





BMJ Open Effectiveness and safety of oral sedation in adult patients undergoing dental procedures: a systematic review

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ABSTRACT

Objectives It can be challenging to manage patients who are anxious during dental procedures. There is a lack of evidence regarding the effectiveness and safety of oral sedation in adults. This study evaluated the effectiveness and safety of oral sedation in patients undergoing dental procedures.

Design Systematic review.

Methods Randomised clinical trials (RCTs) compared the oral use of benzodiazepines and other medications with a placebo or other oral agents in adult patients. A search of the Cochrane (CENTRAL), MEDLINE (via Ovid), EMBASE (via Ovid) and Cumulative Index to Nursing and Allied Health Literature (via Ovid) databases was conducted, without any restrictions on language or date of publication. The primary outcomes included the adverse effects and anxiety level. The secondary outcomes included sedation, satisfaction with the treatment, heart rate, respiratory rate, blood pressure and oxygen saturation. Reviewers, independently and in pairs, assessed each citation for eligibility, performed the data extraction and assessed the risk of bias. A narrative synthesis of the data was provided.

Results A number of RCTs (n=327 patients) assessed the use of benzodiazepines (n=9) and herbal medicines (n=3). We found good satisfaction with treatment after the use of midazolam 7.5 mg or clonidine 150 µg and reduced anxiety with alprazolam (0.5 and 0.75 mg). Midazolam 15 mg promoted greater anxiety reduction than *Passiflora incarnata* L. 260 mg, while *Valeriana officinalis* 100 mg and *Erythrina mulungu* 500 mg were more effective than a placebo. More patients reported adverse effects with midazolam 15 mg. Diazepam 15 mg and *V. officinalis* 100 mg promoted less change in the heart rate and blood pressure than a placebo.

Conclusions Given the limitations of the findings due to the quality of the included studies and the different comparisons made between interventions, further RCTs are required to confirm the effectiveness and safety of oral sedation in dentistry.

PROSPERO registration number CRD42017057142.

INTRODUCTION

Anxiety during dental treatment can cause stress and discomfort in patients and lead to dental treatment avoidance with consequent damage to the oral health of phobic

Strengths and limitations of this study

- We performed a comprehensive systematic review to identify randomised clinical trials that evaluated the effectiveness and safety of oral sedation in patients undergoing dental surgical procedures.
- Anxiety can lead to dental treatment avoidance with consequent exacerbation of poor oral health in phobic patients; therefore, it is important to understand which drugs are effective for anxiety control, as this can contribute to patient compliance to dental treatment.
- Adverse effects from oral sedatives are negative outcomes in dentistry that should be avoided; therefore, it is important that we estimate the risk of such effects so that decision-making regarding conscious sedation can be better informed.
- This study was carried out with methodological rigour, including explicit eligibility criteria, a broad extensive database search, study selection by reviewers working in pairs and independently and evaluation of the risk of bias.
- The quality of the included studies and different comparisons made between interventions were limiting factors for the study findings.

patients.^{1 2} In this context, effective control of anxiety plays a pivotal role in patient compliance to dental treatment. The use of conscious sedation is an important strategy for the behavioural management of patients who suffer from anxiety over dental treatment.³ Conscious sedation is an approach that uses one or more drugs to produce a state of central nervous system depression while maintaining verbal contact with the patient throughout the procedure.⁴ The sedation level should be such that the patient remains conscious and can readily understand and respond to verbal instructions or tactile stimulation.⁵

Indications for the use of conscious sedation include a diagnosis of anxiety and dental phobia, prolonged or traumatic dental

procedures and medical conditions potentially aggravated by stress, which can reduce the patient's ability to cooperate.⁶

Additionally, the release of endogenous catecholamines can increase the cardiovascular system load in patients with a history of angina, whereas asthmatic patients can present stress-induced acute episodes of breathing difficulty induced by stress. These are among some of the patients' profiles that can benefit from conscious sedation in reducing exacerbation risk. The risk–benefit should be determined according to the severity of the patient's condition.⁷

Oral sedation is one of the relatively accessible means for dental professionals to control patient anxiety. However, oral sedation can have inherent limitations due to the pharmacokinetics of the orally administered drug, such as delayed and variable onsets of action.⁸ Moreover, drug interventions to provide conscious sedation should have a sufficient safety margin to preclude consciousness loss.⁹

Benzodiazepines are widely used in oral sedation to induce a state of anxiety in dental procedures.¹⁰ These drugs are among the most commonly prescribed and employed for this purpose worldwide.^{5 8 11 12}

Although benzodiazepines have a similar mechanism of action, their pharmacokinetics differ, which are key factors in selecting the best option to suit the patient.¹³ The different oral sedation options in dentistry include midazolam, diazepam and lorazepam as mainstream drugs, although alprazolam, temazepam and oxazepam have also been used.⁸

Few studies have synthesised the available evidence on the effectiveness and safety of oral sedation in adults undergoing dental procedures. A systematic review evaluated the safety of using drugs for sedation administered by oral, intranasal, sublingual, intramuscular and intravenous routes in adults undergoing dental procedures. However, the data extraction was not performed in pairs and independently, and the risk of bias or quality of the evidence was not assessed.¹⁰ Another systematic review investigated the use of midazolam in dental surgical procedures. Of the ten studies included in the review, only three addressed oral use, while the other studies combined drugs administered orally and via other routes.¹⁴

The hypothesis of this study was that conscious oral sedation is effective and safe for use in dental procedures. The gap in knowledge on the use of drugs for oral sedation in dentistry prompted this systematic review to determine the effectiveness and safety of oral sedation drugs in adult patients undergoing dental surgical procedures.

METHODS

Protocol registration

The protocol of this systematic review was registered on the PROSPERO—*International Prospective Register of Systematic Reviews* and also published.¹⁵

The population, intervention, comparator and outcomes strategy used was as follows: *population*, adults

requiring dental surgical procedures; *intervention*, oral sedation; *comparator*, placebo group or other oral drug administered; and *outcomes*, effectiveness: anxiety, sedation and satisfaction with the treatment and safety: adverse effect, heart rate, respiratory rate, blood pressure and oxygen saturation.

Patient and public involvement

No patients were involved.

Eligibility criteria of the studies

Inclusion criteria

Participants

Adults requiring dental surgical procedures, such as dental extraction, surgery for orthodontic purposes, removal of residual roots and third molars, dental implants and other dental surgical interventions.

Intervention

At least one group used oral sedation with benzodiazepines or other drugs (eg, herbal medicines).

Comparator

Placebo group or other drug administered orally.

Study

Randomised clinical trials (RCTs).

Exclusion criteria

Studies involving adults with respiratory diseases, with contraindications to benzodiazepine; pregnant and/or breastfeeding women; and those with a history of allergies were not included. Studies that combined the administration of different drugs for oral sedation were also excluded.

Outcomes assessed

Primary outcomes

1. Effectiveness was measured by improvement in anxiety by using the Dental Anxiety Scale (DAS), Oral Surgery Confidence Questionnaire (OSCQ) and/or other scales for anxiety symptoms.
2. Safety was measured by the number of participants that reported side effects, number of adverse effects (or adverse drug reactions) and number of participants that dropped out due to side effects.

Secondary outcomes

1. Secondary outcomes of effectiveness were sedation and satisfaction with the treatment.
2. Secondary outcomes of safety were heart rate, respiratory rate, blood pressure and oxygen saturation.

Search method for identifying studies

Electronic database search

The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL), which includes Dentistry and Oral Health Group's Specialized Register; MEDLINE (via Ovid); Excerpta Medica Database (EMBASE) (via Ovid); Cumulative Index to Nursing and

Allied Health Literature (via Ovid), Lilacs (Scielo) and the Capes database (<https://catalogodeteses.capes.gov.br/catalogo-teses/#!/>), without restrictions on language or publication date, with the search encompassing articles published between inception and 12 March 2020.

