Review

Efficacy and Safety of Citalopram Compared to Atypical Antipsychotics on Agitation in patients with BPSD.

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Abstract:

Background: *The psychomotor agitation of the behavioural and psychological symptoms of dementia (BPSD) is one of the common issues in aged care facilities, leading to the poor functional and medical consequences. Psychotropic interventions are the preferred choice of treatment, but which medication should be the prescribers first preference? This review aims to compare pharmacological interventions for psychomotor agitation, judging them according to their effectuality and justifiability profiles. This is to be achieved by retrieving information from Randomised Control Trials (RCTs) and systematic reviews.* ***Objectives:*** *This review evaluates evidence from RCTs, systematic reviews, and meta-analyses of BPSD patients who have taken agitation treatments. Assessing the efficacy of selective serotonin reuptake inhibitors (SSRI) and antipsychotic treatments when compared to each other for the purpose of improving agitation outcomes.* ***Methods:*** *This review includes RCT that compared one or more active ingredient medications with another medication or with a placebo, along with systematic reviews comparing citalopram (SSRI) with antipsychotics such as quetiapine, olanzapine, and risperidone. Studies were extracted by searching and accessing databases, such as PubMed, OVID, and Cochrane with restrictions of date from 2000 to 2021 and English language.* ***Conclusion:*** *There is still limited studies of SSRIs for the treatment of agitation in BPSD. SSRIs such as citalopram were associated with a reduction in symptoms of agitation, and lower risk of adverse effects compared to antipsychotics. Future studies are required to assess the long-term safety and efficacy of SSRI treatments for agitation in BPSD.*

Keywords: BPSD; antipsychotics; SSRIs, dementia, agitation

1. Introduction

A large portion of older people who are diagnosed with dementia are experiencing more than one of the BPSD symptoms during their illness [1]. A recent systematic review stated that more than 80% of BPSD exhibit agitation. Psychomotor agitation is a symptom of mood disorders and motor restlessness, characterised by inappropriate behaviour, be it by verbal or vocal expression, or by physical activity that can be repetitive, aggressive, and often contradictory to social standards [1]. Recent clinical guidelines recommended non-pharmacological interventions as the first attempt to try for managing agitation. However, if the agitation causes distress and potentiates the risk of harm to others, then pharmacological approaches may be considered for alleviating agitation [1]. RCTs have evaluated different psychotropic interventions, such as antidepressants, antipsychotics, cholinesterase inhibitors, benzodiazepines, and anticonvulsants [2,3,4,5,6,7,8]. Most of these studies have been compared among different classes of psychotropics. A few RCTs have stated beneficial effects of citalopram for agitation associated with dementia [2,7,8], and suggested it as a safer alternative to antipsychotics. There is however limited evidence from a direct RCT-double blind study comparing citalopram to other atypical antipsychotics in dementia. Therefore, this review aimed to conduct systematic reviews and RCTs to evaluate the effectiveness, safety, and acceptability of citalopram compared to other antipsychotics for psychomotor agitation in dementia.

