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REVIEW

Pharmacological Interventions for Agitated Behaviors in Patients with Traumatic Brain Injury: An Updated Systematic Review

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Abstract

The aim of this updated systematic review was to assess the efficacy and safety of pharmacological agents in the management of agitated behaviors following traumatic brain injury (TBI). We updated a 2019 systematic review, which originally included 21 studies, by performing a search strategy in MedLine, Embase, PsychInfo, Cinhal, Directory of Open Access Journals, and Latin American and Caribbean Literature on Health Sciences Literature (up to Jan 7th, 2025) for evidence on the risks and benefits of nine medication classes used to control agitated behaviors following TBI. We included all randomized controlled trials, quasi-experimental and observational studies examining the effects of medications administered to control agitated behaviors in TBI patients. Of the 58 studies screened in full-text, 11 additional studies were added to the 21 original studies for a total of 32 studies. Of these new studies, three studies evaluating dexmedetomidine suggested some potential benefits in reducing agitation. New studies on risperidone, olanzapine, carbamazepine, and valproic acid failed to show efficacy compared with control groups. Among studies identified in the first review, propranolol did reduce intensity of agitation but not its frequency. In conclusion, there remain insufficient data to recommend the use of any medications for the management of agitation following TBI. Dexmedetomidine may have potential benefit in an acute setting, and the benefits of antipsychotics, carbamazepine, and amantadine remain unclear. Beta-blockers and valproic have shown benefits, but results are inconsistent. More studies in the acute, rehabilitation, and outpatient settings are needed to assess the efficacy and safety of pharmacological agents for the management of agitated behaviors.

Keywords: acute recovery; agitation; pharmacological intervention; systematic review; traumatic brain injury

Introduction

According to the Centers for Disease Control and Prevention, traumatic brain injury (TBI) can arise from a bump, blow, or jolt to the head or from a penetrating head injury that ultimately impairs the normal function of the brain.[1] TBI is associated with decreased levels of consciousness, post-traumatic amnesia (PTA), and alterations in the mental state, such as confusion and

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disorientation.[2,3] In the clinical setting, TBI can be particularly challenging due to the possible presence of post-traumatic agitation, which can manifest in the form of restlessness, irritability, anger, and verbal and/or physical aggressive behaviors.[4,5] Post-traumatic agitation can occur in the acute setting, often associated with PTA, and may also persist in the longer term, where it can be linked to cognitive impairments, often presenting as aggression and aggressivity. Although agitation is more prevalent in the acute care setting, it is also problematic in the rehabilitation and outpatient setting.[6] The prevalence of agitated behaviors in inpatient and rehabilitative settings was recently estimated at 31.7% [95% Confidence Intervals (CI) 25.3%–39.0%] and 32.2% (95% CI 27.1–37.8), respectively.[6] In addition to patient harm, post-traumatic agitation can also be dangerous for health professionals and family members and thus considerably hinder the rehabilitation process.[7] To manage agitation, pharmacological agents including sedatives, antiepileptics, psychostimulants, and antipsychotics are often used, yet there is limited evidence to support their efficacy and safety.[8–10]

Between 2018 and 2019, a number of systematic reviews evaluated pharmacological agents for the management of agitated behaviors in TBI patients including aggression,[11] agitation,[12] or both.[13,14] In 2019, our group also published a systematic review assessing the efficacy and safety of pharmacological agents to manage agitation following TBI.[15] The review identified 21 studies including eight studies that evaluated the use of pharmacological interventions in which an agitated behavior was the presenting symptom or one of the presenting symptoms. The review failed to recommend any agent because of small sample sizes, heterogeneity and an unclear risk of bias among reviewed studies. In light of the absence of an updated systematic review and new research published on the management of TBI-associated agitation, including additional studies on atypical antipsychotics and alpha-2-adrenergic agonists, the purpose of this systematic review is to update our 2019 review.

Methods

The following review is based on our previous review, is registered in PROSPERO International Prospective Register of Systematic Reviews (CRD42023391456), and follows Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Appendix A1).[15,16] The included studies were randomized controlled, quasi-experimental, and observational studies comprising a majority (>50%) of TBI patients. Case reports, case series, and observational studies with no control groups were excluded. All population types, from children to adults, that were either in the early stages of TBI recovery, in rehabilitation, or outpatients were included. The included studies of this review can be distinctly separated as (1) those that evaluated the use of a pharmacological intervention with agitated behaviors as the presenting symptom; (2) those in which agitated behaviors were not the presenting symptom but still measured as a secondary outcome variable; and (3) those that specifically assessed the safety of pharmacological agents used to treat agitation. In this review, agitated behaviors comprised restlessness, aggressiveness, assaultive behavior, and irritability occurring during confusion or PTA. The pharmacological agents examined in this review were prespecified and consisted of the following: beta-adrenergic blockers, typical and atypical antipsychotics, anticonvulsants, dopamine agonists, psychostimulants, antidepressants, alpha-2-adrenergic agonists, hypnotics, anxiolytics, and cholinesterase inhibitors. Included studies compared the pharmacological agents either with a placebo, a different medication, or a combination of distinct medications.

Search strategy

To update the 2019 review, EMBASE, MedLine, PsychInfo, Cinhal, Directory of Open Access Journals, and Latin American and Caribbean Literature on Health Sciences Literature were searched for abstracts and articles published between Dec 10th, 2018, and January 7th, 2025 (Supplementary Appendix A2). In addition, the references of identified article were screened for additional articles.

Data collection and analysis

Two reviewers (T.K. and D.W.) independently screened titles and abstracts for eligible publications. Then, the same reviewers determined the eligibility of each retained study by reviewing the full-text article. Disagreements of eligibility were resolved by a third reviewer (M.M.B.).

Data extraction and management

Two reviewers (T.K. and C.D.) independently extracted data from all eligible studies using a pretested data extraction form. The variables documented for all studies were: study title, name of the first author, year of publication, country of origin, publication type (journal article, conference proceeding, abstract, thesis), clinical setting (Intensive Care Unit [ICU], hospital ward, rehabilitation unit, outpatient), study design (randomized controlled, blinded or open, non-randomized controlled, prospective or retrospective, crossover), population (paediatric, adult), patient characteristics (age, gender, isolated TBI or multiple trauma including TBI, severity of TBI according to Glasgow Coma Scale, days from TBI at inclusion, inclusion and exclusion criteria), characteristics of the intervention and control treatment (type of pharmacological agent, dose, frequency and duration of treatment), agitation measurement tool, description of the specific agitated behaviors (definition, frequency, duration) and clinical outcomes (length of stay), adverse events, use of physical restraints during ICU stay, length of PTA, cognitive function at ICU discharge and at 1 year, and functional outcome at ICU discharge and at 1 year.

Data synthesis

We qualitatively evaluated the studies for heterogeneity by comparing pharmacological classes, drug doses, allowed co-therapies (antipsychotics, sedatives, analgesics), use of physical restraints, clinical setting, and number of study sites. We also qualitatively evaluated methodological heterogeneity (study design, risk of bias, type of control group). Based on our first systematic review, we expected to observe important clinical and observational heterogeneity in the studies identified. In the absence of important clinical and methodological heterogeneity, we had planned to analyze the study results for statistical heterogeneity and, if the statistical heterogeneity was acceptable ($I^2 < 50\%$), to proceed to a meta-analysis of the data using Review Manager (RevMan 5.3) software (Nordic Cochrane Center, Cochrane Collaboration). Given the clinical and methodological heterogeneity, a meta-analysis was not conducted.

Assessment of risk bias

Two reviewers (T.K. and C.D.) independently evaluated each included study with the revised Cochrane Collaboration tool for randomized controlled trials (RoB 2) and the Risk Of Bias In Non-randomized Studies—of Interventions (ROBINS-I) tool for observational studies, respectively.[17,18] As our 2019 systematic review used the Ottawa-Newcastle tool for observational studies and the Cochrane Collaboration tool for randomized controlled trials (RoB 1), we reassessed the risk of bias of all studies using the ROBINS-I and RoB 2 tools for comparison. In cases of disagreement concerning the risk of bias, a third reviewer (D.W.) was consulted to resolve the issue.

Results

Study selection

Since our last systematic review in 2019, a total of 4516 additional citations were identified from the literature search, of which 58 were retained for full-text review (Fig. 1). Of the 58 retained, 11 additional studies were added to the 21 original studies to be included in the systematic review for a total of 32 studies. The addition of new studies allowed for stratification of the studies by their population setting, namely the acute, rehabilitation, and outpatient settings. Seven of the new studies evaluated the benefit of pharmacological treatments on agitated behaviors as the presenting symptom, increasing the total from 8 to 15 studies.[19–25] Five of the seven new studies were in the acute or rehabilitation setting,[20,22,24,25] and the two remaining studies were conducted in outpatients.[21,23] In two new studies, one in the acute setting and

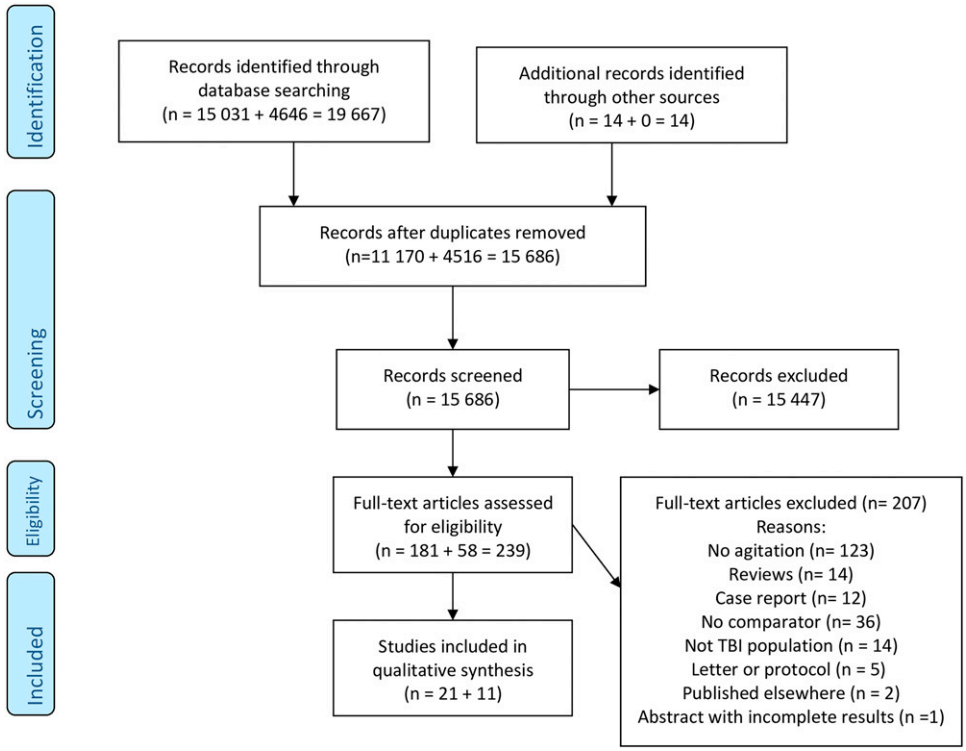


FIG. 1. PRISMA flow diagram. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

one in outpatients, agitated behaviors were not the presenting symptom but were measured as a secondary outcome, increasing the total from 9 to 11 studies.[26,27] Lastly, two new studies, both conducted in the acute setting, assessed the safety of pharmacological agents used for agitated behaviors after TBI, increasing the total from four to six studies.[28,29]

