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Title: Oral medication in agitation of psychiatric origin: A scoping review of randomized controlled trials

April 3, 2017

Dear Dr. Mills:

Thank you for responding so quickly with suggestions that would make our manuscript "Oral medication in agitation of psychiatric origin: A scoping review of randomized controlled trials" more appropriate for publication in your journal.

We have included your recommendations below, followed by the steps we took to revise our manuscript accordingly.

Thank you for your sincere consideration of the editorial comments on this manuscript. You clearly are interested in quality care for an under-represented patient population. This manuscript is such a valuable work of advocacy. We need more information and you have demonstrated that with your work.

Thank you for your understanding and support of our work.

In medicine, we have learned that expert consensus is important but objective data is necessary. We have had some large practice errors that came out of expert consensus without data.

The idea of oral anti-psychotics is good. However, in the clinical practice of Emergency Medicine, they may not be as safe as other options for a lot of reasons. Consider how safe it is to administer an oral medication to a patient who will not contract for safety. Consider the safety of a patient who is refusing oral medications with a staff who feels obligated to administer oral medication. If the oral medication is not as effective, consider the impact on the patient of agreeing to an oral medication then receiving an IM medication anyway. We need objective data to properly advocate for our patients.

The editor's point is well-taken. The issue addressed in the current study is in fact the evidence base for the expert consensus, which while small, is generally supportive of the use of this route of medication. We have revised the manuscript to clarify that the aim of our scoping review is to assess the extent to which expert consensus recommendations regarding oral anti-psychotics have been supported by published data. This point has been made clearer in the "Objectives" section in the abstract, the introduction, and the discussion.

For further details, please see the following manuscripts, which are provided in the references so that readers of the journal can reach their own conclusions regarding this matter:

Allen MH, Currier GW, Hughes DH, Reyes-Harde M, Docherty JP. Expert consensus guideline series: Treatment of behavioral emergencies. Postgrad Med 2001; (Spec No):1-88.

Campillo A, Castillo E, Vilke GM, Hopper A, Ryan V, Wilson MP. First generation antipsychotics are still preferred in the emergency department but are often not administered with adjunctive medications. J Emerg Med. 2015; 49(6):901-906.

Wilson MP, Minassian A, Bahramzi M, Campillo A, Vilke GM. Despite expert recommendations, second-generation antipsychotics are not often prescribed in the emergency department. J Emerg Med. 2014; 46(6):808-13.

Wilson MP, Pepper D, Currier GW, Holloman GH, Feifel D. The psychopharmacology of agitation: Consensus statement of the American Association for Emergency Psychiatry Project BETA Psychopharmacology Workgroup. West JEM. 2012; 13(1):26-34.

Gault TI, Gray SM, Vilke GM, Wilson MP. Graded Evidence-based Medicine Summaries for the Journal of Emergency Medicine (GEMS for JEM): Are oral medications effective in the management of acute agitation? J Emerg Med. 2012; 43(5):854-9.

Please consider some subtle editorial comments below.

Line 50 Please add "of presumed psychiatric origin." to this sentence.

"Of presumed psychiatric origin" has been added.

Line 100 "Although it has been claimed that emergency 101 physicians research common problems in proportion to their frequency," Please add a citation for this claim or delete it.

Citation [21] has been moved to an earlier point in the sentence to avoid ambiguity.

Line 107 "Recommendations for the use of 109 second-generation psychotics in reducing symptoms of acute agitation have therefore likely been 110 extrapolated from other data; " There is a lot of assumption in this sentence. Perhaps the recommendations just come from someone's preference or from someone's personal experience, perhaps not in an ED setting. Would it be more accurate to state "Recommendations for the sue of second-generation.... have not developed out of randomized controlled trials"? Consider revising this statement to make it based on the facts that you have uncovered rather than on further conjecture.

"Likely" has been removed from the sentence above to avoid conjecture and the paragraph has been reworded to reflect that such recommendations have been developed out of only a few randomized trials in addition to other non-randomized, controlled studies.

Line 110: "the oral administration of SGAs to patients experiencing acute 111 agitation in the ED setting merits additional study." This is the crux of all of your hard work. Please make this an independent sentence.

Agreed. This phrase above has been made an independent sentence.

