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ABOUT COVER

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AIMS AND SCOPE

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SYSTEMATIC REVIEWS

Clonidine use during dexmedetomidine weaning: A systematic review

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Abstract

BACKGROUND

Dexmedetomidine is a centrally acting alpha-2A adrenergic agonist that is commonly used as a sedative and anxiolytic in the intensive care unit (ICU), with prolonged use increasing risk of withdrawal symptoms upon sudden discontinuation. As clonidine is an enterally available alpha-2A adrenergic agonist, it may be a suitable agent to taper off dexmedetomidine and reduce withdrawal syndromes. The appropriate dosing and conversion strategies for using enteral clonidine in this context are not known. The objective of this systematic review is to summarize the evidence of enteral clonidine application during dexmedetomidine weaning for prevention of withdrawal symptoms.

AIM

To systematically review the practice, dosing schema, and outcomes of enteral clonidine use during dexmedetomidine weaning in critically ill adults.

METHODS

This was a systematic review of enteral clonidine used during dexmedetomidine weaning in critically ill adults (≥ 18 years). Randomized controlled trials, prospective cohorts, and retrospective cohorts evaluating the use of clonidine to

wean patients from dexmedetomidine in the critically ill were included. The primary outcomes of interest were dosing and titration schema of enteral clonidine and dexmedetomidine and risk factors for dexmedetomidine withdrawal. Other secondary outcomes included prevalence of adverse events associated with enteral clonidine use, re-initiation of dexmedetomidine, duration of mechanical ventilation, and ICU length of stay.

RESULTS
A total of 3427 studies were screened for inclusion with three meeting inclusion criteria with a total of 88 patients. All three studies were observational, two being prospective and one retrospective. In all included studies, the choice to start enteral clonidine to wean off dexmedetomidine was made at the discretion of the physician. Weaning time ranged from 13 to 167 h on average. Enteral clonidine was started in the prospective studies in a similar protocolized method, with 0.3 mg every 6 h. After starting clonidine, patients remained on dexmedetomidine for a median of 1-28 h. Following the termination of dexmedetomidine, two trials tapered enteral clonidine by increasing the interval every 24 h from 6 h to 8h, 12h, and 24 h, followed by clonidine discontinuation. For indicators of enteral clonidine withdrawal, the previously tolerable dosage was reinstated for several days before resuming the taper on the same protocol. The adverse events associated with enteral clonidine use were higher than patients on dexmedetomidine taper alone with increased agitation. The re-initiation of dexmedetomidine was not documented in any study. Only 17 (37%) patients were mechanically ventilated with median duration of 3.5 d for 13 patients in one of the 2 studies. ICU lengths of stay were similar.

CONCLUSION
Enteral clonidine is a strategy to wean critically ill patients from dexmedetomidine. There is an association of increased withdrawal symptoms and agitation with the use of a clonidine taper.

Key Words: Clonidine; Dexmedetomidine; Intensive care unit; Withdrawal; Weaning

Core Tip: In this systematic review of enteral clonidine use during dexmedetomidine weaning in critically ill patients, an association of increased withdrawal symptoms and agitation with the use of a clonidine taper and no difference in intensive care unit length of stay with or without clonidine taper was observed. However, varied techniques and a small total sample size restrict utility of the findings.

INTRODUCTION

In critically ill patients, agitation and delirium lead to poor clinical outcomes, such as prolonged mechanical ventilation, intensive care unit (ICU), and hospital length of stay (LOS)[1,2]. To optimize outcomes related to sedation in ICU patients, the 2018 Society of Critical Care Medicine practice recommendations suggest avoiding benzodiazepines[3]. Dexmedetomidine and propofol are the most commonly used sedatives in this group[3]. They have resulted in a shorter duration of mechanical ventilation as compared to benzodiazepines[3-6].

Dexmedetomidine, an intravenous (IV) alpha-2A adrenergic agonist provides cooperative sedation, sympatholysis, and analgesic-sparing effects without inducing respiratory depression and is frequently used in critically ill patients to treat pain, agitation, and delirium[7,8]. Due to a lack of central depression, dexmedetomidine is an attractive sedative clinically for weaning from mechanical ventilation and awake sedation in non-intubated patients. Dexmedetomidine was licensed by the Food and Drug Administration as a sedative with a 24-h time limit; however, studies have shown that it is safe and effective for up to 5 d with bradycardia and hypotension being the most commonly reported adverse effects[4,9-11]. Other drawbacks have included the cost of drug acquisition and availability only in an IV formulation[12-14]. Sudden cessation of the drug can lead to withdrawal symptoms such as agitation, tachycardia, hypertension, and other hypersympathetic conditions[15]. Clonidine, a

structurally comparable alpha-2A that is widely used as an antihypertensive, sedative, and sympatholytic, could be an alternate enteral medication for patients transitioning from dexmedetomidine[16].

