusion criteria: patients unable to tolerate dental treatment under behavioural management and local anaesthetic or in combination with nitrous oxide use

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Somri 2012 *(Continued)*

	n = 90 Age range = 3 to 10 years Mean age (SD) in years, weight (SD) in kg: Group 1: 5.6 ± 1.85, 19.2 ± 3.68 Group 2: 5.6 ± 1.67, 19.7 ± 3.38 Group 3: 6.2 ± 2.00, 20.3 ± 3.65
Interventions	Group 1: midazolam (0.5 mg/kg) Group 2: midazolam (0.75 mg/kg) Group 3: midazolam (1 mg/kg) All orally
Outcomes	Wisconsin sedation scale, Houpt behavioural rating scale, parent satisfaction
Notes	Immobilisation with manual restraining used Wisconsin level 5 (deep sedation) considered adequate All children received 2 litres of oxygen during treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned by sealed envelope technique"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Unclear risk	Not described
Blinding - Operator/sedationist	Low risk	Nursing staff administering the midazolam, specialist paediatric dentist and anaesthetist performing procedure and post-operative discharge nurses were blinded
Blinding - Outcome assessor	Unclear risk	Not described if the assessor was blinded
Incomplete outcome assessment	Low risk	All participants included in the outcome evaluation
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No other bias

Surendar 2014

Methods	Parallel design RCT Funding: not stated

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Surendar 2014 *(Continued)*

	Location: India
Participants	Inclusion criteria: ASA 1, fearful/anxious and for whom basic behaviour guidance techniques had not been successful in rendering dental treatment, without any history of previous dental treatment under sedation or anaesthesia and whose treatment necessitated the administration of local anaesthesia n = 84 (43 males, 41 females) Age range = 4 to 14 years, weight range = 9 to 27 kg Age range in years, mean age (SD) in years, weight (SD) in kg: Group 1: 4 to 12, 7.34 ± 2.34, 18.29 ± 3.04 Group 2: 4 to 11, 6.71 ± 2.31, 16.52 ± 3.87 Group 3: 4 to 11, 7.76 ± 2.26, 18.57 ± 4.17 Group 4: 4 to 11, 7.24 ± 2.36, 17.71 ± 5.36
Interventions	Group 1: dexmedetomidine (1 µg/ kg) Group 2: dexmedetomidine (1.5 µg/kg) Group 3: midazolam (0.2 mg/kg) Group 4: ketamine (5 mg/kg) All intranasal
Outcomes	Modified AAPD sedation record; behaviour/response to treatment rating scale; Face, Legs, Activity, Cry and Consolability (FLACC) scale
Notes	Sedation was considered unsuccessful if use of physical restraint during the procedure was required

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The order of the drugs was randomized using an online randomization generator"
Allocation concealment (selection bias)	High risk	The anaesthetist administering the drugs was aware of the drug being administered
Blinding - Participant	Low risk	Study described as triple-blinded
Blinding - Operator/sedationist	Low risk	The study is described as triple-blinded therefore the operator is considered to be blinded
Blinding - Outcome assessor	Low risk	Study described as triple-blinded
Incomplete outcome assessment	Low risk	All participants included in the outcome evaluation
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No other bias

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Torres-Perez 2007

Methods	Parallel group RCT Location: Mexico Funding: not stated
Participants	n = 54 Mean age (age range) in years, gender, mean weight (range) kg: Group 1: 3.9 (4-6), 11 males and 7 females, 18.1 (0.9-22) Group 2: 2.83 (1-8), 11 males and 7 females, 15 (10.4-22.5) Group 3: 2.94 (1-10), 10 males and 8 females, 16.33 (10.4-20)
Interventions	Group 1 (n = 18): hydroxyzine (2 mg/kg 2 hours before, 1 mg/kg 20 minutes before) Group 2 (n = 18): midazolam (0.5 mg/kg) + hydroxyzine (1.5 mg/kg) Group 3 (n = 18): chloral hydrate (50 mg/kg) + hydroxyzine (1.5 mg/kg) All oral
Outcomes	Ohio State Behavioral Rating Scale, cardiac rate, oxygen saturation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	High risk	No blinding reported
Blinding - Operator/sedationist	High risk	No blinding reported
Blinding - Outcome assessor	Low risk	Observer "was not informed of the objective of the study"
Incomplete outcome assessment	High risk	Numbers evaluated not stated
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No apparent differences between groups at baseline

Tyagi 2012

Methods	Parallel design RCT

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Tyagi 2012 *(Continued)*

	Funding: not stated Location: India
Participants	Inclusion criteria: Frankl rating 1 (definitely negative) at the initial visit in spite of use of behaviour modification techniques n = 40 Age range = 2 to 10 years
Interventions	Group 1: oral midazolam (0.5 mg/kg) Group 2: oral diazepam (0.5 mg/kg) Group 3: IV midazolam (0.06 mg/kg) Group 4: placebo
Outcomes	Houpt scale, child behaviour questionnaire
Notes	Error in abstract, "Positive behavior of patients in group 2 and 3 did not show significant difference but positive behavior in group 3 was significantly (P < 0.05) more than group 2" Abstract mentions the study as triple-blinded whereas in material and methods study has been classified as double-blinded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised but no details of the randomisation procedure described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	High risk	Blinding not done for IV midazolam group
Blinding - Operator/sedationist	High risk	Sedation procedures and randomisation were performed with the assistance of a registered anaesthetist. The operator was blinded from the type of medication used in group 1, 2 and 4. Blinding not done for IV midazolam group
Blinding - Outcome assessor	High risk	Quote: "Monitoring of vital signs was performed by an evaluator who was blinded for the use of oral sedative agent" Comment: not blinded for IV midazolam group
Incomplete outcome assessment	Low risk	All participants included in the outcome evaluation
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	High risk	Not triple-blinded as IV midazolam group was not included in the blinding, only oral groups were blinded. Demographics at baseline not described

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Veerkamp 1993

Methods	Parallel group RCT Location: the Netherlands Funding: not stated
Participants	Inclusion criteria: healthy Dutch speaking children aged 6 to 11 years, requiring 2 dental treatment sessions; all children had previous treatment session aborted at separate location; scored high on Likert anxiety scale (n = 56) Age range all subjects = 6 to 11 years
Interventions	Group 1 (n = 27): behaviour management Group 2 (n = 29): up to 40:60 nitrous oxide/oxygen Inhalation, interventions administered by dentist
Outcomes	Venham scale
Notes	Dr Veerkamp was contacted to clarify the blinding in this trial and to enquire about any unpublished trials

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Divided randomly into 2 matching (age, sex) groups" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	High risk	Not blinded
Blinding - Operator/sedationist	High risk	Not blinded
Blinding - Outcome assessor	Low risk	Viewed by dentist and psychologist who "were not aware of the objective of the study"
Incomplete outcome assessment	Low risk	All randomised participants included in outcome evaluation
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Unclear risk	Little information on participants in each group at baseline

Wan 2006

Methods	Parallel group RCT Location: China Funding: not stated
Participants	Inclusion criteria: healthy unco-operative children n = 40

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Wan 2006 *(Continued)*

	Mean age (range) in years: all subjects 7.3 (5-10)
	Mean weight (range) in kg: all subjects 22.9 (16-32)
Interventions	Group 1 (n = 19): placebo
	Group 2 (n = 21): midazolam (0.5 mg/kg)
	All oral
Outcomes	Ramsay, Brietkopf and Buttner, Frankl, Houpt scales
Notes	Papoose board

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly divided" - method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Low risk	Study described as double-blind
Blinding - Operator/sedationist	Low risk	Study described as double-blind
Blinding - Outcome assessor	Low risk	Outcomes assessed from videotapes by dentist and anaesthetist unaware of allocated treatment
Incomplete outcome assessment	Low risk	All randomised participants included in outcome assessment
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	Low risk	No apparent differences between groups at baseline

Özen 2012

Methods	Parallel design
	Funding: not stated
	Location: Turkey
Participants	Inclusion criteria: ASA 1; children with definitely or slightly negative behaviour ratings on the Frankl Behaviour Rating Scale and who had prior experience with sedation or general anaesthesia
	n = 240, 116 girls, 124 boys
	Age range = 4 to 6 years
Interventions	Group 1 (n = 60): midazolam (0.20 mg/kg) (40 mg/ml) intranasally, inhalation sedation 50%/50% nitrous oxide/oxygen

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Özen 2012 *(Continued)*

	Group 2 (n = 60): midazolam (0.75 mg/kg) (15 mg/3 ml) orally, inhalation sedation 50%/50% nitrous oxide/oxygen Group 3 (n = 60): midazolam (0.50 mg/kg) (15 mg/3 ml) orally, inhalation sedation 50%/50% nitrous oxide/oxygen Group 4 (n = 60): inhalation sedation 50%/50% nitrous oxide/oxygen
Outcomes	Bispectral Index System; modified scale to classify behaviour; Vancouver Recovery Scale
Notes	Restraint used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding - Participant	Unclear risk	Not described
Blinding - Operator/sedationist	Unclear risk	Not described
Blinding - Outcome assessor	Unclear risk	Not described
Incomplete outcome assessment	High risk	Difficult to gather if dropouts had occurred. Percentage of patients that did not accept route of treatment mentioned
Free of selective reporting	Low risk	All planned outcomes reported
Free of other bias	High risk	Little information on participants in each group as baseline

ASA I/ASA II = American Society of Anesthesiologists (ASA) physical status classification; BIS = bispectral index; DSTG = Dental SedationTeachers Group scale; ITT = intention-to-treat; IV = intravenous; LA = local anaesthesia; min = minute; RCT = randomised controlled trial; SD = standard deviation; SE = standard error.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Al-Zahrani 2009	Cross-over trial
Arya 2002	Participants not randomly assigned
Badalaty 1990	Cross-over trial
Baldinelli 1989	No comparison of groups
Berge 1999	No comparison of groups Ages ranging from 3 to 46 years
Blake 1999	Age unclear, authors did not respond

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
	Review authors assumed the subjects were adults
Campbell 1998	Participants not randomly assigned (explicitly stated)
Canpolat 2017	Described as deep sedation
Cathers 2005	Cross-over trial
Chaushu 2002	No comparison of groups
Coldwell 1999	Evaluates adverse effects only
da Costa 2007	Cross-over trial
Dallman 2001	Cross- over trial
Davila 1990	Review
Doring 1985	Not comparative
Downs 1997	Cross-over trial
Duncan 1984	Survey
Duncan 1994	No comparison of groups
Dunn-Russell 1993	No comparison of groups
el Magboul 1995	Cross-over trial
Erlandsson 2001	No comparison of groups
Evans 1966	Cross-over trial
Flaitz 1985	Cross-over trial
Fuks 1994	Cross-over trial
Fukuta 1993	No comparison of groups Ages 4 to 21 years
Fukuta 1994	Ages from 5 to 20 years
Gallardo 1984	Cross-over trial
Gamonal Aravena 1989	Cross-over trial
Garton 1970	Review
Haas 1996	Cross-over trial
Hall 2006	Adults
Hartgraves 1994	Cross-over trial

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Hasty 1991	Cross-over trial
Heard 2010	Not randomised
Henry 1990	Compares scavenged/non-scavenged groups with regard to levels of ambient nitrous oxide
Houpt 1985a	Cross-over trial
Houpt 1985b	Cross-over trial
Houpt 1989	Cross-over trial
Houpt 1996	Cross-over trial
Hulland 2002	Retrospective
Isik 2008	Looked at the effect of flavouring on acceptability of oral sedatives
Jensen 1998	Retrospective study
Kantovitz 2007	Cross-over trial
Kayalibay 1987	Review
Kerins 2007	Not randomised
Kopel 1971	Not randomised
Koroluk 2000	Retrospective study
Kramer 1991a	No comparison of groups
Kramer 1991b	No comparison of groups
Kupietzky 1996	No relevant outcomes
Lahoud 2001	Pilot study - no comparative group
Leelataweedwud 2001	Retrospective study
Leelataweewud 2000	Cross-over trial
Lima 2003	Cross-over trial
Lindh-Stromberg 2001	No comparison of groups
Lindsay 1980	Cross-over trial
Lindsay 1985	Cross-over trial
Litman 1997	Premedication before general anaesthesia
Litman 1998	Not randomised (author contacted)
Lökken 1994	Cross-over trial

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Machen 1977	No relevant outcomes
Malamed 1989	No comparison of groups
Marshall 1999	The study was based on 56 different treatment attempts on 34 patients. Therefore it was a partial cross-over design as some of the patients would have had more than 1 type of treatment
Martinez 2006	Not randomised
McCann 1996	Cross-over trial
Milnes 2000	No comparison of groups
Moore 1997	No comparison of groups
Musial 2003	Cross-over trial
Myers 1977	No comparison of groups
Myers 2004	Cross-over trial
Nathan 1987	Not randomised
Oei-Lim 1991	No comparison of groups Ages ranging from 23 to 37 years, mental and physical handicapped
Pandey 2010	Cross-over trial
Pisalchaiyong 2005	Cross-over trial
Poorman 1990	Not randomised
Primosch 1999	Cross-over trial
Primosch 2001	Retrospective study No comparison of groups
Quarnstrom 1992	Not randomised
Ram 1999	Cross-over trial
Reinemer 1996	Inappropriate design, partial cross-over with some subjects having both and others only 1 regimen
Robbins 1967	Inappropriate design, partial cross-over with some subjects having both and others only 1 regimen
Roberts 1979	Age range 4 to 17 years No comparison of groups
Roberts 1982	No comparison of groups
Roberts 1992	Inappropriate design, partial cross-over with some subjects having both and others only 1 regimen

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Robertson 1998	Not randomised (quasi-randomisation). First patient randomised by toss of a coin, remaining patients alternated
Roelofse 1990	Premedication before general anaesthesia
Roelofse 1993	Premedication before general anaesthesia
Rohlfing 1998	No comparison of groups
Sams 1992	No relevant outcome
Sams 1993b	Review
Sanders 1997	No comparison of groups
Shapira 1992	Cross-over trial
Shapira 1996	Cross-over trial
Shapira 2004	Cross-over trial
Sharma 1992	Inappropriate design (partial cross-over)
Sheroan 2006	Cross-over trial
Silver 1994	Ages from 3 to 18 years
Songvasin 1990	Cross-over trial
Subramaniam 2017	Interventions not randomised: "Based on the parent preference of the route of administration, children were then randomly divided into 2 groups"
Sullivan 2001	Cross-over trial
Tanaka 2000	General anaesthesia
Tobias 1975	Not randomised
Tsinidou 1992	Cross-over trial
van der Bijl 1991	Adults
Varpio 1991	Not randomised
Veerkamp 1997	Deep sedation
Whitehead 1988	Not randomised (author contacted to confirm)
Wilson 1990	Retrospective study
Wilson 1992	Dose response study measuring physiological outcomes
Wilson 1993	Cross-over trial
Wilson 2000	Retrospective study