2. Materials and Methods

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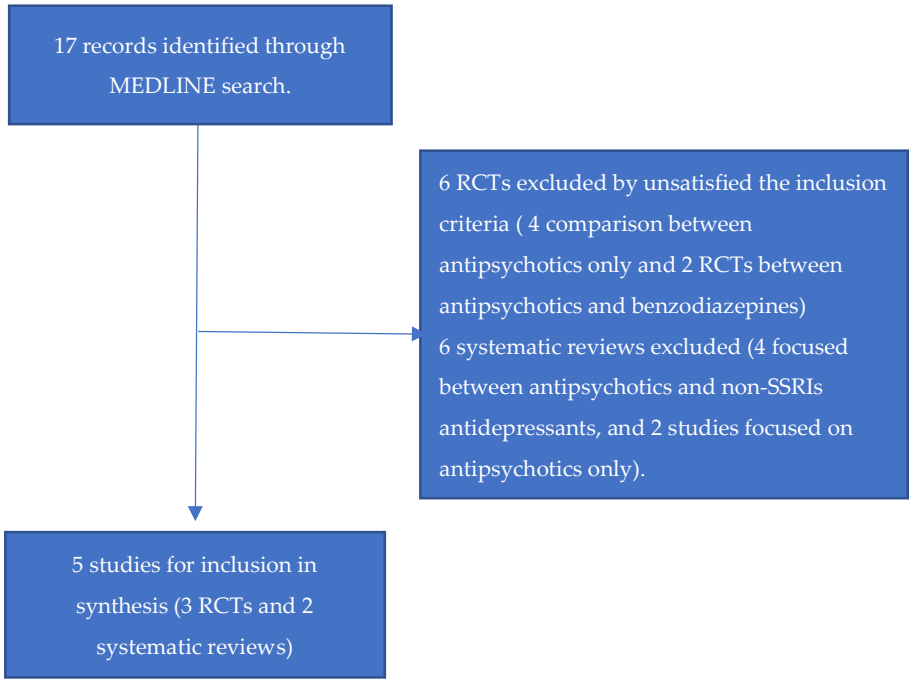
Studies were retrieved by searching electronic databases, including PubMed, OVID MEDLINE, and Cochrane Central Register of Controlled Trials for literature appurtenant to pharmacological interventions for treating agitation in dementia from 2000 until 2021. Search strategies are outlined in appendix 1. MeSH-indexed search terms 'BPSD', 'dementia with agitation', 'psychomotor agitation', 'SSRI', 'citalopram', 'antipsychotics', 'olanzapine', 'haloperidol', 'risperidone', quetiapine'. The results were filtered to include only RCTs, systematic reviews and meta-analysis with English language restriction. After that, the titles and abstracts were manually searched for those compared between SSRIs and antipsychotics. Moreover, the systematic reviews collected from the search were reported in accordance with the PRISMA. The collected data including the details of randomisation, number of participants, dosage, duration of exposure, presence or absences, follow-up/loss of follow-up, adverse effects, and primary outcomes.



3. Results

Six RCTs were excluded as four of six RCTs compared only antipsychotics and two RCTs compared antipsychotics with benzodiazepines. Six systematic reviews are excluded as four focused on antipsychotics and other antidepressants, and two were comparisons of antipsychotics. Thus, the remaining three RCTs and two systematic reviews for inclusion in this synthesis.

Description of systematic reviews

Chaiyakunapruk, et al 2018 [9], designed a systematic review study. The result extracted thirty-six RCTs involving 5585 older people with dementia. Risperidone OR=1.96 (95%CI 1.49-2.59) and SSRI (citalopram) OR=1.61 (95% CI 1.02-2.53) were found to have significant effects compared to placebo. In addition, this review showed haloperidol has less efficacy than other antipsychotics and SSRIs for controlling agitation. The primary outcome of this review stated that risperidone and citalopram showed significant efficacy for agitation in dementia. Haloperidol and oxcarbazepine lack in efficacy and acceptability [9].

Cochrane intervention review performed by Seitz et al, 2011 [10] intensively compared past studies on SSRIs used for agitation in dementia included was five studies (citalopram, fluvoxamine, sertraline, fluoxetine) to a placebo, four studies compared SSRIs to antipsychotics (perphenazine vs citalopram), (haloperidol vs sertraline), (haloperidol vs fluoxetine), and (citalopram vs risperidone). Overall outcome stated that citalopram and sertraline were more effective than placebo and no difference between SSRIs and antipsychotics in treatment of agitation [10].

Description of randomised controlled trials

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There are three recent RCT studies that have explored citalopram as treatment for agitation and aggression in dementia.