The use of enteral clonidine may be a potential strategy for weaning from dexmedetomidine to prevent withdrawal syndromes[17,18]. However, dexmedetomidine has an eight-fold higher affinity for central alpha-2A receptors than clonidine; as a result, the best dosing and conversion strategies for clonidine in this context are unknown[8]. The purpose of this systematic review was to summarize the available evidence regarding the use of enteral clonidine to prevent withdrawal symptoms during dexmedetomidine weaning.

MATERIALS AND METHODS

This was a systematic review designed to assess the use of enteral clonidine to prevent withdrawal syndromes in critically ill adults weaning from dexmedetomidine. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 guidelines[19]. The protocol was *a priori* registered in the PROSPERO database (No. CRD42022330666).

Data sources and eligibility criteria

The systematic search was designed and executed by a skilled medical librarian (DJG). We searched for the concepts of enteral clonidine and dexmedetomidine combined with variant keywords and standardized index terms. The search was performed in April 2022 and included the electronic databases Ovid Evidence-Based Medicine Reviews, Ovid Embase, Ovid Medline, Scopus, and Web of Science Core Collection. The search was limited to the English language and did not include animals or pediatrics. The full search strategy is detailed in the Supplementary Table 1.

Eligible studies to be included were those that reported randomized-, crossover-, or parallel-designed clinical trials, prospective and retrospective longitudinal (cohort) studies, and cross-sectional studies (non-longitudinal studies) that reported on the use of enteral clonidine specifically for the purposes of weaning from dexmedetomidine to avoid withdrawal syndromes. Studies were excluded if they reported on pediatric patients (age < 18 years), animal or other non-clinical experiments, case reports, case series, review articles, editorial, and book chapters. Studies using intravenous clonidine or oral alpha-2A agonists other than clonidine were also excluded. No restrictions were placed on date of publication. In addition, a relevant search was performed by Reference Citation Analysis database (https://www.referencecitationanalysis.com/) to supplement and improve the highlights of the latest cutting-edge research results.

Article selection and data extraction

Article titles and abstracts were screened by two independent reviewers (SSR, MEW) for inclusion based on the pre-defined inclusion and exclusion criteria. Discrepancies between reviewers were adjudicated by a third independent reviewer (EDW) with consultation of a senior investigator (PMW) if necessary. The full text files of the candidate articles were randomly assigned to the two independent reviewers (SSR, MEW) to screen for final inclusion. Discrepancies between reviewers were adjudicated by a third independent reviewer (EDW) with consultation of a senior investigator (PMW) if necessary. All article screening was performed using Covidence software (Melbourne, Australia).

The data from the final articles meeting inclusion criteria were abstracted from full-text documents by two independent abstractors (JAG, LAW). Disagreements were adjudicated by discussion between the abstractors, and consultation of an adjudicator (EDW) when agreement was unattainable with consultation of a senior investigator (PMW) if necessary. The data abstracted included details regarding the publication information, study design, demographic data, details regarding the dosing schema and protocols, and outcomes information.

Risk of bias assessment

The Risk of Bias in Non-randomized Studies of Interventions tool was used to assess for risk of bias[20]. The tool was applied by two independent assessors (JAG, LAW) and disagreements were adjudicated by the senior investigators (PMW, NJS). The risk of bias information was summarized using R version 4.2.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2022) and the robvis version 0.3.0 package[21].

Outcomes and data analysis

The primary outcomes of interest were the dosing and titration schema of enteral clonidine and dexmedetomidine. Secondary outcomes included risk factors for dexmedetomidine withdrawal, incidence of adverse events associated with enteral clonidine use, re-initiation of dexmedetomidine, duration of mechanical ventilation, and ICU LOS. The data were summarized in descriptive format. No inferential analysis was performed.

RESULTS

Trial inclusion

The initial search identified 3427 studies. Following removal of duplicates and excluded records, 29 full-text articles were assessed for eligibility. Three (10.3%) of these met the inclusion criteria and were included in the analysis[22-24]. The results of the systematic search are summarized in Figure 1.

