

REVIEW

Prazosin for the management of behavioural and psychological symptoms of dementia

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Abstract

Prazosin, a centrally acting α_1 adrenoceptor antagonist, has been included in two published algorithms amongst the list of medications that may be used in the management of behavioural and psychological symptoms of dementia (BPSD). However, a review of PubMed, Ovid and Cochrane Collaboration found that there was only one small published randomized controlled trial (RCT) that evaluated the use of prazosin amongst individuals with BPSD. Evidence from this good quality RCT indicates that prazosin appears to benefit individuals with agitation and aggression amongst individuals with BPSD and this medication is well tolerated. When compared to other treatments for BPSD, including atypical antipsychotics, antidepressants, acetylcholinesterase inhibitors, memantine, repetitive transcranial magnetic stimulation and electroconvulsive therapy, where there are multiple studies for each of these treatment modalities, the

data for the use of prazosin for BPSD are limited to just one good quality RCT. Given the limitations in available data, the routine use of prazosin for the treatment of BPSD cannot be recommended at this time. However, prazosin may be used for the management of agitation and aggression amongst individuals with dementia when other medication classes, like acetylcholinesterase inhibitors, memantine, antidepressants and/or atypical antipsychotics, have been ineffective or not tolerated.

Keywords: aggression, agitation, behavioural and psychological symptoms of dementia, prazosin, randomized controlled trial.

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Introduction

Behavioural and psychological symptoms of dementia (BPSD) or neuropsychiatric symptoms of dementia (NPS) describe a group of symptoms and behaviours that are commonly seen amongst individuals with dementia.¹ BPSD cause significant distress to the individual with dementia and their caregivers and impair the care of individuals with dementia in a given environment. BPSD occurs in about a third community-dwelling individuals with dementia and in approximately 80% of individuals with dementia who live at skilled nursing facilities.^{2,3} BPSD tend to fluctuate, with apathy being the most common symptom and psychomotor agitation being the most persistent symptom.⁵⁻⁸

Amongst individuals with dementia, the presence of BPSD is associated with a faster cognitive decline, worsening of activities of daily living, greater rates of institutionalization and

an overall poorer quality of life.⁹⁻¹² In addition, BPSD results in greater caregiver burden and adds significantly to the cost of caring for individuals with dementia.^{2,13-16}

Available evidence indicates that both non-pharmacological and pharmacological treatment strategies have shown benefits in the management of BPSD.^{17,18} In most situations, non-pharmacological strategies are considered as first-line management techniques for BPSD¹⁹ and include the education of caregiver and residential care staff, cognitive stimulation therapy, staff training in behavioural management strategies, mental health consultation and treatment planning, exercise, recreational activities, music therapy, and other forms of sensory stimulation.^{20,21} Amongst individuals with BPSD, the most benefit in managing difficult behaviours occurs with the combination of non-pharmacological and pharmacological treatment strategies.²²

Accumulating evidence indicates that antipsychotics, antidepressants, acetylcholinesterase inhibitors and memantine have shown some benefit in the management of BPSD.²² In a recent network meta-analysis that included data from 17 studies of aripiprazole, olanzapine, quetiapine and risperidone for BPSD, Yunusa et al. found that the use of aripiprazole was associated with improvements in the Neuropsychiatric Inventory (NPI) when compared to placebo (standardized mean difference (SMD) -0.17).²³ The authors did not find any benefit for olanzapine, quetiapine or risperidone on the NPI, but found benefits for aripiprazole (SMD -0.20) and quetiapine (SMD -0.24) and no benefit for olanzapine and risperidone when compared to placebo on the Brief Psychiatric Rating Scale (BPRS). The investigators found benefits for aripiprazole (SMD -0.30) and risperidone (SMD -0.26) on the Cohen Mansfield Agitation Inventory (CMAI), and no benefit for olanzapine or quetiapine on the CMAI, when compared to placebo.

In a meta-analysis of two trials of antidepressants (sertraline and fluoxetine), Seitz et al. found that individuals who received antidepressants did better than individuals receiving placebo on the CMAI (mean difference -0.89 ; $p < 0.00001$).²⁴ The tolerability for antidepressants was good, with withdrawal due to adverse effects being no different between the antidepressant and the placebo group (relative risk 1.07).

