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REVIEW

Propranolol for the management of behavioural and psychological symptoms of dementia

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Abstract

Propranolol is a β-adrenergic antagonist used in the management of hypertension, cardiac arrhythmia, and angina pectoris. There is some evidence that propranolol may benefit individuals with behavioural and psychological symptoms of dementia (BPSD). A total of three case series, one randomized controlled trial and one case report were identified (from a literature search of three major databases: PubMed, Ovid, and Cochrane collaboration) that assessed the use of propranolol for the management of BPSD. From these studies, it appears that propranolol improves BPSD, including agitation and aggression. Propranolol is also well tolerated with no significant bradycardia or hypotension noted in these studies. Current data on the use of propranolol for the management of BPSD are limited in comparison to other pharmacological agents (atypical antipsychotics, antidepressants, acetylcholinesterase inhibitors, memantine, and cannabinoids) and treatment modalities (repetitive transcranial magnetic stimulation and electroconvulsive therapy). The efficacy and safety of these treatments among individuals with BPSD has been evaluated in multiple controlled studies. In clinical practice, the routine use of propranolol among people with BPSD cannot be recommended at this time given the limited data. However, propranolol can be trialled among individuals with BPSD when symptoms have not responded adequately to other medications. Propranolol may also be used prior to embarking on trials of repetitive transcranial magnetic stimulation and electroconvulsive therapy among people with BPSD given the greater acceptance of this medication in the general population.

Keywords: aggression, agitation, behavioural and psychological symptoms of dementia, dementia, propranolol, randomized controlled trial (RCT).

Citation

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Introduction

Behavioural and psychological symptoms of dementia (BPSD) are noted in over 90% of individuals with dementia at some point during the course of the illness and across different aetiologies for dementia.[1] Apathy has been identified in the literature as the most common BPSD.[2] Other common BPSD include depression, aggression, anxiety, and sleep disorders. In individuals with dementia, many of these BPSD can often co-occur.[3] BPSD result in a faster rate of progression of the illness, a greater number of acute care hospital admissions, increased lengths of hospital stay, and higher rates of skilled nursing facility placements.[4] Greater rates of morbidity and mortality are also seen among individuals with BPSD. BPSD tend to worsen caregiver distress and depression and can result in reduced caregiver employment. BPSD are associated with one-third of the care cost for individuals with dementia due to the greater utilization of health services.[4]

Both non-pharmacological strategies and pharmacological agents have shown benefit in the management of people with BPSD.[4] Non-pharmacological strategies are recommended as a first-line option for the management

of BPSD in most situations.[5] The instruction of caregivers and residential home employees in addition to cognitive stimulation therapy have been noted as beneficial in the management of BPSD.[6] Specialized dementia care units are not consistently useful in the management of BPSD, but visual changes to the environment and the unlocking of doors appear to reduce wandering among these individuals.[6]

In one meta-analysis, the investigators noted that non-pharmacological interventions initiated by family caregivers reduced the frequency and severity of BPSD (effect size, 0.34; $p<0.01$) and reduced the caregiving burden (effect size, 0.15; $p=0.006$).[7] A systematic review found that there were beneficial effects noted for staff training, mental health consultation and treatment planning, exercise, recreational activities, music therapy, and other forms of sensory stimulation in the management of BPSD.[8] Benefits have also been noted for music therapy, home-based behavioural management techniques, caregiver-based interventions, staff training in communication skills, person-centred care, and dementia care mapping with supervision in the management of BPSD.[9] The International Delphi consensus has identified the DICE (Describe, Investigate, Create, and Evaluate) intervention and music therapy as the most promising non-pharmacological management approaches for BPSD.[10] In the DICE, BPSD are assessed using a structured method with an evaluation of the underlying aetiologies for BPSD. Additionally, there is care planning, follow-up monitoring, and the training and empowerment of caregivers.

Medication classes that have shown benefit in the management of BPSD include atypical antipsychotics, antidepressants, acetylcholinesterase inhibitors, and cannabinoids.[11] Investigators of a network meta-analysis identified that the use of aripiprazole improved BPSD as rated on the Neuropsychiatric Inventory (NPI) *versus* placebo (standardized mean difference (SMD), -0.17).[12] Improvements on the Brief Psychiatric Rating Scale (BPRS) were noted when compared with placebo with the use of aripiprazole (SMD, -0.20) and quetiapine (SMD, -0.24). Improvements on the Cohen Mansfield Agitation Inventory (CMAI) when compared with placebo were identified with the use of aripiprazole (SMD, -0.30) and risperidone (SMD, -0.26). The surface under the cumulative ranking curve (SUCRA) indicated the highest probability of effectiveness on the NPI for aripiprazole (85.3%). On the BPRS, the highest probability of effectiveness was identified for quetiapine (80.2%) and aripiprazole (72.9%). The highest probabilities of effectiveness on the CMAI were noted for aripiprazole (73.8%) and risperidone (68.6%).