Trial and patient characteristics

Two of the included studies were prospective with one double cohort observational study and the other an observational pilot study[22,23]. The third was a retrospective observational study[24]. A total of 88 participants were included across the 3 studies. All studies were performed in the United States, and publication dates spanned from 2015 to 2020. Characteristics of all the studies included are detailed in Table 1. Males outnumbered females in all studies, with the most common initial diagnosis on admission being respiratory or heart disease, followed by sepsis, gastrointestinal disorders, trauma, neurological issues, and substance abuse. Indications of dexmedetomidine and enteral clonidine taper use were agitation, delirium, substance abuse, post procedural and intolerance of other sedatives.

Dosing and titration schema

The decision to initiate enteral clonidine to wean dexmedetomidine was per clinician discretion in all included studies (Table 2). Bhatt *et al*[22] required at least 72 h of dexmedetomidine prior to enteral clonidine initiation for study inclusion with a median of 167 h [interquartile range (IQR) 115-217.1]; over the entire dexmedetomidine course patients received a mean dose of 0.9 mcg/kg/h and standard deviation of 0.3. Patients in the Gagnon *et al*[23] study had shorter median dexmedetomidine duration prior to enteral clonidine initiation of 33 h (IQR 21-47.5) at a median rate of 1 mcg/kg/h (IQR 0.7-1.2). Dexmedetomidine duration prior to enteral clonidine was shortest in the Terry *et al*[24] study with a median of 24 h (IQR 14.5-39) for patients who had dexmedetomidine discontinued within 8 h of clonidine initiation with a median dose at time of clonidine initiation of 0 mcg/kg/h (IQR 0-0.25). The group requiring more than 8 h of enteral clonidine to wean dexmedetomidine received a median of 13 h (IQR 4-32) of dexmedetomidine at a rate of 0.7 mcg/kg/h (IQR 0.45-0.7). Enteral clonidine was initiated in a similar protocolized fashion by Gagnon *et al*[23] and Bhatt *et al*[22], starting with 0.3 mg every 6 h. Patients with a dexmedetomidine rate < 0.7 mcg/kg/h, weight < 100 kg, or age > 65 years were initiated on 0.2 mg at the same interval. The doses were reduced by 0.1 mg for bradycardia and hypotension and increased by 0.1 mg for agitation. Dexmedetomidine dose was weaned by 25% every 6 h if no agitation requiring rescue medications had occurred. Terry *et al*[24] initiated enteral clonidine at 0.1 mg with non-protocolized uptitration every 6-8 h until the Richmond Agitation-Sedation Scale (RASS) goal was met, or hemodynamics prohibited further uptitration. Dexmedetomidine was weaned as soon as patients responded to clonidine as assessed by RASS, Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), and hemodynamics without a defined protocol.

Patients spent a median of 19 h (IQR 9.5-23) on dexmedetomidine after enteral clonidine initiation in the Bhatt *et al*[22] study. Dexmedetomidine was utilized for a median of 23 h (IQR 2-53) for patients in the Gagnon *et al*[23] study after enteral clonidine was started. Terry *et al*[24] separately evaluated patients able to wean off dexmedetomidine within 8 h of enteral clonidine initiation from those requiring more than 8 h. Of 26 patients included, 17 (65%) were weaned off dexmedetomidine within 8 h with a median transition time of 1 h (IQR 0.5-4.25). Patients requiring more than 8 h to wean off dexmedetomidine after clonidine initiation had a median transition time of 28 h (IQR 20-56.5).

After dexmedetomidine discontinuation, Bhatt *et al*[22] tapered enteral clonidine by increasing the interval every 24 h from 6 h to 8h, then 12h, then 24 h, followed by clonidine discontinuation without any individual dose reduction. Gagnon *et al*[23] also increased the dosing interval in the same manner every 24-48 h without dose reduction. For signs of clonidine withdrawal, the previously tolerated dose was reinitiated for several days and then an attempted taper resumed on the same protocol. Terry *et al* [24] did not describe any subsequent enteral clonidine taper.

Outcomes

Dexmedetomidine re-initiation: No patients had dexmedetomidine restarted for documented enteral clonidine failure, albeit transition failure was identified as inability to wean dexmedetomidine after 8 h (Table 3)[24]. Failed transition had a median transition time of 28 h (IQR = 20-56.5). Patients who failed transition had alcohol withdrawal, septic shock, endocarditis, lung transplant and aortic valve replacement[24]. None of the patients were restarted on dexmedetomidine in the observation pilot trial [23]. Bhatt *et al*[22] showed 93% of patients were able to stop dexmedetomidine within 24 h of enteral clonidine initiation. No explicit details on re-initiation were provided.

