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Pharmacological interventions for agitated behaviors in patients with traumatic brain injury: a systematic review

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Manuscripts

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3 **1 Pharmacological interventions for agitated behaviors in patients with traumatic**
4 **2 brain injury: a systematic review**
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7 4 David R. Williamson, B.Pharm, M.Sc., Ph.D.^{1,2} david.williamson@umontreal.ca
8 5 Anne Julie Frenette, B.Pharm, M.Sc.^{1,2} anne.julie.frenette@umontreal.ca
9 6 Lisa Burry, B.Sc.Pharm, Pharm.D.³ lisa.burry@sinaihealthsystem.ca
10 7 Marc M. Perreault, B.Pharm, M.Sc., Pharm.D.^{2,4} marc.perreault@umontreal.ca
11 8 Emmanuel Charbonney, M.D., Ph.D.^{5,6} emmanuel.charbonney@umontreal.ca
12 9 François Lamontagne, M.D., M.Sc. FRCPC⁷ francois.Lamontagne@USherbrooke.ca
13 10 Marie-Julie Potvin, Ph.D.⁸ mjpotvin@gmail.com
14 11 Jean-François Giguère, M.D., Ph.D. FRSC^{6,9} jean-francois.giguere.1@umontreal.ca
15 12 Sangeeta Mehta, M.D., FRCPC¹⁰ geeta.Mehta@sinaihealthsystem.ca
16 13 Francis Bernard, M.D. FRCPC^{5,6} f.bernard@umontreal.ca
17
18

19 15 ¹ Pharmacy department and Research center, Hôpital du Sacré-Coeur de Montréal

20 16 ² Faculté de pharmacie, Université de Montréal

21 17 ³ Department of Pharmacy and Medicine, Sinai Health System and Leslie Dan Faculty of
22 18 Pharmacy, University of Toronto.

23 19 ⁴ Department of Pharmacy, McGill University Health Center

24 20 ⁵ Department of Critical Care and Research center, Hôpital du Sacré-Coeur de Montréal

25 21 ⁶ Faculté de Médecine, Université de Montréal

26 22 ⁷ Centre de recherche, CHU de Sherbrooke

27 23 ⁸ Department of medicine, Faculté de Médecine, Université de Sherbrooke

28 24 ⁸ Department of Psychology, Hôpital du Sacré-Coeur de Montréal and department of
29 25 Psychology, Université du Québec à Montréal;

30 26 ⁹ Department of Neurosurgery, Hôpital du Sacré-Coeur de Montréal

31 27 ¹⁰ Department of Medicine, Interdepartmental Division of Critical Care Medicine, Mount
32 28 Sinai Hospital and University of Toronto
33
34
35

36 30 Corresponding author:

37 31 David Williamson, Ph.D.

38 32 Pharmacy department and research center

39 33 Hôpital du Sacré-Coeur de Montréal

40 34 5400 Gouin West

41 35 Montreal, Quebec

42 36 Canada, H4J 1C5
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3 43 **Patient and public involvement statement**
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5 44 This research was done without patient involvement. Patients were not invited to
6
7 45 comment on the study design and were not consulted to develop patient relevant
8
9 46 outcomes or interpret the results. Patients were not invited to contribute to the writing or
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11 47 editing of this document for readability or accuracy.
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3 **51 Abstract**

4 **52**
5 **53 Objective:** The aim of this systematic review was to assess the efficacy and safety of
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8 **54** pharmacological agents in the management of agitated behaviors following TBI.

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10 **55 Methods:** We performed a search strategy for published and unpublished evidence on
11
12 **56** the risks and benefits of 9 pre-specified medications classes used to control agitated
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14 **57** behaviors following TBI. We included all randomized controlled trials, quasi-
15
16 **58** experimental and observational studies examining the effects of medications
17
18 **59** administered to control agitated behaviors in TBI patients. Included studies were
19
20 **60** classified into 3 mutually exclusive categories: 1) agitated behavior was the presenting
21
22 **61** symptom; 2) agitated behavior was not the presenting symptom, but was measured as
23
24 **62** an outcome variable and; 3) safety of pharmacological interventions administered to
25
26 **63** control agitated behaviors was measured.

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30 **64 Results:** Among the 181 articles assessed for eligibility, 21 studies were included.
31
32 **65** Propranolol, methylphenidate, valproic acid and olanzapine were the only agents
33
34 **66** suggesting a potential benefit in reducing agitation, anger or irritability. Small sample
35
36 **67** sizes, heterogeneity and an unclear risk of bias were limits.

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39 **68 Conclusions:** There is insufficient data to recommend the use of any agent for the
40
41 **69** management of agitated behaviors following TBI. More studies on tailored interventions
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43 **70** and continuous evaluation throughout acute, rehabilitation and outpatient settings are
44
45 **71** needed.

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49 **72**

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51 **73 Systematic review registration:** Prospero CRD42016033140

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53 **74 Keywords:** Traumatic brain injury, agitation, Pharmacological intervention

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3 76 **Strengths and limitations of this study**
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- 5
6 78 ▪ This systematic review assessed the efficacy and safety of pharmacological agents
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9 79 in the management of agitated behaviors following traumatic brain injury
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11 80 ▪ Randomized controlled trials, quasi-experimental and observational studies were
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13 81 reviewed
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15 82 ▪ The included studies were limited by small sample sizes, variations in the different
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17 83 agitated behaviors and populations studied
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19 84 ▪ The review found insufficient data to recommend the use of any agent for the
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21 85 management of agitated behaviors following TBI
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87 Introduction

88 Traumatic brain injury (TBI) occurs when an external force is applied to the head leading
89 to alterations in brain function including decreased level of consciousness, post-
90 traumatic amnesia, and changes in behavior and cognition that can persist in the long
91 term. In the United States alone, approximately 50,000 people die each year from TBI
92 and more than 5 million live with TBI-related disabilities.^{1, 2} While TBI has a substantial
93 impact on direct healthcare costs, indirect costs from lost productivity also represent a
94 significant economic burden.^{3, 4} Agitated behaviors are a frequent behavioural problem
95 following TBI.^{5, 6} They have been broadly defined as a state of confusion that follows the
96 initial injury and is characterised by disruptive behaviours. A constellation of behaviors
97 has been associated with the term “agitation” in TBI patients, including restlessness,
98 confusion, physical and verbal aggression, impulsivity, perceptual disturbances, and
99 inattention creating a very heterogeneous group of patients to study.⁷ Agitation has been
100 reported in 20-41% of patients during the early stage of recovery in acute care units and
101 up to 70% of patients in rehabilitation units.^{6, 8-13} It can result in harm to patients and
102 caregivers, interfere with treatments, lead to the use of physical and pharmacological
103 restraints, increase hospital length of stay, delay rehabilitation and impede functional
104 independence.^{10-12, 14-16} A variety of agents such as antidepressants, anticonvulsants,
105 stimulants, and antipsychotics have been used for the management of neurobehavioral
106 complications of TBI.^{17, 18} However, preclinical studies have suggested that repeated
107 use of certain agents such as haloperidol, risperidone and diazepam may reduce
108 cognitive and functional recovery.¹⁹⁻²² Thus, it remains unclear which pharmacological
109 agents are the most effective and safest for the management of agitated behaviors in
110 TBI patients. A Cochrane Systematic Review published in 2006 showed a lack of

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3 111 evidence to support any agent.²³ Since then, two additional systematic reviews
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5 112 concluded that the evidence was insufficient and too weak to recommend any specific
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7 113 agent, however they included only French and English studies published before January
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9 114 2016, had incomplete search strategies, and did not include the grey literature.^{24, 25}
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11 115 There is a need for an updated knowledge synthesis in this area that will provide
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13 116 guidance for clinicians and identify knowledge gaps. The aim of this systematic review
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15 117 was to assess the efficacy and safety of pharmacological agents in the management of
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17 118 agitated behaviors following TBI compared to placebo or other treatments.
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24 120 **Methods**

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27 121 The review protocol has been registered in PROSPERO International Prospective
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29 122 Register of Systematic Reviews (CRD42016033140) and published in a peer-reviewed
30
31 123 journal.²⁶ We included all randomized controlled, quasi-experimental, and observational
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33 124 studies with control groups that had a majority (>50%) of patients with TBI. We excluded
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35 125 case reports, case series, and observational studies without control groups. We included
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37 126 studies of all type of patients who suffered a TBI, including children and adults, in both
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39 127 the early stages of recovery and in rehabilitation. We included 3 mutually exclusive
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41 128 types of studies: 1) those evaluating the use of pharmacological interventions in which
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43 129 an agitated behaviour, not further defined, was one of the eligibility criteria for the study;
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45 130 2) those in which an agitated behaviour was not an eligibility criterion, but was measured
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47 131 as an outcome variable; and 3) those specifically assessing the safety of
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49 132 pharmacological agents used to treat agitation in TBI patients. In this systematic review,
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51 133 we considered agitation, aggressiveness, assaultive behaviour, irritability and confusion
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3 134 as part of agitated behaviours. All medications considered in this review were pre-
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5 135 specified and consisted in the following: beta-adrenergic blockers, typical and atypical
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7 136 antipsychotics, anticonvulsants, dopamine agonists, psychostimulants, antidepressants,
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10 137 alpha-2-adrenergic agonists, hypnotics and anxiolytics. Studies were included whether
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12 138 the investigators compared a medication to placebo, a medication to another
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14 139 medication, or various combinations of different medications.

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18 140 The primary outcome was a reduction in severity of the agitated behavior as measured
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20 141 in each study. If feasible, we reported resolution of agitated behaviours as well as
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22 142 changes in duration and type of symptoms (confusion, aggressiveness, inattention,
23
24 143 hallucinations, disorientation, and inappropriate mood or speech). Secondary outcomes
25
26 144 include lengths of stay, (ICU length of stay, hospital LOS for the early rehabilitation
27
28 145 phase), adverse events (extrapyramidal effects, QTc prolongation, cardiac arrhythmias,
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30 146 hypotension, seizures, behavioural effects), use of physical restraints in ICU, cognitive
31
32 147 and functional outcomes at hospital discharge and at one year post-TBI.

33 34 35 36 37 148 *Search strategy*

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41 149 A search strategy was devised with the help of Health Sciences librarian and using the
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43 150 Peer Review for Electronic Search Strategies (PRESS) checklist was conducted in the
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45 151 following databases: PubMed, OvidMEDLINE®, OvidMEDLINE® In-Process & Other Non-
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47 152 Indexed Citations, Embase, CINAHL, PsycINFO, Cochrane Library, Google Scholar,
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49 153 Directory of Open Access Journals, LILACS, Web of Science and Prospero
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51 154 (<http://www.crd.york.ac.uk/PROSPERO/>).²⁷ A grey literature search was also performed
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53 155 using the resources suggested in CADTH's *Grey Matters*

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3 156 (<http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters>). As described in our
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5 157 published protocol, we searched abstracts from annual scientific meetings from relevant
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7 158 groups in the last 5 years.²⁶ Finally, references of identified studies as well as other
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10 159 types of articles (reviews, book chapters) were screened.
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14 161 *Data collection and analysis*
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16 162 Two reviewers (DW, AJF) independently screened titles and abstracts for eligible
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18 163 publications. The same reviewers then assessed the complete report of each retained
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20 164 citations for eligibility. Disagreements were resolved by consensus and discussion with a
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22 165 third reviewer was not required. In the absence of important clinical and methodological
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24 166 heterogeneity, we planned to analyze the study results for statistical heterogeneity. If the
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26 167 statistical heterogeneity was acceptable ($I_2 < 50\%$), we planned to proceed to a meta-
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28 168 analysis.²⁶
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33 169 34 35 170 *Data extraction and management* 36

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38 171 Data from all included studies were extracted by two independent reviewers (AJF and
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40 172 DW) and in duplicate using a pre-tested data extraction form. The following variables
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42 173 were recorded for each study: study title, name of the first author, year of publication,
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44 174 country of origin, language of publication, publication type (journal article, conference
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46 175 proceeding, abstract, thesis), clinical setting (intensive care unit, hospital ward,
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48 176 rehabilitation unit, outpatient), study design (randomized controlled, blinded or open,
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50 177 non-randomized controlled, prospective or retrospective, crossover), population
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52 178 (paediatric, adult), patient characteristics (age, gender, isolated TBI or multiple trauma
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3 179 including TBI, severity of TBI according to Glasgow Coma Scale, days from TBI at
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5 180 inclusion, inclusion and exclusion criteria), characteristics of the intervention and control
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7 181 treatment (type of pharmacological agent, dose, frequency and duration of the therapy),
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10 182 agitation measurement tool, description of the specific agitated behaviours (definition,
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12 183 frequency, duration), and clinical outcomes (length of stay), adverse events, use of
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14 184 physical restraints during ICU stay, duration of post traumatic amnesia, cognitive
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17 185 function at ICU discharge and at one year, and functional outcome at ICU discharge and
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19 186 at one year. We contacted the corresponding author for clarifications when necessary.
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25 188 *Assessment of risk of bias*

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27 189 Two reviewers (DW, AJF) independently evaluated each included study with the
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29 190 Cochrane Collaboration tool for randomized controlled trials and the Ottawa-Newcastle
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31 191 tool for observational studies, respectively.^{28, 29} In case of disagreement concerning the
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33 192 risk of bias, a third reviewer (FB) was consulted to resolve the issue.
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39 194 **Results**

40 195 *Study selection*

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44 199 The database search (up to December 10th 2018) retrieved 11 170 unique citations of
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46 200 which 10 989 were excluded based on title and abstracts (Figure 1). We assessed 181
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48 201 full-text articles for eligibility and 21 studies were included. A total of eight studies
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50 202 evaluated the use of pharmacological interventions in which an agitated behaviour was
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52 203 the presenting symptom or one of the presenting symptoms.³⁰⁻³⁷ In nine other studies,
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54 204 agitated behaviour was not the presenting symptom, but was measured as an outcome
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3 205 variable.³⁸⁻⁴⁶ Finally, four studies specifically assessed the safety of pharmacological
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5 206 agents used for agitated behaviours in TBI.⁴⁷⁻⁵⁰
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8 207 *Agitated behaviors as the presenting symptom*
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10 208
11 209 The eight included studies evaluated various aspects ranging from aggressiveness to
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13 210 irritability and confusion (Table 1).³⁰⁻³⁷. The behaviors were evaluated using the following
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15 211 tools (Table 2): agitated behavior scale (ABS), confusion assessment protocol, State-
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17 212 Trait Anger scale, the overt aggression scale, Richmond Agitation Sedation Scale
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19 213 (RASS) and neuropsychiatric inventory irritability and aggression domains (NPI-I and
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21 214 NPI-A).⁵¹
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216 **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 behaviour as the presenting symptom								
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
Mooney ³¹ 1993 N=38	Published USA	Randomized Pre-post	Anger	Methylphenidate 30mg/day	Placebo	Outpatient	6 months or more (mean 27 +/- 21 months)	Severe blunt TBI
Yablon 2010 ³² N=79	Abstract USA	RCT parallel	Confusion	Amantadine 100mg bid X 14 days	Placebo	Inpatient brain injury unit of a rehabilitation hospital	≤ 6 months	TBI not further defined
Hammond ³⁴ 2014 N=76	Published USA	RCT parallel	Irritability and aggression	Amantadine 100mg bid	Placebo	Outpatient	≥ 6 months following a TBI	Blunt TBI
Beresford ³⁰	Abstract	RCT parallel	Agitation	Valproic acid	Placebo	Outpatient	> 1 year	Mild and

2015 N=50	USA			for level 50-100 mcg/ml			following TBI	moderate TBI
Hammond ³³ 2015 N=168	Published USA	RCT parallel	Irritability and aggression	Amantadine 100mg bid	Placebo	Outpatient	≥ 6 months following a TBI	Blunt TBI
Maturana ³⁷ Waidele 2009 N=31	Published Chili	Prospective double-blind	Restlessness, Irritability, Aggression, Insomnia	Olanzapine (dose not specified)	Placebo	Outpatient	N/A	TBI not further defined
Gramish ³⁵ 2017 N=139	Published USA	Retrospective observational	Agitation	Amantadine 100mg bid	No amantadine	Adult Trauma ICU	Acute TBI	TBI not further defined
2. Agitated behavior is not the presenting symptom								
Study/Year (N)	Publicatio n/Country	Study design	Study focus	Interventional arm	Comparative arm	Location at randomization	Timing from TBI at randomization	TBI description
Schneider ⁴¹ 1999 N=10	Published USA	RCT parallel	Cognitive function and behavior	Amantadine 50mg bid increased to 150mg bid	Placebo	Outpatient	N/A	Moderate and severe TBI

Meythaler ⁴⁰ 2001 N=9	Published USA	RCT Crossover	Recovery and arousal	Sertraline	Placebo	Inpatient rehabilitation	< 2 weeks of TBI	Severe TBI
Meythaler ⁴² 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 ³⁸ 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 ³⁹ 2012 N=184	Published USA, Denmark, Canada	RCT parallel	Functional recovery	Amantadine	Placebo	Inpatients	4 to 16 weeks following TBI	Vegetative or minimally conscious TBI
Tramontana ⁴³ 2014 N=22 but 13 completed the study	Published USA	RCT Crossover	Attention	Lisdexampheta- mine	Placebo	Outpatient	6-34 months (mean 15.6 +/- 10 months) since TBI	Moderate and severe TBI
Johansson ⁴⁵ 2014	Published Sweden	RCT Crossover	Mental fatigue and cognition	Methylphenidate 5mg and 20mg	Placebo	Outpatient	> 12 months following TBI	Mild or moderate

N=48				tid				TBI
Fann ⁴⁴ 2017 N=62	Published USA	RCT parallel	Major depression	Sertraline	Placebo	Level 1 trauma center	< 1 year of TBI	Moderate and severe TBI
Hart ⁴⁶ 2017 N=32	Published USA	RCT parallel	Cognitive function	Dextroampheta mine	Placebo	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 1985 ⁴⁹ 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, benzodiazepine s and neuroleptics	No CNS active medications	Level 1 trauma center and rehabilitation center	From admission	TBI
Kooda ⁵⁰ 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 ⁴⁷	Published	Retrospective	Seizures,	Haloperidol	No	Inpatients	From admission	Moderate

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2016 N=101	USA	cohort	neuroleptic malignant syndrome, QTc prolongation, extrapyramidal symptoms, hematological disturbances		haloperidol			and severe TBI
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218 **Table 2 – Tools used to measure agitated behaviors**

Tools	Description
Agitated behavior scale ⁵²	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.
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.
Belligerence cluster score for the Katz adjustment scale (KAS) ⁵⁷	The KAS is an observer rating scale used to assess the social adjustment of people with traumatic brain injury.
Neuropsychiatric inventory irritability	The NPI is a 40-item scale evaluating 12 behavioral domains including irritability and

<p>(NPI-I) and aggression domains (NPI-A)⁵¹</p>	<p>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.</p>
<p>Neurobehavioral Function Inventory (NFI)⁵⁸</p>	<p>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.</p>
<p>Neurobehavioral rating scale (NRS)⁵⁹</p>	<p>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.</p>
<p>Overt aggression scale (OAS)⁶⁰</p>	<p>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.</p>

Anger-Hostility factor score of the Profile of Mood States (POMS) ³¹	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) ³¹	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.