A meta-analysis of studies involving individuals with BPSD found that those who received sertraline and citalopram improved on the CMAI as compared with individuals who received placebo [mean difference (MD), −0.89; $p<0.001$].[13] The antidepressants were well tolerated, with no difference being noted between the two groups on withdrawal due to adverse effects (RR, 1.07).

One meta-analysis found that people with BPSD receiving acetylcholinesterase inhibitors improved by 1.72 points on the NPI scale *versus* individuals receiving placebo, indicating a small but statistically significant benefit.[14] Another meta-analysis found that individuals with BPSD who received memantine improved by 1.99 points on the NPI scale when compared with placebo ($p=0.04$).[15]

A meta-analysis identified that individuals with BPSD who received cannabinoids did better on the CMAI (SMD, -0.80) when compared with placebo.[16] Benefits were also noted on the NPI total score (SMD, -0.61), the NPI-Agitation/Aggression sub-score (SMD, -0.61), and the nocturnal motor activity (SMD, -1.05) among individuals receiving cannabinoids. Among the adverse effects, only lethargy was potentially related to the use of cannabinoids.

In one meta-analysis, repetitive transcranial magnetic stimulation (rTMS) was found to be beneficial for the management of BPSD (overall effect, -0.58; $p=0.01$).[17] The only adverse effect noted from the rTMS was tiredness, and it was noted as being mild. One systematic review noted that approximately 88% of individuals with BPSD receiving electroconvulsive therapy (ECT) showed improvements on yelling, screaming, agitation, aggression, and food intake.[18]Adverse effects due to ECT were mild and transient, with delirium (5%) and postictal confusion that was severe (2%) in addition to seizures (1%) being infrequent events.

Pharmacotherapy is often used to manage BPSD refractory to non-pharmacological interventions.[19] There are greater benefits noted when non-pharmacological techniques and pharmacotherapy are synergized in the management of BPSD.[20]

Among individuals with Alzheimer's disease (AD), there is an upregulation in the biosynthesis of norepinephrine (NE) among the remaining neurons as a compensatory mechanism for neuronal loss in the locus coeruleus (LC) due to neurodegeneration.[21–23] This compensatory mechanism maintains the normal release of NE from the LC among individuals with AD, as noted by the normal or increased levels of NE and its metabolites in cerebrospinal fluid.[24,25] Peskind et al. found that, among individuals with AD who were treated with yohimbine (an α2-adrenergic antagonist that stimulates noradrenergic activity in the central nervous system by blocking

α2-receptor-mediated NE feedback inhibition of the LC neurons), tension ($p<0.01$), excitement ($p<0.001$), and anxiety ($p<0.01$) were greater among individuals with AD than in the older ($p<0.05$) or younger adult ($p<0.01$) groups of individuals without AD.[26]

It has been postulated that BPSD may also occur due to the dysregulation of noradrenergic signalling, where there is elevation of noradrenergic transmission despite the degeneration of neurons in the LC among individuals with dementia.[27] Additionally, among individuals with AD, it has been noted that there is an increase in α2 receptors in the cerebellum that is correlated with aggressive behaviours.

Propranolol, a β-adrenergic antagonist used to treat hypertension, cardiac arrhythmia, and angina pectoris, has been experimentally shown to reverse stress-related cognitive deficits.[28,29] Experimentally, propranolol has also been shown to reduce amyloid and tau pathologies and restore cognitive functioning.[30] The use of propranolol has been shown to reduce the need for sedatives and opioids among individuals who are critically ill with delirium.[31] The sedative and opioid sparing effects of propranolol are thought to occur due to blocking of the activity of excessive catecholamines that are generated during critical illnesses like delirium. Such neuroprotective effects have also been noted with the use of propranolol among individuals with traumatic brain injury.[32] It is possible that propranolol may also produce such neuroprotective/calming effect among individuals with BPSD by blocking the effect of excessive catecholamines. Beta-blockers have also been noted to reduce aggressive and hypersexual behaviours among individuals with dementia.[33] Although it is unclear as to how beta-blockers can reduce hypersexual behaviours, their proposed mechanisms include reducing testosterone levels in men and acting as a serotonin receptor antagonist in the brain.[34]

The goal of this review is to assess the evidence for the use of propranolol in the management of BPSD. If propranolol is found to have good efficacy and tolerability among individuals with BPSD, then it can be added to the group of medications that can trialled in the management of these complex and distressing behaviours.

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) rules were not followed as this report is not a systematic review.[35] However, an organized search strategy was used to identify articles from the literature. The Jadad scale was used to evaluate the quality of controlled studies that were included in this report.[36]

PubMed, Ovid (Medline [1946-October 3, 2022], Embase [1974-October 3, 2022], APA PsychInfo (1806-September Week 4, 2022]) and Cochrane collaboration databases were searched on June 4, 2022, and October 4, 2022, by authors RRT and DJT. The search of the databases was conducted using the keywords "propranolol", "beta-blocker", "dementia" and "neurodegeneration". All the identified abstracts were independently appraised by authors SAF and SO to select studies for full-text review. Any disagreements between authors SAF and SO on which reports to include for full-text review were resolved after a discussion with the main author (RRT).

