SYSTEMATIC REVIEW AND META-ANALYSIS

Safety of clonidine used for long-term sedation in paediatric intensive care: A systematic review

Sonja Eberl[1] | Gabriele Ahne[1] | Irmgard Toni[1] | Joseph Standing[2] 🔾 | Antje Neubert[1] 🔾

[1]Department of Paediatrics and Adolescents Medicine, University Hospital Erlangen, Erlangen, Germany

[2]UCL Great Ormond Street Institute of Child Health, University College London, London, UK

Correspondence
Antje Neubert, Department of Paediatrics and Adolescent Medicine, Paediatric Clinical Study Centre, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Loschgestrasse 15, 91054. Erlangen, Germany.
Email: antje.neubert@uk-erlangen.de

Funding information
FP7 Health, Grant/Award Number: 602453

Aim: Although not approved, the α-adrenoceptor agonist clonidine is considered an option for long-term sedation protocols in paediatric intensive care. We reviewed adverse effects of clonidine occurring in this indication.

Methods: Relevant literature was systematically identified from PubMed and Embase. We included interventional and observational studies on paediatric patients admitted to intensive care units and systemically long-term sedated with clonidine-containing regimes. In duplicates, we conducted standardised and independent full-text assessment and extraction of safety data.

Results: Data from 11 studies with 909 patients were analysed. The studies were heterogeneous regarding patient characteristics (age groups, comorbidity, or comedication) and sedation regimes (dosage, route, duration, or concomitant sedatives). Just four randomised controlled trials (RCTs) and one observational study had comparison groups, using placebo or midazolam. For safety outcomes, our validity evaluation showed low risk of bias only in three studies. All studies focused on haemodynamic problems, particularly bradycardia and hypotension. Observed incidences or subsequent interventions never caused concerns. However, only two RCTs allowed meaningful comparisons with control groups. Odds ratios showed no significant difference between the groups, but small sample sizes (50 and 125 patients) must be considered; pooled analyses were not reasonable.

Conclusion: All evaluated studies concluded that the use of clonidine in paediatric intensive care units is safe. However, a valid characterisation of the safety profile remains challenging due to limited, biased and heterogeneous data and missing investigation of long-term effects. This evaluation demonstrates the lack of data, which prevents reliable conclusions on the safety of clonidine for long-term sedation in critically ill children. For an evidence-based use, further studies are needed.

KEYWORDS
clonidine, critical care, paediatrics, sedation

1 | INTRODUCTION

In paediatric intensive care, effective sedation management is essential. Patients have to be sedated to facilitate mechanical ventilation and avoid unintentional self-extubation. It is also intended to improve analgesia, enable diagnostic and therapeutic procedures, or reduce the metabolic rate and oxygen demand. Moreover, there are psychological reasons, such as the reduction of distress and anxiety, less disturbed sleep, and a reduction in memory.[1] Among the drugs most commonly used for long-term sedation on paediatric intensive care units (PICUs) are benzodiazepines, opioids and α-**adrenoceptor** agonists.[2] Although the α-adrenoceptor agonist **clonidine** is not approved for sedation in children, it is regarded as a useful sedative or adjuvant. Unlike opioids or benzodiazepines, clonidine is assumed to cause little respiratory depression, does not interfere with natural sleep and there are no concerns about neurotoxic effects, tolerance and dependence.[2,3]

Since clonidine was first introduced as a drug in the 1960s, insights into its mechanism of action have been gained. By stimulating central α_2-adrenoreceptors it can induce sedation and analgesia. Other effects are hypotension and bradycardia. Its hypotensive properties are used therapeutically and it is approved as an antihypertensive for adults. In addition, hypothermia, changes in motor activity and increased regulation of attention and conditioned behaviour may also occur. The latter is the reason for its approval for treatment of attention-deficit hyperactivity disorder in the United States.[4–6] Further effects have also been identified inter alia on peripheral presynaptic α_2-adrenoreceptors, imidazoline binding sites and, if administered at high concentrations, on central α_1-adrenoreceptors.[7,8] Therefore, on the one hand, clonidine is promising for the sedation of paediatric intensive care patients but, on the other hand, other possible unwanted effects must also be considered when it is used as a long-term sedative agent in paediatric intensive care.

Guidelines have recommended clonidine as an alternative sedative agent to midazolam for a long time. However, in the British Consensus guidelines on sedation and analgesia in critically ill children from 2006 the authors indicated that this recommendation was based on a low level of evidence only.[9] In 2016, Barnes et al pointed out that recommendations for the use of clonidine in this indication are based on experience and best practice rather than on high-quality data.[2] In recent years, the available evidence regarding the efficacy of clonidine for long-term sedation has been systematically reviewed.[10–12] First, Chen et al found no eligible study in children.[12] In 2016, Hayden et al concluded that there is potential for the use of clonidine but called for further studies, especially dose finding studies, due to a lack of robust evidence.[10] In this systematic review, only randomised clinical trials were considered and safety profiles were only very briefly examined. The systematic review by Romantsik et al examined efficacy and safety in a population of newborn infants but did not identify any additional evidence.[11] Supplementary safety data from observational pharmacoepidemiological studies were not considered in either review.

The off-label use of clonidine in PICUs has been widely established[13–18] and recently an increase in its utilization in PICUs has been described.[19–21] Thus, although there is an urgent need we did not identify any study that systematically and comprehensively reviewed the literature on the safety of clonidine in paediatric intensive care medicine.

The eligibility of a drug – both for further studies and for off-label use – depends not only on its efficacy but also on its safety profile. Consequently we have initiated this review of available data on the safety profile of clonidine when used for long-term sedation in paediatric intensive care. Both clinical trials as well as pharmacoepidemiological studies should be considered, as the latter can also help to verify and quantify adverse effects. This assessment is intended to support clinical decisions in practice. In addition, it should also identify the need for further studies or assist in designing and implementing future clinical trials. The conduct of paediatric studies in intensive care is complex. On the one hand, ethical requirements have to be met, for example regarding the acceptable risks. On the other hand, the recruitment of patients is quite challenging. This was particularly an issue in the last large-scale planned clonidine studies (SLEEPS and CloSed)[22,23]. As a reason for the disappointing recruitment rates, Wolf et al[22] identified the reluctance of parents to provide consent and the reluctance of clinicians to accept sedation studies in unstable critically ill children. In this context, this comprehensive analysis of the safety profile of clonidine may help in the planning of future studies and enable informed decisions for participation.

The objective of this review is to assess the safety of clonidine used for long-term sedation in paediatric intensive care. We systematically examined the following research question: What are important adverse effects that should be considered as a consequence of long-term sedation with clonidine in children on intensive care units?

2 | METHODS

2.1 | Search strategy

Following our review protocol, we conducted systematic searches in the databases PubMed and Embase to identify relevant literature (primary search January 2019, last update February 2020). The predefined search strategy covered the combined aspects clonidine, sedation and children (see appendix). To obtain a comprehensive collection of literature, we did not limit the time, type or language of publications.

In addition, the reference lists of the included studies were scanned for further relevant studies. Previously published reviews containing the safety of clonidine used for paediatric long-term sedation were also screened. To address publication bias, we additionally searched the databases clinicaltrialsregister.eu, clinicaltrials.gov and the registers of the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished and ongoing trials.

2.2 | Eligibility criteria

We set appropriate inclusion criteria to assess the previously published safety profile and to determine the quantity of the risks of long-term sedation with clonidine in critically ill children. Following the advice of Loke et al, we included interventional studies (randomised

and nonrandomised controlled trials) as well as observational studies (retro- or prospective cohort studies or case control studies).[24,25]

The additional systematic identification of new types of adverse events by analysing case reports and spontaneous reporting databases exceeded the scope of this review. In addition, new findings regarding the spectrum of safety issues are unlikely as clonidine has been used since the 1960s for various indications and patient groups.

We identified studies which included paediatric patients (<18 years of age) who had been admitted to intensive care units. An inclusion criterion involved long-term sedation and mechanical ventilation (ie, actual or planned duration was more than 12 hours). One of the study drugs had to be clonidine for long-term sedation. In addition, the studies were required to report on the safety of clonidine (on at least one of the following aspects: adverse events as defined by the study authors, bradycardia, hypotension, or hypertension, serious adverse event, mortality, haemodynamic changes, delirium or coma, withdrawal symptoms). To focus on the correct indication, we excluded other indications such as procedural sedation, neonatal abstinence syndrome, palliative care, premedication for prevention of withdrawal syndrome and regional anaesthesia (intrathecal). We ensured that studies were performed on intensive care units and therefore excluded studies on different settings. There was no limit to the use of comedication or to dose and frequency of clonidine use. Likewise, there were no limitations regarding the comparison group: studies comparing clonidine with any standard sedative regimen or without a comparator were eligible. As long as a systemic therapy was intended, there was no restriction on the route of administration: intravenous infusion, intravenous boluses, enteral, oral or transdermal route were acceptable.

2.3 | Study identification, data collection and risk of bias assessment

After performing the database queries, one author vetted the titles and abstracts of the identified publications for eligibility. For each potentially relevant publication, the full article was evaluated by two reviewers using a screening checklist. Final inclusion of the studies was decided by consensus. Reasons for in- or exclusions were documented.

Data extraction was performed independently and in duplicate using a data collection form. We collected the following predefined data: the setting of the study, the key patient characteristics, the intervention characteristics (ie characteristics of clonidine therapy regarding dose, route, sedation protocol and adjunctive sedatives) and all reported safety outcome data.

We assessed the applicability and quality of each included study regarding the safety outcomes. This appraisal was based on the Cochrane Collaboration's risk of bias tool[26] for randomised controlled trials (RCTs). In addition, we used for all studies the Risk of bias assessment checklist for studies included in systematic reviews of drug adverse events by Faillie et al.[27]

Possible disagreements during the whole process were resolved by consent. Any remaining issues were settled by consultations with a senior author.

