National Essential Medicine List
Paediatric Hospital Level Medication Review Process
Component: Anaesthetics

MEDICINE REVIEW
TITLE: Clonidine as pre-medication for paediatric patients undergoing surgery.
DATE: June 2022

Key findings

- Midazolam is currently listed in the Paediatric Hospital Level Standard Treatment Guidelines (STGs) as the first line premedication agent for paediatric patients undergoing surgery. Ketamine is listed as an alternative.
- Clonidine is potential alternative and is sometimes preferred as a premedication in private sector and internationally due to its safety profile, especially where midazolam is contraindicated.
- The current EML listing of ketamine for this indication is historical and there are no head-to-head studies comparing clonidine and ketamine and very limited evidence available comparing midazolam and ketamine. We conducted a review of systematic reviews, meta-analyses, and randomized controlled trials comparing clonidine and midazolam as premedication for paediatric patients undergoing surgery.
- We identified ten studies (one Cochrane systematic review, and seven randomised controlled trials and two open label trials). The Cochrane review did not include any of the higher-ranking outcomes (hierarchy of outcomes), thus the evidence obtained from the trials are reported first.
- Most studies included had very small sample sizes and evidence assessed to be of low or very low quality. Overall, we are uncertain if oral clonidine or oral midazolam are superior in terms of efficacy:
- Findings from the trials (RCTs and open label), comparing oral clonidine (4 µg/kg) and oral midazolam (0.5mg/kg):

  Sedation – We found that there may be little or no difference between midazolam and clonidine for mean time in minutes to onset of sedation (MD 8.5 minutes longer for clonidine 95% [1.43 – 15.57 minutes higher]; level of sedation on paediatric sedation scales assessed 60 minutes post-administration (SMD 0.15 points lower level of sedation for clonidine 95% CI [-2.5 points lower to 2.8 points higher]); number achieving adequate sedation 60 minutes post-administration (RR 1.59, 95% CI [0.17 to 14.51] and prior to induction (RR 1.31, 95% CI [1.07 to 1.61]. There may be a little difference in level of sedation on paediatric sedation scales assessed prior to induction (1 RCT reported median difference in favour of clonidine and another RCT reported a mean difference in favour of clonidine).

  Mask acceptance – We found that there may be little or no difference in mask acceptance between clonidine and midazolam: The number achieving satisfactory mask induction/acceptance (RR 0.88, 95% CI [0.73 to 1.04], and level of mask acceptance assessed with paediatric scales (1 RCT reported a median difference in favour of midazolam and another RCT a median difference in favour of clonidine).

  Parental separation – We found that there may be a little difference in parental separation between midazolam and clonidine: The percentage of children with satisfactory parental separation (RR 0.89, 95% CI [0.72 to 1.1].

  Anxiety – We found that there may be little or no difference between clonidine and midazolam in time in minutes to onset of anxiolysis (MD 3 minutes longer for clonidine, 95% CI [0.36 to 6.36 minutes]); and number achieving satisfactory anxiolysis preoperatively (100% achieved for both groups in 2 RCTs, n=119). There may be a little difference in level of anxiety assessed on paediatric anxiety scales (3 RCTs reported a median or mean difference in favour of midazolam, n=254 and 1 RCT a median difference in favour of clonidine, n=30).

Emergence – We found that there may be little or no difference between midazolam and clonidine in percentage of children with emergence excitement (RR 0.39, 95% CI [0.18 to 0.88). There may be a little difference in level of emergence excitement on paediatric emergence excitement scales (One RCT reported a median difference in favour of midazolam (Median difference 0.5 points, n=134)); but mean time to emergence in favour of clonidine (MD 1.5 minutes shorter).

- Findings from systematic review (outcomes include not highest in our hierarchy), comparing oral clonidine (4 µg/kg) and oral midazolam (0.5mg/kg):

  Postoperative pain – The review reported oral clonidine may be superior to oral midazolam is use of rescue analgesia anytime postoperatively. However, there may be no difference between oral clonidine and midazolam in the number of children reported to be pain free in the post-anaesthesia recovery unit (PACU). *In order to be congruent with our quality assessment of the RCTs, assessed the included evidence and for imprecision and risk of bias thus we found that there may be little or no difference for both outcomes: analgesia requirements postoperatively (RR 0.25, 95% CI [0.09 to 0.71]) and number pain free in PACU (RR 1.83 95% CI [0.80 to 4.18]).*

  Postoperative shivering – The review reported that oral clonidine is probably superior to oral midazolam for postoperative shivering. *After assessment of the included evidence, we found that there may be a little difference between clonidine and midazolam in occurrence of postoperative shivering (RR 0.09, 95% CI [0.01 to 0.69].*

  Haemodynamic or respiratory changes requiring intervention – There may be a difference in the number of children requiring supplemental oxygen in PACU (RR 0.55, 95% CI [0.31 – 0.97]).

  Time to discharge: The review found that clonidine may be superior to midazolam in the mean time to discharge. *After assessment of the included evidence, we found that there may be a little or no difference between clonidine and midazolam in time to discharge from PACU (MD 9.85 minutes shorter for clonidine 95% CI [0.09 to 19.61 minutes lower].*

  Postoperative nausea and vomiting – The review reported there is probably no difference between clonidine and midazolam in incidence of post-operative nausea and vomiting (RR 0.67, 95% CI [0.32 to 1.40).

- The cost of clonidine per dose per child is comparable to that of midazolam, based on the current private sector Single Exit Price (SEP), and potentially lower if a 40% discount on the SEP is achieved. The cost of ketamine is comparable to midazolam and clonidine and potentially higher than clonidine if 40% discount of clonidine is achieved.
- The review concluded that there may be no difference between clonidine and midazolam as premedication. The expected cost of clonidine is comparable to or lower than midazolam and ketamine. Midazolam is contra-indicated in certain patient groups and there is limited evidence available for ketamine compared to either clonidine or midazolam thus it is proposed that clonidine be added to the EML/STG for this indication, as an alternative to midazolam. Clonidine may be the preferred option for children with behavioural disorders, autism spectrum disorder and obstructive sleep apnoea and for other conditions for which midazolam is contraindicated. Ketamine is currently widely accepted and been included historically thus it is proposed that in remain on the EML for use in exceptional cases such as the combative child.

Table 1: Summary of Findings Table – Seven key outcomes for clonidine compared to midazolam as premedication for paediatric patients undergoing surgery

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with oral midazolam	**Risk with Oral clonidine**			
Number of participants achieving adequate sedation prior to induction	483 per 1,000	**632 per 1,000** (517 to 777)	**RR 1.31** (1.07 to 1.61)	118 (2 RCTs)	⊕◯◯◯ Very low[a,b]
Number with satisfactory mask induction/acceptance	864 per 1,000	**761 per 1,000** (631 to 899)	**RR 0.88** (0.73 to 1.04)	119 (2 RCTs)	⊕◯◯◯ Very low[a,b]
% with satisfactory parental separation assessed with: Parental separation score	900 per 1,000	**800 per 1,000** (645 to 992)	**RR 0.8889** (0.7169 to 1.1021)	60 (1 RCT)	⊕⊕◯◯ Low[b]
Number of participants achieving adequate preoperative anxiolysis	1,000 per 1,000	**1000 per 1,000** (960 to 1,000)	**RR 1.00** (0.96 to 1.05)	119 (2 RCTs)	⊕◯◯◯ Very low[a,b]
% emergence agitation	286 per 1,000	**111 per 1,000** (51 to 251)	**RR 0.39** (0.18 to 0.88)	99 (2 RCTs)	⊕◯◯◯ Very low[b,c]
Additional postoperative analgesia at any time post-operatively	800 per 1,000	**200 per 1,000** (72 to 568)	**RR 0.25** (0.09 to 0.71)	30 (1 RCT)	⊕◯◯◯ Very low[a,b]
Haemodynamic or respiratory changes requiring intervention	371 per 1,000	**204 per 1,000** (115 to 360)	**RR 0.55** (0.31 to 0.97)	134 (1 RCT)	⊕⊕◯◯ Low[b]

***The risk in the intervention group** (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; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardised mean difference

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

Explanations

a. Downgraded by two levels for risk of bias: Open label trial where patients were not blinded, and no methods described for blinding of outcome assessors.
b. Downgraded by two levels for imprecision: very small sample size
c. Downgraded by two levels for risk of bias: Open label trial where patients were not blinded, and no methods described for blinding of outcome assessors and the RCT did not provide final numbers per group.

1. Executive Summary: Clonidine, oral - Premedication for anaesthesia

Date: June 2022
Medicine (INN): Clonidine, oral
Medicine (ATC): N02CX02
Indication (ICD10 code): Premedication for anaesthesia
Patient population: Pre-anaesthesia paediatric patients in need of premedication
Prevalence of condition: n/a
Level of Care: Hospital level
Prescriber Level: Anaesthetist
Current standard of Care: Oral midazolam and oral ketamine
Efficacy estimates: (preferably NNT): See Summary of Findings Table (Table 1) for key outcomes
Motivator/reviewer name(s): Kim MacQuilkan, Anisa Bhettay, Ameer Hohlfeld, and Jane Riddin

2. Name of Reviewers

Ms Kim MacQuilkan, Dr A Bhettay, Mr A Hohlfeld, Dr Milli Reddy, Dr Jane Riddin

Acknowledgment – Dr T Kredo

3. Author Affiliation and Conflict of Interest Details

- Ms K MacQuilkan (Better Health Programme South Africa, Right to Care) has no interests to declare.
- Dr Bhettay: Department of Anaesthesia and Perioperative Medicine, Division of Paediatric Anaesthesia, Red Cross War Memorial Children's Hospital - Drafting of external guidelines for procedural sedation, bronchospasm, pain, malignant hyperthermia, local anaesthetic toxicity, regional anaesthesia – no financial benefit.
- Mr A Hohlfeld (Cochrane South Africa, South African Medical Research Council, SA GRADE Network) has no interests to declare.
- Dr J Ridden (Affordable Medicines Directorate, National Department of Health) has no interests to declare

Dr T Kredo (Cochrane South Africa, South African Medical Research Council (SAMRC) and Division of Clinical Pharmacology, Department of Medicine and Division of Epidemiology and Biostats, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University; TK is co-director of the South African GRADE Network) has no interests to declare.

4. Introduction/Background

Premedication prior to anaesthesia is needed to minimise distress for patients, families and clinicians. The goals of premedication are to produce anxiolysis, sedation, amnesia, analgesia, salivation reduction, vagolysis, sympathicolysis, to prevent post-operative nausea and vomiting, and reduce gastric secretion and acidity.[1] The Paediatric Standard Treatment Guidelines and Essential Medicines List (EML), 2017,[2] currently recommends using either oral midazolam (IV formulation used orally) or oral ketamine (IV formulation used orally) as premedication prior to anaesthesia. Due to varying onsets, durations of action, safety profiles and benefit with the various premedication prior to anaesthesia agents, alternative options are needed (See Table 1 below). In particular midazolam is contraindicated in children with known hypersensitivity to benzodiazepines, myasthenia gravis, severe respiratory depression, severe respiratory insufficiency and sleep apnoea syndrome.[3,4] There is a limited evidence base for ketamine however it was included historically and is currently widely utilised and accepted. Ketamine has analgesic properties in addition to its sedative and anxiolytic effects and does not cause respiratory depression (Table 1). It is useful in exceptional circumstances for the combative child as an IM where other routes are not possible.

