

Systematic Reviews

Midazolam for sedation before procedures in adults and children: A systematic review update --Manuscript Draft--

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Full Title:	Midazolam for sedation before procedures in adults and children: A systematic review update
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Abstract:	<p>Background Midazolam is used for sedation before diagnostic and therapeutic medical procedures by several routes including oral, intravenous, intranasal and intramuscular. This is an update of a Cochrane review published in 2016, which aimed to determine the evidence on the effectiveness of midazolam for sedation when administered before a diagnostic or therapeutic procedure in adults and children.</p> <p>Methods We searched CENTRAL, MEDLINE, Embase, and two trials registers up to May 2020 together with reference checking to identify additional studies. We imposed no language restrictions. Randomized controlled trials of midazolam in comparison with placebo or other medications used for sedation were included. Two authors independently extracted data and assessed risk of bias for each included study.</p> <p>Results Eight new trials were included in this update, which resulted in changed conclusions for the intravenous midazolam versus placebo, oral midazolam versus chloral hydrate and oral midazolam versus placebo comparisons. Effect estimates for all outcomes within the intravenous midazolam versus placebo (7 trials; 633 adults and 32 children) are uncertain due to concerns about imprecision and risk of bias. Midazolam resulted in a higher level of sedation than placebo (MD 1.05; 95% CI 0.69 to 1.41; 1 study; 100 adults). There was no difference in anxiety (RR 0.43, 95% CI 0.09 to 1.99; I² = 75%; 2 studies; 123 adults). Risk of difficulty performing procedures was lower in the midazolam group (RR 0.5; 95% CI 0.29 to 0.86; I² = 45%; 3 studies; 191 adults and 32 children). There was no difference in discomfort (RR 0.51; 95% CI 0.25 to 1.04; I² = 0%; 2 studies; 190 adults). Five trials with 336 children were included in the oral midazolam versus chloral hydrate comparison. Midazolam was less likely to result in moderate sedation (RR 0.30, 95% CI 0.11 to 0.82; I² = 64%; 2 studies, 228 participants). This effect estimate is highly uncertain due to concerns about the risk of bias, imprecision and inconsistency. There was no difference in ratings of anxiety (SMD -0.26; 95% CI = -0.75 to 0.23; I² = 0%; 2 studies; 68 participants). Midazolam increased risk of incomplete procedures (RR 4.01; 95% CI 1.92 to 8.40; I² = 0%; 4 studies, 268 participants). This effect estimate is uncertain due to concerns about the risk of bias. There were four trials with 359 adults and 77 children included in the oral midazolam versus placebo comparison. Midazolam reduced ratings of anxiety (SMD -1.01; 95% CI -1.86 to -0.16; I² = 92%; 4 studies; 436 participants). It is unclear if midazolam has an effect on difficulty performing procedures. Meta-analysis was not performed because there was only one incomplete procedure in the midazolam group in one of the trials. Midazolam reduced pain in one study with 99 adults (MD -2; 95% CI -2.5 to -1.6; moderate-quality). The effect estimate is uncertain due to concerns about the risk of bias.</p> <p>Conclusion The additional evidence arising from inclusion of new studies in this updated review has not produced sufficient high-quality evidence to determine whether midazolam produces more effective sedation than other medications or placebo in any specific population included in this review. For adults, there was low-quality evidence that intravenous midazolam did not reduce the risk of anxiety or discomfort/pain in comparison to placebo, but the sedation level was higher. By combining results from adults and children, there was low-quality evidence of a large reduction in the risk of procedures being difficult to perform with midazolam in comparison to placebo. The effect estimates for this comparison are uncertain because there was concern about risk of bias and imprecision. There is moderate-quality evidence suggesting that oral</p>

	midazolam produces less effective sedation than chloral hydrate for completion of procedures for children undergoing non-invasive diagnostic procedures. Ratings of anxiety were not different between oral midazolam and chloral hydrate. The extent to which giving oral midazolam to adults or children decreases anxiety during procedures compared with placebo is uncertain due to concerns about risk of bias and imprecision. There was moderate-quality evidence from one study that oral midazolam reduced the severity of discomfort/pain for adults during a brief diagnostic procedure in comparison with placebo.
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Is this study a clinical trial?<hr><i>A clinical trial is defined by the World Health Organisation as 'any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes'.</i>	No

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6 ***Midazolam for sedation before procedures in adults***

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9 ***and children: A systematic review update***

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Abstract

Background

Midazolam is used for sedation before diagnostic and therapeutic medical procedures by several routes including oral, intravenous, intranasal and intramuscular. This is an update of a Cochrane review published in 2016, which aimed to determine the evidence on the effectiveness of midazolam for sedation when administered before a diagnostic or therapeutic procedure in adults and children.

Methods

We searched CENTRAL, MEDLINE, Embase, and two trials registers up to May 2020 together with reference checking to identify additional studies. We imposed no language restrictions. Randomized controlled trials of midazolam in comparison with placebo or other medications used for sedation were included. Two authors independently extracted data and assessed risk of bias for each included study.

Results

Eight new trials were included in this update, which resulted in changed conclusions for the intravenous midazolam versus placebo, oral midazolam versus chloral hydrate and oral midazolam versus placebo comparisons. Effect estimates for all outcomes within the intravenous midazolam versus placebo (7 trials; 633 adults and 32 children) are uncertain due to concerns about imprecision and risk of bias. Midazolam resulted in a higher level of sedation than placebo (MD 1.05; 95% CI 0.69 to 1.41; 1 study; 100 adults). There was no difference in anxiety (RR 0.43, 95% CI 0.09 to 1.99; $I^2 = 75\%$; 2

studies; 123 adults). Risk of difficulty performing procedures was lower in the midazolam group (RR 0.5; 95% CI 0.29 to 0.86; $I^2 = 45\%$; 3 studies; 191 adults and 32 children). There was no difference in discomfort (RR 0.51; 95% CI 0.25 to 1.04; $I^2 = 0\%$; 2 studies; 190 adults). Five trials with 336 children were included in the oral midazolam versus chloral hydrate comparison. Midazolam was less likely to result in moderate sedation (RR 0.30, 95% CI 0.11 to 0.82; $I^2 = 64\%$; 2 studies, 228 participants). This effect estimate is highly uncertain due to concerns about the risk of bias, imprecision and inconsistency. There was no difference in ratings of anxiety (SMD -0.26; 95% CI = -0.75 to 0.23; $I^2 = 0\%$; 2 studies; 68 participants). Midazolam increased risk of incomplete procedures (RR 4.01; 95% CI 1.92 to 8.40; $I^2 = 0\%$; 4 studies, 268 participants). This effect estimate is uncertain due to concerns about the risk of bias. There were four trials with 359 adults and 77 children included in the oral midazolam versus placebo comparison. Midazolam reduced ratings of anxiety (SMD -1.01; 95% CI -1.86 to -0.16; $I^2 = 92\%$; 4 studies; 436 participants). It is unclear if midazolam has an effect on difficulty performing procedures. Meta-analysis was not performed because there was only one incomplete procedure in the midazolam group in one of the trials. Midazolam reduced pain in one study with 99 adults (MD -2; 95% CI -2.5 to -1.6; moderate-quality). The effect estimate is uncertain due to concerns about the risk of bias.