2.4 | Data synthesis and analysis

Initially, aggregation of the data and a meta-analysis was planned. After data extraction, however, we realised that pooled quantitative analyses were not reasonably possible. On the one hand, we identified a high risk of bias in the included observational studies. On the other hand, heterogeneity must be taken into account. First, data from different kind of study types could not be combined due to the different concepts of the studies, resulting in varying reliability and different data collection or comparisons. Second, severe heterogeneity was introduced by different sedation protocols, with different dose regimes, duration of therapy and route of administration. In addition, the studies were heterogeneous regarding the patient parameters of age groups, comorbidities, severity of illness and comedication. For appropriate subgroup analyses, not enough studies could be identified. Therefore, safety information was summarised in a qualitative and descriptive manner. Where applicable, we performed the following analyses. To compare the adverse effects of bradycardia and hypotension between the individual groups that used clonidine, we calculated incidences with 95% confidence interval (95%CI) according to Clopper Pearson using the software RStudio, version 1.1.383. For corresponding comparisons of incidences between clonidine and control groups within the studies, we calculated odds ratios (95%CI) and used visualisations as forest plots based on RevMan5 software, version 5.3.

2.5 | Nomenclature of targets and ligands

Where applicable, we used in this review the nomenclature that corresponds to the IUPHAR/BPS Guide to Pharmacology, according to the online database https://www.guidetopharmacology.org. Key protein targets and ligands in this article are hyperlinked to corresponding entries in https://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

3.1 | Study selection

The database search resulted in a set of 1938 citations. This was reduced to 1585 citations when we removed the duplicates. After initial screening of titles and abstracts, 35 publications were assessed for eligibility. Twelve studies met the predefined criteria and were analysed,[13,14,18,22,28–35] whereas twenty-three studies[15,36–57] were excluded after eligibility assessment. One additional study had to be excluded as it did not provide sufficent information for this review.[33] Although this study included a cohort with the therapeutic option of clonidine, only 20% of patients in this group did receive clonidine and in the safety results it was not differentiated whether the patients had actually received clonidine or not. Figure 1 illustrates the study identification and selection process that led to the 11 studies evaluated.
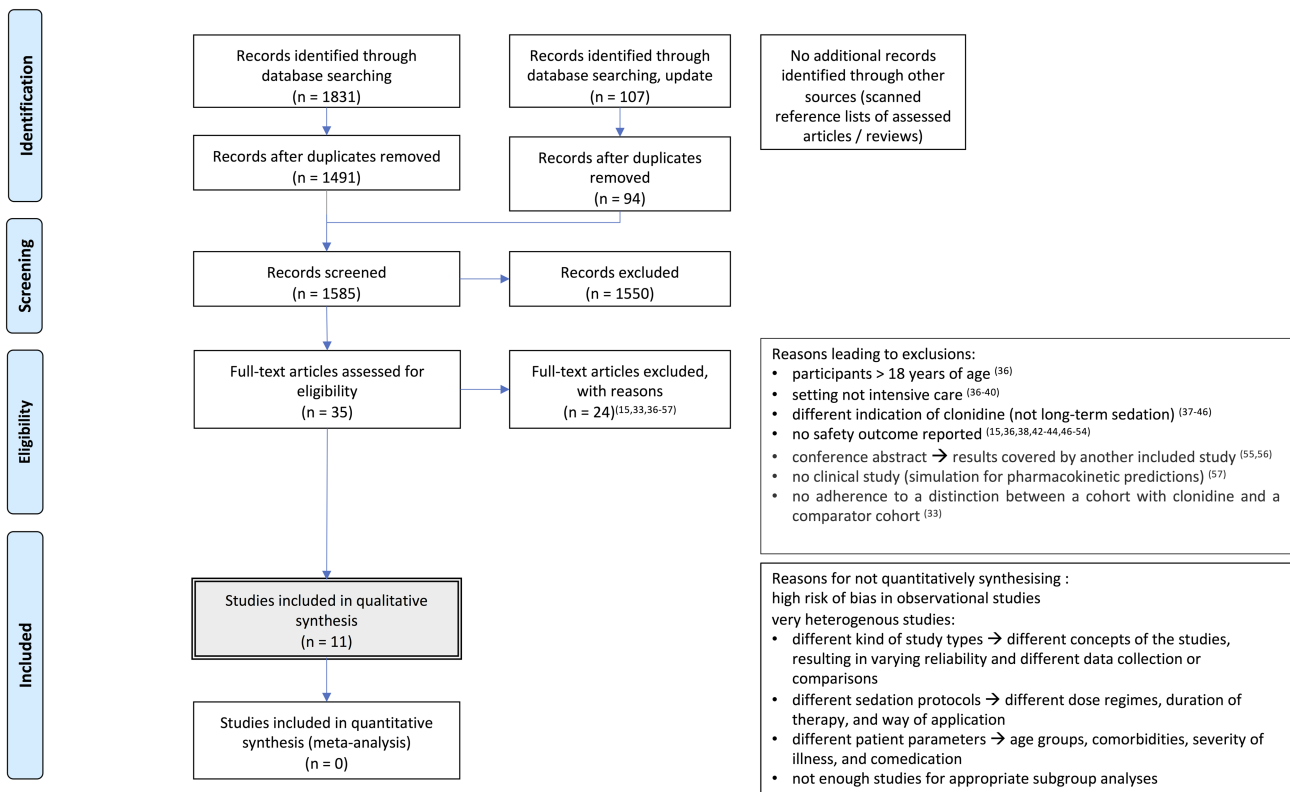
FIGURE 1 Flow diagram of trial identification and selection according to recommendations of preferred reporting items for systematic reviews and meta-analyses[58]

3.2 | Study characteristics

Five of the 11 analysed studies were interventional studies. In a first nonrandomised open dose-ranging study in 2000, Ambrose et al compared different intravenous sedation schemes with clonidine in three small cohorts, including a brief evaluation of side effects.[13] Furthermore, three systematic randomised controlled trials published in 2014 and one published in 2019 were eligible for this review (Duffett et al[30], Hünseler et al[31], Wolf et al[22] and Salarian et al[35]). They investigated safety issues as secondary outcomes. However, the sample sizes only ranged between 50 and 212 patients. Tables 1a and 1b provide summaries of the characteristics of the included interventional trials.

The remaining six studies are observational cohort studies. Safety aspects were addressed as primary outcomes[14,29,34] or as secondary outcomes, when the priority of the studies was effectiveness of sedation or reduction of benzodiazepine doses[18,28,32]. Five of these studies characterised cohorts of clonidine patients without comparison groups. Sample sizes were low and ranged from 14 to 186 patients. Table 1c summarises the characteristics of the included observational cohort studies.

3.3 | Qualitative analysis of safety outcomes

Tables 2a–2c provide an overview of the analysis of the safety outcomes. Overall, the authors mainly focused on the investigation of

haemodynamic aspects. Additionally, mortality and withdrawal symptoms are described. Apart from that, no common safety issues are elaborated in these studies, and further adverse events have not been assessed systematically and are only described individually. The main characteristics and results of the individual studies are summarised in the Supporting Information.

3.4 | Validity of the safety outcomes

The four RCTs could be evaluated using the Cochrane risk of bias tool. Overall, three RCTs were of low risk of bias, while the RCT of Salarian et al[35] was conspicuous by its high risk of bias (see Figure 2).

We assumed a high risk of bias for the Salarian study[35] because of limited confidence in the results. Contradictory information was found in the registration (Iranian Registry of Clinical Trials IRCT20170920036296N1) and in the publication (eg, on organisational issues, on the inclusion criterion of patient age or on the fentanyl dose in the sedation regimen). Furthermore, critical issues were encountered in the publication itself. For example, statistical calculations were not entirely reproducible, significance levels did not coincide in the tables and text, and some results were implausible (eg, data on total doses). Moreover, no details of the safety assessment were described, and exact definitions or the procedure for measurement was not specified. It was therefore not clear whether adverse events have been completely and objectively recorded. This was

TABLE 1a Characteristics of the included nonrandomised interventional cohort study

Study	Group, n (number of patients analysed for safety outcomes):	Patients:	Clonidine (comparator) regime/study duration:	Concomitant sedatives and analgesics:
Ambrose 2000[13] prospective interventional non-randomised without comparator group	"Variable dose, max. 1 μg kg^{-1} h^{-1}" n = 10	Age: Median: 12.5 months (range: 7–38 months) Baseline mortality risk: Nothing reported	Application, dosage: i.v., variable: 0.2–1.0 μg kg^{-1} h^{-1} Duration of study drug exposure: Study duration: 21–222 h	Midazolam
	"Variable dose, max. 2 μg kg^{-1} h^{-1}" n = 10	Age: Median: 2.0 months (range: 1d–15 months) Baseline mortality risk: Nothing reported	Application, dosage: i.v., variable: 0.2–2.0 μg kg^{-1} h^{-1} Duration of study drug exposure: Study duration: 25–181 h	Midazolam
	"Fixed dose 1 μg kg^{-1} h^{-1}" n = 10	Age: ≤ 10 years, no further information Baseline mortality risk: Nothing reported	Application, dosage: i.v. fixed: 1 μg kg^{-1} h^{-1} Duration of study drug exposure: 8 h study duration: 2 h before starting clonidine infusion + 6 h infusion duration	Morphine, chloralhydrate, midazolam

particularly critical as zero cases of bradycardia and hypotension were reported in the intervention group and the results of the placebo group were not explicitly mentioned. Similarly, the incidence of respiratory distress was explicitly reported for the placebo group only.

As we aimed to assess the validity of all studies included in a standardised way, we used the tool of Faillie et al.[27] It has been validated for systematic reviews focusing on adverse drug reactions and is applicable to randomised trials as well to observational studies and allowed for comprehensive standardised testing. Apart from the indicated outcomes, the RCTs of Duffett,[30] Hünseler[31] and Wolf[22] showed a low risk of bias in accordance with the Cochrane tool. In contrast, with the exception of Kleiber et al's[34] evaluation of the haemodynamic profile and tolerance, we considered an overall high risk for the remaining studies.[13,14,18,28,29,32,34,35] This was mostly due to the study design, particularly if only one cohort without comparison group was presented. We also found deficiencies in the definitions of the safety outcomes. Moreover, hardly any additional modifying factors and confounders were taken into account, which implies a high risk of bias. The detailed results of the assessment are presented in Figure 3 and Table 3.

3.5 | Comparability between the different studies

The studies showed considerable heterogeneity regarding the characteristics of the children. Patients of different age groups, with different underlying diseases and thus different comedications, were included. Furthermore, the sedative regimes used differed in terms of sedative comedication, dosages, routes of administration and duration. In addition, if any comparator was involved, it was either placebo[30,31,35] or midazolam.[14,22] Finally, the duration of drug exposure, respectively the observation period, varied.