Other reference search sources

The reviewers (CCB and JOA) manually analysed the reference list or citations of the articles to retrieve and identify other possible eligible studies. The main authors and/or pharmaceutical companies involved in producing the drugs were contacted for information on additional trials, if necessary.

Search strategy

The search was conducted using Medical Subject Headings terms for each oral surgical procedure (such as oral surgery, dental extraction and dental implant), benzodiazepines (and its synonyms) and terms to search for other drugs. The search strategy for MEDLINE (via Ovid) was adapted for each database (online supplemental appendix A).

Study records

Data management

After performing the search strategies on each electronic database, the researchers imported the results from each search into an EndNote library. Duplicate entries were identified and removed.

Study eligibility determination

Relevant data from the eligible studies were independently extracted into Microsoft Excel, using a standardised data extraction form. Four reviewers (JOA and CCB, CCG and NKA), working in pairs and independently, selected potentially relevant titles and abstracts and applied the eligibility criteria. Full texts of the potentially eligible articles were obtained. Similarly, the reviewers checked the eligibility of each study. Disagreements were resolved by consensus and, when necessary, arbitrated by a third reviewer (RHLM or LCL).

Data extraction

The same reviewers (JOA and CCB, CCG and NKA), working in pairs and independently, used a standardised and pretested form for data extraction. Subsequently, the reviewers extracted the patient data, methods, interventions and outcomes. We contacted the authors for articles with incomplete methods and results data, if necessary. Disagreements were resolved by consensus and, when necessary, arbitrated by a third reviewer (RHLM or LCL).

Risk of bias

A modified version of the Cochrane collaboration approach for assessing the risk of bias was used.^{16 17} The same reviewers, again in pairs and independently, evaluated the risk of bias for each clinical trial according to randomisation; allocation concealment; blinding of patients, health professionals and outcome assessors;

incomplete outcome data; selective outcome reporting; and major baseline imbalance characterising the sample.

The same reviewers attributed the standard answers 'definitely yes', 'probably yes', 'probably no' and 'definitely no' for each domain, with 'definitely yes' and 'probably yes' denoting a low risk of bias and 'definitely no' and 'probably no' attributing a high risk of bias.¹⁸ Disagreements were resolved by consensus and, when necessary, arbitrated by a third reviewer (RHLM or LCL).

Data synthesis and analysis of the quality of evidence

A narrative synthesis of the findings was carried out. The extracted data were summarised in the tables with the measures (mean, SD and absolute and relative frequency).

Heterogeneity was explained by drug doses (higher vs lower) with greater effect than expected at higher doses and treatment time (longer vs shorter).¹⁵ Due to the divergences between the drugs prescribed and the doses used and measured outcomes, a meta-analysis was not performed, and the Grading of Recommendations, Assessment, Development and Evaluation could not be produced.^{19 20}

RESULTS

Search strategy results

A total of 3,669 publications were retrieved, of which 49 were included for full-text selection. After application of the eligibility criteria, 10 RCTs were included in the review (figure 1). The studies' characteristics are given in online supplemental appendix B, and the excluded studies are listed in online supplemental appendix C.

Description of the studies included

The 10 RCTs involved 327 patients (58% women) undergoing oral surgery. Most of the RCTs evaluated the use of benzodiazepines (n=9), and three studies assessed the use of herbal medicines for oral sedation. The majority of the studies were conducted by Brazilian researchers between

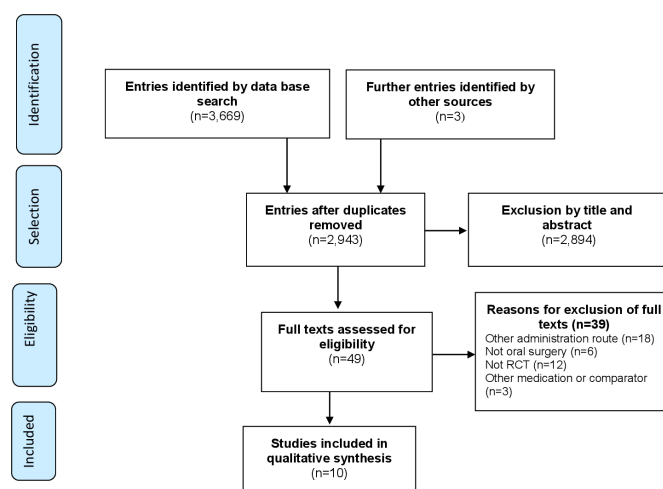


Figure 1 Flow chart of study selection process. RCT, randomised clinical trials.

Table 1 Characteristics of the studies included (n=10 studies)

Variables	Studies (n)	Population (n)
Study population	10	327
Women (n=282)	8	164 (58.2%)
Benzodiazepines		
Alprazolam (0.25, 0.5 and 0.75 mg)	1	36
Diazepam (5, 10 and 15 mg)	3	49
Midazolam (7.5 and 15 mg)	4	97
Lorazepam (1 mg)	1	10
Herbal medicines		
<i>Erythrina mulungu</i> 500 mg	1	30
<i>Passiflora incarnata</i> L. 260 mg	1	40
<i>Valeriana officinalis</i> 100 mg	1	10
Clinical condition		
Dental extraction	6	180
Dental implants	2	45
Other dental surgery	2	102
Country		
Brazil	5	135
USA	1	48
Italy	1	82
Switzerland	1	12
China	1	30
India	1	20
Year of publication		
1979–1988	2	112
1989–1998	1	48
1999–2008	0	0
2009–2017	7	167
Funded by industry		
Yes	1	30
Not specified	4	157
Not funded	5	140

2011 and 2017. Only one study was funded by the pharmaceutical industry (table 1).

Risk of bias

Random sequence generation

Some studies failed to report sufficient data on the randomisation process, precluding any assessment, and exhibited selection bias.^{21–27} Some stated that patients were randomly allocated to groups but did not detail the process used (figure 2).

Allocation concealment

Some studies guaranteed that the random sequence generation of participants was unpredictable since the envelopes handed to participants were sealed and coded.^{22 24 28} By contrast, other clinical trials did not guarantee allocation concealment.^{21 23 25 27 29} Two clinical

trials provided insufficient information on the random sequence generation process employed.^{26 30}

Blinding of the participants and personnel

Rodrigo and Cheung²² and Coldwell *et al*²³ clearly described that the blinding of participants and personnel was ensured and unlikely to have been lost and had no performance bias. The remaining studies stated that they were double-blinded but provided no further details.^{21 24–30} Consequently, these studies were deemed ‘probably yes’ and considered as having a low risk of bias.

Blinding of the outcome assessors

Blinding of the outcome assessors was performed in three studies, making it unlikely that blinding was lost.^{22 27 28} Romano *et al*²⁴ and Pinheiro *et al*³⁰ stated that the professionals were blinded, but it was unclear whether they were

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Branco; Bassualdo 2012	+	+	+	+	+	+	+
Coldwell et al 1997	+	+	+	+	+	+	+
Dantas et al 2017	+	+	+	+	+	+	+
Manani et al 1979	+	+	+	+	+	+	+
Pinheiro et al 2014	+	+	+	+	+	+	+
Rodrigo; Cheung 1987	+	+	+	+	+	+	+
Romano et al 2011	+	+	+	+	+	+	+
Shivananda et al 2014	+	+	+	+	+	+	+
Silveira-Souto et al 2014	+	+	+	+	+	+	+
Studer et al 2012	+	+	+	+	+	+	+

Figure 2 Consensus of the authors about bias risk for each study included.

blinded to the outcome collection. The other studies did not report this information, indicating detection bias.^{21 23 25 26 29}

Incomplete outcomes

For the study by Coldwell *et al*,²³ it was impossible to judge whether incomplete outcome reporting occurred. The remaining studies reported whether any participants were lost to follow-up or excluded for another reason.

