

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Pharmacological interventions for agitated behaviors in patients with traumatic brain injury: a systematic review
<b>AUTHORS</b>	Williamson, David; Frenette, Anne-Julie; Burry, Lisa; Perreault, Marc; Charbonney, Emmanuel; Lamontagne, Francois; Potvin, Marie-Julie; Giguère, Jean-Francois; Mehta, Sangeeta; Bernard, Francis

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Xiaolei Hu Department of Community Medicine and Rehabilitation Umeå University, 901 85 Umeå, Sweden
<b>REVIEW RETURNED</b>	04-Apr-2019

<b>GENERAL COMMENTS</b>	<p>In this systematic reviewer authors extracted data from 21 studies, both randomized controlled trial and non-randomized study of interventions. They found that Propranolol, methylphenidate, valproic acid and olanzapine were the only agents suggesting a potential benefit in reducing agitation, anger or irritability. As others, they claimed that there was insufficient data to draw any conclusion on the management of agitated behaviors following TBI.</p> <p>Some comments for that authors:</p> <p>Abstract: Since the aim was to assess both the efficacy and safety of various medications, both data should be presented in the details in the results. Conclusion need to be more concrete.</p> <p>Introduction: There are already several published systemic reviewers, what is new in the current study?</p> <p>Method: line 149-154 What was the time-window on literature searching?</p> <p>Line 165-168 This part of method didn't perform in the current study, please remove it.</p> <p>Results:</p>
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	<p>Table 1, please add the detail information, such as gender and age of the study populations</p> <p>Discussion: It's interesting to see different tools used to measure agitated behavior in table 2. What are authors' opinions on these tools? Any tool should be recommended in the future?</p> <p>Line 424, you mentioned no language limitation, how did the authors search and handle the non-English literatures?</p> <p>Conclusion: Once again, what's the new and concrete information to add in the field from the results?</p>
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<b>REVIEWER</b>	Adam McKay Monash University
<b>REVIEW RETURNED</b>	18-Apr-2019

<b>GENERAL COMMENTS</b>	<p>This paper details a systematic review of pharmacological treatments of agitation in patients with TBI. In general the paper is well written and balanced in its conclusions. I have the following major comments:</p> <p>1. Novelty. On Page 7, In 3. the authors indicate that two other systematic reviews that are very similar. There is another recent similar review by Hicks et al. (2018) titled: 'Efficacy and Harms of Pharmacological Interventions for Neurobehavioral Symptoms in Post-Traumatic Amnesia after Traumatic Brain Injury: A Systematic Review'. The authors need to be clearer about what this review adds beyond the existing reviews on the same/similar topics.</p> <p>For example, they mention limitations of two existing reviews: 'however they included only French and English studies published before January 2016, had incomplete search strategies, and did not include the grey literature'. It would be helpful if the authors could be clearer about the specific paper that applies to each issue and how this current review address these issues.</p> <p>In the Discussion, it would be helpful if the authors could comment on how the current findings relate to the existing reviews. They do mention the Plantier review but only in relation to olanzapine. A more general perspective would be helpful to know if there are agreements/disagreements between these reviews and potential reasons why.</p> <p>2. Quality. The authors do not indicate whether the review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. The rigour applied to his review would become more apparent to readers if they could report the review according to PRISMA guidelines and reference these within the paper.</p> <p>3. Term agitation. Agitation is most often associated with the early period of recovery after TBI whereas neurobehavioral or neuropsychiatric symptoms characterise behavioural issues more generally. I would recommend the authors change the term from agitation to neurobehavioral or neuropsychiatric as otherwise</p>
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	<p>readers may think this review is focused on patients in the early stages of recovery; instead many of the studies included involve outpatients.</p> <p>Relevant to this issue, their discussion of agitation on page 5 (In 22-42) focusses on the agitation in the early stages of recovery after TBI and does not reflect their operationalising of agitation which extends to the outpatient period.</p> <p>4. Discussion of amantadine. The authors highlight inconsistent findings with amantadine. Could this relate to the timing of recovery, different patients studied? A bit more discussion would be useful.</p> <p>The following are more minor comments</p> <ol style="list-style-type: none"> <li>1. Abstract - Include date from which search was conducted</li> <li>2. Table 1 – Chili should be Chile</li> </ol>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Xiaolei Hu

Institution and Country: Department of Community Medicine and Rehabilitation, Umeå University, 901 85 Umeå, Sweden

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

In this systematic review authors extracted data from 21 studies, both randomized controlled trial and non-randomized study of interventions. They found that Propranolol, methylphenidate, valproic acid and olanzapine were the only agents suggesting a potential benefit in reducing agitation, anger or irritability. As others, they claimed that there was insufficient data to draw any conclusion on the management of agitated behaviors following TBI.