3.6 | Unpublished and ongoing trials

The trials registers did not reveal apparent publication bias and they did not indicate that there will be numerous additional valid safety data in the near future. The CloSed study was terminated due to a lack of recruitment (ClinicalTrials.gov Identifier: NCT0259273, EudraCT Number: 2014–003582-24). There were only two further studies that could provide some safety data subsequently. In a small pilot study at Johns Hopkins University Hospital, Kudchadkar et al aimed to "determine the effective IV dosing scheme of clonidine that can be safely used as an adjunct to analgesic-sedation management for infants and children in the PICU" by comparing a cohort of clonidine-exposed children with a dexmedetomidine cohort in the age strata 0–3, 4–6 and at 7–12 months (ClinicalTrials.gov Identifier: NCT02249039). Data from this trial were planned to inform a larger randomised trial with critically ill infants and children. Recruitment ended in December 2019 with a total number of only 14 patients instead of the originally estimated 30 patients. Results have not yet been published and there is no information as to whether the planned

TABLE 1b Characteristics of the included randomised controlled trials

Study	Group, n (number of patients analysed for safety outcomes):	Patients:	Clonidine (comparator) regime/study duration:	Concomitant sedatives and analgesics:
Duffett 2014[30] comparator: placebo	"Clonidine" n = 25	**Age:** Median: 2.5 years (range: 1 month–16 years) **Baseline mortality risk:** Pediatric risk of mortality PRISM III: Median: 11 (range: 4–31)	**Application, dosage:** Clonidine or placebo: Enteral, 5 µg kg⁻¹ (max 200 µg) every 6 h **Duration of study drug exposure:** Median (IQR) days of study drug exposure clonidine group: 7 d (4–17 d) midazolam group: 8 d (5–12 d) **Follow up time:** Within 48 h after receiving study drug (adverse events); during hospital stay (mortality)	Multiple sedatives at the discretion of attending physicians (no sedation protocol): Benzodiazepine (midazolam, lorazepam), opioids (morphine, fentanyl, hydromorphone), propofol, ketamine, chloral hydrate
	"Placebo" n = 25	**Age:** Median: 2.7 years (range: 1 month–17 years) **Baseline mortality risk:** Pediatric risk of mortality PRISM III: Median: 15 (range: 2–23)		
Hünseler 2014[31] comparator: placebo	"Clonidine" n = 100 "Placebo" n = 112	No separate specification, but no significant differences between the groups regarding age and baseline mortality risk: **Age:** Mean (±SD) age of the ITT population: 86 (±146) days (range: 0–14 months) according to age strata > 50% of the patients 0–28 days **Baseline mortality risk:** Paediatric risk of mortality PRISM III: Mean of all participants: 13.3 ± 6.7 (predicts a mortality rate of 7–8%)	**Application, dosage:** Clonidine or placebo: i.v., continuous infusion, 1 µg kg⁻¹ h⁻¹ **Duration of study drug exposure:** Median (IQR) days of study drug exposure: 7 d (5.3–10 d) for all patients without difference between both study groups (P = 0.964) **Follow up time** (adverse events): Until death or hospital discharge	Standard analgesia and sedation based on fentanyl and midazolam; thiopental sodium was allowed in case of acute agitation Clonidine as comedication: → adjusted dosages of fentanyl and midazolam 6 hourly according to the symptoms
Wolf 2014[22] comparator: midazolam	"Clonidine" n = 64	**Age:** Median: 0.60 years (IQR 0.18–1.84 years) (range: 0.08–13.85 years) **Baseline mortality risk:** Paediatric risk of mortality PRISM III: Not reported	**Application, dosage:** i.v., loading dose over the first hour: Clonidine: 3 µg kg⁻¹ or midazolam: 200 µg kg⁻¹, then continuous infusion: Clonidine: 0–3 µg kg⁻¹ h⁻¹ or midazolam: 0–200 µg kg⁻¹ h⁻¹ **Duration of study drug exposure:** Median (IQR) days of study drug exposure clonidine group: 0.8 d (0.6–1.7 d) midazolam group: 1.5 d (0.8–2.5 d) **Follow up time:** Within 14 d following trial treatment cessation (adverse events/mortality)	Study protocol: Regime with morphine plus clonidine vs midazolam Supplementary analgesia required during sedation: Additional morphine, alfentanil, anaesthetic block, desflurane, diazepam, fentanyl, ibuprofen, isoflurane, ketamine, lorazepam, midazolam, muscle relaxant, paracetamol, propofol, remifentanil, sevoflurane, thiopental sodium
	"Midazolam" n = 61	**Age:** Median: 0.53 years (IQR 0.27–1.30 years) (range: 0.09–9.53 years) **Baseline mortality risk:** Paediatric risk of mortality PRISM III: Not reported		
Salarian 2019[35] comparator: placebo	"Clonidine" n = 46	**Age:** Mean (±SD): 11.7 (±2.5) years (range: 2–15 years) **Baseline mortality risk:** Paediatric risk of mortality PRISM III: Not reported	**Application, dosage:** Clonidine or placebo: Nasogastric tube, 5 µg kg⁻¹ every 6 h **Duration of study drug exposure:** Mean (±SD) days of study drug exposure: clonidine group: 2.2 d (±0.2 d) placebo group: 2.3 d (±0.4 d) **Follow up time** (adverse events): Until discharge from PICU	Standard analgesia and sedation based on fentanyl and midazolam: → adjusted dosages (bolus doses/titration) of fentanyl and midazolam in case with inadequate level of sedation/to maintain target sedation
	"Placebo" n = 50	**Age:** Mean (±SD): 12.4 (±4.3) years (range: 2–14 years) **Baseline mortality risk:** Paediatric risk of mortality PRISM III: Not reported		

TABLE 1c Characteristics of the included observational cohort studies

Study	Group, n (number of patients analysed for safety outcomes):	Patients:	Clonidine (comparator) regime/study duration:	Concomitant sedatives and analgesics:
Arenas-Lopez 2004[28] prospective	n = 14	Age: Median: 3 months (IQR 1.3–15.9 months) (enrolled patients) Baseline mortality risk: PIM-derived mortality risk: 8.0% (5.3–9.8%) (enrolled patients)	Application, dosage: Nasogastric tube at time 0 h as a test dose (1 µg kg⁻¹) to assess the blood pressure response, followed 1 h later by 3–5 µg kg⁻¹ every 8 h Duration of study drug exposure: Median (range) days of ventilation (of analysed patients): 3.4 d (3.3–4.6 d) (no explicit information on study drug exposure)	Morphine, lorazepam
Pohl-Schickinger 2008[29] retrospective	n = 50	Age: Median: 5.0 months (IQR 3.0–9.0 months) Baseline mortality risk: Nothing reported	Application, dosage: i.v. clonidine for sedation, 0.18–3.6 µg kg⁻¹ h⁻¹ Duration of study drug exposure: Median (IQR) days of clonidine exposure: 3 d (2–5 d)	Fentanyl and other opioids, midazolam
Deho 2016[32] retrospective	n = 48	Age: Mean: 2.3 years Baseline mortality risk: Mean paediatric index of mortality 2: Mean 10.2%	Application, dosage: i.v., 0.2–2 µg kg⁻¹ h⁻¹ Duration of study drug exposure: Mean days of clonidine exposure: 8 d	Morphine, midazolam
Kleiber 2016[14] retrospective comparator: midazolam	"Clonidine" n = 23 "Midazolam" n = 10	Age: Median: 22 days (IQR 6–47 days) Baseline mortality risk: Nothing reported Age: Median: 6 days (IQR 0–36 days) Baseline mortality risk: Nothing reported	Application, dosage: Clonidine group: Bolus, 0.5–1 µg kg⁻¹ , max 2 µgkg⁻¹ within 4 h → i.v., 0.5–2 µg kg⁻¹ h⁻¹ comparison group: "Protocol violation" → use of midazolam Duration of study drug exposure: Median (IQR) days of clonidine exposure: 1.3 d (0.5–2.3 d), of midazolam exposure: No information. (Median (IQR) days of intubation: Clonidine group: 2.0 d (1.6–3.7 d) comparison group: 3.7 d (2.0–8.7 d))	Morphine
Kleiber 2018[34] retrospective	n = 186	Age: Median: 12.9 months (IQR 3.5–60.6 months) Baseline mortality risk: Paediatric index of mortality II predicted death rate: Median: 3.1 (IQR 1.3–8.2) paediatric risk of mortality II: Median: 19 (IQR 11–26)	Application, dosage: Boluses, 1–2 µg kg⁻¹ → i.v., 0.5–1 µg kg⁻¹ h⁻¹ up to a max. 2 µg kg⁻¹ h⁻¹ Duration of study drug exposure: Median (IQR) days of clonidine exposure: 2.6 d (1.0–6.5 d)	Morphine (10–30 µg kg⁻¹ h⁻¹), midazolam; other second line sedatives: Esketamine, propofol, phenobarbital

TABLE 1c (Continued)

Study	Group, n (number of patients analysed for safety outcomes):	Patients:	Clonidine (comparator) regime/study duration:	Concomitant sedatives and analgesics:
Michel 2020[18] retrospective	"Pre-modification group" n = 33	Age: Mean (±SD): 2.5 ± 1.8 months; Baseline mortality risk: Nothing reported	Application, dosage: i.v., 0.05 µg kg⁻¹ h⁻¹ starting dose (steps of increase not clear); Duration of study drug exposure: Not reported (mean (±SD) ventilator days: 3.9 ± 3.3 d)	Morphine, midazolam
	"Post-modification group" n = 32	Age: Mean (±SD): 2.9 ± 2.7 months; Baseline mortality risk: Nothing reported	Application, dosage: i.v., 0.2 µg kg⁻¹ h⁻¹ starting dose → bolus/increased infusion by 0.2 µg kg⁻¹ h⁻¹ in case of insufficient sedation; Duration of study drug exposure: Not reported (mean (±SD) ventilator days: 4.5 ± 3.6 d)	Morphine, additional midazolam in case of under-sedation

TABLE 2a Reported safety outcomes of the included non-randomised interventional cohort study