Selective outcome reporting

One RCT recorded their protocol allowing confirmation that there was no selective outcome reporting.³⁰ Although the study protocol was not reported for the other studies, it appears that they reported all the desired outcomes.

Other sources of bias

Only one study cited the source of funding.²² Other studies declared there was no funding.^{21 22 25–28 30} The

remaining studies did not report sufficient information to assess the presence of other sources of bias.^{23 24 29}

Outcomes assessed

The primary and secondary outcomes reported by the studies are described in tables 2–4.

Due to differences between drugs used across groups, a meta-analysis of the data could not be performed, and the results were expressed in the form of a narrative synthesis. None of the studies reported sedation outcomes and respiratory rates.

Of the primary outcomes, five studies reported the anxiety levels,^{23 25 27 28 30} and six studies collected information on the adverse effects.^{21–23 27 29 30}

Table 3 describes the studies that report the percentage of participants who experienced adverse effects. In general, most participants exhibited some adverse effects. Dantas *et al*²⁷ reported the number of adverse effects but did not report the number of patients with adverse effects. Coldwell *et al*²³ did not specify the adverse effect by group. Therefore, we did not include their results in the table.

The number of reports of adverse effects is shown in table 4. In general, a higher number of adverse effects was associated with the use of midazolam compared with *P. incarnata* and a placebo, where the most reported adverse effects were drowsiness, muscular relaxation and dizziness.^{22 27}

The secondary outcomes reported were patient satisfaction with treatment (n=1 study),²⁹ heart rate (n=5 studies),^{21 24 27 28 30} blood pressure (n=5)^{21 27–30} and oxygen saturation (n=3).^{26 28}

Reporting of the outcomes by drug

Alprazolam (0.25, 0.5 and 0.75 mg)

In a placebo-controlled RCT, 48 participants undergoing dental extraction were allocated into four groups (n=12 per group): group I, alprazolam 0.25 mg; group II, alprazolam 0.50 mg; group III, alprazolam 0.75 mg; and group IV, placebo. Anxiety was assessed using the DAS, OSCQ and the Interval Scale of Anxiety Response. The proportion of individuals that reported feeling fairly to very anxious during oral surgery decreased with increased doses of alprazolam. The most commonly observed adverse effect associated with the use of alprazolam at doses of 0.25, 0.50 and 0.75 mg was anterograde amnesia.²³

Diazepam (5, 10 and 15 mg) and lorazepam (1 mg)

In a double-blind and placebo-controlled RCT, 30 participants undergoing dental implant placement surgery were allocated into three groups (n=10 per group). One hour before the procedure, they received the following interventions: group I, diazepam 10 mg; group II, lorazepam 1 mg; and group III, placebo. Anxiety was measured based on Corah's DAS. No significant difference was found between the groups concerning this outcome.²⁵

An RCT allocated 82 patients undergoing outpatient dental surgery to group I, placebo; group II, trazodone 25

Table 2 Primary and secondary outcomes reported by the studies (n=9)

Author (year) (n=participants)	Intervention group (n=participants)	Comparator group (n=participants)	*Primary outcomes (scales)	Primary outcome results	Secondary outcomes	Secondary outcome results
Coldwell <i>et al</i> 1997 ²³ (n=48)	Alprazolam 0.25 mg (n=12) Alprazolam 0.5 mg (n=12) Alprazolam 0.75 mg (n=12)	Placebo (n=12)	Anxiety (DAS, OSCQ and ISAR)	Decrease in number of anxious patients with increasing doses of alprazolam	Not reported	
Branco, Bassualdo 2012 ²⁵ (n=30)	Diazepam 10 mg (n=10) Lorazepam 1 mg (n=10)	Placebo (n=10)	Anxiety (Corah's DAS)	Decreased anxiety compared with baseline levels but no statistical difference between groups	Not reported	
Studer <i>et al</i> 2012 ²⁹ Crossover (washout of 30 days) (n=12)	Midazolam 7.5 mg (n=12)	Clonidine 150 µg (n=12)	Not reported		Satisfaction with the treatment Blood pressure (BP)	77% of patients (midazolam group) versus 75% (clonidine group) No statistical difference between the groups for BP
Silveira-Souto <i>et al</i> 2014 ²⁸ Crossover (washout of 15 days) (n=30)	<i>Erythrina mulungu</i> 500 mg (n=30)	Placebo (n=30)	Anxiety (Corah's DAS)	Decreased anxiety compared with baseline levels but no statistical difference between groups	Heart rate Blood pressure Oxygen saturation	No statistical difference between the groups for outcomes
Dantas <i>et al</i> 2017 ²⁷ Crossover (washout of 15–30 days) (n=40)	<i>Passiflora incarnata</i> L. 260 mg (n=40)	Midazolam 15 mg (n=40)	Anxiety (Corah's DAS)	Decreased anxiety compared with baseline levels but no statistical difference between groups	Heart rate Blood pressure Oxygen saturation	No statistical difference between the groups for outcomes
Pinheiro <i>et al</i> 2014 ³⁰ (n=20)	<i>Valeriana officinalis</i> 100 mg (n=10)	Placebo (n=10)	Anxiety (DAS)	Herbal medicine was more effective than placebo	Heart rate Blood pressure	No statistical difference between the groups for outcomes
Romano <i>et al</i> 2011 ²⁴ (n=40)	Midazolam 15 mg (n=20)	Placebo (n=20)	Not reported		Heart rate	No statistical difference between the groups

Continued

Table 2 Continued

Author (year) (n=participants)	Intervention group (n=participants)	Comparator group (n=participants)	*Primary outcomes (scales)	Primary outcome results	Secondary outcomes	Secondary outcome results
Manani <i>et al</i> 1979 ²¹ (n=82)	Diazepam 15 mg (n=19) Trazodone 25 mg (n=20) Trazodone 50 mg (n=21)	Placebo (n=22)	Not reported		Heart rate Blood pressure	No statistical difference between the groups
Shivananda <i>et al</i> 2014 ²⁶ Crossover (n=20) (washout: not reported)	Diazepam 5 mg (n=20) Diazepam 10 mg (n=20)	Placebo (n=20)	Not reported		Oxygen saturation	No statistical difference between the groups

Dental Anxiety Scale (DAS): categorises participants into not anxious, slightly anxious, fairly anxious and very anxious.

Oral Surgery Confidence Questionnaire (OSCCQ): contains 11 items rated from 0, not at all confident, to 9, extremely confident.

Interval Scale of Anxiety Response (ISAR): contains a 90 mm vertical line labelled with descriptors alongside intervals determined according to estimated magnitude: 'calm, relaxed', 'a little nervous', 'tense, upset', 'afraid', 'very afraid', 'panicked' and 'terrified'.

Corah's Dental Anxiety Scale: contains four questions with five possible answers that assess the patient's feelings, signs and reactions related to the dental procedure, as very little anxious (up to five points), slightly anxious (6–10 points), moderately anxious (11–15 points) points and extremely anxious (16–20 points).

