

Appendix 1. Expertise, roles and responsibilities, and conflicts of interest for the guideline development team members and support staff.

Guideline Member	Expertise	Guideline Role and Section Responsibilities	Conflict(s) of Interest
Guideline development team members			
Lise Bjerre	Family physician (Family Health Team)	<ul style="list-style-type: none"> • Overall lead • Introduction • Key points • Recommendations • Clinical considerations • Conclusion 	None declared
Barbara Farrell	Pharmacist (Geriatric Day Hospital, lead on the Deprescribing guidelines in the elderly project)	<ul style="list-style-type: none"> • Implementation • Gaps in knowledge • Resource implications and cost-effectiveness • Other guidelines 	Dr. Farrell has received research funding for the purposes of developing this guideline; received financial payments from Institute for Healthcare Improvement and Commonwealth Fund for deprescribing guidelines summary and from Ontario Long-Term Care Physicians Association, Ontario Pharmacists Association, Canadian Society of Hospital Pharmacists and European Association of Hospital Pharmacists for speaking engagements
Lyla Graham	Family physician (Long Term Care)	<ul style="list-style-type: none"> • Values and preferences • Clinical considerations 	None declared
Genevieve Lemay	Geriatrician	<ul style="list-style-type: none"> • Clinical considerations 	None declared
Lisa McCarthy	Pharmacist (community and primary care settings)	<ul style="list-style-type: none"> • Resource implications and cost-effectiveness • Other guidelines 	Dr. McCarthy has received funds from the University of Western Ontario for a speaking engagement."
Lalitha Raman-Wilms	Pharmacist (Long Term Care)	<ul style="list-style-type: none"> • Values and preferences 	None declared
Carlos Rojas-Fernandez	Pharmacist (geriatrics, primary and long-term care settings)	<ul style="list-style-type: none"> • Review of review of harms • Clinical considerations 	None declared
Samir Sinha	Geriatrician	<ul style="list-style-type: none"> • Values and preferences 	None declared
Vivian Welch	Clinical epidemiology methodologist	<ul style="list-style-type: none"> • Summary of findings and quality of evidence • GRADE review 	None declared
Andrew Wiens	Geriatric psychiatrist	<ul style="list-style-type: none"> • Clinical considerations 	None declared
Support persons			

Matthew Hogel	Research Associate	<ul style="list-style-type: none"> • Guideline coordinator • Scope • Methods • Summary of findings and quality of evidence • GRADE review 	None declared
Wade Thompson	Pharmacist	<ul style="list-style-type: none"> • Insomnia systematic review • GRADE review 	None declared

Appendix 2. Evidence tables

I. Continuation versus withdrawal of antipsychotic medication for the treatment of BPSD.

Quality assessment							№ of patients	Effect	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Success of withdrawal of antipsychotic medication										
7	randomised trials	not serious	serious	not serious	Not serious	not serious	365	No difference in dropout rate in seven studies. Significant increase in likelihood of relapse in deprescribing group in one study.	⊕⊕⊕O ⁴ MODERATE	
Change in behavioural and psychological symptoms										
6	randomised trials	not serious	serious	not serious	Not serious	not serious	422	No difference in the change in behavioural and psychological symptoms between the deprescribing and the continuation groups.	⊕⊕⊕O ⁴ MODERATE	
Symptoms of withdrawal from antipsychotic medications										
1	randomised trials	not serious	not serious	not serious	very serious	not serious	30	Decreased sleep efficiency in the deprescribing group compared to continuation	⊕⊕OO ¹ LOW	
Adverse events related to antipsychotic medications										
4	randomised trials	not serious	serious	not serious	Not serious	not serious	366	No difference in adverse events between the deprescribing and continuation groups.	⊕⊕⊕O ⁴ MODERATE	
Change in cognitive function										
6	randomised trials	not serious	serious	not serious	Not serious	not serious	422	No difference in the change in cognitive function between the deprescribing and continuation groups.	⊕⊕⊕O ⁴ MODERATE	
Mortality										
2	randomised trials	not serious	serious	not serious	serious	not serious	275	No difference in mortality between the groups in one study. Significant decrease in mortality in the deprescribing group in one study	⊕⊕OO ² LOW	
Change in quality of life										
3	randomised trials	not serious	not serious	serious	not serious	not serious	285	No difference in the change in measures of quality of life between the deprescribing and continuation groups.	⊕⊕⊕O ³ MODERATE	