Conclusion

The additional evidence arising from inclusion of new studies in this updated review has not produced sufficient high-quality evidence to determine whether midazolam produces more effective sedation than other medications or placebo in any specific population

1 included in this review. For adults, there was low-quality evidence that intravenous
2 midazolam did not reduce the risk of anxiety or discomfort/pain in comparison to
3 placebo, but the sedation level was higher. By combining results from adults and
4 children, there was low-quality evidence of a large reduction in the risk of procedures
5 being difficult to perform with midazolam in comparison to placebo. The effect estimates
6 for this comparison are uncertain because there was concern about risk of bias and
7 imprecision. There is moderate-quality evidence suggesting that oral midazolam
8 produces less effective sedation than chloral hydrate for completion of procedures for
9 children undergoing non-invasive diagnostic procedures. Ratings of anxiety were not
10 different between oral midazolam and chloral hydrate. The extent to which giving oral
11 midazolam to adults or children decreases anxiety during procedures compared with
12 placebo is uncertain due to concerns about risk of bias and imprecision. There was
13 moderate-quality evidence from one study that oral midazolam reduced the severity of
14 discomfort/pain for adults during a brief diagnostic procedure in comparison with
15 placebo.

Background

Anxiety at the time of therapeutic or diagnostic medical procedures is a natural response to the unfamiliar environment and experience.(1,2) Anxiety reduction (anxiolysis) may be achieved through pharmacological, and non-pharmacological means, with or without associated sedation.(1,3,4) Anxiolysis without conscious-level depression is termed minimal sedation.(5) If the medication induces an appreciable depression of conscious level (whilst the patient remains responsive), this is termed moderate sedation.(5)

Midazolam is one of the most commonly used medications for inducing anxiolysis or sedation or both, prior to diagnostic and therapeutic procedures.(6,7) This report is an update from a previous version of our Cochrane review.(8) Research interest in using midazolam for sedation before procedures persists, so it is important that new findings are incorporated into our review and disseminated. A comprehensive report of the methods was published with the original review. This report is restricted to highlighting the minor differences in methods which were applied between the previous version and this review, as well as describing the results and conclusions that have changed from the original version.

Methods

A full description of the methods was provided in the original review (8), so we have not repeated them here and instead include them in Additional File 1. The search terms used to identify relevant trials in the original and updated review is presented in

Additional File 2. Table 1 displays a summary of the inclusion and exclusion criteria. In the original review we excluded the comparison between midazolam and dexmedetomidine because there was a Cochrane protocol focusing specifically on that comparison. That protocol has been abandoned. For this reason, we now included the dexmedetomidine comparison.

The other difference in methods between the published Cochrane review and this update was the selection of primary outcomes. For this update, we refined the primary and secondary outcomes based on recommendations from the Sedation Consortium on Endpoints and Procedures for Treatment, Education, and Research Recommendations (SCEPTER) about core outcome domains in clinical trials of in procedural sedation, which were published after our initial review.(9) Recommended core outcomes measures from SCEPTER included sedation level, proceduralist satisfaction and patient-centered outcomes, such as pain.

Table 1. Inclusion and exclusion criteria

Criteria	Description
Studies	<ul style="list-style-type: none">• RCTs in which midazolam was used for sedation before a procedure• No exclusions based on language or publication status
Participants	<ul style="list-style-type: none">• Adults or children• Studies that included participants undergoing dental procedures were excluded
Interventions	<ul style="list-style-type: none">• Studies that used midazolam by any route, at any dose or time, administered before a procedure.• Studies that compared different drugs and different routes were excluded (e.g. intranasal midazolam plus intravenous sedative A versus intranasal sedative A plus intravenous midazolam; intravenous midazolam versus intranasal sedative A)
Outcomes	<p>Primary</p> <ul style="list-style-type: none">• Level of sedation on a sedation assessment scale• Anxiety• Incomplete procedures/difficulty performing procedures• Discomfort/pain <p>Secondary</p> <ul style="list-style-type: none">• Anterograde amnesia• Oversedation• Disinhibition or excitation• Quality of recovery• Allergic or anaphylactoid reactions• Sedation reversal• Tolerance of procedure or participant cooperation• Participant or proceduralist satisfaction

Included studies

We included eight new trials in this updated review. In total, we included 38 trials with 3344 participants, that compared pre-procedure midazolam via the intravenous, oral and intranasal routes of administration, to either a placebo or alternative medication used for sedation (Figure 1). The included trials were conducted in both adults and children. Summaries of the judgements of the risk of bias of included trials in Figure 2 and Figure 3. Details of the included trials are available in Additional File 3. The overall risk of performance bias and detection bias was low for 50% of the included trials. For randomization sequence generation and allocation concealment, the quality assessment yielded low risk of bias for approximately 25% or less of the included trials. The risk of attrition bias for the primary outcomes was low for more than 75% of trials. An expanded description of results for all comparisons included in Additional File 4. Data and results of meta-analyses for all comparisons in the update are in Additional File 5. The remainder of this results section focuses on the comparisons with new evidence available in the update and new comparisons in this update.

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Comparisons with new evidence available in the update

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Intravenous midazolam versus intravenous placebo

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10 Intravenous midazolam was compared with placebo in six trials with 633 adult
11 participants(10–15) and one trial with 32 children.(16) We downgraded the evidence to
12 low quality on all four primary outcomes, due to concerns about the risk of bias and
13 imprecision (Table 2).
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Primary outcomes
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Level of sedation on a sedation assessment scale
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20 One study, which used the Ramsay scale to measure level of sedation, reported on this
21 outcome.(14) Scale scores range from 1 to 6, with higher scores indicating the
22 participant was more sedated. Participants randomized to midazolam were more
23 sedated (MD 1.05; 95% CI 0.6 to 1.4; 1 study; 100 participants; low-quality). The quality
24 of this evidence was downgraded to low quality due to concerns about risk of bias and
25 imprecision.
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Numeric rating scale of anxiety or number of participants rated as anxious
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30 There was no difference in anxiety (risk ratio (RR) 0.43; 95% confidence interval (CI)
31 0.09 to 1.99; $I^2 = 75\%$; 123 adults; 2 studies; low-quality). The quality of this evidence
32 was downgraded to low quality due to concerns about risk of bias and imprecision.
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4 *Proportion of incomplete procedures or where there was difficulty performing the procedures*