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Wilson 2002	Cross-over trial
Wilson 2003	Cross-over trial
Wilson 2006	Cross-over trial
Wilson 2007	Cross-over trial
Yanase 1996	Cross-over trial

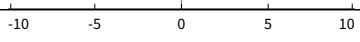
DATA AND ANALYSES

Comparison 1. Sedatives versus placebo

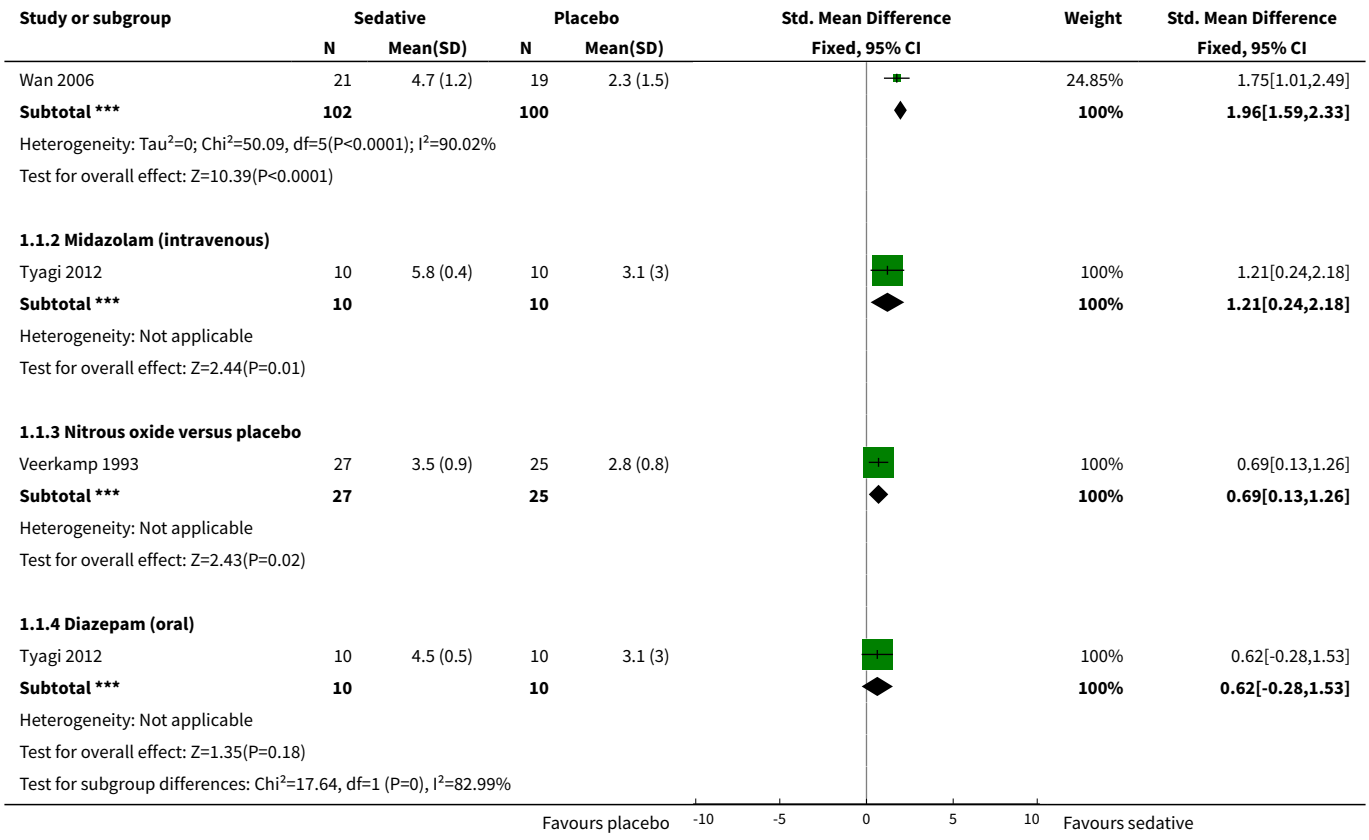
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean Houpt/other behavioural score	7		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Midazolam (oral)	6	202	Std. Mean Difference (IV, Fixed, 95% CI)	1.96 [1.59, 2.33]
1.2 Midazolam (intravenous)	1	20	Std. Mean Difference (IV, Fixed, 95% CI)	1.21 [0.24, 2.18]
1.3 Nitrous oxide versus placebo	1	52	Std. Mean Difference (IV, Fixed, 95% CI)	0.69 [0.13, 1.26]
1.4 Diazepam (oral)	1	20	Std. Mean Difference (IV, Fixed, 95% CI)	0.62 [-0.28, 1.53]
2 Good or better behaviour	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Chloral hydrate	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Meperidine	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Sedatives versus placebo, Outcome 1 Mean Houpt/other behavioural score.

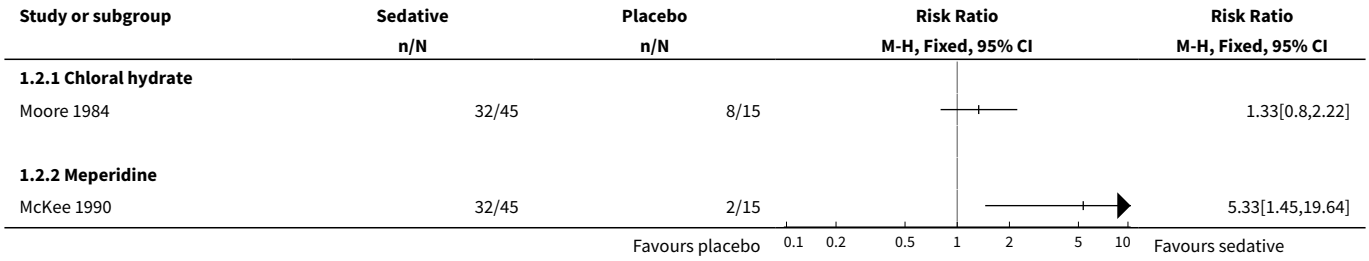
Study or subgroup	Sedative N	Sedative Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
1.1.1 Midazolam (oral)							
Gallardo 1994	16	2.9 (0.3)	16	1.1 (0.3)		4.87%	5.82[4.14,7.49]
Isik 2008a	15	2.6 (0.5)	15	1.3 (0.6)		15.8%	2.18[1.25,3.1]
Kapur 2004	20	1.3 (0.9)	20	0.4 (0.5)		29.58%	1.19[0.52,1.87]
Mortazavi 2009	20	5.1 (0.7)	20	1.6 (0.8)		8.82%	4.67[3.42,5.91]
Tyagi 2012	10	4.9 (0.3)	10	3.1 (3)		16.08%	0.81[-0.11,1.73]



Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.



Analysis 1.2. Comparison 1 Sedatives versus placebo, Outcome 2 Good or better behaviour.



Comparison 2. Chloral hydrate (CH)

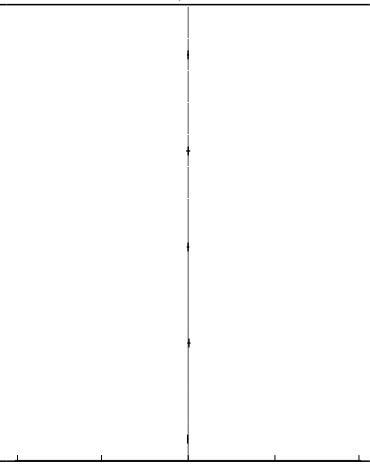
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall behaviour (ordinal scale, Houpt or similar)	5		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 CH vs CH/hydroxyzine	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 CH/hydroxyzine vs triazolam	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 CH/hydroxyzine vs midazolam/acetaminophen	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 CH/promethazine vs meperidine/promethazine	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 CH/hydroxyzine vs CH/hydroxyzine/midazolam	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Good or better behaviour	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 CH vs CH/hydroxyzine	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.24, 1.35]

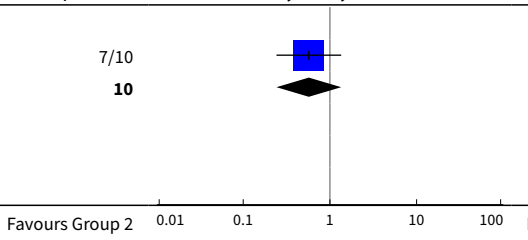
Analysis 2.1. Comparison 2 Chloral hydrate (CH), Outcome 1 Overall behaviour (ordinal scale, Houpt or similar).

Study or subgroup	Group 1 N	Group 1 Mean(SD)	Group 2 N	Group 2 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.1.1 CH vs CH/hydroxyzine						
Avalos-Arenas 1998	20	4.9 (1.1)	20	5 (0.7)		-0.1[-0.67,0.47]
2.1.2 CH/hydroxyzine vs triazolam						
Meyer 1990	20	4.3 (1.9)	20	4.3 (1.9)		0[-1.18,1.18]
2.1.3 CH/hydroxyzine vs midazolam/acetaminophen						
Reeves 1996	20	3.6 (1.2)	20	3.7 (1.2)		-0.1[-0.83,0.63]
2.1.4 CH/promethazine vs meperidine/promethazine						
Sams 1993a	13	4.5 (0.9)	11	4.1 (1.3)		0.4[-0.51,1.31]
2.1.5 CH/hydroxyzine vs CH/hydroxyzine/midazolam						
Park 2006	15	0.5 (0.5)	16	0.8 (0.4)		-0.34[-0.66,-0.02]



Analysis 2.2. Comparison 2 Chloral hydrate (CH), Outcome 2 Good or better behaviour.

Study or subgroup	Group 1 n/N	Group 2 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 CH vs CH/hydroxyzine					
Moody 1986	4/10	7/10		100%	0.57[0.24,1.35]
Subtotal (95% CI)	**10**	**10**		**100%**	**0.57[0.24,1.35]**
Total events: 4 (Group 1), 7 (Group 2)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.27(P=0.2)					



Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Comparison 3. Ketamine

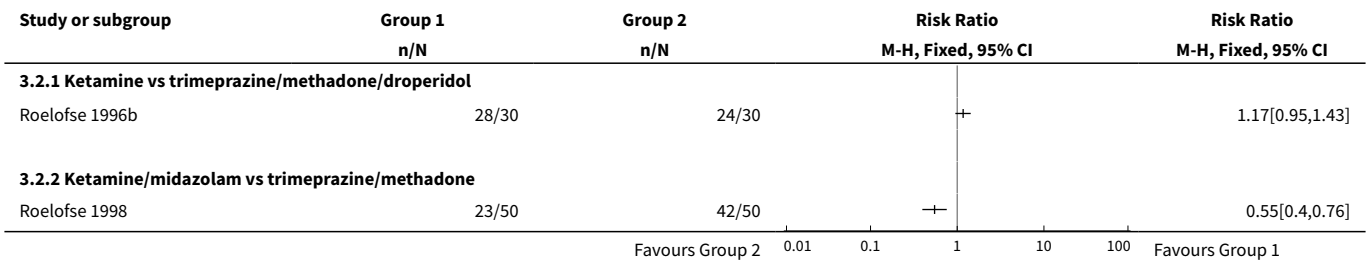
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall behaviour (ordinal scale, Houpt or similar)	5		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Ketamine vs midazolam	2		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Ketamine vs propofol	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Ketamine/midazolam vs trimeprazine/methadone	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Ketamine vs meperidine/promethazine	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.5 Ketamine vs ketamine/promethazine	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Good or better behaviour	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Ketamine vs trimeprazine/methadone/droperidol	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Ketamine/midazolam vs trimeprazine/methadone	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Ketamine, Outcome 1 Overall behaviour (ordinal scale, Houpt or similar).

Study or subgroup	Group 1 N	Group 1 Mean(SD)	Group 2 N	Group 2 Mean(SD)	Std. Mean Difference Random, 95% CI	Std. Mean Difference Random, 95% CI
3.1.1 Ketamine vs midazolam						
Abrams 1993	10	4 (1)	10	4 (1)		0[-0.88,0.88]
Rai 2007	10	5.8 (0.4)	10	3.2 (0.4)		5.93[3.7,8.16]
3.1.2 Ketamine vs propofol						
Rai 2007	10	5.8 (0.4)	10	3.5 (1.1)		2.69[1.41,3.97]
3.1.3 Ketamine/midazolam vs trimeprazine/methadone						
Roelofse 1998	50	2.4 (0.8)	50	3.4 (0.7)		-1.35[-1.78,-0.91]
3.1.4 Ketamine vs meperidine/promethazine						
Alfonzo-Echeverri 1993	20	3.4 (0.9)	20	2.9 (1.2)		0.41[-0.22,1.04]
3.1.5 Ketamine vs ketamine/promethazine						
Bui 2002	11	4.3 (0.5)	11	3.1 (0.3)		2.71[1.49,3.92]
				Favours Group 2	-10 -5 0 5 10	Favours Group 1

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 3.2. Comparison 3 Ketamine, Outcome 2 Good or better behaviour.