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3 220 Of the identified studies, two were conference abstracts that remained unpublished.^{32, 36}
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5 221 The studies evaluated propranolol³⁰, amantadine³²⁻³⁴, methylphenidate³¹, valproic acid³⁶
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7 222 and olanzapine³⁷ in comparison to placebo. Five used a randomized controlled parallel
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9 223 design^{30, 32-34, 36}, one used a randomized pretest posttest control group design³¹, one
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11 224 was a prospective double blind observational study³⁷ and, one was a retrospective
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13 225 observational study.³⁵ All the studies exclusively enrolled adult (16 years or older) TBI
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15 226 patients and three studies excluded older patients (greater than 65 or 75 years)^{33, 34, 36}.
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17 227 The studies mostly included patients in rehabilitation (n=2)^{30, 32} and outpatient (n=5)
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19 228 settings.^{31, 33, 34, 36, 37} Only one study evaluated patients in an intensive care unit (ICU)
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21 229 setting.³⁵ All the studies exclusively studied TBI patients.³⁰⁻³⁷ Three studies identified in
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23 230 an earlier systematic review were excluded (Figure 1) because TBI patients represented
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25 231 less than 50% of the sample.^{23, 61-63}
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33 233 In the eight studies, one randomized trial evaluated the use of propranolol for the
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35 234 treatment of agitation in severe blunt TBI patients (Table 3).³⁰ It reported a reduction in
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37 235 the intensity of agitation episodes and in the use of physical restraints but failed to show
38
39 236 a reduction in the frequency of agitation episodes.³⁰ Amantadine was evaluated for the
40
41 237 management of confusion in a randomized trial, irritability in two randomized trials, and
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43 238 agitation in a retrospective observational study.³²⁻³⁵ The studies reported inconsistent
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45 239 results (Table 3). In one unpublished study in the setting of rehabilitation within 90 days
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47 240 of TBI (n=79), amantadine had no effect on confusion.³² In a pilot study of outpatients
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49 241 who suffered a TBI more than six months ago, amantadine showed significant
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51 242 reductions in irritability and aggression using the Neuropsychiatric Inventory scale
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53 243 (NPI).³⁴ In a follow-up study of 168 outpatients who had suffered a TBI more than 6
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3 244 months ago, no difference in the incidence of irritability at 28 and 60 days using the NPI-
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5 245 I from observers (family member, close friend, or employer) was reported.³³ Participants
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7 246 self-rating at day-60 indicated improvement in irritability ($p<0.04$) but the difference
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10 247 became non-significant when adjusted for multiple comparisons. The Global
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12 248 improvement subscale of the Clinical Global Impressions (CGI), which evaluates general
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14 249 emotional and behavioral function, improved more in the amantadine group than in the
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16 250 placebo group at day 60 ($p=0.0354$). A sub-analysis of patients with anger and
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18 251 aggression (118 of the 168 patients) in the same study was also carried out and
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20 252 reported a statistically significant reduction in participant's self-rated aggression at 60
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22 253 days.⁶⁴ Finally, in a retrospective observational study ($n=139$), patients exposed to
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24 254 amantadine in the ICU reported more agitation episodes defined as a Richmond
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26 255 Agitation Sedation Score of +2 or higher (38% vs 14%) in an unadjusted analysis.³⁵ The
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28 256 use of amantadine was also associated with an increased median ICU length of stay
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30 257 (4.5 vs 3 days; $p=0.01$) when compared to non-exposed patients.
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38 259 The efficacy of olanzapine in the management of restlessness, irritability, aggression
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40 260 and insomnia in outpatients with a history of TBI was evaluated in a prospective double
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42 261 blind study.³⁷ While no reduction in restlessness was reported, the authors did report a
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44 262 significant reduction in irritability and insomnia between weeks 1 and 3 in olanzapine-
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46 263 treated patients. Unfortunately, no statistical comparison with the placebo group was
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48 264 provided. The efficacy of valproic acid in reducing agitated behaviors among mild and
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50 265 moderate TBI outpatients was evaluated in an unpublished randomized controlled study
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52 266 ($n=50$).³⁶ Patients were included more than one year following brain injury and suffered
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54 267 from both affective lability and alcohol dependence. A significant reduction in the
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268 **Table 3 – Efficacy and safety outcomes**

Study/Year/n	Intervention	Agitated behavior measures	Efficacy outcomes	Safety outcomes
1. Agitated behavior as the presenting symptom				
<i>Randomized controlled studies</i>				
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
Mooney 1993 ³¹ 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 effect on side effects
Yablon 2010 ³² N=79	Amantadine	Confusion assessment protocol	No significant differences in the number of symptoms of posttraumatic confusional state as measured by	No patients withdrawn because of safety criteria

		(CAP)	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)	
Hammond 2014 ³⁴ 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 3 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 = .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 = .046).	No difference in adverse events (tremors, appetite, gastrointestinal, aches and pain, sexual problems, disorientation, seizures)
Beresford 2015 ³⁰ 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

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<p>Hammond 2015³³ N=168</p>	<p>Amantadine</p>	<p>NPI-I most problematic by observer and by patient. Global improvement subscale of the Clinical Global Impressions (CGI) by physicians.</p>	<p>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 ($p = 0.0354$).</p>	<p>Well tolerated with no significant differences in adverse events between groups.</p>
<p><i>Observational studies</i></p>				
<p>Maturana Waidele³⁷ 2009 N=31</p>	<p>Olanzapine</p>	<p>Restlessness, irritability, aggressiveness and insomnia. No tool mentioned.</p>	<p>Reduction in irritability ($p < 0.001$), aggressiveness ($p = 0.008$) and insomnia ($p = .0011$) between weeks 1 and 3 in the patients treated with olanzapine</p>	<p>No safety outcomes reported</p>
<p>Gramish 2017³⁵ N=139</p>	<p>Amantadine</p>	<p>RASS score of +2 or higher</p>	<p>Increase in agitation in patients exposed to amantadine (38%) compared to non-exposed (14%); $p = 0.018$. Increase in median ICU length of stay (4.5</p>	<p>No safety outcomes reported</p>

			vs 3 days; p=0.01). Median hospital length of stay was non-significantly increased (14 days vs 10 days; p=0.051)	
2. Agitated behavior is not the presenting symptom				
<i>Randomized controlled studies</i>				
Schneider 1999 ⁴¹ N=10	Amantadine	Neurobehavioral rating scale	No significant difference in behavior scores between amantadine and placebo groups	No safety outcomes reported
Meythaler 2001 ⁴⁰ N=9	Sertraline	Agitated Behavior Scale	No difference in decline of ABS over treatment period	No safety outcomes reported
Meythaler 2002 ⁴² 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> .05, Mann–Whitney U test)	No detrimental effects in hematology or biochemistry laboratories and no seizures.
Banos 2010 ³⁸ 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 2012 ³⁹ N=184	Amantadine	Agitation and restlessness not	A total of 12/87 (14%) patients and 11/97 (11%) patients exposed to amantadine and placebo	No differences in adverse events (seizure, nausea, vomiting,

		further defined	developed agitation (p=NS) over the 4-week period. Restlessness was reported in 8% and 9% of patients exposed to amantadine and placebo, respectively.	constipation, diarrhea, elevated liver function tests, insomnia, rash, congestive heart failure, involuntary muscle contractions)
Tramontana 2014 N=22 but 13 patients completed the study	Lisdexamphetamine	Agitation and restlessness not further defined	No difference in agitation (no cases in each group) or irritability (1/13 case) during placebo) between the Lisdexamphetamine and placebo groups.	Reduced appetite and weight loss of more than 5 lbs more frequent with lisdexamphetamine (7 vs 1 case) p=NS
Johansson 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 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.
Hart 2017	Dextroamphetamine	Agitated Behavior	Increase in agitation with dextroamphetamine over	No significant difference in heart

N=32	mine	Scale	time compared to placebo (p<0.05)	rate or blood pressure.
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3 270 agitated behavior scores (ABS) evaluated by family members at eight weeks (12.9 vs
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5 271 15.5 points; $p=0.03$) was observed. Finally, a crossover study assessed
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7 272 methylphenidate for anger ($n=38$) in TBI rehabilitation center outpatients (six months or
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10 273 more after TBI). After six weeks, methylphenidate significantly reduced the anger score
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12 274 using the State Trait Anger Scale (STAS).³¹

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17 276 Of the eight studies, safety outcomes were reported in four studies.³¹⁻³⁴ When reported,
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19 277 the agents studied were well tolerated with no significant differences observed.
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21 278 Functional and cognitive outcomes were not reported in any of these studies.

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26 280 *Agitated behavior as a secondary measure*

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29 282 We identified nine studies evaluating agitated behaviors as a secondary measure, which
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31 283 were focused on cognitive function and neurological recovery (Table 1).³⁸⁻⁴⁶ In these
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33 284 studies, sertraline^{38, 40, 44}, amantadine^{39, 41, 42}, amphetamines^{43, 46}, and methylphenidate⁴⁵
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35 285 were evaluated versus placebo and reported agitated behaviors as an outcome. Of
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37 286 these studies, 6 used a randomized crossover design and 3 used a randomized
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39 287 controlled parallel design.

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45 289 Sertraline was evaluated in three studies to enhance recovery and increase arousal,
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47 290 ameliorate cognitive and neurobehavioral functioning and to treat major depression
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49 291 (Table 3).^{38, 40, 44} In all these three studies, sertraline had no effect on the incidence of
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51 292 agitation, anger or aggression. In one study, more patients developed
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53 293 agitation/restlessness in the sertraline group (17%) compared to the placebo group (7%)

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3 294 but this difference was not statistically significant ($p=0.42$).⁴⁴ Amantadine was also
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5 295 evaluated in three studies for cognitive and functional recovery.^{39, 41, 42} All three studies
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7 296 found no differences in agitated behaviors compared to placebo. Methylphenidate was
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9 297 evaluated for secondary mental fatigue in mild TBI patients more than six months after
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11 298 injury.⁴⁵ However, it had no effect on irritability and aggression. Lisdexamphetamine and
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13 299 dextroamphetamine were each evaluated for attention deficits in TBI patients and no
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15 300 effect on agitated behaviors was noted with lisdexamphetamine whereas
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17 301 dextroamphetamine increased agitation over time ($p<0.05$).^{43, 46} Among these 9 studies,
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19 302 those evaluating sertraline and amantadine reported no significant differences in
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21 303 adverse events.^{38-42, 44}
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29 305 *Studies evaluating safety outcomes*
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31 306 Finally, the safety of pharmacological agents used for agitated behaviors in TBI patients
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33 307 was evaluated in four retrospective observational studies (Table 4).⁴⁷⁻⁵⁰ Two of these
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35 308 studies focused on the effect of haloperidol and antipsychotic use on post-traumatic
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37 309 amnesia (PTA) duration, whereas a third evaluated the effects of antipsychotics,
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39 310 benzodiazepines and narcotics on PTA duration, and Functional independence measure
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41 311 (FIM) cognitive and motor scores.⁴⁸⁻⁵⁰ In these three studies, haloperidol and other
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43 312 antipsychotics were associated with an increase in PTA duration. Antipsychotics,
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45 313 benzodiazepines and narcotics had no effects on FIM scores.⁴⁸ Finally a fourth study
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47 314 focused on the general safety (seizures, neuroleptic malignant syndrome, QTc
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49 315 prolongation, extrapyramidal symptoms, hematologic disturbances) of haloperidol in ICU
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51 316 TBI patients.⁴⁷ Patients exposed to haloperidol ($n=45$) had no significant increase in
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53 317 adverse events compared to non-exposed patients ($n=56$). Of note, none of the studies
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3 318 adjusted for severity of TBI and other potential confounders.
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8 320 *Risk of bias assessment*

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10 321 Risk of bias scores are reported in Table 5. The analysis of risk of bias of randomized
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12 322 controlled trials with the Cochrane Collaboration's Tool revealed that many studies did
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14 323 not provide sufficient information on sequence, generation and allocation concealment.

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17 324 A majority of studies had other threats to validity including limited sample sizes, no
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19 325 description of patient demographics and loss to follow-up. For six studies evaluated with
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21 326 the Newcastle-Ottawa tool, the number of stars awarded ranged from four to five. Most
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23 327 studies were awarded a score of four stars, indicating a high risk of bias. As none of the
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25 328 six studies were adjusted for potential confounding, all received 0 stars for comparability.
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337 **Table 4 - Studies assessing the safety of pharmacological agents used for agitated behaviors in TBI**

Study/Year/n	Drugs studied	Results
Rao 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 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 ($p<0.01$).
Kooda 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.
Anderson 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 hematologic 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; $p<0.001$)

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339 **Table 5 – Risk of bias assessment**

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1. Randomized controlled trials
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Cochrane Collaboration Tool Risk of bias items							
Study (year)	Sequence generation	Allocation	Blinding of participants and personnel	Blinding of outcome assessment	Outcome data	Selective reporting	Other threats to validity
Brooke 1992	U	U	L	L	L	L	H
Mooney 1993	U	U	L	H	L	U	H
Schneider 1999	U	U	U	U	H	L	H
Meythaler 2001	U	U	L	L	U	U	H
Meythaler 2002	U	U	U	U	L	H	H
Banos 2010	U	U	L	L	L	L	H
Yablon 2010	U	U	L	L	L	U	H
Giacino 2012	U	L	L	L	L	L	L

Hammond 2014	L	L	L	L	U	L	L
Tramontana 2014	H	H	L	L	H	L	H
Johansson 2014	U	H	H	H	H	L	H
Beresford 2015	U	U	L	L	H	L	H
Hammond 2015	L	L	L	L	U	L	L
Fann 2017	L	L	L	L	L	L	H
Hart 2017	U	U	L	L	L	L	L
2. Observational studies							
Study (year)	Newcastle-Ottawa Quality Assessment Scale						
	Number of stars awarded						
	Selection ^a		Comparability ^b			Outcome ^c	
Rao 1985	**					**	

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Maturana Waidele 2009	**		**
Mysiw 2006	**		***
Kooda 2015	**		**
Anderson 2016	**		**
Gramish 2017	***		*

341 For Cochrane Collaboration's Tool:

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

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344 For Newcastle-Ottawa Quality Assessment Scale :

345 ^a Maximum 4 stars

346 ^b Maximum 2 stars

347 ^c Maximum 3 stars.

348 N/A : not applicable

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349 Discussion

350 In this systematic review, we used an exhaustive search strategy and included studies
351 directly or indirectly evaluating pharmacological agents for the management of TBI-
352 associated agitated behaviors as well as studies assessing the safety of
353 pharmacological agents used for these agitated behaviors. Despite the prevalence and
354 importance of this problem, we found a limited number of studies evaluating
355 pharmacological interventions for the management of agitated behaviors. Propranolol,
356 methylphenidate, valproic acid and olanzapine were the only agents suggesting a
357 potential benefit in reducing agitation, anger or irritability.^{30, 31, 36, 37} However, the studies
358 evaluating these agents had limited sample sizes, heterogeneous patient populations
359 and an unclear risk of bias. Amantadine showed mixed results whereas sertraline,
360 lysdexamphetamine and dextroamphetamine showed no benefits.