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7 Risk of difficulty performing procedures was lower in the midazolam group (RR 0.5; 95%
8 CI 0.29 to 0.86; $I^2 = 45\%$; 3 studies; 191 adults and 32 children; low-quality). The quality
9 of this evidence was downgraded to low quality due to concerns about risk of bias and
10 imprecision.
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14 *Discomfort/pain*
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18 There was no difference in discomfort between groups (RR 0.51; 95% CI 0.25 to 1.04; I^2
19 = 0%; 2 studies; 190 participants; low-quality). The quality of this evidence was
20 downgraded to low quality due to concerns about risk of bias and imprecision.
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24 Secondary outcomes
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27 No trials reported results for disinhibition or excitation, quality of recovery, allergy or
28 anaphylactoid reactions and tolerance of procedure or patient co-operation.
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31 Anterograde amnesia (defined by the number of participants who recalled the
32 procedure) There was no difference between groups in one study (RR 0.83; 95% CI
33 0.52 to 1.32; 1 study; 23 participants; low-quality evidence).(13)
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37 *Sedation reversal*
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40 One trial (100 participants) reported that no participants required sedation reversal in
41 either group.(14)
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45 *Participant or proceduralist satisfaction*
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48 Four trials, all conducted with adult participants, reported on participant or proceduralist
49 satisfaction (Bhalla 2006; Manning 2016; Rolo 2012; Yun 1996).(10,13–15) Midazolam
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increased the number of participants who were satisfied with sedation (RR 1.21; 95% CI 1.07 to 1.36; trials = 2; participants = 123; $I^2 = 0\%$; moderate-quality). In the Yuno 1996 trial, participant satisfaction, which was measured on a four-point scale with lower scores indicating greater satisfaction, was better in the midazolam group (MD -1.65; 95% CI -1.75 to -1.55; 40 participants; moderate-quality). Proceduralist satisfaction was also greater in the midazolam group in the same study (MD -1.8; 95% CI -1.9 to -1.7; 1 study; 40 participants; moderate-quality). The effect estimates for this outcome are uncertain due to concerns about the risk of bias.

Oral midazolam versus chloral hydrate

Five trials (Akil 2005; D'Agostino 2000; Derakhshanfar 2013; Salehi 2017; Wheeler 2001), with 336 participants compared oral midazolam with chloral hydrate for sedation of children.(17–21)

Primary outcomes

Level of sedation on a sedation assessment scale

Two trials reported on the rate of reaching a level of moderate sedation. Derakhshanfar et al.(19) reported the number of patients reaching moderate sedation on Wheeler's sedation scale, and Salehi et al.(20) reported the number of patients reaching moderate sedation on the RASS scale. Different scales were used to measure the level of sedation in these studies. Derakhshanfar et al.(19) used Wheeler's sedation level with scores ranging from 1 = agitated to 4 = eyes closing spontaneously but with a response to minor stimuli. Salehi et al.(20) reported using the RASS, with the levels of 'alert and calm', 'drowsy', 'light sedation' and 'moderate sedation'. Based on guidelines from the

American Society of Anesthesiology, the category in the Wheeler scale that corresponds most closely to 'moderate sedation' was level 4 (eyes closing spontaneously but with a response to minor stimuli) (American Society of Anesthesiologists 2014). We used this definition for the meta-analysis to combine results from the two studies. Meta-analysis of results suggested that midazolam was less likely to result in moderate sedation compared with chloral (RR 0.30; 95% CI 0.11 to 0.82; $I^2 = 64\%$; 2 studies; 228 participants; very low-quality). We downgraded the evidence from this meta-analysis to very low quality, due to concerns about the risk of bias, inconsistency and imprecision.

Numeric rating scale of anxiety or number of participants rated as anxious

A numerical rating of anxiety was reported in two trials with 88 participants. The outcome was measured using different scales (by children using a numerical rating scale in D'Agostino et al.(18), and by parents using the Spielberger's Trait Anxiety Inventory in Akil et al.(17)). The standardized mean difference in anxiety rating was not different (SMD -0.26; 95% CI -0.75 to 0.23; $I^2 = 0\%$; 2 studies; 68 participants; low-quality). We downgraded the evidence for this outcome to low, due to concerns about the risk of bias and imprecision. To aid interpretation, we converted the estimate for the SMD to an MD using the numerical rating scale in D'Agostino et al.(18). Scores ranged from 1 - 5 with lower scores indicating less anxiety). The standard deviation for the placebo group in this study was 2.97. The mean difference for the meta-analysis was -0.7 (95% CI -2.2 to 0.7).

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4 *Proportion of incomplete procedures or where there was difficulty performing the procedures*

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7 Four trials (268 participants) reported on this outcome.(17–19,21) Incomplete
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9 procedures were more likely in the midazolam group (RR 4.01; 95% CI 1.92 to 8.40; I² =
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11 0%; 4 studies; 436 participants; moderate-quality). We downgraded the quality of
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13 evidence to moderate, due to concerns about the risk of bias.
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17 *Discomfort/pain*
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20 No trials reported this outcome.
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24 Secondary outcomes
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27 Within this comparison, no trials reported results for anterograde amnesia, quality of
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29 recovery, allergic or anaphylactoid reactions, sedation reversal, and patient or
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31 proceduralist satisfaction.
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35 *Disinhibition or excitation*
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38 There was no difference in disinhibition or excitation between midazolam or chloral
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40 hydrate groups in the Derakhshanfar et al.(19) trial (RR 1.0; 95% CI 0.39 to 2.55; 1
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42 study; 160 participants). No events were observed in either group by Wheeler et al.(21)
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44 (40 participants). Quality of evidence was downgraded to low quality due to concerns
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46 about risk of bias and imprecision.
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50 *Tolerance of procedure or participant co-operation*
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54 Tolerance of the procedure was measured using the Frankl behaviour rating scale
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56 (range 1 to 4, with higher scores indicating better tolerance) by Akil et al.(17). There
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58 was no difference in tolerance between groups (MD 0.25; 95% CI -0.9 to 0.4; 1 study;
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35 participants; low-quality). Participant co-operation was measured using the Hourt
behavioural scale (range 1 to 6, with higher scores indicating better co-operation) in the
Akil et al.(17) trial and there was no difference between groups (MD 0.16; 95% CI -0.54
to 0.86; 1 study; 35 participants; low-quality). The evidence for this outcome was rated
as low quality due to concerns about risk of bias and imprecision.

Oral midazolam versus placebo

Four trials (Akil 2005; Kuganeswaran 1999; Puttapitakpong 2015; Templeton 2010) with
436 participants compared midazolam administered via the oral route with a placebo
(Table 4).(17,22–24) Two trials were conducted with adults and two with children.

