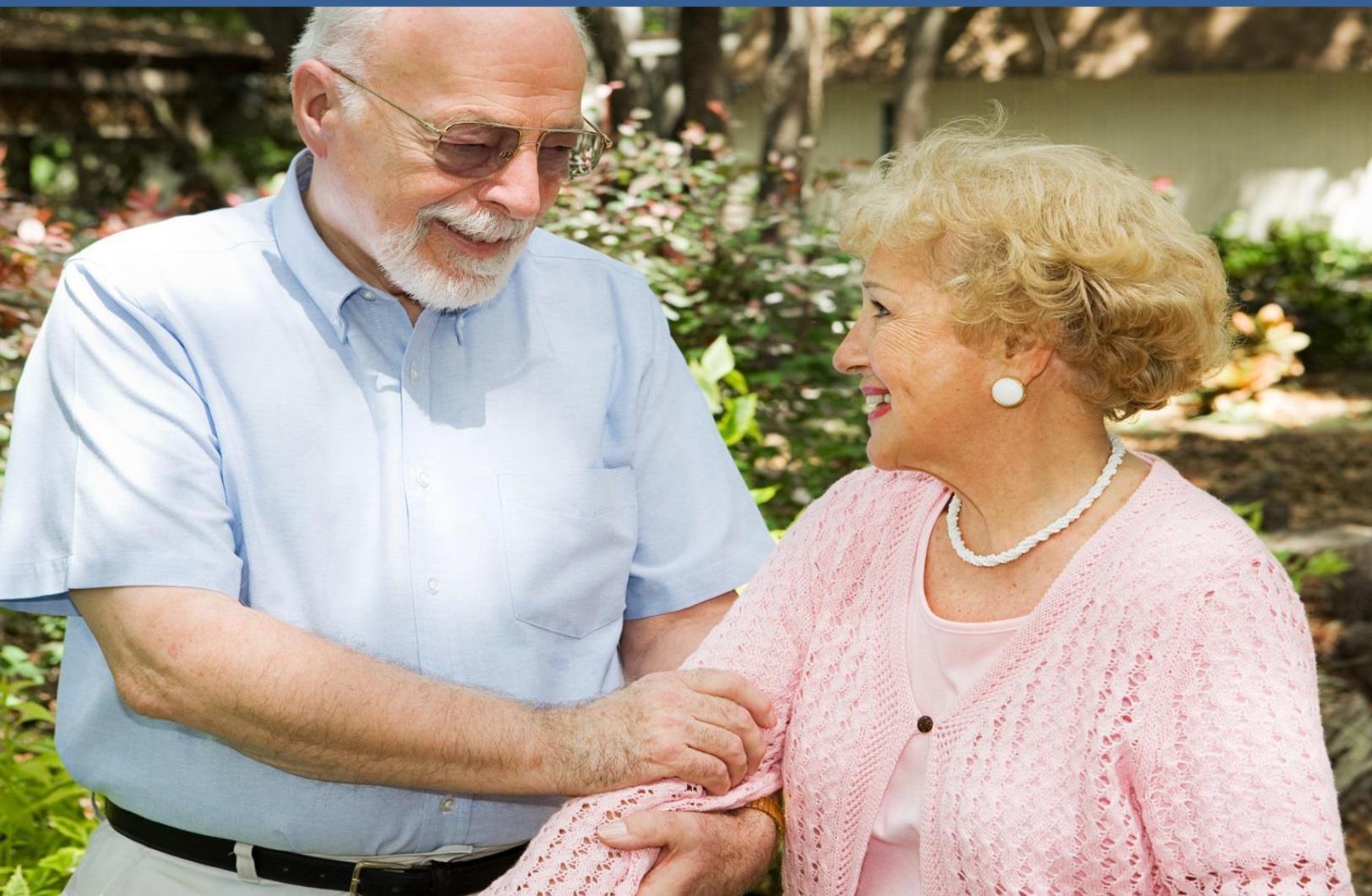


Antipsychotic Use in the Elderly



Final Consolidated Report

June 2015

ODPRN ONTARIO
DRUG POLICY
RESEARCH NETWORK

Ontario Drug Policy Research Network

The Ontario Drug Policy Research Network (ODPRN) is funded to conduct drug class reviews as part of an initiative to modernize the public drug formulary in Ontario. As such, the ODPRN works closely with the Ontario Public Drug Programs (OPDP), Ministry of Health and Long-Term Care to select key priority areas and topics for formulary modernization, then conducts independent drug class reviews and disseminates the results of each of these reviews directly to the OPDP to facilitate informed decision making on public drug funding policies. The drug class reviews may lead to recommendations such as expansion of access to drugs on the formulary, revision or restriction of access to drugs, no change to current listing status and/or education of clinicians regarding appropriate prescribing.

Conflict of Interest Statement

Muhammad Mamdani was a member of an advisory board for Hoffman La Roche, Pfizer, Novartis, GlaxoSmithKline and Eli Lilly Canada.

Paul Oh was a member of an advisory board for Amgen, Astra Zeneca, Janssen, Novartis, Pfizer, Roche and Sanofi.

Tara Gomes, Muhammad Mamdani and David Juurlink received grant funding from the Ministry of Health and Long-term Care.

No other study members report any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that may present a potential conflict of interest in the Atypical Antipsychotic for the Elderly Drug Class Review.

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Note

Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final uncensored reports will be available on the ODPRN website within 6 months of posting of the final reports (www.odprn.ca).

List of Abbreviations

AB	Alberta
BC	British Columbia
BPSD	Behavioural and psychological symptoms of dementia
CI	Confidence interval
CZD	Chlorpromazine dose
CIHI	Canadian Institute for Health Information
EAP	Exceptional Access Program
EPS	Extrapyramidal symptoms
FDA	Food Drug Administration
ICES	Institute for Clinical Evaluative Sciences
LHIN	Local Health Integration Network
LTC	Long-term care
LU	Limited Use
MB	Manitoba
MOHLTC	Ministry of Health and Long-term Care
NB	New Brunswick
NIHB	Non-insured Health Benefits
NL	Newfoundland
NMA	Network meta-analyses
NPI-NH	Neuropsychiatric Inventory-Nursing Home edition
NS	Nova Scotia
NT	Northwest Territories
NU	Nunavut
ODB	Ontario Drug Benefit
ODPRN	Ontario Drug Policy Research Network
ON	Ontario
OPDP	Ontario Public Drug Programs
OR	Odds ratio
PEI	Prince Edward Island
PSW	Personal support worker
QALY	Quality adjusted life year
QC	Quebec
RCT	Randomized controlled trial
SD	Standard deviation
SK	Saskatchewan
SMH	St. Michael's Hospital
SSRIs	Selective serotonin reuptake inhibitors
YK	Yukon Territories

Executive Summary

In Canada, there are nine atypical antipsychotics commercially available: aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone. These medications are primarily indicated for the management of patients with schizophrenia or bipolar disorders. All of these drugs are available as oral formulations and three drugs are available as injectables, either as a regular intramuscular injection (olanzapine) or as an intramuscular depot injection (aripiprazole, paliperidone, risperidone). Only risperidone is indicated for the symptomatic management of inappropriate behaviour in patients with severe dementia of the Alzheimer type. In Ontario, these medications are available as General Benefit on the Ontario Drug Benefit (ODB) formulary. All typical antipsychotics (with the exception of zuclopenthixol) are also listed on the ODB formulary as General Benefit.

Concern has been raised regarding the high utilization of these medications in the elderly, in particular in long-term care facilities.^{1,2} Safety concerns regarding the use of these medications in elderly patients with dementia, such as increased mortality, have been identified.³ As part of the formulary modernization review, an evaluation of atypical antipsychotics for the management of elderly patients with behavioural and psychological symptoms of dementia (BPSD) was undertaken, in order to provide policy recommendations for these products in Ontario.

Key Considerations for Reimbursement Options

Efficacy

Heterogeneity of outcome measures may have limited our ability to find conclusive evidence within the drug class. Overall, our network meta-analyses found that there were no significant differences in the improvement of total BPSD or BPSD subscales for psychosis, aggression and agitation across atypical antipsychotic agents (namely: risperidone, quetiapine, olanzapine, aripiprazole) when compared to placebo among patients with dementia and BPSD. Additionally, in elderly patients with dementia and BPSD, none of the atypical antipsychotics showed significant symptom improvements when compared to each other or haloperidol. There were no significant differences amongst the atypical antipsychotics in the improvement of Global Measures/Impressions, Cognition, or Caregiver Burden outcomes when compared to placebo or any other active comparator. In contrast to our results, previous meta-analyses have found that select atypical antipsychotics may show some benefit in the management of behavioural symptoms of dementia, although their overall effect is small.⁴ Differences between our results and published studies appear to be due to variations in methods of incorporation of subscales (e.g., Cohen-Mansfield Agitation Inventory (CMAI) - aggression subscale) into the analyses.