Line 129 "Although this recommendation may be well-advised, " please consider deleting this portion of the sentence. Again, assumptions are being made here.

This sentence has been similarly revised to avoid conjecture and restate that the evidence base supporting the recommendations of expert consensus panels currently consists of only a small number of randomized, controlled trials.

Thank you again for providing helpful feedback and please let us know if we can make further changes to ensure our manuscript is suitable for publication in your journal.

Sincerely,

Samuel Mullinax, BA
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*Cover Letter

Department of Emergency Medicine
Behavioral Emergencies Research

April 3, 2017

To the editor:

Thank you for considering the revisions to our manuscript "Oral medication in agitation of psychiatric origin: A scoping review of randomized controlled trials". This paper aims to summarize the research pertaining to the use of oral second-generation psychotic medications for the emergent treatment of acute agitation. We look forward to the reviewers' comments.

Sincerely,

Samuel Mullinax, BA
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Oral medication in agitation of psychiatric origin: A scoping review of randomized controlled trials

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The authors have no conflicts of interest to disclose.

Acknowledgments

We would like to thank Mohammad Omer Aslam-Mir for his assistance with this project.

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Acknowledgments

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Oral medication for acute agitation of psychiatric origin: A scoping review of randomized controlled trials

Abstract

Background: Understanding more about the efficacy and safety of oral second-generation antipsychotic medications in reducing the symptoms of acute agitation could improve the treatment of psychiatric emergencies.

Objectives: The objectives of this scoping review are to examine the evidence base underlying expert consensus panel recommendations for the use of oral second-generation antipsychotics to treat acute agitation in mentally ill patients.

Methods: The Cochrane Schizophrenia Group's Study-Based Register was searched for randomized, controlled trials comparing oral second-generation antipsychotics to themselves, benzodiazepines, or first-generation antipsychotics with or without adjunctive benzodiazepines, irrespective of route of administration of the drug being compared. Six articles were included in the final review.

Results: Two oral-second generation antipsychotic medications were studied across the six included trials. While the studies had relatively small sample sizes, oral second-generation antipsychotics similarly effective to IM first-generation antipsychotics in treating symptoms of acute agitation and had similar side effect profiles.

Conclusions: This scoping review identified six randomized trials investigating the use of oral SGAs in the reduction of acute agitation among patients experiencing psychiatric emergencies.

Further research will be necessary to make clinical recommendations due to the overall dearth of randomized trials as well as the small sample sizes of the included studies.

Introduction

Agitated patients in the emergency department pose unique dangers to themselves and challenges for treatment providers. Although precise numbers are hard to determine, it is likely that as many as 1.7 million episodes of acute agitation are treated annually [1-2]. Over the past several years, expert consensus panels, most recently Project BETA, have called for improved humane practices to treat agitated patients [3]. Project BETA ("Best Evidence for the Evaluation and Treatment of Agitation") convened over 35 experts, including emergency psychiatrists, emergency medicine physicians, and mental health clinicians, preferentially recommending second-generation antipsychotics (SGAs) over the more common combination of intramuscular haloperidol + lorazepam [4-7]. SGAs were preferentially recommended orally, both to save patients the unpleasantness of needle sticks and to potentially save injury to nursing staff but the recommendation relied mostly on expert consensus instead of a comprehensive survey of available literature [8].

A previous qualitative review on oral medications in acute agitation concluded that oral medications were at least as effective as intramuscular injections, but it included non-randomized and observational trials [9]. The objective of this study therefore was to survey the literature of randomized controlled trials on oral medications in mentally ill patients suffering from acute agitation, utilizing methodology developed by the Cochrane Collaboration, to examine the amount of evidence for the expert consensus recommendation [10-11].

Methods

A scoping review aims to qualitatively summarize the research on a given topic without necessarily assessing risk of bias or synthesizing quantitative findings. Scoping reviews are particularly useful for clarifying further investigative directions, especially when the topic at hand has not been thoroughly explored in a rigorous fashion and the available evidence that does exist has been acquired through relatively heterogeneous means [12].