Primary outcomes

Level of sedation on a sedation assessment scale

Kuganeswaran et al.(22) reported on level of sedation measured on a 4-point scale with
higher scores indicating a greater sedative effect. Although it was reported that level of
sedation was measured every 5 minutes, summary statistics were reported only for the
timepoint 10 minutes after administration of midazolam. At this timepoint, sedation level
was higher in the midazolam group (MD 0.2; 95% CI 0.19 to 0.21; 101 participants; low-
quality evidence). Numeric rating scale of anxiety or number of participants rated as
anxious A numerical rating of anxiety was reported in all trials included in this
comparison. Standardized mean difference was used for meta-analysis because
different scales were used in each trial. Midazolam reduced ratings of anxiety by one
standard deviation (SMD -1.01; 95% CI -1.86 to -0.16; $I^2 = 92\%$; 4 studies; 436
participants; low quality). The quality of this evidence was downgraded to low quality

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4 due to concerns about the risk of bias and imprecision. To aid interpretation, we
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6 converted the estimate for the SMD to an MD using the numerical rating scale from
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8 Puttapitakpong et al.(23). Scores ranged from 0 to 10, with lower scores indicating less
9 anxiety). The standard deviation for the placebo group in this study was 1.9. The mean
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11 difference for the meta-analysis was -1.9 (95% CI = -3.5 to 0.3).
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17 *Proportion of incomplete procedures or where there was difficulty performing the procedures*
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20 There were no incomplete procedures in either the midazolam or placebo groups in
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22 three trials.(22–24) One procedure (6%) could not be completed in the midazolam
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24 group in Akil et al.(17).
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28 *Discomfort/pain*
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31 In the Kuganeswaran et al.(22) trial, which was conducted with adult participants
32 undergoing sigmoidoscopy, pain was lower in the midazolam group (MD -2; 95% CI -2.5
33 to -1.6; 1 study; 99 participants; moderate-quality). Quality of evidence was downgraded
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35 due to concerns about the risk of bias.
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41 Secondary outcomes
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44 Within this comparison, no trials reported results for disinhibition or excitation, quality of
45 recovery, allergic or anaphylactoid reactions and sedation reversal. Anterograde
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47 amnesia (defined by number of participants who recalled the procedure) There was no
48 overall difference in anterograde amnesia between midazolam and placebo in meta-
49 analysis of two trials that enrolled adults undergoing upper (Puttapitakpong et al.(23)) or
50 lower (Kuganeswaran et al.(22)) endoscopy (RR 0.32, 95% CI 0.01 to 10.12; $I^2 = 99\%$;
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4 2 trials; 359 participants; low-quality). However, the results were inconsistent and
5 imprecise. As such, the quality of evidence was rated as low quality.
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10 *Tolerance of procedure or participant co-operation*

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12 Tolerance of the procedure was measured using the Frankl behaviour rating scale
13 (range 1 to 4, with higher scores indicating better tolerance) in Akil et al.(17). There was
14 no difference in tolerance between groups (MD -0.13, 95% CI -0.5 to 0.76; 1 study; 35
15 participants; low-quality). This effect estimate is uncertain due to concerns about
16 imprecision and the risk of bias. Tolerance of the procedure (defined as not willing to
17 repeat the procedure with the same sedation) was better in the midazolam group in the
18 Puttapitakpong et al.(23) trial. Fewer participants in the midazolam group were not
19 willing to repeat the procedure with the same sedation (RR 0.1 95% CI 0.01 to 0.77; 1
20 study; 260 participants; low-quality). This effect estimate is uncertain due to concerns
21 about imprecision and the risk of bias.
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25 Participant co-operation was measured using the Hourt behavioural scale (range 1 to 6,
26 with higher scores indicating better co-operation) in Akil et al.(17). Participant co-
27 operation between groups was higher in the midazolam group, but the effect estimate
28 was imprecise, and there were concerns about the risk of bias (MD 0.82, 95% CI 0.1 to
29 1.54; 1 study; 35 participants; low-quality).
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33 *Participant or proceduralist satisfaction*

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35 Participant satisfaction (measured by participants' perception that they received
36 inadequate sedation for their procedure) in Kuganeswaran et al.(22), was superior in the
37 midazolam group (RR 0.43 95% CI 0.26 to 0.7; 1 study; 99 participants; low-quality).
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4 This effect estimate is uncertain due to concerns about imprecision and the risk of bias.
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7 In the Puttapitakpong et al.(23) trial, ratings of satisfaction on a scale from 0-10 (higher
8 scores = greater satisfaction) from participants (MD 2.5, 95% CI 2.18 to 2.82; 1 study;
9 10 260 participants; moderate-quality) and proceduralists (MD 2.3 95% CI 2.02 to 2.58; 1
11 study; 260 participants; moderate-quality due to concerns about the risk of bias) were
12 higher in the midazolam group. The effect estimates from this trial are uncertain due to
13 concerns about the risk of bias.
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19 **New comparisons in this update**
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22 **Intranasal midazolam versus dexmedetomidine**
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25 One trial with 38 participants compared intranasal midazolam with intranasal
26 dexmedetomidine for sedation in children before laceration repair.(25) Eighteen
27 participants were randomized to receive 0.4mg/kg of intranasal midazolam, and twenty
28 participants received 2mcg/kg of intranasal dexmedetomidine. Within this comparison,
29 no trials reported results for the level of sedation, incomplete or difficulty performing
30 procedures, discomfort/pain and any of the secondary outcomes.
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33 Participants' level of anxiety during patient positioning for the procedure was measured
34 in this trial by the modified Yale Preoperative Anxiety Scale.(25) Participants were
35 observed for five categories (activity, vocalizations, emotional expressivity, state of
36 apparent arousal, and use of parents) combined to produce a total anxiety score
37 between 23.3 and 100, where higher values indicated greater anxiety. The
38 dexmedetomidine group had a median anxiety score that was significantly lower
39 compared to the midazolam group (23.3 (IQR 23-35) dexmedetomidine; 36.3 (IQR 33-
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4 41) midazolam), with a difference in score of 9.2 points (95% CI 5.0 to 13.3; P = 0.007).
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The proportion of participants who were not anxious during positioning for the procedure was also reported. Participants who scored less than 30 using the modified Yale Preoperative Anxiety Scale were considered “not anxious”. More participants in the dexmedetomidine group were not anxious during positioning compared to those in the midazolam group (14/20 (70%) dexmedetomidine; 2/18 (11%) midazolam, P = 0.00). The odds of participants not being anxious during positioning was 19 times higher in the dexmedetomidine group compared to the midazolam group (OR 19, 95% CI 3 to 108). We rated this evidence as moderate quality, due to concerns about imprecision.