Safety and tolerability

Our network meta-analysis found a significantly higher risk of mortality with the use of atypical antipsychotics (pooled) when compared to placebo [odds ratio 1.90 (95% credible interval 1.19, 3.16)]. No significant differences were found for mortality when active agents were compared to each other or when active comparators were compared to placebo although the number of events was extremely small and these findings should be interpreted with caution. Additionally, no significant differences in

falls or weight change were found when comparing atypical antipsychotics to placebo or any other active comparator in elderly patients with dementia.

Other non-randomized studies have found an increased risk of sedation, falls, fractures, cardiovascular events, renal injury and overall mortality in association with the use of antipsychotics (typical and atypical) in the elderly population. Health Canada has issued several advisories regarding atypical antipsychotics in the elderly including: increased mortality associated with the use of atypical antipsychotic drugs in elderly patients with dementia; a higher risk of cerebrovascular adverse events in patients with mixed and vascular dementia compared to those with dementia of the Alzheimer type treated with any antipsychotic drug (including risperidone); reports of strokes in elderly patients receiving risperidone; increased incidence of cerebrovascular adverse events, such as stroke and transient ischemia attacks, associated with olanzapine in elderly patients with dementia.

Accessibility

In Ontario, all atypical antipsychotics (with the exception of clozapine) are available on the ODB formulary as a General Benefit. As such, no accessibility issues for qualifying patients, including those aged 65 years and older, were identified in our review. Rates of both typical and atypical antipsychotic use in the elderly are substantially higher in the long-term care (LTC) setting (39 and 328 per 1,000 eligible users, respectively) than in the community setting (7 and 22 per 1,000 eligible users, respectively).

Pharmacoeconomics

Budget Impact Analysis: Total OPDP expenditure for atypical antipsychotics in 2013 for patients 65 years and older was just over \$35 million. Expenditure for brand-name only atypical antipsychotics was \$6.1 million or 17.5% of the total atypical antipsychotic expenditure, although only 6% of all elderly users of atypical antipsychotics were using these brand-name only products.

Based on initiatives to reduce antipsychotic use in LTC facilities by 15-30%, the annual expenditure in 2016 for atypical antipsychotics could be reduced by \$2.4 to \$4.8 million.

Final Recommendations

As this drug class review focused on the use of atypical antipsychotics in the elderly for the management of BPSD, proposed recommendations will only consider atypical antipsychotics in this patient population. Expansion of these recommendations to typical antipsychotics in elderly patients with dementia may be appropriate with further review of the evidence to avoid restrictions of atypical agents leading to a rise in the use of typical agents. As well, the impact of these recommendations on utilization of alternative drug classes (e.g., benzodiazepines, typical antipsychotics) was not modeled and should be carefully considered when implementing any policy changes or designing programs aimed at reducing inappropriate prescribing of any one drug class. Note that these recommendations are NOT applicable to the treatment of elderly patients with Health Canada-approved indications such as schizophrenia and bipolar disorder.

Recommendation 1: Implementation of programs to reduce the inappropriate use of antipsychotic drugs for elderly people with dementia

- Although our review did not evaluate the efficacy of non-formulary initiatives to reduce antipsychotic use in elderly with dementia, other organizations have engaged in initiatives that have been shown to reduce the rate of antipsychotic prescribing in LTC facilities by 15-30%. A target of 15-30% has been suggested for Ontario since not all antipsychotic use is considered inappropriate in this population.
- Non-pharmacological initiatives including exercise therapy, environmental changes and music therapy, have been used for patients with dementia and behavioural issues. In some patients, a combination of various treatments (including pharmacological and non-pharmacological) are needed for management of BPSD.
- Educational training for healthcare providers in LTC facilities on dementia care and appropriate use of antipsychotics for BPSD has been used as a tool to reduce the inappropriate use of antipsychotic medications. In addition, information and training specific for caregivers is recommended.

Recommendation 2: Address rising expenditures associated with use of expensive, brand-name only atypical antipsychotics in the elderly

- The efficacy and safety of brand-name only antipsychotics (i.e., Abilify, Saphris, Latuda, Invega, Zeldox) in elderly patients with dementia is similar to genericized atypical antipsychotics (i.e., olanzapine, quetiapine, risperidone). However, the expenditure associated with these newer agents is not proportional to their use. In 2013, brand-name only atypical antipsychotic users (namely Abilify, Invega, Zeldox) comprised approximately 6% of all users of atypical antipsychotics but the expenditure for brand-name only atypical antipsychotics was 17.5% of the total atypical antipsychotic expenditure.
- Rising expenditures associated with the uptake of new, expensive brand-name only drugs should be explored through formulary changes (e.g., requiring Ministry approval to access brand-name only agents) or price negotiations with manufacturers (e.g., price reductions, price-caps). For example, restriction of brand-name only atypical antipsychotics on the Exceptional Access Program for patients 65 years and older for Health Canada-approved indications may result in a conservative cost savings of approximately \$1.4 million annually. Some factors that need to be considered are current pricing agreements between OPDP and manufacturers of brand-name only products, as well as resources required for managing the Exceptional Access Program for brand-name only products.

Recommendation 3: Engage in further research

- This drug class review focused on the pharmacological management of BPSD and associated formulary-based recommendations; use of alternative non-pharmacologic strategies for management of BPSD was not evaluated. Given our findings, a review of non-pharmacological

strategies for management of BPSD, including efficacy and cost-effectiveness, is needed in order to help provide alternatives to antipsychotics that could be incorporated into initiatives designed to reduce antipsychotic prescribing in the elderly.

- Initiatives to decrease the use of antipsychotic use in the elderly have mainly targeted LTC facilities. However, use of these agents in the community setting is substantial, with over 55% of total expenditures for atypical antipsychotics originating from the community. Since a proportion of community-based elderly (up to 54%) receiving atypical antipsychotics do not have a diagnosis of dementia, these agents are presumed to be used for off-label indications, such as insomnia and anxiety. The efficacy and safety of antipsychotics in this population for these off-label indications needs to be further explored including initiatives to decrease inappropriate use.

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Rationale for Review

In Canada, there are nine atypical antipsychotics commercially available: aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone. These medications are primarily indicated for the management of patients with schizophrenia or bipolar disorders. All of these drugs are available as oral formulations and three drugs are available as injectables, either as a regular intramuscular injection (olanzapine) or as an intramuscular depot injection (aripiprazole, paliperidone, risperidone). Only risperidone is indicated for the symptomatic management of inappropriate behaviour in patients with severe dementia of the Alzheimer type. In Ontario, these medications are available as a General Benefit on the Ontario Drug Benefit (ODB) formulary.

Concern has been raised regarding the high utilization of these medications in the elderly, in particular in long-term care (LTC) facilities.^{1,2} As well, safety concerns, such as increased mortality, have been identified with the use of these medications in the elderly with dementia.³ As part of the formulary modernization review, an evaluation of atypical antipsychotics for the management of elderly patients with behavioural and psychological symptoms of dementia (BPSD) was undertaken, in order to provide policy recommendations for these products in Ontario.

This report outlines the key findings for each of the components of the review. More detailed information for each of the reviews can be found on the ODPRN website: <http://www.odprn.ca>

Background Information

With the increase in the aging population, there is a growing number of patients affected with dementia. In Canada, approximately 6-15% of Canadians aged 65 years and older are living with dementia; this is expected to double by 2031.⁵ Dementia causes progressive disability and is a predictor of mortality.⁶ Alzheimer's disease is the most common type of dementia (60-80% of those diagnosed), followed by vascular dementia (10%) and dementia with Lewy bodies (10-25%).⁷ The pharmacological treatment of dementia focuses on cognitive deterioration with memory loss and the management of BPSD. The neuropsychiatric symptoms occur in approximately 90% of patients with dementia and present a challenge for clinicians and caregivers.⁸⁻¹⁰ Disruptive behavioural symptoms are associated with increased risks of cognitive decline, functional decline and institutionalization.¹¹ BPSD includes several symptoms including psychosis, agitation, depression and mood disorders. In patients with dementia, psychosis or agitation predisposes them to worse long-term outcomes, including a higher rate of institutionalization and death.^{11;12} As well, BPSD is associated with poor caregiver outcomes, including quality of life, worse health and reduced income from employment.¹³

Non-pharmacologic approaches are considered first-line in the management of BPSD. A variety of approaches have been suggested including aromatherapy, multisensory stimulation, reminiscence therapy, cognitive stimulation, therapeutic use of music and/or dance and animal-assisted therapy.¹⁴ Additionally, interventions targeting family caregivers have been found to reduce behavioural symptoms

in patients with dementia.¹⁵ Clinical guidelines recommend that pharmacologic treatment options should be utilized when non-pharmacologic approaches have proven ineffective.¹⁶ A number of different agents have been used for the management of BPSD including anticonvulsants, antidepressants, cholinesterase inhibitors and antipsychotics.^{17;18} Antipsychotics are the class of drugs most studied, usually in trials lasting 6 to 12 weeks, for this condition.^{4;19;20}