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362 The use of beta-blockers in patients with organic brain disease and assaultive behaviors
363 or impulsivity has been previously studied in three crossover-randomized trials with
364 some efficacy but TBI represented less than 50% of the total patient population.⁶¹⁻⁶³ In
365 the study presented in this review, propranolol reduced the intensity of agitation but not
366 the frequency.³⁰ One important finding was a reduction in the use of physical restraints.
367 Unfortunately, safety measures such as hypotension and bradycardia were not reported.
368 The Canadian ABIKUS guidelines have recommended beta-blockers for the treatment of
369 aggression following TBI.⁶⁵

370 Although numerous observational studies have reported a reduction in agitation with the
371 use of antipsychotic agents, we found no controlled studies evaluating the efficacy of
372 antipsychotics other than olanzapine.⁶⁶⁻⁶⁸ In a previous systematic review that included

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3 373 case reports and case series evaluating antipsychotics, Lanthier et al. identified 7
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5 374 articles that included a total of 52 patients.²⁴ The lack of a control group excluded these
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8 375 studies from our review. The only study we included that used olanzapine didn't report a
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10 376 reduction in restlessness but did suggest a reduction in irritability.³⁷ Its interpretation is
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12 377 greatly limited given the poor description of methods and a lack of statistical comparison
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14 378 with the placebo group. The four studies assessing safety all evaluated antipsychotic
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16 379 agents and suggested a potential risk of prolonged PTA in unadjusted analyses.⁴⁷⁻⁵⁰
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19 380 None of the studies controlled for potential confounders such as severity of TBI.
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21 381 Although pre-clinical studies have suggested a reduction in cognitive and motor recovery
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23 382 with repeated administration of haloperidol and risperidone, the one study evaluating
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25 383 cognitive and motor scores reported no significant association with antipsychotic use.¹⁹⁻
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27 384 ^{21, 48, 69} In light of these results, both the International Cognitive (INCOG), the Canadian
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29 385 ABIKUS guidelines and the French Society of Physical and Rehabilitation Medicine
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31 386 (SOFMER) guidelines have advised against the use of antipsychotics in TBI patients
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33 387 with agitated behaviors.^{24, 65, 70} Paradoxically, observational studies have suggested
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35 388 antipsychotics are frequently used for the management of agitated behaviors.^{14, 71-73}
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42 390 Anticonvulsants are clinically used as mood stabilizers in bipolar affective disorder and
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44 391 have also been used in TBI-associated agitation.^{74, 75} Case series have reported a
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46 392 reduction in agitation and aggressive behaviors with the use of valproic acid and
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48 393 carbamazepine but were uncontrolled.⁷⁶⁻⁸⁰ We identified one unpublished study of TBI
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50 394 patients with affective lability and alcohol dependence where valproic acid showed
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52 395 effectiveness in reducing weekly ABS rated by spouse or significant other's.
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54 396 Unfortunately, the abstract provided no information on the onset of effect or adverse
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3 397 events associated with its use.
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7 399 Amantadine increases dopaminergic neurotransmission and has been shown to
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10 400 increase the rate of neurological recovery in severe TBI.³⁹ In the 4 studies that evaluated
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12 401 amantadine for irritability, agitation or aggressiveness, results were variable.³²⁻³⁵
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14 402 Although one study suggested a reduction in irritability, a larger study by the same group
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16 403 failed to confirm these results. Interestingly, a recent observational study of patients
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18 404 exposed to amantadine in the ICU reported an increased risk of agitation.³⁵ However,
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20 405 these results were uncontrolled and confounding may explain these differences. In
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22 406 addition, the use of amantadine may have increased arousal and the agitation measured
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24 407 may be part of the natural recovery. In studies in which agitation was not the presenting
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26 408 symptom, no significant differences in behavior scores between amantadine and control
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28 409 groups were reported.^{39, 41, 42}
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35 411 In this review, we found no comparative studies assessing the efficacy of tricyclic
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37 412 antidepressants, dexmedetomidine or benzodiazepines. We also found no studies in
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39 413 children. A search of TBI-associated agitation studies in clinical trial registries revealed
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41 414 ongoing studies with the combination of dextromethorphan and quinidine
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43 415 (ClinicalTrials.gov: NCT03095066) as well as propranolol and clonidine
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45 416 (ClinicalTrials.gov: NCT01322048).⁸¹ Finally, in a recent observational study on the
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47 417 predictors of agitation in TBI rehabilitation, sodium channel antagonist anticonvulsants,
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49 418 second-generation antipsychotics, and gamma-aminobutyric acid anxiolytics were
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51 419 associated with more severe agitation.¹⁴ Although indication bias and residual
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53 420 confounding are probable, these results do suggest an association between suppression
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3 421 of cognition and more agitation.
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7 423 Strengths of this study include an exhaustive search of the literature in the adult and
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10 424 pediatric populations, including grey literature and no language limitation. A risk of bias
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12 425 assessment was performed for each included study. Limits of this study include the
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14 426 presence of significant heterogeneity, variations in the different agitated behaviors
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16 427 (agitation, irritability, and aggression) and populations (acute TBI, rehabilitation,
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18 428 outpatient) evaluated, preventing the authors from proceeding to a meta-analysis. In
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20 429 addition, very little studies reported length of stay and functional outcomes.
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26 431 **Conclusion**
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28 432 In conclusion, there are insufficient data to recommend the use of any medications for
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30 433 the management of agitation following TBI. More studies on tailored interventions and
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32 434 continuous evaluation throughout the acute, rehabilitation and outpatient settings are
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34 435 needed to assess the efficacy and safety of pharmacological agents in both the adult
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36 436 and pediatric TBI populations. In addition, there is a need to better define and
37
38 437 standardize the assessment of agitated behaviors. Propranolol, methylphenidate,
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40 438 valproic acid and olanzapine may offer some benefit, however, they need to be further
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42 439 studied. Newer agents such as dexmedetomidine should also be evaluated.
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50
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53 443 expertise and help with the literature search strategies.
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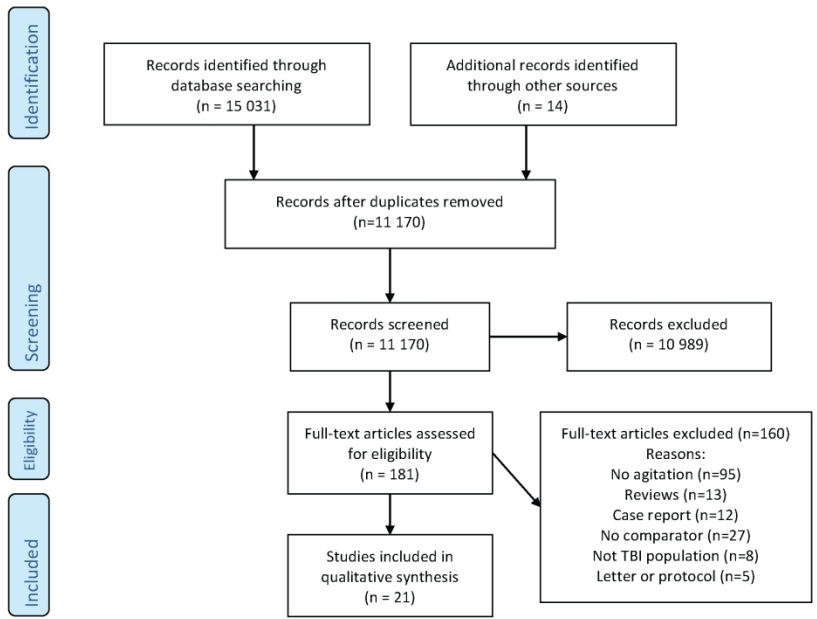
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1 **PRISMA Flow Diagram**

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Pharmacological interventions for agitated behaviors in patients with traumatic brain injury: a systematic review

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Keywords:	Neurological injury < NEUROLOGY, REHABILITATION MEDICINE, Delirium & cognitive disorders < PSYCHIATRY

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Manuscripts

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3 1 **Pharmacological interventions for agitated behaviors in patients with traumatic**
4 2 **brain injury: a systematic review**
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6 4 David R. Williamson, B.Pharm, M.Sc., Ph.D.^{1,2} david.williamson@umontreal.ca
7 5 Anne Julie Frenette, B.Pharm, M.Sc.^{1,2} anne.julie.frenette@umontreal.ca
8 6 Lisa Burry, B.Sc.Pharm, Pharm.D.³ lisa.burry@sinaihealthsystem.ca
9 7 Marc M. Perreault, B.Pharm, M.Sc., Pharm.D.^{2,4} marc.perreault@umontreal.ca
10 8 Emmanuel Charbonney, M.D., Ph.D.^{5,6} emmanuel.charbonney@umontreal.ca
11 9 François Lamontagne, M.D., M.Sc. FRCPC⁷ francois.Lamontagne@USherbrooke.ca
12 10 Marie-Julie Potvin, Ph.D.⁸ potvin.marie_julie@uqam.ca
13 11 Jean-François Giguère, M.D., Ph.D. FRSC^{6,9} jean-francois.giguere.1@umontreal.ca
14 12 Sangeeta Mehta, M.D., FRCPC¹⁰ geeta.Mehta@sinaihealthsystem.ca
15 13 Francis Bernard, M.D. FRCPC^{5,6} f.bernard@umontreal.ca
16 14

17 15 ¹ Pharmacy department and Research center, Hôpital du Sacré-Coeur de Montréal

18 16 ² Faculté de pharmacie, Université de Montréal

19 17 ³ Department of Pharmacy and Medicine, Sinai Health System and Leslie Dan Faculty of
20 18 Pharmacy, University of Toronto.

21 19 ⁴ Department of Pharmacy, McGill University Health Center

22 20 ⁵ Department of Critical Care and Research center, Hôpital du Sacré-Coeur de Montréal

23 21 ⁶ Faculté de Médecine, Université de Montréal

24 22 ⁷ Centre de recherche, CHU de Sherbrooke

25 23 ⁸ Department of medicine, Faculté de Médecine, Université de Sherbrooke

26 24 ⁸ Department of Psychology, Hôpital du Sacré-Coeur de Montréal and department of
27 25 Psychology, Université du Québec à Montréal;

28 26 ⁹ Department of Neurosurgery, Hôpital du Sacré-Coeur de Montréal

29 27 ¹⁰ Department of Medicine, Interdepartmental Division of Critical Care Medicine, Mount
30 28 Sinai Hospital and University of Toronto

31 29
32 30 Corresponding author:

33 31 David Williamson, Ph.D.

34 32 Pharmacy department and research center

35 33 Hôpital du Sacré-Coeur de Montréal

36 34 5400 Gouin West

37 35 Montreal, Quebec

38 36 Canada, H4J 1C5
39 37

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42 40

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3 43 **Patient and public involvement statement**
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5 44 This research was done without patient involvement. Patients were not invited to
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7 45 comment on the study design and were not consulted to develop patient relevant
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9 46 outcomes or interpret the results. Patients were not invited to contribute to the writing or
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11 47 editing of this document for readability or accuracy.
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3 **51 Abstract**

4 **52**
5 **53 Objective:** The aim of this systematic review was to assess the efficacy and safety of
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8 **54** pharmacological agents in the management of agitated behaviors following TBI.

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10 **55 Methods:** We performed a search strategy in PubMed, OvidMEDLINE®, Embase,
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12 **56** CINAHL, PsycINFO, Cochrane Library, Google Scholar, Directory of Open Access
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14 **57** Journals, LILACS, Web of Science and Prospero (up to December 10th 2018) for
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17 **58** published and unpublished evidence on the risks and benefits of 9 pre-specified
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19 **59** medications classes used to control agitated behaviors following TBI. We included all
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21 **60** randomized controlled trials, quasi-experimental and observational studies examining
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24 **61** the effects of medications administered to control agitated behaviors in TBI patients.
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26 **62** Included studies were classified into 3 mutually exclusive categories: 1) agitated
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28 **63** behavior was the presenting symptom; 2) agitated behavior was not the presenting
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30 **64** symptom, but was measured as an outcome variable and; 3) safety of pharmacological
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32 **65** interventions administered to control agitated behaviors was measured.

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35 **66 Results:** Among the 181 articles assessed for eligibility, 21 studies were included. Of
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37 **67** the studies suggesting possible benefits, propranolol reduced maximum intensities of
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39 **68** agitation per week and physical restraint use, methylphenidate improved anger
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41 **69** measures following 6 weeks of treatment, valproic acid reduced weekly agitated
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43 **70** behavior scale ratings and olanzapine reduced irritability, aggressiveness and insomnia
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45 **71** between weeks 1 and 3 of treatment. Amantadine showed variable effects and may
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47 **72** increase the risk of agitation in the critically ill. In 3 studies evaluating safety outcomes,
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49 **73** antipsychotics were associated with an increased duration of post-traumatic amnesia in
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51 **74** unadjusted analyses. Small sample sizes, heterogeneity and an unclear risk of bias
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54 **75** were limits.

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3 76 **Conclusions:** Propranolol, methylphenidate, valproic acid and olanzapine may offer
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5 77 some benefit, however, they need to be further studied. Antipsychotics may increase the
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7 78 length of post-traumatic amnesia. More studies on tailored interventions and continuous
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9 79 evaluation of safety and efficacy throughout acute, rehabilitation and outpatient settings
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11 80 are needed.
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17 82 **Systematic review registration:** Prospero CRD42016033140
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19 83 **Keywords:** Traumatic brain injury, agitation, Pharmacological intervention
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23 85 **Strengths and limitations of this study**

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- 27 87 ▪ This systematic review assessed the efficacy and safety of pharmacological agents
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29 88 in the management of agitated behaviors following traumatic brain injury
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31 89 ▪ Randomized controlled trials, quasi-experimental and observational studies were
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33 90 reviewed
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35 91 ▪ The included studies were limited by small sample sizes, variations in the different
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37 92 agitated behaviors and populations studied
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39 93 ▪ The review found insufficient data to recommend the use of any agent for the
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41 94 management of agitated behaviors following TBI
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96 Introduction

97 Traumatic brain injury (TBI) occurs when an external force is applied to the head leading
98 to alterations in brain function including decreased level of consciousness, post-
99 traumatic amnesia, and changes in behavior and cognition that can persist in the long
100 term. In the United States alone, approximately 50,000 people die each year from TBI
101 and more than 5 million live with TBI-related disabilities.^{1, 2} While TBI has a substantial
102 impact on direct healthcare costs, indirect costs from lost productivity also represent a
103 significant economic burden.^{3, 4} Agitated behaviors are a frequent behavioural problem
104 following TBI.^{5, 6} They have been broadly defined as a state of confusion that follows the
105 initial injury and is characterised by disruptive behaviours. A constellation of behaviors
106 has been associated with the term “agitation” in TBI patients, including restlessness,
107 confusion, physical and verbal aggression, impulsivity, perceptual disturbances, and
108 inattention creating a very heterogeneous group of patients to study.⁷ Agitation has been
109 reported in 20-41% of patients during the early stage of recovery in acute care units and
110 up to 70% of patients in rehabilitation units.^{6, 8-13} It can result in harm to patients and
111 caregivers, interfere with treatments, lead to the use of physical and pharmacological
112 restraints, increase hospital length of stay, delay rehabilitation and impede functional
113 independence.^{10-12, 14-16} In TBI outpatients, neurobehavioral symptoms may be different
114 in nature. Aggressive behaviour and irritability, more than physical agitation are
115 generally reported. A variety of agents such as antidepressants, anticonvulsants,
116 stimulants, and antipsychotics have been used for the management of neurobehavioral
117 complications of TBI.^{17, 18} However, preclinical studies have suggested that repeated
118 use of certain agents such as haloperidol, risperidone and diazepam may reduce
119 cognitive and functional recovery.¹⁹⁻²² Thus, it remains unclear which pharmacological

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3 120 agents are the most effective and safest for the management of agitated behaviors in
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5 121 TBI patients. A Cochrane Systematic Review published in 2006 showed a lack of
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7 122 evidence to support any agent.²³ Since then, two additional systematic reviews
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9 123 concluded that the evidence was insufficient and too weak to recommend any specific
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11 124 agent, however they included only French and English studies published before January
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13 125 2016, had incomplete search strategies, and did not include the grey literature.^{24, 25} To
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15 126 advance this field, we updated and broadened the literature search, included all
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17 127 languages and included studies in which an agitated behaviour was not an eligibility
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19 128 criterion, but was measured as an outcome variable . The aim of this systematic review
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21 129 was to assess the efficacy and safety of pharmacological agents in the management of
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23 130 agitated behaviors following TBI compared to placebo or other treatments.
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132 **Methods**

133 The review protocol has been registered in PROSPERO International Prospective
134 Register of Systematic Reviews (CRD42016033140), conducted according to the
135 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)
136 guidelines and published in a peer-reviewed journal.^{26, 27} We included all randomized
137 controlled, quasi-experimental, and observational studies with control groups that had a
138 majority (>50%) of patients with TBI. We excluded case reports, case series, and
139 observational studies without control groups. We included studies of all type of patients
140 who suffered a TBI, including children and adults, in both the early stages of recovery
141 and in rehabilitation. We included 3 mutually exclusive types of studies: 1) those
142 evaluating the use of pharmacological interventions in which an agitated behaviour, not

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3 143 further defined, was one of the eligibility criteria for the study; 2) those in which an
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5 144 agitated behaviour was not an eligibility criterion, but was measured as an outcome
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7 145 variable; and 3) those specifically assessing the safety of pharmacological agents used
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9 146 to treat agitation in TBI patients. In this systematic review, we considered agitation,
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11 147 aggressiveness, assaultive behaviour, irritability and confusion as part of agitated
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13 148 behaviours. All medications considered in this review were pre-specified and consisted
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15 149 in the following: beta-adrenergic blockers, typical and atypical antipsychotics,
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17 150 anticonvulsants, dopamine agonists, psychostimulants, antidepressants, alpha-2-
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19 151 adrenergic agonists, hypnotics and anxiolytics. Studies were included whether the
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21 152 investigators compared a medication to placebo, a medication to another medication, or
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23 153 various combinations of different medications.
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29 154 The primary outcome was a reduction in severity of the agitated behavior as measured
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31 155 in each study. If feasible, we reported resolution of agitated behaviours as well as
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33 156 changes in duration and type of symptoms (confusion, aggressiveness, inattention,
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35 157 hallucinations, disorientation, and inappropriate mood or speech). Secondary outcomes
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37 158 include lengths of stay, (ICU length of stay, hospital LOS for the early rehabilitation
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39 159 phase), adverse events (extrapyramidal effects, QTc prolongation, cardiac arrhythmias,
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41 160 hypotension, seizures, behavioural effects), use of physical restraints in ICU, cognitive
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43 161 and functional outcomes at hospital discharge and at one year post-TBI.
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49 162 *Search strategy*

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52 163 A search strategy was devised with the help of Health Sciences librarian (supplementary
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54 164 file) and using the Peer Review for Electronic Search Strategies (PRESS) checklist was
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3 165 conducted in the following databases: PubMed, OvidMEDLINE®,OvidMEDLINE®In-
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5 166 Process&OtherNon-Indexed Citations, Embase, CINAHL, PsycINFO, Cochrane Library,
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7 167 Google Scholar, Directory of Open Access Journals, LILACS, Web of Science and
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10 168 Prospero (<http://www.crd.york.ac.uk/PROSPERO/>) up to December 10th 2018.²⁸ A grey
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12 169 literature search was also performed using the resources suggested in CADTH's *Grey*
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14 170 *Matters* (<http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters>). As
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17 171 described in our published protocol, we searched abstracts from annual scientific
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19 172 meetings from relevant groups in the last 5 years.²⁶ Finally, references of identified
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21 173 studies as well as other types of articles (reviews, book chapters) were screened.
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25 26 175 *Data collection and analysis*

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28 176 Two reviewers (DW, AJF) independently screened titles and abstracts for eligible
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30 177 publications. The same reviewers then assessed the complete report of each retained
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32 178 citations for eligibility. Disagreements were resolved by consensus and discussion with a
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34 179 third reviewer was not required.
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39 40 181 *Data extraction and management*

