Can J Anesth/J Can Anesth (2019) 66:318–327
https://doi.org/10.1007/s12630-018-01289-1

REVIEW ARTICLE/BRIEF REVIEW

A systematic review of interventions to facilitate extubation in patients difficult-to-wean due to delirium, agitation, or anxiety and a meta-analysis of the effect of dexmedetomidine

Revue systématique des interventions visant à faciliter l'extubation de patients difficiles à sevrer en raison d'un délirium, d'une agitation ou d'anxiété, et méta-analyse de l'effet de la dexmédétomidine

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Received: 15 May 2018 / Revised: 29 October 2018 / Accepted: 30 October 2018 / Published online: 23 January 2019

Abstract

Background *Delirium, agitation, and anxiety may hinder weaning from mechanical ventilation and lead to increased morbidity and healthcare costs. The most appropriate clinical approach to weaning in these contexts remains unclear and challenging to clinicians. The objective of this systematic review was to identify effective and safe interventions to wean patients that are difficult-to-wean from mechanical ventilation due to delirium, agitation, or anxiety.*

Methods *A systematic review was performed using MEDLINE, EMBASE, and PubMed. Studies evaluating mechanically ventilated patients deemed difficult-to-wean due to delirium, agitation, or anxiety, and comparing the effects of an intervention with a comparator arm were*

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12630-018-01289-1) contains supplementary material, which is available to authorized users.

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sought. Time-to-extubation was the primary outcome while the secondary outcome was intensive care unit (ICU) length of stay.

Results *From 10,860 studies identified, eight met the inclusion criteria: six studies assessed dexmedetomidine while the remaining two assessed loxapine and biofeedback. Pooled analysis of studies assessing dexmedetomidine showed reduced time-to-extubation (six studies, n = 303) by 10.9 hr compared with controls (95% confidence interval [CI], -15.7 to -6.1; I^2 = 68%) and ICU length of stay (four studies, n = 191) by 2.6 days (95% CI, 1.9 to 3.3; I^2 = 0%). Nevertheless, the evidence was deemed to be of low quality given the small sample sizes and high heterogeneity. Studies assessing other interventions did not identify improvements compared with controls. Safety assessment was globally poorly reported.*

Conclusions *This systematic review and meta-analysis provides low quality evidence to suggest the use of dexmedetomidine in patients deemed difficult-to-wean due to agitation, delirium, or anxiety. Insufficient evidence was found regarding other interventions to provide any recommendation.*

Trial registration *PROSPERO (CRD42016042528); registered 15 July, 2016.*

Résumé

Contexte *Le délirium, l'agitation et l'anxiété peuvent compliquer le sevrage de la ventilation mécanique et aboutir à une augmentation de la morbidité et du coût des soins de santé. L'approche clinique la plus adaptée au sevrage dans ces circonstances n'est pas claire et reste un défi pour les cliniciens. L'objectif de cette étude systématique était d'identifier des interventions efficaces et sécuritaires pour sevrer les patients « difficiles à sevrer » de la ventilation mécanique en raison d'un délirium, d'une agitation ou d'anxiété.*

Méthodes *Une revue systématique a été menée en utilisant les bases de données MEDLINE, EMBASE et PubMed. Les études évaluant des patients sous ventilation mécanique jugés difficiles à sevrer en raison d'un délirium, d'une agitation ou d'anxiété, comparant les effets d'une intervention à celle d'un bras comparateur ont été recherchées. Le critère d'évaluation principal a été le délai jusqu'à l'extubation et le critère d'évaluation secondaire a été la durée de séjour en unité de soins intensifs (USI).*

Résultats *À partir de 10 860 études identifiées, huit satisfaisaient les critères d'inclusion : six études ont évalué la dexmédétomidine tandis que les deux dernières ont évalué la loxapine et le biofeedback. L'analyse groupée des études évaluant la dexmédétomidine a montré une réduction du délai d'extubation (six études, n = 303) de 10,9 heures comparativement aux contrôles (intervalle de confiance [IC] à 95 % : -15,7 à -6,1; I^2 = 68 %) et de la durée du séjour en USI (quatre études, n = 191) de 2,6 jours (IC à 95 % : 1,9 à 3,3; I^2 = 0 %). Néanmoins, les résultats sont de faible qualité compte tenu de la petite taille des échantillons et d'une grande hétérogénéité. Les études évaluant d'autres interventions n'ont pas identifié d'améliorations par rapport aux contrôles. D'une manière générale, les évaluations de l'innocuité ont été médiocrement décrites.*