Antipsychotics are generally categorized into typical (also known as first-generation or conventional) and atypical (also known as second-generation). Typical antipsychotics include haloperidol and chlorpromazine, whereas atypical antipsychotics include risperidone, quetiapine, olanzapine and aripiprazole. Antipsychotics are indicated for treatment of schizophrenia, bipolar disorder and/or depression. However, they have also been used “off-label” for other indications such as anxiety disorder, obsessive compulsive disorder, attention deficit hyperactivity disorder, eating disorders, insomnia, post-traumatic stress disorder and dementia.^{4;21;22} Atypical antipsychotics are used more commonly in the pharmacological treatment of BPSD due to potential advantages over typical antipsychotics, such as a lower incidence of extrapyramidal symptoms (EPS) and tardive dyskinesia. However, although atypical antipsychotics have a lower propensity to cause EPS, they are associated with various metabolic adverse effects such as weight gain, diabetes, obesity, dyslipidemia and metabolic syndrome. The risk of metabolic sequelae in the elderly is still unknown.^{23;24} For example, in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE study), second-generation antipsychotics did not appear to affect glucose or triglyceride levels, but clinically significant weight gain ($\geq 7\%$) was observed in the treatment groups compared to the control groups.²⁵

In addition, despite the use of these drugs in the management of patients with BPSD, the safety of antipsychotics has been questioned.^{26;27} Health Canada and other regulatory agencies around the world have issued warnings about the increased likelihood of harm to elderly patients prescribed antipsychotics, including an increased likelihood of mortality.^{23;28-30} Studies have shown an increased rate of mortality with atypical antipsychotics compared to placebo.³¹ More recent observational studies and meta-analyses have shown that typical antipsychotics are associated with an increased risk of death compared to atypical antipsychotics.³²⁻³⁴ However, comparative safety within the antipsychotic drug class and measures of level of risk have largely been inconclusive due to challenges with residual confounding and selection bias that are inherent in observational studies of this population.^{32;35} In general, there is conflicting evidence to support differences between atypical and typical antipsychotics, aside from EPS symptoms.³⁶⁻⁴¹

Public plan reimbursement of atypical antipsychotics in Canada

All atypical antipsychotics are funded by the Ontario Public Drug Programs. Clozapine is funded through a Special Drugs Program (“Clozapine for Schizophrenia”), which covers the full cost of the drug for the specified indication. All other atypical antipsychotics and dosage forms (except Abilify Maintena and Zyprexa Intramuscular, which are not listed) are available as a General Benefit on the ODB formulary. Clozapine, olanzapine, quetiapine and risperidone (oral dosage forms only) are available as generic formulations. All typical antipsychotics (with the exception of zuclopenthixol) are listed on the ODB

formulary as General Benefit.

In Ontario, “Therapeutic Notes” are used with five of the atypical antipsychotics; only aripiprazole and lurasidone indicate that these medications are “not indicated for the treatment of dementia or dementia-related behavioural problems in the elderly”. Therapeutic notes for other atypical antipsychotics include clinical guidance for prescribers for use in schizophrenia or bipolar disorder.

In Canada, most jurisdictions (with the exception of Prince Edward Island), reimburse at least two atypical antipsychotics (namely quetiapine and risperidone) as a general (full) benefit. As noted above, these two medications are available as generic formulations. Olanzapine is restricted (requiring prior authorization) in 6 of 12 jurisdictions, despite its availability as a generic formulation. In all provinces, atypical antipsychotics that require special authorization are limited for the treatment of patients with schizophrenia and/or bipolar disorder. Typical antipsychotics are available in all provinces as general benefit.

Exhibit 1: Public plan listings in Canada for atypical antipsychotics

Drug	Brand/ generic	BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL	YK	NIHB/ NU/ NW
Aripiprazole	Abilify	Res	Ben	Res	Ben	Ben	Ben	Res	Res	Res	Res	Res	Res
	Abilify Maintena	No											
Asenapine	Saphris	Res	Res	Res	No	Ben	No	Res	Res	Res	Res	Res	Res
Clozapine	Generic	Ben	Ben	Res	Ben	Ben	Ben	Ben	Res	Res	Res	Ben	Ben
Lurasidone	Latuda	No	Ben	No	Ben	Ben	Res	Res	Res	No	Res	Res	No
Olanzapine	Zyprexa, Generic	Res	Ben	Res	Ben	Ben	Ben	Res	Res	Res	Res	Ben	Ben
	Zyprexa IM	No											
Paliperidone	Invega	Ben	Ben	No	No	Ben	No						
	Invega Sustenna	Res	Res	Res	No	Ben	Res	Res	Res	No	Res	No	Res
Quetiapine	Seroquel XR, Generic	Ben	No	No	No	Ben							
	Seroquel, Generic	Ben	Res	Ben	Ben	Ben							
Risperidone	Risperdal Consta	Res	Res	Res	No	Ben	Res						
	Risperdal, Generic	Ben	Res	Ben	Ben	Ben							
Ziprasidone	Zeldox	Res	Ben	Ben	Ben	Ben	Ben	Ben	Res	Res	Res	Ben	Res

No=not listed

Res=restricted listing – enforced

Ben=unrestricted listing

Objective

The objective of the drug class review of atypical antipsychotics in the elderly for the management of BPSD is to provide evidence-informed policy recommendations for these drugs in Ontario.

Components of the Drug Class Review

The atypical antipsychotics in the elderly for management of BPSD drug class review is comprised of:

- qualitative analyses of perspectives of patients, pharmacists and prescribers
 - one-on-one semi-structured telephone interviews regarding specific experiences and perceptions relevant to funding policies for atypical antipsychotics
- environmental scans of:
 - national and international drug policies
 - considerations relating to health equity
- analysis of real-world drug utilization using:
 - administrative claims data from Ontario and across Canada
 - summaries of relevant observational literature
- systematic review of the literature and network meta-analyses
- reimbursement-based economic analyses

Results from all of the above components were reviewed and consolidated into a set of policy recommendations.

Overview of Findings

Qualitative Research Team: Perspectives of Family Members and Healthcare Providers

There are multiple factors which may influence the prescription of antipsychotics in dementia care.

Although participating physicians' prescribing decisions were aided by the Canadian consensus guidelines, they emphasized that there are various contextual factors that need to be examined. For example, they may consider responsive behaviour triggers, non-pharmacological approaches, access to health services, type of setting (community or LTC), caregiver burnout, co-morbidities, alternative medications, and the patient's risk of harming themselves or others. Physician participants further explained that if they believe potential benefits outweigh medication risks, they will prescribe atypical antipsychotics. When asked about the atypical antipsychotics black box warnings, most did not perceive that the introduction of these warnings had any significant impact on their prescription habits or those of other physicians across Ontario. They also described their preferences for specific drugs within this class: risperidone and quetiapine were more commonly used compared to olanzapine and aripiprazole. With the exception of two family members, most wished they had more information about the prescription of atypical antipsychotics and the ability to make informed decisions about their loved

ones.

Trends in atypical antipsychotic prescription in dementia care may vary across community, acute care and long term care settings.

Participants perceived that there are significant efforts that are being made to encourage optimal use of antipsychotics. In general, most participants believed that there is a place for atypical antipsychotics in dementia care and it was their opinion that these medications are not grossly misused in every setting across Ontario. However, they acknowledged that there are occasions where atypical antipsychotic use could be avoided or monitored more carefully.

Most participants perceived that atypical antipsychotic use in the community is not as common as in LTC, because dementia patients may be less progressed in their disease. However, there are challenges with monitoring and tapering antipsychotic therapy in patients living in the community because, unlike in acute care and LTC, primary care physicians may only see outpatients once a week or less. As a result, it is difficult to document behaviour and gauge the effectiveness of medication trials. Participants described a greater use of atypical antipsychotics in acute care and LTC due to the severity of dementia patients in these settings and the greater number of responsive behaviour triggers. The environment in acute care and LTC can be over-stimulating (e.g., overcrowding, noise, neighbouring patients) and can trigger more responsive behaviours for patients who are not accustomed to this setting. In most cases, participants described that atypical antipsychotics are prescribed for short term use during acute care stays and longer term use in LTC homes.

“Acute care is for acute care issues. Unfortunately people with dementia sometimes have acute care issues and then, in a new environment, behaviours escalate.” –Primary Care

There are some key barriers to the appropriate use of atypical antipsychotics in dementia care.

Health care provider and family member participants described key barriers to appropriate prescribing which included improper transfer of patient medical information across settings; high staff turnover; limited human resources; limited health care provider expertise; and provider resistance to appropriate prescribing practices. Insufficient collection and transfer of patient medical history can play a key role in the prescription of atypical antipsychotics. In certain cases, lack of information may have influenced physicians to keep patients on a course of atypical antipsychotics for longer than necessary as they transfer from one setting to another (e.g., acute care to LTC). According to patient family members, the inconsistency in staffing in different settings may have acted as a barrier to continuity of care and proper monitoring. Although there is a growing interest in appropriate atypical antipsychotic prescribing, participants described that many primary or LTC clinicians still lack expertise with atypical antipsychotic dosage ranges and some are less enthusiastic about implementing new practices.