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43 182 Data from all included studies were extracted by two independent reviewers (AJF and
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45 183 DW) and in duplicate using a pre-tested data extraction form. The following variables
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47 184 were recorded for each study: study title, name of the first author, year of publication,
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49 185 country of origin, language of publication, publication type (journal article, conference
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51 186 proceeding, abstract, thesis), clinical setting (intensive care unit, hospital ward,
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53 187 rehabilitation unit, outpatient), study design (randomized controlled, blinded or open,
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3 188 non-randomized controlled, prospective or retrospective, crossover), population
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5 189 (paediatric, adult), patient characteristics (age, gender, isolated TBI or multiple trauma
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7 190 including TBI, severity of TBI according to Glasgow Coma Scale, days from TBI at
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9 191 inclusion, inclusion and exclusion criteria), characteristics of the intervention and control
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11 192 treatment (type of pharmacological agent, dose, frequency and duration of the therapy),
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13 193 agitation measurement tool, description of the specific agitated behaviours (definition,
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15 194 frequency, duration), and clinical outcomes (length of stay), adverse events, use of
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17 195 physical restraints during ICU stay, duration of post traumatic amnesia, cognitive
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19 196 function at ICU discharge and at one year, and functional outcome at ICU discharge and
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21 197 at one year. We contacted the corresponding author for clarifications when necessary.
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30 199 *Assessment of risk of bias*
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32 200 Two reviewers (DW, AJF) independently evaluated each included study with the
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34 201 Cochrane Collaboration tool for randomized controlled trials and the Ottawa-Newcastle
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36 202 tool for observational studies, respectively.^{29, 30}. In case of disagreement concerning the
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38 203 risk of bias, a third reviewer (FB) was consulted to resolve the issue.
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41 204 *Patient and public involvement*

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43 205 Patients and or public were not involved in the conduct of this systematic review.
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46 206 **Results**

47 207 *Study selection*

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49 209 The database search (up to December 10th 2018) retrieved 11 170 unique citations of
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51 211 which 10 989 were excluded based on title and abstracts (Figure 1). We assessed 181
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53 212 full-text articles for eligibility and 21 studies were included. A total of eight studies
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3 214 evaluated the use of pharmacological interventions in which an agitated behaviour was
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5 215 the presenting symptom or one of the presenting symptoms.³¹⁻³⁸ In nine other studies,
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7 216 agitated behaviour was not the presenting symptom, but was measured as an outcome
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10 217 variable.³⁹⁻⁴⁷ Finally, four studies specifically assessed the safety of pharmacological
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12 218 agents used for agitated behaviours in TBI.⁴⁸⁻⁵¹
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15 219 *Agitated behaviors as the presenting symptom*
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18 221 The eight included studies evaluated various aspects ranging from aggressiveness to
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20 222 irritability and confusion (Table 1).³¹⁻³⁸. The behaviors were evaluated using the following
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22 223 tools (Table 2): agitated behavior scale (ABS), confusion assessment protocol, State-
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24 224 Trait Anger scale, the overt aggression scale, Richmond Agitation Sedation Scale
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26 225 (RASS) and neuropsychiatric inventory irritability and aggression domains (NPI-I and
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228 **Table 1 – Study characteristics**

Study/Year (N)	Publication/ Country	Study design	Study focus/Population	Interventional arm/Population	Comparative arm/Population	Location at randomization	Timing from TBI at randomization	TBI description
1. Agitated behaviour as the presenting symptom								
Brooke ³⁰ 1992 N=21	Published USA	RCT parallel	Agitation Mean age 31 87 men and 13 women	Propranolol 60- 420mg daily	Placebo	Level 1 trauma and rehabilitation center	N/A	Severe blunt TBI
Mooney ³¹ 1993 N=38	Published USA	Randomize d Pre-post	Anger Mean age 29 ± 10 Male gender 100%	Methylphenidate 30mg/day	Placebo	Outpatient	6 months or more (mean 27 +/- 21 months)	Severe blunt TBI
Yablon 2010 ³² N=79	Abstract USA	RCT parallel	Confusion Age and gender not reported	Amantadine 100mg bid X 14 days	Placebo	Inpatient brain injury unit of a rehabilitation hospital	≤ 6 months	TBI not further defined
Hammond ³⁴ 2014 N=76	Published USA	RCT parallel	Irritability and aggression	Amantadine 100mg bid Mean age 40 +/-	Placebo 38 +/-12 Male gender	Outpatient	≥ 6 months following a TBI	Blunt TBI

				13 Male gender 74.4%	80.5%			
Beresford ³⁰ 2015 N=50	Abstract USA	RCT parallel	Agitation Mean age 47 ± 14 46 men and 4 women	Valproic acid for level 50-100 mcg/ml	Placebo	Outpatient	> 1 year following TBI	Mild and moderate TBI
Hammond ³³ 2015 N=168	Published USA	RCT parallel	Irritability and aggression	Amantadine 100mg bid Mean age 40 ± 13 Male gender 80.5%	Placebo Mean age 38 ± 12 Male gender 74.4%	Outpatient	≥ 6 months following a TBI	Blunt TBI
Maturana ³⁷ Waidele 2009 N=31	Published Chile	Prospective double- blind	Restlessness, Irritability, Aggression, Insomnia	Olanzapine (dose not specified)	Placebo	Outpatient	N/A	TBI not further defined

			Age and gender not reported					
Gramish ³⁵ 2017 N=139	Published USA	Retrospective observational	Agitation	Amantadine 100mg bid 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 behavior is not the presenting symptom								
Study/Year (N)	Publication Country	Study design	Study focus	Interventional arm	Comparative arm	Location at randomization	Timing from TBI at randomization	TBI description
Schneider ⁴¹ 1999 N=10	Published USA	RCT parallel	Cognitive function and behavior Mean age 31 7 men and 3 women	Amantadine 50mg bid increased to 150mg bid	Placebo	Outpatient	N/A	Moderate and severe TBI
Meythaler ⁴⁰ 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 ⁴²	Published	RCT	Neurological	Amantadine	Placebo	Emergency	Between 4 days	Severe blunt

2002 N=35	USA	Crossover	recovery Mean age 31 26 men and 9 women			department	and 6 weeks following TBI	TBI
Banos ³⁸ 2010 N=99	Published USA	RCT parallel	Cognitive function and behavior	Sertraline Mean age: 35 ± 17 Male gender: 79%	Placebo Mean age 35 ± 16 Male gender: 66%	Level 1 trauma center inpatients	< 8 weeks of TBI	Moderate and severe TBI
Giacino ³⁹ 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 to 16 weeks following TBI	Vegetative or minimally conscious TBI
Tramontana ⁴³ 2014 N=22 but 13 completed the study	Published USA	RCT Crossover	Attention Mean age: 29±9 Male gender: 69%	Lisdexampheta- mine	Placebo	Outpatient	6-34 months (mean 15.6 +/- 10 months) since TBI	Moderate and severe TBI

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Johansson ⁴⁵ 2014 N=24	Published Sweden	RCT Crossover	Mental fatigue and cognition Mean age 39±11 Male gender: 50%	Methylphenidate 5mg and 20mg tid	Placebo	Outpatient	> 12 months following TBI	Mild or moderate TBI
Fann ⁴⁴ 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 center	< 1 year of TBI	Moderate and severe TBI
Hart ⁴⁶ 2017 N=32	Published USA	RCT parallel	Cognitive function	Dextroamphetami ne 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 1985 ⁴⁹ N=26	Published USA	Retrospecti ve observation al	Rehabilitation outcomes	Haloperidol Median age: 34 Gender not reported	No haloperidol Median age: 22 Gender not reported	Trauma and rehabilitation center	From admission	Severe closed head injury

1 2 3 4 5 6 7 8 9 10 11 12	Mysiw ⁴⁸ 2006 N=182	Published USA	Retrospecti ve cohort	Cognitive and motor recovery Mean age: 36 Male gender: 74%	Narcotics, benzodiazepines and neuroleptics	No CNS active medications	Level 1 trauma center and rehabilitation center	From admission	TBI
13 14 15 16 17 18 19 20 21	Kooda ⁵⁰ 2015 N=195	Abstract USA	Retrospecti ve observation al	Duration of post- traumatic amnesia Age and gender not reported	Antipsychotics	No antipsychotic	Level 1 trauma center and rehabilitation center	From admission	TBI
22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	Anderson ⁴⁷ 2016 N=101	Published USA	Retrospecti ve cohort	Seizures, neuroleptic malignant syndrome, QTc prolongation, extrapyramidal symptoms, hematological disturbances	Haloperidol Median age 32 Male gender: 87%	No haloperidol Median age 47 Male gender: 61%	Inpatients	From admission	Moderate and severe TBI

230 **Table 2 – Tools used to measure agitated behaviors**

Tools	Description
Agitated behavior scale ⁵³	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.
Brief Anger and Aggression Scale ⁵⁴	A six-item measure developed for the rapid screening and identification of anger and aggression levels.
Confusion assessment protocol ⁵⁵	Combination of orientation, cognition and other clinical measures of early confusion following traumatic brain injury.
Functional independence measure (FIM) ⁵⁶	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) ⁵⁷	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) ⁵⁸	The KAS is an observer rating scale used to assess the social adjustment of people with traumatic brain injury.
Neuropsychiatric inventory irritability	The NPI is a 40-item scale evaluating 12 behavioral domains including irritability and

<p>(NPI-I) and aggression domains (NPI-A)⁵²</p>	<p>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.</p>
<p>Neurobehavioral Function Inventory (NFI)⁵⁹</p>	<p>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.</p>
<p>Neurobehavioral rating scale (NRS)⁶⁰</p>	<p>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.</p>
<p>Overt aggression scale (OAS)⁶¹</p>	<p>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.</p>

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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 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.

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3 232 Of the identified studies, two were conference abstracts that remained unpublished.^{33, 37}
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5 233 The studies evaluated propranolol³¹, amantadine³³⁻³⁵, methylphenidate³², valproic acid³⁷
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7 234 and olanzapine³⁸ in comparison to placebo. Five used a randomized controlled parallel
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9 235 design^{31, 33-35, 37}, one used a randomized pretest posttest control group design³², one
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11 236 was a prospective double blind observational study³⁸ and, one was a retrospective
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13 237 observational study.³⁶ All the studies exclusively enrolled adult (16 years or older) TBI
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15 238 patients and three studies excluded older patients (greater than 65 or 75 years)^{34, 35, 37}.
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17 239 The studies mostly included patients in rehabilitation (n=2)^{31, 33} and outpatient (n=5)
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19 240 settings.^{32, 34, 35, 37, 38} Only one study evaluated patients in an intensive care unit (ICU)
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21 241 setting.³⁶ All the studies exclusively studied TBI patients.³¹⁻³⁸ Three studies identified in
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23 242 an earlier systematic review were excluded (Figure 1) because TBI patients represented
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25 243 less than 50% of the sample.^{23, 62-64}
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33 245 In the eight studies, one randomized trial evaluated the use of propranolol for the
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35 246 treatment of agitation in severe blunt TBI patients (Table 3).³¹ It reported a reduction in
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37 247 the intensity of agitation episodes and in the use of physical restraints but failed to show
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39 248 a reduction in the frequency of agitation episodes.³¹ Amantadine was evaluated for the
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41 249 management of confusion in a randomized trial, irritability in two randomized trials, and
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43 250 agitation in a retrospective observational study.³³⁻³⁶ The studies reported inconsistent
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45 251 results (Table 3). In one unpublished study in the setting of rehabilitation within 90 days
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47 252 of TBI (n=79), amantadine had no effect on confusion.³³ In a pilot study of outpatients
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49 253 who suffered a TBI more than six months ago, amantadine showed significant
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51 254 reductions in irritability and aggression using the Neuropsychiatric Inventory scale
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53 255 (NPI).³⁵ In a follow-up study of 168 outpatients who had suffered a TBI more than 6
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3 256 months ago, no difference in the incidence of irritability at 28 and 60 days using the NPI-
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7 258 self-rating at day-60 indicated improvement in irritability ($p<0.04$) but the difference
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10 259 became non-significant when adjusted for multiple comparisons. The Global
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12 260 improvement subscale of the Clinical Global Impressions (CGI), which evaluates general
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14 261 emotional and behavioral function, improved more in the amantadine group than in the
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16 262 placebo group at day 60 ($p=0.0354$). A sub-analysis of patients with anger and
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18 263 aggression (118 of the 168 patients) in the same study was also carried out and
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20 264 reported a statistically significant reduction in participant's self-rated aggression at 60
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22 265 days.⁶⁵ Finally, in a retrospective observational study ($n=139$), patients exposed to
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24 266 amantadine in the ICU reported more agitation episodes defined as a Richmond
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26 267 Agitation Sedation Score of +2 or higher (38% vs 14%) in an unadjusted analysis.³⁶ The
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28 268 use of amantadine was also associated with an increased median ICU length of stay
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30 269 (4.5 vs 3 days; $p=0.01$) when compared to non-exposed patients.
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38 271 The efficacy of olanzapine in the management of restlessness, irritability, aggression
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40 272 and insomnia in outpatients with a history of TBI was evaluated in a prospective double
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42 273 blind study.³⁸ While no reduction in restlessness was reported, the authors did report a
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44 274 significant reduction in irritability and insomnia between weeks 1 and 3 in olanzapine-
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46 275 treated patients. Unfortunately, no statistical comparison with the placebo group was
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48 276 provided. The efficacy of valproic acid in reducing agitated behaviors among mild and
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50 277 moderate TBI outpatients was evaluated in an unpublished randomized controlled study
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52 278 ($n=50$).³⁷ Patients were included more than one year following brain injury and suffered
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54 279 from both affective lability and alcohol dependence. A significant reduction in the
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280 **Table 3 – Efficacy and safety outcomes**

Study/Year/n	Intervention	Agitated behavior measures	Efficacy outcomes	Safety outcomes
1. Agitated behavior as the presenting symptom				
<i>Randomized controlled studies</i>				
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
Mooney 1993 ³¹ 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 effect on side effects
Yablon 2010 ³² N=79	Amantadine	Confusion assessment protocol	No significant differences in the number of symptoms of posttraumatic confusional state as measured by	No patients withdrawn because of safety criteria

		(CAP)	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)	
Hammond 2014 ³⁴ 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 3 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 = .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 = .046).	No difference in adverse events (tremors, appetite, gastrointestinal, aches and pain, sexual problems, disorientation, seizures)
Beresford 2015 ³⁰ 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

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20	Hammond 2015 ³³ 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 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.
21	<i>Observational studies</i>				
22 23 24 25 26 27 28 29 30 31 32 33 34 35	Maturana Waidele ³⁷ 2009 N=31	Olanzapine	Restlessness, irritability, aggressiveness and insomnia. No tool mentioned.	Reduction in irritability ($p < 0.001$), aggressiveness ($p = 0.008$) and insomnia ($p = .0011$) between weeks 1 and 3 in the patients treated with olanzapine	No safety outcomes reported
36 37 38 39 40 41 42 43 44 45 46 47	Gramish 2017 ³⁵ N=139	Amantadine	RASS score of +2 or higher	Increase in agitation in patients exposed to amantadine (38%) compared to non-exposed (14%); $p = 0.018$. Increase in median ICU length of stay (4.5	No safety outcomes reported

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			vs 3 days; p=0.01). Median hospital length of stay was non-significantly increased (14 days vs 10 days; p=0.051)	
2. Agitated behavior is not the presenting symptom				
<i>Randomized controlled studies</i>				
Schneider 1999 ⁴¹ N=10	Amantadine	Neurobehavioral rating scale	No significant difference in behavior scores between amantadine and placebo groups	No safety outcomes reported
Meythaler 2001 ⁴⁰ N=9	Sertraline	Agitated Behavior Scale	No difference in decline of ABS over treatment period	No safety outcomes reported
Meythaler 2002 ⁴² 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> .05, Mann–Whitney U test)	No detrimental effects in hematology or biochemistry laboratories and no seizures.
Banos 2010 ³⁸ 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 2012 ³⁹ N=184	Amantadine	Agitation and restlessness not	A total of 12/87 (14%) patients and 11/97 (11%) patients exposed to amantadine and placebo	No differences in adverse events (seizure, nausea, vomiting,

		further defined	developed agitation (p=NS) over the 4-week period. Restlessness was reported in 8% and 9% of patients exposed to amantadine and placebo, respectively.	constipation, diarrhea, elevated liver function tests, insomnia, rash, congestive heart failure, involuntary muscle contractions)
Tramontana 2014 N=22 but 13 patients completed the study	Lisdexamphetamine	Agitation and restlessness not further defined	No difference in agitation (no cases in each group) or irritability (1/13 case) during placebo) between the Lisdexamphetamine and placebo groups.	Reduced appetite and weight loss of more than 5 lbs more frequent with lisdexamphetamine (7 vs 1 case) p=NS
Johansson 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 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.
Hart 2017	Dextroamphetamine	Agitated Behavior	Increase in agitation with dextroamphetamine over	No significant difference in heart

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N=32	mine	Scale	time compared to placebo (p<0.05)	rate or blood pressure.
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3 282 agitated behavior scores (ABS) evaluated by family members at eight weeks (12.9 vs
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5 283 15.5 points; $p=0.03$) was observed. Finally, a crossover study assessed
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7 284 methylphenidate for anger ($n=38$) in TBI rehabilitation center outpatients (six months or
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10 285 more after TBI). After six weeks, methylphenidate significantly reduced the anger score
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12 286 using the State Trait Anger Scale (STAS).³²

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17 288 Of the eight studies, safety outcomes were reported in four studies.³²⁻³⁵ When reported,
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19 289 the agents studied were well tolerated with no significant differences observed.
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21 290 Functional and cognitive outcomes were not reported in any of these studies.
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26 292 *Agitated behavior as a secondary measure*
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29 294 We identified nine studies evaluating agitated behaviors as a secondary measure, which
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31 295 were focused on cognitive function and neurological recovery (Table 1).³⁹⁻⁴⁷ In these
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33 296 studies, sertraline^{39, 41, 45}, amantadine^{40, 42, 43}, amphetamines^{44, 47}, and methylphenidate⁴⁶
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35 297 were evaluated versus placebo and reported agitated behaviors as an outcome. Of
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37 298 these studies, 6 used a randomized crossover design and 3 used a randomized
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39 299 controlled parallel design.
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46 301 Sertraline was evaluated in three studies to enhance recovery and increase arousal,
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48 302 ameliorate cognitive and neurobehavioral functioning and to treat major depression
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50 303 (Table 3).^{39, 41, 45} In all these three studies, sertraline had no effect on the incidence of
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52 304 agitation, anger or aggression. In one study, more patients developed
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54 305 agitation/restlessness in the sertraline group (17%) compared to the placebo group (7%)
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3 306 but this difference was not statistically significant ($p=0.42$).⁴⁵ Amantadine was also
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5 307 evaluated in three studies for cognitive and functional recovery.^{40, 42, 43} All three studies
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7 308 found no differences in agitated behaviors compared to placebo. Methylphenidate was
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10 309 evaluated for secondary mental fatigue in mild TBI patients more than six months after
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12 310 injury.⁴⁶ However, it had no effect on irritability and aggression. Lisdexamphetamine and
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14 311 dextroamphetamine were each evaluated for attention deficits in TBI patients and no
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16 312 effect on agitated behaviors was noted with lisdexamphetamine whereas
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18 313 dextroamphetamine increased agitation over time ($p<0.05$).^{44, 47} Among these 9 studies,
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20 314 those evaluating sertraline and amantadine reported no significant differences in
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22 315 adverse events.^{39-43, 45}
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28 317 *Studies evaluating safety outcomes*

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31 318 Finally, the safety of pharmacological agents used for agitated behaviors in TBI patients
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33 319 was evaluated in four retrospective observational studies (Table 4).⁴⁸⁻⁵¹ Two of these
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35 320 studies focused on the effect of haloperidol and antipsychotic use on post-traumatic
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37 321 amnesia (PTA) duration, whereas a third evaluated the effects of antipsychotics,
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39 322 benzodiazepines and narcotics on PTA duration, and Functional independence measure
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41 323 (FIM) cognitive and motor scores.⁴⁹⁻⁵¹ In these three studies, haloperidol and other
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43 324 antipsychotics were associated with an increase in PTA duration. Antipsychotics,
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45 325 benzodiazepines and narcotics had no effects on FIM scores.⁴⁹ Finally a fourth study
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47 326 focused on the general safety (seizures, neuroleptic malignant syndrome, QTc
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49 327 prolongation, extrapyramidal symptoms, hematologic disturbances) of haloperidol in ICU
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51 328 TBI patients.⁴⁸ Patients exposed to haloperidol ($n=45$) had no significant increase in
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53 329 adverse events compared to non-exposed patients ($n=56$). Of note, none of the studies
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3 330 adjusted for severity of TBI and other potential confounders.
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8 332 *Risk of bias assessment*

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10 333 Risk of bias scores are reported in Table 5. The analysis of risk of bias of randomized

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12 334 controlled trials with the Cochrane Collaboration's Tool revealed that many studies did

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14 335 not provide sufficient information on sequence, generation and allocation concealment.

