

## Role of antipsychotics for treating behavioral and psychological symptoms of dementia

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### Abstract

Over the past three decades, concerns about the high prevalence of antipsychotic use in the nursing homes (NHs) for the management of behavioral and psychological symptoms of dementia continue to be emphasized and intervened by many. However, despite the numerous side effects and the recent blackbox warning by the United States Food and Drug Administration about the increased risks for stroke and sudden death associated with the use of antipsychotics in dementia, the prevalence of antipsychotic use in NHs remains high. While the use of antipsychotics appeared to have modest efficacy in reducing symptoms of aggression and psychosis in dementia, there is insufficient evidence to routinely recommend the use of alternative psychopharmacological treatments for these symptoms. Hence, clinicians have to balance the safety warnings against the need to treat these symptoms in order to prevent harm to the resident that may result from his/her dangerous behaviors. Although the use of antipsychotics may be warranted in some cases, organizational, resource and training support should be provided to encourage and equip NH staff to participate in interventions so as to minimize inappropriate use of these medicines in NHs. This review will discuss the place in therapy, the trend and appropriateness of antipsychotic use in NHs, as well as the effectiveness

of current and future strategies for reducing antipsychotic use in the NHs.

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**Key words:** Antipsychotic agents; Psychotropic drugs; Prescribing appropriateness; Dementia; Behavioral and psychological symptoms of dementia; Nursing homes

**Core tip:** While antipsychotics may be used to manage symptoms of severe aggression and psychosis when the safety of the resident is threatened, there should be routine reviews of the appropriateness of antipsychotic use as well as training and support of the care staff in providing psychosocial intervention to treat the symptoms so as to reduce antipsychotic use in nursing homes. Reported studies evaluating interventions to improve antipsychotic use appropriateness in nursing homes are limited by the small sample sizes and absence of control groups. Future research should address these methodological issues while exploring safer therapeutic alternatives to manage these symptoms.

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### OVERVIEW OF BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

With the rapidly aging population worldwide, the number of persons with dementia is projected to double every 20 years, from 35.6 million in year 2010, to 65.7 million, and 115.4 million by years 2030 and 2050 respectively<sup>[1]</sup>. Dementia is marked by features of progressively worsening

memory impairment and cognitive disturbances<sup>[2]</sup>. As the illness advances, the resulting decline in functional capacity naturally exerts its toll on the patient's family and/or the society, demanding significant expenditure in time, energy and resources in caregiving for extended periods. In year 2010, the cost of informal care (unpaid care provided by family and others) and direct cost of social care (provided by care professionals in the community and in residential long-term care institutions) for dementia each contributed to about 42% of the estimated USD 604 billion total cost<sup>[3]</sup>.

In addition to delaying cognitive and functional decline, dementia-related research has become increasingly focused on defining, measuring and managing behavioral and psychological symptoms of dementia (BPSD)<sup>[4]</sup>. BPSD is a term that encompasses a heterogeneous range of non-cognitive symptoms, such as disturbed perception, thought content, mood, and behavior<sup>[4]</sup>; and are broadly classified as "behavioral" or "psychological"<sup>[5]</sup>. These symptoms may be present in up to 97% of persons with dementia over a five-year period<sup>[6]</sup>, and were reported to be a significant source of patient distress, caregiver stress<sup>[7,8]</sup>, increased costs of care and nursing home (NH) admissions<sup>[9]</sup>. Hence, it was not surprising that higher point prevalence of BPSD were reported in the NHs compared to that in the community care setting<sup>[10]</sup>.

## EFFICACY AND SAFETY OF ANTIPSYCHOTICS FOR TREATING BPSD

Over many decades, antipsychotics have been prescribed for managing BPSD, particularly symptoms of severe agitation, aggression and psychosis. Although the precise mechanism of antipsychotics' influence on agitation is not known, their antagonistic effect on postsynaptic dopamine receptors was postulated to play a role in the amelioration of psychotic symptoms in dementia<sup>[11]</sup>. In a meta-analysis, haloperidol appeared to be clinically effective in reducing symptoms of aggression in dementia compared to controls<sup>[12]</sup>. The lack of a significant difference in the overall drop-out rates between the haloperidol treatment and control groups despite more drop-outs from the haloperidol group due to the presence of side effects further suggests the possible effectiveness of the drug<sup>[12]</sup>. However, the authors concluded that the routine use of haloperidol for the treatment of agitation in dementia should not be recommended, due to insufficient evidence of benefits from this treatment<sup>[12]</sup>.