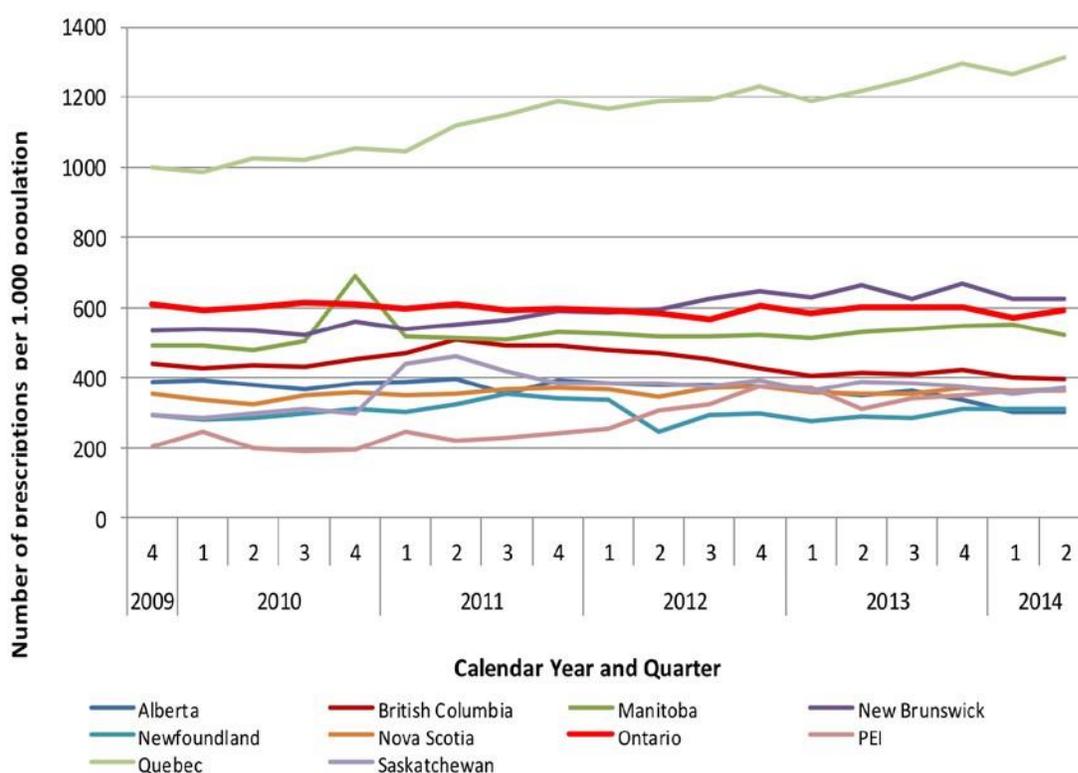
“The ratio in the nursing home is one to ten or more, I mean one PSW to ten residents or even more. So how could you expect this one PSW [Personal Support Worker] to manage 10 people with severe behaviour issues without any medication?” –LTC nurse

Pharmacoepidemiology Team

Current Utilization across Canada

Prescriptions for antipsychotics to elderly patients in Canada have increased by nearly 32% over the past 4 years, from 2,954,248 prescriptions dispensed in the last quarter of 2009 to 3,912,013 prescriptions dispensed by the second quarter of 2014 (See Exhibit 2). A total of \$75 million was spent on antipsychotic prescriptions dispensed to elderly patients nationally in the second quarter of 2014, an increase of approximately 21% since the fourth quarter of 2009 (\$62 million). The majority of antipsychotic prescription costs dispensed to elderly patients in Canada were for atypical antipsychotics (97%). Quebec has the highest rate of antipsychotic prescribing in Canada (1,314 prescriptions per 1000 elderly), with all other provinces having rates ranging between 303 and 625 prescriptions per 1,000 elderly. By the second quarter of 2014, Ontario’s rate of antipsychotic prescribing to elderly patients was 592 prescriptions dispensed per 1,000 eligible patients, which was higher than rates in all provinces except for New Brunswick and Quebec.

Exhibit 2: Population-adjusted utilization of antipsychotics in the elderly in Canada by province



Quetiapine, risperidone, and olanzapine are the three most prescribed atypical antipsychotics and account for 94% of atypical antipsychotic prescriptions (3,351,076 prescriptions in Q4-2014) and 78% of total cost (\$56,555,847 in Q4-2014) across Canada. Use of newer atypical antipsychotics has grown from only 0.2% of all prescriptions at the end of 2009 to 5% of all atypical antipsychotic prescriptions in Q2-2014.

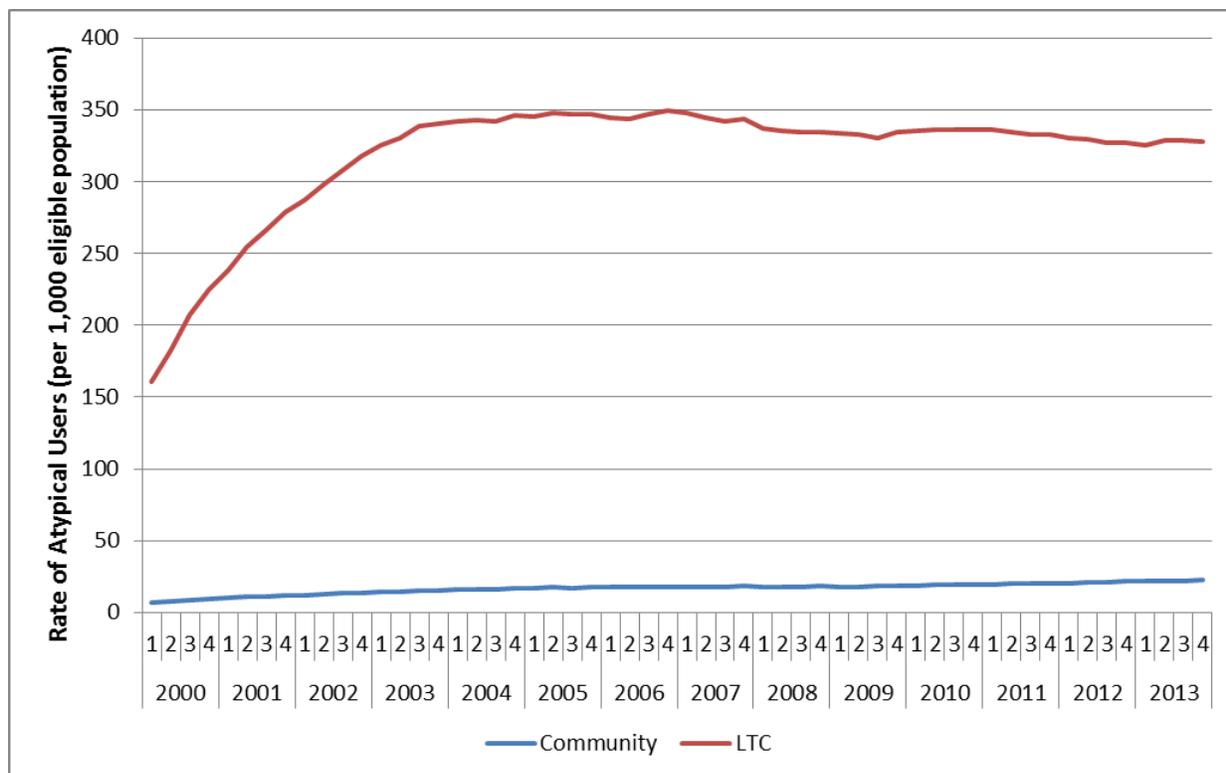
Trends in Provincially-Funded Antipsychotic Products in Ontario

Similar to national trends, Ontario has seen a sharp decrease in the use of typical antipsychotics in the elderly and an increase in the use of atypical antipsychotics. In Ontario, the rate of atypical antipsychotic use has increased by 214% and the rate of typical antipsychotics has decreased by 43% between the Q1-2000 and Q4-2013. This suggests that increases in rate of atypical AP prescribing are not simply due to replacement of typical antipsychotic prescribing. The most commonly used atypical antipsychotics initiated in new users in 2013 were quetiapine (47%), risperidone (40%) and olanzapine (13%). Haloperidol (56%), prochlorperazine (29%) and methotrimeprazine (9%) were the most common typical antipsychotics initiated. Although prochlorperazine is classified as an antipsychotic, it is primarily used as an antiemetic.