Conclusions *Cette étude systématique et la méta-analyse procurent une preuve de qualité basse pour suggérer l'utilisation de la dexmédétomidine chez des patients considérés difficiles à sevrer en raison d'un délirium, d'une agitation ou d'anxiété. Les données probantes concernant les autres interventions ont été jugées insuffisantes pour permettre des recommandations quelconques.*

Enregistrement de l'essai clinique *PROSPERO (CRD42016042528); enregistré le 15 juillet 2016.*

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Mechanical ventilation (MV) is often required in intensive care unit (ICU) patients and represents important healthcare costs.[1] Following resolution of the indication for MV, planning extubation requires a multi-step approach, including the process of weaning.[2] About 40% of total MV time will be spent on weaning, making it a major issue in the ICU.[3,4] Difficult-to-wean (DTW) has been defined as a successful MV separation requiring more than one day but less than seven days after the first separation attempt.[5] Weaning from MV that exceeds seven days refers to prolonged weaning.[5] The reported incidence of DTW and prolonged weaning varies from 10–40% and 6–18%, respectively and both are associated with increased

mortality and ICU length of stay (LOS).[5-8] Causes of prolonged MV can be grouped into the following categories: respiratory, cardiac, neuromuscular, metabolic, and neuropsychologic etiologies.[9] Neuropsychologic complications, which include delirium, agitation, and anxiety, may hinder weaning and lead to increased morbidity and healthcare costs.[1,7,9-12] Delirium itself has recently been independently associated with increased odds of being DTW.[13] Multiple factors such as untreated pain, prolonged immobilisation, sleep deprivation, and psychoactive drugs, among others, have been associated with the development of such psychologic dysfunctions.[2]

There is a lack of consensus concerning the most appropriate clinical approach to these neuropsychologic conditions. Coexistence and interrelation between these psychologic dysfunctions make the approach to weaning more challenging for clinicians. Among potential interventions, dexmedetomidine has been shown to prevent delirium and improve sleep quality in the ICU environment and may represent an option.[14-16] Antipsychotics agents, valproic acid, and clonidine have also been suggested to manage agitation or delirium and may facilitate MV weaning.[17-20] Complementary and alternative medicine strategies such as music therapy are also potential therapies to facilitate MV weaning.[21] The goal of this systematic review and meta-analysis was to search for evidence of efficacious and safe interventions to facilitate MV weaning in patients that are DTW due to delirium, agitation, or anxiety.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed while writing this review.[22] The protocol was registered on PROSPERO (CRD42016042528).[23]

Study identification

Randomized-controlled trials and observational studies were identified using electronic and manual search strategies. In September 2018, MEDLINE, EMBASE, and PubMed were searched from the earliest accessible date. A senior information specialist reviewed the final search strategy. The bibliographies of identified studies and reviews were manually searched for additional studies. The strategy also included searching the last five years' conference proceedings of six different scientific meetings (Society of Critical Care Medicine, European Society of Intensive Care Medicine, American Thoracic Society, International Symposium on Intensive Care and Emergency Medicine, World Federation of Pediatric Intensive and Critical Care Societies, World Federation Societies of Intensive and Critical Care Medicine). The full MEDLINE search strategy is available in the eTable (available as Electronic Supplementary Material).

Eligibility criteria

Studies evaluating MV patients, without age restrictions, identified or deemed DTW due to delirium, agitation, or anxiety, and comparing the effects of any pharmacologic intervention or complementary and alternative medicine strategies with placebo, standard treatment, or another active comparator were sought.

Studies that included patients that were DTW from etiologies other than neuropsychologic causes were also excluded. Studies in which DTW was caused by mixed etiologies, such as ventilator asynchrony or paroxysmal sympathetic hyperactivity, were included if delirium, agitation, or anxiety were also stated as possible causes. DTW was defined by the study authors in each paper. Studies evaluating specific etiologies of psychologic dysfunctions such as pain or drug or substance withdrawal were also screened. No timeframe of MV duration was pre-specified and no spontaneous breathing trial or other specific tests were required to be included in the systematic review. There were no restrictions for date and language of publication. Reasons for exclusions were documented.

Study selection

Two independent reviewers (S.D. and D.B.) screened all citations based on titles and abstracts. Full articles of selected citations were then retrieved for eligibility assessment. Disagreements were resolved by consensus and included a third reviewer (D.R.W.).