Intranasal midazolam versus ketamine

One trial, with 145 children undergoing echocardiography, compared intranasal midazolam with ketamine.(26) There were 73 participants allocated to receive midazolam (0.2mg/kg) and 27 participants to ketamine (4mg/kg). Within this comparison, no trials reported results for anxiety, discomfort/pain and any of the secondary outcomes.

Level of sedation was measured every 15 minutes using the RASS, with levels of ‘awake and calm’, ‘drowsy’ or ‘sedated’. More participants were rated as ‘sedated’ in the midazolam group at 15 minutes (RR 50; 95% CI 3 to 809; 1 trial; 145 participants; low-quality) and 30 minutes (RR 2; 95% CI 1.3 to 3.3; 1 trial; 145 participants; low-quality). There was no difference in the level of sedation between groups at 45 minutes (RR 0.97; 95% CI 0.88 to 1.67; 1 trial; 145 participants; low-quality) and 60 minutes (RR 1.0;

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4 95% CI 0.97 to 1.03; 1 trial; 145 participants; low-quality). The effect estimates for this
5 outcome are uncertain due to concerns about imprecision and the risk of bias.
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10 There was no difference between groups in the number of participants who were
11 insufficiently sedated to be able to perform the procedure (RR 0.99; 95% CI 0.21 to
12 4.73; 1 trial; 145 participants; low quality). This effect estimate is uncertain due to
13 concerns about imprecision and the risk of bias.
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20 Intravenous midazolam versus pethidine hydrochloride

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24 We identified one trial that enrolled 120 participants for this comparison.(27) Forty
25 participants were randomized to midazolam and 39 to pethidine hydrochloride.
26
27 Participants in the midazolam group received intravenous midazolam in 0.5-1.0mg
28 doses administered until a Ramsay score of 3 was achieved for pharyngeal observation.
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30 Participants in the pethidine group received 35mg of intravenous pethidine
31 hydrochloride. Within this comparison, no trials reported results for level of sedation,
32 anxiety, incomplete or difficulty performing procedures, anterograde amnesia,
33 disinhibition or excitation, quality of recovery, allergic or anaphylactoid reactions,
34 sedation reversal, tolerance of procedure or patient co-operation and participant or
35 proceduralist-satisfaction.

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40 Yamasaki et al.(27) reported on participants' discomfort during pharyngeal observation
41 using a visual analogue scale. Participants rated their level of discomfort between 0 mm
42 - 100 mm along a 100 mm horizontal line, where higher values indicated greater pain.
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44 The mean score for discomfort was not significantly different between the midazolam
45 and pethidine groups (MD -0.4; 95% CI -1.39 to 0.59; 1 study; 120 participants; low-
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4 quality). This effect estimate is uncertain due to concerns about imprecision and the risk
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6 of bias.
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10 **Discussion**
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14 *Summary of new evidence for comparisons included in the original review*
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17 Despite inclusion of additional studies in this update, in general, it remains unclear if
18 intravenous midazolam is more effective than placebo for procedural sedation. Overall,
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20 we judged the quality of the evidence for the primary outcomes to be low-quality.
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23 Intravenous midazolam did not reduce the risk of anxiety or discomfort/pain. By
24 combining results from adults and children, there was low-quality evidence of a large
25 reduction in the risk of procedures being difficult to perform with midazolam in
26 comparison to placebo. Also, there was low-quality evidence from multiple studies that
27 midazolam improved participant satisfaction in comparison with placebo. Further studies
28 are needed to increase precision and consequently increase confidence in the effect
29 estimates.
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32 Based on a meta-analysis of four trials(17–19,21), with 268 participants, midazolam was
33 associated with a greater quantity of incomplete procedures in children when compared
34 to chloral hydrate (RR 4.01, 95% CI 1.92 to 8.40). We rated the quality of the evidence
35 as moderate (Summary of findings Table 2). This result is similar to another recently
36 published meta-analysis with different inclusion criteria.(28) However, chloral hydrate
37 was not associated with advantages in any other domain investigated in our review,
38 including the level of pain and level of anxiety. It should be noted that chloral hydrate
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has an inconsistent duration of action and is unavailable in many regions, including the USA.(29)

There was low-quality evidence that oral midazolam reduced anxiety in comparison with placebo in adults and children. There was low-quality evidence of a reduction in discomfort/pain in one of the 4 studies included in this comparison.(23)

Evidence from new comparisons

There was moderate-quality evidence that children who received midazolam for laceration repair had higher ratings of anxiety compared with dexmedetomidine. Additional trials should be conducted in other similar clinical contexts where motion control is required. Such research is needed to confirm these promising initial findings indicating the potential superiority of intranasal dexmedetomidine over midazolam for this indication. Alongside these trials should be a consideration of the cost-effectiveness of dexmedetomidine in comparison to midazolam for pediatric sedation. Another new comparison was intranasal midazolam versus ketamine. One study was identified with 155 children undergoing echocardiography(26). Low-quality evidence indicated that sedation level was higher in the midazolam group earlier after administration, but there was no difference in the number of procedures that could not be completed between groups.

Limitations

Trial protocols were not sought for clarifications regarding risk of bias assessments because many included trials in this review were published prior to the establishment of

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4 clinical trial registries. For this update, we based our selection of primary outcomes on
5 recommendations from the Sedation Consortium on Endpoints and Procedures for
6 Treatment, Education, and Research Recommendations (SCEPTER) about core
7 outcome domains in clinical trials of in procedural sedation.(9) The secondary outcomes
8 we chose to exclude from this update for the review based on these recommendations
9 were: 1) vital signs, based on the fact that they are surrogate outcomes that are likely
10 only important if they lead to clinical outcomes; 2) outcomes related to sedation onset
11 and offset (being duration of sedation, onset of section and offset of sedation); and 3)
12 over-sedation, because this outcome would be more objectively measured by the
13 requirement for sedation reversal which is also an outcome in this review. These
14 decisions about the handling of the data, which we made after seeing it, may have
15 introduced bias to the review process.
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34 Conclusion

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38 The additional evidence arising from inclusion of new studies in this updated review has
39 not produced sufficient high-quality evidence to determine whether midazolam produces
40 more effective sedation than other medications in any specific population included in
41 this review. Moderate-quality evidence demonstrated that midazolam administered
42 orally to children who require sedation for motion control during diagnostic procedures
43 produced less effective sedation compared with chloral hydrate in terms of the ability to
44 complete procedures. Patients appear to prefer to be sedated with midazolam when
45 undergoing a procedure than receive no sedation at all. For this reason, sedation with
46 midazolam could be offered if it is clinically appropriate to do so.
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List of abbreviations

RR: relative risk ratio

95% CI: 95% confidence interval

MD: Mean difference

SMD: Standardized mean difference

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests: The authors declare no competing interests.