Study (group)	Number of events with bradycardia	Number of events with hypotension	Mortality	Further safety outcomes related to the haemodynamic profile	Withdrawal symptoms	Additional information regarding adverse events
Ambrose 2000[13] ("Variable dose, max. 1 µgkg⁻¹ h⁻¹")	0/10	0/10	not reported	nothing reported	nothing reported	nothing reported
Ambrose 2000[13] ("Variable dose, max. 2 µgkg⁻¹ h⁻¹")	0/10	0/10	not reported	nothing reported	nothing reported	nothing reported
Ambrose 2000[13] ("Fixed dose, 1 µgkg⁻¹ h⁻¹")	0/10	0/10	not reported	low dose inotropic support remained the same or were reduced during 8 h study period; no significant changes in trends over 6 h after starting the clonidine infusion: heart rate: 166 (SD 17.9) to 154 (SD 20.2) bpm; blood pressure: 60 (SD 9.8) to 64 (SD 11.1) mm Hg; derived cardiac index: 5.7 (SD 2.2) to 6.0 (SD 1.51) ml m⁻² min⁻¹	nothing reported	nothing reported

TABLE 2b Reported safety outcomes of the included randomised controlled trials

Study (group)	Number of events with bradycardia	Number of events with hypotension	Mortality	Further safety outcomes related to the haemodynamic profile	Withdrawal symptoms	Additional information regarding adverse events
Duffett 2014[30] ("Clonidine")	3/25[a]	5/25[c]	0/25	number of patients with demand for fluid as intervention of bradycardia or hypotension: 2/25, odds ratio (95%CI): 2.1 (0.2–24.6)	withdrawal symptoms requiring treatment: 9/25, odds ratio (95% CI): 1.0 (0.3–3.2)	no withdrawals from the study or discontinuation of the study medication because of adverse effects
Duffett 2014[30] ("Placebo")	2/25[a]	2/25[c]	3/25[e]	number of patients with demand for fluid as intervention of bradycardia or hypotension: 1/25	withdrawal symptoms requiring treatment: 9/25	
Hünseler 2014[31] ("Clonidine")	not reported	not reported	3/100 (6/105)[f]	systolic and mean arterial blood pressures: significantly lower in neonates of clonidine group vs. placebo group - no difference in older age groups; no difference in heart rate levels; no difference in frequency of use and dosage of catecholamines, in the amounts of colloidal and crystalline volume replacements, and diuresis between groups	withdrawal symptoms (Finnegan scores after discontinuation of fentanyl and midazolam): significantly lower in neonates of clonidine group (p = 0.018), with comparable pharmacological treatment - no difference in older age groups	no difference in severe adverse events (not specified) between groups
Hünseler 2014[31] ("Placebo")			6/112 (6/114)[f]			
Wolf 2014[22] ("Clonidine")	1/64[a]	7/64[c] (4 patients affected)	1/64[g]	incidence of inotropic support during the first 12 hours: 5/45 (11.1%), RR (95%CI): 1.93 (0.49–7.61)	withdrawal symptoms requiring treatment: 11/60, relative risk (95%CI): 0.66 (0.34–1.31)	additional adverse events: 6x bradycardia not requiring intervention, number of patients affected: 2; 1x hypertension not requiring intervention; 1x hypertension following cessation of trial treatment additional serious adverse events: 1x accidental extubation; 1x self-extubation not requiring reintubation; 1x failed extubation requiring reintubation: 1x infection requiring antibiotics; 1x postextubation stidor; 1x postoperative wound infection; 1x recurrence of original disease after discharge from hospital; 1x reintubation due to stidor

(Continues)

TABLE 2b (Continued)

Study (group)	Number of events with bradycardia	Number of events with hypotension	Mortality	Further safety outcomes related to the haemodynamic profile	Withdrawal symptoms	Additional information regarding adverse events
Wolf 2014[22] ("Midazolam")	3/61[a] (2 patients affected)	3/60[c]	0/61	incidence of inotropic support during the first 12 hours: 3/52 (5.8%)	withdrawal symptoms requiring treatment: 16/58	additional adverse events: 1x constipation; 1x petechial rash; additional serious adverse events: 1x accidental extubation; 1x self-extubation not requiring reintubation; 1x endotracheal tube migrated downright main bronchus, due to wet retaining tapes
Salarian 2019[35] ("Clonidine")	0/46[b]	0/46[d]	0/46[h]	nothing reported	nothing reported	respiratory distress in 3/50 patients of the placebo group (6%) as the most common adverse effect; clonidine group data not published; no withdrawals from the study due to severe adverse effects
Salarian 2019[35] ("Placebo")	not reported	not reported	0/50[h]			

[a] bradycardia requiring intervention.
[b] severe bradycardia as defined by the study author.
[c] hypotension requiring intervention.
[d] severe hypotension as defined by the study author.
[e] mortality, Duffett 2014[30]: one immunocompromised patient with a viral infection died of severe acute respiratory distress syndrome 5 days after randomisation, the others died 1 and 2 months after the study drug was discontinued of sepsis and refractory seizures, respectively.
[f] mortality, Hünseler 2014[31]: 105 patients assigned to clonidine group, 100 patients received study medication; 114 patients assigned to placebo group, 112 patients received study medication; given information about the 12 patients who died (3 died before receiving study medication): 9 had severe congenital heart disease and 3 patients died of multiple organ failure and had underlying systemic diseases with septicaemia (severe combined immunodeficiency, congenital renal insufficiency, and unknown syndrome).
[g] mortality, Wolf 2014[22]: one patient died from primary disease after active phase of trial completed.
[h] mortality, Salarian 2019[35]: no patient died during PICU stay.

TABLE 2c Reported safety outcomes of the included observational cohort studies

Study (group)	Number of events with bradycardia	Number of events with hypotension	Mortality	Further safety outcomes related to the haemodynamic profile	Withdrawal symptoms	Additional information regarding adverse events
Arenas-Lopez 2004[28]	0/14	0/14	not reported	heart rate decreased significantly, lowest recorded heart rate: 85 bpm; measurements [means (95% CI)] time 0 to time 72 h: 152 (143–160) bpm to 126 (117–135) bpm no significant changes in blood pressure; measurements [means (95%CI)] time 0 to time 72: 69 (62–76) mmHg to 66 (61–70) mmHg	nothing reported	no recorded episodes of hyperglycaemia (only a slight not significant increase was observed: mean (95%CI) time 0 to time 72: 4.1 (3.8–4.4) mmol/l to 5.0 (4.5–5.5) mmol/l)
Pohl-Schickinger 2008[29]	1/50[a]	0/50	not reported	prior to treatment with clonidine, the haemodynamic profile was influenced by prolonged (> 24 h) treatment with midazolam and fentanyl; during clonidine treatment, the haemodynamic profile normalised with a significant reduction of heart rate and mean arterial pressure from the upper norm to the mean within 24 h (no need for additional therapy to reach the target blood pressure) no adverse effects on cardiac rhythm, especially no onset of atrioventricular block	after prolonged (> 24 h) treatment with midazolam and fentanyl, patients showed withdrawal symptoms (including agitation, hypersalivation, tachycardia, hypertension, and fever); after start of clonidine therapy, these symptoms were improved in nearly all patients	according to the authors' appraisal: no major respiratory depressant effect, as the number of reintubations was not higher than that normally found in this patient group
Deho 2016[32]	9/39	8/39	not reported	incidence of both bradycardia and hypotension in a patient: 5/39 haemodynamic instability (bradycardia/hypotension) did not result in increased demand for intravenous fluid or catecholamines 58% of patients who showed haemodynamic instability were less than 1 year old	nothing reported	nothing reported
Kleiber 2016[14] ("Clonidine")	1/23[b]	not reported	0/23[g]	heart rate decreased significantly by 12% [maximal mean decrease: from 149 bpm (SD 17) to 131 bpm (SD 17) at 48h] diastolic blood pressure: there was a significant transient and limited drop of 13% [maximal mean decrease: from baseline mean 42.8 mm Hg (SD 5.9) to 37.1 mm Hg (SD 4.0) at 48h] systolic blood pressure and central venous pressure: no significant changes within 48 h no detrimental changes in other cardiovascular variables apparent (no change in vasoactive inotropic score, volume of fluid bolus, decrease in serum lactate, favourable trend in central venous oxygen saturation and increase in urine output (as indirect markers of organ perfusion)	nothing reported	no instances of accidental extubation, cardiac arrest, or extracorporeal membrane oxygenation

(Continues)

TABLE 2c (Continued)

Study (group)	Number of events with bradycardia	Number of events with hypotension	Mortality	Further safety outcomes related to the haemodynamic profile	Withdrawal symptoms	Additional information regarding adverse events
Kleiber 2016[14] ("Midazolam")	0/10	not reported	0/10[g]	no gradually decrease in heart rate lower systolic and diastolic blood pressure (than clonidine group) higher vasoactive inotropic score and the amount of fluid bolus (than clonidine group) no statistically different serum lactate level between the two groups		
Kleiber 2018[34]	115/179 (moderate) 72/179 (severe)[c]	105/181[e] 90/181[f]	15/186[h]	significant decrease in the parameters, heart rate, blood pressure, vasoactive-inotropic score, after clonidine start age is found as a significant risk factors associated with severe bradycardia, odds ratio (95%CI): 0.74 (0.64–0.85), p < 0.0001 during episodes of severe bradycardia, systolic blood pressure remained stable, mean and diastolic blood pressure decreased only slightly, and vasoactive inotropic score decreased by 19.3% at 6 hours after start of the episode mean blood pressure hypotension and systolic blood pressure hypotension were unrelated to the occurrence of severe bradycardia: mean blood pressure hypotension was found in 53.5% of patients with severe bradycardia (p = 0.56), systolic blood pressure hypotension in 63.4% (p = 0.30)	nothing reported	during clonidine infusion, body temperature increased during clonidine infusion, at day 7 the temperature was significantly higher (mean 38.2°C) than at baseline
Michel 2020[18] ("Pre-modification group")	0/33[d]	not reported	not reported	no incidence of severe cardiac dysrhythmias like junctional ectopic tachycardias, haemodynamically relevant sinus bradycardias or atrioventricular blocks	3/33[i]	no incidence of accidental extubations accidental removal of drains or central lines
Michel 2020[18] ("post-modification group")	0/32[d]	not reported	not reported		5/32[i]	

a bradycardia, Pohl-Schickinger 2008[29]: in one patient clonidine was stopped after sinus bradycardia (55 bpm) that resolved spontaneously within seconds; the authors did not assume a causal relationship with clonidine due to the half-life of clonidine elimination and the time for spontaneous resolution.
b bradycardia, Kleiber 2016[14]: sinus bradycardia (100 bpm) after 35 h of clonidine infusion in a 7 weeks old child, temporary cardiac pacing required, after cessation of clonidine, ongoing well-tolerated sinus bradycardia.
c bradycardia, Kleiber 2018[34]: moderate bradycardia, when the time-weighted average heart rate was below the 10th percentile of normal values for age; severe bradycardia, when below the 1st percentile.
d bradycardia, Michel 2020[18]: haemodynamicallly relevant sinus bradycardias.
e hypotension based on systolic blood pressure.
f hypotension based on mean blood pressure.
g mortality, Kleiber 2016[14]: no deaths within 48 h after PICU admission, no information is available beyond that time.
h mortality, Kleiber 2018[34]: no cause of death of individual patients is mentioned, but it is pointed out that patients with high disease severity were included.
i mortality, Kleiber 2018[34]: duration of follow up time not defined; no cause of death or time not defined.
i incidence of withdrawal symptoms identified by the Sophia Observation withdrawal Symptoms-Paediatric Delirium (SOS-PD) scale.