Among the atypical antipsychotics, risperidone and olanzapine were deemed by Sink and his team to have the best evidence for efficacy in the treatment of aggression and psychosis<sup>[13]</sup>. Specifically, a meta-analysis reported that risperidone (1 to 2 mg/d) was effective in the treatment of aggression and psychosis related to dementia, while the use of olanzapine (5 to 10 mg/d) showed significant benefits in reducing aggression when compared to placebo<sup>[14]</sup>. These findings were consistent with that

reported in another meta-analysis<sup>[15]</sup> and the CATIE-AD trial<sup>[16,17]</sup>. In another randomized, placebo-controlled study, the use of aripiprazole resulted in a reduction of psychotic symptoms<sup>[18]</sup>. Although quetiapine was observed by Tariot and his co-investigators to improve symptoms of agitation<sup>[19]</sup>, this finding was not replicated in other studies<sup>[16,17,20]</sup>.

While typical antipsychotics are primarily D<sub>2</sub> receptor antagonists and inhibit dopaminergic neurotransmission in a dose-dependent manner, atypical antipsychotics vary in their binding affinities to other receptors<sup>[21]</sup>. As a result, each atypical antipsychotic has a different side effect profile. Unlike haloperidol, atypical antipsychotics generally have lesser propensities to cause neuroleptic-induced movement disorders or extrapyramidal symptoms (EPS)<sup>[22]</sup> due to a lower D<sub>2</sub> receptor blocking effect or a partial D<sub>2</sub> agonistic effect<sup>[23]</sup>. However, EPS may become more apparent with risperidone at doses higher than 2 mg/d due to its dose-dependent dopamine receptor blocking effect<sup>[14]</sup>. Other side effects and adverse events of risperidone also included somnolence, peripheral edema, cerebrovascular adverse events, urinary incontinence, urinary tract infection and falls<sup>[14]</sup>. For olanzapine and quetiapine, somnolence side effect was more prominent compared to other antipsychotics due to their higher affinity to block H<sub>1</sub> receptors<sup>[24]</sup>. In addition, significant weight gains, increased waist circumferences and decreased high-density lipoprotein cholesterol levels were also reported as characteristic side effects of olanzapine and quetiapine<sup>[14,25]</sup>. A decline in cognitive function could be a side effect of antipsychotic use, but this was found to be more significant among individuals who were treated with olanzapine and risperidone<sup>[26]</sup>, possibly due to the more pronounced anticholinergic effects of these antipsychotics<sup>[21]</sup>.

Besides the above-mentioned side effects, several studies and reviews have also highlighted the safety concerns regarding the use of antipsychotics in dementia. In a systematic review by Trifiró *et al.*<sup>[27]</sup>, an increase in risk for mortality was reported to be associated with the use of both typical and atypical antipsychotics in a dose-dependent fashion, where the highest risk was estimated to be shortly after exposure<sup>[27]</sup>. Although the related causes were postulated to include cerebrovascular event, pneumonia, peripheral vascular effects and/or metabolic effects, the differential risks of the individual antipsychotics and predisposing patient factors have yet to be established<sup>[27]</sup>.