Herein, we only included studies that specifically assessed the use of propranolol among individuals with dementia who exhibited behavioural and psychological symptoms, irrespective of the study design, date of publication or aetiology for dementia. Additionally, we screened out cases of mild cognitive impairment as this report focuses exclusively on individuals with BPSD. In the final evaluation, we only included reports published in English language journals or those that had an official English translation. Figure 1 describes the flow diagram for the identification of studies from the literature.

Results

From a total of 1133 records that were identified from a search of the PubMed, Ovid, and Cochrane collaboration databases, a total of 5 relevant articles that assessed the use of propranolol in the management of BPSD were picked for inclusion in the final review.[37–41] The articles included 3 case series, 1 randomized controlled study (RCT), and 1 case report. A summary of the included studies is provided in Tables 1 and 2, respectively.

In the first case series, Petrie and Ban discussed the use of propranolol for the management of BPSD among three individuals (one man and two women) who were admitted to an inpatient psychiatric unit.[37] The behaviours that were being treated included wandering, pacing, irritability, physical aggression, and destruction of property. These individuals had failed trials of other psychotropic medications, including haloperidol. They were then treated with propranolol 60–160 mg/day with a resolution of symptoms. In one individual, the discontinuation of propranolol resulted in a recurrence of symptoms. When propranolol was restarted at the previous dose of 60 mg/day, the symptoms resolved. Propranolol appears to have been well tolerated except for a reduction in pulse rate in two of the patients, although the pulse rates are not noted in the report.

Weiler et al. reported a case series of six individuals (two men and four women) with mild to severe dementia

Figure 1. Flow diagram

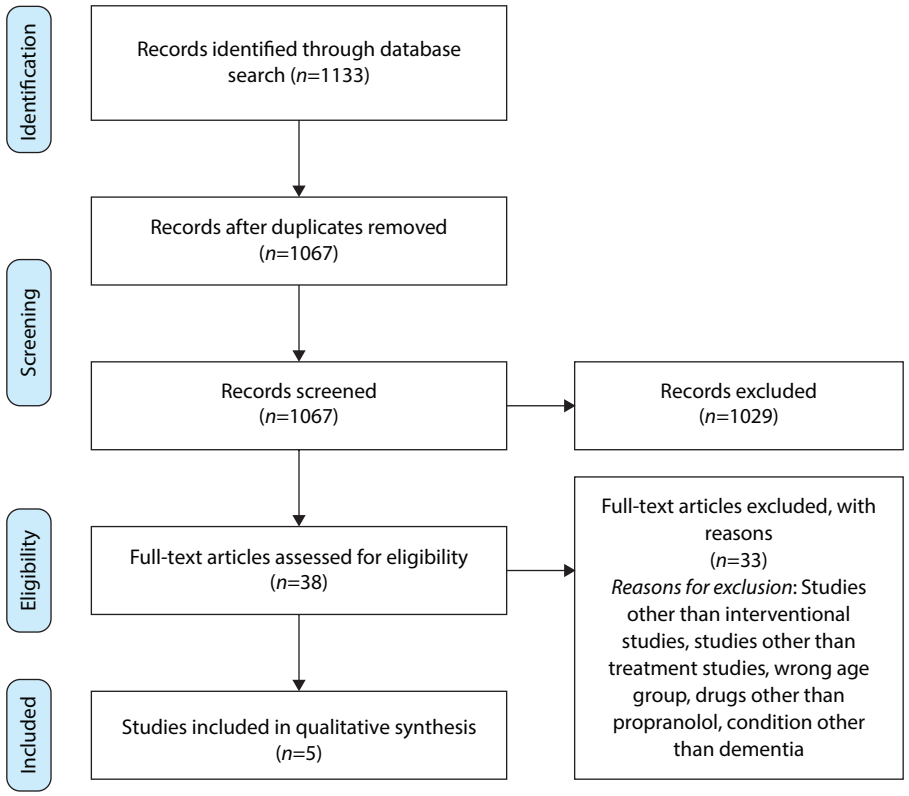

Table 1. Summary of the included trials.