In Ontario, rates of both typical and atypical antipsychotic use in the elderly are substantially higher in the LTC setting (39 and 328 per 1,000 eligible users, respectively) than in the community setting (7 and 22 per 1,000 eligible users, respectively) (see Exhibit 3). Using the most recent five years of available data (2009 to 2013), the overall rate of elderly atypical antipsychotic users was found to have increased by 6%, from 32.4 per 1,000 eligible elderly in Q1-2009 to 34.4 per 1,000 eligible elderly in Q4-2013. In this same time period, the rate of users in the community has increased by 26%, from 17.8 per 1,000 eligible elderly in Q1-2009 to 22.4 per 1,000 eligible elderly in Q4-2013. In contrast, the rate of users in LTC has decreased by 1.7%, from 333.5 per 1,000 eligible elderly in Q1-2009 to 327.7 per 1,000 eligible elderly in Q4-2013.

There was a wide variation in the utilization of AP across Local Health Integration Networks (LHINs) for the elderly living in both the community and in LTC (see our interactive map found on our website www.odprn.ca). Rates of use in LTC residents ranged from 378 per 1,000 population in the Mississauga-Halton LHIN to 518 per 1,000 population in the North West LHIN. In community-dwelling elderly residents, the rate ranged from 32 per 1,000 population in the North West LHIN to 48 per 1,000 population in the North Simcoe Muskoka LHIN.

Exhibit 3: Rate of Atypical Antipsychotic Use among Elderly Public Drug Plan Beneficiaries in Ontario, by setting



Characteristics of Elderly Antipsychotic Users in Ontario

In 2013, 72,488 community-dwelling elderly and 32,580 LTC residents over the age of 65 were users of provincially-funded antipsychotics in Ontario. Among these individuals, 33,143 (45.7%) of those in the community, and 8,055 (24.7%) of those residing in LTC were new users. The average age of users was higher in LTC compared to community (84.3 and 77.4, respectively), which likely reflects different overall age distributions between community-dwelling seniors and LTC residents. The majority of treated patients were using atypical antipsychotics in both the community (N=45,210, 62.4%) and LTC (N=26,903, 82.6%) settings. In both settings, those treated with typical antipsychotics were sicker (higher Charlson comorbidity score), more likely to have visited a hospital in the past year, but less likely to have seen a specialist compared to those treated with atypical antipsychotics.

Users of antipsychotics residing in LTC were more likely to have dementia (88.3%) compared to those residing in the community (34.6%). Atypical antipsychotic users were more likely than typical antipsychotic users to have dementia in both community (46.5% vs. 10.9%) and LTC (89.5% vs. 75.0%) settings. Approximately two-thirds (67.6%) of antipsychotic users in LTC and one half (46.6%) of those residing in the community had concomitant use of an antidepressant. One-third of those in both settings (31.0% and 28.0% in community and LTC, respectively) had concomitant use of a benzodiazepine.

Concomitant use of cognitive enhancers was higher in the LTC setting (36.4%) compared to the community setting (14.7%). Community antipsychotic users were more likely than LTC antipsychotic users to have received their initial prescription from a specialist (16.3% vs. 0.6%, respectively). Atypical antipsychotic users in the community were also more likely to have received their initial prescription from a specialist, when compared to typical antipsychotic users in the community (22.8% vs. 3.4%, respectively).

Patterns of Antipsychotic Use and Discontinuation in the Elderly with Dementia in Ontario

Between April 2008 and March 2013, we found 34,195 community and 24,804 LTC newly-initiated antipsychotic users over the age of 65 with dementia. The age of new users was approximately 85 years and the majority (approximately 80%) of new users, in both the community and LTCs, were initiated on an atypical antipsychotic.

A third of new users were initiated at a dose less than 25 mg chlorpromazine dose (CZD) equivalents in both the community and LTC. Approximately half of new antipsychotic users persisted on therapy for at least one year (50-60%), with 35-40% of new users discontinuing therapy and the remaining 5-10% dying within one year of follow-up. Among the new users living in the community at initiation of antipsychotic therapy, approximately 40% were living in LTC by the end of the year. In both settings (LTC and community), a high mortality rate of close to 10% was observed over the 2 year follow-up period. No major differences in persistence to antipsychotic therapy were found for those living in LTC or community, but patients treated with higher doses at antipsychotic initiation were more likely to discontinue therapy.

Rapid Review Team

Efficacy

Two comprehensive, well-conducted and recently published (2010 and 2011) syntheses of available randomized evidence on the efficacy and safety of atypical antipsychotics in older adults with BPSD were identified.^{42,43} These reports were used as primary evidence synthesis to form the basis for the existing randomized controlled trials (RCTs). Following our own review and update, a total of 37 unique RCTs were included along with 26 companion publications; however, five studies failed to report an efficacy or safety outcome of interest and thus no data was extracted from these studies.

Most studies (28%) included in the analyses were six weeks in duration. Only three studies lasted six months or more. Of the nine atypical antipsychotics of interest, only four were identified in the 32 included studies that reported outcomes of interest (aripiprazole, olanzapine, quetiapine, and risperidone). Risperidone, quetiapine, and olanzapine intervention arms were distributed equally across the included studies and aripiprazole was least frequently used as an intervention. When an atypical antipsychotic was compared to an active comparator, eight unique drugs were identified across the 32 included studies reporting outcome data: namely haloperidol, selective serotonin reuptake inhibitors (SSRIs), rivastigmine, topiramate, lorazepam or promazine.

Overall 68% of participants were female and the mean age of all study participants was 80 years (standard deviation 8.5 years). The total number of study participants was 6,162, of whom 87% had a diagnosis of Alzheimer's disease. Across studies whose participants lived in only one type of setting, the most common type of setting was LTC (61%).

Network meta-analyses (NMA) and pair-wise meta-analysis were conducted for five efficacy outcomes: total symptoms of behaviour and psychological symptoms of dementia (BPSD), caregiver burden, global measures/impressions/cognition and activities of daily living. Additional NMAs were also conducted on three BPSD subscale measures (psychosis, agitation and aggression). The choice of these outcomes was based on input from stakeholder groups (e.g., researchers, healthcare providers) and the sufficiency of the data available to derive robust and consistent network models.

The results of the analysis are as follows (see Exhibit 4):

Behavioural and Psychological Symptoms of Dementia (BPSD):

- In general, there were no significant differences in the improvement of total BPSD across the atypical antipsychotic agents (risperidone, quetiapine, olanzapine, aripiprazole) when compared to placebo.
- Haloperidol, which was a comparator to atypical antipsychotics in our review, was the only agent significantly better than placebo in improving BPSD [mean difference (MD): -5.46, standard deviation (SD) 2.37] on the Neuropsychiatric Inventory-Nursing Home edition (NPI-NH) Scale.
- In elderly patients with dementia and BPSD, none of the atypical antipsychotics compared showed significant symptom improvements when compared to each other or haloperidol.
- Results may differ from clinical practice guidelines or other evidence syntheses as these analyses were based on overall BPSD scales (as opposed to subscales for aggression, agitation and psychosis).
- Additional analyses on BPSD subscales for psychosis, aggression and agitation, showed no significant improvement in any subscale with the atypical antipsychotic agents when compared to any other treatment, each other or placebo. Rivastigmine significantly worsened agitation scores when compared to risperidone (MD 10.13, SD 5.09).

Global Impressions/Impressions, Cognition, and Caregiver Burden:

- There were no significant differences amongst the atypical antipsychotics in the improvement of Global Measures/Impressions, Cognition, or Caregiver Burden outcomes when compared to placebo or any other active comparator.

Activities of Daily Living:

- Five studies reported baseline to end of study differences in Activities of Daily Living; data were reported using a variety of scales. Each of the scales combined for this analysis has different psychometric properties and results should be interpreted with caution.
- Olanzapine is significantly better than placebo, risperidone, quetiapine and haloperidol for

improving Activities of Daily Living outcomes in elderly patients with dementia. The mechanism of action leading to these differences is unclear, and this may be a statistical anomaly and requires further investigation.

- The results of our review differ from other previously published reviews. These differences are largely due to difference in ways that the scores from various subscales were incorporated into our analysis. For example, Ma *et al.* (2014) found that Cohen-Mansfield Agitation Inventory (CMAI) scores (measurement of aggression) for patients taking risperidone significantly improved compared to those who took placebo. Our analysis approach for this outcome differed from Ma *et al.* (2014) in that their analysis incorporated CMAI- aggression subscale change scores when overall scores were not provided by the primary article. By contrast, we restricted our NMA to overall CMAI scores, which could account for the differences in conclusions reached.²⁶ The Agency for Healthcare Research and Quality (AHRQ) completed a meta-analysis of placebo-controlled atypical antipsychotic trials measuring mean change in agitation and psychosis, and found that risperidone was significantly better at improving agitation and psychoses compared to placebo.⁴ AHRQ incorporated a variety of scales and subscales within each of their analyses, whereas we limited our analysis to a single, representative, scale for each outcome. Indeed, this fundamental difference in approach taken to analyze study data could account for the differences in findings for this outcome.