In a meta-analysis of 29 randomized controlled trials (RCTs), Trinh et al. found that individuals with BPSD who were prescribed acetylcholinesterase inhibitors did better on the NPI by 1.72 points when compared to individuals who were prescribed placebo.²⁵ The investigators did not find any difference between the three acetylcholinesterase inhibitors on improvements on the NPI when compared to placebo. There was no tolerability data available for the acetylcholinesterase inhibitors from this meta-analysis. In a meta-analysis of 6 RCTs by Maidment et al., the investigators found that, on the NPI, individuals receiving memantine improved by 1.99 points when compared to individuals receiving placebo ($p = 0.04$).²⁶ This meta-analysis did not include tolerability data for memantine.

There is also growing evidence to indicate the efficacy of cannabinoids in the management of BPSD.^{27,28} In a meta-analysis, Bahji et al. included data from three studies of tetrahydrocannabinol, five studies of dronabinol and one study of nabilone for BPSD²⁷; benefits were noted for cannabinoids on CMAI (SMD -0.80), the NPI total score (SMD -0.61), the NPI-Agitation/Aggression sub-score (SMD -0.61) and on nocturnal motor activity (SMD -1.05). The investigators noted a larger effect size amongst individuals with higher baseline MMSE for the CMAI ($p = 0.001$). Larger effect sizes were noted for older studies on the CMAI ($p = 0.003$). Greater effect sizes were noted for higher total daily doses of cannabinoids ($p < 0.001$) for the NPI total score. On the NPI total score and NPI-Agitation/Aggression sub-score, larger effect sizes were noted for quasi-randomized studies when compared to randomized trials ($p = 0.001$ and $p = 0.047$, respectively). Lethargy was the

only adverse effect noted that could be potentially associated with cannabinoid use. There were no associations noted for weight ($p = 0.76$), systolic blood pressure ($p = 0.20$), diastolic blood pressure ($p = 0.21$) or serious adverse effects ($p = 0.51$) with cannabinoid use. In a meta-analysis of four trials, Bosnjak Kuharic et al. did not find any benefit for cannabinoids (delta-9-tetrahydrocannabinol) and two types of synthetic delta-9-tetrahydrocannabinol analogues (dronabinol and nabilone) on the NPI/NPI-Nursing Home Version (NPI-NH) (mean difference -1.97) when compared to placebo.²⁸ The investigators noted that sedation/lethargy was more common amongst individuals taking nabilone when compared to placebo (OR 2.83). Otherwise, they did not find any difference between cannabinoids and placebo in the number of adverse effects.

Repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT) have also shown benefits in the management of BPSD. A meta-analysis by Vacas et al. that included data from two studies of rTMS amongst individuals with NPS found benefits for rTMS amongst individuals with BPSD (overall effect -0.58 ; $p = 0.01$).²⁹ The investigators found that minor tiredness was the only adverse effect identified from rTMS.

There are no published meta-analyses in the literature on ECT for BPSD. van Den Berg et al., in their systematic review of 17 studies, found clinical improvements in 88% of individuals with BPSD who were treated with ECT.³⁰ Symptoms that improved with ECT included agitation, aggression, yelling/screaming and food intake. Delirium (5%) was the most common serious adverse effect from ECT, followed by severe post ictal confusion (2%) and seizures (1%). In their literature review, Tampi et al. found a total of 20 published reports that evaluated the use of ECT for BPSD.³¹ These reports included a total of 172 individuals with BPSD who were treated with ECT. Forty percent of the study were case reports, which was followed by retrospective chart reviews (25%) and case series (20%). Most individuals with BPSD were diagnosed with AD (40%). This was followed by unspecified dementia (15%) and vascular dementia (13%). The most common electrode placement was bitemporal, which was followed by right unilateral and bilateral electrode placements. Over 90% of the individuals with BPSD responded to ECT. The symptoms that responded included physical aggression and suicidal behaviours. With ECT, adverse effects were uncommon and, if they occurred, were mild and transient. Amongst individuals with BPSD who received ECT, postictal confusion and memory impairment (15%) were the most common adverse effects.