Duration of mechanical ventilation: Seventeen (37%) patients were mechanically ventilated of the 2 studies that reported this data[23,24]. Gagnon *et al*[23] reported duration of mechanical ventilation of 3.5 d (IQR 0-10.5) and mechanical ventilation free days of 24.5 (IQR 15.3, 28)[23]. One study, despite having the bulk of its patients admitted with respiratory diagnosis to the ICU, did not provide data regarding

Table 1 Trial characteristics

Ref.	Type of study	Study dates	Total patients studied	ICU	Admitting diagnosis	Mechanical ventilation	Age (yr)	Sex	Weight (kg)	BMI (kg/m²)	APACHE score
Terry *et al* [24], 2015	Single-center, retrospective, observational study	February 1, 2013-February 28, 2014	26	Cardiac surgery 21 (80.7%), thoracic 3 (11.5%), neurology 1 (3.8%), surgical 1 (3.8%)	Respiratory 4 (15.4%), cardiac 20 (76.9%), trauma 1 (3.8%), substance abuse 1 (3.8%)	4 (14.8%)	54.4 ± 16.9[1]	Male: 17 (63%), female: 9 (37%)	NR	32 ± 3.1[1]	18 (14-22)[2]
Gagnon *et al*[23], 2015	Single-center prospective observational pilot study	January, 2014-March, 2014	20	Mixed medical, surgical, neuro ICU	Respiratory 12 (60%), neurologic 1 (5%), trauma 2 (10%), substance abuse 2 (10%), other 3 (15%)	13 (65%)	62 (54-73)[2]	Male: 13 (65%), female: 7 (35%)	NR	29.9 (26.5-33.1)[2]	62 (54-80)[2]
Bhatt *et al* [22], 2020	Single-center, prospective, double cohort observational study	November, 2017-December, 2018	42	Medical-surgical 10 (67%) *vs* 13 (48%), cardiothoracic 3 (20%) *vs* 8 (30%), neurosurgical 2 (13%) *vs* 6 (22%)	Respiratory 16 (38.1%), cardiac 12 (28.6%), gastroenterological 5 (11.9%), neurologic 2 (4.8%), trauma 1 (2.4%), sepsis/shock 6 (14.3%)	NR	Clonidine taper: 58 (43-66[2] *vs* no taper: 54 (45-66)[2] (*P* = 0.93)	Male: 27 (64%), female: 15 (36%)	Clonidine taper: 86.9 (67.3-94.1)[2] *vs* no taper 91.6 (78.9-101.1)[2] (*P* = 0.19)	NR	NR

[1]Data reported as mean ± SD.

[2]Data reported as median (interquartile range).

NR: Not reported; ICU: Intensive care unit; BMI: Body mass index, APACHE: Acute physiology and chronic health evaluation.

the need for supplemental oxygenation or ventilation[22].

ICU LOS: All three studies reported ICU LOS; two of the studies appear to have similar ICU LOS in patients that had weaning protocol with no comparison[23,24]. Only one study specifically evaluated and found no statistically significant difference in ICU LOS between enteral clonidine taper *vs* no taper (22.7 d *vs* 17 d; *P* = 0.3) and time to discharge after dexmedetomidine wean in either group (7.2 d *vs* 7 d; *P* = 0.69)[22].

Adverse events: Terry *et al*[24] did not specify symptoms associated with enteral clonidine withdrawal. Gagnon *et al*[23] discovered that only one patient met withdrawal criteria (blood pressure > 180/120 mmHg) after stopping enteral clonidine despite a 6-d taper; this patient was also tapering off methadone and clonazepam. Bhatt *et al*[22] provided significant withdrawal data as defined by ³2 of: heart rate > 90, CAM positive, RASS > 1, systolic blood pressure > 140, or Withdrawal Assessment Tool Version 1 (WAT-1) > 2. Patients who experienced at least two withdrawal symptoms from dexmedetomidine during a single assessment during the wean period were not significantly different between the two groups (73% for patients who were given an enteral clonidine taper and 59% for patients who were weaned off dexmedetomidine alone; *P* = 0.27). The most common symptoms reported by both groups on the WAT-1 were loose stools, fever, and agitation. Those on enteral clonidine taper had more withdrawal symptoms, notably agitation (RASS > 1), than patients on