Exhibit 4: Efficacy of atypical antipsychotics for the management of behavioural and psychological symptoms of dementia

	Placebo	Risperidone	Olanzapine	Quetiapine	Aripiprazole	Haloperidol
Placebo		○○○○○	○○○○●	○○○○○	○○	●○○○
Risperidone	○○○○○		○○○○●	○○○○○	○○	○○○○
Olanzapine	○○○○●	○○○○●		○○○○●	○○	○○○○●
Quetiapine	○○○○○	○○○○○	○○○○●		○○	○○○○
Aripiprazole	○○	○○	○○	○○		○○
Haloperidol	●○○○	○○○○	○○○○●	○○○○○	○○	

The five contiguous circles correspond, from LEFT to RIGHT (respectively), to five efficacy outcomes: **BPSD (total), Global Measures/ Impressions, Cognition, Activities of Daily Living, and Caregiver Burden**

- A **green circle** indicates that the “row” antipsychotic is **significantly (statistically) better** compared with the “column” antipsychotic
- A **red circle** indicates that the “row” antipsychotic is **significantly (statistically) worse** compared with the “column” antipsychotic
- An **open circle** indicates that there is **no statistically significant difference** between the “row” and “column” antipsychotic
- A **missing circle** indicates that the **outcome was not available** for analysis

Safety and Tolerability

Four safety outcomes were considered: all-cause mortality (individual atypical antipsychotic agents and pooled), falls, EPS symptoms and weight change (see Exhibit 5).

Mortality, Falls, and Weight Change:

- In general, there are no significant differences in falls or weight change when comparing individual atypical antipsychotics to placebo or any other active comparator.

- An analysis of mortality conducted using pooled atypical antipsychotic agents showed a significantly higher mortality with atypical antipsychotic agents when compared to placebo [odds ratio 1.90 (95% credible interval 1.19, 3.16)]. However, no significant differences were found for mortality when active agents were compared to each other or when active comparators were compared to placebo, although the number of events was small and these findings should be interpreted with caution.
- Previously completed pooled analyses of mortality in patients who took any AAP compared to those who took placebo showed a similar risk increase: OR 1.54, 95% CI 1.06 to 2.23³¹ and OR 1.52, 95% CI 1.06, 2.18.²⁶ A meta-analysis of RCTs by the US Food and Drug Administration (using data not in the public domain) also suggested a significant increase in mortality (OR 1.7).⁴⁴

Extrapyramidal Symptoms (EPS):

- Haloperidol was the only agent to significantly increase EPS symptoms in elderly patients with dementia experiencing BPSD compared to placebo, risperidone, quetiapine, or olanzapine.

Exhibit 5: Safety of atypical antipsychotics for the management of behavioural and psychological symptoms of dementia

	Placebo	Risperidone	Olanzapine	Quetiapine	Aripiprazole	Haloperidol
Placebo		○ ○ ○ ○			○ ○ ○ ○	○ ○ ● ○
Risperidone	○ ○ ○ ○				○ ○ ○ ○	○ ○ ● ○
Olanzapine	○ ○ ○ ○	○ ○ ○ ○		○ ○ ○ ○	○ ○ ○ ○	○ ○ ● ○
Quetiapine	○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○		○ ○ ○ ○	○ ○ ● ○
Aripiprazole	○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○		○ ○ ○ ○
Haloperidol	○ ○ ● ○	○ ○ ● ○	○ ○ ● ○	○ ○ ● ○	○ ○ ○ ○	

The five contiguous circles correspond, from LEFT to RIGHT (respectively), to four safety outcomes: **Mortality (individual atypical antipsychotics), Falls, EPS and Weight Change** outcomes.

- A **green circle** indicates that the “row” antipsychotic is **significantly (statistically) better** compared with the “column” antipsychotic
- A **red circle** indicates that the “row” antipsychotic is **significantly (statistically) worse** compared with the “column” antipsychotic
- An **open circle** indicates that there is **no statistically significant difference** between the “row” and “column” antipsychotic

Antipsychotic safety in the elderly: non-RCT evidence

A robust body of work has found increased risk associated with use of antipsychotics in the elderly population.⁴⁵ Use of antipsychotics in the elderly has been associated with increased risk of sedation, falls⁴⁶, fractures⁴⁷⁻⁴⁹, cardiovascular events⁵⁰, renal injury,⁵¹ and overall mortality.^{31;45;52}

A meta-analysis of 15 RCTs in 2005 concluded that atypical antipsychotics were associated with an increased risk in mortality compared with placebo (OR 1.54; 95% CI 1.06, 2.23)³¹, leading to the issuance of a black box warning for the use of atypical antipsychotics for BPSD.^{3;28} A similar black box warning was issued for typical antipsychotics by the Food Drug Administration (FDA) in the United States in 2008 based on observational studies showing increased risk of mortality in older patients using typical antipsychotics compared to atypical antipsychotics.⁵³ Both atypical and typical antipsychotics have been associated with higher rates of mortality than non-antipsychotic medications, except for

anticonvulsants.⁵⁴ The increased risk has been shown to persist for at least 6-12 months.^{52;54}

Comparative safety within the antipsychotic drug class and measures of level of risk have largely been inconclusive due to challenges with residual confounding and selection bias that are inherent in observational studies of this population.^{32;35} In general, there is conflicting evidence to support differences between atypical and typical antipsychotics, aside from EPS symptoms.³⁶⁻⁴¹ Additionally, no evidence of within-class differences has been found between antipsychotic products.^{55;56} Little evidence is available on the safety of newer atypical antipsychotics (aripiprazole, ziprasidone, paliperidone, asenapine, lurasidone) in this population.

Health Canada and Food Drug Administration (FDA) warnings

- Health Canada issued an “Important Safety Information” advisory on February 18, 2015 regarding a higher risk of cerebrovascular adverse events in patients with mixed and vascular dementia compared to those with dementia of the Alzheimer type treated with any antipsychotic drug (including risperidone).⁵⁷ The indication for risperidone is now limited to “severe dementia of the Alzheimer type”.
- Health Canada issued an advisory in 2005 regarding increased mortality associated with the use of atypical antipsychotic drugs in elderly patients with dementia.³ Based on this advisory, manufacturers of atypical antipsychotic drugs were required to include a warning of the risk in the product monographs.
- In 2002, Health Canada issued an advisory for risperidone in elderly dementia patients regarding reports of strokes in this patient population.⁵⁸ An advisory was issued in 2004 for olanzapine in elderly patients. Use of olanzapine in elderly patients with dementia may be associated with an increased incidence of cerebrovascular adverse events, such as stroke and transient ischemia attacks.⁵⁹
- The United States Food Drug Administration (FDA) issued a Public Health Advisory in 2005 that atypical antipsychotic medications significantly increased the risk of death compared with placebo among elderly patients with dementia. The “Black Box” warning was added to product monographs of all atypical antipsychotics describing these risks and advising that these agents are not approved for use in elderly patients with dementia.²⁸ A similar “Black Box” warning was required in 2008 for manufacturers of conventional antipsychotic drugs.⁴⁴

Pharmacoeconomics Team

Cost-Effectiveness Literature Review

Two studies met the criteria for inclusion in this review^{60;61}. The study by Kirbach et al⁶⁰ was a cost-utility analysis of olanzapine compared with no treatment in patients aged 65 years and over with agitation and psychosis related to Alzheimer’s disease. From a health care system perspective, the incremental cost-utility ratio for olanzapine compared with no treatment was \$49,762 per quality adjusted life year (QALY) in CAD\$ in 2014 [1 USD\$= 1.1571 CAD\$]. From a societal perspective, the incremental cost-utility ratio for olanzapine compared with no treatment was \$17,636 per QALY in CAD\$ in 2014.

The study by Rosenheck et al.⁶¹ was a cost-utility analysis of initiation of therapy with an atypical antipsychotic (olanzapine, quetiapine, or risperidone) compared with watchful waiting (delay in initiation of therapy) in ambulatory outpatients living at home or in assisted living with Alzheimer's disease. The average age of this patient population was 77.9 years and patients had a Mini-Mental State Examination score between 5 and 26. From a health care system perspective, total health costs were lower for watchful waiting compared with olanzapine, quetiapine, or risperidone; and, there was no significant difference in QALYs. Although not a focus of this study, a comparison across the antipsychotics can be made with risperidone appearing less costly and resulting in more QALYs than olanzapine and quetiapine.

Applicability of these studies to the present research question is limited given that they are not from the Canadian perspective, nor do they include any analyses directly comparing active treatments.

Budget Impact Analysis

Total OPDP expenditure for atypical antipsychotics in 2013 for patients 65 years and older was just over \$35 million. This represents 92% of OPDP expenditure on antipsychotics among those aged 65 and over. Broken down by age, 2013 expenditure for atypical antipsychotics was \$15.9 million for patients 65-74 years, \$10.7 million for patients 75-84, and \$8.3 for patients >85 years. Expenditure in 2013 for atypical antipsychotics among patients living in long-term care facilities was lower (\$15.4 million) than for those living in the community (\$19.6 million).

The expenditures for brand name atypical antipsychotics (namely Abilify, Invega, Zeldox) in 2013 for patients 65 years and older was \$6.1 million or 17.5% of the total atypical antipsychotic expenditures; only 0.53% of new users in 2013 were initiated on these brand name atypical antipsychotics. In Q4 2013, 5.7% of all users of atypical antipsychotics were on a brand-name only product.