It has been noted that, amongst individuals with Alzheimer disease (AD) who present with agitation and aggression, there may be increased sensitivity to norepinephrine at the α_1 adrenoreceptor (AR).^{32–35} Prazosin is a centrally acting α_1 AR antagonist that crosses the blood–brain barrier.³⁶ It is FDA approved for the treatment of hypertension as monotherapy or in combination with other agents.³⁷ Two published algorithms have included prazosin amongst the

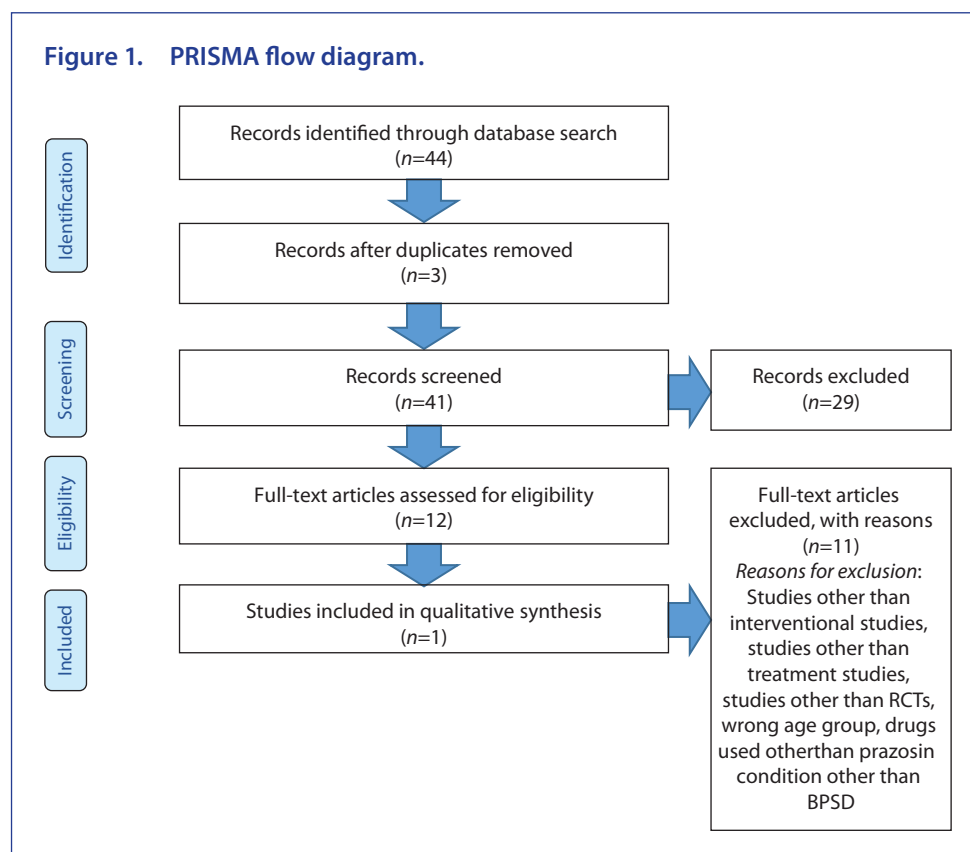
list of medications that can be used to treat individuals with BPSD.^{38,39} The Canadian algorithm recommends that, after the completion of a baseline assessment and discontinuation of medications that are potentially exacerbating BPSD, sequential trials should be performed using risperidone, aripiprazole or quetiapine, carbamazepine, citalopram, gabapentin, and prazosin amongst individuals with AD and mixed dementias presenting with agitation and aggression.³⁸ The Harvard South Shore algorithm describes three separate algorithms for the treatment of BPSD during emergent, urgent and non-urgent situations.³⁹ For emergent BPSD, the authors recommend using intramuscular (IM) olanzapine as first-line treatment with IM haloperidol being recommended as the second choice, followed by the possible use of an IM benzodiazepine. In urgent situations, the recommendation is to use either oral aripiprazole or risperidone as first-line agents. The next option is to use prazosin, with ECT as a final option. For non-emergent agitation, the authors recommend medications in the following order: trazodone followed by donepezil and memantine, then antidepressants like escitalopram and sertraline, atypical antipsychotics, prazosin, and finally carbamazepine.