Table 1: Comparison of clonidine, midazolam, ketamine[9,7,8,5,6]

Outcome	Clonidine	Midazolam	Ketamine
Analgesia	+	-	+
Sedation	+	++	++
Anxiolysis	++	++	++
Amnesia	-	+	-
Onset of action	Long	Intermediate	Intermediate
Duration of action	Long	Short	Intermediate
PONV	Decreased	Nil	Increased
Prolongation regional anaesthesia	+	-	-
Shivering	Decreased	No effect	No effect
Respiratory depression	Nil	Decreased	Nil
Secretions	No effect	No effect	Increased
Hypotension	-	+	-
Bradycardia	+	-	-
Tachycardia	-	-	+

PONV = postoperative nausea and vomiting; + & ++ = Extent of Effect; - = nil effect

Alpha agonists may have many potential benefits in this setting.[7,8] The two alpha agonists used perioperatively are clonidine and dexmedetomidine. Clonidine has been used in paediatric perioperative practice for many years, but recent literature has focused on dexmedetomidine, a more selective alpha agonist which offers a similar effect profile but is prohibitively expensive.[9] In a review by Bergendahl *et al.* (2006), the advantages of clonidine were listed as attenuation of haemodynamic response to tracheal intubation and surgical stimuli, reduced post-operative confusion after sevoflurane anaesthesia, no effect on respiration, no potentiation of opioid-induced respiratory depression, multiple routes of administration, no paradoxical excitation as compared to midazolam, prolongation of analgesia with regional anaesthesia and better acceptance.[5]

A systematic search of literature found no head-to-head studies for clonidine and ketamine as premedication for children undergoing surgery, thus the medicine review aims to compare the efficacy and safety of clonidine and midazolam. The relative costs of clonidine, midazolam and ketamine are also presented for consideration.

5. Purpose/Objective

Research Question

How effective and safe is oral clonidine compared to oral midazolam as pre-medication in paediatric patients undergoing surgery

Table 1. Scope of the technical review

Population	Pre-anaesthesia paediatric patients in need of premedication
Intervention/s and comparisons	Intervention: clonidine Comparator: midazolam
Outcomes	**Outcomes:** - Sedation at anaesthesia induction - Mask acceptance/induction - Separation from parents - Anxiety - Emergence agitation/delirium

	- Duration of emergence - Post-operative pain - Adverse effects/ adverse events - Post-anaesthesia care unit (PACU) stay - Post-operative nausea and vomiting (PONV).
Study designs	Systematic reviews, meta-analyses or randomized control trials (RCTs)

6. Methods

The review focused on the following study designs: randomized controlled trials (RCTs), systematic reviews and meta-analyses of RCTs. The search was conducted in Google Scholar, PubMed and Cochrane Library. The search strategies for the systematic literature searches in PubMed and the Cochrane Library are detailed in Appendix A. Disagreements regarding exclusion and inclusion of studies were handled through discussion. Data from included studies were extracted and analysed.[i] Studies were assessed for risk of bias[ii] and quality in collaboration (KM, JR, AH).[iii]

7. Results

Results of the search

Eighty-two publications were identified. Titles and abstracts were screened, exclusion principles from PICO were applied, and duplicates removed. Fifteen full text publications were reviewed. Two studies were excluded as they included adult patients (>18 years old); one study was excluded as it was a narrative review; one study was excluded due to incorrect dosage form; and one systematic review was excluded. However, it included one study that met the eligibility criteria for this medicine review which we have included into this report for further assessment. The ten sources included in the medicine review included one Cochrane review, seven randomised-controlled trials, and two randomised open label trials. Table 2 lists the excluded studies, and the findings of the included publications are outlined below in the narrative and summarised in Appendix B.

Table 2: List of Excluded Studies

No	Citation	Reason for exclusion
1	Bergendahl H, Lönnqvist PA, Eksborg S. Clonidine in paediatric anaesthesia: review of the literature and comparison with benzodiazepines for premedication. Acta Anaesthesiol Scand. 2006 Feb;50(2):135-43. doi: 10.1111/j.1399-6576.2006.00940.x. PMID: 16430532.	Not a systematic review
2	Dahmani S, Brasher C, Stany I, Golmard J, Skhiri A, Bruneau B, Nivoche Y, Constant I, Murat I. Premedication with clonidine is superior to benzodiazepines. A meta analysis of published studies. Acta Anaesthesiol Scand. 2010 Apr;54(4):397-402. doi: 10.1111/j.1399-6576.2009.02207.x. Epub 2010 Jan 18. PMID: 20085541.	Included individuals over 18 years.
3	Sanchez Munoz MC, De Kock M, Forget P. What is the place of clonidine in anesthesia? Systematic review and meta-analyses of randomized controlled trials. J Clin Anesth. 2017 May;38:140-153. doi: 10.1016/j.jclinane.2017.02.003. Epub 2017 Feb 17. PMID: 28372656.	Focused on adults.
4	Zhang C, Li J, Zhao D, Wang Y. Prophylactic midazolam and clonidine for emergence from agitation in children after emergence from sevoflurane anesthesia: a meta-analysis. Clin Ther. 2013 Oct;35(10):1622-31. doi: 10.1016/j.clinthera.2013.08.016. Epub 2013 Sep 25. PMID: 24075150.	Incorrect dosage form for clonidine group – IV.
5	A systematic review conducted by Hsu et al (2019) in September 2018 included 10 studies; n=9 included a qualitative analysis and n=10 a quantitative analysis. Clonidine was compared to either placebo or benzodiazepines in these trials .	Only one study matched the PICO and that study was included instead (Kumari et al. 2017).

[i] RevMan utilised to pool results where possible - Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020.

[ii] Higgins J P T, Altman D G, Gøtzsche PC, Jüni P, Moher D, Oxman A D et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials BMJ 2011; 343 :d5928 doi:10.1136/bmj.d5928

[iii] GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2021. Available from gradepro.org.

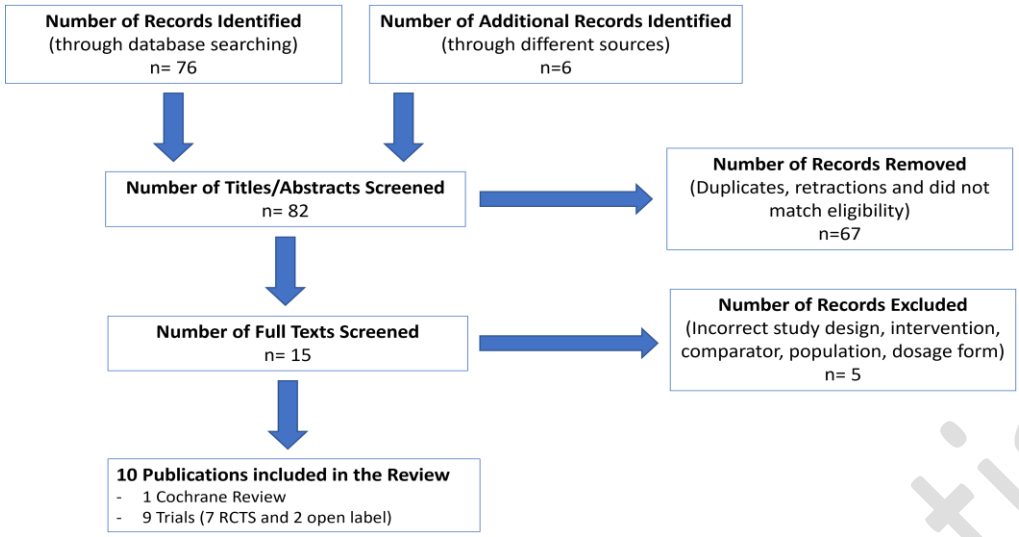


Figure 1: Prisma Diagram of Selection of Studies

Description of included studies

Ten publications were included in this review:

(1) A double-blinded, randomised control trial (RCT) by Bromfalk *et al*. (2020) on 84 children aged 2-6 years old. The RCT compared oral midazolam 0.5 mg/kg, oral clonidine 4 µg/kg and intranasal dexmedetomidine 2 µg/kg on outcomes of anxiety, mask compliance and sedation.[10]

(2) An open randomised trial by Almenrader *et al.* (2007) on 64 children aged 1-6 years old. The trial compared oral clonidine 4 µg/kg and oral midazolam 0.5 mg/kg and assessed drug acceptance, preoperative sedation and anxiolysis, quality of mask acceptance, recovery profile and parental satisfaction.[11]

(3) A double-blinded, RCT by Cao *et al* (2009)[12] on 45 children aged 2-8 years. The RCT compared oral clonidine 2 µg/kg, oral clonidine 4 µg/kg to oral midazolam 0.5mg/kg on outcomes of sedation, mask acceptance, parental separation, post-operative pain and postoperative nausea and vomiting (PONV).[iv]

(4) A double-blinded, RCT by Fazi *et a*l (2001)[13] on 134 children aged 4-12 years. The trial compared oral 4 µg/kg clonidine to oral midazolam and assessed mask acceptance/induction, parental separation, anxiety, postoperative pain, emergence agitation, duration of emergence, PACU stay and PONV.[iv]

(5) A double-blinded, RCT by Qteshat *et al* (2011)[14] on 54 children ages 6-14. The RCT compares oral 4 µg/kg clonidine to oral 0.5 mg/kg midazolam on postoperative pain, sedation, mask acceptance, anxiety, PONV and parental separation.[iv]

(6) An open label clinical trial by Schmidt *et al*. (2007)[15] on 60 children aged 7-12 years. The trial compared oral clonidine 4 µg/kg to oral midazolam 0.5 mg/kg on outcomes of sedation, anxiety, parental separation, emergence agitation, PACU stay and postoperative pain.[iv]

(7) A double-blinded RCT by Tazeroualti *et al*. (2007)[16] on 68 children aged 1-6 years. The RCT compared oral clonidine 4µg/kg to clonidine 2µg/kg and midazolam 0.5 mg/kg on emergence agitation, mask induction and adverse events[v]

(8) A prospective RCT by Trevor *et a*l (2012)[17] on 60 children aged 2-12 years. The trial compared oral clonidine (4 µg/kg) along with oral atropine 0.04 mg/kg to oral midazolam (0.5 mg/kg) along with oral atropine 0.04 mg/kg on outcomes of sedation and anxiety.[v]

[iv] This trial was included in the Lambert *et al*. Cochrane review thus only outcomes not covered in that review will be explored.

[v] This study was excluded from Lambert et al review as it did assess their primary outcome of post-operative pain

(9) A double-blinded RCT by Kumari *et a*l (2017)[18] on 90 children aged 4-12 years. The RCT compared oral clonidine 4 µg/kg to oral midazolam 0.5 mg/kg on outcomes of sedation, anxiety, parental separation, and mask acceptance.

(10) A Cochrane review by Lambert *et al*. (2014) investigated whether clonidine premedication provides pain relief after surgery in children. Eleven randomized controlled studies, (N=742 children), where clonidine (low and high dose) was compared to another medication or placebo were included up to December 2012.[19]

All studies included and excluded in the Lambert *et al.* (2014) Cochrane review were screened for relevance to this medicine review PICO. As the Cochrane review only focused on some of this review's outcomes (postoperative pain, post anaesthesia care unit (PACU) stay and adverse events), studies that evaluated other outcomes relevant to this review were included (sedation, mask acceptance, parental separation, anxiety, emergence agitation and PONV) but data was reported on those specific outcomes only to avoid any duplication.