*The primary outcome 'adverse effect' is reported in tables 3 and 4.

mg; group III, trazodone 50 mg; and group IV, diazepam 15 mg. A comparison of the reported adverse effects for trazodone with diazepam revealed that diazepam was associated with more effects. The main effects reported were drowsiness, vertigo and cognitive impairment. In addition, the number of individuals in use of diazepam reporting adverse effects was also higher. No difference in

the heart rate and blood pressure was observed between the groups.²¹

An RCT with a crossover design (washout not reported) allocated 20 participants undergoing periodontal surgery to group I, diazepam 5 or 10 mg (according to body weight), or group II, placebo, 1 hour before surgery. No significant differences in oxygen saturation were observed between the groups.²⁶

Midazolam (7.5 and 15 mg)

An RCT with a crossover design (washout of 30 days) allocated 12 patients undergoing bilateral surgical third molar extraction to receive the following interventions 1 hour before the procedure: group I, midazolam 7.5 mg, and group II, clonidine 150 µg. The level of satisfaction with the treatment was determined using the Visual Analogue Scale with ratings ranging from 'no satisfaction' (0%) to 'complete satisfaction' (100%). Around 77% of the patients who received midazolam were satisfied compared with 75% of those given clonidine. There was no difference in the number of participants or adverse effects. No significant difference was observed in heart rate between the groups studied.²⁹

Another RCT allocated 15 participants undergoing implant placement to receive either group I, midazolam 15 mg, or group 2, placebo 1 hour before the procedure. The use of midazolam proved ineffective as a premedication anxiolytic for preventing myocardial arrhythmias.²⁴

An RCT with a crossover design allocated 30 patients undergoing bilateral surgical third molar extraction to group I, midazolam 15 mg (single dose), or group II, placebo 45 min before the dental procedure. They reported a higher number of adverse effects with

Table 3 Description of studies that reported the number of participants that experienced adverse effects and dropped out due to adverse effects (n=4)

Authors (year)	Groups	No of participants with adverse effects/total (%)	No of participants that dropped out
Studer <i>et al</i> 2012 ²⁹	Midazolam 7.5 mg	6/12 (50.0)	0
	Clonidine 150 µg	5/12 (41.6)	
Rodrigo and Cheung ²² 1987	Midazolam 15 mg	17/30 (56.6)	0
	Placebo	9/30 (30.0)	
Manani <i>et al</i> 1979 ²¹	Trazodone 25 mg	12/20 (60.0)	0
	Trazodone 50 mg	11/21 (52.3)	
Pinheiro <i>et al</i> 2014 ³⁰	Valeriana officinalis 100 mg	9/10 (90.0)	0
	Placebo	7/10 (70.0)	

Table 4 Description of the adverse effects reported by the included studies (n=5)

Author/year	Intervention group (number of AE)	Description of the effects (number of AE)	Comparator group (number of AE)	Description of the effects (number of AE)
Dantas <i>et al</i> ²⁷	Midazolam 15 mg (54)	Drowsiness (33), muscular relaxation (11), dizziness (7), gastrointestinal problems (1), amnesia (1), insomnia (1)	<i>Passiflora incarnate</i> L. (32)	Drowsiness (20), muscular relaxation (8), dizziness (2), allergy (1), epistaxis (1)
Manani <i>et al</i> ²¹	Diazepam 15 mg (36)	Drowsiness (10), vertigo (3), cognitive impairment (6)	Trazodone 50 mg (28)	Drowsiness (10), vertigo (5), blurred vision (2), cognitive impairment (11)
			Trazodone 25 mg (18)	Drowsiness (15), vertigo (9), blurred vision (6), cognitive impairment (6)
			Placebo (18)	Drowsiness (12), vertigo (1), blurred vision (2), cognitive impairment (3)
Pinheiro <i>et al</i> ³⁰	<i>Valeriana officinalis</i> (16)	Drowsiness (9), muscular relaxation (7)	Placebo (11)	Drowsiness (7), muscular relaxation (4)
Rodrigo, Cheung ²²	Midazolam 15 mg (46)	Drowsiness (17), dizziness (8), memory loss (3), excitability (5), depression (5), nausea (5), vomiting (2), headache (3)	Placebo (29)	Drowsiness (9), dizziness (4), memory loss and excitability (1), depression (1), blurred vision (1), insomnia (5), hallucinations (1), nausea (4), vomiting (1), headache (2)
Studer <i>et al</i> ²⁹	Midazolam 7.5 mg (6)	Dizziness (3); nausea, headache and fatigue (1); cognitive deficit (2)	Clonidine 0.15 mg (6)	Nausea (2), drowsiness (3), fainting (1)

AE, adverse effects.

midazolam compared with placebo, in particular drowsiness, dizziness and excitability.²²

Erythrina mulungu 500 mg

The effectiveness of *E. mulungu* 500 mg (single dose) was assessed in a crossover design RCT (washout period of 15 days) involving 30 patients undergoing bilateral extraction of impacted third molars compared with placebo. Both drugs were administered 1 hour before the dental procedure. Anxiety was determined based on Corah's DAS Scores. Volunteers with higher anxiety levels tended to prefer herbal medicine. The heart rate, systolic and diastolic blood pressure and oxygen saturation were not significantly different between the groups studied.²⁸

Passiflora incarnata L. 260 mg and midazolam 15 mg

An RCT with a crossover design allocated 40 participants undergoing mandibular third molar extraction into two groups (washout period of 15–30 days). Each group received interventions 30 min before the procedure: group I, 260 mg of *P. incarnata* and midazolam 15 mg. Corah's DAS was used before and after the surgical procedure. Both drugs proved to be effective for controlling anxiety, although midazolam 15 mg was more effective than herbal medicine. The most frequent adverse effects, particularly drowsiness and muscular relaxation, occurred with midazolam. The heart rate, systolic and diastolic blood pressure and oxygen saturation were not significantly different between the groups.²⁷

Valeriana officinalis 100 mg

A crossover RCT (washout period of 15 days) allocated 20 participants undergoing bilateral third molar extraction into two groups that received the intervention 1 hour before the procedure: group I, *V. officinalis* 100 mg, and group II, placebo. Anxiety was measured using the DAS. Herbal medicine was more effective in controlling anxiety than a placebo. No differences were reported in the number of adverse effects, with the most common being drowsiness and muscular relaxation. Herbal medicine promoted less change in the heart rate and blood pressure compared with a placebo.³⁰

DISCUSSION

Main findings and literature comparison

This review has evaluated the available evidence on the effectiveness and safety of oral sedation in adults undergoing dental procedures using 10 RCTs. The majority of the RCTs evaluated benzodiazepine class drugs for oral sedation, where the most commonly used was midazolam. Most of the studies were conducted in Brazil, none of which met all the evaluation criteria for risk of bias. The main methodological flaws were related to randomisation and allocation concealment.

The heterogeneity of the interventions and doses precluded a meta-analysis for all the outcomes assessed

being performed. The primary outcomes reported by the studies were anxiety and the adverse effects.^{21–23 25 27–30}

In general, alprazolam (0.5 and 0.75 mg),²³ midazolam 15 mg, *P. incarnata* 260 mg,²⁷ *V. officinalis*,³⁰ and *E. mulungu*²⁸ were considered effective for controlling anxiety.

The results revealed a higher number of adverse effects associated with midazolam use,^{22 27} followed by diazepam.²¹ In addition, a greater number of patients reported adverse effects from these benzodiazepines. However, these findings should be interpreted with caution, given that the high number of reports might be related to the larger number of participants in these studies. Moreover, these findings are based on reports of only one study, where a lack of comparability between studies hampers any meaningful conclusion.

There was no difference in the number of patients that exhibited adverse effects after using midazolam 7.5 mg and clonidine 150 µg,²⁹ but more adverse effects were reported in the group that received midazolam 15 mg than in the placebo group. These results suggest that an increase in midazolam dose may be associated with a higher number of adverse effects.

No difference was found between midazolam 7.5 mg and clonidine 150 µg regarding satisfaction with the treatment.²⁹ The physiological parameters showed no statistical difference by any intervention. No significant differences in the heart rate or blood pressure were evident when comparing *E. mulungu* to placebo,²⁸ *P. incarnata* to midazolam,²⁷ midazolam to clonidine²⁹ and diazepam to placebo or trazodone.²¹ However, the use of *V. officinalis* was associated with less change in these parameters relative to a placebo.³⁰ There was no difference in oxygen saturation for the use of *E. mulungu* versus placebo,²⁸ *P. incarnata* versus midazolam²⁷ or diazepam versus placebo.²⁶

Although there are public policies aimed at herbal medicines in Brazil, such as the National Program for Medicinal Plants and Herbal Medicines (Decree Number 5813 of 2006), the use of herbal medicines is not common in dentistry. Three RCTs with herbal medicines were from Brazil; this is probably because oral sedation is a common practice in dental procedures compared with other countries that use intravenous and other routes for sedation.