Another safety concern was the increased risk for cerebrovascular events (CVEs) associated with antipsychotics, particularly olanzapine and risperidone, which were linked to a threefold increase in risk<sup>[14,28]</sup>. Yet, based on currently reported studies, a fair conclusion on the difference in risks between individual antipsychotic agents cannot be drawn. The plausible mechanisms of antipsychotic-related CVEs were deemed to be linked to side effects of antipsychotics including EPS<sup>[29]</sup>, orthostatic hypotension, hyperprolactinemia<sup>[30]</sup>, thromboem-

bolic events and excessive sedation<sup>[29,31]</sup>. However, while the elevated risk was thought to be temporal with the potential to decrease over time<sup>[32]</sup>, the contribution of predisposing patient factors to the development of CVEs (such as presence of vascular dementia) independent of antipsychotic use was not ascertained<sup>[27]</sup>.

Antipsychotic use was also associated with an increased risk for pneumonia. Specifically, threefold and 1.6-fold increases in risk were observed when atypical and typical antipsychotics were used respectively<sup>[33]</sup>. These could possibly be due to aspiration pneumonia linked to underlying mechanisms of antipsychotic-induced side effects including dysphagia, sedation and EPS<sup>[34]</sup>. Due to the poor prognosis of pneumonia in older persons with dementia, this adverse event may in turn contribute to the increased risk of their mortality associated with the use of these medicines.

## ROLE OF ALTERNATIVE PSYCHOPHARMACOLOGICAL AGENTS

### **Benzodiazepines**

Compared to antipsychotics, there was no or little evidence for recommending the use of other psychopharmacologicals such as benzodiazepines and anticonvulsant mood stabilizers to treat symptoms of severe agitation, aggression and psychosis. Specifically, the use of benzodiazepines among older persons for the treatment of agitation, especially in the presence of dementia, should be avoided as these individuals are more sensitive to side effects including sedation, ataxia and withdrawal symptoms, which may potentiate confusion, falls and fractures leading to adverse clinical outcomes<sup>[35]</sup>. To the authors' knowledge, there are also no published systematic review, meta-analysis or randomized controlled study to provide any evidence to support the treatment of severe agitation, aggression and psychosis in dementia with benzodiazepines.

### **Anticonvulsant mood stabilizers**

With regards to anticonvulsant mood stabilizers, valproate was ineffective in reducing BPSD or agitation symptoms according to two recent reviews<sup>[13,36]</sup> and a meta-analysis<sup>[37]</sup>. Although carbamazepine appeared to have some effect in reducing symptoms of aggression<sup>[38,39]</sup>, these reports were countered by negative findings of another study<sup>[40]</sup>. Furthermore, carbamazepine has clinically significant drug-drug interactions with medicines commonly used by older persons such as verapamil<sup>[41,42]</sup> and warfarin<sup>[43]</sup>. Carbamazepine also carries black box warnings for potentially fatal severe adverse drug reactions, specifically hematologic toxicity and serious dermatologic reactions especially for individuals with HLA-B\*1502 allele<sup>[44,45]</sup>. As such, the clinical use of carbamazepine, especially in the NHs, would be highly inconvenient due to the need for pre-treatment genotype screening and regular hematological monitoring to minimize the occurrence of these serious adverse drug reactions. Therefore,

anticonvulsant mood stabilizers should not be used to treat aggression and psychosis related to dementia.

### **Antidepressants**

While serotonin has been postulated to be involved in the underlying pathophysiological mechanisms for psychosis and aggression<sup>[46,47]</sup>, the evidence for the clinical use of antidepressants is primarily for the treatment of depression in dementia<sup>[48]</sup>. Although Lyketsos and his colleagues observed a beneficial reduction in non-mood behavioral symptom scores of the Neuropsychiatric Inventory (NPI-NM)<sup>[49,50]</sup> among individuals with Alzheimer's disease who had responded fully to the treatment of depression with sertraline, the difference in the reported NPI-NM scores between the treatment and control groups of the study was not statistically significant<sup>[51]</sup>. In a recent meta-analysis<sup>[52]</sup>, the use of serotonin reuptake inhibitors (SSRIs) sertraline and citalopram were associated with a larger mean change in the Cohen Mansfield Agitation Inventory<sup>[53]</sup> score (compared to placebo: -0.89, 95%CI: -1.22 to -0.57) and appeared to be better tolerated than typical and atypical antipsychotics. However, these findings were limited by the small sample sizes<sup>[52]</sup>. Furthermore, an evaluation of the effectiveness of citalopram for the treatment of BPSD noted improvements that were limited to symptoms of agitation and lability. The results were also potentially biased with a high dropout rate of more than 50% due to possible side effects and lack of efficacy<sup>[54]</sup>. Hence, more large-scale studies would be required to ascertain the safety and efficacy of SSRIs in the treatment of aggression and psychotic symptoms in dementia.