A six-month RCT [2], 75 participants at nursing homes were randomised to receive either citalopram, quetiapine, or olanzapine (n=25 each group). Individuals included in the study met criteria of NINCDS-ADRDA; clinically relevant agitation; and have a history of psychotropic drugs before admission. The result of this trial showed citalopram has similar efficacy to quetiapine and olanzapine for managing agitation. Citalopram vs quetiapine (OR 1 95%CI= 0.92,1.7 at P=0.935). Citalopram vs olanzapine (OR=0.98, 95% CI 0.86,1.2 at P=0.849). Citalopram demonstrated lowest all-case hospitalisations than quetiapine (OR=0.92, 95%CI= 0.88,0.95 at P=0.016) and olanzapine (OR=0.78, 95% CI= 0.64,0.92 at P=0.004). Moreover, citalopram also demonstrated a decreased occurrence of falls in comparison with olanzapine (OR=0.81, 95%CI= 0.68,0.97 at P=0.012), but no difference was noted regarding instances of falls between citalopram and quetiapine. In addition, citalopram had the lowest incidence of orthostatic hypotension with; quetiapine (OR=0.8, 95%CI = 0.66,0.95 at P=0.032) and olanzapine (OR=0.75, 95%CI= 0.69,0.91 at P=0.02). This trial revealed no differences observed regarding QT wave prolongation and infections [2].

A twelve-week randomised, double-blind controlled trial done by Pollock et al 2007 was conducted at the University of Pittsburgh Medical Centre [7] comparing citalopram and risperidone for the treatment of psychosis and behavioural symptoms associated with dementia. 103 participants were recruited, all met the criteria of at least one of the following moderate to severe target symptoms; agitation, aggression, delusion, suspiciousness. Blinded randomisation was in two groups, citalopram (n=53) or risperidone (n=50). Before and after mixed model analysis of the outcome measures were conducted using a neurobehavioral rating scale (NBR scale) and side effect rating scale (SER scale) at weekly and fortnightly intervals. The result of this trial showed the agitation and psychosis symptoms decreased in both treatment groups. Neurobehavioral Rating Scale (NBRS) agitation score citalopram vs risperidone (OR 0.11 95%CI= -0.28,0.50 at P=0.57). NBRS psychosis score (OR=0.06, 95%CI= -0.35,0.46 at P=0.79). Udvalg for Kliniske Undersogelser side effect scale (UKU) total score (OR=0.52, 95% CI 0.12,0.91 at P= 0.01). UKU psychotic subscale score (OR=0.55, 95% CI 0.15,0.94 at P= 0.007). UKU neurological subscale score (OR=0.22, 95% CI= -0.17,0.61 at P=0.27). Also, the trial stated that there were significant side effects with risperidone but not with citalopram [7].

CitAD randomised clinical trial is another study examined the effect of citalopram on agitation in Alzheimer's dementia. The study was conducted by Marano et al 2014 [8], as a randomised, parallel group, double-blinded, placebo-controlled trial that recruited 186 participants with Alzheimer's dementia and clinically reported with agitation. The randomisation was achieved by dividing 186 participants into two groups, 92 placebo group participants received psychosocial intervention and 94 intervention group received citalopram for 9 weeks. The intervention group received citalopram at 10mg daily and gradually titrated to 30mg daily over three weeks based on response and tolerability [8]. The result was established on the measures of neuropsychological rating scale agitation subscale (NBRS-A), and modified Alzheimer's disease cooperative study-clinical global impression of change (mADCS-CGIC). Also, this study used other scales such as CMAI, NPI and ADLs for neuropsychiatry agitation and MMSE for mental status. The results of this trial showed significant improvement compared to placebo group. The NBRS-A scale after 9 weeks shown OR -0.93 95%CI= -1.80,-0.06 at P= 0.04. The results of mADCS-CGIC shown 40% of citalopram have improvement with OR 2.13 95%CI= 1.23,3.69 at P=0.01. Moreover, CMAI and NPI scales revealed significant improvement for citalopram group participants. However, QT intervals prolongation were seen at higher rates in the citalopram group than placebo (18.1ms; 95%CI= 6.1,30.1 at P=0.004) [8].