The goal of this report is to identify, from a systematic review of the literature, the evidence for using prazosin in the management of BPSD including agitation and aggression from controlled studies. We also wanted to evaluate where the evidence for using prazosin stands when compared to other treatments for BPSD, including antipsychotics, antidepressants, acetylcholinesterase inhibitors, memantine, rTMS and ECT. If

the evidence indicates that there is good data for the efficacy and tolerability for prazosin in the treatment of any of the symptoms of BPSD from multiple trials, then this medication can be added to the list of medications that can be routinely used for the management of these complex and often distressing behaviours.

Methods

Two of the authors (RRT and DJT) searched PubMed, Ovid (Medline [1946–October 15, 2021], Embase [1974–October 15, 2021] and APA PsychInfo [1806–October Week 2, 2021]) and Cochrane Collaboration on October 16, 2021. The keywords used for the search were “prazosin” and “dementia”. A total of 44 abstracts were obtained for initial review: PubMed (prazosin and dementia, 30); Ovid (prazosin and dementia, 0) and Cochrane (prazosin and dementia, 0). RRT and DJT independently reviewed all the abstracts to select studies for full-text review. All disagreements with regards to which reports to include for full-text review and for final inclusion for the review were resolved by consensus. All articles published in English language journals or those reports with an official English translation that evaluated the use of prazosin amongst individuals with BPSD from RCTs were included. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) rules were followed for this Review (Figure 1).⁴⁰ The Jadad scale was used to assess the quality of included studies.⁴¹



Results

We only identified one published RCT that evaluated the use of prazosin amongst individuals with BPSD.⁴² This was an 8-week double-blind, placebo-controlled, parallel-group study of 22 nursing home and community-dwelling individuals with probable or possible AD who presented with agitation and aggression. The randomized group included 11 individuals each in the prazosin and placebo groups. The randomization schedule was computer-generated. There was a block for the setting where the participants resided – either nursing home or community. Everyone, with the exception of the study pharmacist, was blinded to treatment arms. Prazosin dosing was achieved using a flexible dosing algorithm. The starting dose of prazosin was 1 mg/day and the drug was titrated up in 1–2 mg dose increments every 3–7 days with a maximum dose of 6 mg/day. Increases in dosages of medication were made by the study psychiatrist or physician assistant. The drug was titrated up if the participant did not have any improvements in the target behaviours but they did not report any adverse effects that were attributable to prazosin. Blood pressure and possible adverse effects were monitored by the medication prescriber who was blinded to the treatment condition.

Change from baseline scores on the NPI and BPRS along with the Clinical Global Impression of Change (CGIC) were the primary outcome measures. The secondary outcome measures included the emergence of side-effects, changes in blood pressure and the Lawton–Brody Physical Self-Maintenance Scale (PSMS). All outcomes were assessed by an experienced research nurse who was blinded to the study medication, side-effects and blood pressure. There was an assessment of NPI, BPRS and PSMS at baseline and at weeks 1, 2, 4, 6 and 8. The CGIC was assessed at week 8, or at the last visit, if there was early withdrawal of the participant from the study. A modified intent-to-treat approach was used by the investigators, where all participants with at least one follow-up outcome measure were included in the final analysis.

A total of 24 participants were randomized to either prazosin or placebo (12 in each group). From each randomized group, 1 participant had to drop out due to hypotension prior to the completion of any follow-up assessments. For the final analysis,

data for a total of 22 participants (11 in each group) who had at least one follow-up assessment were available.

The drop-out rates in both groups were 46% during the 8-week study duration. A total of 4 additional participants in the prazosin group dropped out (2 participants moved to a new nursing home, 1 participant had a lower extremity oedema and 1 participant had continuing agitation). A total of 5 participants in the placebo group dropped out during this time (3 participants had continuing agitation, 1 participant had lower extremity oedema and 1 participant had a rash).