### **Acetylcholinesterase inhibitors and memantine**

Besides improving cognitive symptoms, the effects of acetylcholinesterase inhibitors (donepezil, rivastigmine and galantamine) and an N-methyl D-aspartate antagonist (memantine) in reducing BPSD were described in many case reports<sup>[55-57]</sup>, clinical studies<sup>[58-64]</sup>, randomized controlled trials<sup>[65-74]</sup> and systematic reviews<sup>[63,75-77]</sup>. A review on the randomized controlled trials concluded that the findings for donepezil and memantine appeared to be conflicting<sup>[13]</sup>. In addition, there is no landmark head-to-head study to offer a fair comparison for the differences in efficacies of these pharmacological agents. Meta-analyses of these drugs were also limited by different methodologies and measures of BPSD used in the clinical trials of each drug<sup>[78]</sup>. Furthermore, there were also reports of paradoxical worsening of both behavioral symptoms related to the use of donepezil in frontotemporal dementia<sup>[79]</sup> and parkinsonism associated with the use of donepezil in dementia with Lewy bodies<sup>[57]</sup>. Significant side effects of rivastigmine were also observed, which included nausea, vomiting, tremor and dizziness<sup>[66]</sup>. In all, it appears however, that rivastigmine<sup>[64,66,77]</sup> and memantine<sup>[71]</sup> may be safer alternatives for the management of aggression and psychotic symptoms, particularly for individuals with Parkinson's disease dementia and dementia with Lewy bodies, as they are likely to be susceptible to

the severe adverse effects of antipsychotics such as worsening of Parkinsonian symptoms and life-threatening severe neuroleptic malignant syndrome<sup>[80,81]</sup>.

## GUIDELINES AND TRENDS OF ANTIPSYCHOTIC USE IN DEMENTIA

Although there is limited evidence supporting the efficacy of non-pharmacological interventions for reducing aggression and psychosis related to dementia, these are recommended as the first-line strategy over the use of antipsychotics in all practice guidelines<sup>[82-84]</sup>. The obvious reasons are the numerous side effects<sup>[12,25,26,85]</sup> and higher risks for stroke and death associated with antipsychotics, which out-weigh their modest efficacies<sup>[86-89]</sup>, and their limited benefits with long-term use<sup>[90]</sup>. Despite the introduction of the black box warning for antipsychotics by the United States Food and Drug Administration in 2005 against its use in view of the increased risks for stroke and death, the reported prevalence of antipsychotic use in most NHs in the United States remained unchanged<sup>[91]</sup>. A recent report by the Centers for Medicare and Medicaid Services estimated that about 40% of NH residents with dementia were prescribed with antipsychotics in 2010<sup>[92]</sup>. Interestingly, this corresponded with the prevalence of delusion (54%) and hallucination (39%) found among these residents with dementia<sup>[93]</sup>. In a cross-national comparison, while about a quarter of NH residents in the United States were prescribed with antipsychotics, this prevalence varied between 11%-40% in Hong Kong, Canada, Switzerland and Finland and other countries<sup>[94]</sup>.

Within NHs, comparisons between the older persons with dementia residing in special dementia units *vs* traditional care wards found that antipsychotics were used more often in the former, as these residents were more likely to exhibit behavioral problems<sup>[95,96]</sup>. However, no statistical difference in the prevalence of antipsychotic use between these two cohorts of elderly NH residents with dementia was reported in another study, where the researchers attributed it to the effect of increased number of activities and psychosocial interventions which reduced the need for antipsychotics<sup>[97]</sup>.