Agitated behaviors as the primary outcome—acute and rehabilitation settings

Out of the seven new studies, five studies measured agitation in the acute setting (Table 1).[20,22,24,25] The tools used by the new studies to measure agitated behaviors included the Riker Sedation-Agitation Scale (SAS), the Richmond Agitation Sedation Scale, and the Agitated Behavior Scale (Table 2). Four of the seven new studies were randomized controlled trial (RCT) designs[19,20,22,24] and the remaining study was a retrospective cohort.[25] In comparison with our initial systematic review, which included studies evaluating beta-adrenergic blockers[30] and amantadine,[31,32] the new studies evaluated other pharmacological agents (i.e., dexmedetomidine, haloperidol, butorphanol, olanzapine, and valproic acid).[19,20,22,24,25] Among all studies, pharmacological agents were either compared with placebo,[19,24,30,31] no medication,[22,32] another medication,[20] or standard care.[25] All studies enrolled adults (16 years and older), with some studies capping the age limit at 65 years and older.[20,22,23]

Three RCTs, conducted in the ICU setting, evaluated the effects of dexmedetomidine on agitation as the primary symptom (Table 3).[19,20,22] The conditions of the studies differed, as one study compared dexmedetomidine to placebo,[19] one to haloperidol[20] and another compared dexmedetomidine, butorphanol, and their combination to controls.[22] In a study of TBI patients undergoing craniotomy hematoma removal, dexmedetomidine significantly reduced the incidence of agitation and Ramsay sedation scores after 120 min of postoperative treatment.[19] In another study, dexmedetomidine significantly reduced the incidence of delirium at 5–7 days after the intervention compared with haloperidol in moderate TBI ICU patients,[20] whereas the third study of moderate to severe TBI patients reported significantly lower SAS scores in the dexmedetomidine and butorphanol group compared with the control group on postoperative days 3 and 5, but not in the dexmedetomidine group.[22]

In a double-blind controlled trial, olanzapine was compared with placebo in severe TBI patients in PTA suffering from agitation admitted to a rehabilitation unit.[24] As recruitment was limited to 11 out of the initially planned 58 patients, the study was analyzed as a series of *n*-of-1 trials. Although no direct comparisons were made, patients assigned to olanzapine ($n = 5$) demonstrated a reduction in agitation over the PTA period, whereas those assigned to placebo ($n = 6$) did not. However, olanzapine patients demonstrated poorer orientation and memory and a trend toward increased PTA duration. In a retrospective study of TBI ICU patients with agitated delirium, patients who received valproic for more than 48 h did not have more agitation-free days compared with those who received other medications.[25]

Three studies in the acute or rehabilitation setting were identified in our initial systematic review.[30–32] One study evaluated the use of propranolol for treating agitation in patients with severe blunt TBI and reported a reduction in the intensity of agitation episodes and use of physical restraints but did not demonstrate a decrease in agitation frequency (Table 3).[30] One RCT in the brain injury unit of a rehabilitation hospital and one retrospective study in ICU patients compared amantadine with placebo[31] or no amantadine.[32] No significant differences in the number of symptoms of post-traumatic confusional state at 14 days were shown in the randomized controlled study, whereas an increase in agitation in ICU patients exposed to amantadine was reported in the retrospective study (Table 3).[31,32]

Agitated behaviors as the primary outcome—outpatient setting

Two new studies evaluated irritability and aggression in the outpatient setting (Table 1).[21,23] Both studies were randomized controlled designs and evaluated risperidone and carbamazepine in comparison with placebo. The tools used were the Modified Overt Aggression Scale and the Neuropsychiatric inventory irritability (NPI-I) and aggression domains (NPI-A) (Table 2). Both studies enrolled adults (16 years and older), with one study capping the age limit at 65 years and older.[21]

In a multicenter feasibility study conducted in mild, moderate, and severe TBI outpatients with aggression, risperidone was compared with placebo.[21] The study, which included 12 patients, was deemed not feasible and not powered to enable clinical comparisons. A study of olanzapine for restlessness, irritability, aggression, and insomnia in patients with a history of TBI was identified in our first systematic review. Although the study suggested reductions in irritability and insomnia between weeks 1 and 3 in olanzapine-treated patients, no direct comparisons with placebo were made.

In addition to a randomized controlled study of valproic acid in mild to moderate TBI outpatients suffering from alcohol abuse showing a reduction in irritability,[34] we found an additional randomized controlled study of carbamazepine.[23] In complicated mild TBI, moderate or severe outpatients more than 6 months following injury suffering from irritability and aggression, carbamazepine ($n = 35$) titrated up to 400 mg was compared with placebo ($n = 35$) twice daily.[23] Although clinician ratings suggested a benefit for carbamazepine, the anticonvulsant did not show reductions in irritability and aggression according to both observers and participants.

Table 1. Study Characteristics

Study/year (N)	Publication/ country	Study design	Study focus	Interventional arm	Comparative arm	Location at randomization	Timing from TBI at randomization	TBI description
1. Agitated behavior as the presenting symptom								
Acute setting and rehabilitation								
[a]Feng[19] 2022 (*N* = 60)	Published China	RCT parallel	Agitation	Dexmedetomidine 0.5 μg/kg	Saline	Hospital	From admission	TBI not further defined (craniocerebral injury)
[a]Soltani[20]2021 (*N* = 60)	Published Iran	RCT parallel	Agitation	Dexmedetomidine 0.5 μg/kg every other day	Haloperidol 7.5 mg daily	ICU inpatients	From admission	Moderate TBI
[a]Wang[22]2022 (*N* = 104)	Published China	RCT parallel	Agitation	Dexmedetomidine1 μg/kg with 0.2–0.7 μg/kg maintenance, butorphanol 4 mg, dexmedetomidine and butorphanol	No medication	Neurosurgery department	From admission	TBI (Glasgow Coma Scale 5–12)
[a]Swayngim[25] 2024 (*N* = 108)	Published USA	Retrospective cohort	Agitation and delirium	Valproic acid Average dose 1643 mg/day	Other treatments	Hospital	Not applicable	Critically ill patients treated for agitation and delirium. A total of 87.8% and 76.3% were TBIs.
[a]Phyland[24] 2023 (*N* = 11)	Published Australia	RCT parallel	Agitation	Olanzapine Titrated to 10 mg twice daily	Placebo	Inpatient	From admission	Severe to extremely severe TBI
Brooke[30] 1992 (*N* = 21)	Published USA	RCT parallel	Agitation	Propranolol 60-420mg daily	Placebo	Level 1 trauma and rehabilitation center	N/A	Severe blunt TBI
Yablon[31] 2010 (*N* = 79)	Abstract USA	RCT parallel	Confusion	Amantadine 100 mg bid X 14 days	Placebo	Inpatient brain injury unit of a rehabilitation hospital	≤6 months	TBI not further defined
Gramish[32] 2017 (*N* = 139)	Published USA	Retrospective observational	Agitation	Amantadine 100 mg bid	No amantadine	Adult Trauma ICU	Acute TBI	TBI not further defined
Outpatient setting								
[a]Deb[21] 2020 (*N* = 12)	Published UK	RCT parallel	Aggression	Risperidone 1–4 mg daily	Placebo	Outpatient	≥6 months following a TBI	Mild, moderate and severe TBI
[a]Hammond[23]2021 (*N* = 69)	Published USA	RCT parallel	Irritability and aggression	Carbamazepine 200–400 mg bid	Placebo	Outpatient	≥6 months following a TBI	Moderate, severe, or complicated mild TBI
Hammond[33] 2014 *N* = 76	Published USA	RCT parallel	Irritability and aggression	Amantadine 100 mg bid	Placebo	Outpatient	≥6 months following a TBI	Blunt TBI
Beresford[34] 2015 (2022) (*N* = 50)	Abstract USA	RCT parallel	Agitation	Valproic acid for level 50–100 mcg/ml	Placebo	Outpatient	>1 year following TBI	Mild and moderate TBI
Hammond[35] 2015 *N* = 168	Published USA	RCT parallel	Irritability and aggression	Amantadine 100 mg bid	Placebo	Outpatient	≥6 months following a TBI	Blunt TBI
Maturana Waidele[36] 2009 (*N* = 31)	Published Chili	Prospective double-blind	Restlessness, irritability, aggression, insomnia	Olanzapine (dose not specified)	Placebo	Outpatient	N/A	TBI not further defined
Mooney[37] 1993 (*N* = 38)	Published USA	Randomized Pre–post	Anger	Methylphenidate 30 mg/day	Placebo	Outpatient	6 months or more (mean 27 ± 21 months)	Severe blunt TBI
2. Agitated behavior is not the presenting symptom								
Acute setting and rehabilitation								
[a]Nordness[27] 2023 (*N* = 47)	Published USA	RCT parallel	Ventilator free days	Propranolol 4 mg and clonidine 0.2 mg daily	Placebo	ICU inpatient	From admission	Severe TBI
Meythaler[38] 2001 (*N* = 9)	Published USA	RCT Crossover	Recovery and arousal	Sertraline	Placebo	Inpatient rehabilitation	<2 weeks of TBI	Severe TBI
Meythaler[39] 2002 (*N* = 35)	Published USA	RCT Crossover	Neurological recovery	Amantadine	Placebo	Emergency department	Between 4 days and 6 weeks following TBI	Severe blunt TBI
Banos[40] 2010 (*N* = 99)	Published USA	RCT parallel	Cognitive function and behavior	Sertraline	Placebo	Level 1 trauma center inpatients	<8 weeks of TBI	Moderate and severe TBI
Giacino[41] 2012 (*N* = 184)	Published USA, Denmark, Canada	RCT parallel	Functional recovery	Amantadine	Placebo	Inpatients	4–16 weeks following TBI	Vegetative or minimally conscious TBI
Fann[42] 2017 (*N* = 62)	Published USA	RCT parallel	Major depression	Sertraline	Placebo	Level 1 trauma center	<1 year of TBI	Moderate and severe TBI