Previous systematic reviews could not be compared with the present study's findings because the RCTs included in these reviews were not restricted to the oral route.^{10 14} Also, these reviews failed to report most of the outcomes assessed in the present study.

A previous systematic review assessed the safety of using sedation drugs by any administration route in patients undergoing dental procedures. Ten of the studies included were RCTs, but none of these were included in our study because they used a combination of drugs or other routes of administration. Midazolam was the most commonly used drug, irrespective of the administration route. Although the authors stated that the drug appeared to be safe for sedation, the risk of bias of the

studies was not considered, and further clinical trials were suggested to confirm the findings.¹⁰

Another systematic review investigated the anxiolytic effect of midazolam in dental surgery, regardless of the administration route.¹⁴ Of the ten studies reviewed, three involved oral administration, of which only one RCT was included in the present study since the other clinical trials used a combination of different drugs or alternative routes of administration.²⁹

In the literature, no secondary studies that compared outcomes to the treatment and physiological parameters were found.

Study strengths and limitations

This review was carried out with methodological rigour and evaluated the risk of bias, which has not been performed previously in similar reviews.^{10 14} The strengths of the present review include its explicit eligibility criteria, broad extensive database search and study selection by reviewers working both independently and in pairs.

The primary studies included are a limiting factor to the findings due to their methodological quality, the non-reporting of clinical outcomes and different comparator groups. This meant that a meta-analysis could not be conducted. Another notable factor was the heterogeneous method of reporting anxiety outcomes among studies.

It is also noteworthy that the vast majority of the RCTs (90%) failed to consider the patient's anxiety level as a study inclusion criterion. Only one study reported that patients with higher anxiety levels tended to prefer herbal medicine.²⁸ This information is important in that according to the literature, oral sedation can help most patients with mild to moderate levels of fear and anxiety but may be ineffective in patients with high levels of anxiety.^{11 31}

Implications for clinical practice and research

Our findings suggest that benzodiazepines and herbal-based medicines could be safely used for oral sedation in outpatient dental surgical procedures. Dental surgeons should devise surgical plans based on the patient's condition. This requires a detailed analysis in which the patient's level of anxiety and fear concerning the procedure is determined so that the most suitable medication can be administered.

None of the RCTs evaluated all of the outcomes proposed to determine the effectiveness and safety of oral sedation in dental surgical procedures. Also, a comparison between the studies was not possible due to the different drugs investigated. Therefore, further clinical trials adopting more methodological rigorous data collection and methodological guidelines should be conducted.

It is important to point out that although the findings of this review are somewhat limited, benzodiazepines and herbal-based medicines both appear to be safe under the conditions reported in the RCTs included (single dose administered orally).

The present review synthesises the available evidence on the effectiveness and safety of oral sedation in adults undergoing dental surgical procedures. This can help guide the decision-making process in dental practice so as to reduce patient anxiety in clinical procedures.

CONCLUSION

The results suggest that the use of alprazolam, midazolam, *P. incarnate*, *V. officinalis* and *E. mulungu* is effective and safe in controlling anxiety among adult patients undergoing dental interventions. Midazolam was the most studied drug and was associated with the highest rate of adverse effects. However, given the study's limitations concerning the number of studies reviewed, different comparisons between the studies and incomplete outcome reporting, further clinical trials should be conducted to confirm the effectiveness and safety of these drugs.

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APPENDIX A – Search strategy on MEDLINE (via Ovid) database

1.	surgery, maxillofacial.mp. or exp Surgery, Oral/
2.	operative dentistry.mp. or exp Dentistry, Operative/
3.	dentistry, operative.mp. or exp Dentistry, Operative/
4.	prosthesis, surgical dental.mp. or Dental Implants/
5.	prostheses, surgical dental.mp. or exp Dental Implants/
6.	surgical dental prosthesis.mp. or exp Dental Implants/
7.	surgical dental prostheses.mp. or exp Dental Implants/
8.	dental prosthesis, surgical.mp. or exp Dental Implants/
9.	dental prostheses, surgical.mp. or exp Dental Implants/
10.	implant, dental.mp. or exp Dental Implants/
11.	dental implant.mp. or exp Dental Implants/
12.	implants, dental.mp. or exp Dental Implants/
13.	dental implants.mp. or exp Dental Implants/
14.	procedures, maxillofacial.mp. or exp Oral Surgical Procedures/
15.	procedure, maxillofacial.mp. or exp Oral Surgical Procedures/
16.	maxillofacial procedure.mp. or exp Oral Surgical Procedures/
17.	maxillofacial procedures.mp. or exp Oral Surgical Procedures/
18.	exodontics.mp. or exp Surgery, Oral/
19.	procedure, oral surgical.mp. or exp Oral Surgical Procedures/
20.	oral surgical procedure.mp. or exp Oral Surgical Procedures/
21.	surgical procedures, oral.mp. or exp Oral Surgical Procedures/
22.	procedures, oral surgical.mp. or exp Oral Surgical Procedures/
23.	surgical procedures, oral.mp. or exp Oral Surgical Procedures/
24.	oral surgical procedures.mp. or exp Oral Surgical Procedures/
25.	oral surgery.mp. or exp Surgery, Oral/
26.	maxillofacial surgery.mp. or exp Surgery, Oral/
27.	surgery, oral.mp. or exp Surgery, Oral/
28.	1 or 2 or 3 or 4 or 5 or 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 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29.	benzodiazepinones.mp. or exp Benzodiazepinones/
30.	Benzodiazepinones.mp. or exp Benzodiazepinones/
31.	Alprazolam novopharm brand.mp. or exp Alprazolam/
32.	novopharm brand of alprazolam.mp. or exp Alprazolam/
33.	novo alprazol.mp. or exp Alprazolam/
34.	novoalprazol.mp. or exp Alprazolam/
35.	novo-alprazol.mp. or exp Alprazolam/
36.	Alprazolam pfizer brand.mp. or exp Alprazolam/
37.	pfizer brand of alprazolam.mp. or exp Alprazolam/
38.	maleate, midazolam.mp. or exp Midazolam/
39.	midazolam maleate.mp. or exp Midazolam/
40.	midazolam.mp. or exp Midazolam/
41.	effect, antianxiety.mp. or exp Anti-Anxiety Agents/
42.	antianxiety effect.mp. or exp Anti-Anxiety Agents/
43.	effects, anti-anxiety.mp. or exp Anti-Anxiety Agents/
44.	anti anxiety effects.mp. or exp Anti-Anxiety Agents/
45.	anti-anxiety effects.mp. or exp Anti-Anxiety Agents/
46.	effect, anxiolytic.mp. or exp Anti-Anxiety Agents/
47.	anxiolytic effect.mp. or exp Anti-Anxiety Agents/

48.	effects, antianxiety.mp. or exp Anti-Anxiety Agents/
49.	antianxiety effects.mp. or exp Anti-Anxiety Agents/
50.	effects, anxiolytic.mp. or exp Anti-Anxiety Agents/
51.	anxiolytic effects.mp. or exp Anti-Anxiety Agents/
52.	effect, anti-anxiety.mp. or exp Anti-Anxiety Agents/
53.	anti anxiety effect.mp. or exp Anti-Anxiety Agents/
54.	anti-anxiety effect.mp. or exp Anti-Anxiety Agents/
55.	anxiolytics.mp. or exp Anti-Anxiety Agents/
56.	drugs, anti-anxiety.mp. or exp Anti-Anxiety Agents/
57.	anti anxiety drugs.mp. or exp Anti-Anxiety Agents/
58.	anti-anxiety drugs.mp. or exp Anti-Anxiety Agents/
59.	minor tranquillizing agents.mp. or exp Anti-Anxiety Agents/
60.	agents, minor tranquillizing.mp. or exp Anti-Anxiety Agents/
61.	minor tranquilizing agents.mp. or exp Anti-Anxiety Agents/
62.	agents, minor tranquilizing.mp. or exp Anti-Anxiety Agents/
63.	tranquilizing agents, minor.mp. or exp Anti-Anxiety Agents/
64.	agents, anxiolytic.mp. or exp Anti-Anxiety Agents/
65.	anxiolytic agents.mp. or exp Anti-Anxiety Agents/
66.	anti anxiety agents.mp. or exp Anti-Anxiety Agents/
67.	agents, anti-anxiety.mp. or exp Anti-Anxiety Agents/
68.	anti-anxiety agents.mp. or exp Anti-Anxiety Agents/
69.	29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68
70.	69 and 28