Nevertheless, the use of antipsychotics in the NHs will continue due to the lack of alternative evidence-based pharmacological treatments for dementia-related severe agitation, aggression and psychosis for the residents with risk of physical harm as a result of uncontrolled behavior<sup>[98,99]</sup>. In addition, although many guidelines advocate prescribing antipsychotics for a minimal duration with attempts to taper off and discontinue at least once every 6 mo, a recent study suggested that the use of antipsychotics for up to 9 mo in individuals with severe baseline symptoms may confer benefits of having a reduction in symptom relapses compared to those who were taken off antipsychotics after 4 mo<sup>[100]</sup>. Similarly, another review concluded that though antipsychotics can be withdrawn within 6 mo without detrimental effects on behavior for most individuals, the use of antipsychotics

could be extended for those with more severe symptoms at baseline to prevent relapses<sup>[90]</sup>. Yet, concerns regarding the inappropriate use of antipsychotics in NHs were raised, which included the lack of proper documentation (especially pertaining to indications for use)<sup>[92,101,102]</sup>, prescribing of inappropriately high doses<sup>[103]</sup> and inadequate monitoring<sup>[104]</sup> for managing adverse effects and evaluating the need for continued use.

## APPROPRIATENESS OF ANTIPSYCHOTIC PRESCRIBING

While there appears to be a lack of specific clinical guidance for antipsychotic prescribing in dementia<sup>[105]</sup>, the literature is replete with criteria for defining what are considered as “inappropriate”. Firstly, clinicians have to balance the safety warnings associated with antipsychotic use in dementia against the need to alleviate the caregiving stress of providing the basic needs of the aggressive patient and to protect the resident from his/her own dangerous behaviors<sup>[99,106,107]</sup>. A failure to address these needs is considered “inappropriate”<sup>[99,108]</sup>. On the other hand, the patient’s and/or family’s wishes to refrain from antipsychotic use have to be considered and respected<sup>[108]</sup>.

Secondly, antipsychotic prescribing decisions without documented reasons are considered as inappropriate. As suggested in the algorithm by Osborne *et al.*<sup>[102]</sup>, proper documentation of prescribing rationale when initiating antipsychotics would include the specific description of the target behavior and/or symptoms and its impact on the patient that the prescribed medicine was intended to treat and resolve. During subsequent medical follow-ups and reviews, documentation of the patients’ responses to the prescribed treatment in terms of the changes in the details and impact of the target indications would be required to make informed decision for attempting a dose reduction or continuing with the antipsychotic treatment at the minimum effective dose, according to the guiding principle of “start low and go slow”<sup>[109]</sup>. Since the recommended antipsychotic doses for managing aggression and psychosis in dementia is generally much lower than that for treatment of psychiatric conditions, the prescribing of high doses and/or quick upward titration of doses may inappropriately expose the older person with dementia to unnecessary side effects such as drug-induced movement disorders, gait disturbances, and somnolence, potentially contributing to falls and adverse events such as fractures<sup>[12,85,110]</sup>.

Lastly, prescribing of antipsychotics for use in older persons with dementia would be inappropriate without proper monitoring for clinical responses and side effects. As prescribing decisions made during the short consultation time often depend on feedback from the caregivers, detailed and specific accounts of the changes in behavior, symptoms and complaints of patients may prompt timely interventions such as titrating the antipsychotic dose downwards for abating side effects. Specifically in the NH setting, the lack of proper monitoring and feedback

processes may be attributed to the low staff-to-resident ratio<sup>[111]</sup>, nurse-resident miscommunication<sup>[112]</sup>, inadequate training and the lack of a structured monitoring framework for antipsychotic use<sup>[113]</sup>, resulting in a lack of proper documentation of the rationale for antipsychotic use for each resident throughout his stay at the NH<sup>[104]</sup>.