FIGURE 2 Risk of bias assessment according to the Cochrane risk of bias tool for the included RCTs (green "+" indicates a low risk of bias, red "–" indicates a high risk of bias)

3.7 | Synthesis of the safety profile: haemodynamic safety issues

The major safety concerns of the study authors were haemodynamic problems. Figure 4a compares the odds ratios of bradycardia and hypotension in the randomised trials of Duffett et al[30] and Wolf et al.[22] These are the only studies we have identified in which these data have been collected with low risk of bias. The odds ratios show no significant differences between the clonidine and control groups in the incidence of these adverse events.

Figure 4b shows the incidences of bradycardia and hypotension in the clonidine groups of all studies. Since these effects are type 1 adverse reaction, the studies are ordered by increasing dosage.

Rather high incidences of bradycardia and hypotension are notable in the studies by Kleiber et al 2018,[34] Deho et al[32] and Duffett et al.[30] Kleiber et al[34] attributed this to their study population of very severely ill patients. Deho et al[32] gave no explanation, but in their study the treatment duration was relatively long, which on the one hand naturally could lead to a higher incidence and on the other hand could also be an indication for very severe ill patients.

subsequent larger randomized trial will be conducted. Furthermore, clonidine is being investigated in a neonatal intensive care unit setting within the SANNI project of Skane University Hospital by Norman et al (EudraCT Number: 2017–005091-26). This ongoing observational study on 100 preterm infants was initiated in 2018, with an estimated duration of 2 years. It is planned to investigate haemodynamic parameters as a secondary outcome.

Considering the comparison group (see Figure 4a), the incidences of bradycardia and hypotension in Duffett et al[30] were not significantly increased in the clonidine group. Apart from these studies, no significant incidence of bradycardia and hypotension was observed. However, considering the external influences and their risk of bias as described above, valid conclusions can hardly be drawn. The same applies to the influence of doses and routes of administration. Moreover, the comparison of the different studies does not allow to conclusions to be drawn on whether or not younger age is a possible risk factor. This would be of interest since Kleiber et al 2018[34] and Hünseler et al[31] identified younger age as a risk factor for haemodynamic adverse effects.

Overall, all study authors considered the use of clonidine for long-term sedation safe despite the possible risk for bradycardia and hypotension. To this end, several authors evaluated the consequences of haemodynamic instability (bradycardia/hypotension). Thus, they investigated whether interventions such as inotropic support or fluid demand were required more frequently. None of the studies found a considerable increase.[14,22,30,32,34] Duffett et al[30] provided concrete figures in an evaluation of the number of patients with demand for fluid as intervention of bradycardia or hypotension. Moreover, Wolf et al[22] reported the incidence of increased inotropic support required during the first 12 hours after randomisation. These data are shown in Figure 5. With an odds ratio of about 2 in each study, the result is quite consistent and would indicate a more frequent need for intervention in the clonidine groups. However, the analysis is based on a small number of patients and is not significant.

FIGURE 3   Risk of bias assessment according to the checklist of Faillie et al[27] for each included study; where necessary, the outcomes referred to are indicated: Bradycardia (i), hypotension (ii), mortality (iii), outcomes related to haemodynamics (iv), withdrawal symptoms (v), additional adverse events (vi). Green rectangles represent low, yellow triangles unclear, and red circles a high risk of bias

3.8 | Summary of safety issues beside haemodynamics

In six studies,[14,22,30,31,34,35] mortality was a further common safety outcome. However, none of these studies found a causal relationship between the use of clonidine and deaths.

Another concordant outcome measure in five studies was the occurrence of withdrawal symptoms.[18,22,29–31] Two studies identified an advantage of clonidine: After discontinuation of fentanyl and midazolam, Hünseler et al[31] reported fewer symptoms in the neonatal clonidine group compared to the neonatal midazolam group. Pohl-Schickinger et al[29] observed that withdrawal symptoms caused by
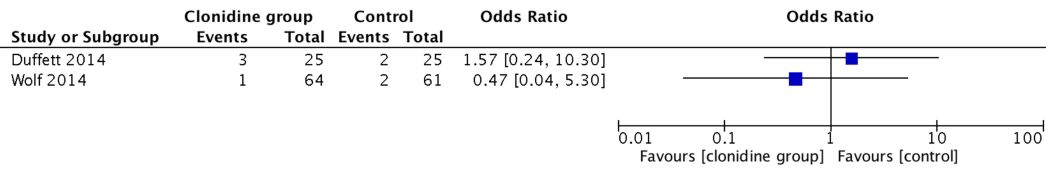
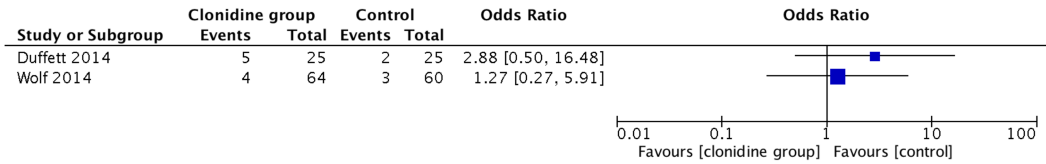**TABLE 3** Comments on the risk of bias assessment shown in figure 3

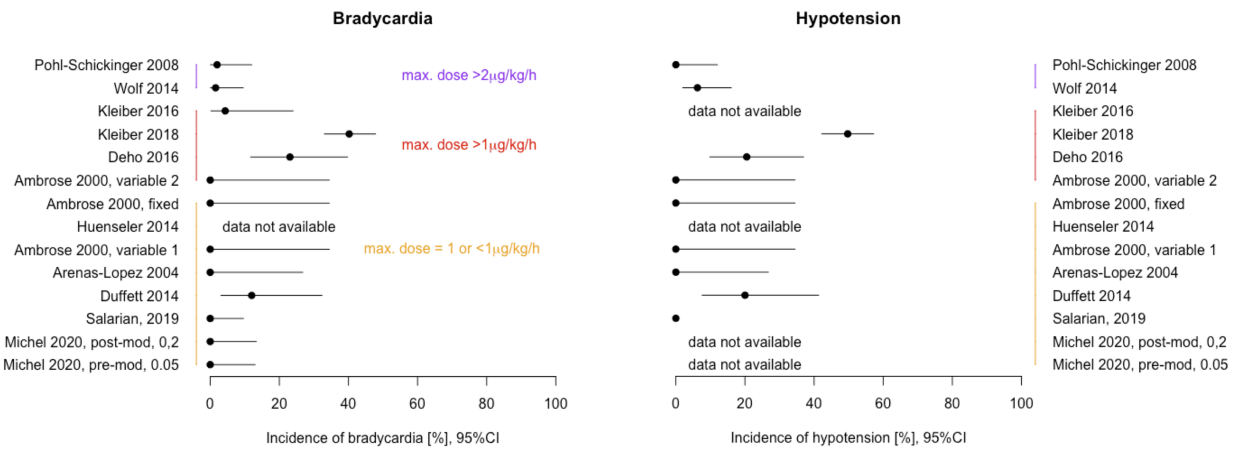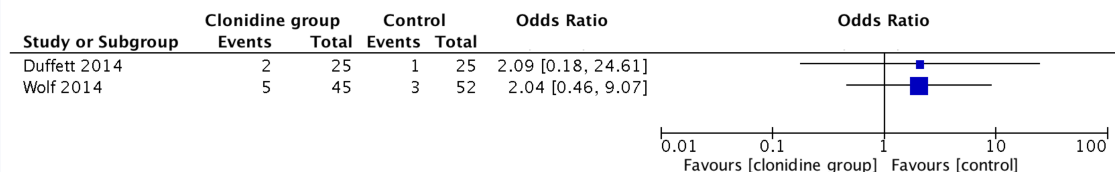| Assessment category	Comments
A) Study design	In six included studies,[13,18,28,29,32,34] only cohorts of patients treated with clonidine without a comparison group were investigated and characterised. But since no data on the baseline risk of the safety outcomes were available, no reliable conclusions could be drawn about the impact of clonidine, especially not about the extent of adverse effects. Therefore, we considered the study design in these six studies to be not appropriate for obtaining valid findings which should quantify safety issues. However, Kleiber et al 2018[34] included the aim of identifying risk factors for bradycardia and evaluated the relationship between haemodynamic parameters in order to assess haemodynamic tolerance. For this purpose, valid outcomes could be expected, despite the design without comparison group.
B) Selection bias	Since Ambrose et al[13] and Deho et al[32] did not describe criteria for the selection process, it was unclear whether selection bias was an issue. In addition, Ambrose et al[13] did not provide information about baseline characteristics. In 2016, Kleiber et al[14] compared patients who have received clonidine in the course of an established sedation regime with patients in whom physicians decided to use midazolam instead of clonidine. The reasons for this protocol deviation was not documented but may affect the outcome. This also introduced an unclear risk of bias in the selection process.
C) Attrition bias	There seemed to be a high risk of attrition bias in the study of Deho et al,[32] since there was no complete flow chart available and the information regarding the number of participants was confusing (48 patients were enrolled, but the outcomes related only to 39 patients, a reason for this was not given.)
D) Information bias regarding the drug safety outcome	In general, unclear information bias occurs when there is no clear definition of an outcome. Indeed, this was difficult to categorise for some outcomes. On the one hand, monitoring of patients and documentation of signs and symptoms on PICUs is generally very accurate and PICUs usually establish internal conventions for diagnosing adverse events such as bradycardia. However, especially in retrospective studies, one has to rely on routine data quality, which may not be standardised and audited. Moreover, there are several underlying international guidelines and the definition of normal values is also subject to constant scientific review and discussion, so that the outcome definitions also evolve. Thus, it is important for the assessment of adverse events to which norm values or guideline the study outcomes refer. For example, Fleming et al 2011[59] evaluated available data on heart rate and respiratory rate and requested a redefinition of these normal values. However, O'Leary's study[60] showed some controversy over defining these normal values in 2015. Likewise, the definition of normal blood pressure values have also been revised.[61] Therefore, we considered an unclear risk of information bias for the denoted outcomes as shown in Figure 3.[13,14,18,22,28–32] In addition, the RCT of Salarian[35] provided no information on the number of adverse events explicitly in both groups and on causality attribution assessment.
E) Other information bias	Other information bias would refer to characteristics other than the outcomes. We did not assume this kind of risk for all included studies.
F) Controlling of confounding	In the included studies without randomisation (Ambrose et al,[13] and the 6 observational studies[14,18,28,29,32,34]) confounding was not excluded by the study design. Therefore, confounding seemed to be introduced e.g. by confounding by indication, or by confounding factors such as age, disease severity, or comedication. In addition, confounding was not addressed in the statistical analyses. Therefore, we saw a high risk of bias. Due to the small sample sizes, a respective evaluation would not have been feasible in most cases. Kleiber et al 2018[34] investigated risk factors for bradycardia and hypotension and evaluated relationships between haemodynamic parameters to evaluate haemodynamic tolerance. Since these dealt with a descriptive research question, confounding was no issue for these outcomes.
G) Statistical issues	When evaluating the study by Salarian et al[35] we recognised some obvious discrepancies and issues regarding the results. Therefore, there were serious doubts about the reliability of the statistical analysis and the results (see above). In some of the other studies, the information on statistical analysis was also a bit minimalistic, but we could not recognize obvious statistical issues. Therefore, we considered a low risk of bias for this aspect for the remaining studies. However, it is noticeable that all the studies only provided information on whether safety issues occurred per patients. This quantity is, of course, important in the treatment decision process. However, none of the studies included the duration of clonidine therapy (or comparative therapy) or the total follow-up time in the statistical evaluation. This means that neither a rate of safety issues per therapy time was determined, nor the time to event was investigated in survival analysis. These would be additionally relevant and very informative data for the drug profile.
H) Conflict of interest	Abrose et al,[13] Deho et al[32] and Salarian et al[35] did not provide enough information to exclude conflicts of interest, but on the other hand there were no indications of conflicts.