Table 2 Dosing schemes reported in study methods

Ref.	Formal protocol	Dexmedetomidine indication	Threshold for clonidine use	Initial clonidine dose	Dexmedetomidine wean	Clonidine taper
Terry *et al*[24], 2015	No	Primarily for sedation after cardiac surgery	No standard	No standard. 0.1 mg three times daily commonly used	No standard	No standard
Gagnon *et al*[23], 2015	Yes	Agitation: 12 (60%); Alcohol withdrawal: 3 (15%); Delirium: 2 (10%); Intolerance to other sedatives: 3 (15%)	Hemodynamically stable patients; Favorable response to DEX for 12-24 h	0.2-0.5 mg every 6 h; Start at 0.2 mg with DEX doses of < 0.7 μg/kg/h, weight < 100 kg or age > 65 yr; Start with 0.5 mg every 6 h for all other patients	Decrease DEX dose by 25% of baseline within 6 h of clonidine administration (as long as no rescue meds were needed for agitation)	Extend the dosing interval to every 8, 12 and 24 h every 1-2 d as tolerated until discontinuation
Bhatt *et al*[22], 2020	Yes	No clear selection criteria; patients with substance withdrawal were excluded	Variable; Clonidine taper and DEX wean started together	0.3 or 0.2 mg every 6 h; Start at 0.2 mg with DEX < 0.7 μg/kg/h, weight < 100 kg, age > 65 yr old; Start with 0.3 mg every 6 h for all other patients	Decrease DEX dose by 25% of baseline from 0 h to 6 h, and continue dose reduction by 25% every 6 h while on clonidine	Extend the dosing interval to every 8, 12 and 24 h every 1-2 d as tolerated until discontinuation

DEX: Dexmedetomidine.

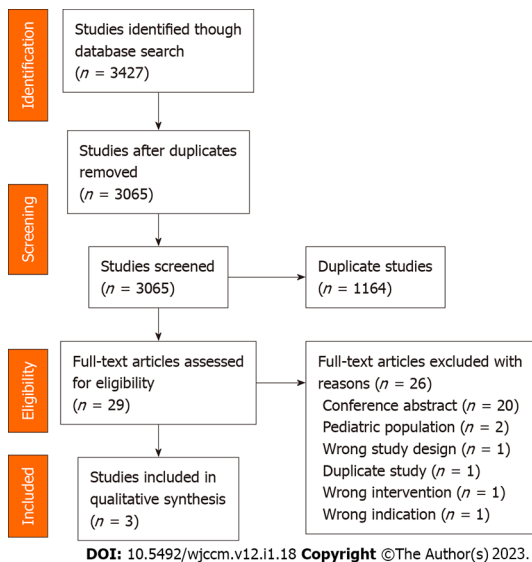**DOI:** 10.5492/wjccm.v12.i1.18 **Copyright** ©The Author(s) 2023.

Figure 1 Study flow diagram.

dexmedetomidine taper (40% *vs* 11%; *P* = 0.05). During the weaning period, there was no difference in the use of propofol, antipsychotics, benzodiazepines, or ketamine between groups. Patients on enteral clonidine taper had a higher average daily dexmedetomidine rate (mcg/kg/h) than patients on a dexmedetomidine alone taper, although the total infusion dose in g/h was not significantly different between groups[22].

Socioeconomic factors: Gagnon *et al*[23] reported an estimated $15360-$52140 cost reduction with enteral clonidine usage based on drug acquisition cost alone assuming a minimum of 24 h of enteral clonidine in place of dexmedetomidine per patient and a maximum of substituting the entire enteral clonidine course with continuous dexmedetomidine[23]. Bhatt *et al*[22] reported an average cost savings of $1553 per patient, also based solely on drug acquisition costs. Gagnon *et al*[23] reported 25% (5/20) of the patients were discharged on enteral clonidine with 20% (4/20) receiving instructions to taper off the medication. Terry *et al*[24] discovered 54% (14/26) of patients were continued on enteral clonidine at ICU transfer with 23% (6/26) of patients being discharged home on clonidine unintentionally.