## INTERVENTIONS TO REDUCE INAPPROPRIATE PRESCRIBING OF ANTIPSYCHOTICS IN NURSING HOMES

In order to reduce inappropriate prescribing of antipsychotics in the NHs, many interventions have been detailed. The first widespread changes in antipsychotic use trends were reported across most NHs in the US during the early 1990s. This was in response to the implementation of the OBRA'87 legislation which restricted the unjustified use of antipsychotics as a chemical restraint in the NHs for the management of difficult behaviors such as wandering, restlessness, anxiety and uncooperativeness<sup>[114]</sup>. In tandem with this legislation was the mandatory conduct of routine drug regimen reviews by pharmacists<sup>[115]</sup>. Although these brought about remarkable reductions in antipsychotic use, evidence of its positive impact on other clinical outcomes such as reduction in adverse events among NH residents was elusive. In contrast, a retrospective cross-sectional study noted that the NH residents in the United States were more likely to sustain falls, despite lower prevalence of psychotropic use, compared to those in Denmark, Iceland, Italy, Japan and Sweden<sup>[116]</sup>. Furthermore, adequate level of staffing could be more crucial towards the successful reduction of antipsychotic use and improved outcomes in the NHs<sup>[117,118]</sup>.

A literature search using a combination of terms “antipsychotics”, “neuroleptics”, “prescribing”, “nursing homes” and “intervention” was conducted to identify original studies that reported interventions targeting to reduce inappropriate antipsychotic use in NHs. A total of 12 interventions involving strategies such as audit-feedback processes, education and training for prescribers and/or nurses, medication review, multi-disciplinary case conferencing, early screening and intervention, structured monitoring program, as well as patient-centered psychosocial interventions are discussed in this review (Table 1).

### Interventions involving audits and feedback

Among the interventions using the audits and feedback approach, Westbury's and Castle's reports showed statistically significant reduction in the use of antipsychotics<sup>[119,120]</sup>. However, Westbury's group postulated that the positive outcome was likely to be attributed to the impact of the academic detailing with physicians, nursing staff training and follow-up medication review component<sup>[119]</sup>, but the outcome was not sustainable after 18 mo and the antipsychotic use prevalence returned to baseline levels<sup>[121]</sup>. This suggests for the management of BPSD

to be a long-term process, requiring constant reviews to ensure the appropriateness of antipsychotic prescribing. Similarly, another study showed that the audit-feedback process resulted in a reduction in antipsychotic use when it was carried out in combination with providing education and practical tools for nurses on how to document behaviors as well as the use of non-pharmacological interventions by nurses to manage agitation and challenging behaviors<sup>[122]</sup>. However, the intervention employed by Castle<sup>[120]</sup> did not include the component of education. Instead, it focused on communicating “important legislative efforts to reduce the prevalence of antipsychotics” as well as each NH's “performance” compared to other NHs across the board, in a manner which facilitated the use of these information by the NHs to change their care processes<sup>[120]</sup>. However, as inadequate information was provided on the selection or randomization of the NHs included in Castle's study, there could be a potential bias of more NHs that are motivated in change in the intervention group.

### Interventions involving education of healthcare professionals

Unlike educational interventions previously reported in the early 1990s<sup>[123,124]</sup>, two studies published more recently in 2005 and 2010 did not report significant reduction of antipsychotic use in the intervention NHs<sup>[125,126]</sup>. Reasons for these could be related to the small sample size of residents using antipsychotics at baseline as well as the use of non comparable control NHs with regards to the BPSD severity and use of antipsychotics of the NH residents. However, Monette *et al.*<sup>[127]</sup> reported a large number of antipsychotic discontinuation and dose reduction following an inter-disciplinary educational intervention, which was coupled with active monthly clinical follow-up by pharmacists to remind physicians to review antipsychotic prescriptions, monthly charting of residents' BPSD severity by nurses, as well as regular inter-disciplinary team meetings. A re-evaluation of this complex intervention involving education and inter-disciplinary efforts five years' later continued to demonstrate a reduction in the prevalence of antipsychotic use from 30.5% in year 2004 to 17.2% in year 2009<sup>[128]</sup>.