Data extraction and quality assessment

Each study was evaluated independently and in duplicate using a pre-tested standardized form. Descriptive variables for each study (language and year of publication, source of funding, sample size and study objectives) were collected. Information regarding study population characteristics, reason for which the patients were deemed DTW, DTW definition, interventions including co-treatments and weaning protocols and outcome measures were collected and analyzed. Information on all reported adverse events and their method of assessment was also collected and considered appropriate if it was prospectively collected or it was a study endpoint. The method of assessing adverse

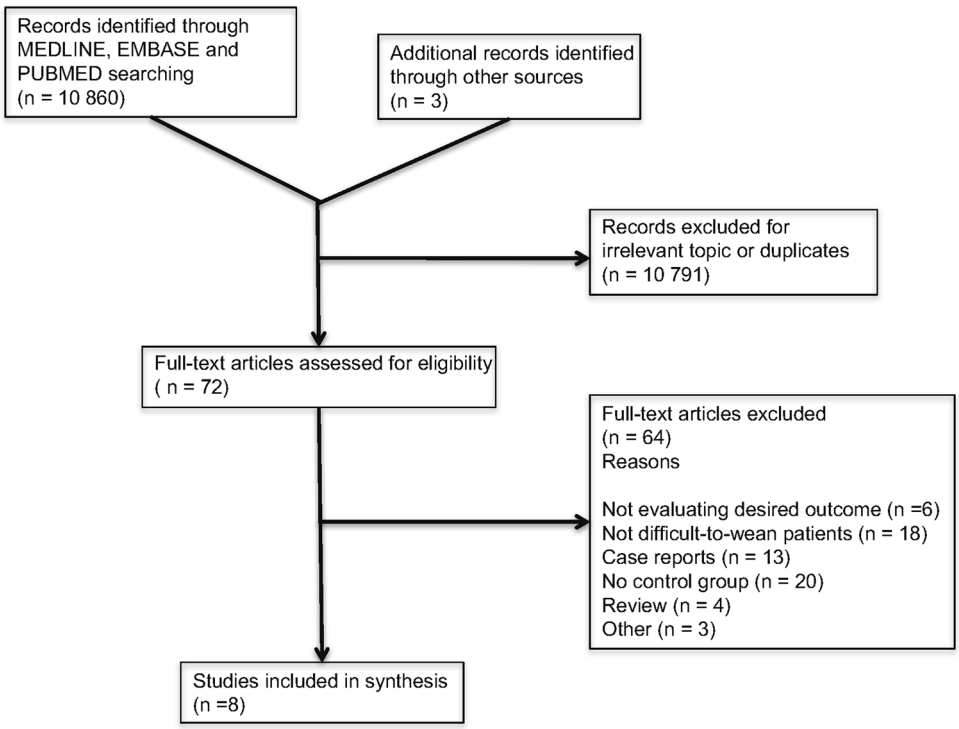

Fig.1 Flow chart of the systematic review

events had to be provided and its timing clinically relevant.[24]

Risk of bias was assessed using the Cochrane Collaboration tool for randomized-controlled trials by two independent reviewers.[25] Disagreements were resolved by consensus including a third reviewer.

Outcomes

The primary outcomes were time-to-extubation (defined as time from the initiation of the intervention to successful extubation) and ventilator-free days at one week (defined as time being alive and not receiving MV). Secondary outcomes were ICU and hospital LOS, and adverse drug reactions specific to the intervention. Outcomes related to delirium, agitation, and anxiety as well as unplanned extubations and reintubation rates were also collected.

Data synthesis

Studies were qualitatively evaluated for methodologic and clinical heterogeneity. In the absence of important methodologic and clinical heterogeneity, outcomes were pooled using Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and forest plots were generated. Statistical heterogeneity was measured using the I^2 statistic. As all pharmacologic studies except one evaluated the effects of dexmedetomidine, the results were solely pooled for dexmedetomidine studies. A random effect model using the DerSimonian and Laird method was used for all outcomes, as the study populations were deemed likely to be heterogeneous. To enable meta-analysis, means and standard deviations of two studies were estimated using medians and interquartile ranges as previously described.[26] Results are presented as mean differences with 95% confidence intervals (CI).