APPENDIX B – CHARACTERISTICS OF STUDIES INCLUDED

Study characteristics	Branco & Bassualdo (2012)
Method	Randomized double-blind placebo-controlled clinical trial. Allocated 30 participants undergoing dental implant placement surgery into 3 different groups (n=10) to receive a drug 1 hour before procedure. Group I – diazepam 10 mg; Group II – lorazepam 1 mg; Group III – placebo.
Participants	30 participants, both genders, mean age 20-64 years, selected for dental implant placement surgery.
Intervention	Three groups of patients underwent surgery for dental implant placement after oral sedation.
Outcomes	Primary outcomes: anxiety. Secondary outcomes: vital signs (blood pressure, heart rate).
Observations	There were no significant differences in reduction of anxiety or in vital signs pre and post-operatively, only trans-operatively. Effective anxiety control was not demonstrated.

Branco & Bassualdo (2012)	Deemed risk of bias	Support for judgement
Random sequence generation	High risk	Randomized, although no detailed report on procedure was provided in study description.
Allocation concealment	High risk	No information or scant description on procedures for concealing allocation of patients into groups.

Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	High risk	The study failed to report this information. The outcomes assessed are subject to influence by lack of blinding.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	Low risk	The study protocol is not available, but the study published clearly included all desired outcomes.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

Study characteristics	Coldwell et al. (1997)
Method	Allocated 48 participants undergoing oral surgery for dental extraction into 4 different groups (n=12). Group 1 – alprazolam 0.25 mg; Group 2 – alprazolam 0.50 mg; Group 3 – alprazolam 0.75 mg; Group 4 – placebo.
Participants	48 participants of both genders were selected for surgical dental extraction of 1-4 molars.
Intervention	Four groups of patients submitted to surgical dental extraction after oral sedation.
Outcomes	Primary outcomes: anxiety, adverse effect (anterograde amnesia).
Observations	The study showed that alprazolam caused memory impairment at doses necessary for producing clinically significant anxiolytic effect during oral surgery.

Coldwell et al. (1997)	Deemed risk of bias	Support for judgement
Random sequence generation	High risk	Randomized, although no detailed report on procedure was provided in study description.
Allocation concealment	High risk	No information or scant description on procedures for concealing allocation of patients into groups.
Blinding of participants and personnel	Low risk	Study not blinded or incomplete blinding, and outcome unaffected by lack of blinding.
Blinding of outcome assessors	High risk	The study failed to report this information. The outcomes assessed are subject to influence by lack of blinding.
Incomplete outcomes	High risk	Insufficient information to judge. The study did not report this information.
Selective outcome reporting	Low risk	The study protocol is not available, but the study published clearly included all desired outcomes.
Other sources of bias	High risk	Insufficient information to judge. The study did not report this information.

Study characteristics	Dantas et al. (2017)
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Method	Randomized double-blind clinically-controlled crossover trial. Allocated 40 participants undergoing surgical extraction of third molars into 2 groups (n=40) receiving orally administered drug 30 mins before procedure. Group I – <i>Passiflora incarnata</i> 260 mg; Group II – midazolam 15 mg.
Participants	40 participants of both genders were selected for third molar extraction.
Intervention	Two groups of patients undergoing surgery for third molar extraction after oral sedation.
Outcomes	Primary outcomes: anxiety, adverse effects. Secondary outcomes: vital signs (blood pressure and heart rate) and oxygen saturation.
Observations	<i>Passiflora incarnata</i> promoted similar anxiolytic effect to midazolam, and participants who received the drug had relatively stable blood pressure, heart rate and oxygen saturation.

Dantas et al. (2017)	Deemed risk of bias	Support for judgement
Random sequence generation	High risk	Randomized, although no detailed report on procedure was provided in study description.
Allocation concealment	High risk	No information or scant description on procedures for concealing allocation of patients into groups.
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	Low risk	Blinding of outcome assessors was done, making it unlikely blinding was lost.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	Low risk	The study protocol is not available, but the study published clearly included all desired outcomes.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

Study characteristics	Manani et al. (1979)
Method	Randomized double-blind clinically-controlled trial. Allocated 82 patients of both genders, age range 20-50 years, undergoing dental procedures into 4 groups according to drug administered for inducing sedation. Group I – placebo; Group II – trazodone 25 mg; Group III – trazodone 50 mg; Group IV – diazepam 15 mg.
Participants	82 participants of both genders, age range 20-50 years, selected for surgery with oral sedation.
Intervention	Group I received placebo (Control Group). Group II received trazodone 25 mg. Group III received trazodone 50 mg. Group IV received diazepam 15 mg. All drugs were prepared and distributed in the form of blue capsules to prevent identification of Group by the participants and professionals.
Outcomes	Primary outcomes: anxiety, sedation, adverse effects (drowsiness, vertigo, headache, blurred vision, cold hands and dry mouth). Secondary outcomes: vital signs (blood pressure and heart rate).
Observations	One hour after administration of drug, there was a significant increase in sedation of patients. No adverse effects were observed in patients of control group or trazodone 25 mg group. Patients using diazepam 15 mg or trazodone 50 mg had greater reduction in

	neurovegetative response and higher rate of adverse effects, proving more marked in the group treated with diazepam.
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Manani et al. (1979)	Deemed risk of bias	Support for judgement
Random sequence generation	High risk	Insufficient information on random sequence generation process to allow judgement. No detailed report on procedure was provided in study description.
Allocation concealment	High risk	No information or scant description on procedures for concealing allocation of patients into groups.
Blinding of participants and personnel	Low risk	The study stated that all drugs were placed into identical capsules, thereby ensuring blinding of participants and personnel.
Blinding of outcome assessors	High risk	The study failed to report this information. The outcomes assessed are subject to influence by lack of blinding.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	Low risk	The study protocol is not available, but the study published clearly included all desired outcomes.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

Study characteristics	Rodrigo & Cheung (1987)
Method	Randomized double-blind clinical trial. Allocated 30 participants undergoing surgical extraction of mandibular third molars to receive orally administered drug midazolam 15 mg or placebo, the surgery was carried out by a single operator, randomly, one side per visit.
Participants	30 participants of both genders were selected for surgical removal of third molars.
Intervention	The patients underwent surgical removal of third molars after oral sedation.
Outcomes	Primary outcomes: adverse effects (amnesia, hiccupping, nausea, drowsiness and dizziness) and satisfaction with treatment.
Observations	Midazolam sedation lasted about 45 minutes, produced good operating conditions and stable vital signs with adequate verbal response.

Rodrigo & Cheung (1987)	Deemed risk of bias	Support for judgement
Random sequence generation	High risk	Randomized, although no detailed report on procedure was provided in study description.

