





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

Jimmy de Oliveira Araújo,<sup>1</sup> Cristiane de Cássia Bergamaschi <sup>2</sup>,  
Luciane Cruz Lopes <sup>2</sup>, Caio Chaves Guimarães <sup>1</sup>, Natalia Karol de Andrade,<sup>1</sup>  
Juliana Cama Ramacciato,<sup>1</sup> Rogério Heládio Lopes Motta <sup>1</sup>

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<sup>1</sup>Division of Pharmacology, Anesthesiology and Therapeutics, Faculdade São Leopoldo Mandic, Instituto de Pesquisas São Leopoldo Mandic, Campinas, Brazil

<sup>2</sup>Department of Pharmaceutical Sciences, Universidade da Sorocaba, Sorocaba, Brazil

## Correspondence to

Professor Rogério Heládio Lopes Motta;  
[rogerio.motta@slmandic.edu.br](mailto:rogerio.motta@slmandic.edu.br)

## 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.<sup>1 2</sup> 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.<sup>3</sup> 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.<sup>4</sup> The sedation level should be such that the patient remains conscious and can readily understand and respond to verbal instructions or tactile stimulation.<sup>5</sup>

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.<sup>6</sup>

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.<sup>7</sup>

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.<sup>8</sup> Moreover, drug interventions to provide conscious sedation should have a sufficient safety margin to preclude consciousness loss.<sup>9</sup>

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

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

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.<sup>10</sup> 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.<sup>14</sup>

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.<sup>15</sup>

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.<sup>16 17</sup> 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.<sup>18</sup> 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).<sup>15</sup> 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.<sup>19 20</sup>

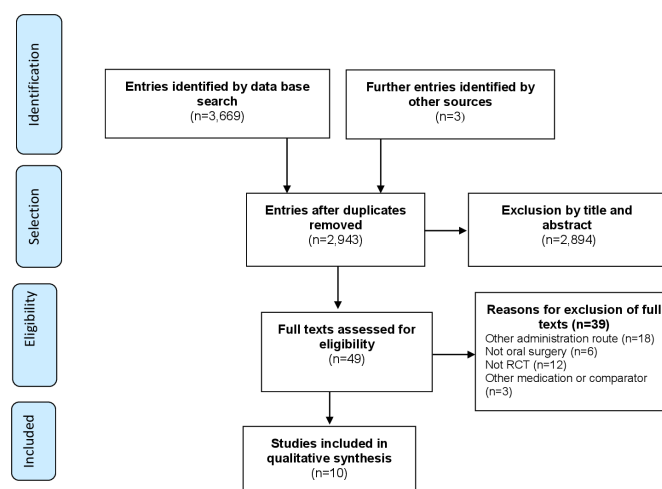
## RESULTS

### 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.<sup>21–27</sup> 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.<sup>22 24 28</sup> By contrast, other clinical trials did not guarantee allocation concealment.<sup>21 23 25 27 29</sup> Two clinical

trials provided insufficient information on the random sequence generation process employed.<sup>26 30</sup>

### Blinding of the participants and personnel

Rodrigo and Cheung<sup>22</sup> and Coldwell *et al*<sup>23</sup> 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.<sup>21 24–30</sup> 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.<sup>22 27 28</sup> Romano *et al*<sup>24</sup> and Pinheiro *et al*<sup>30</sup> 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.<sup>21 23 25 26 29</sup>

### Incomplete outcomes

For the study by Coldwell *et al*,<sup>23</sup> 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.<sup>30</sup> 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.<sup>22</sup> Other studies declared there was no funding.<sup>21 22 25–28 30</sup> The

remaining studies did not report sufficient information to assess the presence of other sources of bias.<sup>23 24 29</sup>

### 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,<sup>23 25 27 28 30</sup> and six studies collected information on the adverse effects.<sup>21–23 27 29 30</sup>

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*<sup>27</sup> reported the number of adverse effects but did not report the number of patients with adverse effects. Coldwell *et al*<sup>23</sup> 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.<sup>22 27</sup>

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

### 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.<sup>23</sup>

#### 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.<sup>25</sup>

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 <sup>23</sup> (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 <sup>25</sup> (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 <sup>29</sup> <b>Crossover</b> (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 <sup>28</sup> <b>Crossover</b> (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 <sup>27</sup> <b>Crossover</b> (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 <sup>30</sup> (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 <sup>24</sup> (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 <sup>21</sup> (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 <sup>26</sup> <b>Crossover</b> (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.<sup>21</sup>

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.<sup>26</sup>

#### 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.<sup>29</sup>

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.<sup>24</sup>

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 <sup>29</sup>	Midazolam 7.5 mg	6/12 (50.0)	0
	Clonidine 150 µg	5/12 (41.6)	
Rodrigo and Cheung <sup>22</sup> 1987	Midazolam 15 mg	17/30 (56.6)	0
	Placebo	9/30 (30.0)	
Manani <i>et al</i> 1979 <sup>21</sup>	Trazodone 25 mg	12/20 (60.0)	0
	Trazodone 50 mg	11/21 (52.3)	
Pinheiro <i>et al</i> 2014 <sup>30</sup>	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> <sup>27</sup>	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> <sup>21</sup>	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> <sup>30</sup>	<i>Valeriana officinalis</i> (16)	Drowsiness (9), muscular relaxation (7)	Placebo (11)	Drowsiness (7), muscular relaxation (4)
Rodrigo, Cheung <sup>22</sup>	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> <sup>29</sup>	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.<sup>22</sup>

#### *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.<sup>28</sup>

#### *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.<sup>27</sup>

#### *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.<sup>30</sup>

## 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.<sup>21–23 25 27–30</sup>

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

The results revealed a higher number of adverse effects associated with midazolam use,<sup>22 27</sup> followed by diazepam.<sup>21</sup> 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,<sup>29</sup> 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.<sup>29</sup> 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,<sup>28</sup> *P. incarnata* to midazolam,<sup>27</sup> midazolam to clonidine<sup>29</sup> and diazepam to placebo or trazodone.<sup>21</sup> However, the use of *V. officinalis* was associated with less change in these parameters relative to a placebo.<sup>30</sup> There was no difference in oxygen saturation for the use of *E. mulungu* versus placebo,<sup>28</sup> *P. incarnata* versus midazolam<sup>27</sup> or diazepam versus placebo.<sup>26</sup>

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.<sup>10 14</sup> 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.<sup>10</sup>

Another systematic review investigated the anxiolytic effect of midazolam in dental surgery, regardless of the administration route.<sup>14</sup> 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.<sup>29</sup>

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.<sup>10 14</sup> 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.<sup>28</sup> 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.<sup>11 31</sup>

## 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.

**Twitter** Luciane Cruz Lopes @lulopesbr

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## ORCID iDs

Cristiane de Cássia Bergamaschi <http://orcid.org/0000-0002-6608-1806>

Luciane Cruz Lopes <http://orcid.org/0000-0002-3684-3275>

Caio Chaves Guimarães <http://orcid.org/0000-0002-1672-528X>

Rogério Heládio Lopes Motta <http://orcid.org/0000-0002-6983-7883>

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