Name of study	Study design	Intervention	Number of participants	Age (years)	Number of men and women	Setting	Duration
Petrie & Ban[37]	Case series	Propranolol	3	54–86	1 and 2	Inpatient unit	10 days–3 weeks
Weiler et al.[38]	Case series	Propranolol	6	66–83	2 and 4	Inpatient unit, nursing home, home	>1 week–11 months
Shankle et al.[39]	Case series	Propranolol	12	54–81	5 and 7	Outpatients	1–14 months
Peskind et al.[40]	Randomized controlled trial	Propranolol *versus* placebo	17 *versus* 14	Mean, 85 ± 7.8	3 and 14; 3 and 11	Nursing home	6 weeks
Summers[41]	Case report	Propranolol	1	74	1 man	Nursing home and inpatient medical/psychiatric unit	12–16 months

who required admission to an inpatient psychiatric unit for BPSD.[38] These individuals were all residents of skilled nursing facilities and had presented with severe BPSD. The BPSD included restlessness, wandering, verbal agitation, and physical aggression, and had not responded to antipsychotics, including haloperidol, or other sedative medications. Propranolol was trialled at doses ranging from 80 to 560 mg/day. The authors justified the high dosing of propranolol stating that a previous study by Greendyke et al. used propranolol up to 520 mg/day among eight individuals with organic brain disease (only one with dementia), who exhibited violent and assaultive behaviour unresponsive to other treatments.[42] In the study by Greendyke et al., 7% of the prescribed doses of

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

Name of study	Dosing	Rating scales/ outcome measures	Results	Tolerability
Petrie & Ban[37]	60–160 mg/day	No specific rating scales, clinical improvement	Improvement in symptoms of wandering in all three patients and agitation in two of the patients where it was present	Propranolol was well tolerated except for a reduction of pulse rate in two patients
Weiler et al.[38]	80–560 mg/day	No specific rating scales, clinical improvement	Agitated behaviours improved significantly in all participants	Well tolerated with no adverse effects reported
Shankle et al.[39]	10–80 mg/day	CMAI CBQ	The overall response rate was 67% (8/12); 60% response rate for agitation; 71% response rate for agitation and aggression	Well tolerated, bradycardia in one participant with heart disease, symptoms resolved when the dose of propranolol was reduced from 60 to 30 mg/day
Peskind et al.[40]	106±38 mg/day	NPI CGIC	At week 6: NPI total score: propranolol *versus* placebo (p=0.01) NPI items: propranolol *versus* placebo 'agitation/aggression' (p=0.06) CGIC mean score: propranolol *versus* placebo (p=0.005) CGIC: markedly improved (n=1), moderately improved (n=7) (p<0.02)	One individual in the propranolol group discontinued treatment due to rash Two individuals in the placebo group treatment discontinued treatment due to hypotension (n=1) or bradycardia (n=1) when compared with none in the propranolol group
Summers[41]	80–180 mg/day	No specific rating scales, clinical improvement	Significant improvements in disruptive vocalizations and episodic violent outbursts	No adverse effects noted from propranolol

CBQ, California Alzheimer's Disease Diagnosis and Treatment Center Behavior Questionnaire; CGIC, Clinical Global Impression of Change; CMAI, Cohen Mansfield Agitation Inventory; NPI, Neuropsychiatric Inventory.

propranolol had to be withheld due to bradycardia or hypotension,[42] and improvement was noted in seven individuals who could tolerate propranolol at adequate drug dosages. In the Weiler et al. study, all individuals had a reduction in their respective agitated and disruptive behaviours that were based on clinical assessment.[38] There were no clinically important adverse events reported from the use of propranolol in this study.

Shankle et al. report a case series of 12 individuals (5 men plus 7 women) with mild to severe dementia who were treated with propranolol for BPSD.[39] Six of the 12 individuals met the National Institute for Neurological Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable or possible AD, and 5 met the Alzheimer's Disease Diagnosis and Treatment Center (ADDTC) criteria for probable or possible vascular dementia and one individual had possible mixed (probable vascular dementia plus possible AD). BPSD that were present included physical, verbal or sexual aggression, anxiety, agitation, pacing, wandering, or hyperactive vocalizations. Ten of the 12 individuals were taking medications for agitation without benefit, and these were discontinued before the trial. Propranolol was started at 10 mg/ twice daily and titrated up every 3 days by an additional 20–30 mg/day until it was reported by the caregivers that the agitation or aggression was no longer a problem or a maximum dose of 80 mg/day (in 2–3 divided doses) was attained. Statistically significant reductions in aggression severity with propranolol (p<0.003) were noted in the study. Clinically, a significant improvement, as rated by the caregiver, was seen in nine individuals. All responses were observed within the first 2 weeks of

initiation of treatment. There was a relapse of BPSD in one of the nine responders after 6 months. Among the responders, CMAI scores indicated an improvement in physical and verbal aggression and wandering and pacing behaviours that were statistically significant ($p<0.04$). California ADDTC Behavior Questionnaire (CBQ) scores showed reductions in agitation in both responders and non-responders ($p<0.05$). There was a correlation noted between treatment efficacy and lower Mini-Mental State Examination (MMSE) scores ($r^2=0.35$). There was no difference in response based on sex. It was also noted that responders to propranolol had relatively greater deficits in frontal, frontal-temporal, and left frontal-temporal functions. Bradycardia was the only adverse effect noted in one participant with heart disease. The bradycardia resolved when the dose of propranolol was reduced from 60 to 30 mg/day in this participant.