Effectiveness and safety of the intervention

COMPARISON 1: 4 µg/kg (high dose) vs Midazolam 0.5 mg/kg

Sedation (6 trials, n=307)

- The evidence regarding the difference in sedation between clonidine and midazolam is uncertain (very low certainty of evidence for all outcomes under sedation except for sedation score prior to induction which was low certainty of evidence):

  - **Onset of sedation** – there may be little or no difference in mean time of onset of sedation in minutes between midazolam and high dose clonidine. One open label trial reported a lower mean in the midazolam group (MD: 8.5 minutes shorter, 95% CI [1.43 - 15.57], P = 0.035), *n=59 (very low quality)*[11].
  - **Outcome Peak sedative effect** – there may be no or little difference in mean time in minutes to peak sedative effect between midazolam and clonidine. One open label trial reported a lower mean in the midazolam group (MD 14.60 minutes shorter, 95% CI [7.44 - 21.76], P = 0.001), *n=59* (very *low quality)*[11].
  - **Mean score on sedation scale 60 minutes post-administration –** there may be little or no difference in sedation based on paediatric sedation scales an hour after administration. Two studies explored this outcome using different scales (Bromfalk et al. 2021[10] - RSS 6-point scale and Kumari et al. 2017[18] - 3-point sedation score). Pooled result higher sedation for midazolam (SMD 0.15 points higher 95% CI [-2.50 - 2.80], P=0.91, i^2=98%), n=114 (very *low quality)* – See Appendix C.
  - **Mean and median score on sedation scores prior to induction** – there may be a little difference between clonidine and midazolam for sedation prior to induction. Two studies reported mean or median on different sedation scales prior to induction. One RCT reported a higher mean score on a 3-point scale in favour of clonidine (MD 0.6 points higher, 95% CI [0.28 – 0.92], P < 0,05), n=30[12]. Another RCT also reported a higher median score on the RSS scale (6-point scale) in favour of clonidine (median difference 1 point higher, clonidine IQR 2-5 midazolam IQR 2-3, p < 0.001), n=54 (low quality)[10].
  - **Number of children achieving adequate sedation at 60 minutes post-administration** – there may be little to no difference in number of children achieving adequate sedation at 60 minutes. Two studies explored this outcome, pooled result in favour of clonidine(RR 1.59 95% CI [0.17, 14.51] – not significant, i^2 = 98%, n=120, [17,18] (very *low quality)* - See Appendix C.
  - **Number of children achieving adequate sedation prior to induction** – there may be little to no difference in number of children achieving adequate sedation prior to induction. Two studies explored this outcome, pooled result in favour of clonidine (RR 1.31 95% CI [1.07-1.61], i^2=0%, P=0.01), n=118 [11,17] (very *low quality)* - See Appendix C.

Mask acceptance/induction (4 trials, n=248)

- The evidence regarding the difference in mask acceptance/induction between clonidine and midazolam is uncertain (very low certainty of evidence for all outcomes):

  - **Mean difference in mask induction/acceptance scales –** There may be little or no difference in mask induction. Two studies explored this outcome however the scales utilised were different (scales size and in different directions), thus data could not be combined. One RCT reported a lower mean on the Induction Compliance Checklist in favour of midazolam (MD 1.2 points lower 95% CI [0.374 - 2.026], P = 0.87), *n=84)* [10]. Another RCT reported a higher mean on a 4-point scale in favour of clonidine (MD 1.5 points higher, CI not provided and could not be determined, p < 0.05), n=45 (very low quality)[12].
  - **Number achieving satisfactory mask induction/acceptance –** there may be little or no difference in number achieving satisfactory mask induction. Two studies explored this outcome and pooled result showed higher number for midazolam (RR 0.88 95% CI [0.73, 1.04], i^2=0%, P=0.14), n=119[11,18]:*(very low quality)* - See Appendix C.

Parental Separation (1 trial, n=60)

- The evidence regarding the difference in parental separation between clonidine and midazolam is uncertain (low certainty of evidence for outcome):

  - **Percentage of children with satisfactory parental separation –** there may a little difference between clonidine and midazolam in satisfactory parental separation. One RCT reported a higher number children with satisfactory parental separation for midazolam (RR 0.889, 95% CI [0.7169 - 1.1021], P=0.46), n=60 (low quality)[18].

Anxiety/Anxiolysis (5 trials, n=363)

- The evidence regarding the difference in anxiolysis between clonidine and midazolam is uncertain (very low certainty of evidence for all outcomes under anxiety except for anxiety score at time of parental separation which was low certainty of evidence):

  - **Onset of anxiolysis** – There may be little or no difference between clonidine and midazolam in onset of anxiolysis. One open label randomised study reported shorter time to anxiolysis (3 or more on an anxiety scale) for midazolam (MD 3 minutes 95% CI [-0.36 - 6.36], p>0.05), *n=59 (very low quality)*[11].
  - **Mean or median difference on an anxiety scale at time of parental separation** – There may be a little difference between midazolam and clonidine in anxiety at parental separation measured by different scales.[vi] One RCT reported a lower mean on the modified Yale Preoperative Anxiety Scale in favour of midazolam (MD 11.1 points 95% CI [4.097 - 18.103], P < 0.05), n= 134[13]. Another RCT also reported a lower mean but on a 4-point anxiety score in favour of midazolam (MD 0.27 points, 95% CI [0.1055 - 0.4345], P=0.018), n = 60[18]. One RCT reported a higher median for midazolam on a four-point scale where a higher score indicated better anxiolysis (Median difference 0.7 points, clonidine 2.7 IQR 1-4, and midazolam 3.4 IQR 1-4, P < 0.05), n=60[17]. One RCT reported a higher mean on a 3-point scale in favour of clonidine (MD 0.6 points, 95% CI [0.187- 1.013], P < 0.05), n=30[12](*low quality)*.
  - **Number with satisfactory anxiolysis before induction** – There may be little or no difference between clonidine and midazolam in achieving satisfactory anxiolysis prior to induction. Two studies explored

[vi] Four studies explored this outcome however scales utilised were very different and in opposite directions. Furthermore, some reported medians and others means thus due to time constraints were not meta-analysed

this outcome and in both studies all participants achieved adequate anxiolysis (RR 1.0 95% CI [0.96 – 1.05]; not significant), n=119 (very low quality)[11,18] – See Appendix C.

Emergence Agitation/excitement (3 trials, n=266)

- The evidence regarding the difference in emergence agitation/excitement between clonidine and midazolam is uncertain (very low certainty of evidence for % of participants with emergence agitation and low certainty of evidence for emergence excitement measured on a scale in PACU):

  - **Median difference for emergence excitement in Phase 1 PACU –** There may be a little difference between clonidine and midazolam in emergence excitement measured with a scale. One RCT reported a lower mean on a 5-point scale in favour of midazolam (Median difference 0.5clonidine 2.5 IQR 0-4 and midazolam 2 IQR 1-4, P < 0.05), n=134 (low quality)[Error! Bookmark not defined.].
  - **Percentage of participants with emergence agitation –** There may be little or no difference between clonidine and midazolam in percentage with emergence agitation. Two studies reported this outcome and both reported a lower percentage for clonidine (RR 0.39 95% CI [0.18 – 0.88], i^2=0%, P=0.02) , n=99 (very low quality)[13,16] – See Appendix C

Emergence Duration (1 trial, n=266)

- The evidence regarding the difference in emergence agitation between clonidine and midazolam is uncertain (low certainty of evidence for time to emergence):

  - **Median difference in time to emergence in minutes –** There may a bit little difference between clonidine and midazolam in time to emergence. One RCT reported a shorter time in minutes to emergence for clonidine (median difference 1.5 minutes, clonidine 7.2 IQR 4-9 and midazolam 8.7 IQR 3-9, P < 0.05), n=134 (low quality)[13].

Post-operative pain (Cochrane systematic review - 11 trials, n=742 children[19])

- The evidence regarding the difference in postoperative pain between clonidine and midazolam is uncertain (very low certainty of evidence):

  - **Additional postoperative analgesia at any time post-operatively** – there may be little or no difference between clonidine and midazolam for analgesia requirements postoperatively. The Cochrane review reported a higher need with midazolam ((RR 0.25, 95% [CI 0.09 - 0.71], P <0.05) – 1 trial, n=30 *(low certainty reported in Cochrane, considered very low quality in this medicine review)*[19].
  - **Number pain free in PACU –** there may be little or no difference between clonidine and midazolam in number of patients pain free in PACU. The Cochrane review reported higher numbers pain free for clonidine (RR 1.83 95% CI [0.80 - 4.18], P=0.15), 1 trial n=40 (very low quality)[19]) - See Appendix C.

Severe or mild adverse events (Cochrane systematic review - 11 trials, n=742 children[19])

- The evidence regarding the difference in adverse events between clonidine and midazolam is uncertain (low certainty of evidence for postoperative shivering and numbers requiring supplemental oxygen):

- **Postoperative shivering**: There may be a little difference between clonidine and midazolam in occurrence of postoperative shivering. The Cochrane review reported a pooled fewer number of patients with postoperative shivering for clonidine (RR 0.09 95% CI [0.01,0.69], i^2 = 0%, P=0.02, n=123 (low quality) – See Appendix C[19].
- **Haemodynamic or respiratory changes requiring intervention:** There may be a little difference in the number of patients between clonidine and midazolam in number of children requiring supplemental oxygen. The Cochrane review reported in one study that participants in the clonidine group had lower

cases requiring supplemental oxygen in PACU (RR 0.55 95% CI [0.31 - 0.97], P=0.05), 1 trial, n=134 (low quality). An RCT reported no significant difference in hypotension, bradycardia or respiratory depression - 1 trial, n=30)[19] – *very low quality*. Another RCT reported no events of hypotension of bradycardia in either group (n=54)[14].

Post-anaesthesia care unit (PACU) stay (Cochrane systematic review - 11 trials, n=742 children[19])

- The evidence regarding the difference in PACU stay between clonidine and midazolam is very uncertain (very low certainty of evidence):

- **Time to discharge from PACU** – There may be little or no difference between clonidine and midazolam in time to discharge in minutes. The Cochrane review reported a pooled lower mean in time to discharge in minutes for clonidine (MD -9.85 95% CI [-19.61 to -0.09], P <0.05), – *2 studies, n = 184 (very low certainty)*[19] - See Appendix C.

Post-operative nausea and vomiting (PONV)
(Cochrane systematic review - 11 trials, n=742 children[19] and 1 trial, n=60[18])

- The evidence regarding the difference in PONV between clonidine and midazolam is very uncertain (very low certainty of evidence):

- **Incidence of PONV:** There may be little or no difference between clonidine and midazolam in incidence of nausea or vomiting. The Cochrane review reported a pooled lower incidence of postoperative nausea and vomiting for clonidine (RR 0.67 95% CI[0.32 - 1.4], i^2=33.58%, P=0.29) – 3 trials, n = 184 (very low quality) – See Appendix C[19].

COMPARISON 2: 2 µg/kg (low dose) vs Midazolam 0.5 mg/kg

One RCT (Cao *et al*. 2009) and the Cochrane review reported findings on the lower dose of clonidine compared to midazolam. Cao *et al*. (2009) reported a higher mean on a 3-point sedation scale in favour of midazolam (MD 0.3 points, unable to estimate CI, P < 0,05), n=45 (very low quality)[12]. The same RCT also reported a higher mean on a 4-point mask induction assessment in favour of clonidine (MD 1.4 points, unable to estimate CI, p < 0.05), n=45 (very low quality)[12]. The Cochrane review reported less additional postoperative analgesia required for midazolam (RR 0.25, 95% CI [0.09 - 0.71], P <0.05), – *1 trial in the review, n=30 patients* (*low quality evidence)*[19].