Comparison 4. Midazolam (versus other)

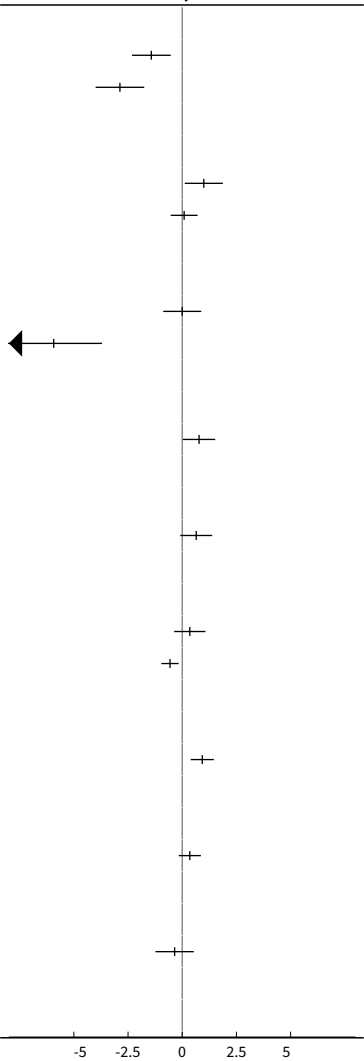
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall behaviour (ordinal scale, Houpt or similar)	12		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Midazolam (low dose) vs midazolam (high dose)	2		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Midazolam (intramuscular) vs midazolam (intranasal)	2		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Midazolam vs ketamine	2		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Midazolam vs nitrous oxide	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.5 Midazolam vs hydroxyzine	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.6 Midazolam vs midazolam/ketamine	2		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.7 Midazolam vs promethazine	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.8 Midazolam vs triclofos	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.9 Midazolam vs propofol	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.10 Midazolam/acetaminophen vs CH/hydroxyzine	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.11 Midazolam/ketamine vs trimeprazine/methadone	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

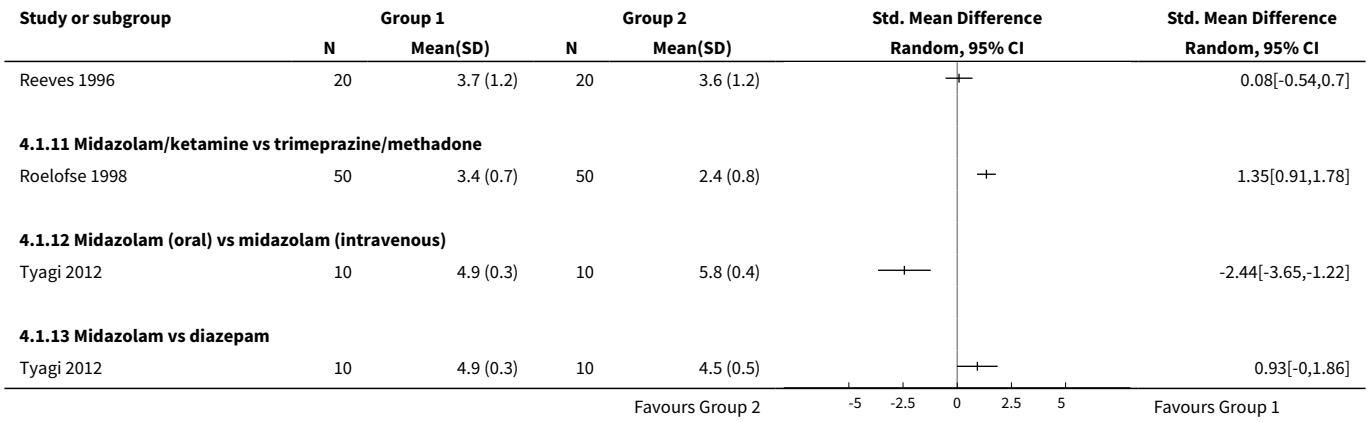
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.12 Midazolam (oral) vs midazolam (intravenous)	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.13 Midazolam vs diazepam	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Good or better sedation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Midazolam (rectal) vs diazepam (rectal)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 Midazolam (versus other), Outcome 1 Overall behaviour (ordinal scale, Houpt or similar).

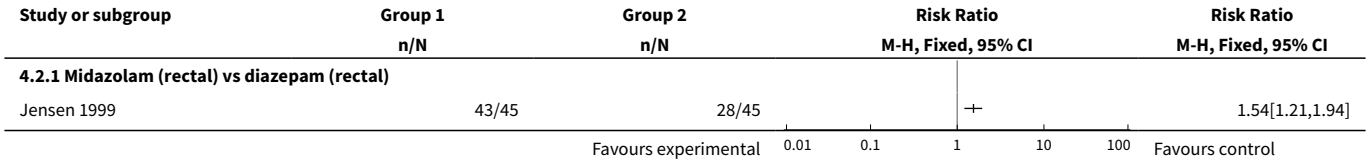
Study or subgroup	Group 1 N	Group 1 Mean(SD)	Group 2 N	Group 2 Mean(SD)	Std. Mean Difference Random, 95% CI	Std. Mean Difference Random, 95% CI
4.1.1 Midazolam (low dose) vs midazolam (high dose)						
Al-Rakaf 2001	12	3.4 (1.3)	13	4.9 (0.6)		-1.43[-2.32,-0.53]
Isik 2008b	14	1.2 (0.4)	13	2.7 (0.6)		-2.87[-4,-1.75]
4.1.2 Midazolam (intramuscular) vs midazolam (intranasal)						
Lam 2005	12	5.1 (0.7)	11	3.9 (1.5)		1[0.12,1.87]
Shashikiran 2006	20	2.2 (0.5)	20	2.2 (0.6)		0.09[-0.53,0.71]
4.1.3 Midazolam vs ketamine						
Abrams 1993	10	4 (1)	10	4 (1)		0[-0.88,0.88]
Rai 2007	10	3.2 (0.4)	10	5.8 (0.4)		-5.93[-8.16,-3.7]
4.1.4 Midazolam vs nitrous oxide						
Baygin 2010	15	2.3 (0.8)	15	1.7 (0.6)		0.78[0.03,1.52]
4.1.5 Midazolam vs hydroxyzine						
Baygin 2010	15	2.3 (0.8)	15	1.8 (0.7)		0.65[-0.09,1.38]
4.1.6 Midazolam vs midazolam/ketamine						
Baygin 2010	15	2.3 (0.8)	15	2 (0.9)		0.35[-0.37,1.07]
Roelofse 1996a	50	3.2 (0.6)	50	3.6 (0.6)		-0.56[-0.96,-0.16]
4.1.7 Midazolam vs promethazine						
Singh 2002	30	3.3 (0.7)	30	2.7 (0.5)		0.92[0.39,1.46]
4.1.8 Midazolam vs triclofos						
Singh 2002	30	3.3 (0.7)	30	3.1 (0.6)		0.35[-0.16,0.86]
4.1.9 Midazolam vs propofol						
Rai 2007	10	3.2 (0.4)	10	3.5 (1.1)		-0.35[-1.24,0.53]
4.1.10 Midazolam/acetaminophen vs CH/hydroxyzine						



Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.



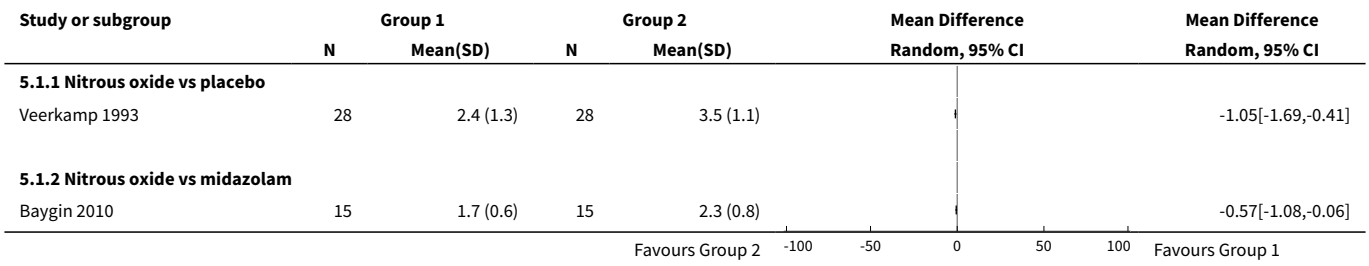
Analysis 4.2. Comparison 4 Midazolam (versus other), Outcome 2 Good or better sedation.



Comparison 5. Nitrous oxide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall behaviour (ordinal scale, Houpt or similar)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Nitrous oxide vs placebo	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Nitrous oxide vs midazolam	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.1. Comparison 5 Nitrous oxide, Outcome 1 Overall behaviour (ordinal scale, Houpt or similar).



Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ADDITIONAL TABLES

Table 1. Placebo study outcomes

Study ID	Sample	Intervention	Outcomes	Results	Treatment completed
Chloral hydrate					
Moore 1984	n = 60 Group 1 (n = 15), mean age 3.6 years, 11 males, 4 females Group 2 (n = 15), mean age 3.3 years, 7 males, 8 females Group 3 (n = 15), mean age 3.8 years, 9 males, 6 females Group 4 (n = 15), mean age 3.9 years, 7 males, 8 females	Group 1: placebo Group 2: chloral hydrate (20 mg/kg) Group 3: chloral hydrate (40 mg/kg) Group 4: chloral hydrate (60 mg/kg) All oral	Behaviour evaluations Completion of treatment Analysed using Chi^2 and Fisher's exact test	No statistically significant difference (P < 0.05) seen between placebo and 60 mg/kg chloral hydrate group for outcome of positive behaviour in operatory. No statistically significant differences between placebo and other groups Data reported as numbers and percentage per group, at different stages of the treatment and displayed in graphical form Adverse effects: not clear, 4 children failed to respond to obstruction (Group 4) after nitrous oxide/oxygen started Monitoring: cardiovascular and respiratory monitoring mentioned	All participants completed treatment
Dexmedetomidine (intranasal)					
Malhotra 2016	n = 36 Age range = 3-9 years Mean age (SD) in years: 4.60 ± 1.99 Mean weight (SD) kg: 15.62 ± 4.21	Group 1: intranasal normal saline, oral midazolam (0.5 mg/kg) + oral ketamine (5 mg/kg) in 30 ml of mango juice Group 2: intranasal dexmedetomidine (1 µ/kg), 30 ml of mango juice Group 3: intranasal normal saline, 30 ml of mango juice	Modified Observer Assessment of Alertness and Sedation (MOAAS) Houpt scale	Significant difference (P = 0.007) in behaviour during treatment compared to baseline in Group 1 and Group 2 Significant difference in the level of sedation in Group 1 and Group 2 when a comparison is made at specific time stages (treatment-baseline and end of treatment-baseline) (e.g. for Group 1 treatment-baseline comparison shows significant difference (P = 0.002) in the level of sedation) No significant difference between Group 1 and Group 2 in sedative efficacy or anxiolysis potential Adverse effects: not reported Monitoring: blood pressure, heart rate, oxygen saturation	-
Diazepam (oral)					

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 1. Placebo study outcomes *(Continued)*

Tyagi 2012	n = 40 Age range = 2-10 years	Group 1: oral midazolam (0.5 mg/kg) Group 2: oral diazepam (0.5 mg/kg) Group 3: intravenous midazolam (0.06 mg/kg) Group 4: placebo	Houpt scale Child behaviour questionnaire	Behaviour was assessed in terms of sleep, crying and movement at 30 minutes post drug administration in Group 1, Group 2 and Group 4 or 5 minutes in Group 3. At placement of blood pressure cuff, during administration of local anaesthesia or use of hand piece and every 15 minutes thereafter (e.g. at administration of local anaesthetic agent or use of hand piece significantly lower ($P < 0.001$) sleep in Group 4 compared to other groups. Significantly less crying in Group 3 compared to Group 1, Group 2 and Group 4 ($P < 0.001$, $P < 0.01$ and $P < 0.05$ respectively)) Overall behaviour rating was significantly better ($P < 0.001$) in Group 3 compared to other groups Positive behaviour post sedation: no significant difference between Group 1 and Group 2. Significant improvement ($P < 0.05$) in Group 3 compared to Group 2 Sleeping mentioned Adverse effects: not reported Monitoring: oxygen saturation, respiratory rate, blood pressure and respiratory rate	-
Melatonin					
Isik 2008a	Mean age (SD) in years, gender, mean weight (SD) in kg: Group 1: n = 15, 4.87 (0.99), 7 males, 8 females, 18.87 (2.5) Group 2: n = 15, 4.93 (1.11), 7 males, 8 females, 17.87 (3.88) Group 3: n = 15, 4.93 (1.10), 8 males, 7 females, 18.6 (3.31) Group 4: n = 15, 5.01 (1.03), 9 males, 6 fe-	Group 1: melatonin (3 mg) Group 2: melatonin (0.5 mg/kg) Group 3: midazolam (0.75 mg/kg) Group 4: placebo All oral	Ramsay Sedation Score Analysed with Kruskal-Wallis	Ramsay Sedation Score significantly higher (i.e. more sedated) for Group 3 versus all other groups ($P < 0.05$). Sedation significantly likely to be scored as satisfactory in Group 3 versus other groups ($P < 0.05$). Data presented graphically. No sedations scored as unsatisfactory in Group 3 Adverse effects: vomiting, hiccupping and coughing seen in all groups, amnesia reported in Group 3 Monitoring: pulse oximeter	-

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 1. Placebo study outcomes *(Continued)*

	males, 19.73 (4.77)				
Meperidine					
McKee 1990	n = 60 Mean age (SE) in months: Group 1: n = 15, 36.5 (2.7) Group 2: n = 15, 41.7 (3) Group 3: n = 15, 35.9 (2.7) Group 4: n = 15, 43 (2.7)	Group 1: placebo Group 2: meperidine (0.25 mg/lb) Group 3: meperidine (0.50 mg/lb) Group 4: meperidine (1 mg/lb) All intramuscular	Modified Houpt Dichotomous Behavior Scale 10-point behaviour scale Global Rating Scale Analysed using Kruskal-Wallis, multivariant analysis of covariance (MANCOVA) and Mann-Whitney U test	Global rating scale (good to excellent) significantly favoured meperidine compared to placebo. All doses of meperidine were significantly better than placebo ($P < 0.05$) for values of global sedation scale. All 3 scales significantly contributed to overall MANCOVA. Global rating reported as individual frequencies Sleep mentioned Adverse effects: sleep/drowsiness (Groups 1 and 3), nausea/vomiting (Groups 3 and 4), hyperexcited (Group 3) Monitoring: precordial stethoscope, automatic sphygmomanometer, pulse oximeter	1 participant from 0.25 mg/lb group and 1 from 0.5 mg/lb group became unmanageable and treatment was not completed
Midazolam (intravenous)					
Tyagi 2012	n = 40 Age range = 2-10 years	Group 1: oral midazolam (0.5 mg/kg) Group 2: oral diazepam (0.5 mg/kg) Group 3: intravenous midazolam (0.06 mg/kg) Group 4: placebo	Houpt scale Child behaviour questionnaire	Behaviour was assessed in terms of sleep, crying and movement at 30 minutes post drug administration in Group 1, Group 2 and Group 4 or 5 minutes in Group 3. At placement of blood pressure cuff, during administration of local anaesthesia or use of hand piece and every 15 minutes thereafter e.g. at administration of local anaesthetic agent or use of hand piece significantly lower ($P < 0.001$) sleep in Group 4 compared to other groups. Significantly less crying in Group 3 compared to Group 1, Group 2 and Group 4 ($P < 0.001$, $P < 0.01$ and $P < 0.05$ respectively) Overall behaviour rating was significantly better ($P < 0.001$) in Group 3 compared to other groups Positive behaviour post sedation: no significant difference between Group 1 and Group 2. Significant improvement ($P < 0.05$) in Group 3 compared to Group 2 Sleeping mentioned Adverse effects: not reported Monitoring: oxygen saturation, respiratory rate, blood pressure and respiratory rate	-
Midazolam (oral)					