In this scoping paper, randomized and controlled trials were included that pertained to the use of oral second-generation psychotics in the treatment of acute agitation of presumed psychiatric origin. Trials were included if they were randomized evaluations of an oral administration of at least one second-generation antipsychotic medication (with or without other medications at same time of administration) and contained an outcome measure of acute agitation with the majority of assessments occurring within 24 hours. Trials were excluded if they were not randomized or if they did not include oral administration of second-generation antipsychotics. Furthermore, studies that switched between different medications or different routes of administration within the same group of patients without analysing the potential differences induced by such changes were excluded. Finally, records of studies with a suspected cohort of patients shared between different studies or those records with patients which were a subset or duplicate analysis of a larger patient cohort were also excluded.

Identification of records

The Cochrane Schizophrenia Group's Study-Based Register was searched on March 11, 2016. This register is compiled and updated by searches of different biomedical databases, including AMED, BIOSIS, EMBASE, MEDLINE, PsycINFO, CINAHL, PubMed and registries of clinical

trials. More information about this source, which contains randomized controlled clinical trials of patients with schizophrenia in addition to other severe mental illnesses, is available via http://schizophrenia.cochrane.org/register-trials. The following keywords were used:

((("Oral* OR " Oral* OR *(Oral* OR *Orodispersible* OR *Tablet* OR *Pill* OR *Sublingu*OR *Sub-Lingu* OR *Sub Lingu* OR *Tongue* OR *Chew* OR *Swallow* OR *Capsule*) in Title or Abstract Field of REFERENCE OR (*(Oral)* OR *Route*) in Intervention Field of STUDY) AND ((*Aggress* OR *Violen* OR *Agitat* OR *Tranq*) in Title OR Abstract of REFERENCE OR (*Aggression* OR *Agitation* OR *Violence*) in Healthcare Condition of STUDY)

After checking the relevancy of search results, the following search terms were not included among the search terms because they did not retrieve any relevant results: Capsule, Swallow, Chew, Under the Tongue, Sustained Release (SR), Extended Release (ER) (XR), and Immediate Release (IR).

Data collection and processing

All full records returned by the database search were inspected for relevance by [blinded for peer review]. Please see Figure 1. Multiple reports of single trials were clustered to avoid double counting.

Results

Of the >20,000 randomised trials on the Cochrane Schizophrenia Group's register (>25,000 reports) only six evaluated oral antipsychotic drugs for people who are agitated or aggressive (Table 1). Trials were small (total n=465, range 20-162) and all studies generated six

comparisons with only one comparison (oral risperidone vs IM haloperidol) likely to have anywhere near adequate power to adequately identify outcomes of direct clinical value (Table 2).

Although all six included studies were prospective clinical trials evaluating agitated patients within 24 hours of medication administration; only two were conducted solely in the ED. Reduction in agitation was assessed using a variety of standardized rating scales; the empirically validated Positive and Negative Syndrome Scale Excited Component was used most frequently [19]. Five studies compared oral second-generation antipsychotics to IM first-generation antipsychotics or IM second-generation antipsychotics. In general, the included studies found that oral second-generation antipsychotics were effective for reducing acute agitation and had side effect profiles that were comparable to first-generation antipsychotics (Table 1).

Discussion

A survey of 56 medical directors of psychiatric emergency services showed a preference for the use of oral atypical antipsychotic agents [20]. Although it has been claimed that emergency physicians research common problems in proportion to their frequency [21], there is a surprisingly small amount of evidence from randomized controlled trials about the use of oral antipsychotics for acute agitation even when searching the literature for articles outside the emergency department.

Perhaps more surprising, the total number of patients randomized worldwide is only 465. Only two randomized trials have been conducted solely in an ED setting, and the only SGAs that have been studied in this manner are risperidone and olanzapine. Recommendations for the use of second-generation antipsychotics in reducing symptoms of acute agitation by expert consensus

panels such as Project BETA [8] have been developed using a small number of randomized controlled trials. As noted by Gault and colleagues, however, there is more evidence when non-randomized studies are included [9]. The oral administration of SGAs to patients experiencing acute agitation in the ED setting merits additional study.

Limitations

There are important limitations of this scoping study. First, this was designed to scope out existing literature; and the risk of bias was not assessed. This survey also did not include sublingual medications and so did not capture any investigations using this formulation, although at least one such trial does exist [22]. In addition, inhaled medications were not included [23]. However, it seems unlikely that large, important, and relevant oral medication studies were missed by this methodology.