The mean doses of prazosin and placebo were 5.7 ± 0.9 mg/day and 5.6 ± 1.2 mg/day, respectively. For those individuals who completed the study, when compared to baseline, individuals who received prazosin appeared to do better on both the NPI and BPRS ($p=0.12$ and $p=0.36$, respectively) at the end of the study when compared to individuals receiving placebo. The differences in CGIC between the prazosin and placebo groups at the end of the study were also statistically significant ($p=0.011$). All the participants in the prazosin group were either doing the same or having shown improvement when compared to 6 of the 11 participants in the placebo group showing some worsening of symptoms. No differences in the PSMS scores were noted between the two groups ($p=0.3$).

Prazosin was well tolerated when compared to placebo, with no significant differences noted between the two groups on blood pressure changes (systolic ($p=0.5$) and diastolic ($p=0.8$)), sedation (3 versus 3) and hallucinations (1 versus 1). Hypotension (2 versus 1), cough (2 versus 0) and dizziness on standing (1 versus 0) were more common in the prazosin group when compared to the placebo group. Confusion (4 versus 1), lower extremity oedema (2 versus 1), headache (2 versus 0) and rash (1 versus 0) were more common in the placebo group when compared to the prazosin group. Tables 1 and 2 describe the details of the included study.

Discussion

This systematic review indicates that there is a significant limitation in evidence for the use of prazosin amongst individuals with BPSD from controlled studies. We only found one published RCT that evaluated the use of prazosin

Table 1. Summary of the included trial.

Name of study	Study design	Intervention	Number of participants	Mean age (years)	Setting	Duration
Wang et al, 2009 (ref. ⁴²)	Double-blind, placebo-controlled, parallel-group study	Prazosin versus placebo	22	80.6±11.2	Nursing home (12 participants) Community dwelling (10 participants)	8 weeks

Table 2. Summary of the results of the included trials.

Name of study	Dosing	Rating scales/ outcome measures	Results	Tolerability
Wang et al., 2009 (ref. ⁴²)	Prazosin (mean dose 5.7±0.9 mg/day) Placebo (mean dose 5.6±1.2 mg/day)	Change from baseline scores on the BPRS and on the NPI score at weeks 1, 2, 4, 6, and 8 The CGIC score at week 8	BPRS (mean change): -9±9 versus -3±5; <i>p</i> =0.036 NPI (mean change): -19±21 versus -2±15; <i>p</i> =0.012 CGIC (mean): 2.6±1.0 versus 4.5; <i>p</i> =0.01	There were no differences noted for blood pressure changes during the study duration between the two treatment groups (systolic [<i>p</i> =0.5] and diastolic [<i>p</i> =0.8]) Sedation, confusion, lower extremity oedema, hypotension, headache, cough, hallucination, dizziness and rash were the adverse effects reported, but were no different between the two groups 1 participant in each group terminated the study early due to oedema 1 participant in each group terminated the study early due to hypotension

BPRS, Brief Psychiatric Rating Scale; CGIC, Clinical Global Impression of Change; NPI, Neuropsychiatric Inventory.

Table 3. Quality of included RCTs.

Name of study	Randomization?	Blinding	An account of all patients
Wang et al., 2009 (ref. ⁴²)	<ul style="list-style-type: none"> 1 point if randomization is mentioned 1 additional point if the method of randomization is appropriate Deduct 1 point if the method of randomization is inappropriate (minimum 0) 	<ul style="list-style-type: none"> 1 point if blinding is mentioned 1 additional point if the method of blinding is appropriate Deduct 1 point if the method of blinding is inappropriate (minimum 0) 	<ul style="list-style-type: none"> The fate of all patients in the trial is known; if there are no data, the reason is stated
	2	2	1

amongst individuals with BPSD. This was a good quality study as assessed by the Jadad scale (5/5).⁴¹ This study indicated that individuals prescribed prazosin responded to treatment when compared to individuals receiving placebo with an improvement in symptoms as noted on the BPRS total score, the NPI total score and the CGIC (*p*=0.036, *p*=0.012 and *p*=0.01, respectively). Prazosin was also well tolerated with individuals taking prazosin having no significant blood pressure changes (systolic (*p*=0.5) and diastolic (*p*=0.8)), sedation (3 versus 3) or hallucinations (1 versus 1) when compared to individuals

taking placebo. Table 3 describes the quality of the included study.