Risk of bias: In the risk of bias assessment, two studies[22,23] were deemed to be moderate risk and one study[24] was deemed to be serious risk (Figure 2). The primary reasons for a serious risk of bias were

Table 3 Outcomes data

Outcomes data	Terry *et al*[24], 2015	Gagnon *et al*[23], 2015	Bhatt *et al*[22], 2020
Breakthrough withdrawal	NR	1[1]	Taper 11 (73%); No taper 16 (59%)[2]
Discharged on clonidine	Out of ICU: 14 (54%); Out of hospital: 6 (23%)	5 (25%)	NR
Use of other agents			
Propofol	NR	No individual data	Taper: 5 (33%); No taper: 8 (30%)
Ketamine	NR	NR	Taper: 1 (6.7%); No taper: 6 (22.2%)
Benzodiazepines	Clonidine: 2 (22%); No clonidine: 5 (29%)	No individual data	Taper: 3 (20%); No taper: 3 (11%)
Antipsychotics	Clonidine: 4 (44%); No clonidine: 3 (18%)	DEX maintenance dose	Taper: 9 (60%); No taper: 10 (37%) (*P* = 0.2)
Opioids	Clonidine: 7 (78%); No clonidine: 13 (76%)	No individual data	No individual data
Hemodynamic changes			
Tachycardia	NR	NR	Taper: 12 (80%); No taper: 20 (74%)
Hypertension	NR	DEX maintenance dose: 0; Transition: 0; Clonidine maintenance: 0; Clonidine taper final day: 0; Post clonidine: 1 (6%)	Taper: 6 (40%); No taper: 8 (30%)
Bradycardia	NR	DEX maintenance dose: 0; Transition: 0; Clonidine maintenance: 1 (5%); Clonidine taper final day: 1 (6%); Post clonidine: 0	0
Hypotension	Clonidine: 4 (44%); No clonidine: 6 (35%)	DEX maintenance dose: 8 (40%); Transition: 7 (35%); Clonidine maintenance: 4 (20%); Clonidine taper final day: 2 (12%); Post clonidine: 2 (25%)	0
Sedation assessment score	RASS; Clonidine: 0 (-2 to 2); No clonidine: 0 (0-2)	SAS Score outside the goal of 3-4; DEX maintenance: 10 (50%); Transition: 10 (50%); Clonidine maintenance: 9 (45%); Clonidine taper final day 13 (76%); Post clonidine: 2 (25%)	NR
CAM ICU	Clonidine: 4 (44%); No clonidine: 3 (18%), *P* = 0.036	DEX maintenance: 10 (50%); Transition: 11 (55%); Clonidine maintenance: 9 (45%); Clonidine taper final day: 13 (76%); Post clonidine: 3 (38%)	Taper: 11 (73%); No taper: 17 (63%)
Duration of mechanical ventilation (d), median (IQR)	NR	3.5 (0, 10.5)	NR
Hospital length of stay (d), median (IQR)	8 (4, 10.5)	16.5 (10.5, 29.5)	NR
ICU length of stay (d), median (IQR)	12.5 (7, 28)	9.5 (5, 16.5)	Taper: 22.7; No taper: 17
Mortality	0	2 (10%)	NR

[1]Systolic blood pressure (SPB) > 180/120 after stopping despite 6-d taper, but was also tapering off methadone and clonazepam so causality if not clear.
[2]Significant withdrawal as defined by paper (≥ 2 heart rate > 90, Confusion Assessment Method positive, Richmond Agitation-Sedation Scale > 1, SBP > 140, Withdrawal Assessment Tool Version 1 > 2).
DEX: Dexmedetomidine; NR: Not reported; SAS: Sedation-Agitation scale.

confounding, participant selection, and deviations from the intended interventions given the observational nature of the design[24]. Additionally, confounding, participant selection, and outcomes measurements were common reasons for a moderate risk of bias in the other studies[22,23].

DISCUSSION

This systematic review of the literature summarized the use of enteral clonidine for weaning of parental dexmedetomidine in the critically ill, dosing and titration schema of enteral clonidine and
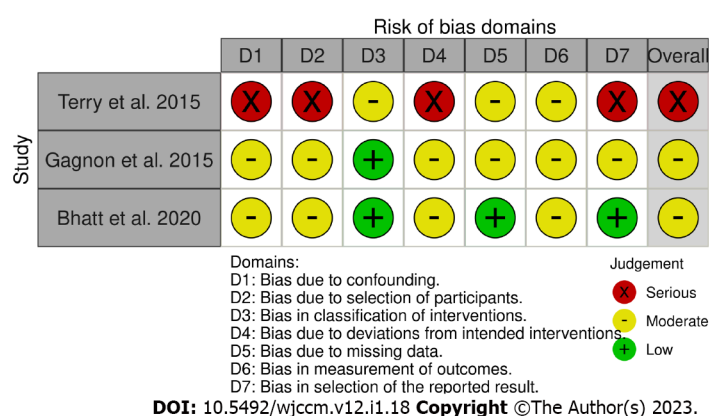
Risk of bias domains