Clarifications

1. Downgraded two levels for imprecision due to lack of optimal information size.
2. Downgraded one level for imprecision due to lack of optimal information size and one level for inconsistency as the two studies reported opposite results.
3. Downgraded one level for imprecision due to of optimal information size.
4. Downgraded one level for inconsistency due to the heterogeneity of the outcome measures.

II. Use of antipsychotic versus placebo for the treatment of insomnia.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quetiapine	Control	Relative (95% CI)	Absolute	
Increase in total sleep time											
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ^{2,3}	none	7	6	-	MD 52.68 higher (27.27 lower to 132.6 higher)	⊕○○○ VERY LOW
Reduction in sleep latency from baseline											
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ^{2,3}	none	7	6	-	MD 72.44 higher (2.65 lower to 147.5 higher)	⊕○○○ VERY LOW
Improvement in sleep satisfaction from baseline											
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ^{2,3}	none	7	6	-	MD 6.16 higher (12.32 lower to 24.64 higher)	⊕○○○ VERY LOW

Clarifications

¹ Concerns regarding baseline imbalance, incomplete outcome data

² Sample size less than 400

³ Uncertainty of results owing to wide confidence intervals

Appendix 3: Ranges of frequency ratios for harms associated with antipsychotics, and related references.

Harm	Odds ratios (and 95% confidence intervals)	Absolute Rates (Drug vs. Placebo)	Reference
CVAEs	2.13 (1.2, 3.75)	1.9% vs 0.9%	[1]
Death	1.54 (1.06, 2.23)	3.5% vs 2.3%	[1]
Abnormal gait	3.42 (1.78,6.56)	10% vs 2%	[1]
Somnolence	2.84 (2.25,3.58)	17% vs 7%	[1]
Drowsiness	2.38 - 8.2 (1.76, 29.9)	Not available	[2]
Edema	1.99 (1.2,3.3)	9% vs 4%	[1]
EPS	1.51 (1.2,1.91)	13% vs 8%	[1]
UTIs	1.28 (1.02,1.61)	16% vs 12%	[1]
Injury or falls	0.93 (0.78,1.11)	21% vs 22%	[1]

Full reference list for eligible systematic reviews reporting on harms of antipsychotic use:

- (1) Schneider LS, Dagerman K, Insel PS. Efficacy and Adverse Effects of Atypical Antipsychotics for Dementia: Meta-analysis of Randomized, Placebo-Controlled Trials. *The American Journal of Geriatric Psychiatry* 2006;14:191-210.
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Appendix 4: Evidence review

Summary of Systematic Review Findings

Deprescribing antipsychotics for the treatment of BPSD

Included studies

The 2013 Cochrane review included nine studies [1-9]. These studies had a median minimum duration of treatment with antipsychotics of 3 months (range 1-6 months; average 3.3 months +/- 1.5 months) prior to attempting withdrawal. Due to differences in study design and BPSD scales, a pooled analysis could not be performed. A narrative summary of the patient-important outcomes of interest is presented in Appendix 2.

Study outcomes

Success of antipsychotic withdrawal, measured as the ability of participants to reach the end of the study phase without removal from the study due to reasons such as death, symptom relapse, adverse effects of antipsychotic medication withdrawal, was evaluated in seven studies comprising a total of 365 participants [1,3,5-9]. There was no difference in the dropout rate in six studies. In one study, there was a higher rate of dropout in the withdrawal group than in the continuation group resulting from symptom relapse. The quality of evidence for success of deprescribing was graded as moderate due to concerns surrounding imprecision relating to the heterogeneity of the results.