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 1. Placebo study outcomes *(Continued)*

Gallardo 1994	n = 32 Age range = 4 to 10 years 17 males and 15 females	Group 1: midazolam (7.5 mg) (regardless of weight) Group 2: placebo All oral	Overall sedation mental attitude Hypnotic effects Motor activity Ease of treatment Analysed using Wilcoxon rank	Midazolam significantly better than placebo (P < 0.001) in all categories. Data presented graphically Sleeping mentioned Adverse effects and monitoring: not mentioned	-
Isik 2008a	Mean age (SD) in years, gender, mean weight (SD) in kg: Group 1: n = 15, 4.87 (0.99), 7 males, 8 females, 18.87 (2.5) Group 2: n = 15, 4.93 (1.11), 7 males, 8 females, 17.87 (3.88) Group 3: n = 15, 4.93 (1.10), 8 males, 7 females, 18.6 (3.31) Group 4: n = 15, 5.01 (1.03), 9 males, 6 females, 19.73 (4.77)	Group 1: melatonin (3 mg) Group 2: melatonin (0.5 mg/kg) Group 3: midazolam (0.75 mg/kg) Group 4: placebo All oral	Ramsay Sedation Score Analysed with Kruskal-Wallis	Ramsay Sedation Score significantly higher (i.e. more sedated) for Group 3 versus all other groups (P < 0.05). Sedation significantly likely to be scored as satisfactory in Group 3 versus other groups (P < 0.05). Data presented graphically. No sedations scored as unsatisfactory in Group 3 Adverse effects: vomiting, hiccupping and coughing seen in all groups, amnesia reported in Group 3 Monitoring: pulse oximeter	-
Kapur 2004	n = 40 Age: younger than 4 years old - no differences at baseline with regards to age, sex and body weight	Group 1: midazolam (0.5 mg/kg) (oral/transmucosal) Group 2: placebo (same volume)	Sedation score, treatment completion, time No statistical tests described	Significantly better sedation in Group 1 (mean 3.75, SD 0.85) compared to Group 2 (mean 4.6, SD 0.5) (P < 0.01). 18 completed Group 1 versus 7 Group 2 (P < 0.01) Monitored with pulse oximeter	-
Mortazavi 2009	n = 40 Mean age (SD) years: 3.99 (0.38)	Group 1: placebo Group 2: midazolam (0.25 mg/kg) All oral	Houpt Analysed using Mann-Whitney U test	Significant improvement in overall behaviour in midazolam group compared to placebo group (5.1 versus 1.6, P < 0.05) Adverse effects: none Monitoring: pulse oximeter, precordial stethoscope	11 out of 20 patients aborted treatment in placebo group

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 1. Placebo study outcomes *(Continued)*

Moreira 2013	n = 44 Average age below 36 months Mean age (SD) in months, gender: Group 1: n = 11, 27.1 (8.3), 6 males, 5 females Group 2: n = 18 (parents refused treatment for 2), 27.7 (5.5), 9 males, 7 females Group 3: n = 15 (parents refused treatment for 1), 27.3 (6.4), 9 males, 4 females	Group 1: midazolam (0.5 mg/kg) + ketamine (3 mg/kg) Group 2: midazolam (1 mg/kg) Group 3: no sedation Group 1 and 2 oral	Ohio State University Behavior Rating Scale (OSUBRS)	Significant difference in behaviour (P = 0.003) between Group 1 and Group 2 and Group 1 and Group 3 (P = 0.03) when sedatives used Behaviour during various stages of treatment sessions was observed e.g. for local anaesthetic administration OSUBRS score for Group 1 was lower than Group 2 (P = 0.06) and Group 3 (P = 0.02) During rubber dam placement OSUBRS score for Group 1 was lower than Group 2 (P = 0.01) and Group 3 (P = 0.07). All groups showed same behavioural pattern at the end of the treatment session (P = 0.25) Sleep mentioned Adverse effects: within 24 hours post-operatively Group 1 presented with agitation and vomiting in 3 children	All participants completed treatment
Tyagi 2012	n = 40 Age range = 2-10 years	Group 1: oral midazolam (0.5 mg/kg) Group 2: oral diazepam (0.5 mg/kg) Group 3: intravenous midazolam (0.06 mg/kg) Group 4: placebo	Houpt scale Child behaviour questionnaire	Behaviour was assessed in terms of sleep, crying and movement at 30 minutes post drug administration in Group 1, Group 2 and Group 4 or 5 minutes in Group 3. At placement of blood pressure cuff, during administration of local anaesthesia or use of hand piece and every 15 minutes thereafter e.g. at administration of local anaesthetic agent or use of hand piece significantly lower (P < 0.001) sleep in Group 4 compared to other groups. Significantly less crying in Group 3 compared to Group 1, Group 2 and Group 4 (P < 0.001, P < 0.01 and P < 0.05 respectively) Overall behaviour rating was significantly better (P < 0.001) in Group 3 compared to other groups Positive behaviour post sedation: no significant difference between Group 1 and Group 2. Significant improvement (P < 0.05) in Group 3 compared to Group 2 Sleeping mentioned Adverse effects: not reported Monitoring: oxygen saturation, respiratory rate, blood pressure and respiratory rate	-

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 1. Placebo study outcomes *(Continued)*

Wan 2006	n = 40 Group 1: n = 19 Group 2: n = 21 Mean age (range) in years all subjects: 7.3 (5-10) Mean weight (range) in kg all subjects: 22.9 (16-32)	Group 1: placebo Group 2: midazolam (0.5 mg/kg) All oral	Ramsey Brietkopf and Buttner scale Frankl scale Houpt scale Analysed using 1-way ANOVA	Scores significantly lower in placebo group for all outcomes (P < 0.001) Adverse effects: 15 subjects reported amnesia - all in the midazolam group Monitoring: blood pressure, pulse oximeter	-
Midazolam and ketamine (oral)					
Malhotra 2016	n = 36 Age range = 3-9 years Mean age (SD) in years: 4.60 ± 1.99 Mean weight (SD) kg: 15.62 ± 4.21	Group 1: intranasal normal saline, oral midazolam (0.5 mg/kg) + oral ketamine (5 mg/kg) in 30 ml of mango juice Group 2: intranasal dexmedetomidine (1 µ/kg), 30 ml of mango juice Group 3: intranasal normal saline, 30 ml of mango juice	Modified Observer Assessment of Alertness and Sedation (MOAAS) Houpt scale	Significant difference (P = 0.007) in behaviour during treatment compared to baseline in Group 1 and Group 2 Significant difference in the level of sedation in Group 1 and Group 2 when a comparison is made at specific time stages (treatment-baseline and end of treatment-baseline) e.g. for Group 1 treatment-baseline comparison shows significant difference (P = 0.002) in the level of sedation No significant difference between Group 1 and Group 2 in sedative efficacy or anxiolysis potential Adverse effects: not reported Monitoring: blood pressure, heart rate, oxygen saturation	-
Moreira 2013	n = 44 Average age below 36 months Mean age (SD) in months, gender: Group 1: n = 11, 27.1 (8.3), 6 males, 5 females Group 2: n = 18 (parents refused treatment for 2), 27.7 (5.5), 9	Group 1: midazolam (0.5 mg/kg) + ketamine (3 mg/kg) Group 2: midazolam (1 mg/kg) Group 3: no sedation Group 1 and 2 oral	Ohio State University Behavior Rating Scale (OSUBRS)	Significant difference in behaviour (P = 0.003) between Group 1 and Group 2 and Group 1 and Group 3 (P = 0.03) when sedatives used Behaviour during various stages of treatment sessions was observed e.g. for local anaesthetic administration OSUBRS score for Group 1 was lower than Group 2 (P = 0.06) and Group 3 (P = 0.02) During rubber dam placement OSUBRS score for Group 1 was lower than Group 2 (P = 0.01) and Group 3 (P = 0.07). All Groups showed same behavioural pattern at the end of the treatment session (P = 0.25) Sleep mentioned	All participants completed treatment

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 1. Placebo study outcomes *(Continued)*

	males, 7 females Group 3: n = 15 (parents refused treatment for 1), 27.3 (6.4), 9 males, 4 females			Adverse effects: within 24 hours post-operatively Group 1 presented with agitation and vomiting in 3 children	
Nitrous oxide					
Nathan 1988	n = 35 Age range = 48 to 72 months	Group 1: no intervention Group 2: placebo inhalation Group 3: 20-50:50 nitrous oxide/oxygen inhalation	Venham Parental questionnaire Behavioral screening instrument Ratings of anxiety and behaviour analysed using 2-way ANOVA	Significantly lower anxiety and behaviour ratings in nitrous oxide group (P < 0.05). Data presented graphically Adverse effects: not mentioned Monitoring: precordial electrodes: heart rate using Epstein's measure of mean heart rate	All participants completed treatment
Veerkamp 1993	n = 56 Group 1: n = 27 Group 2: n = 29 Age range all subjects = 6 to 11 years	Group 1: behaviour management Group 2: up to 40:60 nitrous oxide/oxygen All inhalation	Venham scale Analysed using t-test	Mean Venham scores from T1 p177 transformed for forest plots Significantly better outcome (P < 0.05) in nitrous oxide group (mean overall score Group 1 = 2.84, SD 0.80, Group 2 = 3.45, SD 0.92) Adverse effects and monitoring not mentioned	All participants completed treatment

ANOVA = analysis of variance; MANCOVA = multivariant analysis of covariance; n = number; SD = standard deviation; SE = standard error.

Table 2. Dosage study outcomes

Study ID	Sample	Intervention	Outcomes	Outcome results	Treatment completed
Hydroxyzine					
Faytrouny 2007	n = 30 14 females, 16 males Mean age (SD) months: Group 1 61.9 (11.9) Group 2	Group 1: hydroxyzine (20 mg 24 hours before) + hydroxyzine (3.7 mg/kg at the appointment) Group 2: hydroxyzine (3.7 mg/kg at the appointment)	Houpt. Analysed using ANOVA and Mann-Whitney	No significant differences at any time point. At 20 minutes Houpt Group 1, 5.2 (SD 1.5) and Group 2, 4.6 (SD 1.6) No adverse effects reported in either group Monitoring: pulse oximeter	-

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 2. Dosage study outcomes *(Continued)*

	53.7 (12.8)	All oral			
Midazolam (intranasal)					
Al-Rakaf 2001	n = 38 children Mean age (SD) in years and gender: Group 1 (n = 12) 3.75 (0.75), 6 males, 6 females Group 2 (n = 13) 4.3 (0.65), 6 males, 7 females Group 3 (n = 13) 4 (0.71), 6 males, 7 females	Group 1: midazolam (0.3 mg/kg) Group 2: midazolam (0.4 mg/kg) Group 3: midazolam (0.5 mg/kg) All intranasal	Houpt. Analysed using Tukey's range test and non-parametric 2-factor ANOVA Duration of sedation	Significant difference in Houpt behavioural scores between Group 3 and Group 1 (P < 0.0001) and between Group 3 and Group 2 (P < 0.01) No difference in outcomes between fasting and no-fasting in each group (P = 0.8286) None of the children were asleep Adverse effects: sneezing and coughing during administration and drowsiness (Groups 1 and 2), diplopia (only in Group 3) Monitoring: pulse oximeter	79% 0.3 mg/kg, 96% 0.4 mg/kg and 100% 0.5 mg/kg completed treatment
Lam 2005	n = 23 (12 Group 1, 11 Group 2) Mean age (range) in years: 5.13 (2-9) Mean weight (range) in kg: 21.74 (12-30) 15 males, 7 females	Group 1: midazolam (0.2 mg/kg) (intramuscular) Group 2: midazolam (0.2 mg/kg) (intranasal) All used as premed for unspecified intravenous sedation drug	Houpt. Analysed using Mann-Whitney. Inter-examiner variability assessed using Spearmans rank correlation Good/excellent sedation levels in each group	Patients more deeply sedated in Group 1 at time of local anaesthesia administration and venepuncture (P < 0.048, P < 0.015 respectively). 1 observer found Group 1 (intramuscular) significantly more effective than Group 2 (P < 0.04). Not significant for the second observer (P = 0.056). Individual outcomes for each observer not reported Good/excellent sedation 12/12 (100%) in intramuscular group and 6/11 (54%) in the intranasal group Children more likely to be drowsy in Group 1 Adverse effects: none reported Monitoring: heart rate, respiratory rate, blood pressure, oxygen saturation	Treatment completed by all participants
Lee-Kim 2004	n = 40 Mean age (unclear, possibly SD) in months; mean weight (unclear, possibly SD) in kg; gender: Group 1 (n = 20) 40.8 (11), 17 (3.6), 11 males, 9 females Group 2 (n = 20) 38.5 (9.8), 16.2	Group 1: midazolam (0.7 mg/kg) (oral) Group 2: midazolam (0.3 mg/kg) (nasal)	Modified Houpt - domains of sleep movement and crying but no overall measure. Analysed with ANOVA, Chi^2 statistic and t-test Mean time of onset and mean working time in each group	Data presented on graphs only and text states no significant differences in Houpt using multivariate ANOVA (P = 0.749) Onset of sedation mean 5.55 minutes (SD 2.2) for nasal and mean 15.5 minutes (SD 5) for oral (P < 0.001) Mean working time was 29.3 minutes (SD 11.6) for nasal and & 38.1 min (SD 7.58) for PO (P = 0.007) Adverse effects: none reported, no differences between groups. Monitoring: oxygen saturation, heart rate, respiratory rate	All participants completed

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 2. Dosage study outcomes *(Continued)*