(*continued*)

Table 1. (Continued)

Study/year (N)	Publication/ country	Study design	Study focus	Interventional arm	Comparative arm	Location at randomization	Timing from TBI at randomization	TBI description
Hart[43] 2017 ($N = 32$)	Published USA	RCT parallel	Cognitive function	Dextroamphetamine	Placebo	TBI rehabilitation unit	< 6 months of TBI	Moderate and severe TBI
Outpatient setting								
[a]Brawman-Mintzer[26] 2021 ($N = 94$)	Published USA	RCT parallel	Cognitive function	Rivastigmine 4.6 mg daily for 4 weeks followed by 9.5 mg daily	Placebo	Outpatient	≥ 12 months following a TBI	Mild, moderate and severe TBI
Schneider[44] 1999 ($N = 10$)	Published USA	RCT parallel	Cognitive function and behavior	Amantadine 50 mg bid increased to 150 mg bid	Placebo	Outpatient	N/A	Moderate and severe TBI
Tramontana[45] 2014 ($N = 22$) but 13 completed the study	Published USA	RCT Crossover	Attention	Lysdexampheta-mine	Placebo	Outpatient	6–34 months (mean 15.6 ± 10 months) since TBI	Moderate and severe TBI
Johansson[46] 2014 ($N = 48$)	Published Sweden	RCT Crossover	Mental fatigue and cognition	Methylphenidate 5 mg and 20 mg tid	Placebo	Outpatient	> 12 months following TBI	Mild or moderate TBI
3. Studies assessing the safety of pharmacological agents used for agitated behaviors in TBI								
Acute setting and rehabilitation								
[a]Oommen[28] 2019 ($N = 53$)	Published USA	Retrospective chart review	Cognitive function	Amantadine, methylphenidate, modafinil, zolpidem	None	Inpatient	From admission	TBI
[a]Nguyen[29] 2021 ($N = 200$)	Published USA	Retrospective cohort	Agitation	Phenytoin mean of 318 mg daily	Levetiracetam mean of 1352 mg daily	Level 1 trauma center	From admission	TBI
Rao[47] 1985 ($N = 26$)	Published USA	Retrospective observational	Rehabilitation outcomes	Haloperidol	No haloperidol	Trauma and rehabilitation center	From admission	Severe closed head injury
Mysiw[48] 2006 ($N = 182$)	Published USA	Retrospective cohort	Cognitive and motor recovery	Narcotics, benzodiazepines and neuroleptics	No Central Nervous System active medications	Level 1 trauma center and rehabilitation center	From admission	TBI
Kooda[49] 2015 ($N = 195$)	Abstract USA	Retrospective observational	Duration of post-traumatic amnesia	Antipsychotics	No antipsychotic	Level 1 trauma center and rehabilitation center	From admission	TBI
Anderson[50] 2016 ($N = 101$)	Published USA	Retrospective cohort	Seizures, neuroleptic malignant syndrome, QTc prolongation, extrapyramidal symptoms, hematological disturbances	Haloperidol	No haloperidol	Inpatients	From admission	Moderate and severe TBI

[a]Studies identified in the updated literature search.
TBI, traumatic brain injury; ICU, Intensive Care Unit.

Table 2. Tools Used to Measure Agitated Behaviors

Tools	*Description*
Agitated behavior scale (ABS)[51]	Scale of 14 items with 4 levels of scoring to assess the nature and extent of agitation during the acute recovery of traumatic brain. Total scores greater than 21 are considered as agitation.
Anger-Hostility factor score of the Profile of Mood States (POMS)[37]	The POMS consists of 65 adjectives that describe moods or feelings, to which the patient responds on a 5-point scale that ranges from "Not at all" to "Extremely." The POMS measures six identifiable mood/affective states: tension-anxiety, depression-dejection, anger-hostility, vigor-activity (V); fatigue-inertia (F), and confusion-bewilderment (C).
Belligerence cluster score for the Katz adjustment scale (KAS)[52]	The KAS is an observer rating scale used to assess the social adjustment of people with traumatic brain injury.
Brief Anger and Aggression Scale[53]	A six-item measure developed for the rapid screening and identification of anger and aggression levels.
Confusion assessment protocol[54]	Combination of orientation, cognition and other clinical measures of early confusion following traumatic brain injury.
Functional independence measure (FIM)[55]	Functional assessment measure with a 18-item ordinal scale used in the rehabilitation population. It offers a useful assessment of patient progress during inpatient rehabilitation.
Global improvement subscale of the Clinical Global Impressions (CGI)[56]	The CGI is a 3-item observer-rated scale that measures illness severity (CGIS), global improvement or change (CGIC) and therapeutic response.
Modified overt aggression scale (MOAS)[a] [21]	The MOAS is a 4-item scale measuring verbal and physical aggression toward other people, property and self.
Neurobehavioral Function Inventory (NFI)[57]	The NFI provides information on the frequency of behaviors and symptoms commonly associated with brain injury. Two versions of the NFI are available, one for completion by family members, another for completion by the person with the injury.
Neurobehavioral rating scale (NRS)[58]	The NRS is a 28-item observer-rated instrument that measures a broad range of cognitive and noncognitive symptoms. It measures symptoms associated with psychiatric disorders as well as cognitive impairment and behavioral disturbances.
Neuropsychiatric inventory irritability (NPI-I) and aggression (NPI-A) domains[59]	The NPI is a 40-item scale evaluating 12 behavioral domains including irritability and aggression. The NPI irritability (NPI-I) items include bad temper, rapid mood changes, sudden anger, impatience, crankiness, and argumentative. Raters evaluate frequency and severity of behaviors in the last month. The NPI aggression domain assesses the tendency to get upset, resistance to activities, stubbornness, uncooperativeness, shouting, cursing, and physical behaviors indicative of aggression. The NPI score is the product of frequency and severity. The worst item score provided by the scorer is NPI-I or NPI-A most aberrant.
Overt aggression scale (OAS)[60]	Scale for the objective rating of verbal and physical aggression. The OAS measures aggressive behaviors divided into 4 categories: verbal aggression, physical aggression against objects, physical aggression against self, and physical aggression against others.
Ramsay Sedation Scale[61]	The Ramsay Sedation Scale is a six-point numerical scale of motor response founded on depth of sedation.
Richmond Agitation-Sedation Scale (RASS)[a] [62]	The RASS ranges between −5 (unarousable sedation) to +4 (combative agitation) with 0 representing the appearance of a calm state.
Riker Sedation-Agitation Scale (SAS)[a] [63]	The SAS ranks the level of sedation and agitation of patients from 1 (unarousable sedation) to 7 (dangerous agitation) with 4 being a calm and cooperative state.
State-Trait Anger Scale (STAS)[37]	The STAS is a 20-item self-report scale assessing two types of anger (State and Strait). State anger is comprised of tension, annoyance, irritability or rage. Whereas trait anger is the frequency with which a person feels state anger over time.

[a]Tools from studies added with the updated literature search.

For amantadine, no new studies were identified. Amantadine was evaluated in 2 RCTs and reported inconsistent results.[33,35] In a pilot study, amantadine showed significant reductions in irritability and aggression using the Neuropsychiatric Inventory (NPI) scale.[33] In a follow-up study, there were large improvements in both groups, but no difference in the incidence of irritability at 28 and 60 days using the NPI-I from observers (family member, close friend, or employer) was reported.[35]

Agitated behavior as a secondary outcome—acute and rehabilitation (1.2)

From the new studies evaluated in which agitated behaviors were a secondary outcome; one took place in the acute setting.[27] The study was a RCT and focused on the effects of propranolol and clonidine on mortality in severe TBI patients in the ICU setting.[27] The administration of both propranolol and clonidine failed to significantly impact agitation when compared with placebo.[27] The study reported no serious adverse events, and treatments were well tolerated by the patients.

Agitated behavior as a secondary outcome—outpatient (1.2)

The second study evaluating agitated behaviors as a secondary outcome was a RCT performed in the outpatient setting.[26] The study evaluated the effects of rivastigmine on memory recovery more than 12 months after a mild,