Some comments for that authors:

Abstract:

Since the aim was to assess both the efficacy and safety of various medications, both data should be presented in the details in the results. Conclusion need to be more concrete.

We have added data to the abstract as suggested:

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

We have modified the abstract conclusion as follows:

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

Introduction:

There are already several published systemic reviewers, what is new in the current study?

To highlight the novelty of our systematic review, we have modified the introduction as follows: "Since then, two additional systematic reviews concluded that the evidence was insufficient and too weak to recommend any specific agent, however they included only French and English studies published before January 2016, had incomplete search strategies, and did not include the grey literature.<sup>24, 25</sup> To advance this field, we updated and broadened the literature search, included all languages and included studies in which an agitated behaviour was not an eligibility criterion, but was measured as an outcome variable"

Method:

line 149-154

What was the time-window on literature searching?

We have added the search date in the methods section as suggested

Line 165-168

This part of method didn't perform in the current study, please remove it.

We have removed the section as suggested

Results:

Table 1, please add the detail information, such as gender and age of the study populations

We have added age and sex in Table 1 as suggested.

Discussion:

It's interesting to see different tools used to measure agitated behavior in table 2. What are authors' opinions on these tools? Any tool should be recommended in the future?

We thank the reviewer for this comment. However, as our systematic review was not designed to evaluate the quality of the different tools, we feel it would not be appropriate to recommend a specific tool. Thus, a scoping review of tools used to measure agitated behaviors would be an excellent idea that we plan to pursue.

Line 424, you mentioned no language limitation, how did the authors search and handle the non-English literatures?

The literature search was conducted as described in the methods section. In the case of an abstract not available in English, the research team included authors fluent in French, Spanish, German, and Italian, who were able to read the abstract. Among selected articles, only one article in Spanish was included. The article was reviewed by authors fluent in Spanish.

Conclusion:

Once again, what's the new and concrete information to add in the field from the results?

To add

We have modified the conclusion to include more concrete information:

In conclusion, there are insufficient data to recommend the use of any medications for the management of agitation following TBI. Propranolol, methylphenidate, valproic acid and olanzapine may offer some benefit, however, they need to be further studied. The use of amantadine in the acutely ill may increase the risk of agitation whereas antipsychotics may prolong post-traumatic amnesia. More studies on tailored interventions and continuous evaluation throughout the acute, rehabilitation and outpatient settings are needed to assess the efficacy and safety of pharmacological agents for the management of agitated behaviours in both the adult and pediatric TBI populations. In addition, there is a need to better define and standardize the assessment of agitated behaviors. Newer agents such as dexmedetomidine should also be evaluated.

Reviewer: 2

Reviewer Name: Adam McKay

Institution and Country: Monash University

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This paper details a systematic review of pharmacological treatments of agitation in patients with TBI. In general the paper is well written and balanced in its conclusions. I have the following major comments:

1. Novelty. On Page 7, In 3. the authors indicate that two other systematic reviews that are very similar. There is another recent similar review by Hicks et al. (2018) titled: 'Efficacy and Harms of Pharmacological Interventions for Neurobehavioral Symptoms in Post-Traumatic Amnesia after Traumatic Brain Injury: A Systematic Review'. The authors need to be clearer about what this review adds beyond the existing reviews on the same/similar topics.

For example, they mention limitations of two existing reviews: 'however they included only French and English studies published before January 2016, had incomplete search strategies, and did not include the grey literature'. It would be helpful if the authors could be clearer about the specific paper that applies to each issue and how this current review address these issues.

The review by Hicks is not specific to agitated behaviors but is rather focused on post-traumatic amnesia. Hence, it did not evaluate trials that evaluated agitated behaviors after post-traumatic amnesia. To highlight the novelty of our systematic review, we have modified the introduction as follows: "Since then, two additional systematic reviews concluded that the evidence was insufficient and too weak to recommend any specific agent, however they included only French and English studies published before January 2016, had incomplete search strategies, and did not include the grey literature.<sup>24, 25</sup> To advance this field, we updated and broadened the literature search, included all languages and included studies in which an agitated behaviour was not an eligibility criterion, but was measured as an outcome variable"

In the Discussion, it would be helpful if the authors could comment on how the current findings relate to the existing reviews. They do mention the Plantier review but only in relation to olanzapine. A more general perspective would be helpful to know if there are agreements/disagreements between these reviews and potential reasons why.