### Interventions involving medication review

In the United States, pharmacist-conducted medication reviews yielded a positive impact on improving the appropriateness of antipsychotic use in nursing homes<sup>[116]</sup>. This effect was also observed in Northern Ireland where a significant reduction in antipsychotic use was observed among NH residents receiving a structured pharmacist-led medication review program compared to those receiving usual care with no pharmacist intervention<sup>[129]</sup>. Despite the involvement of resident interviews and multidisciplinary meetings with nurses and physicians, this intervention was estimated to be more cost-effective than usual care<sup>[130]</sup>. Positive reduction in antipsychotic use was also reported in a medication review intervention led by

**Table 1** Selected original intervention studies aimed to improve antipsychotic use in the nursing home

Intervention type	Study design	Study duration	Healthcare disciplines providing intervention	Changes in antipsychotic use
Audit-feedback				
Castle <sup>[120]</sup>	CT	1 yr	NA	4.8% reduction in intervention group; SS
Westbury <i>et al</i> <sup>[119]</sup>	CT	26 wk	P, Ph, N	1.7% reduction in intervention group; SS
Watson-Wolfe <i>et al</i> <sup>[122]</sup>	SSBAS	2 mo	N	4.9% reduction
Education				
Hagen <i>et al</i> <sup>[126]</sup>	CT	1 yr	Ph	Increases in antipsychotic use; no SS in intervention group but SS in control group
Testad <i>et al</i> <sup>[125]</sup>	CRCT	1 yr	P	Increases in antipsychotic use; no SS
Monette <i>et al</i> <sup>[127]</sup>	SSBAS	7 mo	P, Psy, Ph, N	49% discontinued antipsychotics, 13.6% had dose reduction
Medication review				
Patterson <i>et al</i> <sup>[129]</sup>	CRCT	1 yr	P, Ph, N	9.4% reduction in intervention group; odds ratio of antipsychotic use for intervention group <i>vs</i> control = 0.26 (95%CI: 0.14–0.49); SS
Chakraborty <i>et al</i> <sup>[131]</sup>	MSBAS	2 yr	Psy, N	13.4% reduction
Case conferencing				
Dahl <i>et al</i> <sup>[133]</sup>	SSBAS	1 yr	P, Ph, N	1.3% reduction
Structured monitoring				
Yap <i>et al</i> <sup>[104]</sup>	SSBAS	24 wk	P, Ph, N	4 times increase in antipsychotic prescribing decisions due to side-effects reported; SS
Psychosocial intervention				
Fossey <i>et al</i> <sup>[134]</sup>	CRCT	10 mo	Psychologist, occupational therapist, N	19.1% reduction in intervention group; lower prevalence in intervention group (19.1% <i>vs</i> 42.1%); SS
Bird <i>et al</i> <sup>[135]</sup>	CT	9 mo	P, Psy, N, Psychologist	15.7% reduction in intervention group; SS

CRCT: Cluster-randomized controlled trial; CT: Controlled trial (non-randomized); MSBAS: Multi-site, before-and-after study; N: Nurse; NA: Not assessed; P: Physician; Ph: Pharmacist; Psy: Psychiatrist; SSBAS: Single site, before-and-after study; SS: Statistically significant.

psychiatrists and nurses<sup>[131]</sup>. However, the study did not include a control group or cost-effective analysis. The frequency and duration of visits by the psychiatrist-nurse team was also not known. Interestingly, the NHs in this study had an overall higher prevalence of antipsychotic use compared to non-nursing residential homes. This could be attributed to NH residents having more severe BPSD, which supports the continuous need to identify safer and more effective approaches to manage BPSD in NHs.