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Author contributions:

Co-ordinating the review: AC
Undertaking manual searches: AC, KC
Screening search results: AC, JS
Organizing retrieval of papers: AC
Screening retrieved papers against inclusion criteria: AC, JS, KC
Appraising quality of papers: AC, JS, KC
Abstracting data from papers: AC, JS, KC, SM
Interpretation of data: AC, JS, KC, SM
Statistical inferences:

AC, JS,KC,SM Writing the review: AC, JS,KC,SM. All authors read and approved the final manuscript.

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Figure legend

Figure 1. PRISMA flow diagram

Figure 2. Risk of bias across studies

Figure 3. Risk of bias within studies

Additional files

Filename	Title	Description
Additional file 1	Methods	Expanded description of methods used in the original and updated review
Additional file 2	Search strategy	Search terms used for the original and updated review
Additional file 3	Study characteristics	Sample and intervention characteristics and outcome descriptions as well as risk of bias assessments for each study included in the updated review.
Additional file 4	Results	Expanded description of results for all comparisons included in the updated review.
Additional file 5	Data and analyses	All data and results of meta-analyses

Table 2. Intravenous midazolam compared to intravenous placebo

Intravenous midazolam compared to placebo for sedation before procedures						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Intravenous midazolam				
Level of sedation on a sedation assessment scale The Ramsay scale was used (numerical scale that ranged from 1 to 6 with higher scores indicating the participant was more sedated)	1.19	1 higher (from 0.6 higher to 1.4 higher)		100 (1 study)	low ¹ ⊕⊕⊖⊖	
Numeric rating of anxiety or number of participants rated as anxious Number of participants rated as anxious.	333 per 1000	143 per 1000 (30 to 663)	RR 0.43 (0.09 to 1.99)	123 (2 studies)	low ² ⊕⊕⊖⊖	
Proportion of incomplete procedures or where there was difficulty performing the procedures	216 per 1000	108 per 1,000 (63 to 186)	RR 0.50 (0.29 to 0.86)	223 (3 studies)	low ³ ⊕⊕⊖⊖	
Discomfort/pain	168 per 1000	86 per 1000 (42 to 175)	RR 0.51	190 (2 studies)	low ⁴ ⊕⊕⊖⊖	

			(0.25 to 1.04)			
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*The basis for the **assumed risk** is the control group risk across studies or the average risk for pooled data and the control group risk for single studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Footnotes

¹Downgraded two levels due to concerns about the risk of bias (it was unclear how the allocation sequence was generated and concealed and how participants were blinded to the allocation) and imprecision (optimal information size was not met - single study with a small number of participants, no confidence intervals were reported).

²Downgraded two levels due to concerns about risk of bias (it was unclear in one study how the allocation sequence was generated and concealed and how participants were blinded to the allocation) and imprecision (optimal information size was not met - single study with a small number of participants, wide confidence intervals crossing the line of no effect, and including the potential for both benefit and harm)

³Downgraded two levels due to concerns about the risk of bias (it was unclear in one study how the allocation sequence was concealed) and imprecision (optimal information size was not met - wide confidence intervals including the potential for a very large benefit or very small degree of harm)

⁴Downgraded two levels due to concerns about the risk of bias (it was unclear in one study how the allocation sequence was concealed) and imprecision (optimal information size was not met - wide confidence intervals including the potential for a very large benefit or very small degree of harm)

Table 3. Oral midazolam compared to oral chloral

Oral midazolam compared to chloral hydrate for sedation before procedures						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chloral hydrate	Oral midazolam				
Level of sedation on sedation assessment scale <u>Derakhshanfar 2013</u> reported the number of patients reaching moderate sedation on Wheeler's sedation scale and <u>Salehi 2017</u> reported the number of patients reaching moderate sedation on the RASS scale.	596 per 1000	179 per 1,000 (66 to 489)	RR 0.3 (0.11 to 0.82)	228 (2)	very low¹ ⊕⊖⊖⊖	
Numeric rating of anxiety or number of participants rated as anxious (Numerical rating scale of 1 - 5 with lower scores indicating less anxiety)	2.5	MD was 0.77 lower² (2.2 lower to 0.68 higher)		88 (2)	low³ ⊕⊕⊖⊖	The assumed and corresponding risks were estimated from the SMD, which was -0.26 (95% CI = -0.75 to 0.23).

Proportion of incomplete procedures or where there was difficulty performing the procedures	56 per 1000	226 per 1000 (108 to 474)	RR 4.01 (1.92 to 8.4)	268 (4)	moderate⁴ ⊕⊕⊕⊖	
Discomfort/Pain (as defined/measured by the authors of the trial)						No studies reported on this outcome.

*The basis for the **assumed risk** is the control group risk across studies or the average risk for pooled data and the control group risk for single studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Footnotes

¹Downgraded three levels due to concerns about risk of bias (both studies had unclear and high risk of bias for multiple domains), inconsistency (although the effect estimates for both studies indicated midazolam was less likely to result in moderate sedation, the I² value was high) and imprecision (wide confidence intervals indicating the effect could be either very large or small).

²Studies in this comparison used different instruments to measure anxiety. We used the SMD for meta-analysis. We selected the D'Agostino 2000 trial as our representative study in order to calculate the assumed risk and corresponding risk for the summary of findings table. The standard deviation for the placebo group in this study was 2.97, measured on a scale ranging from 1 to 5.

³Downgraded three levels due to concerns about risk of bias (both studies had unclear and high risk of bias for multiple domains) and imprecision (optimal information size was not met - only a small number of participants, wide confidence intervals crossing the line of no effect, and including the potential for both benefit and harm).

⁴Downgraded one level due to concerns about risk of bias (all studies had unclear and high risk of bias for multiple domains).

Table 4 Oral midazolam compared to oral placebo for sedation before procedures

Oral midazolam compared to oral placebo for sedation before procedures						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Midazolam				
Level of sedation on a sedation assessment scale (as defined/measured by the authors of the trial)						No studies reported on this outcome.
Numeric rating of anxiety or number of participants rated as anxious (as defined/measured by the authors of the trial)	4.6 ² (measured on a scale that ranged from 0 to 10 with higher scores representing worse anxiety)	MD was 1.9 lower (3.5 lower to 0.3 lower)		436 (4)	low¹ ⊕⊕⊖⊖	The assumed and corresponding risks were estimated from the SMD, which was -1 (95% CI -1.86 to -0.16).
Proportion of incomplete procedures or where there was difficulty performing				439 (4 studies)	low¹ ⊕⊕⊖⊖	Relative effect was not able to be conducted because there was only one

the procedures (as defined/measured by the authors of the trial)						incomplete procedure in the midazolam group in one of the four trials that reported on this outcome.
Discomfort/Pain (as defined/measured by the authors of the trial) Scores ranged from 0 to 10 with higher score indicating more pain	4.62	MD was 2 lower (2.5 lower to 1.6 lower)		99 (1 study)	moderate¹ ⊕⊕⊕⊖	