This is an excellent and helpful comment. We have added the following sentences:

In comparison to the two most recent systematic reviews, we used a more rigorous and broader search strategy. As such, we restricted our search to randomized controlled, quasi-experimental, and observational studies with control groups that had a majority (>50%) of patients with TBI, thus excluding case reports, case series and uncontrolled observational studies. Our updated and broadened literature search enabled the identification of two additional studies from the grey literature, three recently published studies and one non-English study.<sup>24, 25, 33, 36, 37, 45, 47</sup> Our search strategy also included studies evaluating agitated behaviors as a secondary measure and identified 9 more studies, thus adding to previous systematic reviews. Furthermore, we included studies where the safety of pharmacological agents for the management of agitated behaviors was assessed and identified four such studies.

2. Quality. The authors do not indicate whether the review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. The rigour applied to his review would become more apparent to readers if they could report the review according to PRISMA guidelines and reference these within the paper.

The systematic review was conducted according to PRISMA guidelines and we have added this statement and reference in the methods section.

3. Term agitation. Agitation is most often associated with the early period of recovery after TBI whereas neurobehavioral or neuropsychiatric symptoms characterise behavioural issues more generally. I would recommend the authors change the term from agitation to neurobehavioral or neuropsychiatric as otherwise readers may think this review is focused on patients in the early stages of recovery; instead many of the studies included involve outpatients.

We agree with the reviewer's comments that characterizing agitation in TBI is not simple as many overlapping concepts have been suggested and are used in clinical trials. Defining these concepts over time is another important challenge. As we concentrated our literature search on "agitated behaviors" (specifically agitation, aggressiveness, assaultive behaviour, irritability and confusion), we feel using the term neurobehavioral symptoms may be too broad and not adequately characterize the scope of our systematic review. Hence, this is why we used "agitated behaviors" rather than simply agitation. Although we did not foresee identifying as many outpatient studies, they did respond to our inclusion criteria. In conclusion, we feel term "agitated behaviors" is more appropriate for our manuscript.

Relevant to this issue, their discussion of agitation on page 5 (ln 22-42) focusses on the agitation in the early stages of recovery after TBI and does not reflect their operationalising of agitation which extends to the outpatient period.

We have added the following sentence to introduction:

In TBI outpatients, neurobehavioral symptoms may be different in nature mostly include aggressiveness and irritability, more than physical agitation.

4. Discussion of amantadine. The authors highlight inconsistent findings with amantadine. Could this relate to the timing of recovery, different patients studied? A bit more discussion would be useful.

Thanks for this pertinent comment. We have modified the discussion as follows:

In the 4 studies that evaluated amantadine for irritability, agitation or aggressiveness, results were variable.<sup>33-36</sup> Although one study suggested a reduction in irritability in outpatients, a larger study by the same group failed to confirm these results.<sup>34, 35</sup> Interestingly, a recent observational study of patients exposed to amantadine in the ICU reported an increased risk of agitation.<sup>36</sup> Although these effects were not observed in a multicenter trial that started amantadine at least four weeks after TBI, the early use of amantadine in the ICU may explain these findings.<sup>36, 40</sup> However, these results were uncontrolled and confounding may also explain these differences. In addition, the use of amantadine may have increased arousal and the agitation measured may be part of the natural recovery. In studies in which agitation was not the presenting symptom, no significant differences in behavior scores between amantadine and control groups were reported.<sup>40, 42, 43</sup>

The following are more minor comments

1. Abstract - Include date from which search was conducted

We have added the date as suggested

2. Table 1 – Chili should be Chile

We have corrected the typo. Thanks.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Xiaolei Hu Umeå university, Sweden
<b>REVIEW RETURNED</b>	08-Jun-2019

<b>GENERAL COMMENTS</b>	The answer to my previous question (Line 424) concerning non-English literatures should be added into the method part to clarify the issue.
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## VERSION 2 – AUTHOR RESPONSE

Reviewer 1

2) We have added the following sentence to the Methods section:

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