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Terry et al. 2015	X	X	-	X	-	-	X	X
Gagnon et al. 2015	-	-	+	-	-	-	-	-
Bhatt et al. 2020	-	-	+	-	+	-	+	-

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
X Serious
- Moderate
+ Low

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Figure 2 Risk of bias assessment.

dexmedetomidine, prevalence of adverse events associated with clonidine use, re-initiation of dexmedetomidine, duration of mechanical ventilation and ICU LOS. Meta-analysis was not feasible due to differences in methodology, patients, and procedures that led to variation in the reported results between studies.

Weaning off dexmedetomidine with enteral clonidine has gained much attention for the potential benefits of reduced ICU LOS and costs. Clonidine has shown promise in minimizing the withdrawal symptoms associated with cessation of prolonged dexmedetomidine[25]. Clonidine, like dexmedetomidine, is a centrally acting alpha 2 agonist and has a longer half-life (8-12 h *vs* 2 h); however, dexmedetomidine has an eight-fold higher affinity for central alpha receptors than clonidine[8]. Clonidine is thought to reduce central nervous system hyperactivity after dexmedetomidine withdrawal due to its alpha 2 agonist actions and decreased affinity for the alpha 2 receptors. Our review focusing on enteral clonidine for dexmedetomidine weaning in adults resulted in three studies, two prospective and one retrospective. Importantly, no randomized controlled trials were identified.

The results of this systematic review leave many unanswered questions regarding the optimal utility of enteral clonidine in the setting of dexmedetomidine weaning. It is difficult to draw comparisons among the available data from the three studies due to the heterogeneity of the groups studied. There seems to be a common dosing scheme for enteral clonidine in the setting of weaning from dexmedetomidine based on Gagnon *et al*[23] and their institutional experience with the medication. However, the process of determining who received enteral clonidine in the reviewed studies was largely left to clinician discretion, limiting the ability to draw conclusions about the impact of clonidine. For example, although Bhatt *et al*[22] demonstrated a higher incidence of agitation and rescue antipsychotic dosing in the patient group receiving enteral clonidine, potential confounders include unknown patient factors that led to higher dexmedetomidine dosing and the clinician's need to provide clonidine as a treatment rather than to evaluate its comparative effect vs. dexmedetomidine taper alone.

Dexmedetomidine is typically restricted to use in areas with critical care personnel and monitoring available such as the ICU and the perioperative care area. While it is valuable to have a study design with an inclusive patient population, the inclusion of both medical and postoperative patients in the studies reviewed pose challenges to the generalizability of the findings. For example, the sedation needs for a cardiac surgery patient in a rapid recovery protocol and the rapidity of sedation and mechanical ventilation liberation is often quite different than the medical patient requiring both treatment and stability after an acute cardiorespiratory insult requiring escalation to critical care needs. Terry *et al*[24] was highly skewed toward a post cardiac surgery population, whereas Gagnon *et al*[23] and Bhatt *et al* [22] included more mixed medical-surgical patients. The numerically lower total duration of dexmedetomidine in Terry *et al*[24] may have allowed for a lower general dose of enteral clonidine (*i.e.* 0.1 mg per dose) compared to the standard 0.2-0.3 mg clonidine doses used in the other two studies. However, given the lack of detail regarding exact dosing plan and the liberty clinicians were allotted regarding dosing selection, it is difficult to draw specific conclusions beyond the generalities offered in the study methods.

Adverse events from dexmedetomidine withdrawal included anxiety, agitation, decreased sleep, loose stools, emesis, tremors, and increased secretions[26]. Similarly, well-described phenomenon attributed to cessation of adrenal catecholamine secretion blockade and a subsequent surge in their circulating levels is associated with clonidine withdrawal resulting in rise in blood pressure, agitation, insomnia, and palpitations[27]. Risk factors for withdrawal are not known and were not identified in the studies reviewed. Further understanding of the risk factors for withdrawal and targeting appropriate patients for weaning could help minimize harm and improve quality of care. Patients on the enteral clonidine taper appeared to have more withdrawal symptoms than patients on dexmedetomidine taper. Re-initiation of dexmedetomidine was not explicitly addressed in any of the studies for withdrawal and should be an area of further investigation.