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16 336 A majority of studies had other threats to validity including limited sample sizes, no

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18 337 description of patient demographics and loss to follow-up. For six studies evaluated with

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20 338 the Newcastle-Ottawa tool, the number of stars awarded ranged from four to five. Most

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22 339 studies were awarded a score of four stars, indicating a high risk of bias. As none of the

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24 340 six studies were adjusted for potential confounding, all received 0 stars for comparability.

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349 **Table 4 - Studies assessing the safety of pharmacological agents used for agitated behaviors in TBI**

Study/Year/n	Drugs studied	Results
Rao 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 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).
Kooda 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.
Anderson 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 hematologic 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)

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351 **Table 5 – Risk of bias assessment**

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1. Randomized controlled trials
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	Cochrane Collaboration Tool Risk of bias items						
Study (year)	Sequence generation	Allocation	Blinding of participants and personnel	Blinding of outcome assessment	Outcome data	Selective reporting	Other threats to validity
Brooke 1992	U	U	L	L	L	L	H
Mooney 1993	U	U	L	H	L	U	H
Schneider 1999	U	U	U	U	H	L	H
Meythaler 2001	U	U	L	L	U	U	H
Meythaler 2002	U	U	U	U	L	H	H
Banos 2010	U	U	L	L	L	L	H
Yablon 2010	U	U	L	L	L	U	H
Giacino 2012	U	L	L	L	L	L	L

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Hammond 2014	L	L	L	L	U	L	L
Tramontana 2014	H	H	L	L	H	L	H
Johansson 2014	U	H	H	H	H	L	H
Beresford 2015	U	U	L	L	H	L	H
Hammond 2015	L	L	L	L	U	L	L
Fann 2017	L	L	L	L	L	L	H
Hart 2017	U	U	L	L	L	L	L

2. Observational studies

Study (year)	Newcastle-Ottawa Quality Assessment Scale					
	Number of stars awarded					
	Selection ^a		Comparability ^b		Outcome ^c	
Rao 1985	**				**	

Maturana Waidele 2009	**		**
Mysiw 2006	**		***
Kooda 2015	**		**
Anderson 2016	**		**
Gramish 2017	***		*

353 For Cochrane Collaboration's Tool:

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

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356 For Newcastle-Ottawa Quality Assessment Scale :

357 ^a Maximum 4 stars

358 ^b Maximum 2 stars

359 ^c Maximum 3 stars.

360 N/A : not applicable

361 Discussion

362 In this systematic review, we used an exhaustive search strategy and included studies
363 directly or indirectly evaluating pharmacological agents for the management of TBI-
364 associated agitated behaviors as well as studies assessing the safety of
365 pharmacological agents used for these agitated behaviors. Despite the prevalence and
366 importance of this problem, we found a limited number of studies evaluating
367 pharmacological interventions for the management of agitated behaviors. Propranolol,
368 methylphenidate, valproic acid and olanzapine were the only agents suggesting a
369 potential benefit in reducing agitation, anger or irritability.^{31, 32, 37, 38} However, the studies
370 evaluating these agents had limited sample sizes, heterogeneous patient populations
371 and an unclear risk of bias. Amantadine showed mixed results whereas sertraline,
372 lysdexamphetamine and dextroamphetamine showed no benefits. In comparison to the
373 two most recent systematic reviews, we used a more rigorous and broader search
374 strategy. As such, we restricted our search to randomized controlled, quasi-
375 experimental, and observational studies with control groups that had a majority (>50%)
376 of patients with TBI, thus excluding case reports, case series and uncontrolled
377 observational studies. Our updated and broadened literature search enabled the
378 identification of two additional studies from the grey literature, three recently published
379 studies and one non-English study.^{24, 25, 33, 36, 37, 45, 47} Our search strategy also included
380 studies evaluating agitated behaviors as a secondary measure and identified 9 more
381 studies, thus adding to previous systematic reviews. Furthermore, we included studies
382 where the safety of pharmacological agents for the management of agitated behaviors
383 was assessed and identified four such studies.

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3 385 The use of beta-blockers in patients with organic brain disease and assaultive behaviors
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5 386 or impulsivity has been previously studied in three crossover-randomized trials with
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7 387 some efficacy but TBI represented less than 50% of the total patient population.⁶²⁻⁶⁴ In
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9 388 the study presented in this review, propranolol reduced the intensity of agitation but not
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11 389 the frequency.³¹ One important finding was a reduction in the use of physical restraints.
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13 390 Unfortunately, safety measures such as hypotension and bradycardia were not reported.
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15 391 The Canadian ABIKUS guidelines have recommended beta-blockers for the treatment of
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17 392 aggression following TBI.⁶⁶
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19 393 Although numerous observational studies have reported a reduction in agitation with the
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21 394 use of antipsychotic agents, we found no controlled studies evaluating the efficacy of
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23 395 antipsychotics other than olanzapine.⁶⁷⁻⁶⁹ In a previous systematic review that included
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25 396 case reports and case series evaluating antipsychotics, Lanthier et al. identified 7
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27 397 articles that included a total of 52 patients.²⁴ The lack of a control group excluded these
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29 398 studies from our review. The only study we included that used olanzapine didn't report a
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31 399 reduction in restlessness but did suggest a reduction in irritability.³⁸ Its interpretation is
32
33 400 greatly limited given the poor description of methods and a lack of statistical comparison
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35 401 with the placebo group. The four studies assessing safety all evaluated antipsychotic
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37 402 agents and suggested a potential risk of prolonged PTA in unadjusted analyses.⁴⁸⁻⁵¹
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39 403 None of the studies controlled for potential confounders such as severity of TBI.
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41 404 Although pre-clinical studies have suggested a reduction in cognitive and motor recovery
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43 405 with repeated administration of haloperidol and risperidone, the one study evaluating
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45 406 cognitive and motor scores reported no significant association with antipsychotic use.¹⁹⁻
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47 407 ^{21, 49, 70} In light of these results, both the International Cognitive (INCOG), the Canadian
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49 408 ABIKUS guidelines and the French Society of Physical and Rehabilitation Medicine
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3 409 (SOFMER) guidelines have advised against the use of antipsychotics in TBI patients
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5 410 with agitated behaviors.^{24, 66, 71} Paradoxically, observational studies have suggested
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7 411 antipsychotics are frequently used for the management of agitated behaviors.^{14, 72-74}
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12 413 Anticonvulsants are clinically used as mood stabilizers in bipolar affective disorder and
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14 414 have also been used in TBI-associated agitation.^{75, 76} Case series have reported a
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16 415 reduction in agitation and aggressive behaviors with the use of valproic acid and
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18 416 carbamazepine but were uncontrolled.⁷⁷⁻⁸¹ We identified one unpublished study of TBI
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20 417 patients with affective lability and alcohol dependence where valproic acid showed
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22 418 effectiveness in reducing weekly ABS rated by spouse or significant other's.
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24 419 Unfortunately, the abstract provided no information on the onset of effect or adverse
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26 420 events associated with its use.
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33 422 Amantadine increases dopaminergic neurotransmission and has been shown to
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35 423 increase the rate of neurological recovery in severe TBI.⁴⁰ In the 4 studies that evaluated
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37 424 amantadine for irritability, agitation or aggressiveness, results were variable.³³⁻³⁶
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39 425 Although one study suggested a reduction in irritability in outpatients, a larger study by
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41 426 the same group failed to confirm these results.^{34, 35} Interestingly, a recent observational
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43 427 study of patients exposed to amantadine in the ICU reported an increased risk of
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45 428 agitation.³⁶ Although these effects were not observed in a multicenter trial that started
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47 429 amantadine at least four weeks after TBI, the early use of amantadine in the ICU may
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49 430 explain these findings.^{36, 40} However, these results were uncontrolled and confounding
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51 431 may also explain these differences. In addition, the use of amantadine may have
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53 432 increased arousal and the agitation measured may be part of the natural recovery. In
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3 433 studies in which agitation was not the presenting symptom, no significant differences in
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5 434 behavior scores between amantadine and control groups were reported.^{40, 42, 43}
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10 436 In this review, we found no comparative studies assessing the efficacy of tricyclic
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12 437 antidepressants, dexmedetomidine or benzodiazepines. We also found no studies in
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14 438 children. A search of TBI-associated agitation studies in clinical trial registries revealed
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16 439 ongoing studies with the combination of dextromethorphan and quinidine
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18 440 (ClinicalTrials.gov: NCT03095066) as well as propranolol and clonidine
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20 441 (ClinicalTrials.gov: NCT01322048).⁸² Finally, in a recent observational study on the
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22 442 predictors of agitation in TBI rehabilitation, sodium channel antagonist anticonvulsants,
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24 443 second-generation antipsychotics, and gamma-aminobutyric acid anxiolytics were
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26 444 associated with more severe agitation.¹⁴ Although indication bias and residual
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28 445 confounding are probable, these results do suggest an association between suppression
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30 446 of cognition and more agitation.
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56 447
57 448 Strengths of this study include an exhaustive search of the literature in the adult and
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59 449 pediatric populations, including grey literature and no language limitation. A risk of bias
60 450 assessment was performed for each included study. Limits of this study include the
451 presence of significant heterogeneity, variations in the different agitated behaviors
452 (agitation, irritability, and aggression) and populations (acute TBI, rehabilitation,
453 outpatient) evaluated, preventing the authors from proceeding to a meta-analysis. In
454 addition, very little studies reported length of stay and functional outcomes.

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456 **Conclusion**

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3 457 In conclusion, there are insufficient data to recommend the use of any medications for
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5 458 the management of agitation following TBI. Propranolol, methylphenidate, valproic acid
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7 459 and olanzapine may offer some benefit, however, they need to be further studied. The
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9 460 use of amantadine in the acutely ill may increase the risk of agitation whereas
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11 461 antipsychotics may prolong post-traumatic amnesia. More studies on tailored
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13 462 interventions and continuous evaluation throughout the acute, rehabilitation and
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15 463 outpatient settings are needed to assess the efficacy and safety of pharmacological
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17 464 agents for the management of agitated behaviours in both the adult and pediatric TBI
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19 465 populations. In addition, there is a need to better define and standardize the assessment
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21 466 of agitated behaviors. Newer agents such as dexmedetomidine should also be
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23 467 evaluated.
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30 469 **Acknowledgements**

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32
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34
35 471 expertise and help with the literature search strategies.
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37 472 **Figure 1: Prisma Flow Diagram**

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33 693

694 **Contribution statement**

695 DRW, AJF, LB, MMP, EC, FL, MJP, JFG, SM and FB participated in the design, writing
696 of the the review protocol and contributed to the final manuscript. DW wrote the search
697 strategy and undertook the literature search. DW, AJF and FB conducted the title and
698 abstract screening and full article screening for final study inclusion. DRW and AJF
699 conducted data collection and cleaning, LB, MMP and EC advised on methods and
700 interpretation of findings.

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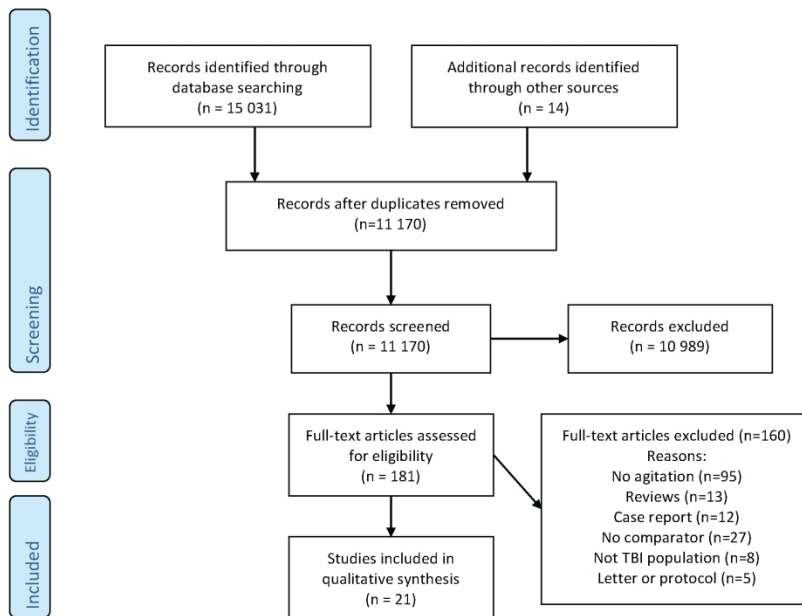
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1 **PRISMA Flow Diagram**

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Supplementary file: search strategy in MedLine

Concept	Description of concept	Research terms
A	Agitation/delirium	Confusion/ OR Delirium/ OR Psychomotor agitation/ OR attention/ OR hallucinations/ or hallucinat\$.mp OR delirium.mp OR confusion.mp OR Disorientation.mp OR agitation.mp OR confusional.mp OR Restlessness.mp OR Psychomotor Hyperactivity.mp OR Psychomotor Excite\$.mp OR Akathisia.mp OR attention.mp
B	Traumatic brain injury	Craniocerebral Trauma/ OR Craniocerebral Traumas.mp OR Craniocerebral Trauma.mp OR Craniocerebral injury.mp OR Craniocerebral injuries.mp OR Head Injury.mp OR Head Injuries.mp OR head trauma.mp OR head traumas.mp OR Parietal Region Trauma.mp OR Parietal Region Traumas.mp OR Skull Injury.mp OR Skull Injuries.mp OR Head Injury.mp OR Head Injuries.mp OR Occipital Region Trauma.mp OR Occipital Region Traumas.mp OR Occipital Trauma.mp OR Occipital Traumas.mp OR Temporal Region Trauma.mp OR Temporal Region Traumas.mp OR Frontal Region Trauma.mp OR Frontal Region Traumas.mp OR Forehead Trauma.mp OR Forehead Traumas.mp OR Brain Concussion.mp OR Brain Concussions.mp OR Diffuse Axonal Injury.mp OR Diffuse Axonal Injuries.mp OR Traumatic Intracranial Hemorrhage.mp OR Traumatic Intracranial Hemorrhages.mp OR Traumatic Intracranial Hematoma.mp OR Traumatic Intracranial Hematomas.mp OR Glasgow Coma Scale/ OR Glasgow Coma scale.mp OR Brain Damage, Chronic/ OR Brain Damage.mp OR Brain Damages.mp Epilepsy, Post-Traumatic/ OR Post-Traumatic Epilepsy/ OR Post-Traumatic Epilepsies/ OR Posttraumatic Epilepsy/ OR Posttraumatic Epilepsies.mp OR Post-Traumatic Seizure Disorder.mp OR Post-Traumatic Seizure Disorders.mp OR Posttraumatic Seizure Disorder.mp OR Posttraumatic Seizure Disorders.mp OR Traumatic Epilepsy.mp OR Traumatic Epilepsies.mp OR Traumatic Seizure Disorder.mp OR Traumatic Seizure Disorders.mp OR Late Post-Traumatic Seizure.mp OR Late Post-Traumatic Seizures.mp OR Late Posttraumatic Seizure.mp OR Late Posttraumatic Seizures.mp OR Impact Seizure.mp OR Impact Seizures.mp OR Convulsive Convulsion.mp OR Convulsive Convulsions.mp OR Early Post-Traumatic Seizure.mp OR Early Post-Traumatic Seizures.mp OR Early Posttraumatic Seizure.mp OR Early Posttraumatic Seizures.mp
C	Pharmacological treatment	Antipsychotic Agents/ OR Tranquilizing Agents/ OR Anti-Anxiety Agents/ OR Antimanic Agents/ acepromazine OR amoxapine OR asenapine OR azaperone OR benperidol OR butaclamol OR chlorpromazine OR chlorprothixene OR clopenthixol OR clozapine OR droperidol OR flupenthixol OR fluphenazine OR fluspirilene OR haloperidol OR levomepromazine OR loxapine OR loxapine succinate OR mesoridazine OR methiothepin OR methotrimeprazine OR molindone OR olanzapine OR paliperidone OR penfluridol OR perazine OR perphenazine OR pimozide OR prochlorperazine OR promazine OR quetiapine OR remoxipride OR reserpine OR risperidone OR ritanserine OR spiperone OR sulpiride OR thioridazine OR thiothixene OR tiapride hydrochloride OR trifluoperazine OR trifluoperidol OR trifluopromazine OR ziprasidone OR Lithium