	(4), 10 males, 10 females				
Shashikiran 2006	n = 40 Group 1: 11 males, 9 females, mean age (SD) in years 3.4 (0.6), mean weight (SD) in kg 12.2 (1.2) Group 2: 8 males, 12 females, mean age (SD) in years 3.5 (0.7), mean weight (SD) in kg 12.6 (1.4)	Group 1: midazolam (0.2 mg/kg) (intramuscular) Group 2: midazolam (0.2 mg/kg) (intranasal)	Houpt and Fukuta. Analysed using Chi^2 statistic and Mann-Whitney U test	No difference in behaviour between groups (Chi^2 = 0.37, P = 0.83), but both groups showed improvement from baseline. Intranasal midazolam was significantly faster acting at all time points and allowed a shorter treatment time overall (P < 0.001) Mean onset times 15.7 ± 2.0 minutes intramuscular versus 10.8 ± 2.0 minutes intranasal Adverse effects: 2 patients in the intramuscular group and 6 patients in the intranasal group showed instances of sneezing/coughing/hiccups after the administration of the sedative (difference not statistically significant) No fasting pretreatment and no vomiting in either group Monitoring: heart rate, respiratory rate	Score 3 given to excellent, 2 to satisfactory, 1 to unsatisfactory
Shanmugaavel 2016a	n = 20 Age range = 4-7 years Group 1 (n = 10) Group 2 (n = 10)	Group 1: midazolam (0.2 mg/kg) (intranasal) Group 2: midazolam (0.2 mg/kg) (sublingual)	Venham's Clinical Anxiety Scale Salivary cortisol level	Significant decrease in anxiety in Group 1 (P = 0.004) and Group 2 (P = 0.0.003) 20 minutes after drug administration Group 1 showed statistically significant decrease in anxiety at each of the 4 points of measurement during operative procedure (T1, T2, T3, T4), whereas Group 2 did not show statistically significant change at T1, T2 and T3 No significant difference in salivary cortisol levels before and after drug administration in Group 1 and Group 2 (P = 0.07, P = 0.38 respectively) No significant correlation between decrease in clinical anxiety and salivary cortisol level in Group 1 and Group 2 (P = 0.554, P = 0.457 respectively) Adverse effects: not reported	-
Shanmugaavel 2016b	n = 40 Mean age (SD) in years, gender, weight (SD) in kg: Group A: 5.1 (1.07), 12 males and 8 females, 17.5 (4.39)	Group A: midazolam (0.2 mg/kg) (intranasal) Group B: midazolam (0.2 mg/kg) (sublingual)	Venham's Clinical Anxiety Scale Acceptance (Al-Rakaf 2001)	No statistically significant difference in Venham's anxiety score between groups at baseline or at the end time point (T4) Mean (SD) Venham's score at T4 in Group A 0.35 (0.59) and Group B 0.45 (1.10) P = 0.001 Statistically significant difference in acceptance with better acceptance in Group B compared to Group A (95% versus 40%, P = 0.001)	-

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 2. Dosage study outcomes *(Continued)*

	Group B: 5.2 (1.15), 12 males and 8 females, 17.4 (4.33)			Adverse effects not reported	
Midazolam (oral)					
Aydintug 2004	n = 50 Mean age (unclear, possibly SD) in years; mean weight (unclear, possibly SD) in kg; gender: Group 1 (n = 25), 5.36 (1.7), 19.068 (3.43), 18 males and 7 females Group 2 (n = 25), 4.96 (1.513), 17.804 (3.08), 12 males and 13 females	Group 1: midazolam (0.5 mg/kg) (oral) Group 2: midazolam (0.35 mg/kg) (rectal)	Ramsay Sedation Score, acceptance of application, acceptance of local anaesthesia, operating conditions, state of amnesia Analysed using Chi^2 test	Acceptance of application significantly better in oral group (72% excellent in oral group compared to 20% excellent in rectal group, P < 0.05) No significant difference seen (P > 0.05) between acceptance of local anaesthesia, state of amnesia or operating conditions. Ramsay's Sedation Scores not reported Adverse effects: no significant difference (P > 0.05) in adverse effects between groups (56% oral, 44% rectal, included hypoxaemia, vomiting and nausea, disinhibition) Monitoring: oxygen saturation, heart rate, blood pressure	Treatment completed by all participants
Isik 2008b	Mean age (SD) in years, gender, mean weight (SD) in kg: Group 1 (n = 14), 4.6 (1.2), 7 males and 7 females, 15.6 (2.8) Group 2 (n = 13), 4.4 (1.0), 8 males and 5 females, 16.2 (2.4) Group 3 (n = 13), 4.4 (0.9), 6 males and 7 females, 16.1 (2.4) Group 4 (n = 13), 4.3 (0.9), 5 males and 8 females, 15.8 (2.6)	Group 1: midazolam (0.2 mg/kg) Group 2: midazolam (0.5 mg/kg) Group 3: midazolam (0.75 mg/kg) Group 4: midazolam (1 mg/kg) All oral	Ramsay Sedation Score Analysed using Kruskal-Wallis, Mann-Whitney U test	At the 20 minute time point, mean Ramsay Sedation Score was 1.2 (0.4), 1.6 (0.5), 2.2 (0.6), 2.7 (1.0) in Groups 1-4 respectively. Children in Groups 3 and 4 were more sedated than children in Groups 1 and 2 (P < 0.05) Sedation considered inadequate in 12/14, 5/13, 3/13 and 5/13 in Groups 1-4 respectively Mean recovery time was 45 (0), 45 (0), 47.3 (8.3), and 57.7 (42.8) minutes in Groups 1-4 respectively Adverse effects: most of the adverse effects were seen in Group 4 with 1 patient desaturating and 3 presenting with delayed recovery, no adverse effects in Group 1 and "very few" in Groups 2 and 3 Monitoring: pulse oximeter	-
Somri 2012	n = 90 (30 per group) Age range = 3-10 years Mean age (SD) in years, weight (SD) in kg:	Group 1: midazolam (0.5 mg/kg) Group 2: midazolam (0.75 mg/kg)	Wisconsin Sedation Scale Houpt behavioural rating scale Parent satisfaction	Sedation and behaviour co-operation scores were noted at baseline, 15 minutes, 30 minutes and 45 minutes. Significant difference with sedation scores in Group 1 lower than Group 2 and Group 3 (P < 0.001)	Group 1 20% (n = 6), Group 2 6.7% (n = 2) did not complete treatment

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 2. Dosage study outcomes *(Continued)*

	Group 1: 5.6 ± 1.85 years, 19.2 ± 3.68 kg Group 2: 5.6 ± 1.67 years, 19.7 ± 3.38 kg Group 3: 6.2 ± 2.00 years, 20.3 ± 3.65 kg	Group 3: midazolam (1 mg/kg)		No significant difference (P < 0.001) in sedation score of Group 2 and Group 3 except at baseline Behavioural co-operation score was significantly lower (P < 0.001) in Group 1 compared to Group 2 and Group 3. Significant difference (P < 0.001) in behaviour scores of Group 2 and Group 3 with Group 2 having lower scores at baseline and 45 minutes Significant difference (P = 0.025) in completion scores between Group 1 and Group 3 No significant difference (P = 0.43) in duration between the groups Significant difference in discharge time between the groups. Group 1 had shorter mean inpatient stay (85 minutes ± 18.5, P < 0.001) compared to Group 2 (103.7 ± 13.3 minutes) and Group 3 (137 ± 14.7 minutes) Significant difference in parent satisfaction (P < 0.001) where Group 1 is lower than Group 2 and Group 3. No significant difference (P = 0.147) between Group 2 and Group 3 Adverse effects: respiratory events Group 2 (3/30), Group 3 (10/30) Nausea and drowsiness Group 1 (3/30), Group 2 (7/30), Group 3 (12/30)	

ANOVA = analysis of variance; n = number; SD = standard deviation.

Table 3. Drug comparison study outcomes

Study ID	Sample	Intervention	Outcomes	Outcome results	Treatment completed
Chloral hydrate/hydroxyzine versus					
Avalos-Arenas 1998	n = 40 Mean age (SD) in months and gender: Group 1 (n = 20), 27.7 (2.9), 13 males and 7 females Group 2 (n = 20), 29.2 (3.6), 14 males and 6 females	Group 1: chloral hydrate (70 mg/kg) Group 2: chloral hydrate (70 mg/kg) + hydroxyzine (2 mg/kg) All oral	Houpt. Analysed using Kruskal-Wallis and Mann-Whitney U tests	No significant difference (P > 0.05) for overall behaviour evaluation (mean values reported at 7 different time intervals e.g. at injection mean behaviour Group 1 = 4.9 (SD 1.1), Group 2 = 5.0 (SD 0.68) Crying and movement evaluations significantly better (P < 0.05) at 45-60 minutes after application of rubber dam for Group 1 Sleep mentioned	All participants completed treatment

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 3. Drug comparison study outcomes *(Continued)*

				Adverse effects: Group 1 15%-30% children has oxygen saturation < 90% but in Group 2 range was 10%-45% Monitoring: precordial stethoscope, pulse oximeter and sphygmomanometer	
Meyer 1990	n = 40 Mean age (age range) in months: Group 1 (n = 20), 44 (21 to 74) Group 2 (n = 20), 42 (23 to 64)	Group 1: chloral hydrate (40 mg/kg) + hydroxyzine (25 mg) Group 2: triazolam (0.02 mg/kg) All oral	Houpt. Analysed using ANOVA and Chi^2 test	No significant differences between groups (mean overall behaviour Group 1 and Group 2 the same with a value of 4.3 (SE 0.4354) Sleeping mentioned Adverse effects: vomiting (1 child in Group 1) Monitoring: pulse oximeter and precordial stethoscope	-
Moody 1986	n = 30 Mean age in months: Group 1 (n = 10), 39.6 Group 2 (n = 10), 42 Group 3 (n = 10), 38.4	Group 1: chloral hydrate (50 mg/kg) (oral) Group 2: chloral hydrate (50 mg/kg) (rectal) Group 3: chloral hydrate (30 mg/kg) + hydroxyzine (25 mg) (oral) All received nitrous oxide inhalation 30%-50%	Modified Barker Overall quality sedation Behavioural data not statistically analysed	Good or excellent sedation achieved in 4/10, 7/10 and 7/10 of children in oral chloral hydrate, rectal chloral hydrate and oral chloral hydrate/hydroxyzine groups respectively Adverse effects: not mentioned Monitoring: precordial stethoscope and pulse oximeter	-
Park 2006	n = 31 Mean age in months (SD), gender, mean weight in kg (SD): CH Group 44.5 (14.1), 6 males and 9 females, 15.6 (2.7) CH-M Group 34.3 (9.3), 11 males and 5 females, 15.1 (2.6)	CH Group: chloral hydrate (60 mg/kg) + hydroxyzine (1 mg/kg) (both oral) CH-M Group: chloral hydrate (60 mg/kg oral) + hydroxyzine (1 mg/kg oral) + midazolam (0.1 mg/kg submucosal) All received nitrous oxide inhalation 50%	Houpt Requirement for restraint	Subjects in the CH-M Group showed better overall behaviour as measured by Houpt. Mean score 0.47 (SD 0.5) in CH Group versus 0.81 (0.39) in CH-M Group, P = 0.004 Less restraint was required in the CH-M Group (P < 0.05) Adverse effects: not reported Monitoring: pulse oximeter	-
Reeves 1996	n = 40 Mean age (age range) in months, gender:	Group 1: chloral hydrate (50 mg/kg) + hydroxyzine (25 mg)	Modified Houpt Analysed using Wilcoxon	Subjects in chloral hydrate/hydroxyzine group were in a significantly deeper sleep (P < 0.05). Data presented graphically. Sleeping mentioned	Dental treatment aborted in 1 participant from chloral hy-

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 3. Drug comparison study outcomes *(Continued)*

	Group 1 (n = 20), 48 (32 to 73), 11 males and 9 females Group 2 (n = 20), 42 (27 to 70), 10 males and 10 females	Group 2: midazolam (0.5 mg/kg) + acetaminophen (10 mg/kg) All oral	matched pairs test and Chi^2 test	Adverse effects: not reported Monitoring: pulse oximeter, precordial stethoscope and capnograph	drate/hydroxyzine group
Torres-Perez 2007	n = 54 Mean age (age range) in years; mean weight (range) in kg; gender: Group 1: 3.9 (4-6), 11 males, 7 females, 18.1 (0.9-22) Group 2: 2.83 (1-8), 11 males, 7 females, 15 (10.4-22.5) Group 3: 2.94 (1-10), 10 males, 8 females, 16.33 (10.4-20)	Group 1: hydroxyzine (2 mg/kg 2 hours before, 1 mg/kg 20 minutes before) Group 2: midazolam (0.5 mg/kg) + hydroxyzine (1.5 mg/kg) Group 3: chloral hydrate (50 mg/kg) + hydroxyzine (1.5 mg/kg) All oral	Ohio State Behavioral Rating Scale Analysed using Wilcoxon matched pairs test and Kruskal Wallis	"Significantly quieter" (mean cardiac rate 152, 146 and 137 in Group 1, Group 2 and Group 3 respectively (no P value given). Data presented graphically suggesting less movement in Group 3 Adverse effects: in Group 3 1/18 experienced oxygen saturation < 90% Monitoring: oxygen saturation and cardiac rate	-
Chloral hydrate/promethazine versus					
Sams 1993a	n = 24 Mean age (SD) in months: Group 1 (n = 13), 31.0 (8.6) Group 2 (n = 11), 35.8 (10.6)	Group 1: chloral hydrate (50 mg/kg) + promethazine (1 mg/kg) Group 2: meperidine (1 mg/kg) + promethazine (1 mg/kg) All oral	Modified Houpt Analysed using Hotelings T test and 2-sample t-test	Chloral hydrate/promethazine group significantly "better" (P < 0.05) for overall evaluation at 4 of the 10 measured time intervals (e.g. mean overall behaviour 15 minutes post-injection Group 1 = 5.2 (SD 1.1), Group 2 = 4.4 (SD 1.3), P < 0.05) Adverse effects: not reported Significantly more sleep in Group 1 than Group 2	All participants completed treatment and mean treatment duration was 50.8 (SD 13.3) and 50.9 (SD 17.6) in Groups 1 and 2 respectively
Dexmedetomidine versus					
Malhotra 2016	n = 36 Age range = 3-9 years Mean age (SD) in years: 4.60 ± 1.99	Group 1: intranasal normal saline, oral midazolam (0.5 mg/kg) + oral ketamine (5 mg/kg) in 30 ml of mango juice Group 2: intranasal	Modified Observer Assessment of Alertness and Sedation (MOAAS) Houpt scale	Significant difference (P = 0.007) in behaviour during treatment compared to baseline in Group 1 and Group 2 Significant difference in the level of sedation in Group 1 and Group 2 when a comparison is made at specific time stages (treatment-baseline and, end of treatment-baseline) e.g. for Group 1 treatment-baseline comparison shows	-