Although cost-effectiveness data is limited, the anticipated cost savings from drug acquisition ranged from $819 to $2338 per patient in two of the studies that reported data[22,23]. This price solely includes the drug acquisition cost and excludes the additional costs associated with dexmedetomidine, such as a dedicated ICU service line, monitoring, and titration. As a result, the shorter time on dexmedetomidine infusion following clonidine commencement may be greatly understated by these values.

Notably, in the two studies that reported information on enteral clonidine continuation at discharge from the hospital, approximately 25% of patients were still taking the medication[23,24]. Terry *et al*[24] also reported over half of patients were still taking enteral clonidine upon transfer from the intensive care unit. Several medications started in the ICU to expedite discharge, including antipsychotics and midodrine, are frequently prolonged without proper indication during transfer and upon discharge[28, 29]. An order set and medication reconciliation during transitions of care may be helpful techniques for preventing the unintentional continuation of clonidine.

Strengths of this systematic review include the identification of a feasible enteral clonidine dosing strategy protocolized by Gagnon *et al*[23] that has been applied to other institutions as evidenced by Bhatt *et al*[22] and the elucidation of areas that could be optimized when utilizing enteral clonidine for dexmedetomidine weaning such as appropriate discontinuation prior to hospital discharge and the potential association of increased hypersympathetic withdrawal symptoms with its use. This systematic review has several limitations. All three studies have insufficient sample sizes, preventing the detection of withdrawal symptoms. Only one study had a matched control group, despite selection bias based on withdrawal risk assessment, which was not reported in any of the studies. Indications for weaning protocol varied according to the patient group and ICU site. There was heterogeneity of the research and data regarding the start date of clonidine weaning. The broad use of clinician discretion in the determination of enteral clonidine use and dosing limits the ability to systematically evaluate the available literature. Lastly, due to the heterogeneity in the reporting of the outcomes, quantitative meta-analysis was not possible.

CONCLUSION

Enteral clonidine has been utilized as a strategy to wean patients from parenteral dexmedetomidine due to similar mechanisms of action and potential for reduced costs and shorter ICU requirements. However, guidance on an appropriate taper strategy and resultant outcomes is limited. This systematic review investigated the literature related to weaning dexmedetomidine with and without an enteral clonidine taper. While there are some patterns in dosing schedules among the studies included, there is no consensus regarding an ideal taper strategy and the decision to utilize an enteral clonidine taper is left to clinical judgment. There may be an association of increased withdrawal symptoms and agitation with the use of an enteral clonidine taper, however we did not observe any appreciable difference in ICU LOS with or without a clonidine taper. Further research into risk factors for withdrawal, dose, and duration of dexmedetomidine use followed with appropriate clonidine dose and taper is needed.

ARTICLE HIGHLIGHTS

Research background
Clonidine, an enterally available alpha-2A adrenergic agonist, may be a suitable agent to taper off parenteral dexmedetomidine (centrally acting alpha-2A adrenergic agonist) and reduce withdrawal syndromes. This could lead to reduced intensive care unit (ICU) length of stay (LOS), among other outcomes. However, limited data exist on this topic.

Research motivation
To determine if oral clonidine is useful to wean off parenteral dexmedetomine and reduce ICU LOS.

Research objectives
To systematically review the practice, dosing schema, and outcomes of enteral clonidine use during dexmedetomidine weaning in critically ill adults.

Research methods
This was a systematic review of randomized controlled trials, prospective and retrospective cohorts, on the use of enteral clonidine during dexmedetomidine weaning in critically ill adults (≥ 18 years). The primary outcomes of interest were dosing and titration schema of enteral clonidine and dexmedetomidine and risk factors for dexmedetomidine withdrawal.

Research results

Three observational studies were included (two prospective and one retrospective). Weaning time ranged from 13 to 167 h on average. The adverse events associated with enteral clonidine use were higher than patients on dexmedetomidine taper alone with increased agitation. The re-initiation of dexmedetomidine was not documented in any study. Only 17 (37%) patients were mechanically ventilated with median duration of 3.5 d for 13 patients in one of the 2 studies. ICU lengths of stay were similar.

Research conclusions

Enteral clonidine is a strategy to wean critically ill patients from parenteral dexmedetomidine. However, there is an association of increased withdrawal symptoms and agitation with the use of a clonidine taper.

Research perspectives

It is unclear if oral clonidine is useful in weaning from dexmedetomidine. More data are needed in terms of both dosing schedule and outcomes.

FOOTNOTES

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