Allocation concealment	Low risk	The pills were sealed and coded in envelopes and thus information on procedures confirmed concealment of allocation of patients into groups.
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was incomplete, but the authors claimed outcome was unaffected by the lack of blinding.
Blinding of outcome assessors	Low risk	Blinding of outcome assessors was done, making it unlikely blinding was lost.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	High risk	Study protocol not available and there was insufficient information to allow judgement.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

Study characteristics	Pinheiro et al. (2014)
Method	Randomized double-blind clinically-controlled study. Allocated 20 participants undergoing bilateral extraction of third molars into 2 groups (n=10) orally administered drug 1 hour before procedure. Group I – <i>Valeriana officinalis</i> 100 mg; Group II – placebo.
Participants	20 Participants aged 17-31 years of both genders were selected for bilateral extraction of impacted third lower molars.
Intervention	Two patient groups underwent surgery for extraction of third molars after oral sedation.
Outcomes	Primary outcomes: anxiety, adverse effects (drowsiness, fear and muscle relaxation). Secondary outcomes: vital signs (systolic and diastolic blood pressure, heart rate).
Observations	Pre-operative dose of <i>Valeriana officinalis</i> had greater anti-anxiety effect than placebo.

Pinheiro et al. (2014)	Deemed risk of bias	Support for judgement
Random sequence generation	Low risk	Medications with the same concentrations, size and appearance were placed in envelopes, thus there was sufficient information on the method used for random sequence generation.
Allocation concealment	High risk	Insufficient information on random sequence generation process to allow judgement. It was stated that envelopes were used, but it remained unclear whether these were sealed, opaque or numbered sequentially.
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	High risk	Insufficient information to judge. The study did not report this information.
Incomplete outcomes	Low risk	There was no loss of outcome data.

Selective outcome reporting	Low risk	The study protocol was available and all pre-specified primary and secondary outcomes of interest in the review were reported as proposed.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

Study characteristics	Romano et al. (2011)
Method	Randomized double-blind clinical trial. Allocated 15 participants undergoing dental implant were orally administered the drug midazolam 15 mg or placebo 1 hour before the procedure. The surgery was carried out by the same operator in 2 surgical visits with 30-day interval between sessions.
Participants	15 participants age 21-50 years of both genders were selected for dental implant placement.
Intervention	Two patient groups underwent surgery for dental implant placement after oral sedation.
Outcomes	Secondary outcomes: vital signs (heart rate).
Observations	No difference for use of 15 mg midazolam versus placebo, with no advantage for incidence of arrhythmias. Anxiolytic premedication failed to prevent arrhythmia.

Romano et al. (2011)	Deemed risk of bias	Support for judgement
Random sequence generation	High risk	There was insufficient information on procedures for concealing allocation of patients into groups.
Allocation concealment	Low risk	It was stated that envelopes were sealed, providing information on procedures concealing allocation of patients into groups.
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	High risk	Insufficient information to judge. The study did not report this information.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	Low risk	The study protocol is not available, but the study published clearly included all desired outcomes.
Other sources of bias	High risk	Insufficient information to assess whether there was relevant risk of bias.

Study characteristics	Silveira-Souto et al. (2014)
Method	Randomized double-blind crossover clinical study. Allocated 30 participants undergoing surgery for extraction of third

	molars to receive orally administered medication <i>E. mulungu</i> 500 mg or placebo, 1 hour before procedure, at first or second surgical intervention, left or right side, compared to placebo group.
Participants	30 participants of both genders were selected for extraction of third molars.
Intervention	Patients underwent surgery for extraction of third molars after oral sedation.
Outcomes	Primary outcomes: anxiety and satisfaction with treatment. Secondary outcomes: vital signs (blood pressure) and oxygen saturation.
Observations	<i>E. mulungu</i> can be considered a viable alternative, having produced no meaningful changes in physiological parameters (respiratory depression or motor abnormalities).

Silveira-Souto et al. (2014)	Deemed risk of bias	Support for judgement
Random sequence generation	Low risk	Randomization was performed using randomized computer-generated numbers, thus there was sufficient information about the method used for generating the random sequence.
Allocation concealment	Low risk	Information was given on procedures for concealing allocation of patients into groups, through coding in protocols
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	Low risk	Blinding of outcome assessors was done, making it unlikely blinding was lost.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	Low risk	The study protocol is not available, but the study published clearly included all desired outcomes.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

Study characteristics	Studer et al. (2012)
Method	Randomized double-blind crossover study. Allocated 12 participants undergoing surgery for bilateral extraction of third molars to receive drug orally administered 1 hour before procedure. Group I – midazolam 7.5 mg; Group II – clonidine 150 ug. The procedure was performed by the same dental surgeon during two surgical visits with follow-up of 7 days.
Participants	12 participants of both genders were selected for bilateral extraction of third molars.
Intervention	The patients underwent surgery for extraction of third molars after oral sedation.
Outcomes	Primary outcomes: anxiety, adverse effects (dizziness, nausea, headache, fatigue, metallic taste and concentration difficulties). Secondary outcomes: satisfaction with treatment.
Observations	The two medications were rated similar for patient satisfaction. Oral administration of clonidine 150 ug and midazolam 7.5 mg

	medications promoted similar anxiolytic effects before surgery with local anaesthesia.
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Studer et al. (2012)	Deemed risk of bias	Support for judgement
Random sequence generation	Low risk	Randomization was performed using randomized computer-generated list, thus there was sufficient information about the method used for generating the random sequence.
Allocation concealment	High risk	No information or scant description on procedures for concealing allocation of patients into groups.
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	High risk	The study failed to report this information. Outcomes assessed were subject to influence by the lack of blinding.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	Low risk	The study is not available, but the study published clearly included all the desired outcomes.
Other sources of bias	High risk	Insufficient information to assess whether there was relevant risk of bias.

Characteristics of studies	Shivananda et al. (2014)
Method	Randomized double-blind crossover clinical trial. Allocated 20 participants undergoing periodontal surgery. Twenty subjects requiring minimum 2 sextants of flap surgery were selected for the study. Each sextant was randomly assigned into experimental and control sites.
Participants	20 participants of both genders were selected for periodontal surgery, experimental group under 68 kg received diazepam 5 mg and over 68 kg 10 mg - the night before and 1 hour before surgery.
Intervention	Modified widman flap surgery was performed in experimental site with pre-operative oral diazepam sedation and local anaesthesia. Similar surgery was performed in the control site with pre-operative oral placebo and using local anaesthesia only.
Outcomes	Secondary outcomes: oxygen saturation
Observations	There was no statistically significant difference between sedated and non-sedated patients for oxygen saturation. Oral conscious sedation can be used for anxious patients during periodontal surgery for alleviation of anxiety and for better patient acceptance during surgical procedures without significant respiratory depression.

Shivananda et al. (2014)	Deemed risk of bias	Support for judgement
Random sequence generation	High risk	There was insufficient information on procedure concealing allocation of patients into groups.

Allocation concealment	High risk	No information or scant description on procedures for concealing allocation of patients into groups.
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	High risk	The study failed to report this information. Outcomes assessed were subject to influence by lack of blinding.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	High risk	The study protocol was not available, thus there was insufficient information to allow judgement.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