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 3. Drug comparison study outcomes *(Continued)*

	Mean weight (SD): 15.62 ± 4.21	dexmedetomidine (1 µ/kg), 30 ml of mango juice Group 3: intranasal normal saline, 30 ml of mango juice		significant difference (P = 0.002) in the level of sedation No significant difference between Group 1 and Group 2 in sedative efficacy or anxiolysis potential Adverse effects: not reported Monitoring: blood pressure, heart rate, oxygen saturation	
Surendar 2014	n = 84 Age range in years, mean age (SD) in years: Group 1 (n = 21) 7.34 (2.34) Group 2 (n = 21) 6.71 (2.31) Group 3 (n = 21) 7.76 (2.26) Group 4 (n = 21) 7.24 (2.36)	Group 1: dexmedetomidine (1 µg/kg) Group 2: dexmedetomidine (1.5 µg/kg) Group 3: midazolam (0.2 mg/kg) Group 4: ketamine (5 mg/kg) All intranasal	Modified AAPD Sedation Record Face, Legs, Activity, Cry and Consolability (FLACC) scale	No significant difference (P = 0.378) in overall behaviour was observed No significant difference (P = 0.242 and P = 0.120) in overall success rate of treatment and distribution of sedation levels between the groups Significant difference (P > 0.05) in intra and postoperative analgesic effects reported with Group 1, Group 2 and Group 4 significantly better than Group 3 e.g. intraoperative analgesia score Group 3 = 5.62 (SD 1.12) compared to Group 1 = 3.81 (0.81), Group 2 = 3.67 (0.91) and Group 4 = 3.52 (0.68) Significant difference (P > 0.05) in onset time, recovery time, pulse rate and systolic blood pressure of Group 1 and Group 2 compared to Group 3 and Group 4 was observed Adverse effects: not reported Monitoring: oxygen saturation, respiratory rate, blood pressure and respiratory rate	-
Ketamine versus					
Abrams 1993	n = 30 (10 per group with sufentanil divided into 2 subgroups of 5 each) Age range = 17 to 62 months	Group 1: ketamine (3 mg/kg) Group 2: midazolam (0.4 mg/kg) Group 3: sufentanil (1 µg) Group 4: sufentanil (1.5 µg) All intranasal	Sedation scoring criteria No statistical tests used	Groups 1 to 3 had mean sedation score of 4 (acceptable sedation), Group 4 had mean sedation score of 7 (heavy sedation) Mean recovery times (± SD) were 7 (± 7), 3 (± 2), 7 (± 13), and 58 (± 40) minutes for Groups 1-4 respectively Sleeping mentioned Adverse effects: drowsiness (Group 1), mild obtundation and deep sedation (Group 3), desaturations in 4/5 children on high dose sufentanil Monitoring: pulse oximeter, automatic blood pressure and if necessary capnograph	-

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 3. Drug comparison study outcomes *(Continued)*

Rai 2007	n = 30 (10 per group) Age range 3-6 years	Group 1: midazolam (0.1 mg/kg) (bolus) + 0.004 mg/kg/min (infusion) Group 2: propofol (1 mg/kg) (bolus) + 0.06 mg/kg/min (infusion) Group 3: ketamine (0.5 mg/kg) (bolus) + 0.01 mg/kg/min (infusion) All intravenous All children had premedication 1 hour before of 0.5 mg/kg midazolam and atropine (0.6 mg)	Houpt Analysed Kruskal Wallis	The maximum level of co-operation was seen with ketamine then propofol and then midazolam (P < 0.001) At treatment end mean scores were 5.8 ± 0.42, 3.5 ± 1.08 and 3.2 ± 0.42 in ketamine, propofol and midazolam groups respectively Propofol showed the fastest postoperative recovery score followed by ketamine and the midazolam. Sleeping was reported Adverse effects: pain on injection with propofol and intermittent cough Monitoring: vital signs	-
Roelofse 1996a	n = 100 Mean age (SD) in years, gender: Group 1 (n = 50), 4.3 (1), 24 males and 26 females Group 2 (n = 50), 4.3 (1.1), 22 males and 28 females	Group 1: ketamine (5 mg/kg) + midazolam (0.35 mg/kg) Group 2: midazolam (1 mg/kg) All rectal	Ramsay Sedation Score Movement Crying Overall sedation and behaviour Analysed using McNewman's test (sic), Chi^2 and Fisher's Exact tests	Significant differences in level of sedation with 71% subjects in Group 2 "orientated and calm" compared to 14% in Group 1 30 minutes after administration Significantly less movement and crying (P < 0.05) in Group 1 (58% no movement at all compared to 14% in Group 2) Sleep mentioned Adverse effects: hallucination (Groups 1 (14%) and 2 (42%)), nausea (Group 1) Monitoring: pulse oximeter	Dental treatment aborted in 1 participant (ketamine/midazolam group)
Roelofse 1996b	n = 60 Mean age (SD) in years, gender: Group 1 (n = 30), 4.8 (1.3), 14 males and 16 females Group 2 (n = 30), 4.9 (1.3), 16 males and 14 females	Group 1: 0.5 ml/kg of trimeprazine 6 mg/ml + physeptone (methadone) (0.4 mg/ml) + droperidol (0.1 mg/kg) Group 2: ketamine (12.5 mg/kg) All oral	Anxiety Level of sedation Movement Crying Overall behaviour Analysed using McNemar test, Chi^2 and Fisher's Exact tests	Sedation was significantly "better" (very good/excellent 80% and 93% of Group 1 and Group 2 respectively) Overall evaluation good/very good in 67% and 90% of Group 1 and Group 2 respectively Sleeping mentioned Adverse effects: hallucination (9 and 5), restless/irritation 4 and 1, in Group 1 and Group 2 Ketamine also 2 vomiting/nausea, 4 visual disturbances and 4 excess salivation Monitoring: pulse oximeter	All participants completed treatment

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 3. Drug comparison study outcomes *(Continued)*

Roelofse 1998	n = 100 Mean age (SD) in years, gender: Group 1 (n = 50), 4.1 (1.3), 27 males and 23 females Group 2 (n = 50), 4 (1.2), 29 males and 21 females	Group 1: ketamine (5 mg/kg) + midazolam (0.35 mg/kg) Group 2: trimeprazine (3 mg/kg) + methadone (0.2 mg/kg) All oral	Modified Houpt, Ramsay Sedation Score Analysed using McNemar's test, Chi^2 and Fisher's Exact tests	Significant differences (P < 0.05) in level of sedation immediately before treatment with 46% participants in Group 1 "oriented and calm" compared to 84% in Group 2 Overall surgeons rated 94% versus 78% of sedations as good/very good in Group 1 versus Group 2 Sedation rated as poor in significantly more children in Group 2 (24%) than Group 1 (6%) Sleeping mentioned Adverse effects: vomiting (n = 2) and hallucination (n = 10) in Group 1 Monitoring: pulse oximeter	All participants completed treatment
Singh 2014	n = 112 Age range = 1-10 years Mean age (SD) in years, gender and weight (SD) in kg: Group 1 (n = 28), 6.54 (1.79), 14 males and 14 females, 18.89 (4.33) Group 2 (n = 28), 6.93 (2.05), 13 males and 15 females, 17.04 (5.33) Group 3 (n = 28), 7.21 (1.98), 11 males and 17 females, 16.93 (4.22) Group 4 (n = 28), 6.82 (2.22), 14 males and 14 females, 16.61 (4.92)	Group 1: ketamine (8 mg/kg^{-1}) Group 2: dexmedetomidine (3 µg/kg^{-1}) Group 3: dexmedetomidine (4 µg/kg^{-1}) Group 4: dexmedetomidine (5 µg/kg^{-1}) All oral	Onset time, recovery time Sedation rating scale modified from AAPD guidelines Face, Legs, Activity, Cry and Consolability Pain Scale (FLACC) Anterograde amnesia Behaviour score	Group 4 had highest "adequate" depth of sedation and "satisfactory" completion of treatment (82.1%, 85.7% respectively), but was not significantly different to Group 1, Group 2 and Group 3 Significant difference (P < 0.001) in lowering of pulse rate and systolic blood pressure in Group 2, Group 3 and Group 4 compared to Group 1 Significant difference (P < 0.001) in onset time, recovery time (except Group 1 and Group 4), intra and postoperative pain scores when comparing the groups e.g. postoperative pain score in Group 1 = 1.54 (0.63) and Group 4 = 1.79 (0.74) were lower compared to Group 2 = 2.43 (0.88) and Group 3 = 2.11 (1.19) Adverse effects: in office vomiting (Group 1 n = 5, Group 4 n = 1), emergency reaction (Group 1 n = 2) Monitoring: oxygen saturation, respiratory rate, blood pressure and respiratory rate	-
Alfonzo-Echeverri 1993	n = 40 Mean age (SD) in months: Group 1 (n = 20) 40.4 (10.2) Group 2 (n = 20) 37.5 (10.6)	Group 1: ketamine (6 mg/kg) Group 2: meperidine (2.0 mg/kg) + promethazine (0.5 mg/kg) All oral	Modified Houpt Analysed using Chi^2 test	"Good sedation" in 65% of ketamine group and 45% of meperidine/promethazine Overall no statistically significant difference in distribution of sedation outcomes between groups (P = 0.07)	Dental treatment aborted in 4 children receiving meperidine and none

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 3. Drug comparison study outcomes *(Continued)*

		All received nitrous oxide 30%-50%		Sedation onset time and recovery time both shorter for ketamine (P < 0.001 and P = 0.08 respectively) Adverse effects: vomiting (Groups 1 (n = 8) and 2 (n = 1)) Monitoring: precordial stethoscope and pulse oximeter	in ketamine group
Bui 2002	n = 22 Mean age (SD) in months: Group 1 (n = 11) 34 (6.28) Group 2 (n = 11) 33 (6.65)	Group 1: ketamine (10 mg/kg) + promethazine (1.1 mg/kg) Group 2: ketamine (10 mg/kg) All oral All received nitrous oxide 50%	Houpt Analysed using Mann-Whitney U test	Statistically significant difference in mean Houpt score favouring ketamine group (mean score 4.27, SD 0.5) (Group 1 (mean score 3.12, SD 0.29)) (P < 0.05) Adverse effects: 3 patients from Group 2 vomited. Most of the patients reported as being drowsy or asleep after 25 minutes	Dental treatment aborted in 1 participant from Group 1 due to violent physical movement and crying
Ketamine/midazolam versus					
Gomes 2017	Mean age (SD) in years, gender, mean weight (25% median to 75%) in kg: Group 1 (n = 13), 4.7 (0.6), 10 males, 3 females, 16.5 (15.7-19.6) Group 2 (n = 14), 5.2 (0.8), 8 males, 6 females, 19.6 (16.7-23.9)	Group 1: midazolam (0.5 mg/kg) + ketamine (3 mg/kg) (oral) Group 2: midazolam (0.5 mg/kg) (oral) + ketamine (3 mg/kg) (oral) + sevoflurane (0.1%-0.4% inhalation)	Houpt Analysed using Mann-Whitney U test Adverse events Analysed using Chi^2 test	No significant difference in overall Houpt score between the 2 groups (P > 0.05 data presented graphically) Adverse events: more children in Group 1 reported adverse events at 24 hours than Group 2 (Group 1 n = 10, Group 2 n = 4; P = 0.01) Adverse events seen in all children included: excessive drowsiness 22% (n = 6), vomiting 22% (n = 6) No apnoea /drop in oxygen saturation seen Monitoring: pulse oximeter	Treatment not completed in 1 child from Group 1 due to poor co-operation
Midazolam (oral) versus					
Baygin 2010	n = 60 Mean age (unclear, possibly SD) in years, mean weight (unclear, possibly SD) in kg, gender: Group 1 (n = 15), 5.33 (0.62), 18.93 (2.31), 10 males and 5 females Group 2 (n = 15), 5.27 (0.80)	Group 1: hydroxyzine (1 mg/kg) (oral) Group 2: midazolam (0.7 mg/kg) Group 3: ketamine (3 mg/kg) + midazolam (0.25 mg/kg) Group 4: no oral premedication 40% nitrous oxide oxygen was	Ramsay Sedation Score, Bispectral Index System	Ramsay Sedation Scores (RSS) were significantly greater in Group 2 compared to Groups 1, 3 and 4 (P < 0.05) RSS satisfactory/mid-level satisfactory/unsatisfactory was as follows: Group 1: 13.3%/53.3%/33.3% Group 2: 54%/20%/26% Group 3: 33.3%/33.3%/33.3% Group 4: 6.7%/60%/33.3% P value or significance not reported	Figure 5 used to extrapolate data with score 3 given to satisfactory, 2 middle level, 1 unsatisfactory All participants completed treatment

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 3. Drug comparison study outcomes *(Continued)*

	19.07 (3.62), 11 males and 4 females Group 3 (n = 15), 5.20 (0.41), 18.20 (2.34), 9 males and 6 females Group 4 (n = 15), 5.53 (0.99), 20.01 (3.99), 6 males and 9 females	administered to all participants		Adverse effects: nausea/vomiting (n = 1/2/3/4), cough (4/4//), hiccough (/1//5), enuresis (/2//), bronchospasm (/1//), hypersalivation (//8/), otalgia (///2), hallucination (//2/), and epistaxis (///1) in patients in groups 1, 2, 3, and 4, respectively Monitoring: pulse oximeter	
Bhatnagar 2012	n = 60 Age range = 3-9 years	Group 1: midazolam (0.5 mg/kg) Group 2: tramadol (2 mg/kg) Group 3: triclofos (70 mg/kg) Group 4: zolpidem (0.4 mg/kg) All oral	Sedation rating scale Ease of treatment completion	Significant difference (P < 0.001) in the level of sedation (median scores) with Group 4 > Group 3 > Group 2 = Group 1 Mean score in the ease of treatment shown in the table of results reports Group 4 > Group 3 > Group 2 > Group 1 No statistical difference between (P > 0.05) between Group 1, Group 2, Group 3 in ease of treatment. Group 4 was found to have a statistical difference compared to the other groups (P < 0.001) Adverse effects: not mentioned	-
Moreira 2013	n = 44 Average age below 36 months Mean age (SD) in months, gender: Group 1 (n = 11), 27.1 (8.3), 6 males and 5 females Group 2 (n = 18, parents refused treatment for 2), 27.7 (5.5), 9 males and 7 females Group 3 (n = 15, parents refused treatment for 1), 27.3 (6.4), 9 males and 4 females	Group 1: midazolam (0.5 mg/kg) + ketamine (3 mg/kg) Group 2: midazolam (1 mg/kg) Group 3: no sedation Group 1 and 2 oral	Ohio State University Behavior Rating Scale (OSUBRS)	Significant difference in behaviour (P = 0.003) between Group 1 and Group 2 and Group 1 and Group 3 (P = 0.03) when sedatives used Behaviour during various stages of treatment sessions was observed e.g. for local anaesthetic administration OSUBRS score for Group 1 was lower than Group 2 (P = 0.06) and Group 3 (P = 0.02) During rubber dam placement OSUBRS score for Group 1 was lower than Group 2 (P = 0.01) and Group 3 (P = 0.07). All Groups showed same behavioural pattern at the end of the treatment session (P = 0.25) Sleep mentioned Adverse effects: within 24 hour postoperatively Group 1 presented with agitation and vomiting in 3 children	All participants completed treatment