Sensitivity analyses were performed according to cause of DTW (excluding trials with mixed etiologies), risk of bias (excluding studies at high risk of bias), data transformation (excluding studies that reported medians and interquartile ranges), and study blinding (excluding open-label studies). Due to the small number of included studies, an Egger's test was not performed to assess publication bias.[27] However, we explored the possibility of publication bias using a funnel plot.

Results

Search results

The literature search yielded 10,860 records (7,564 after removal of duplicates) and three additional articles were identified through proceedings of scientific meetings and cross-reference strategy. After screening, 72 full-text articles were further assessed for eligibility. Among them, 64 studies were excluded for reasons listed in

Table Characteristics of included studies

Study/Country/ICU type	Patient description	DTW definition	Intervention, comparator, and target sedation	Results
Conti 2016/Italy /Unspecified (n = 20)[28]	Mean 69 yr 55% male	SBT failure secondary to various causes including anxiety and agitation	I: Dexmedetomidine 0.2-1.4 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ C: Propofol 0.3-4 $mg \cdot kg^{-1} \cdot hr^{-1}$ Target: RASS -2 to 1	Similar time-to-extubation (25.2 *vs* 57.3 hr, P = 0.958) Similar ICU LOS (6.0 *vs* 10.0 d, P = 0.742)
Gupta 2015/India /Surgical ICU (n = 40)[29]	Mean 41yr 63% male	SBT failure secondary to various causes including anxiety	I: Dexmedetomidine 0.2-0.7 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ C: Midazolam 0.04-0.2 $mg \cdot kg^{-1} \cdot hr^{-1}$ Target: Ramsay 2 to 4	↓ time-to-extubation (24.2 *vs* 31.4 hr, P = 0.026)
Lu 2016/China /Medical ICU (n = 80)[30]	Mean 63 yr 49% male	DTW based on clinician assessment and secondary to agitation	I: Dexmedetomidine 0.2-1.0 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ C: Midazolam infusion Target: RASS -2 to 1	↓ time-to-extubation (3.0 *vs* 4.3 d, $P < 0.05$) ↓ ICU LOS (5.4 *vs* 8.0 d, $P < 0.05$) ↓ Hospital LOS (10.1 *vs* 15.3 d, $P < 0.05$) ↓ Delirium at extubation (8 *vs* 18 cases, P = 0.017)
Reade 2009/Australia /Mixed ICU (n = 20)[31]	Median 60 yr 85% male	DTW based on clinician assessment and secondary to agitation	I: Dexmedetomidine 0.2-0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$ C: Haloperidol 0.5- 2 $mg \cdot hr^{-1}$ Target: RASS 0	↓ time-to-extubation (19.9 *vs* 42.5 hr, P = 0.016) ↓ ICU LOS (4.4 *vs* 8.0 d, P = 0.009)
Reade 2016/Australia /Mixed ICU (n = 71)[32]	Median 57 yr 75% male	DTW based on clinician assessment and secondary to agitated delirium	I: Dexmedetomidine up to 1.5 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ C: Placebo (saline) at equivalent rates Target: RASS 0	↓ time-to-extubation (21.9 *vs* 44.3 hr, P < 0.001) ↑ ventilator-free time at seven days (17.0 hr; 95% CI, 4.0 to 33.2 hr) Similar ICU LOS (2.9 vs 4.1 d, P = 0.09) Similar hospital LOS (8.5 *vs* 9.5 d, P = 0.96) ↓ time to resolution of delirium (23.3 *vs* 40.0 hr, P = 0.01) Similar bradycardia events (5.3% *vs* 0%, P = 0.50)
Yapici 2011/Turkey /Cardiac surgery ICU (n = 72)[33]	Mean 60 yr 38% male	Failed local extubation protocol secondary to agitation and delirium	I: Dexmedetomidine 0.3–0.7 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ C: Midazolam 0.05–0.2 $mg \cdot kg^{-1} \cdot hr^{-1}$ Target: not specified	↓ time-to-extubation (49.6 *vs* 58.4 hr, P < 0.001)
Gaudry 2017/France /Unspecified (n = 87)[34]	Mean 55 yr 76% male	SBT failure secondary to agitation	I: Loxapine 150 mg per tube × 1, then varying doses repeated according to protocol C: Placebo per tube × 1, then varying doses repeated according to protocol Target: not specified	Similar time-to-extubation (3.2 *vs* 5.0 d, P = 0.45) Similar ventilator-free days in the first 14 days (5.8 *vs* 5.5 d, P = 0.9)
Li 2015/Taiwan/unspecified (n = 47)[35]	Mean 69 yr 60% male	DTW based on clinical assessment and secondary anxiety, fear, and perceived control	I: Biofeedback (four sessions per day) C: Usual care Target: not specified	Similar time to wean from MV (9.0 *vs* 13.1 d, NS)