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Adrenergic alpha-2 Receptor Agonists/ OR OR "Dexmedetomidine/
Klofenil OR Clofenil OR Chlophazolin OR Clonidine OR "Clonidine
Dihydrochloride" OR "Clonidine Hydrochloride" OR "Clonidine
Monohydrochloride" OR "Clonidine Monohydrobromide" OR Guanfacine OR
Lofexidine OR Gemiton OR Hemiton OR Isoglaucan OR Klofelin OR
Clopheline OR Clofelin OR Catapres OR Catapressan OR Catapresan OR
Dixarit OR Precedex OR Dixarit
Adrenergic beta-Antagonists/ OR propranolol OR metoprolol OR pindolol

Central Nervous System Stimulants/

Metadate OR Equasym OR Methylin OR Modafinil OR Concerta OR
Phenidylate OR Ritalin OR Ritaline OR Tsentedrin OR Centedrin OR Daytrana
OR "Methylphenidate Hydrochloride"

Amphetamines/

Dopamine Agonists/ OR Dopamine Receptor Agonists/ OR "Dopaminergic
Agonists" OR dopamine agents/

Amantadine OR Apomorphine OR Bromocriptine OR Metergoline OR
Piribedil OR Gabapentin OR "Gabapentin enacarbil" OR Neurontin

Anticonvulsants/ OR Anticonvulsive OR "Anti-convulsive" OR Anticonvulsant
OR Anticonvulsants OR "Anti-convulsant" OR "Anti-convulsants" OR
Antiepileptic OR Antiepileptics OR "Anti-epileptic" OR "Anti-epileptics"
"valproic acid" OR carbamazepine OR phenytoin OR lamotrigine OR
Pregabalin

Antidepressive Agents/ OR Antidepressants OR "Anti-depressant" OR "Anti-
depressants" OR "Anti-depressive" OR amitryptiline OR desipramine OR
doxepin OR imipramine

Serotonin Uptake Inhibitors/ OR fluoxetine OR fluvoxamine OR sertraline OR
citalopram OR Trazodone OR buspirone

Search strategy

« A » & « B » & « C »



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A



PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 3 and 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

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BMJ Open

Pharmacological interventions for agitated behaviors in patients with traumatic brain injury: a systematic review

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-029604.R2
Article Type:	Research
Date Submitted by the Author:	12-Jun-2019
Complete List of Authors:	Williamson, David ; Université de Montréal, Pharmacy; Hôpital du Sacré-Coeur de Montréal, Pharmacy Frenette, Anne-Julie; Université de Montréal, Pharmacy; Hôpital du Sacré-Coeur de Montréal, Pharmacy Burry, Lisa; Mount Sinai Hospital Pharmacy Department; University of Toronto Leslie Dan Faculty of Pharmacy Perreault, Marc; Université de Montréal, Pharmacy; McGill University Health Centre, Pharmacy Charbonney, Emmanuel; Université de Montréal Faculté de médecine Lamontagne, François; Université de Sherbrooke, Médecine Potvin, Marie-Julie; Hôpital du Sacré-Coeur de Montréal, Psychologie Giguère, Jean-François; Hôpital du Sacré-Coeur de Montréal, Neurosurgery; Université de Montréal, Médecine Mehta, Sangeeta; University of Toronto, Department of Medicine, Interdepartmental Division of Critical Care Medicine Bernard, Francis; Hôpital du Sacré-Coeur de Montréal, Critical Care; Université de Montréal, Médecine
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Neurology, Mental health
Keywords:	Neurological injury < NEUROLOGY, REHABILITATION MEDICINE, Delirium & cognitive disorders < PSYCHIATRY

SCHOLARONE™
Manuscripts

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3 1 **Pharmacological interventions for agitated behaviors in patients with traumatic**
4 2 **brain injury: a systematic review**
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6 4 David R. Williamson, B.Pharm, M.Sc., Ph.D.^{1,2} david.williamson@umontreal.ca
7 5 Anne Julie Frenette, B.Pharm, M.Sc.^{1,2} anne.julie.frenette@umontreal.ca
8 6 Lisa Burry, B.Sc.Pharm, Pharm.D.³ lisa.burry@sinaihealthsystem.ca
9 7 Marc M. Perreault, B.Pharm, M.Sc., Pharm.D.^{2,4} marc.perreault@umontreal.ca
10 8 Emmanuel Charbonney, M.D., Ph.D.^{5,6} emmanuel.charbonney@umontreal.ca
11 9 François Lamontagne, M.D., M.Sc. FRCPC⁷ francois.Lamontagne@USherbrooke.ca
12 10 Marie-Julie Potvin, Ph.D.⁸ potvin.marie_julie@uqam.ca
13 11 Jean-François Giguère, M.D., Ph.D. FRSC^{6,9} jean-francois.giguere.1@umontreal.ca
14 12 Sangeeta Mehta, M.D., FRCPC¹⁰ geeta.Mehta@sinaihealthsystem.ca
15 13 Francis Bernard, M.D. FRCPC^{5,6} f.bernard@umontreal.ca
16 14

17 15 ¹ Pharmacy department and Research center, Hôpital du Sacré-Coeur de Montréal

18 16 ² Faculté de pharmacie, Université de Montréal

19 17 ³ Department of Pharmacy and Medicine, Sinai Health System and Leslie Dan Faculty of
20 18 Pharmacy, University of Toronto.

21 19 ⁴ Department of Pharmacy, McGill University Health Center

22 20 ⁵ Department of Critical Care and Research center, Hôpital du Sacré-Coeur de Montréal

23 21 ⁶ Faculté de Médecine, Université de Montréal

24 22 ⁷ Centre de recherche, CHU de Sherbrooke

25 23 ⁸ Department of medicine, Faculté de Médecine, Université de Sherbrooke

26 24 ⁸ Department of Psychology, Hôpital du Sacré-Coeur de Montréal and department of
27 25 Psychology, Université du Québec à Montréal;

28 26 ⁹ Department of Neurosurgery, Hôpital du Sacré-Coeur de Montréal

29 27 ¹⁰ Department of Medicine, Interdepartmental Division of Critical Care Medicine, Mount
30 28 Sinai Hospital and University of Toronto

31 29
32 30 Corresponding author:

33 31 David Williamson, Ph.D.

34 32 Pharmacy department and research center

35 33 Hôpital du Sacré-Coeur de Montréal

36 34 5400 Gouin West

37 35 Montreal, Quebec

38 36 Canada, H4J 1C5
39 37

40 38 **Author Disclosure Statement**

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42 40

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For peer review only

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3 45 **Abstract**

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5 47 **Objective:** The aim of this systematic review was to assess the efficacy and safety of
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7 48 pharmacological agents in the management of agitated behaviors following TBI.

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10 49 **Methods:** We performed a search strategy in PubMed, OvidMEDLINE®, Embase,
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12 50 CINAHL, PsycINFO, Cochrane Library, Google Scholar, Directory of Open Access
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14 51 Journals, LILACS, Web of Science and Prospero (up to December 10th 2018) for
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16 52 published and unpublished evidence on the risks and benefits of 9 pre-specified
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18 53 medications classes used to control agitated behaviors following TBI. We included all
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20 54 randomized controlled trials, quasi-experimental and observational studies examining the
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22 55 effects of medications administered to control agitated behaviors in TBI patients. Included
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24 56 studies were classified into 3 mutually exclusive categories: 1) agitated behavior was the
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26 57 presenting symptom; 2) agitated behavior was not the presenting symptom, but was
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28 58 measured as an outcome variable and; 3) safety of pharmacological interventions
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30 59 administered to control agitated behaviors was measured.

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33 60 **Results:** Among the 181 articles assessed for eligibility, 21 studies were included. Of the
34
35 61 studies suggesting possible benefits, propranolol reduced maximum intensities of
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37 62 agitation per week and physical restraint use, methylphenidate improved anger measures
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39 63 following 6 weeks of treatment, valproic acid reduced weekly agitated behavior scale
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41 64 ratings and olanzapine reduced irritability, aggressiveness and insomnia between weeks
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43 65 1 and 3 of treatment. Amantadine showed variable effects and may increase the risk of
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45 66 agitation in the critically ill. In 3 studies evaluating safety outcomes, antipsychotics were
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47 67 associated with an increased duration of post-traumatic amnesia in unadjusted analyses.
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49 68 Small sample sizes, heterogeneity and an unclear risk of bias were limits.

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3 69 **Conclusions:** Propranolol, methylphenidate, valproic acid and olanzapine may offer
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5 70 some benefit, however, they need to be further studied. Antipsychotics may increase the
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7 71 length of post-traumatic amnesia. More studies on tailored interventions and continuous
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9 72 evaluation of safety and efficacy throughout acute, rehabilitation and outpatient settings
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11 73 are needed.
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17 75 **Systematic review registration:** Prospero CRD42016033140
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19 76 **Keywords:** Traumatic brain injury, agitation, Pharmacological intervention
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22 78 **Strengths and limitations of this study** 23 24 79

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27 80 ▪ This systematic review assessed the efficacy and safety of pharmacological agents in
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29 81 the management of agitated behaviors following traumatic brain injury
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31 82 ▪ Randomized controlled trials, quasi-experimental and observational studies were
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33 83 reviewed
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35 84 ▪ The included studies were limited by small sample sizes, variations in the different
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37 85 agitated behaviors and populations studied
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39 86 ▪ The review found insufficient data to recommend the use of any agent for the
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41 87 management of agitated behaviors following TBI
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89 Introduction

90 Traumatic brain injury (TBI) occurs when an external force is applied to the head leading
91 to alterations in brain function including decreased level of consciousness, post-traumatic
92 amnesia, and changes in behavior and cognition that can persist in the long term. In the
93 United States alone, approximately 50,000 people die each year from TBI and more than
94 5 million live with TBI-related disabilities.^{1, 2} While TBI has a substantial impact on direct
95 healthcare costs, indirect costs from lost productivity also represent a significant economic
96 burden.^{3, 4} Agitated behaviors are a frequent behavioural problem following TBI.^{5, 6} They
97 have been broadly defined as a state of confusion that follows the initial injury and is
98 characterised by disruptive behaviours. A constellation of behaviors has been associated
99 with the term “agitation” in TBI patients, including restlessness, confusion, physical and
100 verbal aggression, impulsivity, perceptual disturbances, and inattention creating a very
101 heterogeneous group of patients to study.⁷ Agitation has been reported in 20-41% of
102 patients during the early stage of recovery in acute care units and up to 70% of patients
103 in rehabilitation units.^{6, 8-13} It can result in harm to patients and caregivers, interfere with
104 treatments, lead to the use of physical and pharmacological restraints, increase hospital
105 length of stay, delay rehabilitation and impede functional independence.^{10-12, 14-16} In TBI
106 outpatients, neurobehavioral symptoms may be different in nature. Aggressive behaviour
107 and irritability, more than physical agitation are generally reported. A variety of agents
108 such as antidepressants, anticonvulsants, stimulants, and antipsychotics have been used
109 for the management of neurobehavioral complications of TBI.^{17, 18} However, preclinical
110 studies have suggested that repeated use of certain agents such as haloperidol,
111 risperidone and diazepam may reduce cognitive and functional recovery.¹⁹⁻²² Thus, it
112 remains unclear which pharmacological agents are the most effective and safest for the

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3 113 management of agitated behaviors in TBI patients. A Cochrane Systematic Review
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5 114 published in 2006 showed a lack of evidence to support any agent.²³ Since then, two
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7 115 additional systematic reviews concluded that the evidence was insufficient and too weak
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9 116 to recommend any specific agent, however they included only French and English studies
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11 117 published before January 2016, had incomplete search strategies, and did not include the
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13 118 grey literature.^{24, 25} To advance this field, we updated and broadened the literature
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15 119 search, included all languages and included studies in which an agitated behaviour was
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17 120 not an eligibility criterion, but was measured as an outcome variable . The aim of this
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19 121 systematic review was to assess the efficacy and safety of pharmacological agents in the
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21 122 management of agitated behaviors following TBI compared to placebo or other
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23 123 treatments.
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31 **Methods**

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34 126 The review protocol has been registered in PROSPERO International Prospective
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36 127 Register of Systematic Reviews (CRD42016033140), conducted according to the
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38 128 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines
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40 129 and published in a peer-reviewed journal.^{26, 27} We included all randomized controlled,
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42 130 quasi-experimental, and observational studies with control groups that had a majority
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44 131 (>50%) of patients with TBI. We excluded case reports, case series, and observational
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46 132 studies without control groups. We included studies of all type of patients who suffered a
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48 133 TBI, including children and adults, in both the early stages of recovery and in rehabilitation.
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50 134 We included 3 mutually exclusive types of studies: 1) those evaluating the use of
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52 135 pharmacological interventions in which an agitated behaviour, not further defined, was
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3 136 one of the eligibility criteria for the study; 2) those in which an agitated behaviour was not
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5 137 an eligibility criterion, but was measured as an outcome variable; and 3) those specifically
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7 138 assessing the safety of pharmacological agents used to treat agitation in TBI patients. In
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10 139 this systematic review, we considered agitation, aggressiveness, assaultive behaviour,
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12 140 irritability and confusion as part of agitated behaviours. All medications considered in this
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14 141 review were pre-specified and consisted in the following: beta-adrenergic blockers, typical
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16 142 and atypical antipsychotics, anticonvulsants, dopamine agonists, psychostimulants,
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18 143 antidepressants, alpha-2-adrenergic agonists, hypnotics and anxiolytics. Studies were
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20 144 included whether the investigators compared a medication to placebo, a medication to
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22 145 another medication, or various combinations of different medications.
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27 146 The primary outcome was a reduction in severity of the agitated behavior as measured in
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29 147 each study. If feasible, we reported resolution of agitated behaviours as well as changes
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31 148 in duration and type of symptoms (confusion, aggressiveness, inattention, hallucinations,
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33 149 disorientation, and inappropriate mood or speech). Secondary outcomes include lengths
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35 150 of stay, (ICU length of stay, hospital LOS for the early rehabilitation phase), adverse
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37 151 events (extrapyramidal effects, QTc prolongation, cardiac arrhythmias, hypotension,
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39 152 seizures, behavioural effects), use of physical restraints in ICU, cognitive and functional
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41 153 outcomes at hospital discharge and at one year post-TBI.
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46 154 **Patient and public involvement statement**

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49 155 This research was done without patient involvement. Patients were not invited to
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51 156 comment on the study design and were not consulted to develop patient relevant
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53 157 outcomes or interpret the results. Patients were not invited to contribute to the writing or
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55 158 editing of this document for readability or accuracy.
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159 *Search strategy*

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

172 *Data collection and analysis*

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

178 *Data extraction and management*

179 Data from all included studies were extracted by two independent reviewers (AJF and
180 DW) and in duplicate using a pre-tested data extraction form. The following variables were
181 recorded for each study: study title, name of the first author, year of publication, country

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3 182 of origin, language of publication, publication type (journal article, conference proceeding,
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5 183 abstract, thesis), clinical setting (intensive care unit, hospital ward, rehabilitation unit,
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7 184 outpatient), study design (randomized controlled, blinded or open, non-randomized
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9 185 controlled, prospective or retrospective, crossover), population (paediatric, adult), patient
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11 186 characteristics (age, gender, isolated TBI or multiple trauma including TBI, severity of TBI
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13 187 according to Glasgow Coma Scale, days from TBI at inclusion, inclusion and exclusion
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15 188 criteria), characteristics of the intervention and control treatment (type of pharmacological
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17 189 agent, dose, frequency and duration of the therapy), agitation measurement tool,
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19 190 description of the specific agitated behaviours (definition, frequency, duration), and clinical
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21 191 outcomes (length of stay), adverse events, use of physical restraints during ICU stay,
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23 192 duration of post traumatic amnesia, cognitive function at ICU discharge and at one year,
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25 193 and functional outcome at ICU discharge and at one year. We contacted the
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27 194 corresponding author for clarifications when necessary. In the case of an abstract not
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29 195 available in English, the research team included authors fluent in French, Spanish,
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31 196 German, and Italian, who were able to read the abstract. Among selected articles, only
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33 197 one article in Spanish was included. The article was reviewed by authors fluent in Spanish.
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42 199 *Assessment of risk of bias*

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44 200 Two reviewers (DW, AJF) independently evaluated each included study with the
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46 201 Cochrane Collaboration tool for randomized controlled trials and the Ottawa-Newcastle
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48 202 tool for observational studies, respectively.^{29, 30} In case of disagreement concerning the
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50 203 risk of bias, a third reviewer (FB) was consulted to resolve the issue.
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54 204 *Patient and public involvement*

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56 205 Patients and or public were not involved in the conduct of this systematic review.
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3 2064 207 **Results**

5 208

6 209 *Study selection*

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8 211 The database search (up to December 10th 2018) retrieved 11 170 unique citations of

9 212 which 10 989 were excluded based on title and abstracts (Figure 1). We assessed 181

10 213 full-text articles for eligibility and 21 studies were included. A total of eight studies

11 214 evaluated the use of pharmacological interventions in which an agitated behaviour was

12 215 the presenting symptom or one of the presenting symptoms.³¹⁻³⁸ In nine other studies,

13 216 agitated behaviour was not the presenting symptom, but was measured as an outcome

14 217 variable.³⁹⁻⁴⁷ Finally, four studies specifically assessed the safety of pharmacological15 218 agents used for agitated behaviours in TBI.⁴⁸⁻⁵¹

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17 220 *Agitated behaviors as the presenting symptom*

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19 222 The eight included studies evaluated various aspects ranging from aggressiveness to

20 223 irritability and confusion (Table 1).³¹⁻³⁸ The behaviors were evaluated using the following

21 224 tools (Table 2): agitated behavior scale (ABS), confusion assessment protocol, State-Trait

22 225 Anger scale, the overt aggression scale, Richmond Agitation Sedation Scale (RASS) and

23 226 neuropsychiatric inventory irritability and aggression domains (NPI-I and NPI-A).⁵²

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227 **Table 1 – Study characteristics**