Table 1: Psychotropics-related outcomes of three randomised controlled trials

Citation, year	Number of participants	Duration	Active ingredient	Lost Follow-up	Difference between groups	Outcome

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Viscogliosi et al, 2017	75 (citalopram n=25), (olanzapine n=25), (quetiapine n=25)	26 weeks	Citalopram, olanzapine, quetiapine	Short duration of follow-up (no details)	Efficacy against agitation: Citalopram vs quetiapine (OR 1 95%CI= 0.92,1.7 at P=0.935). Citalopram vs olanzapine (OR=0.98, 95% CI= 0.86,1.2 at P=0.849). Hospitalization: quetiapine (OR=0.92, 95%CI= 0.88,0.95 at P=0.016), olanzapine (OR=0.78, 95% CI= 0.64,0.92 at P=0.004). Occurrence of falls: olanzapine (OR=0.81, 95%CI= 0.68,0.97 at P=0.012). Incidence of orthostatic hypotension: quetiapine (OR=0.8, 95%CI = 0.66,0.95 at P=0.032) and olanzapine (OR=0.75, 95%CI= 0.69,0.91 at P=0.02).	citalopram has similar efficacy to quetiapine and olanzapine. Citalopram shown less all-case hospitalisations than both quetiapine and olanzapine. Citalopram shown also the lest occurrence of falls than olanzapine but no difference in lowering falls between citalopram and quetiapine. Citalopram showed lower incidence of orthostatic hypotension than quetiapine and olanzapine.
Pollock et al, 2007	103 (citalopram n=53), (risperidone n=50)	12 weeks	Citalopram, risperidone	N=31 lost follow-up in risperidone group. N=38 lost follow-up in citalopram group	NBRS agitation score citalopram vs risperidone (OR 0.11 95%CI= -0.28,0.50 at P=0.57). NBRS psychosis score (OR=0.06, 95%CI= -0.35,0.46 at P=0.79). UKU total score (OR=0.52, 95% CI 0.12,0.91 at P= 0.01). UKU psychotic subscale score (OR=0.55, 95% CI 0.15,0.94 at P= 0.007). UKU neurological subscale score (OR=0.22, 95% CI= -0.17,0.61 at P=0.27).	The result of this trial shown the agitation and psychosis symptoms decreased in both treatment groups. Also, the trial stated that there was a significant side effect risperidone but not with citalopram.
Marano et al 2014	186 (citalopram n= 94), (psychotherapy n=92).	9 weeks	Citalopram vs placebo	After week-9 visit, n=8 lost follow-up in citalopram group and n=9 in psychotherapy group.	The NBRS-A scale after 9 weeks shown OR -0.93 95%CI= -1.80,-0.06 at P= 0.04. The results of mADCS-CGIC shown 40% of citalopram have marked improvement with OR 2.13 95%CI= 1.23,3.69 at P=0.01.	The results of this trial showed significant improvement in citalopram group compared to placebo group. Moreover, CMAI and NPI scales were shown significant improvement for citalopram group participants. However, QT intervals

					QT intervals prolongation were seen in the citalopram group than placebo (18.1ms; 95%CI= 6.1,30.1 at P=0.004).	prolongation were seen in the citalopram group than placebo.

4. Discussion

Quality of evidence

- **Methodological quality of the systematic reviews**

The systematic reviews by Seitz et al., [10] and Chaiyakunapruk et al., [9] were of high quality, scoring 14/16 and 12/16 respectively on the AMSTAR2 assessment tool. Both reviews searched the PICO question and clearly stated the inclusion criteria. Both reviews expressed their methodology prior to conducting the articles refining and both significantly justified the protocols. The authors of both reviews explained their study designs, adequately justifying exclusions, and use comprehensive literature search strategies.
Seitz et al. review applied the 'risk of bias tool' to assess bias results by methodological quality and summary graphs. Moreover, bias in this review was assessed by visual screening of funnel plots of the primary outcomes. Chaiyakunapruk et al. review examined the selected study bias by using (Rob version 2) the revised Cochrane risk of bias tool for randomisation trials.
This tool measures deviation from intended interventions, bias in the measurements, bias due to results outcomes, bias due to missed outcome data. In general, the risk of bias of the selected studies in this review was classified at low risk. The authors of both reviews provide a satisfactory explanation, discussion in the results. Both reviews reported potential conflict of interest, but there is no information about the sources of funding they received for conducting the review.