*The basis for the **assumed risk** is the control group risk across studies or the average risk for pooled data and the control group risk for single studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

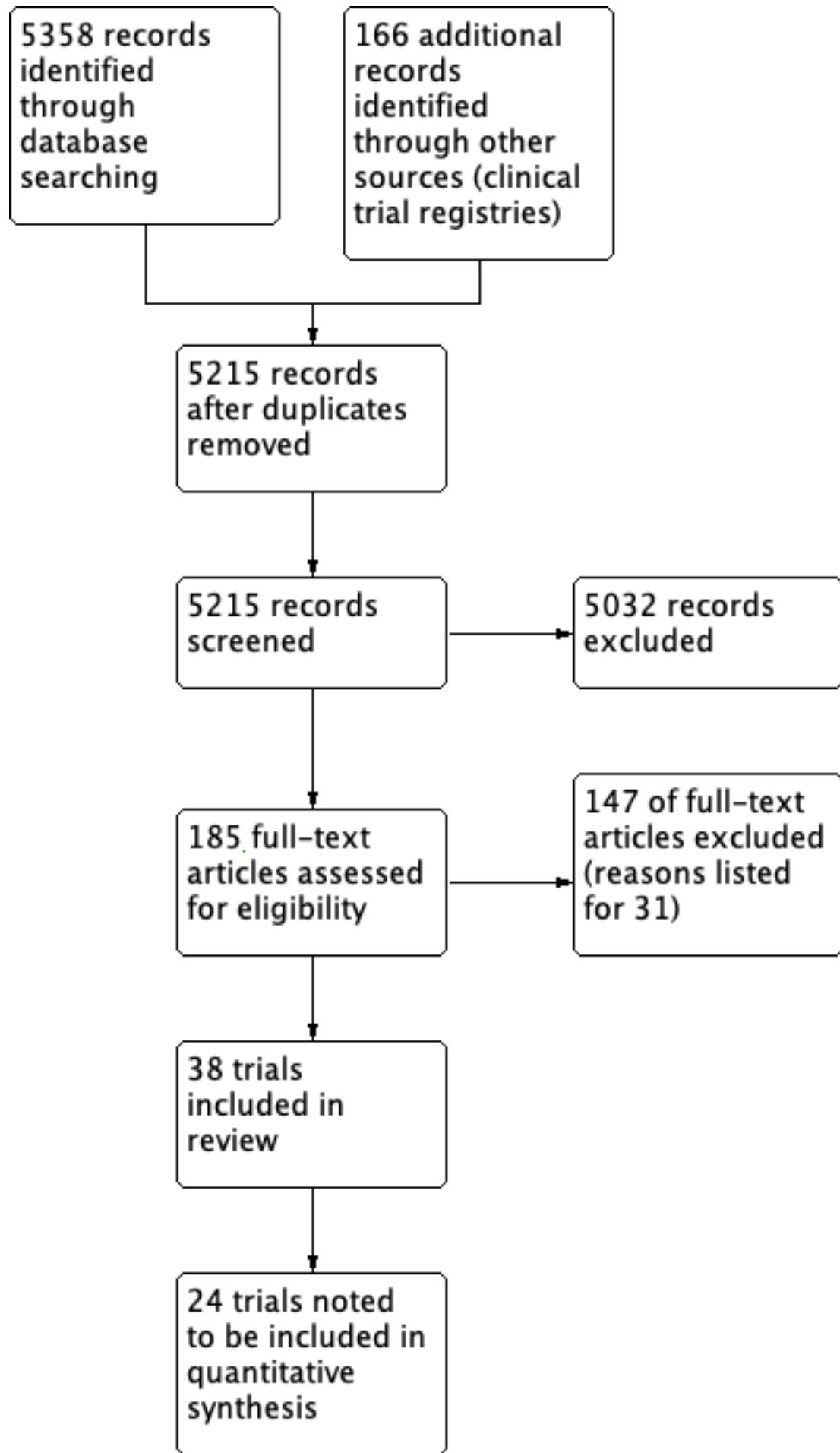
Footnotes

¹Downgraded two levels due to concerns about the risk of bias and imprecision.

²Studies in this comparison used different instruments to measure anxiety. We used the SMD for meta-analysis. We selected the Puttapitakpong 2015 trial as our representative study in order to calculate the assumed risk and corresponding risk for the summary of findings table. The standard deviation for the placebo group in this study was 1.9, measured on a scale ranging from 0 to 10.

²Downgraded one level due to concerns about the risk of bias.

Figure 1

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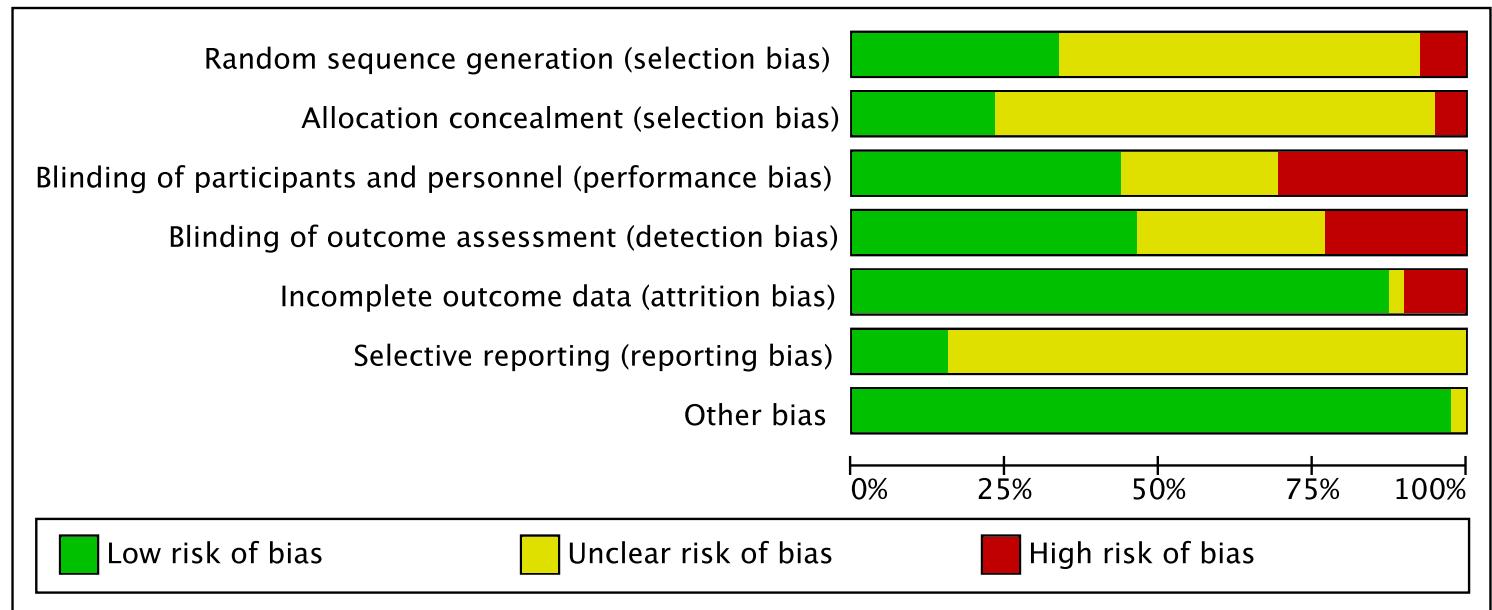