Study/Year (N)	Publication/ Country	Study design	Study focus/Population	Interventional arm/Population	Comparative arm/Population	Location at randomization	Timing from TBI at randomization	TBI description
1. Agitated behaviour as the presenting symptom								
Brooke ³⁰ 1992 N=21	Published USA	RCT parallel	Agitation Mean age 31 87 men and 13 women	Propranolol 60- 420mg daily	Placebo	Level 1 trauma and rehabilitation center	N/A	Severe blunt TBI
Mooney ³¹ 1993 N=38	Published USA	Randomize d Pre-post	Anger Mean age 29 ± 10 Male gender 100%	Methylphenidate 30mg/day	Placebo	Outpatient	6 months or more (mean 27 +/- 21 months)	Severe blunt TBI
Yablon 2010 ³² N=79	Abstract USA	RCT parallel	Confusion Age and gender not reported	Amantadine 100mg bid X 14 days	Placebo	Inpatient brain injury unit of a rehabilitation hospital	≤ 6 months	TBI not further defined
Hammond ³⁴ 2014 N=76	Published USA	RCT parallel	Irritability and aggression	Amantadine 100mg bid	Placebo 38 +/-12	Outpatient	≥ 6 months following a TBI	Blunt TBI

				Mean age 40 +/- 13 Male gender 74.4%	Male gender 80.5%			
Beresford ³⁰ 2015 N=50	Abstract USA	RCT parallel	Agitation Mean age 47 ± 14 46 men and 4 women	Valproic acid for level 50-100 mcg/ml	Placebo	Outpatient	> 1 year following TBI	Mild and moderate TBI
Hammond ³³ 2015 N=168	Published USA	RCT parallel	Irritability and aggression	Amantadine 100mg bid Mean age 40 ± 13 Male gender 80.5%	Placebo Mean age 38 ± 12 Male gender 74.4%	Outpatient	≥ 6 months following a TBI	Blunt TBI
Maturana ³⁷ Waidele 2009	Published Chile	Prospective double- blind	Restlessness, Irritability,	Olanzapine (dose not specified)	Placebo	Outpatient	N/A	TBI not further defined

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N=31			Aggression, Insomnia Age and gender not reported					
Gramish ³⁵ 2017 N=139	Published USA	Retrospective observational	Agitation	Amantadine 100mg bid 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 behavior is not the presenting symptom								
Study/Year (N)	Publication/Country	Study design	Study focus	Interventional arm	Comparative arm	Location at randomization	Timing from TBI at randomization	TBI description
Schneider ⁴¹ 1999 N=10	Published USA	RCT parallel	Cognitive function and behavior Mean age 31 7 men and 3 women	Amantadine 50mg bid increased to 150mg bid	Placebo	Outpatient	N/A	Moderate and severe TBI
Meythaler ⁴⁰ 2001 N=9	Published USA	RCT Crossover	Recovery and arousal	Sertraline	Placebo	Inpatient rehabilitation	< 2 weeks of TBI	Severe TBI

			Age and gender not reported					
Meythaler ⁴² 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 ³⁸ 2010 N=99	Published USA	RCT parallel	Cognitive function and behavior	Sertraline Mean age: 35 ± 17 Male gender: 79%	Placebo Mean age 35 ± 16 Male gender: 66%	Level 1 trauma center inpatients	< 8 weeks of TBI	Moderate and severe TBI
Giacino ³⁹ 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 to 16 weeks following TBI	Vegetative or minimally conscious TBI
Tramontana ⁴³ 2014	Published USA	RCT Crossover	Attention Mean age: 29±9 Male gender: 69%	Lysdexampheta- mine	Placebo	Outpatient	6-34 months (mean 15.6 +/-	Moderate and severe TBI

1 2 3 4 5 6 7 8 9 10	N=22 but 13 completed the study						10 months) since TBI	
11 12 13 14 15 16 17	Johansson ⁴⁵ 2014 N=24	Published Sweden	RCT Crossover	Mental fatigue and cognition Mean age 39±11 Male gender: 50%	Methylphenidate 5mg and 20mg tid	Placebo	Outpatient	> 12 months following TBI Mild or moderate TBI
18 19 20 21 22 23 24 25 26 27	Fann ⁴⁴ 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 center	< 1 year of TBI Moderate and severe TBI
28 29 30 31 32 33 34 35 36 37	Hart ⁴⁶ 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
38 39 40 41 42 43 44 45 46 47	3. Studies assessing the safety of pharmacological agents used for agitated behaviours in TBI							

1 2 3 4 5 6 7 8 9 10 11 12	Rao 1985 ⁴⁹ N=26	Published USA	Retrospecti ve observation al	Rehabilitation outcomes	Haloperidol Median age: 34 Gender not reported	No haloperidol Median age: 22 Gender not reported	Trauma and rehabilitation center	From admission	Severe closed head injury
13 14 15 16 17 18 19 20 21	Mysi ^w ⁴⁸ 2006 N=182	Published USA	Retrospecti ve cohort	Cognitive and motor recovery Mean age: 36 Male gender: 74%	Narcotics, benzodiazepines and neuroleptics	No CNS active medications	Level 1 trauma center and rehabilitation center	From admission	TBI
22 23 24 25 26 27 28 29 30 31	Kooda ⁵⁰ 2015 N=195	Abstract USA	Retrospecti ve observation al	Duration of post- traumatic amnesia Age and gender not reported	Antipsychotics	No antipsychotic	Level 1 trauma center and rehabilitation center	From admission	TBI
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	Anderson ⁴⁷ 2016 N=101	Published USA	Retrospecti ve cohort	Seizures, neuroleptic malignant syndrome, QTc prolongation,	Haloperidol Median age 32 Male gender: 87%	No haloperidol Median age 47 Male gender: 61%	Inpatients	From admission	Moderate and severe TBI

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			extrapyramidal symptoms, hematological disturbances					
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229 **Table 2 – Tools used to measure agitated behaviors**

Tools	Description
Agitated behavior scale ⁵³	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.
Brief Anger and Aggression Scale ⁵⁴	A six-item measure developed for the rapid screening and identification of anger and aggression levels.
Confusion assessment protocol ⁵⁵	Combination of orientation, cognition and other clinical measures of early confusion following traumatic brain injury.
Functional independence measure (FIM) ⁵⁶	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) ⁵⁷	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) ⁵⁸	The KAS is an observer rating scale used to assess the social adjustment of people with traumatic brain injury.

<p>Neuropsychiatric inventory irritability (NPI-I) and aggression domains (NPI-A)⁵²</p>	<p>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.</p>
<p>Neurobehavioral Function Inventory (NFI)⁵⁹</p>	<p>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.</p>
<p>Neurobehavioral rating scale (NRS)⁶⁰</p>	<p>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.</p>
<p>Overt aggression scale (OAS)⁶¹</p>	<p>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.</p>

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.

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3 231 Of the identified studies, two were conference abstracts that remained unpublished.^{33, 37}
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5 232 The studies evaluated propranolol³¹, amantadine³³⁻³⁵, methylphenidate³², valproic acid³⁷
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7 233 and olanzapine³⁸ in comparison to placebo. Five used a randomized controlled parallel
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9 234 design^{31, 33-35, 37}, one used a randomized pretest posttest control group design³², one was
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11 235 a prospective double blind observational study³⁸ and, one was a retrospective
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13 236 observational study.³⁶ All the studies exclusively enrolled adult (16 years or older) TBI
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15 237 patients and three studies excluded older patients (greater than 65 or 75 years)^{34, 35, 37}.
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17 238 The studies mostly included patients in rehabilitation (n=2)^{31, 33} and outpatient (n=5)
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19 239 settings.^{32, 34, 35, 37, 38} Only one study evaluated patients in an intensive care unit (ICU)
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21 240 setting.³⁶ All the studies exclusively studied TBI patients.³¹⁻³⁸ Three studies identified in
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23 241 an earlier systematic review were excluded (Figure 1) because TBI patients represented
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25 242 less than 50% of the sample.^{23, 62-64}
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33 244 In the eight studies, one randomized trial evaluated the use of propranolol for the
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35 245 treatment of agitation in severe blunt TBI patients (Table 3).³¹ It reported a reduction in
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37 246 the intensity of agitation episodes and in the use of physical restraints but failed to show
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39 247 a reduction in the frequency of agitation episodes.³¹ Amantadine was evaluated for the
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41 248 management of confusion in a randomized trial, irritability in two randomized trials, and
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43 249 agitation in a retrospective observational study.³³⁻³⁶ The studies reported inconsistent
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45 250 results (Table 3). In one unpublished study in the setting of rehabilitation within 90 days
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47 251 of TBI (n=79), amantadine had no effect on confusion.³³ In a pilot study of outpatients who
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49 252 suffered a TBI more than six months ago, amantadine showed significant reductions in
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51 253 irritability and aggression using the Neuropsychiatric Inventory scale (NPI).³⁵ In a follow-
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53 254 up study of 168 outpatients who had suffered a TBI more than 6 months ago, no difference
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3 255 in the incidence of irritability at 28 and 60 days using the NPI-I from observers (family
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5 256 member, close friend, or employer) was reported.³⁴ Participants self-rating at day-60
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7 257 indicated improvement in irritability ($p < 0.04$) but the difference became non-significant
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9 258 when adjusted for multiple comparisons. The Global improvement subscale of the Clinical
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11 259 Global Impressions (CGI), which evaluates general emotional and behavioral function,
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13 260 improved more in the amantadine group than in the placebo group at day 60 ($p = 0.0354$).
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15 261 A sub-analysis of patients with anger and aggression (118 of the 168 patients) in the same
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17 262 study was also carried out and reported a statistically significant reduction in participant's
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19 263 self-rated aggression at 60 days.⁶⁵ Finally, in a retrospective observational study ($n = 139$),
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21 264 patients exposed to amantadine in the ICU reported more agitation episodes defined as
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23 265 a Richmond Agitation Sedation Score of +2 or higher (38% vs 14%) in an unadjusted
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25 266 analysis.³⁶ The use of amantadine was also associated with an increased median ICU
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27 267 length of stay (4.5 vs 3 days; $p = 0.01$) when compared to non-exposed patients.
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35 269 The efficacy of olanzapine in the management of restlessness, irritability, aggression and
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37 270 insomnia in outpatients with a history of TBI was evaluated in a prospective double blind
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39 271 study.³⁸ While no reduction in restlessness was reported, the authors did report a
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41 272 significant reduction in irritability and insomnia between weeks 1 and 3 in olanzapine-
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43 273 treated patients. Unfortunately, no statistical comparison with the placebo group was
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45 274 provided. The efficacy of valproic acid in reducing agitated behaviors among mild and
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47 275 moderate TBI outpatients was evaluated in an unpublished randomized controlled study
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49 276 ($n = 50$).³⁷ Patients were included more than one year following brain injury and suffered
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51 277 from both affective lability and alcohol dependence. A significant reduction in the
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278 **Table 3 – Efficacy and safety outcomes**

Study/Year/n	Intervention	Agitated behavior measures	Efficacy outcomes	Safety outcomes
1. Agitated behavior as the presenting symptom				
<i>Randomized controlled studies</i>				
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
Mooney 1993 ³¹ 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 effect on side effects

1 2 3 4 5 6 7 8 9 10 11 12 13 14	Yablon 2010 ³² N=79	Amantadine	Confusion assessment protocol (CAP)	No significant differences in the number of symptoms of posttraumatic 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
15 16 17 18 19 20 21 22 23 24 25 26 27 28 29	Hammond 2014 ³⁴ 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 3 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 = .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 = .046).	No difference in adverse events (tremors, appetite, gastrointestinal, aches and pain, sexual problems, disorientation, seizures)
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	Beresford 2015 ³⁰ 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

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Hammond 2015 ³³ 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 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.
<i>Observational studies</i>				
Maturana Waidele ³⁷ 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=-.0011) between weeks 1 and 3 in the patients treated with olanzapine	No safety outcomes reported
Gramish 2017 ³⁵ N=139	Amantadine	RASS score of +2 or higher	Increase in agitation in patients exposed to amantadine (38%) compared to non-exposed (14%);	No safety outcomes reported

			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)	
2. Agitated behavior is not the presenting symptom				
<i>Randomized controlled studies</i>				
Schneider 1999 ⁴¹ N=10	Amantadine	Neurobehavioral rating scale	No significant difference in behavior scores between amantadine and placebo groups	No safety outcomes reported
Meythaler 2001 ⁴⁰ N=9	Sertraline	Agitated Behavior Scale	No difference in decline of ABS over treatment period	No safety outcomes reported
Meythaler 2002 ⁴² 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> .05, Mann–Whitney U test)	No detrimental effects in hematology or biochemistry laboratories and no seizures.
Banos 2010 ³⁸ 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

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<p>Giacino 2012³⁹ N=184</p>	<p>Amantadine</p>	<p>Agitation and restlessness not further defined</p>	<p>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.</p>	<p>No differences in adverse events (seizure, nausea, vomiting, constipation, diarrhea, elevated liver function tests, insomnia, rash, congestive heart failure, involuntary muscle contractions)</p>
<p>Tramontana 2014 N=22 but 13 patients completed the study</p>	<p>Lisdexamphetamine</p>	<p>Agitation and restlessness not further defined</p>	<p>No difference in agitation (no cases in each group) or irritability (1/13 case) during placebo) between the Lisdexamphetamine and placebo groups.</p>	<p>Reduced appetite and weight loss of more than 5 lbs more frequent with lisdexamphetamine (7 vs 1 case) p=NS</p>
<p>Johansson 2014 N=48</p>	<p>Methylphenidate</p>	<p>Aggression, restlessness and irritability not further defined</p>	<p>No difference in aggression, restlessness and irritability in patients treated with methylphenidate</p>	<p>A significant increase in heart rate was found. No significant changes were found in blood pressure or QT intervals.</p>
<p>Fann 2017 N=62</p>	<p>Sertraline</p>	<p>Brief Anger and Aggression Scale</p>	<p>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</p>	<p>No significant difference in safety outcomes. More patients in the sertraline group (17%)</p>

		and agitation/restlessness not further defined		developed gas/flatulence vs the placebo group (0%) p=0.052.
Hart 2017 N=32	Dextroamphetamine	Agitated Behavior Scale	Increase in agitation with dextroamphetamine over time compared to placebo (p<0.05)	No significant difference in heart rate or blood pressure.

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3 280 agitated behavior scores (ABS) evaluated by family members at eight weeks (12.9 vs 15.5
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5 281 points; $p=0.03$) was observed. Finally, a crossover study assessed methylphenidate for
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7 282 anger ($n=38$) in TBI rehabilitation center outpatients (six months or more after TBI). After
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10 283 six weeks, methylphenidate significantly reduced the anger score using the State Trait
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12 284 Anger Scale (STAS).³²

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17 286 Of the eight studies, safety outcomes were reported in four studies.³²⁻³⁵ When reported,
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19 287 the agents studied were well tolerated with no significant differences observed. Functional
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21 288 and cognitive outcomes were not reported in any of these studies.

22 23 24 289 25 26 290 *Agitated behavior as a secondary measure*

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29 292 We identified nine studies evaluating agitated behaviors as a secondary measure, which
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31 293 were focused on cognitive function and neurological recovery (Table 1).³⁹⁻⁴⁷ In these
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33 294 studies, sertraline^{39, 41, 45}, amantadine^{40, 42, 43}, amphetamines^{44, 47}, and methylphenidate⁴⁶
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35 295 were evaluated versus placebo and reported agitated behaviors as an outcome. Of these
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37 296 studies, 6 used a randomized crossover design and 3 used a randomized controlled
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39 297 parallel design.

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45 299 Sertraline was evaluated in three studies to enhance recovery and increase arousal,
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47 300 ameliorate cognitive and neurobehavioral functioning and to treat major depression (Table
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49 301 3).^{39, 41, 45} In all these three studies, sertraline had no effect on the incidence of agitation,
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51 302 anger or aggression. In one study, more patients developed agitation/restlessness in the
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53 303 sertraline group (17%) compared to the placebo group (7%) but this difference was not
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3 304 statistically significant ($p=0.42$).⁴⁵ Amantadine was also evaluated in three studies for
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5 305 cognitive and functional recovery.^{40, 42, 43} All three studies found no differences in agitated
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7 306 behaviors compared to placebo. Methylphenidate was evaluated for secondary mental
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9 307 fatigue in mild TBI patients more than six months after injury.⁴⁶ However, it had no effect
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11 308 on irritability and aggression. Lisdexamphetamine and dextroamphetamine were each
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13 309 evaluated for attention deficits in TBI patients and no effect on agitated behaviors was
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15 310 noted with lisdexamphetamine whereas dextroamphetamine increased agitation over time
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17 311 ($p<0.05$).^{44, 47} Among these 9 studies, those evaluating sertraline and amantadine
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19 312 reported no significant differences in adverse events.^{39-43, 45}
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26 314 *Studies evaluating safety outcomes*

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28 315 Finally, the safety of pharmacological agents used for agitated behaviors in TBI patients
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30 316 was evaluated in four retrospective observational studies (Table 4).⁴⁸⁻⁵¹ Two of these
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32 317 studies focused on the effect of haloperidol and antipsychotic use on post-traumatic
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34 318 amnesia (PTA) duration, whereas a third evaluated the effects of antipsychotics,
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36 319 benzodiazepines and narcotics on PTA duration, and Functional independence measure
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38 320 (FIM) cognitive and motor scores.⁴⁹⁻⁵¹ In these three studies, haloperidol and other
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40 321 antipsychotics were associated with an increase in PTA duration. Antipsychotics,
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42 322 benzodiazepines and narcotics had no effects on FIM scores.⁴⁹ Finally a fourth study
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44 323 focused on the general safety (seizures, neuroleptic malignant syndrome, QTc
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46 324 prolongation, extrapyramidal symptoms, hematologic disturbances) of haloperidol in ICU
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48 325 TBI patients.⁴⁸ Patients exposed to haloperidol ($n=45$) had no significant increase in
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50 326 adverse events compared to non-exposed patients ($n=56$). Of note, none of the studies
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52 327 adjusted for severity of TBI and other potential confounders.
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5 329 *Risk of bias assessment*
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8 330 Risk of bias scores are reported in Table 5. The analysis of risk of bias of randomized
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10 331 controlled trials with the Cochrane Collaboration's Tool revealed that many studies did not
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12 332 provide sufficient information on sequence, generation and allocation concealment. A
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14 333 majority of studies had other threats to validity including limited sample sizes, no
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17 334 description of patient demographics and loss to follow-up. For six studies evaluated with
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19 335 the Newcastle-Ottawa tool, the number of stars awarded ranged from four to five. Most
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21 336 studies were awarded a score of four stars, indicating a high risk of bias. As none of the
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24 337 six studies were adjusted for potential confounding, all received 0 stars for comparability.
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346 **Table 4 - Studies assessing the safety of pharmacological agents used for agitated behaviors in TBI**

Study/Year/n	Drugs studied	Results
Rao 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 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 ($p < 0.01$).
Kooda 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.
Anderson 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 hematologic 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; $p < 0.001$)

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348 **Table 5 – Risk of bias assessment**

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1. Randomized controlled trials
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Cochrane Collaboration Tool Risk of bias items							
Study (year)	Sequence generation	Allocation	Blinding of participants and personnel	Blinding of outcome assessment	Outcome data	Selective reporting	Other threats to validity
Brooke 1992	U	U	L	L	L	L	H
Mooney 1993	U	U	L	H	L	U	H
Schneider 1999	U	U	U	U	H	L	H
Meythaler 2001	U	U	L	L	U	U	H
Meythaler 2002	U	U	U	U	L	H	H
Banos 2010	U	U	L	L	L	L	H
Yablon 2010	U	U	L	L	L	U	H
Giacino 2012	U	L	L	L	L	L	L

Hammond 2014	L	L	L	L	U	L	L
Tramontana 2014	H	H	L	L	H	L	H
Johansson 2014	U	H	H	H	H	L	H
Beresford 2015	U	U	L	L	H	L	H
Hammond 2015	L	L	L	L	U	L	L
Fann 2017	L	L	L	L	L	L	H
Hart 2017	U	U	L	L	L	L	L

2. Observational studies

Study (year)	Newcastle-Ottawa Quality Assessment Scale					
	Number of stars awarded					
	Selection ^a		Comparability ^b		Outcome ^c	
Rao 1985	**				**	

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Maturana Waidele 2009	**		**
Mysiw 2006	**		***
Kooda 2015	**		**
Anderson 2016	**		**
Gramish 2017	***		*

350 For Cochrane Collaboration's Tool:

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

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353 For Newcastle-Ottawa Quality Assessment Scale :

354 ^a Maximum 4 stars

355 ^b Maximum 2 stars

356 ^c Maximum 3 stars.