AMSTAR Assessment tool

AMSTAR 2 TOOL	Seitz et al, 2011	Chaiyakunapruk et al, 2018
Include PICO components and research questions	YES	YES
Comprehensive details about methodology before conducting the review	YES	YES
Description of the inclusion criteria	YES	YES
Comprehensive details about searching strategies	YES	YES
Performed study selection in duplicate	YES	NO
Data extraction in duplicate	YES	YES
Describe exclusion criteria	NO	YES
Describe inclusion studies in detail	YES	YES
Satisfactory technique for assessing risk of bias	YES	YES
Report the source of funding	NO	NO

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Use an appropriate statistical technique for meta-analysis combination of RCT results	YES	YES
Assess the potential impact of RoB on each individual RCT study	NO	YES
Account RoB in each individual study when discussing the result	YES	YES
Satisfactory explanation for RCT results in the review	YES	YES
Perform an adequate investigation of potential risk of bias in quantitative studies	YES	YES
Reported any potential conflict of interest and funding	YES	YES

- **Methodological quality of most recent trials**

The trial by Viscogliosi et al. 2017 [2] was conducted with 75 participants. They had selected after inclusion criteria was satisfied, including a diagnosis of Alzheimer's dementia paired with clinically relevant agitation. The method used to generate the random allocation sequences was conducted by two experienced geriatricians who randomized the participants into three equal groups (n=25 each group). However, there is no information on whether blocking or stratification was reported during randomization; and no information whether any participants in the group were concealed until interventions were assigned. The authors did not specify what aspects of the trial were blinded, and if the persons administering the interventions, or those investigating outcomes had knowledge of what substance each patient was given. Regarding participants flow in this study, a diagram was absent, and there was a noted absence of information regarding what had happened to the groups for a period of 6 months during the trial. Also, there was a distinct lack of information regarding how many participants did not engage in follow-up. The strong point of this study has demonstrated the baseline demographic and clinical characteristics of inclusion and exclusion criteria. The numbers of participants in each group were compared and analysed into two tables and graphs. The report also provides clear outcomes and a summary of results for each group [2].

The objective and the hypotheses of the trial by Pollock et al., 2007 [7] are well-explained, comparing risperidone and citalopram for the treatment of agitation and psychosis in dementia. The hypotheses of this trial stated that citalopram is more effective for agitation while risperidone proved more effective for psychosis. The period of the trial is 12 weeks, randomised 103 dementia patients. The eligibility criteria for participants along with the settings and locations where the data was collected are mentioned in detail. The participants were randomised to either risperidone (n=50) or citalopram (n=53). The randomisation was generated by a biostatistician at the beginning of the trial and the stratification of randomisation might consider based on the presence or absence of the psychotic symptoms [7]. Only the research pharmacist has access to the information regarding the treatment assigned to each group, participants, and investigators. Only the assessors in this trial remained blind throughout the study. After randomisation, the assigned participants were assessed after receiving citalopram or risperidone for three, and seven days, then once a week for five weeks, then once fortnightly, and at the discharge from hospital. Also, the authors explained the details of intent-to-treat principles after randomisation. In addition, the participants continued to administrate the medications even after discharged under rigorous maintenance of the double-blinded conditions. The flow of participants through each stage of the trial was explained clearly in the methods and discussion, illustrated by a diagram. The author successfully demonstrated that each group reported the numbers of randomly assigned participants, intended treatments, follow-up, completed and analysed for the primary outcomes. The limitation

of this trial is that it has no placebo, and it was established on the efficacy of citalopram and risperidone on evidence of only two previous trials [7].