Figure 3

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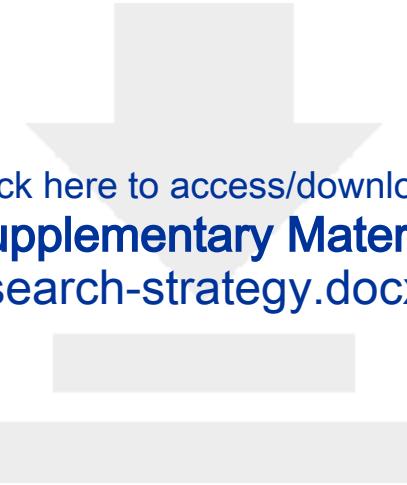
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Akil 2005	?	?	-	-	+	?	+
Aktogu 1994	?	?	?	?	+	?	+
Alp 2019	-	-	-	+	+	?	+
Bell 1988	?	?	?	?	+	?	+
Bhalla 2006	+	?	+	+	+	?	+
Bianchi Porro 1988	?	?	+	+	+	?	+
Cole 1983	?	?	+	+	+	?	+
Coll-Vinent 2003	+	+	-	-	+	?	+
Córdova 1992	?	?	?	?	+	?	+
D'Agostino 2000	+	?	+	+	+	?	+
De Alencar 2010	?	?	-	-	+	?	+
Demiraran 2007a	+	-	-	+	+	+	+
Derakhshanfar 2013	?	?	-	-	+	?	+
Eisapour 2015	-	?	?	?	+	+	+
Everitt 2002	?	?	+	+	?	?	+
Fakheri 2010	?	?	-	-	-	?	?
Gilvarry 1990	?	?	-	+	+	?	+
Hollenhorst 2001	?	?	+	?	+	?	+
Korttila 1985	?	?	+	+	+	?	+
Kuganeswaran 1999	+	?	+	+	+	?	+
Lavies 1988	?	?	+	?	+	?	+
Lazaraki 2007	?	?	?	+	+	?	+
Lee 1989	?	?	-	-	+	?	+
Manning 2016	+	+	+	+	+	+	+
Mignonsin 1994	-	?	-	-	+	?	+
Neville 2016	+	+	+	+	+	+	+
Puttapitakpong 2015	+	?	+	+	+	+	+
Rolo 2012	?	?	?	?	+	?	+
Sainpy 1984	?	+	?	?	+	?	+
Salehi 2017	?	?	?	+	-	?	+
Stokland 2003	?	+	+	?	+	?	+
Takrouri 1988	+	?	-	-	+	?	+
Templeton 2010	+	+	+	?	-	?	+
Tolia 1990	?	?	+	+	-	?	+
Wheeler 2001	+	?	+	?	+	?	+
Whitwam 1983	?	?	?	+	+	?	+
Yamasaki 2017	+	+	-	-	+	+	+
Younge 2001	+	+	+	+	+	?	+
Yuno 1996	?	+	?	?	+	?	+



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17 September 2020

Systematic reviews
Editorial Board

To the editor,

Thank you for considering our manuscript for publication. We report results of an update of our Cochrane systematic review on Midazolam for Sedation before Procedures, which was published in 2016. Since this time, new relevant evidence has become available that we consider is important to highlight. Also, the citation metrics for the original review (63 citations in Google Scholar since 2016, including 14 citations in 2020) indicate research interest in using midazolam for sedation before procedures persists, so it is important that new findings are incorporated into our review and disseminated.

Please note that, in accordance with the journal's instructions regarding article formatting for 'Systematic Review Updates', we have attempted to be 'innovative' in our reporting. The article is restricted to highlighting the minor differences in methods which were applied between the previous version and this update, as well as describing the results and conclusions that have changed from the original version. We provide full descriptions of the complete methods and results (not just those comparisons with new evidence) in the Additional Files.

Also, as an Associate Editor for *Systematic Reviews*, I am all too aware that it can sometimes be challenging to find reviewers for manuscripts. As such, I have provided below a list of reviewers with content and methods expertise that is relevant to our review. Please don't hesitate to reach out for more reviewer recommendations if required.

Potential reviewer	Email address	Reason/Expertise
Chaipichit	iamkeang@hotmail.com	Author of one of the included RCTs
Puttapitakpong		
Ali Ebrahimzadeh	Ebrahimzadehali@yahoo.com	Author of one of the included RCTs
Lingli Zhang	zhanglingli@scu.edu.cn	Author of recent systematic review on midazolam
Paul Ashley	p.ashley@ucl.ac.uk	Author of Cochrane systematic review of dental sedation
Choong Yi Fong	choongyi@hotmail.com; cyfong@ummc.edu.my	Author of Cochrane systematic review of chloral hydrate for sedation
Desiree Neville	desiree.neville@chp.edu	Author of one of the included RCTs
Kalev Freeman	kalev.freeman@uvm.edu	Author of one of the included RCTs
Tianyang Dai	daitianyang12345@163.com	Author of recent meta-analysis of sedation for bronchoscopy
Igor Braga Ribeiro	igorbraga1@gmail.com	Author of recent meta-analysis of sedation for endoscopy
Ji-Feng Feng	604282082@qq.com	Author of recent meta-analysis of dexmedetomidine for sedation
Lukas Kreienbühl	lukas.kreienbuehl@helios-gesundheit.de	Author of systematic review of patient-controlled sedation

Potential reviewer	Email address	Reason/Expertise
Basavana Gouda	goudrab@uphs.upenn.edu	Author of systematic review of non-anaesthesia provided sedation
Hyuk Lee	leehyuk@skku.edu	Author of systematic review of BIS monitoring for sedation
Yan Zheng	Yan_Zheng88@163.com	Author of systematic review of propofol for colonoscopy
Douglas G. Adler	Douglas.Adler@hsc.utah.edu	Author of systematic review of propofol for colonoscopy

Regards,



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