(A)

(B)

FIGURE 4 (a) Odds ratios (95%CI) of bradycardia and hypotension according to Duffett et al[30] and Wolf et al,[22] visualised by forest plots (software: RevMan5) (b) Incidence of bradycardia and hypotension, with 95%CI (Clopper Pearson) in the different study (sub-)groups that used clonidine (software: R). The studies are presented by increasing maximum clonidine dose. According to the summary measure of age, neonate children were only predominantly in the study of Kleiber.[14] In the studies of Arenas-Lopez,[28] Hünseler,[31] Ambrose[13] (group: "variable dose, max. 2 µg kg^{-1}h^{-1}") and Michel[18] (both groups) the children were predominantly no more than 3 months of age. In the studies of Ambrose[13] (group: "variable dose, max. 1 µg kg^{-1}h^{-1}"), Deho,[32] Kleiber,[34] Wolf[22] and Pohl-Schickinger[29] the children were predominantly no more than 2 years of age. The median age of the children enrolled in the study of Duffett[30] was 2.5 years. With children older than 10 years, Ambrose[13] (group: "fixed dose, 1 µg kg^{-1}h^{-1}") and Salarian[35] included the highest age groups

FIGURE 5 Interventions due to bradycardia and hypotension: Events at Duffett et al[30] are number of patients with demand for fluid as intervention of bradycardia or hypotension; events at Wolf et al[22] are number of patients with increased inotropic support required during the first 12 hours after randomisation (software: RevMan5)

midazolam and fentanyl improved when starting clonidine therapy. Otherwise, no information on withdrawal effects caused by clonidine could be found. This could mean that clonidine does not cause significant withdrawal problems, but to draw a valid conclusion – also regarding a possible positive effect – further investigations are needed. Moreover, it is important to mention that Wolf et al[22] identified a case of mild rebound hypertension after stopping clonidine treatment. The authors, however, did not consider this a significant problem.

Interestingly, Salarian et al reported cases of respiratory distress in the control group. Unfortunately, there was no explicit information on the clonidine patients, but possibly this meant that this group was not affected by respiratory problems.[35] This would be in line with the appraisal of Pohl-Schickinger et al, as no significant respiratory depressive effect due to clonidine was assumed in this study either.[29] However, objective monitoring is also lacking here, as this judgement was based on the fact that the number of reintubations was not higher than it is normally found to be in this patient group. Also, with regard to this problem, valid data would be required in future studies, in particular to assess whether there is an advantage of clonidine compared to the alternative midazolam.

The remaining individually reported adverse events are listed in Table 2. It should be emphasised that suspected hyperglycaemia did not occur in the Arenas-Lopez study – only a slight, insignificant increase in blood glucose levels was observed.[28] In addition, Kleiber et al reported a significant increase in body temperature. Nevertheless, there is no evidence of a relationship with clonidine due to other possible factors.[34]

3.9 | Study populations and generalizability

Notably, the studies excluded patients with suspected haemodynamic problems and patients requiring extracorporeal life support. Furthermore, patients with brain injuries or severe neurological problems were also excluded. To be able to conduct feasible (eg, with regard to sedation assessment) and also safe and thus ethically acceptable studies, the exclusions are certainly inevitable. However, this naturally leads to limitations of the generalisability of the safety results.

4 | DISCUSSION

This literature review was conducted to assess the available evidence on the safety of long-term sedation with clonidine in critically ill children. Although no critical, uncontrollable issues have been documented, only limited high-quality data are available. This prevents reliable and quantitative conclusions on the occurrence of adverse effects.

We systematically reviewed the literature and identified 11 studies, including four RCTs, which reported on adverse events of clonidine. All studies identified focused on cardiovascular outcomes. Particularly haemodynamic problems, such as bradycardia and hypotension, have been described. This was expected due to the established effect on blood pressure. Indeed, clonidine has been approved for the treatment

of hypertension and hypertensive crises in adults.[4] For children and adolescents, it is used as an off-label drug in this indication.[62,63] The dose ranges for the indications blood pressure reduction and sedation may be close to each other (eg, dose range for intravenous bolus for the treatment of hypertension crises 2–6 μg kg^{-1} per dose[62] vs loading dose for sedation up to 3 μg kg^{-1} over 1 hour[22]).

However, the sample size from the available studies is not sufficient to show an increased incidence of hypotension (ie, the crude increase from 5/85 to 9/89 cases, see Figure 4a). In total, in RCTs, adverse events were only studied in 235 patients receiving clonidine compared to 248 control patients. To demonstrate that the observed increased incidence of hypotension is significant, a much larger sample size would be required. A simple sample size calculation[64] would result in a minimum of 640 patients per group. Additionally, the number would increase if weightings and heterogeneity of the studies would have to be taken into account. For example, the RCTs identified used different comparison groups and event predefinitions. Moreover, influencing factors such as sedation regime, age, concomitant diseases and medication were very heterogeneous. Although we also analysed observational studies, they did not contribute to more evidence for the same reasons. In addition, they were much biased, particularly with regard to study design, information bias and confounding.

In the studies analysed a wide range of dosing regimens was used. The range of continuous intravenous clonidine varied from 0.05 to 3.6 μg kg^{-1} h^{-1} [13,14,18,22,29,31,32,34] with additional loading doses from 0.5 to 3 μg kg^{-1} h^{-1} in some studies.[14,22,34] Nasogastric or oral doses were administered as 3–5 μg kg^{-1} every 8 hours[14] or 5 μg kg^{-1} every 6 hours[30,35] and were thus rather lower, especially if an oral bioavailability of 55% for clonidine is assumed.[65] Due to other external influences such as patient age, severity of illness, different comorbidities or comedication and the risk of bias, no conclusions can be drawn from the data regarding maximum tolerated doses and optimal routes of administration. Based on their kinetics study, Arenas-Lopes et al argued for intravenous administration to achieve a fast and reliable sedation because oral absorption of clonidine may be slowed down in critically ill children.[45] Recently, Hayden et al conducted a simulation study that considered the effective target plasma concentration to evaluate clonidine dosing regimens. As a result, they proposed the following dosing regimen: "Clonidine titrated infusions with a loading dose of 2 μg kg^{-1} followed by a continuous infusion of up to 2 μg kg^{-1} h^{-1} are recommended in hemodynamically stable PICU patients to achieve adequate sedation. Doses should be halved in neonates."[66] Hayden et al assumed this to be an optimized and safe regime but emphasised that cardiovascular stability must be ensured. In this context, the authors also discussed the high incidence of bradycardia and hypotension in the study of Kleiber,[34] as the patients were treated with a dose regimen in the recommended range. They did not anticipate a critical safety problem, as haemodynamic stability did not appear to be compromised by clonidine administration. This was explained by compensation mechanisms and it was concluded that the general PICU population tolerates the recommended dosage well, at least, in none of the studies analysed did the authors consider cardiovascular events a critical safety concern. Some authors

underpinned this view by investigating the clinical consequences, ie, the number of interventions due to bradycardia or hypotension, as shown in Figure 5. The nonsignificant increase in the clonidine groups did not concern the authors in both studies.

In addition, as with Kleiber's approach,[34] further influencing factors for haemodynamic problems must be identified and the consequences should be quantified to detect high-risk patients. Looking at the incidence for bradycardia and hypotension of all studies included, the large variability is particularly noticeable in the observational studies. We attributed this to the risk of bias and the heterogeneity of the study designs. However, there are also patient individual effects that cannot be reasonably standardised, eg, individually titrated clonidine dosages, additional sedation drugs, concomitant diseases, other concomitant medication, and individual distress or anxiety, with physiological reactions, such as tachycardia, which would negate bradycardic side effects. Therefore, very high sample sizes are necessary to ensure valid results.