In their RCT, Peskind et al. included 31 individuals (6 men and 25 women) with a mean age of 85±7.8 years who met NINCDS-ADRDA criteria for probable ($n=22$) or possible AD ($n=9$) and had ≥4 weeks of persistently disruptive behaviour that was rated ≥4 on the 'agitation/aggression', 'irritability/lability', and/or 'aberrant motor activity' items of the NPI.[40] All participants had been residents of a skilled nursing care facility for a minimum of 2 months. Individuals with prominent psychotic symptoms or those who met DSM-IV criteria for delirium, major depression, history of schizophrenia, or bipolar disorder or had unstable medical illness were excluded from this study. The investigators allowed previously prescribed psychotropics to be continued during the study. Participants were randomized using computer-generated randomization, were scheduled to receive either propranolol ($n=17$) or placebo ($n=14$), and were followed for 6 weeks under double-blind conditions. Propranolol was started at 10 mg tablets dosed three times a day and increased by an additional tablet every 3 days to a maximum of four tablets three times a day (120 mg/day). The primary outcome measures were changes from baseline to the end of the study at 6 weeks for the NPI total score and on the Clinical Global Impression of Change (CGIC). The investigators found that propranolol augmentation was better than placebo on improving the total NPI score ($p=0.01$) and CGIC mean score ($p=0.005$), respectively. Among individual NPI items, significant improvement with propranolol when compared with placebo was only seen for the 'agitation/aggression' item ($p=0.06$). On the CGIC, in the propranolol group, one individual showed marked improvement in symptoms and seven individuals had moderately improved symptoms whereas, in the placebo, none had markedly improved symptoms and only one showed moderate improvement in their symptoms ($p<0.02$). Additionally, individuals in the propranolol group remained in the double-blind study longer than individuals in the placebo group ($p<0.02$). A total of five individuals in the propranolol group and nine in the placebo group did not complete the study, as the staff at the facility were not willing to tolerate the ongoing or increasingly difficult behaviours. Overall, propranolol was well tolerated. One individual in the propranolol group discontinued treatment due to rash. Two individuals in the placebo group discontinued treatment due to hypotension ($n=1$) or bradycardia ($n=1$) when compared with none in the propranolol group. After 6 months of open-label propranolol treatment, improvement of overall behavioural status among those individuals rated as having markedly improved ($n=1$) or moderately improved ($n=7$) symptoms on the CGIC had substantially diminished to moderately improved ($n=1$), minimally improved ($n=3$), unchanged ($n=3$), or minimally worse ($n=1$) symptoms.

Summers, in his case report, described the treatment of a man with a diagnosis of AD (late stage) and disruptive vocalizations and episodic violent outbursts who was stabilized using propranolol 180 mg/day.[41] The individual was stable at a nursing home for 12 months on propranolol. All antipsychotics administered had been discontinued. He was also receiving rivastigmine, citalopram, doxepin, and gabapentin in addition to propranolol. The patient then needed multiple medical hospitalizations and at least two psychiatric hospitalizations for worsening delirium and BPSD. The propranolol was initially discontinued but needed to be reinitiated as the individual did not respond well to antipsychotics, chlorpromazine, haloperidol, quetiapine, and olanzapine. His behaviours improved with the reinitiation of propranolol at doses 120–180 mg/day. Unfortunately, the patient died 119 days after his initial medical hospitalization. At the time of his death, the patient was not receiving any propranolol. No adverse effects with the use of propranolol were noted in this case report.

Discussion

This review indicates that there is limited data for the use of propranolol among individuals with BPSD. We identified a total of three case series, one RCT, and one case report from the literature search.[37–41] The three case series involved a total of 21 people with BPSD.[37–39] The individuals in the case series responded well to propranolol with a resolution in BPSD at doses of 60–560 mg/day. Propranolol was well tolerated with bradycardia being the major adverse effect noted in three of the individuals in these reports. In one of the individuals, a woman with heart disease, bradycardia resolved when the dose of propranolol was reduced from 60 to 30 mg/day.[39]

This literature search identified only one RCT that assessed the efficacy and tolerability of propranolol among

individuals with BPSD.[40] Based on the JADAD scale (5/5), this was a good quality study.[32] In this trial, individuals with BPSD exhibited good response to management with propranolol in comparison to people receiving placebo. BPSD were identified as having improved as per the NPI total score (p=0.01) and the CGIC mean score (p=0.005) by the end of the study period. Significant improvements were also noted with propranolol when compared with placebo on the 'agitation/aggression' NPI item (p=0.06). In the propranolol group, one individual was identified as having markedly improved symptoms and seven individuals were noted to have moderately improved symptoms on the CGI scale *versus* no one being identified as having markedly improved symptoms and only one person having moderately improved symptoms in the placebo group (p<0.02). Propranolol was also well tolerated with none of the individuals in this group discontinuing the study due to hypotension or bradycardia as compared with one individual each in the placebo group discontinuing treatment due to hypotension and bradycardia. The quality of the included RCT is described in Table 3.

In the only case report included in this review, propranolol was beneficial in managing BPSD in a 74-year-old man with severe AD.[41] The person had 12 months of stability on propranolol 180 mg/day. There were no adverse effects identified with the use of propranolol in this individual.