CI = confidence interval; d = day; DTW = difficult-to-wean; ICU = intensive care unit; LOS = length of stay; NS = not significant; RASS = Richmond Agitation Sedation Scale; SBT = spontaneous breathing trials

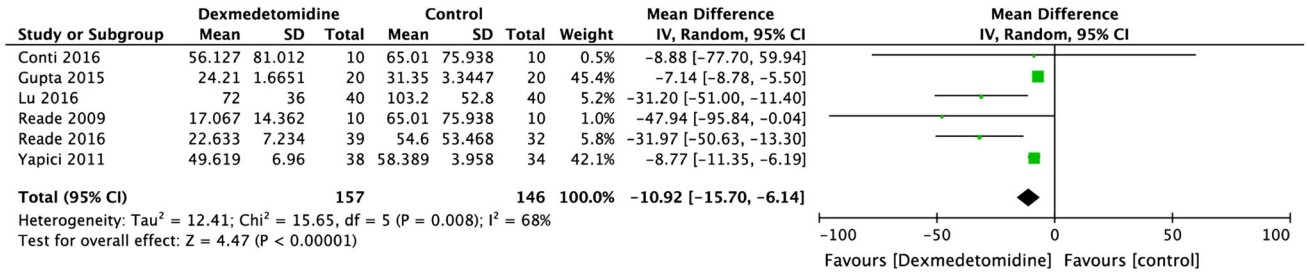

Fig. 2 Meta-analysis of dexmedetomidine *vs* control in difficult-to-wean patients: time-to-extubation

Fig. 1, leaving eight studies included in the review. These eight studies were all randomized-controlled trials and regrouped 437 patients.[28-35] One of the studies was only available in abstract form, and the authors were successfully contacted for missing data when needed.[35]

Patient characteristics

The main characteristics of included studies are shown in the Table. All studies included adult patients, most reporting median ages in the fifties or sixties. Difficult-to-wean patients were identified solely based on a clinicians' assessment without objective criteria in four trials,[30-32,35] while the others included patients who failed one spontaneous breathing trial[28,29,34] or failed an in-house extubation protocol.[33] Agitation was the reason for DTW in three studies and was measured using the Richmond Agitation Sedation Scale (RASS).[30,32,34] Agitated delirium was an inclusion criteria in two studies and was assessed using a combination of a positive CAM-ICU and an evaluation with either the RASS[33] or the Mindful Attention Awareness Scale.[32] One study included patients that were DTW due to anxiety and used the State Anxiety Scale.[35] Patients were included with mixed DTW etiologies, including anxiety or agitation, in two studies.[28,29]

Study interventions

Dexmedetomidine was the most frequent pharmacologic intervention evaluated.[28-33] Intravenous dexmedetomidine up to a maximum of 1.5 $\mu g \cdot kg^{-1} \cdot hr^{-1}$, was compared with either an infusion of midazolam 0.04–0.2 $mg \cdot kg^{-1} \cdot hr^{-1}$,[29,30,33] propofol 0.3–4 $mg \cdot kg^{-1} \cdot hr^{-1}$[28] haloperidol 0.5–2 $mg \cdot hr^{-1}$[31] or placebo.[32] Another compared the effects of a single 150 mg dose of oral loxapine with placebo.[34]

Biofeedback was the only non-pharmacologic intervention reported.[35] Biofeedback, which was compared with usual care, consisted of 20-min sessions that were performed four times per day and focused on diaphragmatic breathing.

Open-label acetaminophen,[28,29,33] non-steroidal anti-inflammatory drugs,[33] benzodiazepines,[28,31,32,34] propofol,[31,32] or narcotic analgesics[32,34] were mentioned as permitted in both study groups in some trials. Open-label antipsychotics were permitted in one trial assessing dexmedetomidine.[32] Other trials did not mention if co-treatments were permitted or prescribed.[30,35] Weaning protocols were not described in any trial except one where rapid shallow breathing indexes and spontaneous breathing trials were regularly performed.[30,35] Non-pharmacologic measures to alleviate delirium (e.g., early mobilization, sleep promotion, etc.) were not mentioned in any trial.