Finally, this survey did not scrutinize the methodology of these articles in detail, and so the effect sizes of the interventions were not summarized. It is theoretically possible that some interventions which have a low number of participants may have nonetheless a large effect size, thus making further study unwarranted. However, even if considerable effect were reported for any one of the ten possible comparisons within the six trials, selecting a treatment based on the findings of one study is often ill-advised.

Conclusions

Expert consensus panels such as Allen et al and the BETA project [4,9] have preferentially recommended oral administration of SGAs for acute agitation in the ED. Although the existing evidence has generally supported the use of oral medication thus far, the available research is

limited. Only six small randomized trials investigating the use of oral SGAs among patients with mental illnesses have been undertaken worldwide, and only two of those trials have taken place entirely in an ED. Further study of this issue is needed.

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Article Summary

1. **Why is this topic important?**

Patients experiencing an episode of acute agitation pose risks to themselves and staff, distress other patients, and consume ED resources until they are sedated. This topic is important because it explores treatment approaches for rapidly and humanely managing agitation among mentally ill patients in an acute setting.

2. **What does this study attempt to show?**

This study summarizes existing literature pertaining to the use of oral second-generation antipsychotics in the treatment of acute agitated patients with psychiatric conditions and suggests directions for future research.

3. **What are the key findings?**

Oral second-generation antipsychotics were found to be similarly effective to IM first-generation antipsychotics with similar side effect profiles by the included trials. However, only six randomized trials with small sample sizes were included, so further research is needed before clinical recommendations can be made.

4. **How is patient care impacted?**

Patient care will not be directly impacted until this topic is studied further. If more evidence emerges supporting the use oral second-generation drugs to treat acute agitation, doing so would be in line with a recent expert consensus panel as well as patient preference; patients with schizophrenia and schizoaffective disorder surveyed about antipsychotic medication have reported that they perceive receiving oral medication as less coercive than receiving an injection [24].

Table 1: Included trials and their results

Study tag	Comparison				Setting	Total N	Primary assessment tool(s)	Results
	Oral		Intramuscular					
Currier 2004	Risperidone (2mg) + lorazepam (2mg)		Haloperidol (4mg) + lorazepam (2mg)		24 sites, ED/inpatients United States	162	Positive and Negative Syndrome Scale (PANSS) 5-item acute-agitation cluster	Similar tolerability and reductions in agitation from 30 to 120 minutes
Hatta 2008*	Risperidone solution (3mg)	Olanzapine disintegrating tablet (10mg)			7 EDs Japan	87	Excited Component for PANSS (PANSS-EC)	Similar reductions in agitation from 0 to 60 minutes; Olanzapine provided greater recovery from tachycardia
Herrera 2005	Risperidone solution (10mg) + IM placebo		Haloperidol (10mg) + oral placebo		Inpatients, acute ward Mexico	20	PANSS-EC and Brief Psychiatric Rating Scale (BPRS)	Similar tolerability and reductions in agitation
Hsu 2010	Risperidone solution (3mg)	Olanzapine (10mg)	Haloperidol (7.5mg)	Olanzapine (10mg)	Inpatients, acute ward Taiwan	42	PANSS-EC	Greater reductions in agitation from 15 to 90 minutes with oral and IM olanzapine than with IM haloperidol
Lim 2010	Risperidone (2mg)		Haloperidol (5mg)		ED/inpatients Korea	124	PANSS-EC and Clinical Global Impression-Severity of Illness Scale (CGI-S)	Similar tolerability and reductions in agitation
Veser 2006	Risperidone (2mg)	Placebo	Lorazepam (2mg)		1 ED United States	30	PANSS and BPRS	Similar tolerability and reductions in agitation from 30 to 90 minutes

***** Pseudorandomized study design

Table 2. Comparisons generated from identified studies

Comparison	Study tag	Estimates of total number or participants within comparison
Oral risperidone vs IM haloperidol	Currier 2004, Herrera 2005, Hsu 2010, Lim 2010	326
Oral risperidone vs oral placebo	Veser 2006	20
Oral risperidone vs IM lorazepam	Veser 2006	20
Oral risperidone vs oral olanzapine	Hatta 2008, Hsu 2010	109
Oral risperidone vs IM olanzapine	Hsu 2010	20
Oral placebo vs IM lorazepam	Veser 2006	20