8. Evidence Quality

All studies were assessed for risk of bias (See Appendix B) and outcomes assessed with GRADE (See Summary of findings table – Appendix D). Risk of bias was considered not serious in 4 of the studies, serious in 2 of the studies and very serious in 3 of the studies (outcomes not fully reported and/or randomisation and allocation concealment not fully described, assessors of outcomes not reported). All studies had very small samples sizes resulting in downgrading for serious imprecision. There was some unexplained heterogeneity in the outcomes. Population and settings for studies were quite different however it could not be determined for certain if this could explain the difference in results. Overall certainty in the evidence was assessed to be low to very low.

9. Alternative agents

Dexmedetomidine is also an alternative, but its cost precludes consideration at this point.

10. Cost Comparison

Table 5: Costing of oral clonidine and oral midazolam per dose

Agent	Strength		Pack Size		Cost	Price per tablet/mL	Dose	Dose in 15 kg child		Number of tabs/mL#	Cost per dose
Clonidine	0.025	mg	100	Tablets	R268.37*	R2.68	0.003-0.005mg/kg	0.06	mg	2.5	R6.70
										3~	R8.04
Midazolam	5	mg	5	ml	R5.75^	R1.15	0.5mg/kg	7.5	mg	10	R11.50
	5	mg	5	ml	R6.21***	R1.24	0.5mg/kg	7.5	mg	10	R12.42
	50	mg	10	ml	R19.25**	R.1.93	0.5mg/kg	7.5	mg	7.10	R19.25
	15	mg	3	ml	R7.50**	R2.50	0.5mg/kg	7.5	mg	7.3	R7.50
	15	mg	3	ml	R8.17***	R2.72	0.5mg/kg	7.5	mg	3	R8.17
Ketamine	100	mg/ml	10	ml	R78.43~	R7.84	3-5 mg/kg	60	mg	0.6	R4.71
	10	mg/ml	20	ml	R29.52~	R1.48	3-5 mg/kg	60	mg	6	R8.86
	50	mg/ml	10	ml	R39.22~	R3.92	3-5 mg/kg	60	mg	1.2	R4.71

**Item not on contract - Single Exit Price 2021 (incl VAT) (Menograine)*
*** MHPL March 2022, assumes vials are not shared (Pharma-Q)*
**** MHPL March 2022, assumes vials are not shared (Adcock)*
^MHPL March 2022, assumes vials are not shared (Accord)
 # assumed no vial sharing, ~ assumes wastage of half tablet
~ National Contact: RT297-2019 – Injections

Note: no current national contract is in place for clonidine oral tablets, thus only the Single Exit Price (SEP) is available. It can be expected that the contract price would be more favourable compared to SEP due to economies of scale. It is generally estimated as between 40-60% of SEP, see table below.

Table 6: Adjusted costing of oral clonidine and oral midazolam per dose

Agent	Strength		Pack Size		Cost	Price per tablet/mL	Dose	Dose in 15 kg child		Number of tabs/mL	Cost per dose
Clonidine	0.025	mg	100	Tablets	R107.35*	R1.07	0.003-0.005mg/kg	0.06	mg	2.5	R2.68
										3	R3.21
Clonidine	0.025	mg	100	Tablets	R161.02**	R1.61	0.003-0.005mg/kg	0.06	mg	2.5	R4.03
										3	R4.83

***40%** of Single Exit Price ****60%** of Single Exit Price*

Table 7: Current buyout price for oral clonidine

Agent	Strength		Pack Size		Cost	Price per tablet/mL	Dose	Dose in 15 kg child		Number of tabs/mL	Cost per dose
Clonidine	0.025	mg	100	Tablets	R228.73*	R2.29	0.003-0.005mg/kg	0.06	mg	2.5	R5.72
										3	R6.87

**Nelson Mandela Children's hospital current buy out price*

12. Discussion and Conclusion

Overall, the quality of evidence was low or very low, with small sample sizes in most trials. There may be little or no difference between midazolam and clonidine as premedication for paediatric patients undergoing surgery. Midazolam may potentially be superior for anxiolysis and mean time to sedation.

Clonidine potentially may have a better safety profile compared to midazolam and potentially superior in time to discharge, postoperative shivering as well as need for supplemental oxygen in the PACU. Clonidine thus may be superior for specific patient groups such as those with obstructive sleep apnoea where risk of respiratory depression is a concern as well as in patients in which midazolam is contraindicated. Ketamine was the historical recommended alternative and could be utilised in these patient populations however there are no head-to-head studies comparing ketamine and clonidine and limited exploring midazolam and ketamine. Ketamine is widely accepted and the only option in certain circumstances such as the combative child. The expected cost of clonidine is similar to midazolam, and potentially lower if a comparable discount on SEP is achieved. The cost of ketamine is comparable to clonidine and midazolam. It is thus proposed that clonidine be added as a recommended alternative agent to midazolam and ketamine be utlised in exceptional circumstances for example as IM for the combative child who refuses alternative routes of administration.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	2 open label studies and 7 RCTs, 1 Cochrane review. Overall quality of evidence was low to very low. *See Summary of Findings Table (Table 1 for seven main outcomes and Appendix D for all outcomes)*
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☒ None ☐	The size of effect for most outcomes were small or none between clonidine and midazolam. **Sedation** Number of participants achieving adequate sedation prior to induction (MD 8.5 minutes longer for clonidine 95% [1.43 – 15.57 minutes higher) **Mask Acceptance** The number achieving satisfactory mask induction/acceptance (RR 0.88, 95% CI [0.73 to 1.04] **Parental Separation** The percentage of children with satisfactory parental separation is probably not significantly different (RR 0.89, 95% CI [0.72 to 1.1]). **Anxiety** Number achieving satisfactory anxiolysis preoperatively (100% achieved for both groups in 2 RCTs, n=119) **Emergence** Percentage of children with emergence excitement (RR 0.39, 95% CI [0.18 to 0.88). **Postoperative pain** Additional postoperative analgesia at any time post-operatively (RR 0.25, 95% CI [0.09 to 0.71]) ***See Summary of Findings Table (Table 1 for main outcomes and Appendix D for all outcomes)***

QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High: [ ] Moderate: [ ] Low: [ ] Very low: [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	2 open label studies and 7 RCTs, 1 Cochrane review. Overall quality of evidence was low to very low. ***See Summary of Findings Table (Table 1 for seven main outcomes and Appendix D for all outcomes)***
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: [ ] Moderate: [ ] Small: [X] None: [ ]	**Haemodynamic or respiratory changes requiring intervention** Number of children requiring supplemental oxygen in PACU (RR 0.55, 95% CI [0.31 – 0.97]). **Postoperative shivering** Occurrence of postoperative shivering (RR 0.09, 95% CI [0.01 to 0.69]. **Time to discharge** Time to discharge from PACU (MD 9.85 minutes shorter for clonidine 95% CI [0.09 to 19.61 minutes lower] ***See Summary of Findings Table (Table 1 for main outcomes and Appendix D for all outcomes)***
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention: [ ] Favours control: [ ] Intervention = Control *or* Uncertain: [X]	There may be little or no difference between clonidine and midazolam as premedication but clonidine may be superior in terms of safety especially for certain patient populations in which respiratory depression is a concern and in which midazolam is contra-indicated.
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes: [X] No: [ ] Uncertain: [ ]	
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [ ] Uncertain/Similar: [X]	See cost comparison above. No current National Contract for clonidine. At full SEP prices are comparable. At 40% and 60% reduction in SEP, clonidine is less resource intensive.
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: [ ] Major: [ ] Uncertain: [X] **Is the option acceptable to key stakeholders?** Yes: [X] No: [ ] Uncertain: [ ]	Although no evidence is available on preferences and acceptability, clonidine is expected to be an acceptable alternative to existing options (where IV solutions are used off-label, administered orally).
EQUITY	**Would there be an impact on health inequity?** Yes: [ ] No: [X] Uncertain: [ ]	No expected impact on health equity

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☒	☐	☐

Recommendation

The Paediatric Hospital Level Expert Review Committee recommends adding clonidine to the Essential Medicines List for pre-medication for paediatric patients undergoing surgery as an alternative to midazolam, oral, especially in children in which midazolam is contra-indicated. Ketamine is recommended as an alternative to midazolam or clonidine only in exceptional circumstances.

Rationale:

There is insufficient evidence to show that there is a difference between clonidine and midazolam as premedication however clonidine may be favourable in specific patients due to its safety profile and midazolam is patients in which anxiolysis or time to onset of sedation is of highest concern. Agents are comparable in terms of costs. There is limited evidence to support ketamine as the alternative for midazolam and is recommended only for certain circumstances.

Level of Evidence:

Low to very low-quality trials and one good quality Cochrane review.

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
☐	X	☐

VEN status:

Vital	Essential	Necessary
☐	X	☐

Monitoring and evaluation considerations

Research priorities

Appendix A

Database: PubMed
Date: November 2021

Search	Query	Results
#1	(((clonidine[Title/Abstract]) AND (midazolam[Title/Abstract])) AND (preanesthetic medication[MeSH Terms])) AND (child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescenc*[Title/Abstract])	14
#4	(((clonidine[Title/Abstract]) AND (midazolam[Title/Abstract])) AND (preanesthetic medication[MeSH Terms])) AND (child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescenc*[Title/Abstract])	12
#5	(((clonidine[Title/Abstract]) AND (midazolam[Title/Abstract])) AND (preanesthetic medication[MeSH Terms])) AND (child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescenc*[Title/Abstract])	2
#6	(((clonidine[Title/Abstract]) OR (midazolam[Title/Abstract])) AND (preanesthetic medication[MeSH Terms])) AND (child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescenc*[Title/Abstract])	288
#9	(((clonidine[Title/Abstract]) OR (midazolam[Title/Abstract])) AND (preanesthetic medication[MeSH Terms])) AND (child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescenc*[Title/Abstract])	189
#10	(((clonidine[Title/Abstract]) OR (midazolam[Title/Abstract])) AND (preanesthetic medication[MeSH Terms])) AND (child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescenc*[Title/Abstract])	7
#21	((((clonidine[Title/Abstract]) OR (midazolam[Title/Abstract])) AND (surgery[Title/Abstract] OR operati*[Title/Abstract])) AND (anxioly*[Title/Abstract] OR sedati*[Title/Abstract])) AND (child*[Title/Abstract] OR adolscenc*[Title/Abstract] OR infan*[Title/Abstract])	399
#24	((((clonidine[Title/Abstract]) OR (midazolam[Title/Abstract])) AND (surgery[Title/Abstract] OR operati*[Title/Abstract])) AND (anxioly*[Title/Abstract] OR sedati*[Title/Abstract])) AND (child*[Title/Abstract] OR adolscenc*[Title/Abstract] OR infan*[Title/Abstract])	175
#25	((((clonidine[Title/Abstract]) OR (midazolam[Title/Abstract])) AND (surgery[Title/Abstract] OR operati*[Title/Abstract])) AND (anxioly*[Title/Abstract] OR sedati*[Title/Abstract])) AND (child*[Title/Abstract] OR adolscenc*[Title/Abstract] OR infan*[Title/Abstract])	17
#26	((((clonidine[Title/Abstract]) AND (midazolam[Title/Abstract])) AND (surgery[Title/Abstract] OR operati*[Title/Abstract])) AND (anxioly*[Title/Abstract] OR sedati*[Title/Abstract])) AND (child*[Title/Abstract] OR adolescenc*[Title/Abstract] OR infan*[Title/Abstract])	25
#29	((((clonidine[Title/Abstract]) AND (midazolam[Title/Abstract])) AND (surgery[Title/Abstract] OR operati*[Title/Abstract])) AND (anxioly*[Title/Abstract] OR sedati*[Title/Abstract])) AND (child*[Title/Abstract] OR adolescenc*[Title/Abstract] OR infan*[Title/Abstract])	12
#30	((((clonidine[Title/Abstract]) AND (midazolam[Title/Abstract])) AND (surgery[Title/Abstract] OR operati*[Title/Abstract])) AND (anxioly*[Title/Abstract] OR sedati*[Title/Abstract])) AND (child*[Title/Abstract] OR adolescenc*[Title/Abstract] OR infan*[Title/Abstract])	5

Database: Cochrane Library
Date: November 2021
Search Name: Clonidine versus midazolam
Date Run: 16/11/2021 11:55:33

ID	Search	Hits
#1	(clonidine):ti,ab,kw OR (midazolam):ti,ab,kw AND (child OR infant OR children OR adolescent):ti,ab,kw	6486
#2	MeSH descriptor: [Preanesthetic Medication] explode all trees	1728
#3	#1 AND #2	369
#4	#3 in Cochrane Reviews	3

APPENDIX B – Summary tables for included studies

The tables below summarise the evidence for the ten publications included in this review.