Efficacy outcomes

Time-to-extubation was evaluated in all the included studies.[28-35] As presented in Fig. 2, pooled estimates of randomized-controlled trials assessing dexmedetomidine showed a reduced time-to-extubation of 10.9 hr compared with control arm (95% CI, -15.7 to -6.1; I^2 = 68%). Dexmedetomidine significantly reduced ventilator-free time by 17.0 hr (95% CI, 4.0 to 33.2) within seven days after randomization in the only study that reported this outcome.[32] The use of dexmedetomidine also decreased ICU LOS by 2.6 days (95% CI, 1.9 to 3.3; I^2 = 0%) (Fig. 3), whereas hospital LOS was not statistically different in the two trials evaluating this outcome (-2.9 days; 95% CI, -7.6 to 1.75; I^2 = 91%).[30,32] Prevalence of delirium at extubation was reduced from 45% to 20% in one study (P = 0.017)[30] and median time to resolution of delirium was shorter in a second one (23.3 hr *vs* 40.0 hr, P = 0.01).[32] Reade *et al.* also reported less adjunct antipsychotics use (36.8% *vs* 65.6%, P = 0.02) in the dexmedetomidine group.[32] In a sensitivity analysis removing studies that were unblinded,[28,29,31,33] a 31.6 hr (95% CI, 18.0 to 45.2; $P < 0.001$) reduction in time-to-extubation was noted in the remaining two studies. Removing studies that included patients because of mixed etiologies[28,29] increased the pooled estimate to 24.8 hr (95% CI, -42.9 to -6.7). When removing the studies necessitating data transformation,[28,31,32] the pooled results remained similar (-10.5 hr; 95% CI, -15.1 to -5.8). Finally,

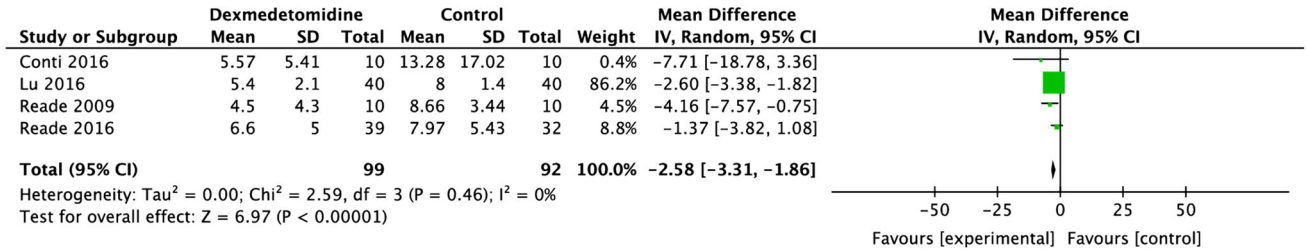

Fig. 3 Meta-analysis of dexmedetomidine *vs* control in difficult-to-wean patients: intensive care unit length of stay

excluding the study from Lu *et al.*,[30] which was at high risk of bias and had an important weight, did not affect the results (-9.2 hr; 95% CI, -13.2 to -5.2).

In the only study evaluating loxapine, time-to-extubation (3.2 days *vs* 5 days; $P = 0.45$) and ventilator-free days in the first 14 days (5.8 days *vs* 5.5 days, $P = 0.9$) were similar between the treatment and control arms. Also, more sedation was required in the placebo group in the first 24 hr after randomization (44% *vs* 17%, $P = 0.01$).[34] Biofeedback sessions, while improving anxiety in patients, did not show a significant difference in time to wean from MV.[35]

Safety outcomes

Reporting on safety outcomes was not pre-specified in most studies. In studies assessing dexmedetomidine, reduction in heart rate was seen in three studies[29,30,33] and decreased mean arterial pressure in two.[29,30] Bradycardia was reported for a single patient with dexmedetomidine in another trial.[28] Only one study systematically reported occurrence of clinically important adverse events related to bradycardia, hypotension, or agitation with dexmedetomidine, which did not differ significantly compared with placebo.[32] Unplanned extubation rates were similar (13% *vs* 18%, $P = 0.5$) in the loxapine trial[34] and did not occur in two other studies where reported.[31,32] Reintubation rates were rare where reported as the trachea of only one patient was reintubated in a single trial.[31,32] Adverse events were not reported in one trial.[35]