Although this was a well-conducted study, it had some major limitations. This was a single-site study that included a limited number of participants (*n*=22). Additionally, this was a short study that lasted a total of 8 weeks. A formal exploratory analysis of subitems in the BPRS and NPI was not conducted and therefore it is difficult to conclude as to which specific psychiatric or behavioural symptoms improved with the use

of prazosin when compared to placebo. Furthermore, the definitive dosing range for prazosin for use amongst individuals with BPSD is unclear but, based on the only available evidence, 1–6 mg a day would be appropriate. Whether BPSD symptoms would respond to prazosin amongst individuals with other aetiologies of dementia, including vascular, mixed, Lewy body disease or frontotemporal dementia, is unclear from the available evidence. As a significant number of participants were also taking other psychotropic medications, including atypical antipsychotics, cholinesterase inhibitors, memantine, antidepressants, buspirone, benzodiazepines and divalproex, and these were well tolerated by the participants of the study, it is possible we could judiciously co-prescribe prazosin with other psychotropic medications.

We also found a report on a second study of prazosin that was presented as a poster presentation in *Alzheimer's & Dementia*.⁴³ In this study, 17 individuals with probable or possible AD were randomized to receive prazosin (8 mg/day in divided doses). The investigators reported that the improvements in NPI were numerically greater for prazosin (-28 ± 12) when compared to placebo (-19 ± 11). They also reported that prazosin was well tolerated when compared to placebo. It was reported that the medication did not cause any symptomatic reduction in blood pressure in this study. The limitations of this report are that it was not peer reviewed or published and its limited number of participants ($n=17$). Furthermore, the duration of the study is unclear.

There are multiple published trials that have assessed the efficacy and adverse effects of atypical antipsychotics, antidepressants, acetylcholinesterase inhibitors and memantine, cannabinoids, and rTMS and ECT amongst individuals with BPSD. In comparison, the evidence for using prazosin for BPSD is limited to only one published study. Although this is a good quality study, it is limited by the small number of participants and short duration. Based on this data, we recommend caution with the routine use of prazosin amongst individuals with BPSD. Prazosin could be used to possibly treat agitation and aggression amongst individuals with BPSD who have failed to adequately respond to other medication classes, including atypical

antipsychotics, antidepressants, acetylcholinesterase inhibitors and memantine. Prazosin could be used prior to the trials of cannabinoids, rTMS or ECT, as there is greater acceptability of its use amongst patients, their caregivers and medical professionals given its wide and decades-long use in the treatment of hypertension.³⁷

There is a recent study called 'Prazosin for disruptive agitation in Alzheimer's disease (PEACE-AD)', which is a phase IIb multicentre, randomized, double-blind, placebo-controlled trial of 12-week treatment with prazosin for disruptive agitation in approximately 186 individuals with AD who live in long-term care settings or at home with full-time caregiving.⁴⁴ This study is currently active but is not enrolling any participants. The results of this study are awaited.

Conclusion

Available evidence indicates that there is only one RCT of prazosin amongst individuals with BPSD. This study showed benefits for prazosin when compared to placebo amongst individuals with BPSD and prazosin was well tolerated. However, this was a small study and of short duration. Additionally, it is unclear which symptoms of BPSD are most responsive to prazosin. Furthermore, it remains to be studied whether the symptoms of BPSD in dementias other than AD will respond adequately to treatment with prazosin. Based on available evidence, it is our recommendation that prazosin could be used to treat BPSD symptoms, possibly for agitation and aggression, amongst individuals with dementia who have failed to adequately respond to other medication classes, including atypical antipsychotics, antidepressants, acetylcholinesterase inhibitors and memantine. Prazosin could be tried prior to using cannabinoids, rTMS or ECT amongst individuals with BPSD. We would also recommend using this medication in conjunction with non-pharmacological management strategies to maximize treatment outcomes. Prazosin could also be used cautiously in conjunction with other psychotropic medication classes, including cognitive enhancers, antidepressants, atypical antipsychotics and mood stabilizers, with close monitoring for efficacy and adverse effects.

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