Characteristics of Included Studies (Systematic reviews)

Author, date	Type of study	N	Population	Comparators	Primary outcome	Effect sizes	Comments
Lambert et.al. 2014[19]	Cochrane Review	11 trials, 742 patients	Children < 18 years presenting for anaesthesia for surgical/ other invasive interventions	Clonidine versus placebo or midazolam, or in addition to fentanyl n=9 trials clonidine oral n=2 trials clonidine rectally	• Requirement of additional analgesia post-anaesthesia • Sedation requiring intervention • Secondary outcome – nausea and vomiting • Secondary outcome: time to discharge from PACU • Secondary outcome - haemodynamic or respiratory changes requiring intervention	*Need for additional analgesia was reduced* **Clonidine 4 µg/kg vs midazolam 0.5mg/kg**: RR 0.25, 95% CI 0.09 to 0.71 *(1 small study, n=30, P<0.05, NNT=2[14])* **Clonidine 4 µg/kg (high dose) vs clonidine 2 µg/kg (low dose):** RR 0.38, 95% CI 0.23 to 0.65 *(single higher-quality trial)* *Nausea and vomiting* **Clonidine 2 µg/kg vs midazolam 0.5mg/kg**: RR 0.27 [0.03,2.51] in favour of clonidine, P=0.25[14] (**not statistically significant**) **Clonidine 4 µg/kg vs midazolam 0.5mg/kg**: RR 0.67 [0.32,1.4] in favour of clonidine, P=0.29**Error! Bookmark not defined.** 16 **Error! Bookmark not defined.** (**not statistically significant**) *Time to discharge from PACU* **Clonidine 4 µg/kg vs midazolam 0.5mg/kg**: MD -9.85 [-19.61 to -0.09] in favour of clonidine, P=0.05 (*two studies low quality n=40**Error! Bookmark not defined.** and n=134[16]*). *Haemodynamic or respiratory changes requiring intervention* **Clonidine 4 µg/kg vs midazolam 0.5mg/kg**: One trial (n=30) no significant difference found between groups for hypotension, bradycardia and respiratory depression[14]. One trial (n=134) reported a statistically significant difference in need for supplemental	Risk of bias **low** or **unclear** in all except 2 studies which had **high risk of bias**. • **Allocation Bias** – adequate in 6 of 11 trials. • **Blinding** – adequate blinding of 8/11 trials. 2/11 trials had no information about binding. n=1 trial was open label • **Incomplete outcome data** – 8/11 accounted for missing outcome data • **Selective Reporting** – 10/11 studies reported the outcomes stated in the respective materials and methods section and 1 study – no information was available

Author, date	Type of study	N	Population	Comparators	Primary outcome	Effect sizes	Comments
						oxygen (RR 0.55, 95% CI 0.31 to 0.97, in favour of clonidine, p=0.05, NNT = 6[16])	

Characteristics of Included Studies (randomized trials)

Citation	Study design and methods	Population and setting	Intervention and comparison	Main outcomes of interest	Comments
Bromfalk et al. [10]	Randomised, double-blind, controlled trial	Children 2-6 years scheduled for elective ear-, nose-and-throat surgery	*Oral clonidine, 4 µg/ kg 60 min preoperatively* *OR* *Oral midazolam, 0.5 mg/kg 40 min preoperatively* *OR* *Intra-nasal dexmedetomidine 2 µg/kg 40 min preoperatively*	Anxiety modified Yale Preoperative Anxiety Scale (mYPAS) • During anaesthesia preparation, the mYPAS score increased significantly compared to the baseline in the clonidine group (p = 0.016) no change was observed in the midazolam group (no children had an increased score). Mask Induction/Acceptance Induction compliance checklist (ICC) • No significant difference found between the clonidine and midazolam groups for mask compliance (MID, 0.4 ± 1.3; CLO, 1.6 ± 1.7; p = .87) Sedation Ramsay sedation scale (RSS) • At 60 minutes after baseline clonidine group had a higher RSS score compared to the midazolam group (MID, 2.26 ± 0.45; C LO,3.56 ± 1.12; p < .001).	Limitations include: • Early termination of study • Small sample (90) ***Authors Conclusions:*** In preschool children aged 2–6 years, premedication with midazolam resulted in a more effective anxiolysis, thereby requiring less sedation compared with premedication with clonidine and dexmedetomidine. **Risk of Bias** ***Random Sequence Generation (Selection Bias)***: ''randomization function in Microsoft Excel, with randomization in blocks of 15'' – Low Risk ***Allocation Concealment (Selection Bias)***: ''Randomization was performed by opening a sequentially numbered envelope containing the group assignment'' – Low Risk ***Blinding of Participants and Personnel (Performance Bias)***: ''The interventions were triple-blinded; that is, blinded for the patient, care providers, and researchers.''– Low Risk ***Blinding of Outcome Assessment (Detection Bias)***: ''The interventions were triple-blinded; that is, blinded for the patient, care providers, and researchers".– Low Risk ***Incomplete Outcome Data (Attrition Bias)***: 3 subjects in each of the clonidine and midazolam groups refused medication and were not included in the analysis – (10% of clonidine group) - Low Risk ***Selection Reporting (Reporting Bias)***: All reported - Low Risk

Citation	Study design and methods	Population and setting	Intervention and comparison	Main outcomes of interest	Comments
					Other Bias: No other detected - **Low Risk**

Citation	Study design and methods	Population and setting	Intervention and comparison	Main outcomes of interest	Comments
Almenrader et al. [11]	Randomised, open trial	Children 1-6 years, scheduled for inguinal herniorrhaphy, hydrocele repair, circumcision, or orchidopexy	*Oral clonidine, 4 µg/ kg prior to induction* *OR* *Oral midazolam, 0.5 mg/kg prior to induction*	<u>Anxiety</u> 4-point anxiety score (1 = crying, very anxious, 2 = anxious, not crying, 3 = calm, but not cooperative, 4 = calm, cooperative or asleep). • No significant difference found between midazolam (29 children) and clonidine (30 children) groups for anxiolysis (score greater or equal to 3; p>0.05). <u>Mask Induction/Acceptance</u> 5-point scale (1 = combative, crying, 2 = moderate fear of the mask, not easily calmed, 3 = cooperative with reassurance, 4 = calm, cooperative, 5 = asleep, steal-induction). • A satisfactory mask induction was achieved in 86% of midazolam group and in 83% of clonidine group and there was no significant difference between groups (P=0.51). <u>Sedation</u> Onset of sedation and Peak sedative effect. Level of sedation 3-point scale (1 = awake, 2 = drowsy, and 3 = asleep). • The onset of sedation for the midazolam group was significantly shorter than for the clonidine group (30.0 ± 13.1; 38.5 ± 14.6; P = 0.035). • The peak sedative effect was significantly shorter in the midazolam group than in the clonidine group (31.4 ± 12.2; 46.0 ± 15.7; P = 0.001). • Level of sedation was significantly better in the clonidine group than in the midazolam group (90% of patients were asleep prior to induction compared with 10% and 24% of patients in the midazolam group remained awake, but none in clonidine group P < 0.0001). <u>Emergence agitation</u> 3-point scale (1 = agitated, crying, 2 = crying, but easily consoled, 3 = calm or asleep). No significant difference found between groups (P = 0.13).	Limitations include: • Lack of a blinded observer for evaluation of preoperative sedation and anxiolysis scores • Small Sample (n=64) ***Authors Conclusions:*** In conclusion, our data suggest that oral clonidine premedication has clinical advantages compared with oral midazolam premedication. Quality of mask induction was equally successful in both groups, but oral clonidine was better accepted by the child, produced more effective preoperative sedation, showed a trend towards a better recovery profile and had a higher degree of parental satisfaction. **<u>Risk of Bias</u>** ***Random Sequence Generation (Selection Bias)***: ''randomly assigned by a computer-generated list''– **Low Risk** ***Allocation Concealment (Selection Bias)***: Not described – **Unclear Risk** ***Blinding of Participants and Personnel (Performance Bias)***: open label - **High Risk** ***Blinding of Outcome Assessment (Detection Bias)***: open label - **High Risk** ***Incomplete Outcome Data (Attrition Bias)***: All participants completed - **Low Risk** ***Selection Reporting (Reporting Bias)***: All reported - **Low Risk** ***Other Bias***: No other detected - **Low Risk**

Citation	Study design and methods	Population and setting	Intervention and comparison	Main outcomes of interest	Comments
Cao *et al*. [12]	Double blind RCT	45 ASA I-II patients, aged 2-8 years, undergoing ventriculoperitoneal shunt insertion	*Oral clonidine, 2 µg/ kg prior to induction* *OR* *Oral clonidine, 4 µg/ kg prior to induction* *OR* *Oral midazolam, 0.5 mg/kg prior to induction*	<u>Sedation</u> 3-point preoperative sedation score (1 = crying and struggle, 2 = alert, 3 = drowsy) before induction • Mean was significantly higher in the oral clonidine *2 µg/kg and 4 µg/kg* groups compared to oral midazolam (*2 µg/kg* clonidine *m*ean 2.4 ± 0.6 and midazolam mean 2.1 ± 0.5; P < 0,05 in favour of clonidine & 4 *µg/kg* clonidine mean 2.7 ± 0.4 and midazolam 2.1 ± 0.5; P < 0.05 in favour of clonidine) <u>Mask acceptance/induction</u> 4-point scale for evaluation of mask acceptance (3): 1 = combative, angry, 2 = fear of the mask, not easily calmed, 3 = fear of the mask, easily calmed, 4 = calm, cooperative. • Mean was significantly higher in the oral clonidine *2 µg/kg and 4 µg/kg* groups compared to oral midazolam (*2 µg/kg* clonidine *m*ean 2.8 ± 0.8 and midazolam mean 1.4 ± 0.6; P < 0.05 in favour of clonidine & 4 *µg/kg* clonidine mean 2.9 ± 1 and midazolam 1.4 ± 0.6; P < 0.05 in favour of clonidine) <u>Anxiety at parental separation</u> 3-point scale: 1 = anxiety and struggle, 2 = anxiety, easily calmed, 3 = drowsy and calm. • Mean was significantly higher in the oral clonidine *2 µg/kg and 4 µg/kg* groups compared to oral midazolam (*2 µg/kg* clonidine *m*ean 2.1 ± 0.6 and midazolam mean 1.6 ± 0.5; P < 0,05 in favour of clonidine & 4 *µg/kg* clonidine mean 2.2 ± 0.6 and midazolam 1.6 ± 0.5; P < 0,05 in favour of clonidine)	Article included in Lambert et al study but on post-op outcomes included. Limitations include: • Small Sample (n=45) ***Authors Conclusions:*** Authors conclusion: In conclusion, in this study, premedication with oral clonidine appeared to be superior to oral midazolam. Oral clonidine premedication provided better sedation, anti-anxiety, postoperative analgesia, and prevented postoperative shivering with few adverse effects. **<u>Risk of Bias</u>** ***Random Sequence Generation (Selection Bias)***: Children randomised but not described – **Unclear Risk** ***Allocation Concealment (Selection Bias)***: Children randomised but not described – **Unclear Risk** ***Blinding of Participants and Personnel (Performance Bias)***: The premedication was mixed with 5 mL syrup, children - **Low Risk** ***Blinding of Outcome Assessment (Detection Bias)***: ''Assessment was performed by a consultant anaesthetist who had no knowledge of the type of premedication''. - **Low Risk** ***Incomplete Outcome Data (Attrition Bias)***: All participants completed - **Low Risk** ***Selection Reporting (Reporting Bias)***: All reported - **Low Risk** ***Other Bias***: No other detected - **Low Risk**