Although the included RCT was a good quality study, it had some shortcomings. It was a single-site study that only included 31 participants.[40] The study also lasted only for a total of 6 weeks. Furthermore, all participants in the study had possible or probable AD. Based on this study alone, it cannot be confirmed that BPSD would be responsive to management with propranolol among people with other aetiologies of dementia, including vascular dementia, mixed dementia, Lewy body disease, or frontotemporal dementia.

Based on these reports, it can be concluded that the dosing range of propranolol for the treatment of BPSD varies between 60 and 560 mg/day. What is unclear from these reports is the type of symptom or individual characteristics that will respond to a particular dose of propranolol and the reasons for this response. Although participants in the studies included in this report appear to tolerate propranolol well, with no significant bradycardia or hypotension, caution must be exercised when using any new medication in the elderly. There is potential for serious drug interactions and exacerbation of drug-induced adverse effects, as older adults are often taking multiple different medications and are susceptible to developing these adverse effects.[43] This is especially true when combining medications like propranolol with acetylcholinesterase inhibitors, where there is a potential risk for significant bradycardia or hypotension.[44]

This current review on the use of propranolol for the management of BPSD has some limitations. Although there was an organized methodology for searching the literature to identify potential articles for inclusion, we did not follow the PRISMA guidelines, as this report was not intended as a systematic review. The other major limitation is the lack of statistical analyses based on available studies. We also did not include any reports of individuals with mild cognitive impairment who were presenting with behavioural and psychological symptoms, as we wanted this report to focus exclusively on BPSD. The strength of this report is the use of a definitive plan in searching three major databases (PubMed, Ovid, and Cochrane) and identifying appropriate studies for inclusion in the final review.

In summary, available evidence for using propranolol in the management of BPSD is limited when compared with other medication classes and treatment modalities that are currently being used for the management of BPSD. These medication classes and treatments have multiple trials to assess their efficacy and adverse effects among individuals with BPSD.[12–18] However, evidence for the use of propranolol for the management of BPSD is similar to the evidence available for using prazosin

Table 3. Quality of included randomized controlled trials.

Name of study	Randomization 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)	Blinding 1 point if blinding is mentioned; 1 additional point is if the method of blinding is appropriate; deduct 1 point if the method of blinding is inappropriate (minimum 0)	An account of all patients The fate of all patients in the trial is known; if there are no data, the reason is stated
Peskind et al.[40]	2	2	1

among people with BPSD, where there is only one small but good quality RCT.[45] It is foreseeable that, in certain situations where prazosin is not effective in managing BPSD, propranolol could be used or vice versa.

Conclusions

Based on available evidence, the routine use of propranolol in the management of BPSD cannot be recommended. However, in situations where the BPSD have not responded adequately to other medication trials, propranolol can be used. Propranolol can also be used before trialling cannabinoids, rTMS, or ECT in the management of BPSD. There is greater acceptability for the use of propranolol among medical professionals and the general public when compared with the use of cannabinoids, rTMS, or ECT in individuals with dementia. It is also possible to use propranolol in combination with other psychotropic medications among people with BPSD as a significant number of participants in the included RCT were also taking other psychotropic medications. Participants in the trial tolerated the combination of propranolol and other medications well. However, caution must be exercised when prescribing propranolol to individuals with BPSD given the potential for adverse effects, including bradycardia and hypotension. This is especially true when combining propranolol with medications like acetylcholinesterase inhibitors, which are often prescribed to individuals with dementia.