Risk of bias assessment

Risk of bias assessment of included studies is summarized in Fig. 4. One study presented a low risk of bias.[32] A high risk or unclear risk of bias was found in most of the studies.[28-31,33-35] Open-label trials as well as missing information on patient recruitment or co-interventions used were the main threats to validity. The study assessing loxapine was terminated early because of insufficient enrolment.[34]

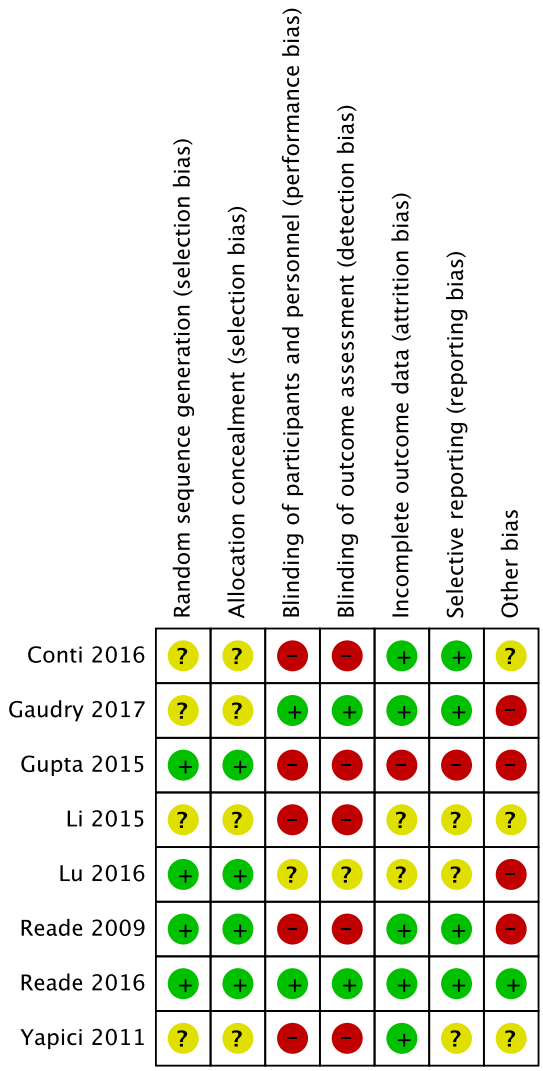

Fig. 4 Risk of bias and methodologic assessment of included studies. Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias.

An exploratory funnel plot (eFigure; available as Electronic Supplementary Material) represented by studies assessing dexmedetomidine showed an asymmetric distribution; therefore publication bias could not be excluded.

Discussion

Mortality in DTW patients is estimated as high as 25% and has been associated with important morbidity and higher hospital costs.[1,36,37] Therefore, it is crucial to rapidly identify and resolve the etiology of weaning difficulty.[9] This systematic review sought to identify interventions that could facilitate weaning from MV that was difficult due to agitation, delirium, or anxiety. In the present meta-analysis, dexmedetomidine was found to reduce time-to-extubation as well as ICU LOS in these DTW patients.

Dexmedetomidine is a selective alpha-$_2$ receptor agonist, which mainly induces light sedation, provides light analgesia with opioid sparing effects, and blunts stress response through its sympatholytic properties.[38,39] Clinical benefits of dexmedetomidine can be explained by the conscious sedation it induces, promoting better patient collaboration. The benefit could also result from the attenuation of iatrogenic withdrawal from sedatives and opiates.[40] Furthermore, the absence of respiratory depression combined with its anxiolytic properties might reduce ventilator asynchrony and provide faster and safer extubation.[28]

Surprisingly, clinical benefit from dexmedetomidine regarding time-to-extubation appears modest compared with the important reduction in ICU LOS. These conclusions might be observed from a faster time to resolution of delirium, thereby leading to an earlier discharge from the ICU.[30,32] Nevertheless, resolution of delirium was not specifically assessed in this study and thus its impact on ICU LOS remains speculative. The small magnitude of the effect for time-to-extubation outcome can also be explained by the fact that the studied neuropsychologic conditions were rapidly reversed. Delirium in ICU patients has been associated with increased mortality, ICU and hospital LOS, and MV duration.[41] Compared with either benzodiazepines or propofol, when used as a long-term sedative in the ICU, dexmedetomidine led to shorter times to extubation and less delirium than comparative arms in various trials.[42-44] Differences in ICU LOS in these trials were not significantly different, but the magnitude of effect was similar to that found in this review.