Citation	Study design and methods	Population and setting	Intervention and comparison	Main outcomes of interest	Comments
Fazi *et al*. [13]	Double blind RCT	134 ASA physical status I-II children, aged 4–12 yr, scheduled for tonsillectomy with or without adenoidectomy	*Oral clonidine 4 µg/kg 60–90 min and equal volume placebo 30 min before induction* *OR* *Placebo 60–90 min and oral midazolam 0.5 mg/kg (maximum 15 mg) 30 min before induction.*	<u>Anxiety</u> modified Yale Preoperative Anxiety Scale scores (higher more anxious) • Mean was significantly higher at parental separation in the oral clonidine group compared to oral midazolam (clonidine mean 38.9 ± 25 vs midazolam mean 27.8 ± 15.2; P < 0.05 in favour of midazolam). • Mean was significantly higher at induction in the oral clonidine group compared to oral midazolam (clonidine mean 42.9 ± 27.50 and midazolam 28.2 ± 16.2; P < 0.05 in favour of midazolam). <u>Emergence agitation</u> Modified CHEOPS (Children's Hospital of Eastern Ontario Pain Scale) – higher more agitation • Median was significantly higher in the oral clonidine group compared to oral midazolam (clonidine median 2.5 IQR 0-4 and midazolam 2 IQR 1-4, P < 0.05 in favour of midazolam). <u>Duration of emergence</u> • Median was significantly lower in the oral clonidine group compared to oral midazolam (clonidine median 7.2 IQR 4-9 and midazolam 8.7 IQR 3-9, P < 0.05 in favour of clonidine).	Article included in Lambert et al study but on post-op outcomes included. ***Authors Conclusions:*** In conclusion, clonidine did not offer a better recovery profile or an equivalent preoperative profile in comparison with oral midazolam under the conditions of this study. We would recommend the preferential use of oral midazolam as a preanesthetic medication in children undergoing tonsillectomy. <u>**Risk of Bias**</u> ***Random Sequence Generation (Selection Bias)***: ''Computer-generated random numbers table''– **Low Risk** ***Allocation Concealment (Selection Bias)***: Not described – **Unclear Risk** ***Blinding of Participants and Personnel (Performance Bias)***: ''Group A subjects received oral clonidine4 mg/kg (maximum 300 mg) 60–90 min and equal volume placebo 30 min before induction and Group B received placebo 60–90 min and oral midazolam 0.5 mg/kg (maximum 15 mg) 30 min before induction. The medications were diluted to a fixed volume by the pharmacist to maintain the double-blinded nature of the study'' – **Low Risk** ***Blinding of Outcome Assessment (Detection Bias)***: ''An observer blinded to the group assignment....'' - **Low Risk** ***Incomplete Outcome Data (Attrition Bias)***: All participants completed - **Low Risk** ***Selection Reporting (Reporting Bias)***: All reported - **Low Risk** ***Other Bias***: No other detected - **Low Risk**

Citation	Study design and methods	Population and setting	Intervention and comparison	Main outcomes of interest	Comments
Kumari *et al.* [18]	Double blind RCT	90 children age group of 4–12 years and the American Society of Anesthesiologists Physical status I, posted for ophthalmic surgery	*Oral clonidine, 4 µg/ kg* *OR* *Oral midazolam, 0.5 mg/kg*	<u>Sedation</u> Three-point scale: 1=awake, 2=drowsy, 3=asleep. • Mean sedation score at 30 minutes post-administration was significantly lower in the clonidine group compared to midazolam (clonidine mean 1.2 ± 0.45 vs midazolam 2.00 ± 0.26; P < 0.001 in favour of midazolam). • Mean sedation score at 60 minutes post-administration was significantly lower in the clonidine group compared to midazolam (clonidine mean 2.33 ± 0.55 vs midazolam 2.87 ± 0.3; P < 0.001 in favour of midazolam). • No significant difference between clonidine and midazolam group in number of children achieving adequate sedation at 60 minutes (parental separation) (clonidine n=29 vs midazolam n=30; P = 0.637). <u>Parental separation</u> the parental separation anxiety scale (PSAS): 1=Easy separation; 2=Whimper but easily reassured; 3=Cries and cannot be easily reassured, but not clinging to parents; 4=cries and clings to parents. • No significant difference found in number of children with acceptable separation (1 or 2) between clonidine and midazolam groups (clonidine 80%, midazolam 90%; P = 0.46). • Percentage of children with excellent parental separation was significantly lower in the clonidine group (clonidine 50%, midazolam 83.3%; P = 0.028 in favour of midazolam) <u>Anxiety</u> 5-point anxiety score: 1 = Quiet and comfortable; 2 =uneasy; 3=worried or anxious; 4=very worried or very upset; 5=frightened or terrified • Mean anxiety score at 30 minutes was significantly higher in the clonidine group compared to midazolam (clonidine mean 2.13 ± 0.77 vs midazolam 1.4 ± 0.49; P < 0.001 in favour of midazolam). • Mean anxiety score at 60 minutes was significantly higher in the clonidine group compared to midazolam (clonidine mean 1.27 ± 0.45 vs midazolam 1.00 ± 0; P < 0.018 in favour of midazolam). • Number participants with satisfactory score at 60 minutes (parental separation) prior to induction was no different between groups (all participants had a satisfactory score). No significant different in POV reported between groups.	Adverse events reported to be not significant but specific details not provided, article included in HSU et al. which was excluded. ***Authors Conclusions:*** We conclude that oral dexmedetomidine 4 µg/kg is comparable to oral midazolam 0.5 mg/kg and superior to oral clonidine 4 µg/kg for providing acceptable, separation from parents in children. All the three drugs were comparable for providing satisfactory mask acceptance. Oral midazolam was superior to the other two drugs for providing easy separation from parents and excellent mask acceptance in children. Oral midazolam had faster onset of sedation and provided higher sedation scores and lower anxiety scores as compared to the other two groups. All three drugs are safe and effective for premedication in children when given orally. **<u>Risk of Bias</u>** ***Random Sequence Generation (Selection Bias)***: ''Patients were randomly allocated by computer- generated random numbers to one of the three groups..''– **Low Risk** ***Allocation Concealment (Selection Bias)***: Not described – **Unclear Risk** ***Blinding of Participants and Personnel (Performance Bias)***: Double-blind study, IV agents were all mixed with apple juice, diluted to total volume of 0.2 ml/kg body weight, and given orally.- **Low Risk** ***Blinding of Outcome Assessment (Detection Bias)***: ''The anaesthesiologist who monitored the patient, scored the patient's behavior, and collected the data was blind to the study drug administered''. - **Low Risk** ***Incomplete Outcome Data (Attrition Bias)***: All participants completed - **Low Risk** ***Selection Reporting (Reporting Bias)***: All outcomes reported, granular data on adverse events not reported but was not a primary or secondary outcome.- **Low Risk** ***Other Bias***: No other detected - **Low Risk**

Citation	Study design and methods	Population and setting	Intervention and comparison	Main outcomes of interest	Comments
Qteshat *et al*. [14]	Double blinded RCT	54 children ages 6-14, presenting for tonsillectomy	*Oral clonidine, 4 µg/kg* *OR* *Oral midazolam, 0.5 mg/kg*	<u>Parental separation</u> The average time from the administration of oral clonidine and midazolam to separation from parents was 65 and 38 minutes respectively – no P value reported. <u>Adverse events</u> • There were no clinically significant episodes of bradycardia or hypotension in either group. • Intraoperative averages of the mean blood pressure were significantly decreased in the clonidine group. No p value provided No outcomes could be included in the medicine review due to insufficient details reported.	• Not all outcomes reported. • Article included in lambert for post-operative pain. • Small Sample (n=54) ***Authors Conclusions:*** Oral midazolam was superior to clonidine in relieving preoperative anxiety and shortening the time of separation from parents. Clonidine decreased the incidence of emesis and shortened the duration of surgery and anesthesia **<u>Risk of Bias</u>** ***Random Sequence Generation (Selection Bias)***: Stated that it is a randomised trial but methods not described– **Unclear Risk** ***Allocation Concealment (Selection Bias)***: Not described – **Unclear Risk** ***Blinding of Participants and Personnel (Performance Bias)***: Not described – **Unclear Risk** ***Blinding of Outcome Assessment (Detection Bias)***: Not described – **Unclear Risk** ***Incomplete Outcome Data (Attrition Bias)***: Not described – **Unclear Risk** ***Selection Reporting (Reporting Bias)***: Two outcomes not reported - sedation and emesis – **High Risk** ***Other Bias***: No other detected - **Low Risk**

Citation	Study design and methods	Population and setting	Intervention and comparison	Main outcomes of interest	Comments
Schmidt et al. [15]	Randomised, open trial	60 ASA I-II children, 7-12 years old, undergoing general or combined general/regional anaesthesia for various surgeries.	*Oral clonidine, 4 µg/ kg prior to induction* *OR* *Oral midazolam, 0.5 mg/kg prior to induction* *OR* *transmucosal dexmedetomidine (DEX)*	<u>Sedation</u> Sedation [a four-point scale: (i) none, angry, or crying; (ii) slight, awake but calm; (iii) moderate, responding to verbal commands; and (iv) intense, sleepy] • No significant difference found in median sedation score before induction between clonidine and midazolam groups (clonidine median 2.5 IQR 2-5 vs midazolam 2 IQR 1.5-2.5). <u>Parental separation</u> Separation from parents [(i) very difficult; (ii) restlessness; (iii) realizing the separation without restlessness; and (iv) does not realize, remaining calm]. • Data points not provided but reported that no significant difference was found <u>Anxiety</u> State-Trait Anxiety Inventory for Children (STAIC) postoperatively emergence agitation • No significant difference found in mean for clonidine compared to midazolam (clonidine mean 27.6 ± 5.9 vs midazolam 31.7 ± 10.3; P = 0.35).	Article included in Lambert SR for postoperative pain. Limitations include: • Open label • Small Sample (n=60) ***Authors Conclusions:*** These findings indicate that children receiving clonidine or DEX preoperatively have similar levels of anxiety and sedation postoperatively as those receiving midazolam. However, children given a2-agonists had less perioperative sympathetic stimulation and less postoperative pain than those given midazolam. **<u>Risk of Bias</u>** ***Random Sequence Generation (Selection Bias)***: ''Randomization was performed according to a computer-generated random list''.– **Low Risk** ***Allocation Concealment (Selection Bias)***: Open label – **High Risk** ***Blinding of Participants and Personnel (Performance Bias)***: open label - **High Risk** ***Blinding of Outcome Assessment (Detection Bias)***: open label - **High Risk** ***Incomplete Outcome Data (Attrition Bias)***: All participants completed - **Low Risk** ***Selection Reporting (Reporting Bias)***: All outcomes reported, only one outcome emergence agitation didn't provide granular detail stating just that no significant difference was found - **Low Risk** ***Other Bias***: No other detected - **Low Risk**