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References

1. Kales HC, Gitlin LN, Lyketsos CG, et al. Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel. *J Am Geriatr Soc*. 2014;62(4):762–769. https://doi.org/10.1111/jgs.12730
2. Zhao QF, Tan L, Wang HF, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: systematic review and meta-analysis. *J Affect Disord*. 2016;190:264–271. https://doi.org/10.1016/j.jad.2015.09.069
3. Savva GM, Zaccai J, Matthews FE, et al. Prevalence, correlates and course of behavioural and psychological symptoms of dementia in the population. *Br J Psychiatry*. 2009;194(3):212–219. https://doi.org/10.1192/bjp.bp.108.049619
4. Gerlach LB, Kales HC. Managing behavioral and psychological symptoms of dementia. *Clin Geriatr Med*. 2020;36(2):315–327. https://doi.org/10.1016/j.cger.2019.11.010
5. Dyer SM, Harrison SL, Laver K, Whitehead C, Crotty M. An overview of systematic reviews of pharmacological and non-pharmacological interventions for the treatment of behavioral and psychological symptoms of dementia. *Int Psychogeriatr*. 2018;30(3):295–309. https://doi.org/10.1017/S1041610217002344
6. Livingston G, Johnston K, Katona C, et al. Systematic review of psychological approaches to the management of neuropsychiatric symptoms of dementia. *Am J Psychiatry*. 2005;162(11):1996–2021. https://doi.org/10.1176/appi.ajp.162.11.1996
7. Brodaty H, Arasaratnam C. Meta-analysis of nonpharmacological interventions for neuropsychiatric symptoms of dementia. *Am J Psychiatry*. 2012;169(9):946–953. https://doi.org/10.1176/appi.ajp.2012.11101529
8. Seitz DP, Brisbin S, Herrmann N, et al. Efficacy and feasibility of nonpharmacological interventions for neuropsychiatric symptoms of dementia in long term care: a systematic review. *J Am Med Dir Assoc*. 2012;13(6):503–506.e2. https://doi.org/10.1016/j.jamda.2011.12.059
9. Abraha I, Rimland JM, Trotta FM, et al. Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series. *BMJ Open*. 2017;7(3):e012759. https://doi.org/10.1136/bmjopen-2016-012759
10. Kales HC, Lyketsos CG, Miller EM, Ballard C. Management of behavioral and psychological symptoms in people with Alzheimer's disease: an international Delphi consensus. *Int Psychogeriatr*. 2019;31(1):83–90. https://doi.org/10.1017/S1041610218000534
11. Tampi RR, Jeste DV. Dementia is more than memory loss: neuropsychiatric symptoms of dementia and their nonpharmacological and pharmacological management. *Am J Psychiatry*. 2022;179(8):528–543. https://doi.org/10.1176/appi.ajp.20220508
12. Yunusa I, Alsumali A, Garba AE, Regestein QR, Eguale T. Assessment of reported comparative effectiveness and safety of atypical antipsychotics in the treatment of behavioral and psychological symptoms of dementia: a network meta-analysis. *JAMA Netw Open*. 2019;2(3):e190828. https://doi.org/10.1001/jamanetworkopen.2019.0828
13. Seitz DP, Adunuri N, Gill SS, et al. Antidepressants for agitation and psychosis in dementia. *Cochrane Database Syst Rev*. 2011;(2):CD008191. https://doi.org/10.1002/14651858.CD008191.pub2
14. Trinh NH, Hoblyn J, Mohanty S, Yaffe K. Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a meta-analysis. *JAMA*. 2003;289(2):210–216. https://doi.org/10.1001/jama.289.2.210
15. Maidment ID, Fox CG, Boustani M, et al. Efficacy of memantine on behavioral and psychological symptoms related to dementia: a systematic meta-analysis. *Ann Pharmacother*. 2008;42(1):32–38. https://doi.org/10.1345/aph.1K372
16. Bahji A, Meyyappan AC, Hawken ER. Cannabinoids for the neuropsychiatric symptoms of dementia: a systematic review and meta-analysis. *Can J Psychiatry*. 2020;65(6):365–376. https://doi.org/10.1177/0706743719892717
17. Vacas SM, Stella F, Loureiro JC, et al. Noninvasive brain stimulation for behavioural and psychological symptoms of dementia: a systematic review and meta-analysis. *Int J Geriatr Psychiatry*. 2019;34(9):1336–1345. https://doi.org/10.1002/gps.5003
18. van den Berg JF, Kruithof HC, Kok RM, et al. Electroconvulsive therapy for agitation and aggression in dementia: a systematic review. *Am J Geriatr Psychiatry*. 2018;26(4):419–434. https://doi.org/10.1016/j.jagp.2017.09.023
19. Bessey LJ, Walaszek A. Management of behavioral and psychological symptoms of dementia. *Curr Psychiatry Rep*. 2019;21(8):66. https://doi.org/10.1007/s11920-019-1049-5
20. Magierski R, Sobow T, Schwertner E, Religa D. Pharmacotherapy of behavioral and psychological symptoms of dementia: state of the art and future progress. *Front Pharmacol*. 2020;11:1168. https://doi.org/10.3389/fphar.2020.01168