357 N/A : not applicable

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358 Discussion

359 In this systematic review, we used an exhaustive search strategy and included studies
360 directly or indirectly evaluating pharmacological agents for the management of TBI-
361 associated agitated behaviors as well as studies assessing the safety of pharmacological
362 agents used for these agitated behaviors. Despite the prevalence and importance of this
363 problem, we found a limited number of studies evaluating pharmacological interventions
364 for the management of agitated behaviors. Propranolol, methylphenidate, valproic acid
365 and olanzapine were the only agents suggesting a potential benefit in reducing agitation,
366 anger or irritability.^{31, 32, 37, 38} However, the studies evaluating these agents had limited
367 sample sizes, heterogeneous patient populations and an unclear risk of bias. Amantadine
368 showed mixed results whereas sertraline, lysdexamphetamine and dextroamphetamine
369 showed no benefits. In comparison to the two most recent systematic reviews, we used a
370 more rigorous and broader search strategy. As such, we restricted our search to
371 randomized controlled, quasi-experimental, and observational studies with control groups
372 that had a majority (>50%) of patients with TBI, thus excluding case reports, case series
373 and uncontrolled observational studies. Our updated and broadened literature search
374 enabled the identification of two additional studies from the grey literature, three recently
375 published studies and one non-English study.^{24, 25, 33, 36, 37, 45, 47} Our search strategy also
376 included studies evaluating agitated behaviors as a secondary measure and identified 9
377 more studies, thus adding to previous systematic reviews. Furthermore, we included
378 studies where the safety of pharmacological agents for the management of agitated
379 behaviors was assessed and identified four such studies.

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3 381 The use of beta-blockers in patients with organic brain disease and assaultive behaviors
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5 382 or impulsivity has been previously studied in three crossover-randomized trials with some
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7 383 efficacy but TBI represented less than 50% of the total patient population.⁶²⁻⁶⁴ In the study
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10 384 presented in this review, propranolol reduced the intensity of agitation but not the
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12 385 frequency.³¹ One important finding was a reduction in the use of physical restraints.
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14 386 Unfortunately, safety measures such as hypotension and bradycardia were not reported.
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17 387 The Canadian ABIKUS guidelines have recommended beta-blockers for the treatment of
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19 388 aggression following TBI.⁶⁶
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21 389 Although numerous observational studies have reported a reduction in agitation with the
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23 390 use of antipsychotic agents, we found no controlled studies evaluating the efficacy of
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25 391 antipsychotics other than olanzapine.⁶⁷⁻⁶⁹ In a previous systematic review that included
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27 392 case reports and case series evaluating antipsychotics, Lanthier et al. identified 7 articles
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29 393 that included a total of 52 patients.²⁴ The lack of a control group excluded these studies
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31 394 from our review. The only study we included that used olanzapine didn't report a reduction
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33 395 in restlessness but did suggest a reduction in irritability.³⁸ Its interpretation is greatly limited
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35 396 given the poor description of methods and a lack of statistical comparison with the placebo
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37 397 group. The four studies assessing safety all evaluated antipsychotic agents and
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39 398 suggested a potential risk of prolonged PTA in unadjusted analyses.⁴⁸⁻⁵¹ None of the
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41 399 studies controlled for potential confounders such as severity of TBI. Although pre-clinical
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43 400 studies have suggested a reduction in cognitive and motor recovery with repeated
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45 401 administration of haloperidol and risperidone, the one study evaluating cognitive and
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47 402 motor scores reported no significant association with antipsychotic use.^{19-21, 49, 70} In light
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49 403 of these results, both the International Cognitive (INCOG), the Canadian ABIKUS
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51 404 guidelines and the French Society of Physical and Rehabilitation Medicine (SOFMER)

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3 405 guidelines have advised against the use of antipsychotics in TBI patients with agitated
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5 406 behaviors.^{24, 66, 71} Paradoxically, observational studies have suggested antipsychotics are
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7 407 frequently used for the management of agitated behaviors.^{14, 72-74}
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12 409 Anticonvulsants are clinically used as mood stabilizers in bipolar affective disorder and
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14 410 have also been used in TBI-associated agitation.^{75, 76} Case series have reported a
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16 411 reduction in agitation and aggressive behaviors with the use of valproic acid and
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18 412 carbamazepine but were uncontrolled.⁷⁷⁻⁸¹ We identified one unpublished study of TBI
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20 413 patients with affective lability and alcohol dependence where valproic acid showed
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22 414 effectiveness in reducing weekly ABS rated by spouse or significant other's.
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24 415 Unfortunately, the abstract provided no information on the onset of effect or adverse
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26 416 events associated with its use.
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32 418 Amantadine increases dopaminergic neurotransmission and has been shown to increase
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34 419 the rate of neurological recovery in severe TBI.⁴⁰ In the 4 studies that evaluated
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36 420 amantadine for irritability, agitation or aggressiveness, results were variable.³³⁻³⁶ Although
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38 421 one study suggested a reduction in irritability in outpatients, a larger study by the same
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40 422 group failed to confirm these results.^{34, 35} Interestingly, a recent observational study of
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42 423 patients exposed to amantadine in the ICU reported an increased risk of agitation.³⁶
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44 424 Although these effects were not observed in a multicenter trial that started amantadine at
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46 425 least four weeks after TBI, the early use of amantadine in the ICU may explain these
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48 426 findings.^{36, 40} However, these results were uncontrolled and confounding may also explain
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50 427 these differences. In addition, the use of amantadine may have increased arousal and the
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52 428 agitation measured may be part of the natural recovery. In studies in which agitation was
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3 429 not the presenting symptom, no significant differences in behavior scores between
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5 430 amantadine and control groups were reported.^{40, 42, 43}
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10 432 In this review, we found no comparative studies assessing the efficacy of tricyclic
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12 433 antidepressants, dexmedetomidine or benzodiazepines. We also found no studies in
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14 434 children. A search of TBI-associated agitation studies in clinical trial registries revealed
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17 435 ongoing studies with the combination of dextromethorphan and quinidine
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19 436 (ClinicalTrials.gov: NCT03095066) as well as propranolol and clonidine
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21 437 (ClinicalTrials.gov: NCT01322048).⁸² Finally, in a recent observational study on the
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24 438 predictors of agitation in TBI rehabilitation, sodium channel antagonist anticonvulsants,
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26 439 second-generation antipsychotics, and gamma-aminobutyric acid anxiolytics were
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28 440 associated with more severe agitation.¹⁴ Although indication bias and residual
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31 441 confounding are probable, these results do suggest an association between suppression
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33 442 of cognition and more agitation.
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37 444 Strengths of this study include an exhaustive search of the literature in the adult and
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39 445 pediatric populations, including grey literature and no language limitation. A risk of bias
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42 446 assessment was performed for each included study. Limits of this study include the
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45 447 presence of significant heterogeneity, variations in the different agitated behaviors
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47 448 (agitation, irritability, and aggression) and populations (acute TBI, rehabilitation,
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49 449 outpatient) evaluated, preventing the authors from proceeding to a meta-analysis. In
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51 450 addition, very little studies reported length of stay and functional outcomes.
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55 56 452 **Conclusion**

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3 453 In conclusion, there are insufficient data to recommend the use of any medications for the
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5 454 management of agitation following TBI. Propranolol, methylphenidate, valproic acid and
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7 455 olanzapine may offer some benefit, however, they need to be further studied. The use of
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9 456 amantadine in the acutely ill may increase the risk of agitation whereas antipsychotics
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11 457 may prolong post-traumatic amnesia. More studies on tailored interventions and
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13 458 continuous evaluation throughout the acute, rehabilitation and outpatient settings are
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15 459 needed to assess the efficacy and safety of pharmacological agents for the management
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17 460 of agitated behaviours in both the adult and pediatric TBI populations. In addition, there is
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19 461 a need to better define and standardize the assessment of agitated behaviors. Newer
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21 462 agents such as dexmedetomidine should also be evaluated.
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30
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32
33 466 and help with the literature search strategies.
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35 467 **Figure 1: Prisma Flow Diagram**

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689 **Contribution statement**

690 DRW, AJF, LB, MMP, EC, FL, MJP, JFG, SM and FB participated in the design, writing of
691 the the review protocol and contributed to the final manuscript. DW wrote the search
692 strategy and undertook the literature search. DW, AJF and FB conducted the title and
693 abstract screening and full article screening for final study inclusion. DRW and AJF
694 conducted data collection and cleaning, LB, MMP and EC advised on methods and
695 interpretation of findings.

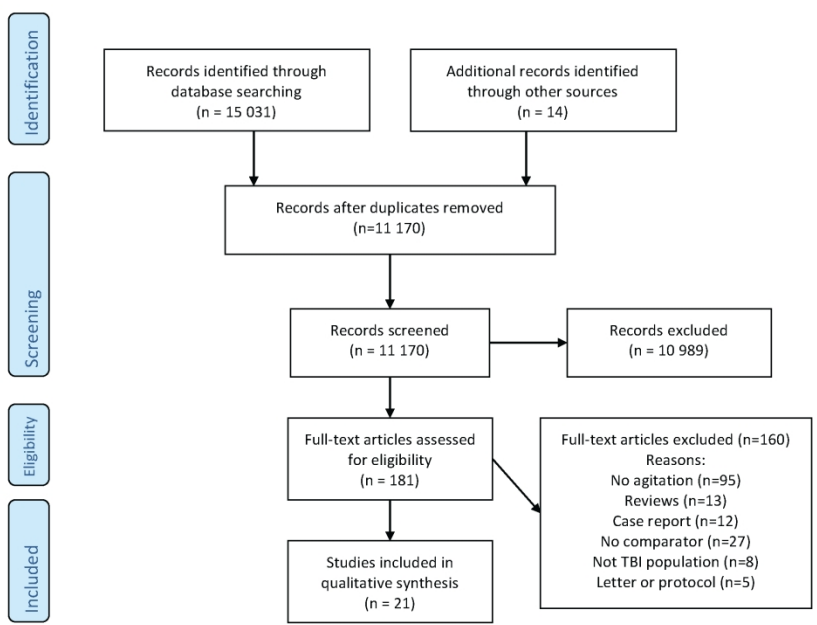
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1 PRISMA Flow Diagram
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Supplementary file: search strategy in MedLine

Concept	Description of concept	Research terms
A	Agitation/delirium	Confusion/ OR Delirium/ OR Psychomotor agitation/ OR attention/ OR hallucinations/ or hallucinat\$.mp OR delirium.mp OR confusion.mp OR Disorientation.mp OR agitation.mp OR confusional.mp OR Restlessness.mp OR Psychomotor Hyperactivity.mp OR Psychomotor Excite\$.mp OR Akathisia.mp OR attention.mp
B	Traumatic brain injury	Craniocerebral Trauma/ OR Craniocerebral Traumas.mp OR Craniocerebral Trauma.mp OR Craniocerebral injury.mp OR Craniocerebral injuries.mp OR Head Injury.mp OR Head Injuries.mp OR head trauma.mp OR head traumas.mp OR Parietal Region Trauma.mp OR Parietal Region Traumas.mp OR Skull Injury.mp OR Skull Injuries.mp OR Head Injury.mp OR Head Injuries.mp OR Occipital Region Trauma.mp OR Occipital Region Traumas.mp OR Occipital Trauma.mp OR Occipital Traumas.mp OR Temporal Region Trauma.mp OR Temporal Region Traumas.mp OR Frontal Region Trauma.mp OR Frontal Region Traumas.mp OR Forehead Trauma.mp OR Forehead Traumas.mp OR Brain Concussion.mp OR Brain Concussions.mp OR Diffuse Axonal Injury.mp OR Diffuse Axonal Injuries.mp OR Traumatic Intracranial Hemorrhage.mp OR Traumatic Intracranial Hemorrhages.mp OR Traumatic Intracranial Hematoma.mp OR Traumatic Intracranial Hematomas.mp OR Glasgow Coma Scale/ OR Glasgow Coma scale.mp OR Brain Damage, Chronic/ OR Brain Damage.mp OR Brain Damages.mp Epilepsy, Post-Traumatic/ OR Post-Traumatic Epilepsy/ OR Post-Traumatic Epilepsies/ OR Posttraumatic Epilepsy/ OR Posttraumatic Epilepsies.mp OR Post-Traumatic Seizure Disorder.mp OR Post-Traumatic Seizure Disorders.mp OR Posttraumatic Seizure Disorder.mp OR Posttraumatic Seizure Disorders.mp OR Traumatic Epilepsy.mp OR Traumatic Epilepsies.mp OR Traumatic Seizure Disorder.mp OR Traumatic Seizure Disorders.mp OR Late Post-Traumatic Seizure.mp OR Late Post-Traumatic Seizures.mp OR Late Posttraumatic Seizure.mp OR Late Posttraumatic Seizures.mp OR Impact Seizure.mp OR Impact Seizures.mp OR Concussive Convulsion.mp OR Concussive Convulsions.mp OR Early Post-Traumatic Seizure.mp OR Early Post-Traumatic Seizures.mp OR Early Posttraumatic Seizure.mp OR Early Posttraumatic Seizures.mp
C	Pharmacological treatment	Antipsychotic Agents/ OR Tranquilizing Agents/ OR Anti-Anxiety Agents/ OR Antimanic Agents/ acepromazine OR amoxapine OR asenapine OR azaperone OR benperidol OR butaclamol OR chlorpromazine OR chlorprothixene OR clopenthixol OR clozapine OR droperidol OR flupenthixol OR fluphenazine OR fluspirilene OR haloperidol OR levomepromazine OR loxapine OR loxapine succinate OR mesoridazine OR methiothepin OR methotrimeprazine OR molindone OR olanzapine OR paliperidone OR penfluridol OR perazine OR perphenazine OR pimozone OR prochlorperazine OR promazine OR quetiapine OR remoxipride OR reserpine OR risperidone OR ritanserine OR spiperone OR sulpiride OR thioridazine OR thiothixene OR tiapride hydrochloride OR trifluoperazine OR trifluoperidol OR trifluopromazine OR ziprasidone OR Lithium

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Adrenergic alpha-2 Receptor Agonists/ OR OR "Dexmedetomidine/
Klofenil OR Clofenil OR Chlophazolin OR Clonidine OR "Clonidine
Dihydrochloride" OR "Clonidine Hydrochloride" OR "Clonidine
Monohydrochloride" OR "Clonidine Monohydrobromide" OR Guanfacine OR
Lofexidine OR Gemiton OR Hemiton OR Isoglucon OR Klofelin OR
Clopheline OR Clofelin OR Catapres OR Catapressan OR Catapresan OR
Dixarit OR Precedex OR Dixarit
Adrenergic beta-Antagonists/ OR propranolol OR metoprolol OR pindolol

Central Nervous System Stimulants/

Metadate OR Equasym OR Methylin OR Modafinil OR Concerta OR
Phenidylate OR Ritalin OR Ritaline OR Tsentedrin OR Centedrin OR Daytrana
OR "Methylphenidate Hydrochloride"

Amphetamines/

Dopamine Agonists/ OR Dopamine Receptor Agonists/ OR "Dopaminergic
Agonists" OR dopamine agents/

Amantadine OR Apomorphine OR Bromocriptine OR Metergoline OR
Piribedil OR Gabapentin OR "Gabapentin enacarbil" OR Neurontin

Anticonvulsants/ OR Anticonvulsive OR "Anti-convulsive" OR Anticonvulsant
OR Anticonvulsants OR "Anti-convulsant" OR "Anti-convulsants" OR
Antiepileptic OR Antiepileptics OR "Anti-epileptic" OR "Anti-epileptics"
"valproic acid" OR carbamazepine OR phenytoin OR lamotrigine OR
Pregabalin

Antidepressive Agents/ OR Antidepressants OR "Anti-depressant" OR "Anti-
depressants" OR "Anti-depressive" OR amitryptiline OR desipramine OR
doxepin OR imipramine

Serotonin Uptake Inhibitors/ OR fluoxetine OR fluvoxamine OR sertraline OR
citalopram OR Trazodone OR buspirone

Search strategy

« A » & « B » & « C »



PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	N/A



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 3 and 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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