Because withdrawal effects are a major concern some study authors assessed withdrawal symptoms after stopping long-term sedation. Despite not proving it, they emphasised the positive effect of clonidine on withdrawal symptoms caused by concomitant sedatives (midazolam and/or opioids). However, after abrupt withdrawal of clonidine, the risk of acute rebound hypertension and other withdrawal symptoms (eg, tachycardia, arrhythmia, nervousness, agitation, headache or tremor) is well known. Actually, mild rebound hypertension was observed in one patient in the SLEEPS study.[22] However, this incident did not require treatment and the authors of the study did not consider this as a significant problem. Overall, no study author was concerned about rebound phenomena and withdrawal symptoms of clonidine itself. Preventive measures (eg, weaning for 48 hours with clonidine therapy longer than 48 hours) were apparently effective but should definitely be implemented.

On a qualitative level, the studies reviewed did not reveal hitherto unexpected additional risks. However, some further important safety issues still need to be addressed. Unlike midazolam,[67] clonidine is not yet approved for long-term sedation in paediatric intensive care. It is important to justify an off-label use compared to this alternative. A frequently cited advantage of clonidine is the lower risk of respiratory depressant effects.[68,69] However, even for clonidine a minimal respiratory depressant effect was not entirely excluded experimentally,[70,71] and respiratory symptoms have been described in children after clonidine poisoning.[72–74] Salarian et al[35] included monitoring of respiratory depression, but did not provide reliable results. All other reviewed studies did not focus on this risk. Only two of the studies mentioned this issue in their safety outcomes, but they did not consider it a problem.[22,29] Nevertheless, it would be reasonable to explicitly document and verify respiratory effects in future studies. Unfortunately, information on other less well-known side effects is very sparse: hyperglycaemia and increased body temperature have been considered, but the brief investigations without comparison groups did not allow for reliable conclusions.

In addition, clonidine was considered to be preferred over midazolam to avoid neurotoxicity.[33] However, the observation periods of the studies reviewed were insufficiently long to conclude on this, and we did not found other studies that have explicitly examined neurotoxicity. Watson et al investigated long-term sequelae in paediatric patients with PICU stays because of acute respiratory failure.[75] Besides aetiology of respiratory failure and duration of mechanical ventilation, clonidine was identified as a risk factor during hospitalisation for functional decline. However, this correlation may not allow causal conclusions but should give rise to further research. Therefore, for paediatric long-term sedation, long-term safety issues should also be well investigated and should be essentially included as an outcome in future studies.[76,77]

5 | CONCLUSION

To conclude, the results published to date suggest a safe use, but due to the limitations evidence to support this conclusion is lacking. This review reveals the limited availability of safety data on clonidine used for paediatric long-term sedation. However, valid information on the type, extent, (temporal) predictability, clinical consequences and manageability of adverse effects would be among the prerequisites for standard use. Therefore, further clinical studies are justified and recommended. Until additional data are available, caution is warranted, especially with younger children, with cardiovascular conditions or with polymedication.

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

S.E., J.S. and A.N. contributed to the concept and design of the study. S.E. and G.A. contributed to data acquisition and analyses. All authors contributed to the interpretation of the data. S.E. and A.N. prepared the draft. All authors contributed to the revision and gave final approval to the manuscript.

ORCID

Joseph Standing https://orcid.org/0000-0002-4561-7173
Antje Neubert https://orcid.org/0000-0001-6575-1452

REFERENCES

1. Playfor SD, Vyas H. Sedation in critically ill children. *Curr Paediatr*. 2000;10(1):1-4.
2. Barnes S, Yaster M, Kudchadkar SR. Pediatric sedation management. *Pediatr Rev*. 2016;37(5):203-212.
3. Nguyen V, Tiemann D, Park E, Salehi A. Alpha-2 agonists. *Anesthesiol Clin*. 2017;35(2):233-245.

4. Boehringer Ingelheim Pharma GmbH &Co. KG. Fachinformation Catapresan®. 2018. Available at: http://www.fachinfo.de. Accessed February 2, 2020.

5. Gyires K, Zádori ZS, Török T, Mátyus P. α2-Adrenoceptor subtypes-mediated physiological, pharmacological actions. *Neurochem Int*. 2009;55(7):447-453.

6. Ming X, Mulvey M, Mohanty S, Patel V. Safety and efficacy of clonidine and clonidine extended-release in the treatment of children and adolescents with attention deficit and hyperactivity disorders. *Adolesc Health Med Ther*. Published online. September 2011;2:105-112.

7. Szabo B. Imidazoline antihypertensive drugs: a critical review on their mechanism of action. *Pharmacol Ther*. 2002;93(1):1-35.

8. Bousquet P, Hudson A, García-Sevilla JA, Li J-X. Imidazoline receptor system: the past, the present, and the future. *Pharmacol Rev*. 2020; 72(1):50-79.

9. Playfor S, Jenkins I, Boyles C, et al. Consensus guidelines on sedation and analgesia in critically ill children. *Intensive Care Med*. 2006;32(8): 1125-1136.

10. Hayden JC, Breatnach C, Doherty DR, et al. Efficacy of α2-agonists for sedation in pediatric critical care: a systematic review. *Pediatr Crit Care Med*. 2016;17(2):e66-e75.

11. Romantsik O, Calevo MG, Norman E, Bruschettini M. Clonidine for sedation and analgesia for neonates receiving mechanical ventilation. *Cochrane Database Syst Rev*. 2017;2017:CD012468.

12. Chen K, Lu Z, Xin YC, Cai Y, Chen Y, Pan SM. Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients. *Cochrane Database Syst Rev*. 2015;1:CD010269.

13. Ambrose C, Sale S, Howells R, et al. Intravenous clonidine infusion in critically ill children: dose-dependent sedative effects and cardiovascular stability. *Br J Anaesth*. 2000;84(6):794-796.

14. Kleiber N, de Wildt SN, Cortina G, et al. Clonidine as a first-line sedative agent after neonatal cardiac surgery: retrospective cohort study. *Pediatr Crit Care Med*. 2016;17(4):332-341.

15. Hayden JC, Doherty DR, Dawkins I, et al. The effectiveness of α2 agonists as sedatives in pediatric critical care: a propensity score-matched cohort study. *Crit Care Med*. 2019;47(7):e580-e586.

16. Pereira L, Pinto C, Naughton I, O'Callaghan M, Thiruchelvam T. A five-year observational data analysis of sedation and analgesic requirements for neonatal and paediatric patients supported on ECMO for respiratory failure >7days. *Perfus Ger*. 2019;34(1):228-229.

17. Sanavia E, Mencía S, Lafever SN, Solana MJ, Garcia M, López-Herce J. Sedative and analgesic drug rotation protocol in critically ill children with prolonged sedation. Evaluation of implementation and efficacy to reduce withdrawal syndrome. *Pediatr Crit Care Med*. 2019; 20(12):1111-1117.

18. Michel J, Hofbeck M, Peper A-K, Kumpf M, Neunhoeffer F. Evaluation of an updated sedation protocol to reduce benzodiazepines in a pediatric intensive care unit. *Curr Med Res Opin*. 2020;36(1):1-6.

19. Shein SL, Slain K, Wilson-Costello D, McKee B, Rotta AT. Temporal changes in prescription of Neuropharmacologic drugs and utilization of resources related to neurologic morbidity in mechanically ventilated children with bronchiolitis. *Pediatr Crit Care Med*. 2017;18(12): e606-e614.

20. Blatz A, Rotta A, Wilson-Costello D, Shein S. Trends in neuropharmacologic medications in mechanically ventilated children with medical diseases. *Crit Care Med*. 2019;47(1):468.

21. Pradhan S, Blatz A, Rotta A, Wilson-Costello D, Shein S. Trends in neuropharmacologic agent use in mechanically ventilated young cardiac surgery patients. *Crit Care Med*. 2019;47(1):121.

22. Wolf A, McKay A, Spowart C, et al. Prospective multicentre randomised, double-blind, equivalence study comparing clonidine and midazolam as intravenous sedative agents in critically ill children: the SLEEPS (safety profilLe, efficacy and equivalence in Paediatric intensive care sedation) study. *Health Technol Assess (Winch Eng)*. 2014; 18(71):1-212.

23. Neubert A, Baarslag MA, van Dijk M, et al. The CLOSED trial; CLOnidine compared with midazolam for SEDation of paediatric patients in the intensive care unit: study protocol for a multicentre randomised controlled trial. *BMJ Open*. 2017;7:e016031.

24. Loke YK, Price D, Herxheimer A. Systematic reviews of adverse effects: framework for a structured approach. *BMC Med Res Methodol*. 2007;7:32.

25. Loke YK, Golder SP, Vandenbroucke JP. Comprehensive evaluations of the adverse effects of drugs: importance of appropriate study selection and data sources. *Ther Adv Drug Saf*. 2011;2(2):59-68.

26. Higgins JPT, Green S. (Eds.). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.2 (Updated June 2017)*. http://www. training.cochrane.org/handbook. Accessed January 12, 2018.

27. Faillie J-L, Ferrer P, Gouverneur A, et al. A new risk of bias checklist applicable to randomized trials, observational studies, and systematic reviews was developed and validated to be used for systematic reviews focusing on drug adverse events. *J Clin Epidemiol*. 2017;86: 168-175.

28. Arenas-López S, Riphagen S, Tibby SM, et al. Use of oral clonidine for sedation in ventilated paediatric intensive care patients. *Intensive Care Med*. 2004;30(8):1625-1629.

29. Pohl-Schickinger A, Lemmer J, Hübler M, et al. Intravenous clonidine infusion in infants after cardiovascular surgery. *Paediatr Anaesth*. 2008;18(3):217-222.

30. Duffett M, Choong K, Foster J, et al. Clonidine in the sedation of mechanically ventilated children: a pilot randomized trial. *J Crit Care*. 2014;29(5):758-763.

31. Hünseler C, Balling G, Röhlig C, et al. Continuous infusion of clonidine in ventilated newborns and infants: a randomized controlled trial. *Pediatr Crit Care Med*. 2014;15(6):511-522.

32. Deho A, Sadozai L, Dauger S, Prot-Labarthe S. Use of continuous infusion of clonidine for sedation in critically ill children: indications, efficacy and side effects. *Ann Intensive Care*. 2016;6:107.