### Interventions involving multi-disciplinary case conferencing

A regular multidisciplinary team intervention study reported a significant decrease in the prevalence (-19%) of antipsychotic use<sup>[132]</sup>. However, at the end of the study, the prevalence of use remained at 19% after the intervention study period, while only 5% of the study population had psychotic disorders. Additional tools for facilitating the assessment, documentation of symptoms and reporting during multi-disciplinary meetings were described in other published studies<sup>[104,133]</sup>. In order to circumvent the challenge of coordinating the schedules of visiting physicians, psychiatrists and pharmacists for face-to-face case conferencing at the NHs, the intervention reported by Yap's group<sup>[104]</sup> emphasized on the process of monitoring, documentation and feedback of changes in residents' behavior, clinical responses and side effects to the prescribed antipsychotics by the nursing staff, including nursing aides and healthcare attendants. These

caregivers were motivated in providing the intervention as the monitoring-feedback processes were readily incorporated into their usual duties and did not require them to perform additional interviews or physical assessments on the residents. This resulted in a significant increase in prescribing decisions, specifically dose reduction and switching of agents to one with less propensity for drug-induced movement disorders, in response to side effects of antipsychotics reported by the nursing staff. Hence, this intervention would be useful in settings with low staff-to-resident ratios and where potential language and/or cultural barriers between the care staff and residents are present.

### Interventions involving psychosocial intervention

The use of psychosocial care was found to be an effective alternative to the use of antipsychotics in managing BPSD according to two studies. Specifically, the use of person-centred care approach for managing BPSD demonstrated significant reduction in antipsychotic use in NHs<sup>[134,135]</sup>. However, it may be challenging for NHs with staffing caps to implement full psychosocial care in managing BPSD as it is labor-intensive. The provision of continuous support from prescribers and NH administrators as well as training of staff<sup>[134]</sup> and adequate staff-to-resident ratio is needed<sup>[135]</sup>.

Overall, the majority of the published interventions with positive outcomes of reducing inappropriate antipsychotic use involved education for clinicians and care staff. While nurses were involved in all the interventions

with positive changes in antipsychotic use, they were not part of those interventions which reported no significant reduction in antipsychotic use. This observation suggests that interventions should involve healthcare providers from more than one discipline, especially the nursing staff, as their input as direct caregivers would be a significant influence on antipsychotic prescribing in the NHs<sup>[136]</sup>. Furthermore, it was noted that many interventions focused on reducing the use of antipsychotics, which is synonymous with preventing the “overuse” and “mis-use” of antipsychotics, while only the intervention reported by Yap’s group<sup>[104]</sup> expressly addressed the potential “underuse” of antipsychotics due to under- or mis-identification of symptoms such as psychosis, which could respond to short-term antipsychotic treatment<sup>[83]</sup>.

Most of the intervention studies cited in this review employed a variety of intervention types and methodological designs, and some are limited by small sample sizes and the lack of a suitable control. As only one study evaluated the cost-effectiveness of the pharmacist-led medication review intervention<sup>[130]</sup>, the comparisons of effectiveness in the other studies were descriptive at best. However, a study making direct comparison of the 4 interventions, namely medication review, recreational therapy, exercise and patient-centered care is ongoing<sup>[137]</sup>. Its results would provide deeper insights on the effectiveness of these interventions. Although some of the intervention studies<sup>[125,127,134]</sup> included in this review measured the change in BPSD using various instruments, positive results for this outcome measure can not be entirely attributed to the appropriateness of antipsychotic use as BPSD, specifically agitation, is intermittent in nature<sup>[138]</sup>. Hence, future studies should address the highlighted methodological concerns and measure the long-term effects of reducing antipsychotic use on BPSD and adverse outcomes among NH residents<sup>[139]</sup>.

## CONCLUSION

It appears that despite the modest efficacy and concerns for adverse outcomes of antipsychotic use in the management of BPSD, the use of these medications in the NHs is inevitable. However, future research should continue to explore the use of safer alternatives for the treatment of these symptoms. Although current guidelines recommend the use of psychosocial care over antipsychotics for the management of BPSD, organizational, resource and training support are essential to encourage and equip the NH staff to participate and provide these interventions. At present, there is no alternative solution to antipsychotic treatment and no gold standard in clinical practice to reduce inappropriate antipsychotic use. While the use of antipsychotics to manage BPSD symptoms may be warranted in cases when the safety of the NH resident and others around him/her is threatened, multidisciplinary interventions such as routine medication reviews to promote the appropriate use of antipsychotics may contribute as a long-term sustainable solution.

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