A single trial evaluating an antipsychotic medication, loxapine, was included.[34] The trial was terminated early because of low recruitment and did not result in positive clinical outcomes, possibly reflecting a lack of power. Antipsychotic drugs assessed in the treatment of delirium in the ICU have failed to show positive outcomes, although they may have a role in preventing delirium in a high-risk surgical population.[45]

Biofeedback during MV weaning focuses on helping patients understand their respiratory situation, providing psychologic support and improving their breathing patterns. In the only trial included, biofeedback improved anxiety control and the rapid shallow breathing index, but it did not reduce the time-to-extubation.[35] Although it did not prove clinically useful in hastening patient extubation, it would be interesting to assess if biofeedback can improve mid and long-term neurologic outcomes in patients (for example, post-traumatic stress disorder).

Strengths and limitations

This is the first systematic review identifying interventions that could provide clinical benefits in DTW patients. The review was very inclusive and permitted inclusion of several interventions. The review was accomplished using rigorous methodology and the many sensitivity analyses all yielded similar results, suggesting robustness and increasing the confidence in the estimates of the measured effects.

The current review does have limitations. There is significant clinical and statistical heterogeneity, as the studies included different DTW etiologies or definitions and different comparator arms. An older definition of difficult weaning proposed by the International Consensus Conference in 2007 specifically took spontaneous breathing trials into account, which are not systematically used by clinicians.[2] Therefore, the lack of a definition reflecting clinical practice can partially explain the wide range of definitions used in the studies. To overcome this problem, a new definition of DTW has recently been proposed by the *Réseau Européen de Recherche en Ventilation Artificielle* (REVA) Network.[5] Unfortunately, all included studies were performed before publication of this new definition. The lack of a pre-specified definition for DTW in half of the included studies may have introduced an important selection bias and limited the external validity of the meta-analysis.

Small study samples and their overall low quality could have led to overestimation of benefits seen with dexmedetomidine. As shown on the exploratory funnel plot, publication bias cannot be excluded and we remain concerned that negative studies may not have been published.

Most of the results in the studies were presented as medians with interquartile ranges (possibly because of the small sample sizes) and non-parametric distribution of results, which limits possibilities for meta-analyzing. Means and standard deviations had to be estimated from these to enable meta-analysis.[26]

Safety was not systematically addressed in most of the studies. Nevertheless, dexmedetomidine has already been shown to induce hypotension and bradycardia.[42-44]

Moreover, details on effective non-pharmacologic co-interventions were lacking in all studies. For example, early physical and occupational therapy has been associated with more ventilator-free days and shorter duration of delirium.[46] Nevertheless, it would not be expected that intervention groups were treated differently than control groups in the trials.

Conclusion

In summary, this review provides evidence to recommend the use of dexmedetomidine in DTW patients due to agitation, delirium, or anxiety, since it seems to reduce time-to-extubation and ICU LOS in these patients compared with control arms. Nevertheless, the evidence was deemed low quality given the small sample sizes and high heterogeneity. Not enough evidence was found among other interventions to provide any recommendation. Furthermore, as trials in the review mostly evaluated short-term outcomes, performing additional trials assessing effects of interventions on long-term neurocognitive outcomes as well as other important clinical issues such as mortality would be of interest.

Acknowledgements We thank Patrice Dupont, senior information specialist at University of Montreal, for providing helpful comments on the search strategy.

Competing interests Dave Brindamour received consulting honoraria from Pfizer; Anne Julie Frenette received speaker honoraria from Pfizer; David R. Williamson is supported by a Fonds de recherche du Québec – Santé (FRQ-S) clinical scientist career grant and received an investigator-initiated research grant from Pfizer. The remaining authors have disclosed that they do not have conflicts of interest.

Editorial responsibility This submission was handled by Dr. Gregory L. Bryson, Deputy Editor-in-Chief, *Canadian Journal of Anesthesia.*

Author contributions *Sébastien Dupuis* and *Dave Brindamour* conceived the study design, performed the search, selected studies, extracted and analyzed the data, and wrote the manuscript. *Stephanie Karzon* performed the search, selected studies, extracted the data, and revised the manuscript. *Anne Julie Frenette* and *David R. Williamson* conceived the study design, extracted the data, analyzed the data, and revised the manuscript. *Marc M. Perreault*, *Lisa Burry*, *Emmanuel Charbonney*, and *Patrick Bellemare* extracted and checked data, helped with the interpretation of data, and critically revised the manuscript.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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