Citation	Study design and methods	Population and setting	Intervention and comparison	Main outcomes of interest	Comments
Tazeroualti et al. [16]	Double blinded RCT	68 ASA I–II children undergoing circumcision	*Oral clonidine, 2 µg/ kg* *OR* *Oral clonidine, 4 µg/ kg* *OR* *Oral midazolam, 0.5 mg/kg*	Mask induction • Percentage of participants categorised to have had 'good' quality mask induction was significantly better in midazolam group compared to both clonidine groups (midazolam 70%, clonidine *2 µg/kg 50%* and 4 *µg/kg* 30%; P=0.041 in favour of midazolam however actual data points not provided) Emergence agitation • Percentage of children with emergence agitation in the first hour after surgery significantly less in the higher dose clonidine group compared to midazolam however not in the lower dose clonidine group (clonidine *2 µg/kg 40%,* 4 *µg/kg* 25% vs midazolam 60%; P=0.025 in favour of high dose clonidine however actual data points not provided) • Percentage of children displaying agitation for >15 min during the first hour after post-anaesthetic care unit admission significantly less in the higher dose clonidine group compared to midazolam however not in the lower dose clonidine group (clonidine *2 µg/kg 30%,* 4 *µg/kg* 20% vs midazolam 50%; P=0.025 in favour of high dose clonidine however actual data points not provided)	Article excluded from Lambert SR as it did not include post-operative pain. Limitations include: • Actual numbers in each group not provided • Small Sample (n=68) ***Authors Conclusions:*** In conclusion, oral clonidine 4 mg kg21 administered 30 min before sevoflurane anaesthesia in preschool children significantly reduced emergence agitation. Further studies are required to define the optimal time of administration of clonidine in order to produce adequate sedation at the time of anaesthetic induction. **Risk of Bias** ***Random Sequence Generation (Selection Bias)***: Randomisation but method not described – **Unclear Risk** ***Allocation Concealment (Selection Bias)***: ''An anaesthesiologist not involved in the clinical protocol prepared the randomization envelopes. For each child included in the study, the anaesthesiologist responsible for the protocol (NT) drew the sealed envelope and administered the premedication''. – **Low Risk** ***Blinding of Participants and Personnel (Performance Bias)***: ''This premedication was mixed with3–5 ml of syrup''.- **Low Risk** ***Blinding of Outcome Assessment (Detection Bias)***: ''An independent observer evaluated the child in the recovery room for 2 h after surgery...'' - **Low Risk** ***Incomplete Outcome Data (Attrition Bias)***: ''Sixty-eight children were enrolled in this study. Seven children were excluded because of ineffective penile block at the time of incision and one child because of a study protocol violation''. However final numbers per group not described - **Unclear Risk** ***Selection Reporting (Reporting Bias)***: Outcomes reported however final numbers per group not provided- **Unclear Risk** ***Other Bias***: No other detected - **Low Risk**

Citation	Study design and methods	Population and setting	Intervention and comparison	Main outcomes of interest	Comments
Trevor et al. [17]	Prospective, randomized, observational study	60 ASA class I and II between the age group of 2-12 years scheduled for elective surgery	*Oral clonidine, 4 µg/ kg along with oral atropine 0.04 mg/kg* *OR* *Oral midazolam, 0.5 mg/kg along with oral atropine 0.04 mg/kg*	Sedation 4-point sedation score (1=alert, 2=awake, 3=drowsy, 4=asleep) 3 or 4 = adequate sedation • Number of children with adequate sedation at the time of parental separation was significantly lower in the clonidine group compared to midazolam (clonidine n=24 vs midazolam n=9; P<0.001 in favour of clonidine). • Number of children with adequate sedation at time of induction was significantly higher in the clonidine group compared to midazolam (clonidine n=8 vs midazolam n=6; P<0.05 in favour of clonidine). Anxiety 4-point score, 1=poor (afraid and agitated and difficult to control, panicky), 2=fair (fearful, moderate apprehension, moaning), 3=good (slightly apprehensive, but withdrawn from the surroundings), 4=excellent (no fear, calm and sleepy, friendly) • Median anxiety score at parental separation significantly lower in the clonidine group compared to midazolam (clonidine median 2.7 IQR 1-4 vs midazolam 3.4 IQR 1-4; P < 0.05 in favour of midazolam) • Median anxiety score at mask induction significantly lower in the clonidine group compared to midazolam (clonidine 3 IQR 1-4 vs midazolam 3.4 IQR 1-4; P < 0,05 in favour of midazolam)	Article excluded from Lambert SR as did not include Post-operative pain. Limitations include: • Small Sample (n=60) ***Authors Conclusions:*** We conclude that under the conditions of the study, oral midazolam is superior to clonidine as an anxiolytic in pediatric population. Clonidine with its sedative action especially at the time of separation from parents along with its other perioperative benefits cannot be discounted. **Risk of Bias** ***Random Sequence Generation (Selection Bias)***: Randomisation but method not described– **Unclear Risk** ***Allocation Concealment (Selection Bias)***: Not described – **Unclear Risk** ***Blinding of Participants and Personnel (Performance Bias)***: ''The medications were diluted to a fixed volume with honey to mask the bitter taste by the pharmacist to maintain the double-blinded nature of the study''. - **Low Risk** ***Blinding of Outcome Assessment (Detection Bias)***: Not described – **Unclear Risk** ***Incomplete Outcome Data (Attrition Bias)***: All participants completed - **Low Risk** ***Selection Reporting (Reporting Bias)***: All reported - **Low Risk** ***Other Bias***: No other detected - **Low Risk**

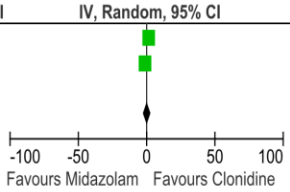
APPENDIX C - FOREST PLOTS

Oral clonidine high dose 4µg/kg compared to oral midazolam 0.5mg/kg

Mean sedation score on a scale 60 minutes post-administration (pooled in RevMan 5.4)

Study or Subgroup	Experimental - Clonidine Mean	SD	Total	Control - Midazolam Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bromfalk2021	3.56	1.12	27	2.26	0.45	27	49.9%	1.50 [0.89, 2.11]
Kumari2017	2.33	0.55	30	2.87	0.3	30	50.1%	-1.20 [-1.76, -0.65]
Total (95% CI)			57			57	100.0%	0.15 [-2.50, 2.80]

Heterogeneity: Tau² = 3.57; Chi² = 41.51, df = 1 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.11 (P = 0.91)

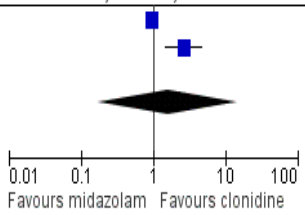


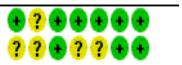
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Number achieving adequate sedation 60 minutes post-administration (pooled in RevMan 5.4)

Study or Subgroup	Experimental - Clonidine Events	Total	Control - Midazolam Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumari2017	29	30	30	30	50.8%	0.97 [0.88, 1.06]
Trevor2012	24	30	9	30	49.2%	2.67 [1.50, 4.74]
Total (95% CI)		60		60	100.0%	1.59 [0.17, 14.51]
Total events	53		39			

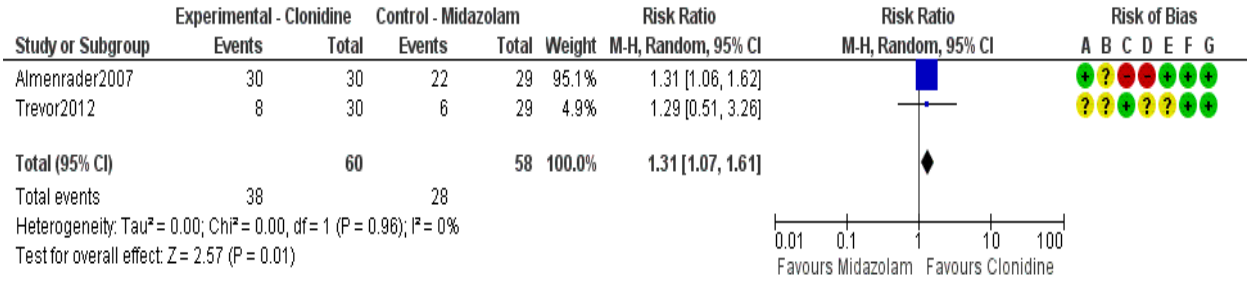
Heterogeneity: Tau² = 2.50; Chi² = 57.60, df = 1 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.41 (P = 0.68)





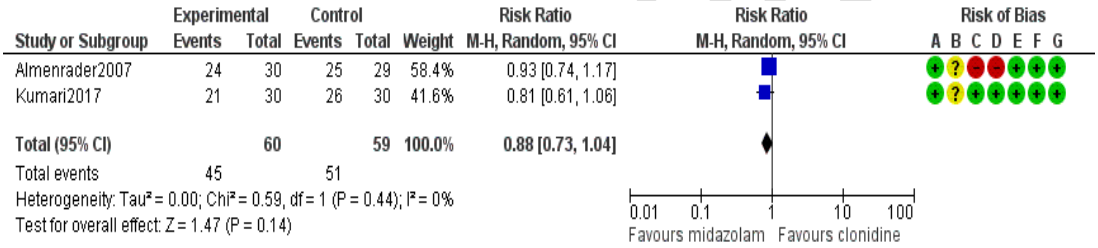
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Number achieving adequate sedation at induction (pooled with RevMan 5.4)



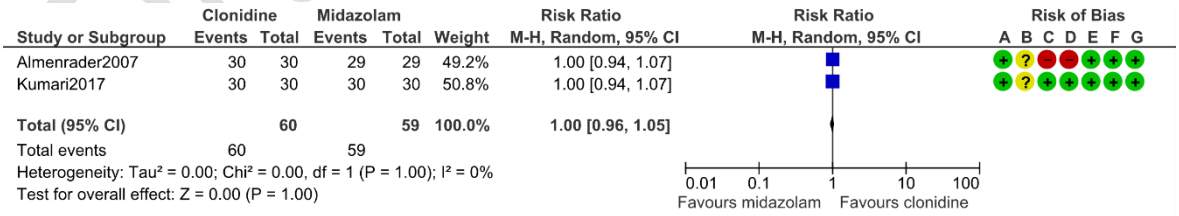
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Number achieving satisfactory induction/mask compliance (pooled in RevMan 5.4)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