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 3. Drug comparison study outcomes *(Continued)*

Koirala 2006	n = 120 (20 per group) Age range: 2-9 years	Group 1: midazolam (9.5 mg/kg) Group 2: ketamine (5 mg/kg) Group 3: zolpidem (0.4 mg/kg) Group 4: midazolam (0.4 mg/kg) + ketamine (3 mg/kg) Group 5: midazolam (0.5 mg/kg) + tramadol (2 mg/kg) Group 6: zolpidem (0.4 mg/kg) + tramadol (2 mg/kg) All oral	Onset of action Level of sedation Ease of treatment completion	Group 4 and 5 the "best" and Groups 3 and 6 the "worst" when compared on level of sedation (P < 0.001) Group 4 had the shortest time of onset of sedation (Data presented graphically) No adverse effects were reported	-
Singh 2002	n = 90 (30 per group) Age range: 3-9 years	Group 1: midazolam (0.5 mg/kg) Group 2: triclofos (70 mg/kg) Group 3: promethazine (1.2 mg/kg) All oral	Degree of sedation Time of onset, time of recovery Statistical techniques not described	Transformed sedative scores Group 1: 3.3 ± 0.7 (best) Group 2: 3.07 ± 0.6 Group 3: 2.73 ± 0.5 Both Groups 1 and 2 were statistically significantly better than Group 3 (P < 0.05) Time of onset and time of recovery were both shortest in Group 1 Adverse effects: not mentioned Monitoring: blood pressure, heart and respiratory rate	-
Özen 2012	n = 240 (n = 60 per group) Mean age (SD) in months 57.02 (9.31)	Group 1: midazolam (0.20 mg/kg (40 mg/ml)) (intranasally) + inhalation sedation 50%–50% nitrous oxide/oxygen Group 2: midazolam (0.75 mg/kg (15 mg/3 ml)) (orally) + inhalation sedation 50%–50% nitrous oxide/oxygen	Bispectral Index System (BIS) Modified scale to classify behaviour Vancouver Recovery Scale	Modified scale used to classify behaviour/ respond to treatment/sedation was highest in Group 1 (87%) followed by Group 2 (79%), Group 3 (72%) and Group 4 (55%) respectively No significant difference (P = 0.230 and P = 0.399) in overall success rate between Group 1 and Group 2, Group 2 and Group 3 respectively. Significant difference (P < 0.05) between Group 1 and Group 3. Significant difference Group 4 compared to all other groups BIS values recorded every 5 minutes, Group 2 was most sedated except for at 30 minutes. From 15 minutes to end	-

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 3. Drug comparison study outcomes *(Continued)*

		Group 3: midazolam (0.50 mg/kg (15 mg/3 ml)) (orally) + inhalation sedation 50%–50% nitrous oxide/oxygen Group 4: inhalation sedation 50%–50% nitrous oxide/oxygen		of treatment all groups had BIS value above 90 Recovery time in minutes was shorter for intranasal midazolam (22.3) compared to 0.50 mg/kg oral midazolam (27.5) and 0.75 mg/kg oral midazolam (29.2) Sleep mentioned Adverse effects: - drug administration: vomiting in oral midazolam group (4), nose bleeding intranasal midazolam group (1), transient burning and discomfort nasal midazolam group (not reported) - recovery period: vomiting in oral midazolam group (7), coughing in intranasal midazolam group (1), transient burning and discomfort nasal midazolam group (not reported) - after discharge: irritability (42%), crying (34%), sleepiness (31%), nausea (5%)	
Tyagi 2012	n = 40 Age range = 2-10 years	Group 1: midazolam (0.5 mg/kg) (oral) Group 2: diazepam (0.5 mg/kg) (oral) Group 3: midazolam (0.06 mg/kg) (intravenous) Group 4: placebo	Houpt scale Child behaviour questionnaire	Behaviour was assessed in terms of sleep, crying and movement at 30 minutes postdrug administration in Group 1, Group 2 and Group 4 or 5 minutes in Group 3. At placement of blood pressure cuff, during administration of local anaesthesia or use of hand piece and every 15 minutes thereafter e.g. at administration of local anaesthetic agent or use of hand piece significantly lower ($P < 0.001$) sleep in Group 4 compared to other groups. Significantly less crying in Group 3 compared to Group 1, Group 2 and Group 4 ($P < 0.001$, $P < 0.01$ and $P < 0.05$ respectively) Overall behaviour rating was significantly better ($P < 0.001$) in Group 3 compared to other groups Positive behaviour postsedation: no significant difference between Group 1 and Group 2. Significant improvement ($P < 0.05$) in Group 3 compared to Group 2 Sleeping mentioned Adverse effects: not reported Monitoring: oxygen saturation, respiratory rate, blood pressure and respiratory rate	-

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 3. Drug comparison study outcomes *(Continued)*

Midazolam (intravenous) versus					
Kaviani 2015	n = 38 Age range = 4-9 years Gender, mean age in years: Group 1 (n = 18), 8 males and 10 females, 6.27 Group 2 (n = 20), 12 males and 8 females, 6.75	Group 1: midazolam (0.05 mg/kg) + ketamine (0.5 mg/kg) Group 2: midazolam (0.05 mg/kg) + fentanyl (0.5 µg/kg) All intravenous, administered by an anaesthesiologist	Dental Sedation Teacher Groups System Frankl behaviour rating scale	No significant difference (P > 0.05) in intraoperative sedation score and score of operative conditions at 10th, 20th, 30th and 40th minute Significant difference (P < 0.05) in the sedation score and score of operating condition in Group 1 and Group 2 at 10-20 minutes, 10-30 minutes Adverse effects: not reported	-
Eshghi 2016	n = 32 Age range = 3-7 years Mean age (SD) in years: 4.36 (1.6) Group 1 (n = 16), 7 males and 9 females Group 2 (n = 16), 8 males and 8 females	Group 1: remifentanil (0.1 µg/kg/min) + midazolam (0.01 mg/kg) + propofol (0.5 mg/kg) Group 2: ketamine (0.5 mg/kg) + midazolam (0.1 mg/kg) + propofol (0.5 mg/kg) All intravenous	Bispectral Index System (BIS) DSTG scale	Significant difference (P = 0.003) with higher BIS values in Group 1 compared to Group 2 DSTG score noted at 9 different time intervals was 5 (eyes closed, no response to mild physical stimulus) in Group 1 and Group 2 Heart rate and respiratory rate showed no significant difference between Group 1 and Group 2 (P = 0.884, P = 0.775 respectively) Significant difference (P < 0.001) with Group 1 having quicker recovery compared to Group 2 (9.23 ± 2.77, 30.83 ± 5.96 minutes) Adverse effects: severe nausea and vomiting was reported in Group 1, number not reported Monitoring: heart rate, respiratory rate, oxygen saturation	-
Midazolam (rectal) versus					
Jensen 1999	n = 90 Median age (age range) in months and gender: Group 1 (n = 45), 32 (18 to 44), 23 males and 22 females Group 2 (n = 45),	Group 1: diazepam (0.7 mg/kg) Group 2: midazolam (0.3 mg/kg) All rectal	Wilton's sedation scale Acceptance of treatment (Holst) Analysed using Wilcoxon matched pair test and Fisher's exact test	No difference in acceptance of dental procedures (P = 0.07) At 1 hour significantly more children agitated in the diazepam group 13/45 (29%) versus 1/45 (2%) (P = 0.006) Data presented graphically Adverse effects: lasting effect: aggressiveness, tiredness and unco-ordinated movements in diazepam group, children unusually quiet or lively on next day in Group 2	Some children did not complete treatment however, it is not possible to extract exact numbers as these data were only presented as bar chart

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 3. Drug comparison study outcomes *(Continued)*

	29 (15 to 44), 23 males and 22 females				
Sevoflurane versus					
Lahoud 2002	n = 411 Mean age (SD) in years: Group 1 (n = 170), 6.2 (1.9) Group 2 (n = 241), 6 (1.7)	Group 1: 40:60 nitrous oxide/oxygen Group 2: 40:60 nitrous oxide/oxygen + 0.1%-0.3% sevoflurane All inhalation	Venham scale level of sedation and failure rate Analysed using Mann-Whitney U test and Chi^2 test	Effective sedation: Group 1 215/241 (89%); Group 2 89/170 (52%); (P < 0.0001) Venham scale - relaxed: Group 1 = 32%; Group 2 = 67% Significantly less failure in sevoflurane/nitrous oxide Group 1 48% failed (P < 0.0001); Group 2 11% failed Adverse effects: none mentioned Monitoring: pulse oximeter, capnograph, pretracheal stethoscope, visual assessment, auscultation and visualization of chest movements	89% sevoflurane group completed treatment compared to 52% of nitrous oxide group
Averley 2004a	n = 65 Gender, mean weight (SD) in kg, mean age (SD) in years: Group 1: 13 males and 7 females, 33.6 (11.2), 9.3 (2.2) Group 2: 15 males and 5 females, 37.6 (14.6), 9.6 (2.3) Group 3: 4 males and 16 females, 36.1 (11.8), 9.9 (2.2)	Group 1: midazolam (0.5 mg/min) (intravenous) + air (nasal inhalation) Group 2: midazolam (0.5 mg/min) (intravenous) + nitrous oxide (40%) (nasal inhalation) Group 3: midazolam (0.5 mg/min) (intravenous) + nitrous oxide (40%) (nasal inhalation) + sevoflurane (0.3%) (nasal inhalation)	Primary: completion of treatment Secondary: level of co-operation during treatment, recovery time, perception of anxiety and pain and parent's satisfaction Analysed using Chi^2 test	Treatment completion: Group 1: 10/20 (50%) Group 2: 16/22 (73%) Group 3: 19/23 (83%) (Chi^2 = 5.53, df = 2, P = 0.07) Of the 16 treatment failures in Groups 1 and 2, 9 were subsequently successfully treated with the addition of sevoflurane + nitrous oxide No adverse effects reported Monitoring: pulse oximeter, blood pressure, ECG	-
Averley 2004b	n = 664 Gender, mean weight (SD) in kg, mean age (SD) in years: Group 1 (n = 222), 81 males, 36.3 (13.4), 9.1 (2.7) Group 2 (n = 306), 127	Group 1: midazolam (0.5 mg/min) (intravenous) + air (nasal inhalation) Group 2: midazolam (0.5 mg/min) (intravenous) + nitrous oxide (40%) (nasal inhalation)	Primary: completion of treatment Secondary: level of co-operation during treatment, recovery time, perception of anxiety and pain and par-	Treatment completion: Group 1: 94/174 (54%) Group 2: 204/256 (80%) Group 3: 249/267 (93%) Chi^2 = 9.64, df = 2, P < 0.001 Adverse effects: 1 faint in Group 1, 6 vomited in Group 3	-

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 3. Drug comparison study outcomes *(Continued)*

males, 37.8 (14.1), 9.5 (2.7) Group 3 (n = 320), 103 males, 37.7 (14), 9.6 (2.5)	Group 3: midazolam (0.5 mg/min) (intravenous) + nitrous oxide (40%) (nasal inhalation) + sevoflurane (0.3%) (nasal inhalation)	ent's satisfaction Analysed using Chi^2 test	Monitoring: pulse oximeter, blood pressure, ECG

AAPD = American Academy of Pediatric Dentistry; DSTG scale = Dental Sedation Teachers Group scale; df = degrees of freedom; ECG = electrocardiogram; n = number; SD = standard deviation; SE = standard error.