Table 3. Efficacy and Safety Outcomes

Study/year/n	*Intervention*	*Agitated behavior measures*	*Efficacy outcomes*	*Safety outcomes*
1. Agitated behavior as the presenting symptom				
Randomized controlled studies				
Acute and rehabilitation setting				
Phyland[24] 2023[a] ($N = 11$)	Olanzapine	Agitated behavior scale (ABS)	No significant differences were recorded on measures of agitation (mean ABS over treatment period, number of agitated days, and agitation at discharge).	No significant difference in adverse events was recorded between the groups.
Feng[19] 2022[a] ($N = 60$)	Dexmedetomidine	Riker sedation-agitation scale (SAS) and the Ramsay sedation scale (RSS)	Incidence of agitation was significantly lower in the dexmedetomidine group (16%) in comparison with the saline group (76%) ($p < 0.05$). SAS and RSS scores were statistically lower in the dexmedetomidine group throughout the recording post-surgery (2 h).	Cases of chills and delirium were significantly lower in the dexmedetomidine group vs the saline group ($p < 0.05$).
Wang[22] 2022[a] ($N = 104$)	Dexmedetomidine, butorphanol, dexmedetomidine and butorphanol	Riker sedation-agitation scale (SAS)	At the 3rd and 5th days post-operation, SAS scores were significantly improved in the dexmedetomidine and butorphanol combination group in comparison with the control group ($p < 0.05$).	Vital signs were significantly improved in the combination group compared with the control group ($p < 0.05$).
Soltani[20] 2021[a] ($N = 60$)	Dexmedetomidine, haloperidol	Richmond agitation-sedation scale (RASS)	Three to seven days after the intervention, RASS scores showed that dexmedetomidine patients were less agitated and more stable than haloperidol patients ($p < 0.05$). Delirium was also lower in the dexmedetomidine group ($p < 0.05$).	No safety outcomes reported.
Yablon[31] 2010 ($N = 79$)	Amantadine	Confusion assessment protocol (CAP)	No significant differences in the number of symptoms of post-traumatic confusional state as measured by the CAP at 14 days (amantadine 2.56 vs placebo 2.7; $p = 0.57$). Mean difference in time to first "nonconfused" CAP score between groups approached significance (amantadine 7.7 days and placebo 9.3 days; $p = 0.053$)	No patients withdrawn because of safety criteria
Brooke[30] 1992 ($N = 21$)	Propranolol	Overt aggression scale	Significant reduction in maximum intensities of agitation per week ($p < 0.05$). No significant difference in average number of agitation episodes per week. Significant reduction in physical restraint use during the study ($p < 0.05$)	No safety outcomes reported
Outpatient setting				
Hammond[23] 2021[a] ($N = 69$)	Carbamazepine	Neuropsychiatric inventory irritability (NPI-I) and aggression domains (NPI-A)	Observer- and participant-rated irritability/aggression was not reduced compared to placebo. Clinician ratings suggest benefit.	No statistical difference in subjects with serious adverse advents in the intent-to-treat ($p = 0.11$) and therapeutic sample ($p = 0.26$) compared with placebo. Non-serious adverse events related to carbamazepine were more common in the intent-to-treat sample ($p = 0.01$).
Deb[21] 2020[a] ($N = 12$)	Risperidone	Modified overt aggression scale (MOAS)	No difference in MOAS scores between the risperidone and placebo groups.	No severe adverse events were reported.

(*continued*)

Table 3. (Continued)

Study/year/n	Intervention	Agitated behavior measures	Efficacy outcomes	Safety outcomes
Beresford[64] 2015 ($N = 50$)	Valproic acid	Agitated Behavior Scale by spouse or significant other	Significant others' weekly Agitated Behavior Scale ratings were statistically lower, indicating less agitation in the valproic acid group, 12.9 ± 4.9, than in the placebo group, 15.5 ± 6.6, with significance at $p = 0.0367$.	No safety outcomes reported
Hammond[35] 2015 ($N = 168$)	Amantadine	NPI-I most problematic by observer and by patient. Global improvement subscale of the Clinical Global Impressions (CGI) by physicians.	Observer ratings were not different at day 28 or 60. Participants rating at day 60 showed improvement in NPI-I most problematic ($p < 0.04$; but non-significant when adjusted for multiple comparisons). Physician's assessment of global improvement improved more in the amantadine group than the placebo group at 60 days ($p = 0.0354$).	Well tolerated with no significant differences in adverse events between groups.
Hammond[33] 2014 ($N = 76$)	Amantadine	NPI-I most aberrant and most problematic Irritability (NPI-I) and aggressiveness (NPI-A)	Significant reduction in irritability (80.56% improved at least three points on the NPI-I, compared with 44.44% in the placebo group; $p = 0.0016$). Mean change in NPI-I was −4.3 in the amantadine group and −2.6 in the placebo group ($p = 0.0085$). When excluding individuals with minimal to no baseline aggression, mean change in NPI-A was −4.56 in the amantadine group and −2.46 in the placebo group ($p = 0.046$).	No difference in adverse events (tremors, appetite, gastrointestinal, aches and pain, sexual problems, disorientation, seizures)
Mooney[37] 1993 ($N = 38$)	Methylphenidate	State-Trait Anger Scale, Belligerence cluster score for the Katz adjustment scale and the Anger-Hostility factor score, Organic Signs and Symptoms Inventory	Significant difference in the comparison of methylphenidate and placebo group on all the anger measures before and after 6 weeks in a multivariate analysis ($p = 0.02$).	No significant side effects
Observational studies				
Acute and rehabilitation setting				
Swayngim 2024[a25] ($N = 108$)	Valproic acid	RASS score ≥2 and positive on the Confusion Assessment Method for the ICU (CAM-ICU)	There were no significant differences in agitation-free days.	Hepatotoxicity was evident in 6.1% of patients who received valproic acid, thrombocytopenia in 12.2%, and 0 patients had laboratory evidence of hyperammonemia.
Gramish[32] 2017 ($N = 139$)	Amantadine	RASS score of +2 or higher	Increase in agitation in patients exposed to amantadine (38%) compared with non-exposed (14%); $p = 0.018$. Increase in median ICU length of stay (4.5 vs 3 days; $p = 0.01$). Median hospital length of stay was non-significantly increased (14 days vs 10 days; $p = 0.051$)	No safety outcomes reported
Outpatient setting				
Maturana Waidele[36] 2009 ($N = 31$)	Olanzapine	Restlessness, irritability, aggressiveness and insomnia. No tool mentioned.	Reduction in irritability ($p < 0.001$), aggressiveness ($p = 0.008$), and insomnia ($p = -0.0011$) between weeks 1 and 3 in the patients treated with olanzapine	No safety outcomes reported

(*continued*)

Table 3. (Continued)

Study/year/n	Intervention	Agitated behavior measures	Efficacy outcomes	Safety outcomes
2. Agitated behavior is not the presenting symptom				
Randomized controlled studies				
Acute and rehabilitation setting				
Nordness[27] 2023[a] ($N = 47$)	Propranolol and clonidine	Richmond agitation-sedation scale (RASS)	No significant differences in secondary outcomes of agitation were detected.	No cardiac or other serious adverse event happened.
Hart[43] 2017 ($N = 32$)	Dextroamphetamine	Agitated behavior scale	Increase in agitation with dextroamphetamine over time compared with placebo ($p < 0.05$).	No significant difference in heart rate or blood pressure.
Fann[42] 2017 ($N = 62$)	Sertraline	Brief anger and aggression scale and agitation/restlessness not further defined	No difference in the anger and aggression scale. More patients developed agitation/restlessness in the sertraline group (17%) vs the placebo group (7%) $p = 0.42$	No significant difference in safety outcomes. More patients in the sertraline group (17%) developed gas/flatulence vs the placebo group (0%) $p = 0.052$.
Giacino[41] 2012 ($N = 184$)	Amantadine	Agitation and restlessness not further defined	A total of 12/87 (14%) patients and 11/97 (11%) patients exposed to amantadine and placebo developed agitation (p = NS) over the 4-week period. Restlessness was reported in 8% and 9% of patients exposed to amantadine and placebo, respectively.	No differences in adverse events (seizure, nausea, vomiting, constipation, diarrhea, elevated liver function tests, insomnia, rash, congestive heart failure, involuntary muscle contractions)
Banos[40] 2010 ($N = 99$)	Sertraline	Aggression self-report and family report according to the neurobehavioral function inventory	No significant differences between sertraline and placebo in patient self-report and family report.	No safety outcomes reported
Meythaler[39] 2002 ($N = 35$)	Amantadine	Agitated behavior scale	There were no statistically significant changes or trends in the ABS during the first 6 weeks or the second 6 weeks of the study ($p > 0.05$, Mann–Whitney U test).	No detrimental effects in hematology or biochemistry laboratories and no seizures.
Meythaler[38] 2001 ($N = 9$)	Sertraline	Agitated behavior scale	No difference in decline of ABS over treatment period.	No safety outcomes reported
Outpatient setting				
Brawman-Mintzer[26] 2021[a] ($N = 94$)	Rivastigmine	Neurobehavioral function inventory (NFI)-aggression	Change from baseline to 12-week aggression in the rivastigmine group was significantly more in the rivastigmine group (+0.5) compared to the placebo group (−1.5) ($p = 0.04$).	Rivastigmine was generally well tolerated with 10 patients developing mild or moderate adverse effects in the rivastigmine group and 4 in the placebo group. No serious adverse events were attributed to the medication.
Tramontana[45] 2014 (N =) 22 but 13 patients completed the study	Lysdexamphetamine	Agitation and restlessness not further defined	No difference in agitation (no cases in each group) or irritability (1/13 case during placebo) between the Lysdexamphetamine and placebo groups.	Reduced appetite and weight loss of more than 5 lbs more frequent with lysdexamphetamine (7 vs 1 case) p = NS
Johansson[46] 2014 ($N = 48$)	Methylphenidate	Aggression, restlessness and irritability not further defined	No difference in aggression, restlessness, and irritability in patients treated with methylphenidate	A significant increase in heart rate was found. No significant changes were found in blood pressure or QT intervals.
Schneider[44] 1999 ($N = 10$)	Amantadine	Neurobehavioral rating scale	No significant difference in behavior scores between amantadine and placebo groups.	No safety outcomes reported
3. Studies assessing the safety of pharmacological agents used for agitated behaviors in TBI				
Acute and rehabilitation setting				
Nguyen[29] 2021[a] ($N = 200$)	Phenytoin, levetiracetam	No statistical difference in neurobehavioral side effects (including agitation) between the phenytoin and levetiracetam groups was recorded ($p = 0.520$).		
Oommen[28] 2019[a] ($N = 53$)	Amantadine, methylphenidate, modafinil, zolpidem	Few adverse events were associated with all four agents with agitation occurring in two modafinil patients and one zolpidem patient as well as hypertension occurring in one modafinil patient.		

(*continued*)

Table 3. (Continued)

Study/year/n	Intervention	Agitated behavior measures	Efficacy outcomes	Safety outcomes
Anderson[50] 2016 ($N = 101$)	Haloperidol	In an unadjusted analysis, there was no significant increase in adverse events (QT prolongation, seizures, neuroleptic malignant syndrome, extrapyramidal symptoms, or hematological disturbances) associated with haloperidol use. Patients in the haloperidol group who developed complications received a higher mean daily dose [$p = 0.013$]. There was no difference in length of mechanical ventilation but the haloperidol group had a longer hospital length of stay (22 vs 11 days; $p < 0.001$)		
Kooda[49] 2015 ($N = 195$)	Antipsychotics	Fifty-two patients received antipsychotics (26.7%) within 7 days of TBI, mostly quetiapine. In an unadjusted analysis, duration of PTA was significantly longer (19.6 vs 12.3 days; $p = 0.013$) in patients treated with antipsychotics.		
Mysiw[48] 2006 ($N = 182$)	Narcotics, benzodiazepines and neuroleptics	Narcotics, benzodiazepines and neuroleptics had no effect on the Function Independence Measures (FIM) motor and independence scores. In an unadjusted analysis, narcotics and neuroleptics increased duration of PTA by more than 7 days ($p < 0.01$).		
Rao[47] 1985 ($N = 26$)	Haloperidol	Twenty-five patients exhibited agitation and 11 patients required haloperidol. In an unadjusted analysis, the haloperidol patients have a significantly longer period (8 vs 4 weeks; $p < 0.03$) of post-traumatic amnesia (PTA).		

[a]Studies identified in the updated literature search.

moderate, or severe TBI. The study found a significant increase in the Neurobehavioral Function Inventory—aggression scores from baseline at 12 weeks in comparison with placebo.[26] No serious adverse events were reported, and rivastigmine was well tolerated by the patients. The compound had no consistent effect on the incidence of agitation, anger, or aggression.

Studies evaluating safety outcomes

Out of the 11 new studies, two primarily assessed the safety of pharmacological agents used for agitated behaviors in TBI.[28,29] In one study, safety outcomes of amantadine, methylphenidate, modafinil, and zolpidem were evaluated with a retrospective chart review.[28] The study was conducted in a single center inpatient setting and used an adult population. Although two modafinil and one zolpidem patients experienced agitation, and one modafinil patient experienced hypertension, amantadine, methylphenidate, modafinil, and zolpidem were associated with few adverse events.[28] A retrospective cohort study evaluated the neurobehavioral side effects of phenytoin and levetiracetam in patients with TBI for seizure prophylaxis.[29] In this study, phenytoin ($n = 95$) and levetiracetam ($n = 105$) showed no differences in neurobehavioral side effects (including agitation).[29]

From the nine remaining new studies, seven studies reported safety outcomes and indicated that the agents were well tolerated with no outstanding adverse events. In a retrospective study, 6.1% and 12.2% of patients who received valproic acid developed hepatotoxicity and thrombocytopenia, respectively.[25] Unfortunately, this study did not report safety outcomes for the control group.

Risk of Bias Assessment

Risk of bias is reported in Figure 2 and Figure 3. The analysis of risk of bias of RCTs with the Cochrane Collaboration's Risk of Bias Tool (ROB2) revealed that most studies had some concerns, and the overall risk of bias was low only in a minority of studies. Missing information regarding the randomization process and risk of selective reporting were the most common risks. A majority of studies had other threats to validity including limited sample sizes, no description of patient demographics and loss to follow-up. For eight studies evaluated with the ROBBINS-I tool, the overall risk of bias was serious or critical. Bias due to confounding and bias in the selection of reported results accounted for much of the risk.

Discussion

In this updated systematic review, the pharmacological management of agitation, aggression, and irritability after TBI was investigated through an updated literature search from our initial 2019 systematic review. Both the effects of the pharmacological agents on TBI agitation and safety were considered in the acute, rehabilitation, and outpatient settings. In the previous review, although beta-blockers and valproic acid showed beneficial effects in rehabilitation and outpatients, there were insufficient data to clearly recommend any pharmacological agent to mediate agitation after TBI.[15] Of the 11 additional studies included in this updated review, a majority of agents assessed were new relative to those previously evaluated in the 2019 systematic review. From these newly studied medications, risperidone, carbamazepine, phenytoin, levetiracetam, and clonidine failed to show any significant changes in agitation, aggression, or irritability. However, studies using the alpha-2-receptor agonist dexmedetomidine in critically ill TBI patients showed significant decreases in agitation.[19,20,22]

Acute/rehabilitation

Dexmedetomidine has attractive pharmacological properties and has shown positive results in various clinical

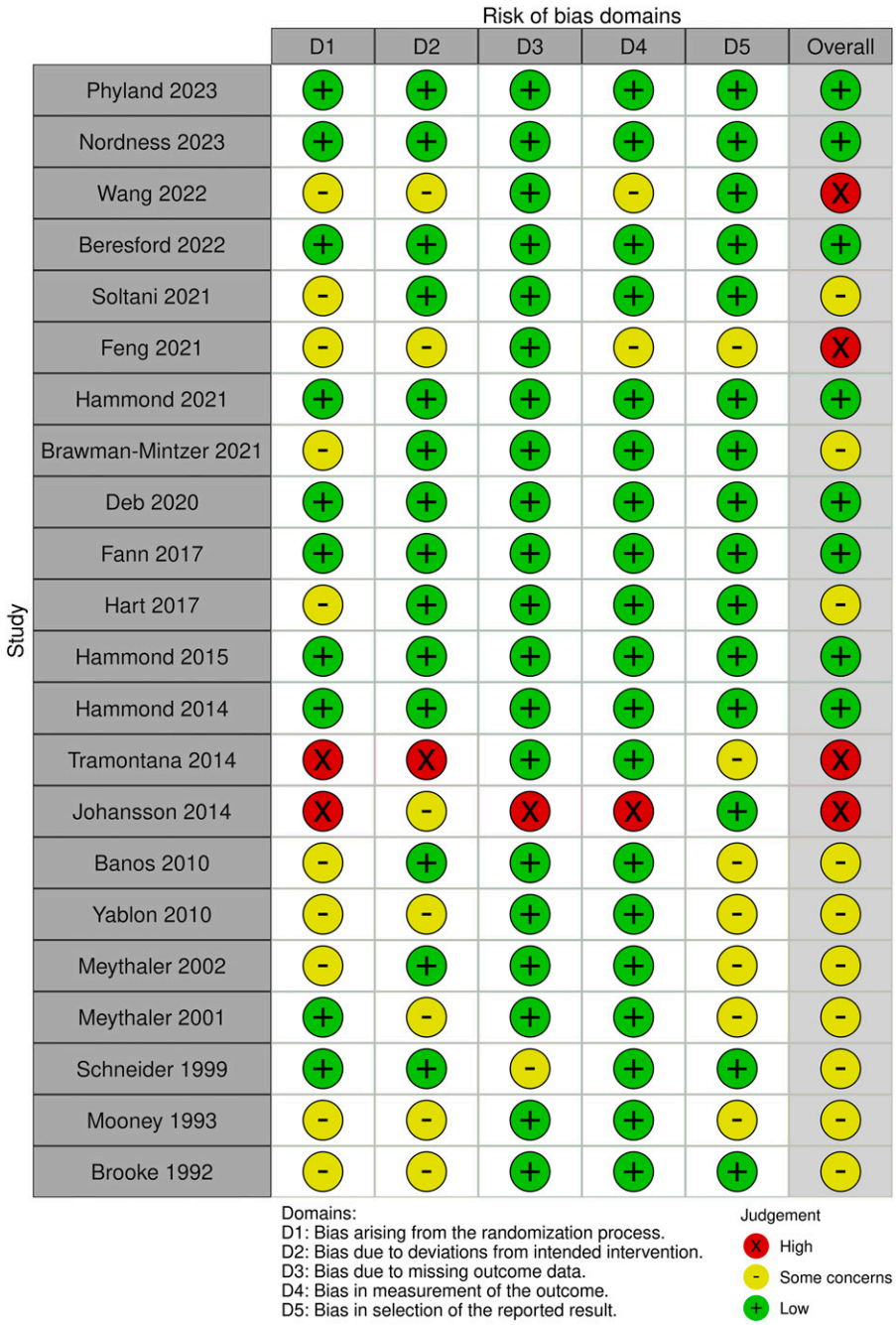


FIG. 2. Cochrane risk-of-bias tool for randomized trials (RoB 2).

settings that may explain the results found in this review.[65–67] Among interesting pharmacological properties, dexmedetomidine does not induce respiratory depression or deep sedation, facilitating the cooperation between patients and caregivers.[68] In addition, dexmedetomidine has been shown to reduce time to extubation, risk and duration of delirium as well as ICU length of stay in non-brain–injured ICU patients.[65,66,69–72] In pre-clinical studies, dexmedetomidine has been shown to enhance neurological recovery and reduce neuroinflammation, neuronal death, and secondary brain damage.[73–77] In accordance with studies of this review using dexmedetomidine,[19,20,22] observational studies support the safety of administering dexmedetomidine in TBI patients.[78–81] Although dexmedetomidine shows promise, this agent is administered as an intravenous infusion and needs hemodynamic monitoring; it would be mostly useful in acute settings. Interestingly, one recent study has successfully

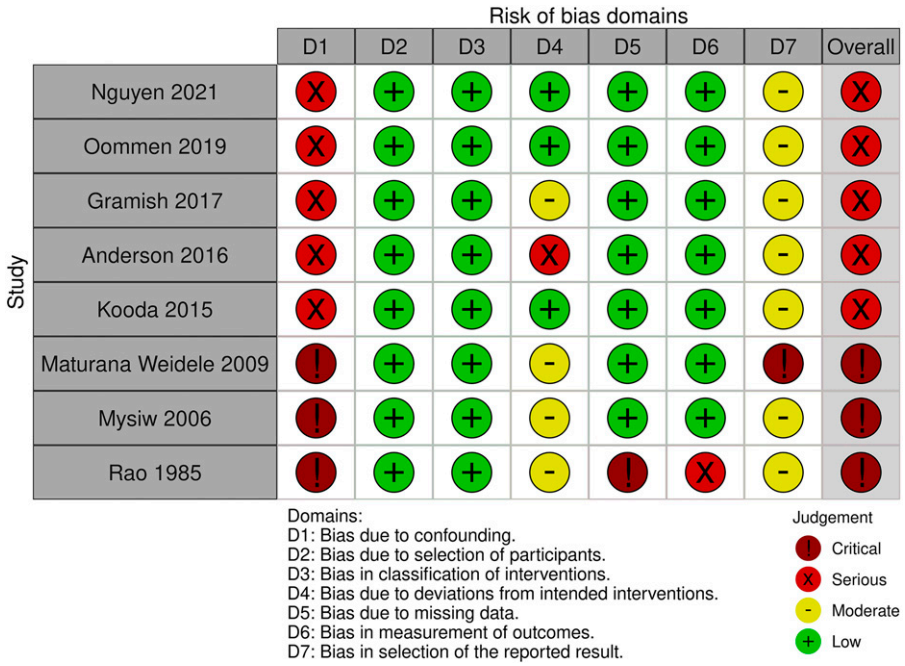


FIG. 3. Risk Of Bias In Non-randomized Studies—of Interventions (ROBINS-I).

shown the efficacy of sublingual dexmedetomidine for the management of acute agitation associated with bipolar disorder.[82] Unfortunately, studies included in the review used dexmedetomidine either for a short post-operative period, in combination with butorphanol, in comparison with haloperidol, or as an every-other-day 0.5 mcg/kg infusion, limiting the applicability of the results.[19,20,22] In addition, all three dexmedetomidine studies had some concerns with regard to risk of bias related to methodological issues and small sample sizes. As such, future investigations that build on the weaknesses of the aforementioned studies should be conducted to explore the effects of dexmedetomidine infusions for the management of agitation in critically ill TBI patients. The safety and efficacy of sympathetic blockade with combined clonidine, another alpha-2-receptor agonist, and propranolol on ventilator-free days after severe TBI were evaluated in one randomized controlled feasibility study ($n = 47$). Interestingly, clonidine 0.1 mg per tube twice daily in combination with propranolol 1 mg intravenously every 6 h failed to detect a difference in the secondary outcome of agitation.[27] The small drug doses used in this study as well as the small sample size may explain this lack of effect. Studies of clonidine and/or propranolol for agitation probably necessitate a higher dosing strategy, as evidenced by the earlier study of propranolol for aggression, which used 60 mg to 420 mg per day.[30] Pre-clinical studies have suggested propranolol may improve cognitive and motor functions in TBI and thus may offer potential benefits for the management of post-TBI agitation.[83]

Despite being frequently used for the management of post-TBI agitation, the efficacy of antipsychotics remains unclear.[84–86] In the review update, we identified one additional study evaluating olanzapine in the acute phase of TBI.[21,24] Unfortunately, the study was unable to complete recruitment because of the COVID-19 pandemic.[24] An *n*-of-1 analysis suggested a reduction in agitation over the PTA period.[24] However, olanzapine patients also demonstrated poorer orientation and memory and a trend toward increased PTA duration.

We identified one retrospective observational study evaluating valproic acid, which showed no significant differences in agitation-free days.[25] A number of observational studies have suggested potential benefits of valproic acid in critically ill patients, but there have been no RCTs evaluating efficacy.[87–90]

Outpatient

In addition to the study on olanzapine in the acute setting, a study evaluating the antipsychotic risperidone in the outpatient setting was performed.[21,24] Unfortunately, slow recruitment in the study prevented the completion of recruitment, and no difference in agitation scores was measured.[21] As pre-clinical and clinical data have suggested potential detrimental effects of antipsychotics such as haloperidol and risperidone on cognitive recovery, adequately powered RCTs are warranted to evaluate

their efficacy and safety in the acute, rehabilitation, and ambulatory settings.[48,91] Interestingly, antipsychotics lacking D2 antagonist activity such as aripiprazole have shown a more interesting safety profile in pre-clinical studies.[92] Until these studies are conducted, clinicians should follow the recent INCOG 2.0 recommendations and minimize the use of antipsychotics to treat agitation or aggression in TBI patients.[93] Similarly, the recently updated Canadian guideline for the rehabilitation of adults with moderate to severe TBI suggests avoiding first-generation antipsychotics and using second generation agents such as quetiapine, ziprasidone, olanzapine, and risperidone for severe agitation or aggression that threatens patient safety.[94]

In addition to a study of valproic acid in TBI veterans with affective lability and alcohol dependence identified in the initial systematic review, one randomized controlled study evaluating carbamazepine was identified.[23,34] Clinician ratings of carbamazepine support a potential benefit, but the study also showed no statistical improvements in observer- and participant-rated irritability and aggression, as high placebo effects were reported.[23] Before anticonvulsants can be recommended for the management of TBI-associated agitation, further studies are warranted.

In the 2019 review, we identified four studies evaluating amantadine and one study with methylphenidate for the management of anger, aggressivity or agitation, mostly in the outpatient setting. In our update, we found no additional studies evaluating psychostimulants. In one study focusing on the effects of rivastigmine on memory recovery after TBI, no decrease in agitation or aggression was observed. A search of TBI-associated agitation studies in clinical registries revealed ongoing studies for the management of agitation, aggression, or irritability with dexmedetomidine (NCT06620393), deudextromethorphan hydrobromide/quinidine sulfate (NCT03095066), and buspirone (NCT01821690).

Strengths and limitations

Strengths of this systematic review include an updated search of the literature in the adult and pediatric populations with no language limitation. A risk of bias assessment was performed and updated from the initial systematic review with the newer RoB 2 and ROBBINS-1 tools. Limitations of this systematic review include the presence of significant heterogeneity with variations in the different agitated behaviors (agitation, irritability, and aggression), TBI severities (mild, moderate, and severe), agitation measurement tools, and populations (acute TBI, rehabilitation, and outpatient), precluding a meta-analysis. Further limiting interpretability, comparators varied between studies from placebo for a majority to other treatments such as butorphanol[22] or haloperidol[20] in studies evaluating dexmedetomidine. Few studies reported length of hospital stay or functional outcomes, and no studies were conducted in the pediatric population. Finally, as the risk of bias assessment of many of the RCTs had at least some concerns and all of the observational studies had serious or critical risks of bias, the results of these studies need to be interpreted in light of these limitations.

Since the 2019 review, this update shows ongoing research in the field, with new pharmacological agents being tested and different behavioral scales being used. While the novelty of these different tools is important to push the field forward, it remains that new studies are very heterogenous, thus hindering possible comparisons. To facilitate future comparisons, core outcome sets specific to agitated behaviors for the acute, rehabilitation, and outpatient TBI periods are needed. In addition, better knowledge on the most optimal treatment strategies must be provided to clinicians. For example, studies in the acute and rehabilitation setting are typically in single-center settings and underpowered. Given that there are more patients susceptible to agitation in these acute phases, larger studies similar to those in the outpatient setting are needed.

Conclusion

In conclusion, there remain insufficient data to recommend the use of any medications for the management of agitation following TBI. In this updated review, dexmedetomidine was identified as an agent with potential benefit in an acute setting with monitoring; however, it needs to be further studied. The benefits of antipsychotics still remain unclear, with official recommendations suggesting to minimize their use. Beta-blockers and valproic acid have shown benefits, but results are inconsistent. Carbamazepine and amantadine have both shown clinician-rated benefits in the outpatient setting, although patient- and observer-reported outcomes were not improved. More studies on tailored interventions and continuous evaluation throughout the acute, rehabilitation, and outpatient settings are needed to assess the efficacy and safety of pharmacological agents for the management of agitated behaviors in both the adult and pediatric TBI populations. In addition, there is a need to better define and standardize the assessment of agitated behaviors in TBI, especially during the acute phase. Newer agents such as dexmedetomidine should also continue to be evaluated.

Transparency, Rigor, and Reproducibility

Summary

This updated systematic review is registered in PROSPERO International Prospective Register of Systematic Reviews (CRD42023391456). We followed the PRISMA guidelines for systematic reviews, and the protocol for the initial systematic review was published (Syst Rev 2016;5:193). The

MedLine search strategy is available in the supplements, and two reviewers screened each article at both steps of the screening process and discussed conflicts with a third reviewer in the screening process to come to a consensus decision for each article. All the selected articles were evaluated for risk of bias.

Authors' Contributions

D.W., L.B., M.P., M.J.P., and F.B. participated in the design and writing of the review protocol and contributed to the final article. D.W. wrote the search strategy and undertook the literature search. D.W. and T.K. conducted the title and abstract screening and full article screening for final study inclusion. D.W., T.K., and C.D. conducted data collection and cleaning. T.K., C.D., and D.W. conducted the risk of bias analysis. L.B., C.A., M.P., A.C., and M.M.B. advised on methods and interpretation of findings. All the authors critically reviewed the article.

Patient and Public Involvement Statement

Patients and/or the public were not involved in the design, conduct, or reporting of this research.

Author Disclosure Statement

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Supplementary Material

Supplementary Appendix A1
Supplementary Appendix A2

References

1. Marr A, Coronado V. Central nervous system injury surveillance data submission standards—2002. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2004.
2. Menon DK, Schwab K, Wright DW, et al.; Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health. Position statement: Definition of traumatic brain injury. Arch Phys Med Rehabil 2010;91(11):1637–1640; doi: 10.1016/j.apmr.2010.05.017
3. Pavlovic D, Pekic S, Stojanovic M, et al. Traumatic brain injury: Neuropathological, neurocognitive and neurobehavioral sequelae. Pituitary 2019;22(3):270–282; doi: 10.1007/s11102-019-00957-9
4. Oberholzer M, Müri RM. Neurorehabilitation of Traumatic Brain Injury (TBI): A Clinical Review. Med Sci (Basel) 2019;7(3):47; doi: 10.3390/medsci7030047
5. Capizzi A, Woo J, Verduzco-Gutierrez M. Traumatic brain injury: An overview of epidemiology, pathophysiology, and medical management. Med Clin North Am 2020;104(2):213–238; doi: 10.1016/j.mcna.2019.11.001
6. Phyland RK, Ponsford JL, Carrier SL, et al. Agitated behaviors following traumatic brain injury: A systematic review and meta-analysis of prevalence by post-traumatic amnesia status, hospital setting, and agitated behavior type. J Neurotrauma 2021;38(22):3047–3067; doi: 10.1089/neu.2021.0257
7. Carrier SL, Ponsford J, McKay A. Managing agitation during early recovery following traumatic brain injury: Qualitative interviews with clinicians. Disabil Rehabil 2023;45(22):3686–3695; doi: 10.1080/09638288.2022.2135771
8. Rahmani E, Lemelle TM, Samarbafzadeh E, et al. Pharmacological treatment of agitation and/or aggression in patients with traumatic brain injury: A systematic review of reviews. J Head Trauma Rehabil 2021; 36(4):E262–E283; doi: 10.1097/HTR.0000000000000656
9. Hicks AJ, Clay FJ, Hopwood M, et al. Efficacy and harms of pharmacological interventions for neurobehavioral symptoms in post-traumatic Amnesia after traumatic brain injury: A systematic review. J Neurotrauma 2018;35(23):2755–2775; doi: 10.1089/neu.2018.5738
10. Saavedra-Mitjans M, Frenette AJ, McCredie VA, et al. Physicians' beliefs and perceived importance of traumatic brain injury-associated agitation in critically ill patients: A survey of Canadian intensivists. Can J Anaesth 2024;71(2):264–273; doi: 10.1007/s12630-023-02666-1
11. Hicks AJ, Clay FJ, Hopwood M, et al. The efficacy and harms of pharmacological interventions for aggression after traumatic brain injury-systematic review. Front Neurol 2019;10:1169; doi: 10.3389/fneur.2019.01169
12. Mehta S, McIntyre A, Janzen S, et al. Pharmacological management of agitation among individuals with moderate to severe acquired brain injury: A systematic review. Brain Inj 2018;32(3):287–296; doi: 10.1080/02699052.2017.1419377
13. Nash RP, Weinberg MS, Laughon SL, et al. Acute pharmacological management of behavioral and emotional dysregulation following a traumatic brain injury: A systematic review of the literature. Psychosomatics 2019;60(2):139–152; doi: 10.1016/j.psym.2018.11.009
14. Ter Mors BJ, Backx APM, Spauwen P, et al. Efficacy of amantadine on behavioural problems due to acquired brain injury: A systematic review. Brain Inj 2019;33(9):1137–1150; doi: 10.1080/02699052.2019.1631482
15. Williamson D, Frenette AJ, Burry LD, et al. Pharmacological interventions for agitated behaviours in patients with traumatic brain injury: A systematic review. BMJ Open 2019;9(7):e029604; doi: 10.1136/bmjopen-2019-029604
16. Williamson DR, Frenette AJ, Burry L, et al. Pharmacological interventions for agitation in patients with traumatic brain injury: Protocol for a systematic review and meta-analysis. Syst Rev 2016;5(1):193; doi: 10.1186/s13643-016-0374-6
17. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355: i4919; doi: 10.1136/bmj.i4919
18. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898; doi: 10.1136/bmj.l4898
19. Feng X, Zhao B, Wang Y. Effect evaluation of dexmedetomidine intravenous anesthesia on postoperative agitation in patients with craniocerebral injury by magnetic resonance imaging based on sparse reconstruction algorithm. Contrast Media Mol Imaging 2022; 2022(pagination):5161703; doi: 10.1155/2022/5161703
20. Soltani F, Tabatabaei S, Jannatmakan F, et al. Comparison of the effects of haloperidol and dexmedetomidine on delirium and agitation in patients with a traumatic brain injury admitted to the intensive care unit. Anesth Pain Med 2021;11(3):e113802; doi: 10.5812/aapm.113802
21. Deb S, Aimola L, Leeson V, et al. Risperidone versus placebo for aggression following traumatic brain injury: A feasibility randomised controlled trial. BMJ Open 2020;10(9):e036300; doi: 10.1136/bmjopen-2019-036300
22. Wang X, Wang Z, Sun C, et al. Clinical study of dexmedetomidine in combination with butorphanol for the treatment of Traumatic Brain Injury (TBI). Turk Neurosurg 2024;34(1):14–19; doi: 10.5137/1019-5149.JTN.36585-21.2
23. Hammond FM, Zafonte RD, Tang Q, et al. Carbamazepine for irritability and aggression after traumatic brain injury: A randomized, placebo-controlled study. J Neurotrauma 2021;38(16):2238–2246; doi: 10.1089/neu.2020.7530
24. Phyland RK, McKay A, Olver J, et al. Use of olanzapine to treat agitation in traumatic brain injury: A series of n-of-one trials. J Neurotrauma 2023; 40(1–2):33–51; doi: 10.1089/neu.2022.0139
25. Swayngim R, Preslaski C, Dawson J. Use of valproic acid for the management of delirium and agitation in the intensive care unit. J Pharm Pract 2024;37(1):118–122; doi: 10.1177/08971900221128636
26. Brawman-Mintzer O, Tang XC, Bizien M, et al. Rivastigmine transdermal patch treatment for moderate to severe cognitive impairment in veterans with traumatic brain injury (RiVET Study): A randomized clinical trial. J Neurotrauma 2021;38(14):1943–1952; doi: 10.1089/neu.2020.7146
27. Nordness MF, Maiga AW, Wilson LD, et al. Effect of propranolol and clonidine after severe traumatic brain injury: A pilot randomized clinical trial. Crit Care 2023;27(1):228; doi: 10.1186/s13054-023-04479-6
28. Oommen JK, Wang S, Axelrad A, et al. Efficacy of modafinil, methylphenidate, amantadine, and zolpidem in consciousness recovery in

intensive care unit patients with traumatic brain injury. P and T 2019; 44(11):676–681.
29. Nguyen JV, Yaw T, Gratton H. Incidence of neurobehavioral side effects associated with levetiracetam compared to phenytoin in traumatic brain injury patients. Brain Inj 2021;35(8):902–906; doi: 10.1080/02699052.2021.1927184
30. Brooke MM, Patterson DR, Questad KA, et al. The treatment of agitation during initial hospitalization after traumatic brain injury. Arch Phys Med Rehabil 1992;73(10):917–921.
31. Yablon S, Sherer M, Nakase-Richardson R, et al. Amantadine hydrochloride for treatment of symptoms of the posttraumatic confusional state: A randomized, double-blind, placebo-controlled trial. Arch Phys Med Rehabil 2010;91(E3).
32. Gramish JA, Kopp BJ, Patanwala AE. Effect of Amantadine on agitation in critically Ill patients with traumatic brain injury. Clin Neuropharmacol 2017;40(5):212–216; doi: 10.1097/wnf.0000000000000242
33. Hammond FM, Bickett AK, Norton JH, et al. Effectiveness of amantadine hydrochloride in the reduction of chronic traumatic brain injury irritability and aggression. J Head Trauma Rehabil 2014;29(5):391–399; doi: 10.1097/01.HTR.0000438116.56228.de
34. Beresford T, Ronan PJ, Hipp D, et al. A double-blind placebo-controlled, randomized trial of divalproex sodium for posttraumatic irritability greater than 1 year after mild to moderate traumatic brain injury. J Neuropsychiatry Clin Neurosci 2022;34(3):224–232; doi: 10.1176/appi.neuropsych.19070159
35. Hammond FM, Sherer M, Malec JF, et al.; Amantadine Irritability Multisite Study Group. Amantadine effect on perceptions of irritability after traumatic brain injury: Results of the amantadine irritability multisite study. J Neurotrauma 2015;32(16):1230–1238; doi: 10.1089/neu.2014.3803
36. Maturana Waidele R, Maturana Rodillo R. Control de la agresividad con olanzapina en pacientes post tec / Aggressiveness control using olanzapine in post tbi patients. Cienc Trab 2009;31:22–24.
37. Mooney GF, Haas LJ. Effect of methylphenidate on brain injury-related anger. Arch Phys Med Rehabil 1993;74(2):153–160.
38. Meythaler JM, Depalma L, Devivo MJ, et al. Sertraline to improve arousal and alertness in severe traumatic brain injury secondary to motor vehicle crashes. Brain Inj 2001;15(4):321–331; doi: 10.1080/026990501750111274
39. Meythaler JM, Brunner RC, Johnson A, et al. Amantadine to improve neurorecovery in traumatic brain injury-associated diffuse axonal injury: A pilot double-blind randomized trial. J Head Trauma Rehabil 2002; 17(4):300–313.
40. Banos JH, Novack TA, Brunner R, et al. Impact of early administration of sertraline on cognitive and behavioral recovery in the first year after moderate to severe traumatic brain injury. J Head Trauma Rehabil 2010; 25(5):357–361; doi: 10.1097/HTR.0b013e3181d6c715
41. Giacino JT, Whyte J, Bagiella E, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. N Engl J Med 2012;366(9): 819–826; doi: 10.1056/NEJMoa1102609
42. Fann JR, Bombardier CH, Temkin N, et al. Sertraline for major depression during the year following traumatic brain injury: A randomized controlled trial. J Head Trauma Rehabil 2017;32(5):332–342; doi: 10.1097/HTR.0000000000000322
43. Hart T, Whyte J, Watanabe T, et al. Effects of dextroamphetamine in subacute traumatic brain injury: A randomized, placebo-controlled pilot study. J Neurosci Res 2018;96(4):702–710; doi: 10.1002/jnr.24102
44. Schneider WN, Drew-Cates J, Wong TM, et al. Cognitive and behavioural efficacy of amantadine in acute traumatic brain injury: An initial double-blind placebo-controlled study. Brain Inj 1999;13(11):863–872.
45. Tramontana MG, Cowan RL, Zald D, et al. Traumatic brain injury-related attention deficits: Treatment outcomes with lisdexamfetamine dimesylate (Vyvanse). Brain Inj 2014;28(11):1461–1472; doi: 10.3109/02699052.2014.930179
46. Johansson B, Wentzel AP, Andrell P, et al. Evaluation of dosage, safety and effects of methylphenidate on post-traumatic brain injury symptoms with a focus on mental fatigue and pain. Brain Inj 2014;28(3): 304–310; doi: 10.3109/02699052.2013.865267
47. Rao N, Jellinek HM, Woolston DC. Agitation in closed head injury: Haloperidol effects on rehabilitation outcome. Arch Phys Med Rehabil 1985; 66(1):30–34.
48. Mysiw WJ, Bogner JA, Corrigan JD, et al. The impact of acute care medications on rehabilitation outcome after traumatic brain injury. Brain Inj 2006;20(9):905–911; doi: 10.1080/02699050600743972
49. Kooda K, Aho J, Weber D, et al. The effect of antipsychotic use post-traumatic brain injury on duration of post-traumatic amnesia. Crit Care Med 2015;43(12 SUPPL. 1):289; doi: 10.1097/01.ccm.0000474980.38145.7b
50. Anderson RL, Birrer KL, Liu-De Ryke X. Haloperidol use in acute traumatic brain injury: A safety analysis. Intensive & Crit Care 2016;02(02):1–6.
51. Corrigan JD. Development of a scale for assessment of agitation following traumatic brain injury. J Clin Exp Neuropsychol 1989;11(2):261–277; doi: 10.1080/01688638908400888
52. Katz M, Lyerly S. Methods of measuring adjustment and social behavior in the community: I. Rationale, description, discrimination validity and scale development. Psychol Rep 1963;13(2)(:503–535.
53. Maiuro R, Vitaliano P, Cahn T. A brief measure for the assessment of anger and aggression. J Interpersonal Violence 1987;2:166–178.
54. Sherer M, Nakase-Thompson R, Yablon SA, et al. Multidimensional assessment of acute confusion after traumatic brain injury. Arch Phys Med Rehabil 2005;86(5):896–904; doi: 10.1016/j.apmr.2004.09.029
55. Keith RA, Granger CV, Hamilton BB, et al. The functional independence measure: A new tool for rehabilitation. Adv Clin Rehabil 1987;1:6–18.
56. Busner J, Targum SD. The clinical global impressions scale: Applying a research tool in clinical practice. Psychiatry (Edgmont) 2007;4(7):28–37.
57. Kreutzer J, Seel R, Marwitz J. The Neurobehavioral Functioning Inventory. The Psychological Corporation. San Antonio, TX; 1999.
58. Levin HS, High WM, Goethe KE, et al. The neurobehavioural rating scale: Assessment of the behavioural sequelae of head injury by the clinician. J Neurol Neurosurg Psychiatry 1987;50(2):183–193.
59. Cummings JL, Mega M, Gray K, et al. The neuropsychiatric inventory: Comprehensive assessment of psychopathology in dementia. Neurology 1994;44(12):2308–2314.
60. Yudofsky SC, Silver JM, Jackson W, et al. The overt aggression scale for the objective rating of verbal and physical aggression. Am J Psychiatry 1986;143(1):35–39; doi: 10.1176/ajp.143.1.35
61. Ramsay MA, Savege TM, Simpson BR, et al. Controlled sedation with alphaxalone-alphadolone. Br Med J 1974;2(5920):656–659; doi: 10.1136/bmj.2.5920.656
62. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond agitation-sedation scale: Validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166(10):1338–1344; doi: 10.1164/rccm.2107138
63. Riker RR, Picard JT, Fraser GL. Prospective evaluation of the sedation-agitation scale for adult critically ill patients. Crit Care Med 1999;27(7): 1325–1329.
64. Beresford T, Schmidt BK, Buchanan J, et al. A double-blind trial of divalproex sodium for affective lability and ethanol use following traumatic brain injury. APA Abstracts 2015.
65. Lewis K, Alshamsi F, Carayannopoulos KL, et al.; GUIDE group. Dexmedetomidine vs other sedatives in critically ill mechanically ventilated adults: A systematic review and meta-analysis of randomized trials. Intensive Care Med 2022;48(7):811–840; doi: 10.1007/s00134-022-06712-2
66. Riker RR, Shehabi Y, Bokesch PM, et al.; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Dexmedetomidine vs midazolam for sedation of critically ill patients: A randomized trial. JAMA 2009;301(5):489–499; doi: 10.1001/jama.2009.56
67. Burry LD, Cheng W, Williamson DR, et al. Pharmacological and non-pharmacological interventions to prevent delirium in critically ill patients: A systematic review and network meta-analysis. Intensive Care Med 2021;47(9):943–960; doi: 10.1007/s00134-021-06490-3
68. Keating GM. Dexmedetomidine: A review of its use for sedation in the intensive care setting. Drugs 2015;75(10):1119–1130; doi: 10.1007/s40265-015-0419-5
69. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: The MENDS randomized controlled trial. JAMA 2007;298(22):2644–2653; doi: 10.1001/jama.298.22.2644
70. Reade MC, Eastwood GM, Bellomo R, et al.; Australian and New Zealand Intensive Care Society Clinical Trials Group. Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: A randomized clinical trial. JAMA 2016;315(14):1460–1468; doi: 10.1001/jama.2016.2707
71. Skrobik Y, Duprey MS, Hill NS, et al. Low-Dose nocturnal dexmedetomidine prevents ICU delirium. A randomized, placebo-controlled trial. Am J Respir Crit Care Med 2018;197(9):1147–1156; doi: 10.1164/rccm.201710-1995OC
72. Dupuis S, Brindamour D, Karzon S, et al. 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. Can J Anaesth 2019;66(3):318–327; doi: 10.1007/s12630-018-01289-1
73. Feng X, Ma W, Zhu J, et al. Dexmedetomidine alleviates early brain injury following traumatic brain injury by inhibiting autophagy and neuroinflammation through the ROS/Nrf2 signaling pathway. Mol Med Rep 2021;24(3):661; doi: 10.3892/mmr.2021.12300
74. Huang GR, Hao FG. Dexmedetomidine inhibits inflammation to alleviate early neuronal injury via TLR4/NF-κB pathway in rats with traumatic brain injury. Crit Rev Eukaryot Gene Expr 2021;31(1):41–47; doi: 10.1615/CritRevEukaryotGeneExpr.2021037390
75. Wang X, Ji J, Fen L, et al. Effects of dexmedetomidine on cerebral blood flow in critically ill patients with or without traumatic brain injury: A prospective controlled trial. Brain Inj 2013;27(13–14):1617–1622; doi: 10.3109/02699052.2013.831130
76. Hu Y, Zhou H, Zhang H, et al. The neuroprotective effect of dexmedetomidine and its mechanism. Front Pharmacol 2022;13:965661; doi: 10.3389/fphar.2022.965661
77. Zhao Z, Ren Y, Jiang H, et al. Dexmedetomidine inhibits the PSD95-NMDA receptor interaction to promote functional recovery following traumatic brain injury. Exp Ther Med 2021;21(1):4; doi: 10.3892/etm.2020.9436
78. Humble SS, Wilson LD, Leath TC, et al. ICU sedation with dexmedetomidine after severe traumatic brain injury. Brain Inj 2016;30(10):1266–1270; doi: 10.1080/02699052.2016.1187289
79. Pajoumand M, Kufera JA, Bonds BW, et al. Dexmedetomidine as an adjunct for sedation in patients with traumatic brain injury. J Trauma Acute Care Surg 2016;81(2):345–351; doi: 10.1097/ta.0000000000001069
80. Hatfield J, Soto AL, Kelly-Hedrick M, et al. Safety, efficacy, and clinical outcomes of dexmedetomidine for sedation in traumatic brain injury: A scoping review. J Neurosurg Anesthesiol 2024;36(2):101–108; doi: 10.1097/ana.0000000000000907
81. Bilodeau V, Saavedra-Mitjans M, Frenette AJ, et al. Safety of dexmedetomidine for the control of agitation in critically ill traumatic brain injury patients: A descriptive study. J Clin Pharm Ther 2021;46(4):1020–1026; doi: 10.1111/jcpt.13389
82. Preskorn SH, Zeller S, Citrome L, et al. Effect of sublingual dexmedetomidine vs placebo on acute agitation associated with bipolar disorder: A randomized clinical trial. JAMA 2022;327(8):727–736; doi: 10.1001/jama.2022.0799
83. Jae J, Li Y, Sun C, et al. Preclinical studies on mechanisms underlying the protective effects of propranolol in traumatic brain injury: A systematic review. J Neuroimmune Pharmacol 2024;19(1):33; doi: 10.1007/s11481-024-10121-1
84. Bogner J, Barrett RS, Hammond FM, et al. Predictors of agitated behavior during inpatient rehabilitation for traumatic brain injury. Arch Phys Med Rehabil 2015;96(Suppl 8):S274–S281.e4; doi: 10.1016/j.apmr.2015.04.020
85. Pisa FE, Cosano G, Giangreco M, et al.; Group for the Study of Medication Use in Centers for Post-acute Brain Injury Rehabilitation. Prescribing practice and off-label use of psychotropic medications in post-acute brain injury rehabilitation centres: A cross-sectional survey. Brain Inj 2015;29(4):508–516; doi: 10.3109/02699052.2014.992474
86. Williamson D, Perreault MM, Rose L, et al. Antipsychotics use in critically Ill TBI patients: A Canadian multicenter observational cohort Study. Neurocrit Care 2019;31(S29).
87. Gagnon DJ, Fontaine GV, Smith KE, et al. Valproate for agitation in critically ill patients: A retrospective study. J Crit Care 2017;37:119–125; doi: 10.1016/j.jcrc.2016.09.006
88. Kim E, Humaran TJ. Divalproex in the management of neuropsychiatric complications of remote acquired brain injury. J Neuropsychiatry Clin Neurosci 2002;14(2):202–205; doi: 10.1176/jnp.14.2.202
89. White G, Adessky N, Chen FW, et al. Valproic acid for agitation in the intensive care unit: An observational study of psychiatric consults. Int J Clin Pharm 2024;46(1):177–185; doi: 10.1007/s11096-023-01661-2
90. Wroblewski BA, Joseph AB, Kupfer J, et al. Effectiveness of valproic acid on destructive and aggressive behaviours in patients with acquired brain injury. Brain Inj 1997;11(1):37–47.
91. Cataford G, Monton LA, Karzon S, et al. Cognitive and motor function effects of antipsychotics in traumatic brain injury: A systematic review of pre-clinical studies. Neurotrauma Rep 2024;5(1):181–193; doi: 10.1089/neur.2023.0108
92. Phelps TI, Bondi CO, Mattiola VV, et al. Relative to typical antipsychotic drugs, aripiprazole is a safer alternative for alleviating behavioral disturbances after experimental brain trauma. Neurorehabil Neural Repair 2017;31(1):25–33; doi: 10.1177/1545968316650281
93. Ponsford J, Trevena-Peters J, Janzen S, et al.; INCOG Expert Panel. INCOG 2.0 guidelines for cognitive rehabilitation following traumatic brain injury, part I: Posttraumatic Amnesia. J Head Trauma Rehabil 2023;38(1):24–37; doi: 10.1097/HTR.0000000000000840
94. MacKenzie HM, Velikonja D, Devito J, et al. Updated Canadian clinical practice guideline for the rehabilitation of adults with moderate to severe traumatic brain injury: Behavioral recommendations. J Head Trauma Rehabil 2024;39(5):382–394; doi: 10.1097/HTR.0000000000000973