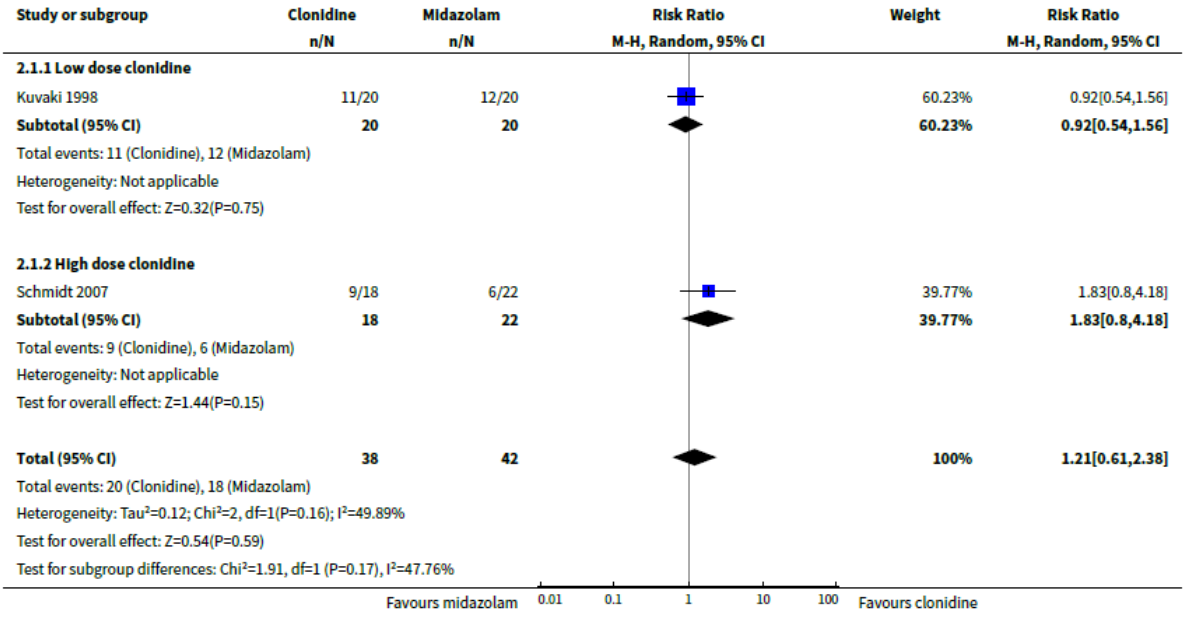
Number achieving adequate anxiolysis prior to induction (pooled in RevMan 5.4)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

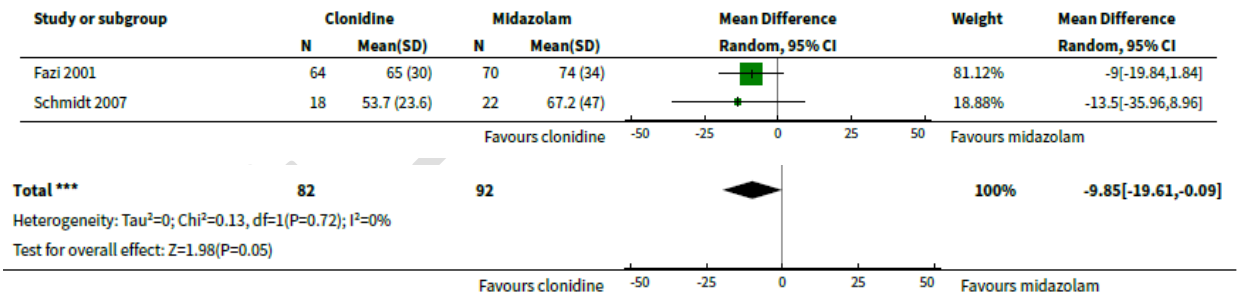
Number pain free in PACU for postoperative pain (From Cochrane Review)

Analysis 2.1. Comparison 2 Clonidine versus midazolam, Outcome 1 Number pain-free in PACU.



Time to discharge from PACU (From Cochrane Review)

Analysis 2.4. Comparison 2 Clonidine versus midazolam, Outcome 4 Time to discharge from PACU.



APPENDIX D – Summary of Findings Table for all Outcomes

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with oral midazolam	**Risk with Oral clonidine**			
Mean time to onset of sedation in minutes	-	MD **8.5 minutes higher** (1.43 higher to 15.57 higher)	-	59 (1 RCT)	⊕◯◯◯ Very low[a,b]
Peak sedative effect in minutes	-	MD **14.6 higher** (7.44 higher to 21.76 higher)	-	59 (1 RCT)	⊕◯◯◯ Very low[a,b]
Mean score on a sedation scale 60 minutes post administration - assessed with: sedation scales	-	SMD **0.15 higher** (2.5 lower to 2.8 higher)	-	114 (2 RCTs)	⊕◯◯◯ Very low[b,c]
Mean or median score on a sedation scale prior to induction - assessed with: Sedation scales	Studies were not meta-analysed due to time constraints as one reported a median and the other a mean. Total numbers 84 (42 in each group) Cao et al. 2009: n=30, mean difference 0.6 on a 3-point scale (in favour of clonidine) 95% CI [0.28 – 0.92], P < 0,05) Bromfalk et al. 2021: n=54, median difference of 1 on the RSS 6-point scale (in favour of clonidine) clonidine IQR 2-5 midazolam IQR 2-3, p < 0.001			84 (2 RCTs)	⊕⊕◯◯ Low[b]
Number of participants achieving adequate sedation at 60 minutes	650 per 1,000	**1000 per 1,000** (111 to 1,000)	**RR 1.59** (0.17 to 14.51)	120 (2 RCTs)	⊕◯◯◯ Very low[b,d]
Number of participants achieving adequate sedation prior to induction	483 per 1,000	**632 per 1,000** (517 to 777)	**RR 1.31** (1.07 to 1.61)	118 (2 RCTs)	⊕◯◯◯ Very low[a,b]
Mean difference in mask induction on induction scales	Studies were not meta-analysed due to time constraints as scales utilised were different, numbered in different directions and studies reported with a mean or median. Total numbers 84 (42 in each group) Bromfalk et al. 2021: n=54, median difference of 1.2 points on ICC 10-point scale (in favour of midazolam), 95% CI [0.374 - 2.026], p = 0.87Cao et al. 2009: n=30, median difference of 1.5 points on 4-point scale (in favour of clonidine), p<0.05.			(2 RCTs)	⊕◯◯◯ Very low[b,c]
Number with satisfactory mask induction/acceptance	864 per 1,000	**761 per 1,000** (631 to 899)	**RR 0.88** (0.73 to 1.04)	119 (2 RCTs)	⊕◯◯◯ Very low[a,b]
% with satisfactory parental separation assessed with: Parental separation score	900 per 1,000	**800 per 1,000** (645 to 992)	**RR 0.8889** (0.7169 to 1.1021)	60 (1 RCT)	⊕⊕◯◯ Low[b]
Onset of anxiolysis in minutes	-	MD **3 minutes higher** (0.36 lower to 6.36 higher)	-	(1 RCT)	⊕◯◯◯ Very low[a,b]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with oral midazolam	**Risk with Oral clonidine**			
Mean or median score on anxiety scale at time of parental separation assessed with different scales	Studies were not meta-analysed as scales utilised were different and numbered in different directions. Total numbers 284 (139 clonidine 145 midazolam) Fazi et al. 2001: n=134, MD of 11.1 points on modified Yale Preoperative Anxiety Scale (in favour of midazolam), 95% CI [4.097 - 18.103], P < 0.05) Kumari et al. 2017: n=60, MD 0.27 points on 4-point scale (in favour of midazolam), 95% CI [0.1055 - 0.4345], P=0.018). Trevor et al. 2012: n=60, Median difference of 0.7 points on a four-point scale (clonidine 2.7 IQR 1-4,and midazolam 3.4 IQR 1-4) in favour of midazolam, P < 0.05). Cao et al. 2009: n=30, MD of 0.6 points on a 3-point scale (in favour of clonidine), 95% CI [0.187- 1.013], P < 0,05)			194 (4 RCTs)	⊕⊕◯◯ Low[b,e]
Number of participants achieving adequate preoperative anxiolysis	1,000 per 1,000	**1000 per 1,000** (960 to 1,000)	**RR 1.00** (0.96 to 1.05)	119 (2 RCTs)	⊕◯◯◯ Very low[a,b]
Median difference on emergence excitement scale in PACU - assessed with 5-point scale	1 study, n=134 Median difference of 0.5 in favour of midazolam (clonidine 2.5 IQR 0-4 and midazolam 2 IQR 1-4), P < 0.05			134 (1 RCT)	⊕⊕◯◯ Low[b]
% emergence agitation	286 per 1,000	**111 per 1,000** (51 to 251)	**RR 0.39** (0.18 to 0.88)	99 (2 RCTs)	⊕◯◯◯ Very low[b,f]
Median difference in time to emergence	1 study n=134. Mean difference of 1.5 minutes in favour of clonidine (clonidine 7.2 IQR 4-9 and midazolam 8.7 IQR 3-9, P < 0.05)			134 (1 RCT)	⊕⊕◯◯ Low[b]
Additional postoperative analgesia at any time post-operatively	800 per 1,000	**200 per 1,000** (72 to 568)	**RR 0.25** (0.09 to 0.71)	30 (1 RCT)	⊕◯◯◯ Very low[a,b]
Number pain free in the PACU	273 per 1,000	**499 per 1,000** (218 to 1,000)	**RR 1.83** (0.80 to 4.18)	40 (1 RCT)	⊕◯◯◯ Very low[a,b]
Postoperative shivering	133 per 1,000	**12 per 1,000** (1 to 92)	**RR 0.09** (0.01 to 0.69)	123 (2 RCTs)	⊕⊕◯◯ Low[b]
Haemodynamic or respiratory changes requiring intervention	371 per 1,000	**204 per 1,000** (115 to 360)	**RR 0.55** (0.31 to 0.97)	134 (1 RCT)	⊕⊕◯◯ Low[b]
Time to discharge from PACU	-	MD **9.85 minutes lower** (19.61 lower to 0.09 lower)	-	174 (2 RCTs)	⊕◯◯◯ Very low[a,b]
Postoperative nausea and vomiting	215 per 1,000	**144 per 1,000** (69 to 302)	**RR 0.67** (0.32 to 1.40)	257 (3 RCTs)	⊕◯◯◯ Very low[a,b,g]

Explanations

a. Downgraded by two levels for risk of bias: Open label trial where patients were not blinded and no methods described for blinding of outcome assessors.
b. Downgraded by two levels for imprecision: very small sample size
c. Downgraded by one level for unexplained inconsistent results. One trial favours midazolam and one favours clonidine but there are also different age children undergoing different procedures - it is not clear which of these factors may impact the results.
d. Downgraded by one level for unexplained inconsistent results. One trial favours clonidine and one trial favours midazolam. The ages of the children were similar however undergoing different procedures - it is not clear if this may have impacted the results.
e. Decided not to downgrade as 3 out of the 4 results are consistent and the inconsistency of the one trial may be explained by the severity of the operation being undertaken (Cao et al. 2009).
f. Downgraded by two levels for risk of bias: Open label trial where patients were not blinded and no methods described for blinding of outcome assessors and the RCT did not provide final numbers per group.
g. Downgraded by one level for unexplained inconsistent results. Two trials favour clonidine and one trial favours midazolam. The ages of the children included differ and undergoing different operations - it is not clear if this may have impacted the results.

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