21. Bondareff W, Mountjoy CQ, Roth M. Loss of neurons of origin of the adrenergic projection to cerebral cortex (nucleus locus ceruleus) in senile dementia. *Neurology*. 1982;32(2):164–168. https://doi.org/10.1212/wnl.32.2.164
22. Chan-Palay V, Asan E. Alterations in catecholamine neurons of the locus coeruleus in senile dementia of the Alzheimer type and in Parkinson's disease with and without dementia and depression. *J Comp Neurol*. 1989;287(3):373–392. https://doi.org/10.1002/cne.902870308
23. Hoogendijk WJ, Feenstra MG, Botterblom MH, et al. Increased activity of surviving locus ceruleus neurons in Alzheimer's disease. *Ann Neurol*. 1999;45(1):82–91. https://doi.org/10.1002/1531-8249(199901)45:1<82::aid-art14>3.0.co;2-t
24. Raskind MA, Peskind ER, Halter JB, Jimerson DC. Norepinephrine and MHPG levels in CSF and plasma in Alzheimer's disease. *Arch Gen Psychiatry*. 1984;41(4):343–346. https://doi.org/10.1001/archpsyc.1984.01790150033006
25. Elrod R, Peskind ER, DiGiacomo L, et al. Effects of Alzheimer's disease severity on cerebrospinal fluid norepinephrine concentration. *Am J Psychiatry*. 1997;154(1):25–30. https://doi.org/10.1176/ajp.154.1.25
26. Peskind ER, Wingerson D, Murray S, et al. Effects of Alzheimer's disease and normal aging on cerebrospinal fluid norepinephrine responses to yohimbine and clonidine. *Arch Gen Psychiatry*. 1995;52(9):774–782. https://doi.org/10.1001/archpsyc.1995.03950210068012
27. Lanari A, Amenta F, Silvestrelli G, et al. Neurotransmitter deficits in behavioural and psychological symptoms of Alzheimer's disease. *Mech Ageing Dev*. 2006;127(2):158–165. https://doi.org/10.1016/j.mad.2005.09.016
28. Roozendaal B, Hahn EL, Nathan SV, de Quervain DJ, McGaugh JL. Glucocorticoid effects on memory retrieval require concurrent noradrenergic activity in the hippocampus and basolateral amygdala. *J Neurosci*. 2004;24(37):8161–8169. https://doi.org/10.1523/JNEUROSCI.2574-04.2004
29. Aisa B, Tordera R, Lasheras B, Del Río J, Ramírez MJ. Cognitive impairment associated to HPA axis hyperactivity after maternal separation in rats. *Psychoneuroendocrinology*. 2007;32(3):256–266. https://doi.org/10.1016/j.psyneuen.2006.12.013
30. Dobarro M, Orejana L, Aguirre N, Ramírez MJ. Propranolol restores cognitive deficits and improves amyloid and Tau pathologies in a senescence-accelerated mouse model. *Neuropharmacology*. 2013;64:137–144. https://doi.org/10.1016/j.neuropharm.2012.06.047
31. Shiotsuka J, Steel A, Downar J. The sedative effect of propranolol on critically ill patients: a case series. *Front Med*. 2017;4:44. https://doi.org/10.3389/fmed.2017.00044
32. Ammar MA, Hussein NS. Using propranolol in traumatic brain injury to reduce sympathetic storm phenomenon: a prospective randomized clinical trial. *Saudi J Anaesth*. 2018;12(4):514–520. https://doi.org/10.4103/sja.SJA_33_18
33. Jensen CF. Hypersexual agitation in Alzheimer's disease. *J Am Geriatr Soc*. 1989;37(9):917. https://doi.org/10.1111/j.1532-5415.1989.tb02278.x
34. Deepmala, Agrawal M. Use of propranolol for hypersexual behavior in an adolescent with autism. *Ann Pharmacother*. 2014;48(10):1385–1388. https://doi.org/10.1177/1060028014541630
35. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4(1):1. https://doi.org/10.1186/2046-4053-4-1
36. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1–12. https://doi.org/10.1016/0197-2456(95)00134-4
37. Petrie WM, Ban TA. Propranolol in organic agitation. *Lancet*. 1981;1(8215):324. https://doi.org/10.1016/s0140-6736(81)91930-9
38. Weiler PG, Mungas D, Bernick C. Propranolol for the control of disruptive behavior in senile dementia. *J Geriatr Psychiatry Neurol*. 1988;1(4):226–230. https://doi.org/10.1177/089198878800100408
39. Shankle WR, Nielson KA, Cotman CW. Low-dose propranolol reduces aggression and agitation resembling that associated with orbitofrontal dysfunction in elderly demented patients. *Alzheimer Dis Assoc Disord*. 1995;9(4):233–237.
40. Peskind ER, Tsuang DW, Bonner LT, et al. Propranolol for disruptive behaviors in nursing home residents with probable or possible Alzheimer disease: a placebo-controlled study. *Alzheimer Dis Assoc Disord*. 2005;19(1):23–28. https://doi.org/10.1097/01.wad.0000155067.16313.5e
41. Summers WK. The management of agitation in demented patients with propranolol. *J Alzheimers Dis*. 2006;9(1):69–75. https://doi.org/10.3233/jad-2006-9107
42. Greendyke RM, Schuster DB, Wooton JA. Propranolol in the treatment of assaultive patients with organic brain disease. *J Clin Psychopharmacol*. 1984;4(5):282–285.

43. Levy RH, Collins C. Risk and predictability of drug interactions in the elderly. *Int Rev Neurobiol*. 2007;81:235–251. https://doi.org/10.1016/S0074-7742(06)81015-9
44. Paulison B, Léos CL. Potential cardiotoxic reaction involving rivastigmine and beta-blockers: a case report and review of the literature. *Cardiovasc Toxicol*. 2010;10(4):306–310. https://doi.org/10.1007/s12012-010-9088-5
45. Tampi RR, Tampi DJ, Farheen SA, Adnan M, Dasarathy D. Prazosin for the management of behavioural and psychological symptoms of dementia. *Drugs Context*. 2022;11:2022-3-3. https://doi.org/10.7573/dic.2022-3-3