Marano et al. 2014 conducted an RCT study that showed citalopram reduced agitation when compared to placebo [8]. The objective of this trial was to assess the efficacy of citalopram for agitation in Alzheimer's dementia. The study was involving 186 patients in a double blinded, randomised, placebo-controlled trial. The participants satisfied the inclusion criteria (>65 years, and diagnosed with Alzheimer's dementia and reported with clinically significant agitation). The authors mentioned that the participants were randomised, however, there is no explanation of the method had used to generate the random allocation sequence, and no details regarding whether the randomisation exposed any restriction, blocking or stratification [8]. It is mentioned in this study that the trial is a double-blinded treatment assignment with adherence to mask rating. But there are no details about whether or not the participants in both intervention and control groups, and those assessing the outcome were blinded, how blinding was achieved, and how blinding success was evaluated. 186 participants were randomised to receive a psychosocial intervention, and either placebo or citalopram for a duration of 9 weeks. The initial dose is 10mg for citalopram with gradual titration to a maximum of 30mg daily over three weeks based on individual response. The flow of participants through each stage of the trial was mentioned in detail and illustrated by a diagram specifically for each group. This diagram also reported the numbers of randomly assigned participants, who received citalopram or placebo, steps of follow-up, and numbers who were absent in the follow-up in each check-up visit. The primary outcome of this trial was based on scores from the neurobehavioral rating scale agitation subscale (NBRS-A) and mADCS-CGIC scale, CMAI scores, NPI, ADLs, MMSE and adverse effects. In general, despite of QT prolongation was reported in citalopram group, the participants showed significant improvement of agitation compared to placebo [8].

5. Conclusions

Traditionally, atypical antipsychotics have been used as the primary method for treating the episodes of agitation and psychosis for people with dementia. However, despite the effectiveness of these agents in managing the agitation, they still provide undesirable side effects and an increased risk of mortality. As a result, there is continued campaigns to reduce the use of antipsychotics in older people and promoting the use of alternative agents such as SSRIs. Although there is limited evidence collected in this review, the findings from the two systematic reviews and the three clinical trials, indicated that SSRI antidepressants (citalopram), not only showed efficacy for treating BPSD. but were better tolerated compared to antipsychotics. This review also presented that citalopram reduces the symptoms of agitation when compared to placebo and it has less adverse effects compared with atypical antipsychotics such as risperidone, quetiapine, and olanzapine. The outcome of this review suggests that further studies involving more participants from aged care facilities should be conducted. With a longer duration of the trials to assess the safety and the efficacy of citalopram for managing agitation in dementia in long term use.

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Conflict of interest

The authors declare that there are no conflict of interest

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, H.Q. and M.S.; methodology, H.Q.; validation, H.Q., M.S. ; formal analysis, H.Q.; investigation, H.Q., M.S.; resources, H.Q.; data curation, H.Q., M.S.; writing—original draft preparation, H.Q.; writing—review and editing, H.Q., M.S.; supervision, H.Q., M.S. All authors have read and agreed to the published version of the manuscript."

Appendix A

1. "anatomy (non mesh)"/or exp behavioural symptoms/	Exploding captures lower branches including behavioural symptoms/
2. exp Serotonin Uptake Inhibitors/ exp antidepressants/	Two different MeSH terms used

3. exp Antipsychotic Agents/	NB: One MeSH terms used
4. exp Psychomotor Agitation/ exp Delirium/ exp Dementia	Three different MeSH terms used
4. ((Antipsychotic Agents OR SSRI OR Antidepressants) Agitation management).tw.	Proximity search
5. Agitation Management.tw.	
6. 1 and 2 and 3 and 4	Will find papers using ANY of those Population MeSH terms / free-text phrases
7. 1 and 2 and 3 and 4 and 5 and 6	For papers covering all PICO components
8. 2 and 3 and 4 and 6	For papers covering all PICO components
9. 2 and 3 and 5 and 6	For papers covering all PICO components
10. (Behavioural and Psychological Symptoms). Mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms].	
11. 2 and 3 and 6 and 11	For papers covering all PICO components
12. (Behavioural and Psychological Symptoms).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms].	
13. 2 and 3 and 4 and 13	
14. 6 AND 10 AND 13	For papers covering all PICO components

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