APPENDIX C – LIST OF EXCLUDED STUDIES AND MAIN REASONS FOR EXCLUSION

Other administration route	<ol style="list-style-type: none"> 1. Barclay JK, Hunter KM, Jones H. Diazepam and lorazepam compared as sedatives for out patient third molar surgery. <i>British Journal of Oral Surgery</i>. 1980;18:141-149. 2. Bavisha KA, Elias M, Paris S, Leon AR, Flynn PJ. Comparison of patient-controlled and operator-controlled conscious sedation for restorative dentistry. <i>European Journal of Anaesthesiology</i>. 2004;21:284-288. 3. Cheung CW, Ying CLA, Chiu WK, Wong GTC, Ng KFJ, Irwin MG. A comparison of dexmedetomidine and midazolam for sedation in third molar surgery. <i>Anaesthesia</i>. 2007;62:1132-1138. 4. Fan TWV, Ti LK, Islam I. Comparison of dexmedetomidine and midazolam for conscious sedation in dental surgery monitored by bispectral index. <i>British Journal of Oral and Maxillofacial Surgery</i>. 2013;51:428-433. 5. Hosie HE, Brook IM, Nimmo WS. Comparison of sedation with temazepam by mouth and diazemuls I.V. for dental surgery. <i>Br J Anaesth</i>. 1988;60:18-23. 6. Luyk NH, Whitley BD. Efficacy of oral midazolam prior to intravenous sedation for there moval of third molars. <i>Int J Oral Maxillofac Surg</i>. 1991;20:264-267. 7. Ochs MW, Tucker MR, White RP, Anderson JA. Recovery following sedation with midazolam or diazepam alone or in combination with fentanyl for out patient surgery. <i>Anesthesia Progress</i>. 1986;230-234. 8. Osborne GA, Rudkin GE, Curtis NJ, Vickers D, Craker AJ. Intra-operative patient-controlled sedation. <i>Anaesthesia</i>. 1991;46:553-556. 9. Rodrigo MRC, Tong CKA. A comparison of patient and anasthetist controlled midazolam sedation for dental surgery. <i>Anaesthesia</i>. 1994;49:241-244. 10. Richmond MN, Daum REO. Premedication with oral slow release morphine in dental anaesthesia: A comparison with temazepam. <i>Anaesthesia</i>. 1988;43:694-696. 11. Stopperich PS, Moore PA, Finder RL, McGirl BE, Weyant RJ. Oral triazolam pretreatment for intravenous sedation. <i>Anesth Prog</i>. 1993;40:117-121.
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	<p>12. Rubim J, Schweggmann I, Uys P. Lorazepam as a premedicant in dental surgery. <i>S Afr Med J</i>. 1980;58(3):124-126.</p> <p>13. Mohamad EM. Midazolam versus but or phanolaslocal an anesthetic adjuncts in oral surgery: a clinical assessment. <i>Egyptian Dental Journal</i>. 1987;33(4):363-374.</p> <p>14. Zanette G, Manani G, Favero L, Stellini E, Mazzoleni S, Cocilovo F, et al. Conscious sedation with Diazepam and midazolam for dental patient: priority to diazepam. <i>Minerva Stomatol</i>. 2013;62:355-374.</p> <p>15. Manani G, Baldinelli L, Cordioli G, Consolati E, Luisetto F, Galzigna L. Premedication with Chlordemethyldiazepam and anxiolytic effect of diazepam in implantology. <i>AnesthProg</i>. 1995;42:107-112.</p> <p>16. Lieblch SE, Horswell B. Attenuation of anxiety in ambulatory oral surgery patients with oral triazolam. <i>J Oral Maxillofac Surg</i>. 1991;49:792-795.</p> <p>17. Luyk NH, Weaver JM, Beck FM, Loetscher CA, Sacks J. The effectiveness of flurazepam as night sedation prior to there moval of third molars. <i>Int J Oral Maxillofac Surg</i>. 1988;17:347-351.</p> <p>18. O'Boyle CA, et al. Comparison of midazolam by mouth and diazepam I.V. in out patient oral surgery. <i>Br J Anaesth</i>. 1987;59:746.</p>
Not oral surgery	<p>19. Ahmed N, Khan FA. Evaluation of oral midazolam as pre-medication in day care surgery in adult Pakistani patients. <i>J Pak Med Assoc</i>. 1995;45(9):239-241.</p> <p>20. Hargreaves J. Benzodiazepine premedication in minorday-case surgery: comparison of oral midazolam and temazepam with placebo. <i>Br J Anaesth</i>. 1988; 61:611-616.</p> <p>21. Patel T, Kurdi MS. A comparative study between oral melatonin and oral midazolam on preoperative anxiety, cognitive, and psychomotor functions. <i>Journal of Anaesthesiology Clinical Pharmacology</i>. 2015;31(1):37-43.</p> <p>22. Baird ES, Curson I. Orally administered diazepam in conservative dentistry. <i>British Dental Journal</i>. 1970;128:25-27.</p> <p>23. Irjala J, Kanto J, Irjala K, Salonen M, Viinamaki O. Temazepam versus flunitrazepam as na oral premedication in adult surgical patients. <i>European Journal of Anesthesiology</i>. 1987;4:435-440.</p> <p>24. Raybould D, Bradshaw EG. Premedication for day case surgery: a study of oral midazolam. <i>Anaesthesia</i>. 1987;42:591.</p>
Not RCT (n=12)	<p>25. Johren P, Jackowski J, Gangler P, Sartory G, Thom A. Fear reduction in patients with dental treatment phobia. <i>British Journal of Oral and Maxillofacial Surgery</i>. 2000;38:612-616.</p> <p>26. Ochs MW, Tucker MR, White RP. A comparison of amnesia in outpatients sedated with midazolam or diazepam alone or in combination with fentanyl during oral surgery. <i>JADA</i>. 1986;113:894-897.</p> <p>27. Khosla VM, Boren W. Diazepam (Valium) as preoperative medication in oral surgery. <i>Anesthesiology</i>. 1969;28(5):671-679.</p> <p>28. Debernardi G, Debernardi C. Sperimentazione clinicasull'azione di una benzodiazepine (Lexotan) sulcomportamento del paziente ansiosonell'ambulatorio odonto stomatologico. <i>Min Stom</i>. 1985; 34:323-328.</p> <p>29. Noguchi T, Hayano Y, Iwasaka H, Miyamoto M, Habu A, Tsuzaki K, et al. A study of clinical efficacy of triazolam as preanesthetic medication. 1985;34(4):493-499.</p> <p>30. Shane SM, Baltimore. Amnesia for brief exodontia procedures using small doses of diazepam and methohexital with local block anesthesia for ambulatory patients. <i>J Oral Surgery</i>. 1971;29:191-193.</p> <p>31. Skelly AM, Boscoe MJ, Dawling S, Adams AP. A comparison of diazepam and midazolam as sedatives for minor oral surgery. <i>European Journal of Anaesthesiology</i>. 1984;(1):253-267.</p>

	<p>32. Wahlmann UW, Dietrich U, Fischer W. Zurfrage der oral em sedierung mit midazolam bei ambulante zahnarztlich-chirurgischen eingriffen. Disch Zahnarztl Z. 1992;47:66-68.</p> <p>33. Reinhardt LC, Felberg RV, Lemes CHJ. Comparative study of bone response guided tissue regeneration clinical evaluation of the anxiety and cardiovascular parameters with the use of anxiolytic in the pre-operative in bucomaxilofacial surgery. Full Dentistry in Science. 2010;1(4):328-331.</p> <p>34. Aeschliman SD, Blue MS, Williams KB, Cobb CM, MacNeill SR. A preliminary study on oxygen saturation levels of patients during periodontal surgery with and without oral conscious sedation using diazepam. J Periodontol. 2003;74(7):1056-1059.</p> <p>35. Moorthi RK, Kumar MPS. Pre- and post-operative anxiety in patients undergoing dental extractions. Drug lvention Today. 2018;10(12):2445-2449.</p> <p>36. James D, Nazar N. Role of anti- anxiety drugs patient cooperation during minor surgical procedure. Research J. Pharm. and Tech.2018; 11(8): 3389-3391</p>
Other medication or comparator	<p>37. Kanto D, Salo M, Happonen RP, Vahlberg T, Kanto J. Tramadol premedication in operative extraction of the mandibular third molar: a placebo-controlled crossover study. Acta Odontologica Scandinavica. 2005; 63:43-49.</p> <p>38. White CS, Dolwick MF, Gravenstein N, Paulus DA. Incidence of oxygen desaturation during oral surgery out patient procedures. J Oral Maxillofac Surg. 1989;47:147-149.</p> <p>39. Dellovo AG, Souza LMA, Oliveira JS, Amorim KS, Groppo FC. Effects of auriculotherapy and midazolam for anxiety control in patients submitted to third molar extraction. Int J Oral Maxillofac Surg. 2018;18:1-6.</p>