Behavioural and psychological symptoms of dementia were evaluated in six studies involving 422 participants using a variety of validated scales (see table) as well as using counts of instances of

aggressive behavior [1-4,8,9]. The time period over which these symptoms were evaluated ranged from 1-12 months (median = 3). There was no significant difference in the change in BPSD

Table – Scales used in BPSD systematic review

BPSD Scales	
BDS	Blessed Dementia Scale
BEHAVE-AD	Behavioural Pathology in Alzheimer's disease rating scale
BPRS	Brief Psychiatric Rating Scale
CGI	Clinical Global Impression
CMAI	Cohen-Mansfield Agitation Inventory
NPI	Neuropsychiatric Inventory
Adverse Events Scales	
AIMS	Abnormal Involuntary Movement Scale
ESRS	Extrapyramidal Symptom Rating Scale
M-UPDS	Modified Unified Parkinson's Disease Scale
	Physical Self-Maintenance Scale
TESS	Treatment of Emergent Symptoms Scales
Cognitive Function Scales	
ADAS-Cog	Alzheimer's Disease Assessment Scale - cognitive
CAS	Cognitive Assessment Scale
LPRS	London Psychogeriatric Rating Scale
MDRS	Mattis Dementia Rating Scale
MMSE	Mini-Mental State Examination
SCAGS	Sandoz Cognitive Assessment Geriatric Scale
SIB	Severe Impairment Battery
SMMSE	Standardized Mini-Mental State Examination
Quality of Life Scales	
ADL	Bristol Activities of Daily Living
BFAS	Blessed Functional Activity Scale
DCM	Dementia Care Mapping

between the continuation and withdrawal group in any of the six studies. The quality of evidence was moderate due to concerns about imprecision relating to the variance in scales used to evaluate this outcome.

Change in cognitive function was measured in six studies, which involved 422 participants [2,4-7,9]. Cognitive function was measured using various scales (see table). There was no difference in the change in cognitive function between the continuation and the withdrawal group in any of the six studies. The quality of evidence was rated as moderate due to the variation in the scales used across the studies to measure cognitive function.

Mortality was measured in two studies consisting of 275 participants [2,6]. One of these studies showed no significant difference in mortality (2/70 in the continuation group vs. 1/67 in the deprescribing group; RR 1.91 [0.18-20.62]) between groups after 32 weeks of having been randomized to continue or stop taking antipsychotics. The second study reported a significant decrease in mortality (39/83 who continued treatment vs. 27/82 in the deprescribing group; HR 0.58 [0.36-0.92]) in the group withdrawn from antipsychotic medication compared to the group continued on antipsychotic medication after a period lasting up to 54 months. The quality of evidence for this outcome was rated as low. It was rated down one level for imprecision due to the limited number of participants in the two studies, and was rated down one level for inconsistency due to the conflicting results in the two studies.

Change in quality of life measured in individuals removed from antipsychotics versus those continued on the drugs was evaluated in three studies involving 285 participants using several scales (see table) [1,2,5]. No significant difference was observed between groups in any of the three studies. The quality of evidence was rated as moderate due to the limited number of participants in the studies which evaluated this outcome.

Withdrawal symptoms in antipsychotic deprescribing trials

Symptoms of withdrawal from antipsychotic medication were reported in one study consisting of 30 participants [8]. This study reported that those withdrawn from their antipsychotic medication experienced decreased sleep efficiency when compared to those who continued on their antipsychotic medication. The quality of evidence was very low, as serious concerns existed about the low number of participants in the single study used to evaluate the outcome.

Adverse effects of continued antipsychotic use in deprescribing trials

Some adverse effects of antipsychotic medications were prospectively measured in four studies, which included 366 participants, using a variety of validated scales (see table) [2,4,6,9]. There was no difference in adverse effects between groups in any of the four studies that measured it. The quality of evidence was rated as moderate owing to the heterogeneity in scales used to evaluate this outcome.

Use of antipsychotics for the treatment of insomnia

Included study and study outcomes

Our systematic review found one study, with 13 participants, that met inclusion criteria [10]. The study reported increases in total sleep time [52.68 min (95% confidence interval (CI): -27.27 to 132.6)] and sleep satisfaction [6.16 out of 100 (95% CI: -12.32 to 24.64)], and a decrease in latency to sleep [72.44 min (95% CI: -2.65 to 147.5)] in the group prescribed an antipsychotic compared to the group given placebo, however, none were significant. Summary of findings tables with further details are presented in Appendix 2. The quality of evidence for all outcomes of antipsychotic effectiveness in insomnia was judged to be very low, due to concerns about high risk

of bias (attrition, reporting and other), small sample size and subsequent imprecise results. The authors did not report rates of adverse effects nor nighttime awakenings, and did not have this data available when contacted. There were also baseline imbalances with respect to sleep parameters – the quetiapine group had a lower total sleep time, longer sleep latency and poorer sleep satisfaction at baseline.

Harms of continued antipsychotic use

In addition to the well-known side effects of antipsychotics (drowsiness, headache, extrapyramidal symptoms, weight gain, etc. [11]), there has been a heightened awareness of more serious adverse effects since the mid-2000s. A review of reviews of harms associated with antipsychotic drugs was conducted; a librarian conducted an English only literature search (strategy available upon request) and 2 research assistants independently reviewed the results using the following inclusion criteria to identify relevant literature: systematic reviews of RCTs or observational studies, and any outcomes resulting in harms. The search retrieved 741 publications, of which 21 were retained and 720 were excluded (see Appendix 3). Of those 21, five contained quantitative data on the occurrence of adverse events in patients taking antipsychotics. The range of frequency ratios from these studies are outlined in Appendix 3. The most concerning harms are the 1.5-2.0 fold increase in risk of death and the 2-fold increased risk of cerebrovascular events (CVAEs), though it is important to bear in mind that the absolute risks [3.5% vs. 2.3 % and 1.9% vs. 0.9% (medication vs. placebo), respectively] are low [12], which translates to an NNH_{1year} of 83-100. These data led the FDA and HC to issue warnings about the increased risk for CVAEs and death in this population [13,14].

It should also be noted that results in the review of observational studies were highly heterogeneous [15] and in many cases, recent observational studies have failed to confirm serious outcomes (death, CVAEs) with antipsychotic use [16-21].

Values and preferences related to antipsychotics

Reasons for use

Family members of community-dwelling individuals with dementia consulted during care reviews believe that antipsychotics use is intended to aid sleep, help family members manage care tasks and help principal care givers cope; others were unaware of the reasons for prescribing antipsychotics [22]. Amongst front-line LTC providers and family members, the reasons most cited during interviews for the use of antipsychotics are the presence of physically or verbally aggressive behaviours and problems with daily care [23]. Results from surveys of front-line care providers and family members reported that on average, about half of their patients/residents or family members with dementia and behavioral disturbances were expected to benefit from antipsychotics [24]. This likely explains a general feeling that the benefits of using antipsychotics outweigh the risks of side-effects [24,25].

Awareness of harms and benefits

Both family members and professional caregivers appear to understand the potential negative outcomes associated with using antipsychotics. Family members reported in interviews that the sedating effects of antipsychotics are distressing, unhelpful and that antipsychotics can be harmful even in the absence of severe side effects, with some family members and primary caregivers feeling patients' quality of life is better without antipsychotics [26]. In interviews and focus groups, some relatives reported removing individuals from residential settings to protect them

against being prescribed antipsychotics [27]. Other studies, using tests as well as patient and caregiver interviews, also suggest that use of antipsychotics, including in an institutional setting [28], is an independent predictor of worsened patient quality of life (QOL) [26,29].

Despite awareness of the negative outcomes of using antipsychotics for BPSD, there is evidence that they can have a positive impact on the caregivers. An RCT with three different treatment arms that evaluated the efficacy of haloperidol and trazodone against placebo for treating agitation in Alzheimer's Disease showed that the combined effect of antipsychotic treatment versus placebo resulted in a small but statistically significant reduction in caregiver burden [30].

Although the negative effects of antipsychotics are apparent to providers, caregivers, and family members, they also seem to have an understanding of the difficulties involved in discontinuing the use of antipsychotics. These barriers include the need for education of physicians, staff, and families [31] as well as inadequate staffing and other resources to support effective non-pharmacological approaches to managing behavioural issues [31,32]. The latter may be the primary reasons for continuing treatment [33]. Primary care physicians may be reluctant to discontinue antipsychotics if they were initially prescribed by another physician [34-37]. This represents a significant challenge if there is little communication between health care providers during transitions in care, without adequate identification of indications for prescribing antipsychotics [32]. Schultz (2008) notes that treatment decisions about antipsychotics are usually influenced by the expectations of clinicians and families [38], therefore, when attempting to withdraw antipsychotics, support from family and care providers can increase everyone's comfort level in doing so and enable a more effective outcome [22].

Resource implications and cost-effectiveness

In Canada, \$75 million was spent on antipsychotics for seniors during the second quarter of 2014. This represents an increase of 21% in costs over the last four years, despite the cost of individual medications declining due to the introduction of generic prices as patent protection expires. Ninety-seven percent (97%) of these costs were attributable to atypical antipsychotics, 78% to quetiapine, risperidone and olanzapine [39]. There is significant variability within Canada with respect to antipsychotic spending between provinces (after adjustments for age), with Quebec being at the high end (60% above the average for the rest of Canada) and Newfoundland and Labrador being well below average (27% below the average for the rest of Canada) [40]. In 2013, in Ontario alone, approximately \$35 million was spent on antipsychotics for patients aged 65 and over and significant variability amongst LTC facilities with respect to antipsychotic use persists [41].

In terms of volume, atypical antipsychotics are prescribed at higher numbers in the community than in LTC facilities, however, the rate of prescribing is 14 times higher in LTC facilities (22 per 1000 community patients vs. 328 per 1000 LTC residents) [42]. In a March 2013 survey of Ontario LTC homes, the prevalence of antipsychotic use amongst residents averaged 28.8% per LTC, with a maximum reported rate of 67.2% [41]. One in four of these long-term care residents taking an antipsychotic do not have a diagnosis of psychosis [43], and 22.4 % of residents in Canadian long-term care homes in 2014 were taking antipsychotics chronically [44].

Cost-effectiveness studies examining treatment options for BPSD show that behavioural interventions, such as cognitive stimulation therapy, are projected to reduce costs. A 2011 UK analysis reported that behavioural interventions resulted in a net benefit of approximately £54.9

million (approximately \$87 million CDN at that time) per year compared to antipsychotic use for BPSD, when the value of health care costs savings, from avoided falls and strokes, and quality of life improvements were considered [45]. For caregivers, antipsychotics have been shown to have a small but significant effect on caregiver burden, as they have been associated with reduced time for caregivers spent in direct caregiving roles [46,47]. These benefits, however, are similar to the effect of support groups and psychoeducational interventions for caregivers [46]. The cost implications are less clear, partly because estimates of the value of informal caregiving are highly variable, ranging from \$41,669 to \$56,290 USD (\$53,833 to \$74,019 CDN) depending on the method used to value informal care [48]. The economic value of informal caregiving is much greater than spending for formal home health care and nursing home care [46].

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