Table 4. Frequency of studies in which drug regimens were tested

Drug regimen tested	Study frequency
Chloral hydrate	3
Chloral hydrate + hydroxyzine	6
Chloral hydrate + hydroxyzine + midazolam	1
Chloral hydrate + promethazine	1
Dexmedetomidine	2
Diazepam	1
Hydroxyzine	3
Ketamine	7
Ketamine + promethazine	1
Ketamine + midazolam	3
Ketamine + midazolam + sevoflurane	1
Melatonin	1
Meperidine	1
Meperidine + promethazine	2
Midazolam	27
Midazolam + acetaminophen	1
Midazolam + fentanyl	1
Midazolam + hydroxyzine	1
Midazolam + nitrous oxide/oxygen	1

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 4. Frequency of studies in which drug regimens were tested *(Continued)*

Midazolam + ketamine	5
Midazolam + sevoflurane + nitrous oxide/oxygen	2
Midazolam + tramadol	1
Nitrous oxide/oxygen	5
Promethazine	1
Propofol	1
Sevoflurane + nitrous oxide/oxygen	1
Sufentanil	1
Tramadol	1
Triazolam	1
Triclofos	2
Trimeprazine + methadone	1
Trimeprazine + physeptone	1
Zolpidem	2
Zolpidem + tramadol	1

Table 5. Comparison of behaviour/sedation rating scales

Score	Ramsay Sedation Scale	Briekopf and Buttner Emotional Status Scale	Frankl Behaviour Rating Scale	Houpt Behaviour Rating Scale
1	Awake, anxious and agitated, restless or both	Irritated: awake, restless, crying	Refusal/distress	Aborted: no treatment rendered
2	Awake, co-operative, orientated, tranquil	Normal: awake, calm	Unco-operative/reluctant	Poor: treatment interrupted, only partial treatment was completed
3	Awake responds to commands only	Inactive: tired, hardly moving	Co-operative/reserved	Fair: treatment interrupted but eventually completed
4	Asleep, brisk response	Sleepy: drowsy, with reaction but rousable	Interested/enjoyed	Good: difficult but all treatment was performed
5	Asleep, sluggish response			Very good: some limited crying and movement
6	Asleep, no response			Excellent: no crying or movement

From Wan 2006.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 6. Outcome measures used (excluding physiological parameters)

Name	Studies used	Characteristics
Houpt	Avalos-Arenas 1998; Bui 2002; Faytrouny 2007; Gomes 2017; Lam 2005; Malhotra 2016; Meyer 1990; Mortazavi 2009; Park 2006; Rai 2007; Reeves 1996; Sams 1993a; Shashikiran 2006; Somri 2012; Tyagi 2012; Wan 2006	3-point scale for sleep (awake to asleep); 4-point scale for movement (1 = violent movement to 4 = no movement); 4-point scale for crying (1 = hysterical crying to 4 = no crying); 6-point scale for overall behaviour (1 = no treatment rendered to 4 = difficult but all treatment completed to 6 = excellent/no crying or movement)
Modified from Houpt	Alfonzo-Echeverri 1993; McKee 1990	4-point scale ranging from 1 = treatment aborted, 2 = poor (treatment frequently interrupted), 3 = fair (planned treatment completed), 4 = good (all treatment completed without crying or movement)
Modified from Houpt	Lee-Kim 2004	Modification not specified
Dichotomous behaviour scale	McKee 1990; Moore 1984	Dichotomous behavioural scale rates specific events of treatment as satisfactory or unsatisfactory
Ohio State University Behavior Rating Scale	Moreira 2013; Torres-Perez 2007	4-point scale ranging from quiet to crying and struggling
Venham scale	Lahoud 2002; Shanmugaavel 2016a; Shanmugaavel 2016b; Veerkamp 1993	6-point scale ranging from 0 = relaxed to 5 = out of control
Mental attitude, hypnotic effect, motor activity and overall sedation	Gallardo 1994	2-point scale for mental attitude (relaxed or agitated); 3-point scale for hypnotic effect (asleep to or awake); 3-point scale for motor activity (absent to remarkable); 3-point scale for sedation (excellent to unsatisfactory)
Ramsay Sedation Scale, movement, crying, overall sedation and behaviour	Aydintug 2004; Baygin 2010; Isik 2008a; Isik 2008b; Roelofse 1996a; Roelofse 1998; Wan 2006	6-point scale for Ramsay (patient anxious and agitated to no response); 3-point scale for movement (continuous movement to no movement); 4-point scale for crying (hysterical crying to no weeping); 4-point scale for overall sedation (impossible to very good)
Sedation scoring system	Abrams 1993	10-point scale ranging from 1 = unmanageable, unable to examine/treat, to 10 = obtunded: apneic where 5 is ideal (well sedated, co-operative with normal oximetry)
Sedation scoring system	Kapur 2004; Koirala 2006	5-point scale ranging from asleep to awake
Sedation scoring system	Roelofse 1996b	4-point scale for level of sedation
Wilton's sedation scale	Jensen 1999	4-point scale for Wilton (drowsy to agitated)
Acceptance of treatment (Holst, 1987)	Jensen 1999; McKee 1990	4-point scale for Holst (positive to no)

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 6. Outcome measures used (excluding physiological parameters) *(Continued)*

Acceptance of treatment (Al Rakaf, 2001)	Shanmugaavel 2016b	4-point scale
Frankl	Kaviani 2015; Wan 2006	4-point scale for Frankl (definitely negative to definitely positive)
Modification Barker sedation scoring system, overall quality sedation	Moody 1986	Barker sedation score calculated by summing scores given at intervals throughout the treatment; 4-point rating scale for sedation quality (poor to excellent)
Global rating scale of overall behaviour	McKee 1990	5 ratings from excellent to poor-aborted
Sedation rating scale	Singh 2002	7-point scale ranging from sleep to excited
Brietkopf and Buttner	Wan 2006	4-point scale ranging from irritated to sleepy
Fukuta	Shashikiran 2006	7-point scale ranging from asleep to violent rejection
Sedation rating scale	Bhatnagar 2012	8-point scale ranging from sleep to excited
Modified scale to classify behaviour/response to treatment/sedation	Özen 2012	4-point scale ranging from success to not accepting treatment
Behaviour/response to treatment rating scale	Surendar 2014	5-point scale ranging from excellent to prohibitive
Modified Dental Sedation Teachers Groups Scale (Ransford, 2010)	Kaviani 2015	4-point scale measuring operating conditions ranging from 1 = good to 4 = impossible

APPENDICES

Appendix 1. Cochrane Oral Health's Trials Register search strategy

From January 2017, searches of the Cochrane Oral Health's Trials Register for this review were undertaken using the Cochrane Register of Studies and the search strategy below:

1. ((sedation or sedative* or "pre anesthetic medication" or "pre anaesthetic medication" or hypnotic* or "anti anxiety agent*" or barbiturate* or benzodiazepine* or "relative analgesia" or "nitrous oxide" or "nitrous-oxide" or midazolam or diazepam or "chloral hydrate" or hydroxyzine or temazepam or ketamine or meperidine or promethazine or triazolam or trimeprazine or metaclopramide or flunitrazepam or sevoflurane)) AND (INREGISTER)
2. ((anxiety or anxious or fear* or fright* or distress* or phobi* or uncopoperative or un-cooperative or un-cooperative)) AND (INREGISTER)
3. ((child* or infant* or adolescen* OR pediatric* or paediatric*)) AND (INREGISTER)
4. #1 and #2 and #3 (INREGISTER)

Previous searches were undertaken using the Procite software, and the search strategy below:

((sedation or sedative* or "pre anesthetic medication" or "pre anaesthetic medication" or hypnotic* or "anti anxiety agent*" or barbiturate* or benzodiazepine* or "relative analgesia" or "nitrous oxide" or "nitrous-oxide" or midazolam or diazepam or "chloral hydrate" or hydroxyzine or temazepam or ketamine or meperidine or promethazine or triazolam or trimeprazine or metaclopramide or flunitrazepam or sevoflurane) OR (anxiety or anxious or fear* or fright* or distress* or phobi* or uncopoperative or un-cooperative or un-cooperative) AND (child* or infant* or adolescen* OR pediatric* or paediatric*))

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 MeSH descriptor Oral Surgical Procedures explode all trees

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

#2 MeSH descriptor Tooth explode all trees
#3 (dental* or dentist* or oral) and (surgery or surgical or orthodont* or endodont* or pulpot* or carie* or carious)
#4 ((dental or tooth or teeth) and (filling* or restor* or extract* or treat*))
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Conscious Sedation, this term only
#7 MeSH descriptor Preanesthetic Medication, this term only
#8 ("preanesthetic medication" or "preanaesthetic medication")
#9 sedat*
#10 MeSH descriptor Hypnotics and Sedatives explode all trees
#11 MeSH descriptor Anti-Anxiety Agents explode all trees
#12 MeSH descriptor Barbiturates explode all trees
#13 MeSH descriptor Benzodiazepines explode all trees
#14 "relative analgesia"
#15 MeSH descriptor Anxiety, this term only
#16 MeSH descriptor Dental Anxiety, this term only
#17 ((anxiety or anxious or fear* or fright* or stress* or distress* or phobi* or uncooperative or un-cooperative or unco-operative) and (dental* or dentist*))
#18 ("nitrous oxide" or midazolam or diazepam or "chloral hydrate" or hydroxyzine or temazepam or ketamine or meperidine or promethazine or triazolam or trimeprazine or metaclopramide or flunitrazepam or sevoflurane)
#19 (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)
#20 MeSH descriptor Child explode all trees
#21 MeSH descriptor Infant, this term only
#22 MeSH descriptor Adolescent, this term only
#23 pediatric* or paediatric*
#24 child* or infant* or adolescent*
#25 (#20 OR #21 OR #22 OR #23 OR #24)
#26 (#5 AND #19 AND #25)

Appendix 3. MEDLINE Ovid search strategy

1. exp Oral Surgical Procedures/
2. exp tooth/
3. (((((dental$ or dentist$ or oral) adj4 surgery) or oral) adj4 surgical$) or orthodont$ or endodont$ or pulpot$ or carie$ or carious).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4. ((dental or tooth or teeth) or (filling$ or restor$ or extract$ or treat$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
5. or/1-4
6. Conscious sedation/
7. Preanesthetic medication/
8. (preanesthetic medication or preanaesthetic medication).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
9. sedat$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
10. exp "Hypnotics and Sedatives"/
11. exp Anti-Anxiety Agents/
12. exp Barbiturates/
13. exp Benzodiazepines/
14. relative analgesia.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
15. Anxiety/
16. Dental anxiety/
17. ((anxiety or anxious or fear$ or fright$ or stress$ or distress$ or phobi$ or uncooperative or un-cooperative or unco-operative) and (dental$ or dentist$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
18. (nitrous oxide or midazolam or diazepam or chloral hydrate or hydroxyzine or temazepam or ketamine or meperidine or promethazine or triazolam or trimeprazine or metaclopramide or flunitrazepam or sevoflurane).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
19. or/6-18
20. exp Child/
21. Infant/
22. Adolescent/
23. (pediatric or paediatric).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
24. (child$ or infant$ or adolescen$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
25. or/20-24
26. 5 and 19 and 25

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

This subject search was linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the*Cochrane Handbook for Systematic Reviews of Interventions,* Version 5.1.0 (updated March 2011) (Lefebvre 2011).

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Appendix 4. Embase Ovid

1. exp Oral Surgical Procedures/
2. exp Tooth/
3. (((((dental$ or dentist$ or oral) adj4 surgery) or oral) adj4 surgical$) or orthodont$ or endodont$ or pulpot$ or carie$ or carious).mp.
4. ((dental or tooth or teeth) and (filling$ or restor$ or extract$ or treat$)).mp.
5. or/1-4
6. Conscious sedation/
7. Preanesthetic medication/
8. ("preanesthetic medication" or "preanaesthetic medication").mp.
9. sedat$.mp.
10. exp "Hypnotics and Sedatives"/
11. exp Anti-Anxiety Agents/
12. exp Barbiturates/
13. exp Benzodiazepines/
14. "relative analgesia".mp.
15. Anxiety/
16. Dental anxiety/

This subject search was linked to an adapted version of the Cochrane Centralised Search Project filter for identifying randomised controlled trials in Embase Ovid (see www.cochranelibrary.com/help/central-creation-details.html for information):

1. Randomized controlled trial/
2. Controlled clinical study/
3. Random$.ti,ab.
4. randomization/
5. intermethod comparison/
6. placebo.ti,ab.
7. (compare or compared or comparison).ti.
8. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
9. (open adj label).ti,ab.
10. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
11. double blind procedure/
12. parallel group$1.ti,ab.
13. (crossover or cross over).ti,ab.
14. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant $1)).ti,ab.
15. (assigned or allocated).ti,ab.
16. (controlled adj7 (study or design or trial)).ti,ab.
17. (volunteer or volunteers).ti,ab.
18. trial.ti.
19. or/1-18
20. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
21. 19 not 20

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Appendix 5. US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov) search strategy

sedation and child* and dental

Appendix 6. World Health Organization International Clinical Trials Registry Platform search strategy

sedation and child* and dental

WHAT'S NEW

Date	Event	Description
22 February 2018	New citation required and conclusions have changed	Changes to author byline. Review update including 14 new studies bringing the total to 50 included studies. Methods updated. 'Summary of findings' tables included. Slight change to review's conclusions.
22 February 2018	New search has been performed	Searches updated to February 2018.

HISTORY

Protocol first published: Issue 4, 2002
Review first published: Issue 2, 2005

Date	Event	Description
13 January 2012	New citation required and conclusions have changed	Major revision to tables and text including addition of meta-analysis of oral midazolam and use of forest plots as another way of displaying data. Susan Furness now added as author. All cross-over studies removed from the review and 11 new studies added.
13 January 2012	New search has been performed	Searches updated to August 2011.
28 July 2008	Amended	Converted to new review format.
15 November 2005	New citation required but conclusions have not changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

- Paul F Ashley contributed to all aspects of this review, in particular data extraction, analysis and interpretation of data and entering data into Review Manager.
- Mohsin Chaudhary contributed to all aspects of this review, in particular data extraction, interpretation of data and entering data into Review Manager.
- Liege Lourenço-Matharu contributed to all aspects of this review, in particular data collection and interpretation of data.

DECLARATIONS OF INTEREST

Paul F Ashley: no interests to declare.
Mohsin Chaudhary: no interests to declare.
Liege Lourenço-Matharu: no interests to declare.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

SOURCES OF SUPPORT

Internal sources

- Eastman Dental Institute, UK.

External sources

- National Institute for Health Research (NIHR), UK.

  This project was supported by the NIHR, via Cochrane Infrastructure funding to Cochrane Oral Health. The views and opinions expressed herein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, the NIHR, the NHS or the Department of Health.
- Cochrane Oral Health Global Alliance, Other.

  The production of Cochrane Oral Health reviews has been supported financially by our Global Alliance since 2011 (oralhealth.cochrane.org/partnerships-alliances). Contributors over the past year have been the American Association of Public Health Dentistry, USA; AS-Akademie, Germany; the British Association for the Study of Community Dentistry, UK; the British Society of Paediatric Dentistry, UK; the Canadian Dental Hygienists Association, Canada; the Centre for Dental Education and Research at All India Institute of Medical Sciences, India; the National Center for Dental Hygiene Research & Practice, USA; New York University College of Dentistry, USA; NHS Education for Scotland, UK; and the Swiss Society for Endodontology, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Cross-over trials are now excluded from this review, as they are not an appropriate study design when the intervention can have a long lasting effect (Higgins 2011). The relationship between pain and anxiety is well established, it is clear that the child's experience of any procedure will have an impact on any subsequent one (Shashikiran 2006).

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics, Non-Narcotic [administration & dosage]; Anti-Anxiety Agents [administration & dosage] [*therapeutic use]; Chloral Hydrate [administration & dosage]; Dental Anxiety [*drug therapy]; Dental Care for Children [methods] [*psychology]; Hydroxyzine [administration & dosage]; Hypnotics and Sedatives [administration & dosage] [*therapeutic use]; Meperidine [administration & dosage]; Midazolam [administration & dosage]; Nitrous Oxide [administration & dosage]; Preanesthetic Medication [methods]; Randomized Controlled Trials as Topic

MeSH check words

Child; Humans

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.