33. Kleiber N, De Wildt SN, Cortina G, et al. A comparative analysis of preemptive versus targeted sedation on cardiovascular stability after high-risk cardiac surgery in infants. *Pediatr Crit Care Med*. 2016;17(4): 321-331.

34. Kleiber N, van Rosmalen J, Tibboel D, de Wildt SN. Hemodynamic tolerance to IV Clonidine infusion in the PICU. *Pediatr Crit Care Med*. 2018;19(8):e409-e416.

35. Salarian S, Khosravi R, Khanbabaei G, Bagheri B. Impact of oral clonidine on duration of opioid and benzodiazepine use in mechanically ventilated children: a randomized, double-blind, placebo-controlled study. *Iran J Pharm Res*. 2019;18(4):2157-2162.

36. Prause A, Wappler F, Scholz J, Bause H, Schulte am Esch J. Respiratory depression under long-term sedation with sufentanil, midazolam and clonidine has no clinical significance. *Intensive Care Med*. 2000; 26(10):1454-1461.

37. Mikawa K, Nishina K, Maekawa N, Takao Y, Asano M, Obara H. Attenuation of the catecholamine response to tracheal intubation with oral clonidine in children. *Can J Anaesth*. 1995;42(10):869-874.

38. Blackburn L, Ottaway K, Anderson BJ. The impact of clonidine on sedation after adenotonsillectomy: a prospective audit. *Paediatr Anaesth*. 2014;24(12):1268-1273.

39. Cardesín A, Pontes C, Rosell R, et al. Hypotensive anaesthesia and bleeding during endoscopic sinus surgery: an observational study. *Eur Arch Otorhinolaryngol*. 2014;271(6):1505-1511.

40. Beringer RM, Guard BC, Hawkins R, Segar P. Randomized controlled pilot study: does intraoperative clonidine reduce the incidence of post-hospitalization negative behaviour changes in children who are distressed during induction of general anaesthesia? *Br J Anaesth*. 2015;115(5):795-797.

41. Bergendahl HTG, Eksborg S, Lönnqvist PA. Low-dose intravenous clonidine in children: plasma concentrations and haemodynamic response. *Acta Anaesthesiol Scand*. 1997;41(3):381-384.

42. Ivanova L, Tanchev P. Autohemotransfusion and controlled hypotension in operations of the spine. *Ortop Travmatol*. 2000;36(2):454-457.

43. Jenkins IA, Playfor SD, Bevan C, Davies G, Wolf AR. Current United Kingdom sedation practice in pediatric intensive care. *Paediatr Anaesth*. 2007;17(7):675-683.

44. Molon M, Piva J, Karcher P, Baldissera T. Clonidine associated to morphine and midazolam in children submitted to mechanical ventilation: randomized, double blind and placebo controlled study. *Rev Bras Ter Intensiva*. 2007;19(3):284-291.

45. Arenas-Lopez S, Mulla H, Manna S, Durward A, Murdoch IA, Tibby SM. Enteral absorption and haemodynamic response of clonidine in infants post-cardiac surgery. *Br J Anaesth*. 2014;113(6): 964-969.

46. Karmaniolou I, Krishnan R, Galtrey E, Cleland S, Vijayaraghavan R. Perioperative management and outcome of patients with Rett syndrome undergoing scoliosis surgery: a retrospective review. *J Anesth*. 2015;29(4):492-498.

47. Müller C, Pataky M, Wiesen M, Hünseler C, Roth B. Pharmacokinetics (PK) of clonidine (CLD) as a comedication in analgesia of long-term ventilated neonates and infants. *Monatsschr Kinderheilkd*. 2011;159:71.

48. Kimland E, Nydert P, Odlind V, Böttiger Y, Lindemalm S. Paediatric drug use with focus on off-label prescriptions at Swedish hospitals - a nationwide study. *Acta Paediatr*. 2012;101(7):772-778.

49. Long D, Erickson S. Baby spice: sedation practice in paediatric intensive care evaluation in Australia and New Zealand. *Pediatr Crit Care Med*. 2014;15(4):19.

50. Zimmerman KO, Hornik CP, Ku L, et al. Sedatives and analgesics given to infants in neonatal intensive care units at the end of life. *J Pediatr*. 2015;167(2):299-304.e3.

51. Hayden J, Dawkins I, Breatnach C, et al. A descriptive observational study of sedation outcomes and practices in mechanically ventilated children in an Irish PICU to inform future sedative effectiveness research studies. *Eur J Pediatr*. 2016;175(11):1640-1641.

52. Kleiber N, Mathôt RAA, Ahsman M, Wildschut ED, Tibboel D, De Wildt SN. Sedation with clonidine during pediatric extracorporeal membrane oxygenation (ECMO): a population pharmacokinetic model. *Eur J Pediatr*. 2016;175(11):1476.

53. Kleiber N, Mathôt RAA, Ahsman MJ, Wildschut ED, Tibboel D, de Wildt SN. Population pharmacokinetics of intravenous clonidine for sedation during paediatric extracorporeal membrane oxygenation and continuous venovenous hemofiltration. *Br J Clin Pharmacol*. 2017; 83(6):1227-1239.

54. Hayden J, Breatnach C, Dawkins I, et al. α2 agonists in paediatric critical care sedation: a multi-site retrospective cohort study. *Pediatr Crit Care Med*. 2018;19(6):197.

55. Duffett M, Choong K, Foster J, Menon K, Meade M, Cook DJ. Adjunctive clonidine in the sedation of mechanically ventilated children: a pilot randomized trial. *Intensive Care Med*. 2013;39:S150-S151.

56. Kleiber NK, Clifford MC, Larson GL, Millar JM. The haemodynamic effects of clonidine infusion after neonatal cardiac surgery. *Pediatr Crit Care Med*. 2014;15(4):122.

57. Sheng Y, Standing JF. Pharmacokinetic reason for negative results of clonidine sedation in long-term-ventilated neonates and infants. *Pediatr Crit Care Med*. 2015;16(1):92-93.

58. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.

59. Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. *The Lancet*. 2011;377(9770): 1011-1018.

60. O'Leary F, Hayen A, Lockie F, Peat J. Defining normal ranges and centiles for heart and respiratory rates in infants and children: a cross-sectional study of patients attending an Australian tertiary hospital paediatric emergency department. *Arch Dis Child*. 2015;100(8):733-737.

61. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140(3):e20171904.

62. Seeman T, Hamdani G, Mitsnefes M. Hypertensive crisis in children and adolescents. *Pediatr Nephrol*. 2019;34(12):2523-2537.

63. Sica DA. Centrally acting antihypertensive agents: an update. *J Clin Hypertens*. 2007;9(5):399-405.

64. Noordzij M, Tripepi G, Dekker FW, Zoccali C, Tanck MW, Jager KJ. Sample size calculations: basic principles and common pitfalls. *Nephrol Dial Transplant*. 2010;25(5):1388-1393.

65. Larsson P, Nordlinder A, Bergendahl HTG, et al. Oral bioavailability of clonidine in children. *Paediatr Anaesth*. 2011;21(3):335-340.

66. Hayden JC, Bardol M, Doherty DR, et al. Optimizing clonidine dosage for sedation in mechanically ventilated children: a pharmacokinetic simulation study. Goobie S, ed. *Pediatr Anesth*. 2019;29(10):1002-1010. https://doi.org/10.1111/pan.13715

67. Roche Pharma AG. Fachinformation Dormicum Injektionslösung®. 2018. Available at: http://www.fachinfo.de. Accessed February 10, 2020.

68. Bailey P, Sperry R, Johnson K, et al. Respiratory effects of Clonidine alone and combined with morphine, in humans. *Anesthesiology*. 1991; 74(1):43-48.

69. Pichot C, Ghignone M, Quintin L. Dexmedetomidine and Clonidine: from second- to first-line sedative agents in the critical care setting? *J Intensive Care Med*. 2012;27(4):219-237.

70. Hall JE, Uhrich TD, Ebert TJ. Sedative, analgesic and cognitive effects of clonidine infusions in humans. *Br J Anaesth*. 2001;86(1):5-11.

71. Ooi R, Pattison J, Feldman SA. The effects of intravenous clonidine on ventilation. *Anaesthesia*. 1991;46(8):632-633.

72. Wang GS, Le Lait M-C, Heard K. Unintentional pediatric exposures to central alpha-2 agonists reported to the national poison data system. *J Pediatr*. 2014;164(1):149-152.

73. Lange R, LeRoy JM, Cole J. Apnea in a child following dermal exposure to compounded pain cream. *Clin Toxicol*. 2017;55(7):733.

74. Sullivan R, Ryzewski M, Hodzic E, Holland MG, Marraffa JM. Compounded ointment results in severe toxicity in a pediatric patient. *Clin Toxicol*. 2012;50(7):599-600.

75. Watson RS, Asaro LA, Hutchins L, et al. Risk factors for functional decline and impaired quality of life after pediatric respiratory failure. *Am J Respir Crit Care Med*. 2019;200(7):900-909.

76. Rappaport BA, Suresh S, Hertz S, Evers AS, Orser BA. Anesthetic neurotoxicity — clinical implications of animal models. *N Engl J Med*. 2015;372(9):796-797.

77. Schiller RM, Allegaert K, Hunfeld M, van den Bosch GE, van den Anker J, Tibboel D. Analgesics and sedatives in critically ill newborns and infants: the impact on long-term neurodevelopment. *J Clin Pharmacol*. 2018;58:S140-S150.

78. Leclercq E, Leeflang MMG, van Dalen EC, Kremer LCM. Validation of search filters for identifying pediatric studies in PubMed. *J Pediatr*. 2013;162(3):629-634.e2.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

APPENDIX A.: Search terms

The search terms combined patients (children) and the intervention (clonidine used for sedation). For the search term "children" in PubMed we applied the validated search term of Leclercq et al.[78]

	PubMed	Embase
Clonidine	(clonidine[MeSH terms] OR clonidin* OR clofelin)	('clonidine'/exp OR clonidin* OR clofelin)
	AND	AND
Sedation	(sedation OR anesthesia[MeSH terms] OR anaesthesia OR anesthesia OR sedat*)	('anesthesiological procedure'/exp OR 'sedation'/exp OR 'anaesthesia' OR 'anesthesia' OR 'sedat*')
	AND	AND
Children	(Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school [tiab] OR school*[tiab] OR prematur* OR preterm* OR PICU OR NICU)	([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim)