

BMJ Open Pharmacological interventions for agitated behaviours in patients with traumatic brain injury: a systematic review

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ABSTRACT

Objective The aim of this systematic review was to assess the efficacy and safety of pharmacological agents in the management of agitated behaviours following traumatic brain injury (TBI).

Methods We performed a search strategy in PubMed, OvidMEDLINE, Embase, CINAHL, PsycINFO, Cochrane Library, Google Scholar, Directory of Open Access Journals, LILACS, Web of Science and Prospero (up to 10 December 2018) for published and unpublished evidence on the risks and benefits of 9 prespecified medications classes used to control agitated behaviours following TBI. We included all randomised controlled trials, quasi-experimental and observational studies examining the effects of medications administered to control agitated behaviours in TBI patients. Included studies were classified into three mutually exclusive categories: (1) agitated behaviour was the presenting symptom; (2) agitated behaviour was not the presenting symptom, but was measured as an outcome variable; and (3) safety of pharmacological interventions administered to control agitated behaviours was measured.

Results Among the 181 articles assessed for eligibility, 21 studies were included. Of the studies suggesting possible benefits, propranolol reduced maximum intensities of agitation per week and physical restraint use, methylphenidate improved anger measures following 6 weeks of treatment, valproic acid reduced weekly agitated behaviour scale ratings and olanzapine reduced irritability, aggressiveness and insomnia between weeks 1 and 3 of treatment. Amantadine showed variable effects and may increase the risk of agitation in the critically ill. In three studies evaluating safety outcomes, antipsychotics were associated with an increased duration of post-traumatic amnesia (PTA) in unadjusted analyses. Small sample sizes, heterogeneity and an unclear risk of bias were limits.

Conclusions Propranolol, methylphenidate, valproic acid and olanzapine may offer some benefit; however, they need to be further studied. Antipsychotics may increase the length of PTA. More studies on tailored interventions and continuous evaluation of safety and efficacy throughout acute, rehabilitation and outpatient settings are needed.

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Strengths and limitations of this study

- This systematic review assessed the efficacy and safety of pharmacological agents in the management of agitated behaviours following traumatic brain injury (TBI).
- Randomised controlled trials, quasi-experimental and observational studies were reviewed.
- The included studies were limited by small sample sizes, variations in the different agitated behaviours and populations studied.
- The review found insufficient data to recommend the use of any agent for the management of agitated behaviours following TBI.

INTRODUCTION

Traumatic brain injury (TBI) occurs when an external force is applied to the head leading to alterations in brain function including decreased level of consciousness, post-traumatic amnesia (PTA) and changes in behaviour and cognition that can persist in the long term. In the USA alone, ~50 000 people die each year from TBI and >5 million live with TBI-related disabilities.^{1 2} While TBI has a substantial impact on direct health-care costs, indirect costs from lost productivity also represent a significant economic burden.^{3 4} Agitated behaviours are a frequent behavioural problem following TBI.^{5 6} They have been broadly defined as a state of confusion that follows the initial injury and is characterised by disruptive behaviours. A constellation of behaviours has been associated with the term ‘agitation’ in TBI patients, including restlessness, confusion, physical and verbal aggression, impulsivity, perceptual disturbances and inattention creating a very heterogeneous group of patients to study.⁷ Agitation has been reported in 20%–41% of patients during the early stage of recovery

in acute care units and up to 70% of patients in rehabilitation units.^{6 8-13} It can result in harm to patients and caregivers, interfere with treatments, lead to the use of physical and pharmacological restraints, increase hospital length of stay, delay rehabilitation and impede functional independence.^{10-12 14-16} In TBI outpatients, neurobehavioral symptoms may be different in nature. Aggressive behaviour and irritability, more than physical agitation are generally reported. A variety of agents such as antidepressants, anticonvulsants, stimulants and antipsychotics have been used for the management of neurobehavioral complications of TBI.^{17 18} However, preclinical studies have suggested that repeated use of certain agents such as haloperidol, risperidone and diazepam may reduce cognitive and functional recovery.¹⁹⁻²² Thus, it remains unclear which pharmacological agents are the most effective and safest for the management of agitated behaviours in TBI patients. A Cochrane Systematic Review published in 2006 showed a lack of evidence to support any agent.²³ Since then, two additional systematic reviews concluded that the evidence was insufficient and too weak to recommend any specific agent; however, they included only French and English studies published before January 2016, had incomplete search strategies and did not include the grey literature.^{24 25} To advance this field, we updated and broadened the literature search, included all languages and included studies in which an agitated behaviour was not an eligibility criterion, but was measured as an outcome variable. The aim of this systematic review was to assess the efficacy and safety of pharmacological agents in the management of agitated behaviours following TBI compared with placebo or other treatments.

METHODS

The review protocol has been registered in PROSPERO International Prospective Register of Systematic Reviews, conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines and published in a peer-reviewed journal.^{26 27} We included all randomised controlled, quasi-experimental and observational studies with control groups that had a majority (>50%) of patients with TBI. We excluded case reports, case series and observational studies without control groups. We included studies of all type of patients who suffered a TBI, including children and adults, in both the early stages of recovery and in rehabilitation. We included three mutually exclusive types of studies: (1) those evaluating the use of pharmacological interventions in which an agitated behaviour, not further defined, was one of the eligibility criteria for the study; (2) those in which an agitated behaviour was not an eligibility criterion, but was measured as an outcome variable; and (3) those specifically assessing the safety of pharmacological agents used to treat agitation in TBI patients. In this systematic review, we considered agitation, aggressiveness, assaultive behaviour, irritability and confusion as part of agitated behaviours. All medications considered in this review

were prespecified and consisted in the following: beta-adrenergic blockers, typical and atypical antipsychotics, anticonvulsants, dopamine agonists, psychostimulants, antidepressants, alpha-2-adrenergic agonists, hypnotics and anxiolytics. Studies were included whether the investigators compared a medication to placebo, a medication to another medication or various combinations of different medications.

The primary outcome was a reduction in severity of the agitated behaviour as measured in each study. If feasible, we reported resolution of agitated behaviours as well as changes in duration and type of symptoms (confusion, aggressiveness, inattention, hallucinations, disorientation and inappropriate mood or speech). Secondary outcomes include lengths of stay (intensive care unit (ICU) length of stay, hospital LOS for the early rehabilitation phase), adverse events (extrapyramidal effects, QTc prolongation, cardiac arrhythmias, hypotension, seizures, behavioural effects), use of physical restraints in ICU, cognitive and functional outcomes at hospital discharge and at 1 year post-TBI.

Patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Search strategy

A search strategy was devised with the help of Health Sciences librarian (online supplementary file 1) and using the Peer Review for Electronic Search Strategies checklist was conducted in the following databases: PubMed, Ovid-MEDLINE, OvidMEDLINEIn-Process & Other Non-Indexed Citations, Embase, CINAHL, PsycINFO, Cochrane Library, Google Scholar, Directory of Open Access Journals, LILACS, Web of Science and Prospero (<http://www.crd.york.ac.uk/PROSPERO/>) up to 10 December 2018.²⁸ A grey literature search was also performed using the resources suggested in CADTH's *Grey Matters* (<http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters>). As described in our published protocol, we searched abstracts from annual scientific meetings from relevant groups in the last 5 years.²⁶ Finally, references of identified studies as well as other types of articles (reviews, book chapters) were screened.

Data collection and analysis

Two reviewers (DW, A-JF) independently screened titles and abstracts for eligible publications. The same reviewers then assessed the complete report of each retained citations for eligibility. Disagreements were resolved by consensus and discussion with a third reviewer was not required.

Data extraction and management

Data from all included studies were extracted by two independent reviewers (A-JF and DW) and in duplicate

using a pretested data extraction form. The following variables were recorded for each study: study title, name of the first author, year of publication, country of origin, language of publication, publication type (journal article, conference proceeding, abstract, thesis), clinical setting (ICU), hospital ward, rehabilitation unit, outpatient), study design (randomised controlled, blinded or open, non-randomised 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 the therapy), agitation measurement tool, description of the specific agitated behaviours (definition, frequency, duration) and clinical outcomes (length of stay), adverse events, use of physical restraints during ICU stay, duration of PTA, cognitive function at ICU discharge and at 1 year, and functional outcome at ICU discharge and at 1 year. We contacted

the corresponding author for clarifications when necessary. In the case of an abstract not available in English, the research team included authors fluent in French, Spanish, German and Italian, who were able to read the abstract. Among selected articles, only one article in Spanish was included. The article was reviewed by authors fluent in Spanish.

Assessment of risk of bias

Two reviewers (DW, A-JF) independently evaluated each included study with the Cochrane Collaboration tool for randomised controlled trials and the Ottawa-Newcastle tool for observational studies, respectively.^{29 30} In case of disagreement concerning the risk of bias, a third reviewer (FB) was consulted to resolve the issue.

RESULTS

Study selection

The database search (up to 10 December 2018) retrieved 11 170 unique citations of which 10 989 were excluded

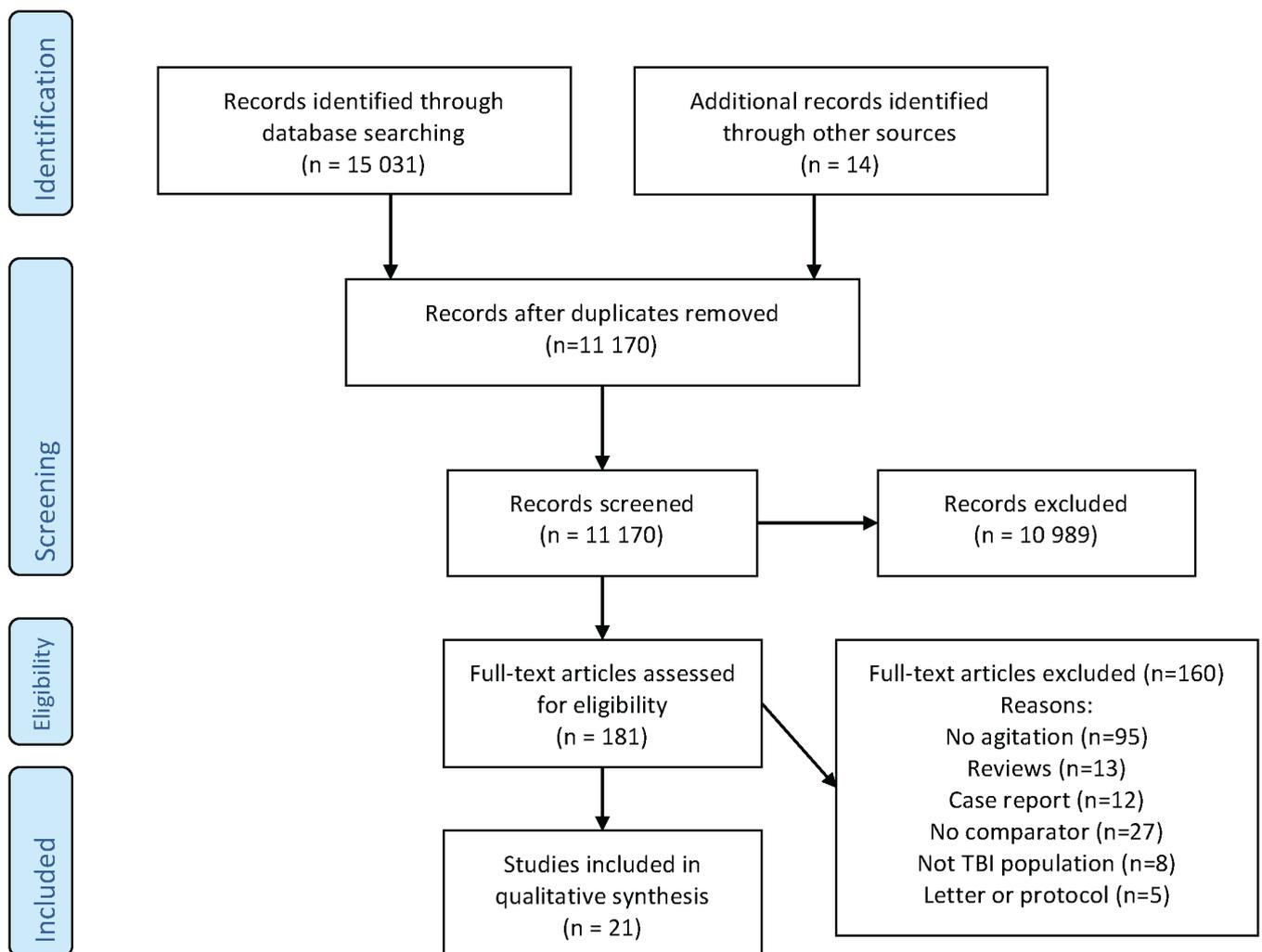


Figure 1 PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis; TBI, traumatic brain injury.

based on title and abstracts (figure 1). We assessed 181 full-text articles for eligibility and 21 studies were included. A total of eight studies evaluated the use of pharmacological interventions in which an agitated behaviour was the presenting symptom or one of the presenting symptoms.^{31–38} In nine other studies, agitated behaviour was not the presenting symptom, but was measured as an outcome variable.^{39–47} Finally, four studies specifically assessed the safety of pharmacological agents used for agitated behaviours in TBI.^{48–51}

Agitated behaviours as the presenting symptom

The eight included studies evaluated various aspects ranging from aggressiveness to irritability and confusion (table 1).^{31–38} The behaviours were evaluated using the following tools (table 2): Agitated Behaviour Scale (ABS), confusion assessment protocol, State-Trait Anger Scale, the overt aggression scale, Richmond Agitation Sedation Scale and neuropsychiatric inventory irritability (NPI-I) and neuropsychiatric inventory aggression domains.⁵²

Of the identified studies, two were conference abstracts that remained unpublished.^{33 37} The studies evaluated propranolol,³¹ amantadine,^{33–35} methylphenidate,³² valproic acid³⁷ and olanzapine³⁸ in comparison to placebo. Five used a randomised controlled parallel design,^{31 33–35 37} one used a randomised pretest posttest control group design,³² one was a prospective double blind observational study³⁸ and, one was a retrospective observational study.³⁶ All the studies exclusively enrolled adult (16 years or older) TBI patients and three studies excluded older patients (>65 or 75 years).^{34 35 37} The studies mostly included patients in rehabilitation (n=2)^{31 33} and outpatient (n=5) settings.^{32 34 35 37 38} Only one study evaluated patients in an ICU setting.³⁶ All the studies exclusively studied TBI patients.^{31–38} Three studies identified in an earlier systematic review were excluded (figure 1) because TBI patients represented <50% of the sample.^{23 53–55}

In the eight studies, one randomised trial evaluated the use of propranolol for the treatment of agitation in severe blunt TBI patients (table 3).³¹ It reported a reduction in the intensity of agitation episodes and in the use of physical restraints but failed to show a reduction in the frequency of agitation episodes.³¹ Amantadine was evaluated for the management of confusion in a randomised trial, irritability in two randomised trials and agitation in a retrospective observational study.^{33–36} The studies reported inconsistent results (table 3). In one unpublished study in the setting of rehabilitation within 90 days of TBI (n=79), amantadine had no effect on confusion.³³ In a pilot study of outpatients who suffered a TBI >6 months ago, amantadine showed significant reductions in irritability and aggression using the Neuropsychiatric Inventory scale (NPI).³⁵ In a follow-up study of 168 outpatients who had suffered a TBI >6 months ago, 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.³⁴ Participants self-rating at day 60 indicated improvement in irritability (p<0.04) but

the difference became non-significant when adjusted for multiple comparisons. The Global improvement subscale of the Clinical Global Impressions (CGI), which evaluates general emotional and behavioural function, improved more in the amantadine group than in the placebo group at day 60 (p=0.0354). A subanalysis of patients with anger and aggression (118 of the 168 patients) in the same study was also carried out and reported a statistically significant reduction in participant's self-rated aggression at 60 days.⁵⁶ Finally, in a retrospective observational study (n=139), patients exposed to amantadine in the ICU reported more agitation episodes defined as a Richmond Agitation Sedation Score of +2 or higher (38% vs 14%) in an unadjusted analysis.³⁶ The use of amantadine was also associated with an increased median ICU length of stay (4.5 vs 3 days; p=0.01) when compared with non-exposed patients.

The efficacy of olanzapine in the management of restlessness, irritability, aggression and insomnia in outpatients with a history of TBI was evaluated in a prospective double blind study.³⁸ While no reduction in restlessness was reported, the authors did report a significant reduction in irritability and insomnia between weeks 1 and 3 in olanzapine-treated patients. Unfortunately, no statistical comparison with the placebo group was provided. The efficacy of valproic acid in reducing agitated behaviours among mild and moderate TBI outpatients was evaluated in an unpublished randomised controlled study (n=50).³⁷ Patients were included >1 year following brain injury and suffered from both affective lability and alcohol dependence. A significant reduction in the ABS evaluated by family members at eight weeks (12.9 vs 15.5 281 points; p=0.03) was observed. Finally, a crossover study assessed methylphenidate for 282 anger (n=38) in TBI rehabilitation centre outpatients (6 months or more after TBI). After 283 6 weeks, methylphenidate significantly reduced the anger score using the State Trait 284 Anger Scale (STAS).³² Of the eight studies, safety outcomes were reported in four studies.^{32–35} When reported, the agents studied were well tolerated with no significant differences observed. Functional and cognitive outcomes were not reported in any of these studies.

Agitated behaviour as a secondary measure

We identified nine studies evaluating agitated behaviours as a secondary measure, which were focused on cognitive function and neurological recovery (table 1).^{39–47} In these studies, sertraline,^{39 41 45} amantadine,^{40 42 43} amphetamines^{44 47} and methylphenidate⁴⁶ were evaluated versus placebo and reported agitated behaviours as an outcome. Of these studies, six used a randomised crossover design and three used a randomised controlled parallel design.

Sertraline was evaluated in three studies to enhance recovery and increase arousal, ameliorate cognitive and neurobehavioral functioning and to treat major depression (table 3).^{39 41 45} In all these three studies, sertraline had no effect on the incidence of agitation, anger or aggression. In one study, more patients developed

Table 1 Study characteristics

Study/year (N)	Publication/country	Study design	Study focus/population	Interventional arm/population	Comparative arm/population	Location at randomisation	Timing from TBI at randomisation	TBI description
1. Agitated behaviour as the presenting symptom								
Brooke, <i>et al</i> ³¹ /1992 (n=21)	Published USA	RCT parallel	Agitation Mean age: 31 87 men and 13 women	Propranolol 60–420 mg/day	Placebo	Level 1 trauma and rehabilitation centre	N/A	Severe blunt TBI
Mooney, Hass ³² /1993 (n=38)	Published USA	Randomised Pre-post	Anger Mean age: 29±10 Male gender: 100%	Methylphenidate 30 mg/day	Placebo	Outpatient	6 months or more (mean 27±21 months)	Severe blunt TBI
Yablon, <i>et al</i> ³³ /2010 (n=79)	Abstract USA	RCT parallel	Confusion Age and gender not reported	Amantadine 100 mg twice daily x 14 days	Placebo	Inpatient brain injury unit of a rehabilitation hospital	≤6 months	TBI not further defined
Hammond, <i>et al</i> ³⁴ /2014 (n=76)	Published USA	RCT parallel	Irritability and aggression	Amantadine 100 mg twice daily Mean age: 40±13 Male gender: 74.4%	Placebo 38±12 Male gender: 80.5%	Outpatient	≥6 months following a TBI	Blunt TBI
Beresford, <i>et al</i> ³⁷ /2015 (n=50)	Abstract USA	RCT parallel	Agitation Mean age: 47±14 46 men and 4 women	Valproic acid for level 50–100 µg/mL	Placebo	Outpatient	>1 year following TBI	Mild and moderate TBI
Hammond, <i>et al</i> ³⁵ /2015 (n=168)	Published USA	RCT parallel	Irritability and aggression	Amantadine 100 mg twice daily Mean age: 38±12 Male gender: 74.4%	Placebo Mean age: 38±12 Male gender: 74.4%	Outpatient	≥6 months following a TBI	Blunt TBI
Maturana Waidele, Maturana Rodillo ³⁸ /2009 (n=31)	Published Chile	Prospective double-blind	Restlessness, irritability, aggression, insomnia Age and gender not reported	Olanzapine (dose not specified)	Placebo	Outpatient	N/A	TBI not further defined
Gramish, <i>et al</i> ³⁶ /2017 (n=139)	Published USA	Retrospective observational	Agitation	Amantadine 100 mg twice daily Mean age: 42±17 Male gender: 81.4%	No amantadine Mean age: 48±21 Male gender: 76.8%	Adult trauma ICU	Acute TBI	TBI not further defined
2. Agitated behaviour is not the presenting symptom								
Study/year (N)	Publication/country	Study design	Study focus	Interventional arm	Comparative arm	Location at randomisation	Timing from TBI at randomisation	TBI description
Schneider ⁴² /1999 (n=10)	Published USA	RCT parallel	Cognitive function and behaviour Mean age: 31 7 men and 3 women	Amantadine 50 mg twice daily increased to 150 mg twice daily	Placebo	Outpatient	N/A	Moderate and severe TBI
Meythaler, <i>et al</i> ⁴¹ /2001 (n=9)	Published USA	RCT crossover	Recovery and arousal Age and gender not reported	Sertraline	Placebo	Inpatient rehabilitation	<2 weeks of TBI	Severe TBI
Meythaler, <i>et al</i> ⁴³ /2002 (n=35)	Published USA	RCT crossover	Neurological recovery Mean age: 31 26 men and 9 women	Amantadine	Placebo	Emergency department	Between 4 days and 6 weeks following TBI	Severe blunt TBI
Banos, <i>et al</i> ³⁹ /2010 (n=99)	Published USA	RCT parallel	Cognitive function and behaviour	Sertraline Mean age: 35±17 Male gender: 79%	Placebo Mean age: 35±16 Male gender: 66%	Level 1 trauma centre inpatients	<8 weeks of TBI	Moderate and severe TBI

Continued

Table 1 Continued

Study/year (N)	Publication/country	Study design	Study focus/population	Interventional arm/ population	Comparative arm/ population	Location at randomisation	Timing from TBI at randomisation	TBI description
Giacino, <i>et al</i> ⁴⁰ /2012 (n=184)	Published USA, Denmark, Canada	RCT parallel	Functional recovery	Amantadine Mean age: 35±15 Male gender: 74%	Placebo Mean age: 37±15 Male gender: 71%	Inpatients	4–16 weeks following TBI	Vegetative or minimally conscious TBI
Tramontana, <i>et al</i> ⁴⁴ /2014 (n=22 but 13 completed the study)	Published USA	RCT crossover	Attention Mean age: 29±9 Male gender: 69%	Lisdexamfetamine	Placebo	Outpatient	6–34 months (mean 15.6±/-10 months) since TBI	Moderate and severe TBI
Johansson, <i>et al</i> ⁴⁶ /2014 (n=24)	Published Sweden	RCT Crossover	Mental fatigue and cognition Mean age 39±11 Male gender: 50%	Methylphenidate 5 mg and 20 mg tid	Placebo	Outpatient	>12 months following TBI	Mild or moderate TBI
Fann, <i>et al</i> ⁴⁵ /2017 (n=62)	Published USA	RCT parallel	Major depression	Sertraline Mean age: 38±12 Male gender: 74%	Placebo Mean age: 37±13 Male gender: 77%	Level 1 trauma centre	<1 year of TBI	Moderate and severe TBI
Hart, <i>et al</i> ⁴⁷ /2017 (n=32)	Published USA	RCT parallel	Cognitive function	Dextroamphetamine Mean age: 39±16 Male gender: 65%	Placebo Mean age: 39±18 Male gender: 100%	TBI rehabilitation unit	<6 months of TBI	Moderate and severe TBI
3. Studies assessing the safety of pharmacological agents used for agitated behaviours in TBI								
Rao, <i>et al</i> ⁵⁰ /1985 (n=26)	Published USA	Retrospective observational	Rehabilitation outcomes	Haloperidol Median age: 34 Gender not reported	No haloperidol Median age: 22 Gender not reported	Trauma and rehabilitation centre	From admission	Severe closed head injury
Mysiw, <i>et al</i> ⁴⁹ /2006 (n=182)	Published USA	Retrospective cohort	Cognitive and motor recovery Mean age: 36 Male gender: 74%	Narcotics, benzodiazepines and neuroleptics	No CNS active medications	Level one trauma centre and rehabilitation centre	From admission	TBI
Kooda, <i>et al</i> ⁵¹ /2015 (n=195)	Abstract USA	Retrospective observational	Duration of post-traumatic amnesia Age and gender not reported	Antipsychotics	No antipsychotic	Level one trauma centre and rehabilitation centre	From admission	TBI
Anderson, <i>et al</i> ⁴⁸ /2016 (n=101)	Published USA	Retrospective cohort	Seizures, neuroleptic malignant syndrome, QTc prolongation, extrapyramidal symptoms, haematological disturbances	Haloperidol Median age: 32 Male gender: 87%	No haloperidol Median age: 47 Male gender: 61%	Inpatients	From admission	Moderate and severe TBI

CNS, Central Nervous System; RCT, Randomized controlled trial; TBI, traumatic brain injury.

Table 2 Tools used to measure agitated behaviours

Tools	Description
Agitated Behaviour Scale ⁷⁴	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 >21 are considered as agitation.
Brief Anger and Aggression Scale ⁷⁵	A six-item measure developed for the rapid screening and identification of anger and aggression levels.
Confusion assessment protocol ⁷⁶	Combination of orientation, cognition and other clinical measures of early confusion following traumatic brain injury.
Functional independence measure ⁷⁷	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) ⁷⁸	The CGI is a 3-item observer-rated scale that measures illness severity (CGIS), global improvement or change (CGIC) and therapeutic response.
Belligerence cluster score for the Katz adjustment scale (KAS) ⁷⁹	The KAS is an observer rating scale used to assess the social adjustment of people with traumatic brain injury.
Neuropsychiatric inventory irritability (NPI-I) and aggression domains (NPI-A) ⁵²	The NPI is a 40-item scale evaluating 12 behavioural domains including irritability and aggression. The NPI-I items include bad temper, rapid mood changes, sudden anger, impatience, crankiness and argumentative. Raters evaluate frequency and severity of behaviours in the last month. The NPI aggression domain assesses the tendency to get upset, resistance to activities, stubbornness, uncooperativeness, shouting, cursing and physical behaviours 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.
Neurobehavioral Function Inventory (NFI) ⁸⁰	The NFI provides information on the frequency of behaviours 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) ⁸¹	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 behavioural disturbances.
Overt aggression scale (OAS) ⁸²	Scale for the objective rating of verbal and physical aggression. The OAS measures aggressive behaviours divided into 4 categories: verbal aggression, physical aggression against objects, physical aggression against self and physical aggression against others.
Anger-Hostility factor score of the Profile of Mood States (POMS) ³²	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).
State-Trait Anger Scale (STAS) ³²	The STAS is a 20-item self-report scale assessing two types of anger (State and Trait). 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.

agitation/restlessness in the sertraline group (17%) compared with the placebo group (7%) but this difference was not statistically significant ($p=0.42$).⁴⁵ Amantadine was also evaluated in three studies for cognitive and functional recovery.^{40 42 43} All three studies found no differences in agitated behaviours compared with placebo. Methylphenidate was evaluated for secondary mental fatigue in mild TBI patients >6 months after injury.⁴⁶ However, it had no effect on irritability and aggression. Lisdexamfetamine and dextroamphetamine were each evaluated for attention deficits in TBI patients and no effect on agitated behaviours was noted with lisdexamfetamine whereas dextroamphetamine increased agitation over time ($p<0.05$).^{44 47} Among these nine studies, those

evaluating sertraline and amantadine reported no significant differences in adverse events.^{39–43 45}

Studies evaluating safety outcomes

Finally, the safety of pharmacological agents used for agitated behaviours in TBI patients was evaluated in four retrospective observational studies (table 4).^{48–51} Two of these studies focused on the effect of haloperidol and antipsychotic use on PTA duration, whereas a third evaluated the effects of antipsychotics, benzodiazepines and narcotics on PTA duration, and Functional independence measure (FIM) cognitive and motor scores.^{49–51} In these three studies, haloperidol and other antipsychotics were associated with an increase in PTA duration. Antipsychotics, benzodiazepines and narcotics had no effects on

Table 3 Efficacy and safety outcomes

Study /year/n	Intervention	Agitated behaviour measures	Efficacy outcomes	Safety outcomes
1. Agitated behaviour as the presenting symptom				
Randomised controlled studies				
Brooke, <i>et al</i> ³¹ /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
	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 effect on side effects
Mooney, Haas ³² /1993/n=38				
Yablon, <i>et al</i> ³³ /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 'non-confused' 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
Hammond, <i>et al</i> ³⁵ /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)
	Valproic acid	Agitated Behaviour Scale by spouse or significant other	Significant others' weekly Agitated Behaviour 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
Beresford, <i>et al</i> ³⁷ /2015/n=50				
	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 NS for 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, <i>et al</i> ³⁴ /2015/n=168				
Observational studies				
Maturana Waidele, Maturana Rodillo ³⁸ /2009/n=31	Olanzapine	Restlessness, irritability, aggressiveness and insomnia. No tool mentioned	Reduction in irritability ($p<0.001$), aggressiveness ($p=0.008$) and insomnia ($p=0.011$) between weeks 1 and 3 in the patients treated with olanzapine.	No safety outcomes reported
	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
Gramish, <i>et al</i> ³⁶ /2017/n=139				
2. Agitated behaviour is not the presenting symptom				
Randomised controlled studies				

Continued

Table 3 Continued

Study /year/n	Intervention	Agitated behaviour measures	Efficacy outcomes	Safety outcomes
Schneider, <i>et al</i> ⁴² /1994/n=10	Amantadine	Neurobehavioral rating scale	No significant difference in behaviour scores between amantadine and placebo groups.	No safety outcomes reported
Meythaler, <i>et al</i> ⁴¹ /2001/n=9	Sertraline	Agitated Behaviour Scale	No difference in decline of ABS over treatment period	No safety outcomes reported
Meythaler, <i>et al</i> ⁴³ /2002/n=35	Amantadine	Agitated Behaviour 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 haematology or biochemistry laboratories and no seizures
Baños, <i>et al</i> ³⁹ /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
Giacino, <i>et al</i> ⁴⁰ /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, diarrhoea, elevated liver function tests, insomnia, rash, congestive heart failure, involuntary muscle contractions)
Tramontana ⁴⁴ /2014/n=22 but 13 patients completed the study	Lisdexamfetamine	Agitation and restlessness not further defined	No difference in agitation (no cases in each group) or irritability (1/13 case) during placebo) between the lisdexamfetamine and placebo groups.	Reduced appetite and weight loss of >5 lbs more frequent with lisdexamfetamine (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
Fann ⁴⁵ /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%) versus the placebo group (7%) $p=0.42$.	No significant difference in safety outcomes. More patients in the sertraline group (17%) developed gas/flatulence versus the placebo group (0%) $p=0.052$
Hart ⁴⁷ /2017/n=32	Dextroamphetamine	Agitated Behaviour Scale	Increase in agitation with dextroamphetamine over time compared with placebo ($p<0.05$).	No significant difference in heart rate or blood pressure

RASS, Richmond Agitation Sedation Scale.

FIM scores.⁴⁹ Finally, a fourth study focused on the general safety (seizures, neuroleptic malignant syndrome, QTc prolongation, extrapyramidal symptoms, haematological disturbances) of haloperidol in ICU TBI patients.⁴⁸ Patients exposed to haloperidol ($n=45$) had no significant increase in adverse events compared with non-exposed patients ($n=56$). Of note, none of the studies adjusted for severity of TBI and other potential confounders.

Risk of bias assessment

Risk of bias scores are reported in [table 5](#). The analysis of risk of bias of randomised controlled trials with the Cochrane Collaboration's Tool revealed that many studies did not provide sufficient information on sequence,

generation and allocation concealment. A majority of studies had other threats to validity including limited sample sizes, no description of patient demographics and loss to follow-up. For six studies evaluated with the Newcastle-Ottawa tool, the number of stars awarded ranged from 4 to 5. Most studies were awarded a score of 4 stars, indicating a high risk of bias. As none of the six studies were adjusted for potential confounding, all received 0 stars for comparability.

DISCUSSION

In this systematic review, we used an exhaustive search strategy and included studies directly or indirectly

Table 4 Studies assessing the safety of pharmacological agents used for agitated behaviours in TBI

Study/year/n	Drugs studied	Results
Rao ⁵⁰ /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).
Mysiw ⁴⁹ /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 >7 days (p<0.01).
Kooda ⁵¹ /2005/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.
Anderson ⁴⁸ /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 haematological 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).

TBI, traumatic brain injury.

evaluating pharmacological agents for the management of TBI-associated agitated behaviours as well as studies assessing the safety of pharmacological agents used for these agitated behaviours. Despite the prevalence and importance of this problem, we found a limited number of studies evaluating pharmacological interventions for the management of agitated behaviours. Propranolol, methylphenidate, valproic acid and olanzapine were the only agents suggesting a potential benefit in reducing agitation, anger or irritability.^{31 32 37 38} However, the studies evaluating these agents had limited sample sizes, heterogeneous patient populations and an unclear risk of bias. Amantadine showed mixed results whereas sertraline, lisdexamfetamine and dextroamphetamine showed no benefits. In comparison to the two most recent systematic reviews, we used a more rigorous and broader search strategy. As such, we restricted our search to randomised controlled, quasi-experimental and observational studies with control groups that had a majority (>50%) of patients with TBI, thus excluding case reports, case series and uncontrolled observational studies. Our updated and broadened literature search enabled the identification of two additional studies from the grey literature, three recently published studies and one non-English study.^{24 25 33 36 37 45 47} Our search strategy also included studies evaluating agitated behaviours as a secondary measure and identified nine more studies, thus adding to previous systematic reviews. Furthermore, we included studies where the safety of pharmacological agents for the management of agitated behaviours was assessed and identified four such studies.

The use of beta-blockers in patients with organic brain disease and assaultive behaviours or impulsivity has been previously studied in three crossover-randomised trials with some efficacy but TBI represented <50% of the total patient population.^{53–55} In the study presented in this review, propranolol reduced the intensity of agitation but

not the frequency.³¹ One important finding was a reduction in the use of physical restraints. Unfortunately, safety measures such as hypotension and bradycardia were not reported.

The Canadian ABIKUS (Acquired Brain Injury Knowledge Uptake Strategy) guidelines have recommended beta-blockers for the treatment of aggression following TBI.⁵⁷

Although numerous observational studies have reported a reduction in agitation with the use of antipsychotic agents, we found no controlled studies evaluating the efficacy of antipsychotics other than olanzapine.^{58–60} In a previous systematic review that included case reports and case series evaluating antipsychotics, Planthier *et al* identified seven articles that included a total of 52 patients.²⁴ The lack of a control group excluded these studies from our review. The only study we included that used olanzapine did not report a reduction in restlessness but did suggest a reduction in irritability.³⁸ Its interpretation is greatly limited given the poor description of methods and a lack of statistical comparison with the placebo group. The four studies assessing safety all evaluated antipsychotic agents and suggested a potential risk of prolonged PTA in unadjusted analyses.^{48–51} None of the studies controlled for potential confounders such as severity of TBI. Although preclinical studies have suggested a reduction in cognitive and motor recovery with repeated administration of haloperidol and risperidone, the one study evaluating cognitive and motor scores reported no significant association with antipsychotic use.^{19–21 49 61} In light of these results, both the International Cognitive, the Canadian ABIKUS guidelines and the French Society of Physical and Rehabilitation Medicine guidelines have advised against the use of antipsychotics in TBI patients with agitated behaviours.^{24 57 62} Paradoxically, observational studies have suggested antipsychotics are frequently used for the management of agitated behaviours.^{14 63–65}

Table 5 Risk of bias assessment

1. Randomised controlled trials

Study (year)	Cochrane Collaboration Tool Risk of bias items						
	Sequence generation	Allocation	Blinding of participants and personnel	Blinding of outcome assessment	Outcome data	Selective reporting	Other threats to validity
Brooke ¹⁶ (1992)	U	U	L	L	L	L	H
Mooney ³² (1993)	U	U	L	H	L	U	H
Schneider ⁴² (1999)	U	U	U	U	H	L	H
Meythaler ⁴¹ (2001)	U	U	L	L	U	U	H
Meythaler ⁴³ (2002)	U	U	U	U	L	H	H
Baños ³⁹ (2010)	U	U	L	L	L	L	H
Yablon ³³ (2010)	U	U	L	L	L	U	H
Giacino ⁴⁰ (2012)	U	L	L	L	L	L	L
Hammond ³⁵ (2014)	L	L	L	L	U	L	L
Tramontana ⁴⁴ (2014)	H	H	L	L	H	L	H
Johansson ⁴⁶ (2014)	U	H	H	H	H	L	H
Beresford ³⁷ (2015)	U	U	L	L	H	L	H
Hammond ¹⁷ (2015)	L	L	L	L	U	L	L
Fann ⁴⁵ (2017)	L	L	L	L	L	L	H
Hart ⁴⁷ (2017)	U	U	L	L	L	L	L

2. Observational studies

Study (year)	Newcastle-Ottawa Quality Assessment Scale No of stars awarded		
	Selection*	Comparability†	Outcome‡
Rao ⁵⁰ (1985)	**		**
Maturana Waidele ³⁸ (2009)	**		**
Mysiw ⁴⁹ (2006)	**		***
Kooda ⁵¹ (2015)	**		**
Anderson ⁴⁸ (2016)	**		**
Gramish ³⁶ (2017)	***		*

For Cochrane Collaboration's Tool: For Newcastle-Ottawa Quality Assessment Scale.

*Maximum four stars.

†Maximum two stars.

‡Maximum three stars.

H, high risk of bias; L, low risk of bias; U, unclear risk of bias.

Anticonvulsants are clinically used as mood stabilisers in bipolar affective disorder and have also been used in TBI-associated agitation.^{66 67} Case series have reported a reduction in agitation and aggressive behaviours with the use of valproic acid and carbamazepine but were uncontrolled.^{68–72} We identified one unpublished study of TBI patients with affective lability and alcohol dependence where valproic acid showed effectiveness in reducing weekly ABS rated by spouse or significant other's. Unfortunately, the abstract provided no information on the onset of effect or adverse events associated with its use.

Amantadine increases dopaminergic neurotransmission and has been shown to increase the rate of neurological recovery in severe TBI.⁴⁰ In the four studies that

evaluated amantadine for irritability, agitation or aggressiveness, results were variable.^{33–36} Although one study suggested a reduction in irritability in outpatients, a larger study by the same group failed to confirm these results.^{34 35} Interestingly, a recent observational study of patients exposed to amantadine in the ICU reported an increased risk of agitation.³⁶ Although these effects were not observed in a multicentre trial that started amantadine at least 4 weeks after TBI, the early use of amantadine in the ICU may explain these findings.^{36 40} However, these results were uncontrolled and confounding may also explain these differences. In addition, the use of amantadine may have increased arousal and the agitation measured may be part of the natural recovery. In studies

in which agitation was not the presenting symptom, no significant differences in behaviour scores between amantadine and control groups were reported.^{40 42 43}

In this review, we found no comparative studies assessing the efficacy of tricyclic antidepressants, dexmedetomidine or benzodiazepines. We also found no studies in children. A search of TBI-associated agitation studies in clinical trial registries revealed ongoing studies with the combination of dextromethorphan and quinidine (ClinicalTrials.gov: NCT03095066) as well as propranolol and clonidine (ClinicalTrials.gov: NCT01322048).⁷³ Finally, in a recent observational study on the predictors of agitation in TBI rehabilitation, sodium channel antagonist anticonvulsants, second-generation antipsychotics and gamma-aminobutyric acid anxiolytics were associated with more severe agitation.¹⁴ Although indication bias and residual confounding are probable, these results do suggest an association between suppression of cognition and more agitation.

Strengths of this study include an exhaustive search of the literature in the adult and paediatric populations, including grey literature and no language limitation. A risk of bias assessment was performed for each included study. Limits of this study include the presence of significant heterogeneity, variations in the different agitated behaviours (agitation, irritability and aggression) and populations (acute TBI, rehabilitation, outpatient) evaluated, preventing the authors from proceeding to a meta-analysis. In addition, very little studies reported length of stay and functional outcomes.

CONCLUSION

In conclusion, there are insufficient data to recommend the use of any medications for the management of agitation following TBI. Propranolol, methylphenidate, valproic acid and olanzapine may offer some benefit; however, they need to be further studied. The use of amantadine in the acutely ill may increase the risk of agitation whereas antipsychotics may prolong PTA. 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 behaviours in both the adult and paediatric TBI populations. In addition, there is a need to better define and standardise the assessment of agitated behaviours. Newer agents such as dexmedetomidine should also be evaluated.

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