Figure 1
Click here to download high resolution image

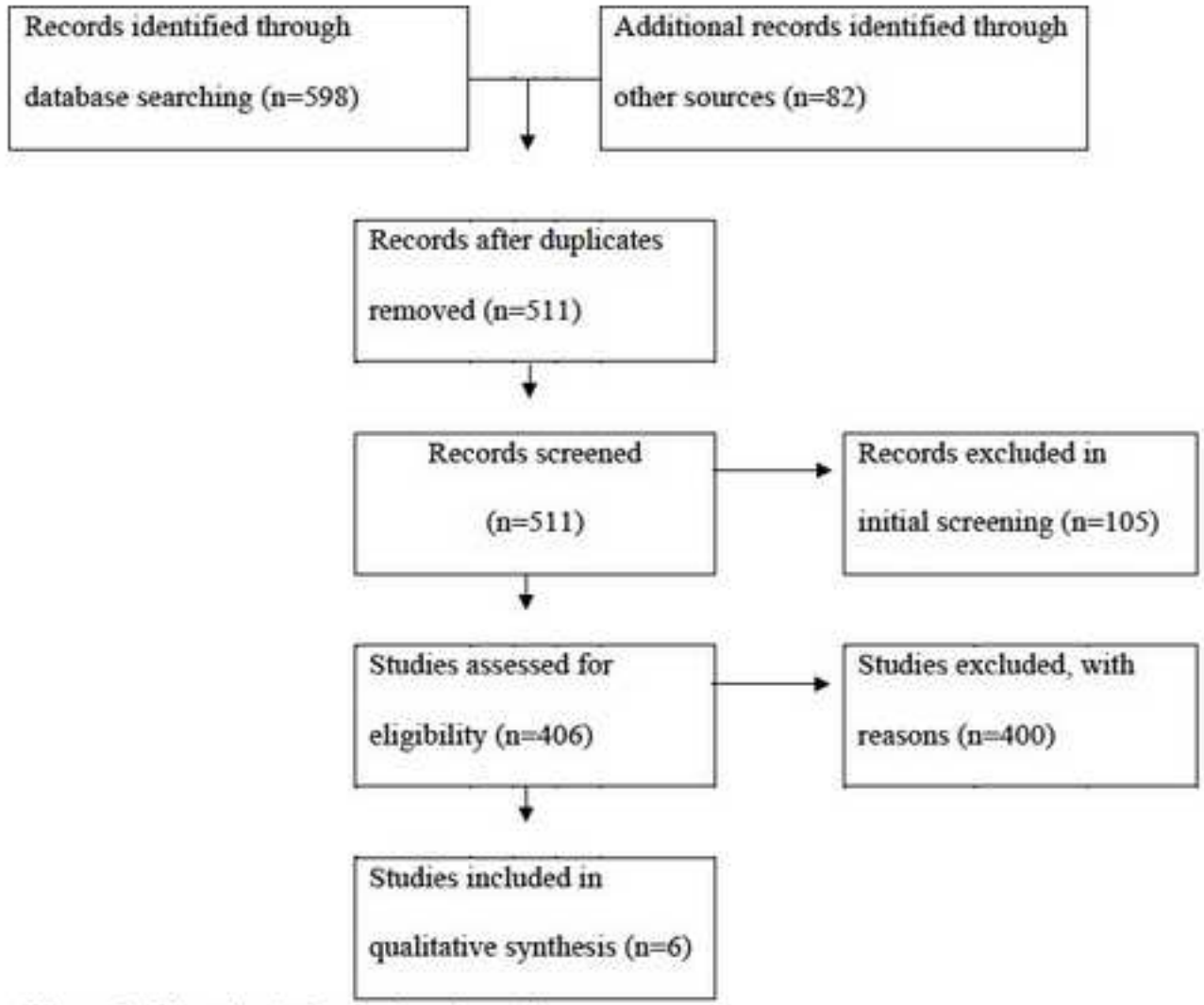

Figure 1. Flowchart of search and results