Estimates of the impact of various initiatives to reduce the use of antipsychotics in long-term care facilities were explored using forecast data for 2016. Based three such initiatives, we estimate that expenditure for all atypical antipsychotics could be reduced by up to \$4.8 million.⁶²⁻⁶⁵

Exhibit 6: Estimated cost-savings on initiatives to reduce the inappropriate use of antipsychotics among elderly patients in long-term care with dementia

ANTIPSYCHOTIC MEDICATION	FORECAST DATA	SCENARIOS FOR REDUCING ANTIPSYCHOTIC USE		
		2016	15% reduction	25% reduction
Atypicals (cost/savings)	\$17,984,704.95	\$15,570,258.31 (\$2,414,446.64)	\$13,960,627.22 (\$4,024,077.73)	\$13,155,811.67 (\$4,828,893.28)
Typicals (cost/savings)	\$904,052.15	\$802,346.28 (\$101,705.87)	\$658,262.97 (\$245,789.18)	\$700,640.42 (\$203,411.73)
Total (cost/savings)	\$18,888,757.10	\$16,372,604.60 (\$2,516,152.51)	\$14,618,890.19 (\$4,269,866.91)	\$13,856,452.09 (\$5,032,305.01)

Health Equity Issues

No major health equity issues were identified in this review. See Appendix A for Health Equity Considerations.

Accessibility of Atypical Antipsychotics for the Elderly

No accessibility issues were identified in Ontario in our review for atypical antipsychotics in the elderly; all atypical antipsychotics (with the exception of clozapine available through the Special Drugs Program, and Abilify Maintena and Zyprexa IM, which are not listed) are available as a general benefit on the ODB formulary.

Recommendations for Consideration

Key Considerations

Efficacy

- Heterogeneity of outcome measures may have limited our ability to find conclusive evidence within the drug class.
- Our network analysis found that there were no significant differences in the improvement of total BPSD or BPSD subscales for psychosis, aggression and agitation across the atypical antipsychotic agents (namely, risperidone, quetiapine, olanzapine, aripiprazole) when compared to placebo.
- In elderly patients with dementia and BPSD, none of the atypical antipsychotics compared showed significant symptom improvements when compared to each other or haloperidol.
- There were no significant differences amongst the atypical antipsychotics in the improvement of Global Measures/Impressions, Cognition, or Caregiver Burden outcomes when compared to placebo or any other active comparator.
- In contrast to our results, other meta-analyses have found that select atypical antipsychotics may show some benefit in the management of behavioural symptoms of dementia, although their overall effect is small.⁴

Safety and tolerability

- A significantly higher mortality was observed with atypical antipsychotic agents (pooled) when compared to placebo [odds ratio 1.90 (95% credible interval 1.19, 3.16)]. No significant differences were found when active agents were compared to each other or when active comparators were compared to placebo.
- Our meta-analysis found that there are no significant differences in falls or weight change when comparing atypical antipsychotics to placebo or any other active comparator.
- Haloperidol was the only agent to significantly increase EPS in elderly patients with dementia experiencing BPSD compared to placebo, risperidone, quetiapine, or olanzapine.
- Health Canada has issued several advisories regarding atypical antipsychotics in the elderly including: increased mortality associated with the use of atypical antipsychotic drugs in elderly

patients with dementia; a higher risk of cerebrovascular adverse events in patients with mixed and vascular dementia compared to those with dementia of the Alzheimer type treated with any antipsychotic drug (including risperidone); reports of strokes in elderly patients receiving risperidone; increased incidence of cerebrovascular adverse events, such as stroke and transient ischemia attacks, associated with olanzapine in elderly patients with dementia.

- Based on non-RCT studies, an increased risk of harm has been associated with the use of antipsychotics (typical and atypical) in the elderly population. Use of antipsychotics in the elderly has been associated with increased risk of sedation, falls, fractures, cardiovascular events, renal injury and overall mortality.

Accessibility

- In Ontario, all atypical and typical antipsychotics (with the exception of clozapine, which is available through the Special Drugs Program, and Abilify Maintena, Zyprexa IM and zuclopenthixol which are not listed) are available on the ODB formulary as a general benefit. As such, no accessibility issues for qualifying patients, including those aged 65 years and older, were identified in our review.
- Rates of both typical and atypical AP use in the elderly are substantially higher in the LTC setting (39 and 328 per 1,000 eligible users, respectively) than in the community setting (7 and 22 per 1,000 eligible users, respectively).

Pharmacoeconomics

- *Budget Impact Analysis:* Total OPDP expenditure for atypical antipsychotics in 2013 for patients 65 years and older was just over \$35 million. Based on initiatives to reduce antipsychotic use in LTC facilities by 15-30%, the annual expenditure in 2016 for atypical antipsychotics could be reduced by \$2.4 to \$4.8 million.

Stakeholder Review

The ODPRN Citizen's Panel rated each of the policy options for atypical antipsychotic use for the behavioural and psychological symptoms of dementia in the elderly (see Appendix B for reimbursement options considered by Citizen's Panel) on factors related to acceptability, accessibility and affordability, and ranked options from most to least preferable from a societal viewpoint. Overall, the most preferred choice was option B (Limited Use), but this was closely followed by option C (Exceptional Access Program). Option A (General Benefit), was chosen as the least acceptable choice.

Exhibit 7: Overall reimbursement option rating by Citizen's Panel

	Mean Ranking (1 = Most Acceptable 3 = Least Acceptable)
Option A: General Benefit (GB) listing for antipsychotics	2.5
Option B: Limited Use (LU) for all prescriptions in the elderly for atypical antipsychotics	1.5
Option C: Exceptional Access Program (EAP) for brand-name atypical antipsychotics	1.9

Respondents felt that Option A (General Benefit) would allow for the greatest access to the drugs, but would put the highest burden on the healthcare system. Option 2 (Limited Use) and Option 3 (Exceptional Access Program) were well-rounded overall and ranked very similarly. They scored high on affordability and reducing the burden on the healthcare system. The largest discrepancy between the two options was in “the policy adequately provides coverage for the appropriate types/quantity/doses” category, as respondents felt that Option B would be more restricting than Option C.

Final Recommendations

As this drug class review focused on the use of atypical antipsychotics in the elderly for the management of behavioural and psychological symptoms associated with dementia, proposed recommendations will only consider atypical antipsychotics in this patient population. Expansion of these recommendations to typical antipsychotics in elderly patients with dementia may be appropriate with further review of the evidence to avoid restrictions of atypical agents leading to a rise in the use of typical agents. As well, impact of these recommendations on utilization of alternative drug classes (e.g., benzodiazepines, typical antipsychotics) was not modeled and should be carefully considered when implementing any policy changes or designing programs aimed at reducing inappropriate prescribing of any one drug class. Note that these recommendations are NOT applicable to the treatment of elderly patients with Health Canada-approved indications such as schizophrenia and bipolar disorder.

All atypical antipsychotics are currently available on the ODB formulary as general benefit (exception: clozapine through Special Drugs Program; Abilify Maintena, Zyprexa IM not listed). Due to the open listing for coverage of these medications and their widespread use, limited reimbursement options are available for this drug class. For example, making all of the atypical antipsychotics available only through the Exceptional Access Program may not be feasible due to the large number of users of this drug class. Therefore, the Ontario MOHLTC may have to consider alternative recommendations. As well, there may be opportunities for the OPDP to engage with other departments within the MOHLTC to help reduce the

use of antipsychotic drugs in the elderly.

Given the lack of clear clinical benefit, safety considerations and increasing use of brand-name only atypical antipsychotics, three recommendations are proposed.

Recommendation 1: Implementation of programs to reduce the inappropriate use of antipsychotic drugs for elderly people with dementia

- Although our review did not evaluate the efficacy of non-formulary initiatives to reduce antipsychotic use in elderly with dementia, other organizations have engaged in initiatives that have been shown to reduce the rate of antipsychotic prescribing in dementia in long-term care facilities by 15-30%. A target of 15-30% has been suggested in Ontario since not all antipsychotic use is considered inappropriate in this population.
- Non-pharmacological initiatives including exercise therapy, environmental changes and music therapy, have been used for patients with dementia and behavioural issues. In some patients, a combination of various treatments (including pharmacological and non-pharmacological) are needed for management of BPSD.
- Educational training for healthcare providers on dementia care and appropriate use of antipsychotics for BPSD has been used as a tool to reduce the inappropriate use of antipsychotic medications. In addition, information and training specific for caregivers is recommended.

Recommendation 2: Address rising expenditures associated with use of expensive, brand-name only atypical antipsychotics in the elderly

- The efficacy and safety of brand-name only antipsychotics in elderly patients with dementia is similar to genericized atypical antipsychotics (i.e., olanzapine, quetiapine, risperidone). However, the expenditure associated with these newer agents is not proportional to their use. In 2013, brand-name only atypical antipsychotic users (namely Abilify, Invega, Zeldox) comprised approximately 6% of all users of atypical antipsychotics but the expenditure for brand-name only atypical antipsychotics was 17.5% of the total atypical antipsychotic expenditure. Addressing rising expenditures associated with the uptake of new, expensive brand-name only drugs can be explored through formulary changes (e.g., requiring Ministry approval to access brand-name only agents) or price negotiations with manufacturers (e.g., price reductions, price-caps). For example, restriction of brand-name only atypical antipsychotics on the Exceptional Access Program for patients 65 years and older for Health Canada-approved indications may result in a conservative cost savings of approximately \$1.4 million annually. Some factors that need to be considered are current pricing agreements between OPDP and manufacturers of brand-name only products, as well as resources required for managing the Exceptional Access Program for brand-name only products.

Recommendation 3: Engage in further research

- This drug class review focused on the pharmacological management of BPSD and associated formulary-based recommendations; use of alternative non-pharmacologic strategies for

management of BPSD was not evaluated. Given our findings, a review of non-pharmacological strategies for management of BPSD, including efficacy and cost-effectiveness, is needed, in order to help provide efficacious alternatives to antipsychotics that could be incorporated into initiatives designed to reduce antipsychotic prescribing in the elderly.

- Initiatives to decrease the use of antipsychotic use in the elderly have mainly targeted long-term care facilities. However, use of these agents in the community setting is substantial, with over 55% of total expenditures for atypical antipsychotics originating from the community. Since a proportion of community-based elderly (up to 54%) receiving atypical antipsychotics do not have a diagnosis of dementia, these agents are presumed to be used for off-label indications, such as insomnia and anxiety. The efficacy and safety of antipsychotics in this population for these off-label indications needs to be further explored including initiatives to decrease inappropriate use.

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Appendix A: Health Equity Considerations for Atypical Antipsychotics in the Elderly

Populations Identify which populations may experience significant unintended health impacts (positive or negative) as a result of the planned policy, program or initiative.	Comments: Proposed Atypical Antipsychotic recommendations
Aboriginal peoples (e.g., First Nations, Inuit, Métis, etc.)	No accessibility issues identified. Coverage of medications, including atypical antipsychotics, for Aboriginal peoples is available through Ontario Ministry of Health and Long-term Care.
Age-related groups (e.g., children, youth, seniors, etc.)	Elderly: No restrictions for atypical antipsychotic use in the elderly were identified.
Disability (e.g., physical, D/deaf, deafened or hard of hearing, visual, intellectual/developmental, learning, mental illness, addictions/substance use, etc.)	No accessibility issues identified. Patients with disability and receiving Ontario Disability Support Program Income Support, receive prescription drug coverage (including ICS+LABAs) through ODB.
Ethno-racial communities (e.g., racial/racialized or cultural minorities, immigrants and refugees, etc.)	No accessibility issues identified.
Francophone (including new immigrant francophones, deaf communities using LSQ/LSF, etc.)	No accessibility issues identified.
Homeless (including marginally or under-housed, etc.)	Not eligible for ODB coverage.
Linguistic communities (e.g., uncomfortable using English or French, literacy affects communication, etc.).	No accessibility issues identified.
Low income (e.g., unemployed, underemployed, etc.)	No accessibility issues identified; low income individuals who receive public drug coverage will have access to atypical antipsychotics through ODB.
Religious/faith communities	No accessibility issues identified.
Rural/remote or inner-urban populations (e.g., geographic or social isolation, under-served areas, etc.)	No accessibility issues identified.
Sex/gender (e.g., male, female, women, men, trans, transsexual, transgendered, two-spirited, etc.)	No accessibility issues identified for sex/gender in the review.
Sexual orientation , (e.g., lesbian, gay, bisexual, etc.)	No accessibility issues identified.
Other: please describe the population here.	None identified.

(based on Health Equity Impact Assessment <http://www.health.gov.on.ca/en/pro/programs/hea/>)

Appendix B: Assessment of Reimbursement Options Presented to the Citizen's Panel

	Option 1: General Benefit (Status quo): with Therapeutic Note*	Option 2: Limited Use for antipsychotics in the elderly (for approved indications)	Option 3: Exceptional Access Program for brand-name antipsychotics
Description	<p>No change in listing status for atypical antipsychotics. Currently, all atypical antipsychotics are available on the ODB formulary as general benefit (exception: Abilify Maintena, Zyprexa IM which are not listed and clozapine available under the Special Drugs Program).</p> <p>Therapeutic Note section for all atypical antipsychotics be aligned.*</p>	<p>All atypical antipsychotics that are currently listed on the ODB formulary be listed as Limited Use for patients 65 years and older.</p> <p>For those under 65 years of age, antipsychotics would continue to be available as general benefit.</p>	<p>All brand-name only atypical antipsychotics and formulations that are currently listed on the ODB formulary (i.e., Abilify, Saphris, Latuda, Invega, Zeldox) be available through EAP for Health Canada approved indications for patients 65 years and older.</p> <p>For patients under 65 years of age, no change in listing of brand-name only atypical antipsychotics that are currently listed on the ODB formulary.</p> <p>Olanzapine, quetiapine, risperidone be available as General Benefit (with Therapeutic Note*).</p>

	Option 1: General Benefit (Status quo): with Therapeutic Note*	Option 2: Limited Use for antipsychotics in the elderly (for approved indications)	Option 3: Exceptional Access Program for brand-name antipsychotics
Accessibility	<p>Widespread use in the elderly (data from 2013: 72,488 community-dwelling and 32,580 in long-term care).</p> <p>Allow for greatest accessibility to all ODB patients and for all indications (approved and off-label indications)</p> <p>Inclusion of a “Therapeutic Note” may help provide guidance for prescribers, but studies have shown limited impact of Therapeutic Note on physician prescribing.⁶⁶</p>	<p>Passive restrictions to access for elderly patients for specific indications (i.e., schizophrenia, bipolar disorder, depression); no prior approval/review would be required but use of Limited Use may be a barrier to ensure more appropriate prescribing in the elderly</p> <p>Since atypical antipsychotics are currently available as general benefit, restricting their use via LU listing may result in delay in care.</p>	<p>Generic atypical antipsychotics (olanzapine, quetiapine, risperidone) are available as general benefit for patients 65 years and older</p> <p>For patients under 65 years of age, no change in listing of brand-name only atypical antipsychotics that are currently listed on the ODB formulary.</p>
Budget Impact (current annual expenditures approximately \$38 million for all antipsychotics)	<p>Assuming reductions of 15-30% in patients with dementia in LTC facilities, cost savings of \$2.4-4.8 million forecasted for 2016 for atypical antipsychotics</p>	<p>Limited Use may aid in the reduction of inappropriate antipsychotic use</p> <p>Assuming reductions of 15-30% in patients with dementia in LTC facilities, cost savings of \$2.4-4.8 million for 2016 for atypical antipsychotics</p>	<p>In 2013, for elderly patients in Ontario, expenditures for brand-name atypical antipsychotics was \$6.1 million or 17.5% of the total atypical antipsychotic expenditure but only 5% of all users were on brand-name (innovator) atypical antipsychotics</p>
Safety concerns (Increased risk of cerebrovascular events and mortality in patients with dementia)	<p>This option results in the greatest number of patients exposed to antipsychotics, resulting in increased number of deaths and additional adverse events</p>	<p>LU listing may decrease the number of elderly patients prescribed antipsychotics outside of approved indications, thereby reducing the number of cerebrovascular events and mortality</p>	<p>Availability through EAP may decrease the number of elderly patients prescribed antipsychotics, thereby reducing the number of cerebrovascular events and mortality; however, since olanzapine, quetiapine and risperidone would be available as general benefit, a shift in prescribing may occur with these generic atypical antipsychotics used in place of the brand-name atypicals</p>

	Option 1: General Benefit (Status quo): with Therapeutic Note*	Option 2: Limited Use for antipsychotics in the elderly (for approved indications)	Option 3: Exceptional Access Program for brand-name antipsychotics
Alignment with other jurisdictions	MB	None**	None**
Prescribing Criteria	No prescribing criteria used with general benefit	Unenforced prescribing criteria used	Enforced prescribing criteria used
Use of alternative treatment options	Since all antipsychotics available as general benefit, use of alternative treatment options may not be as readily considered by the clinician	Limited Use criteria may help to guide the clinician to choose non-pharmacological treatment options for BPSD. However, this option may also lead the clinician to choose more readily available (general benefit) non-antipsychotic treatment options, such as antidepressants or typical antipsychotics for BPSD, and trazodone or antihistamines for insomnia	Restricted access for brand-name only (“innovator”) atypical antipsychotics would decrease the use of these drugs for non-approved indications. However, this option may also lead the clinician to choose more readily available (general benefit) atypical antipsychotics (quetiapine, risperidone, olanzapine) and typical antipsychotics as well as non-antipsychotic treatment options, such as antidepressants for BPSD, and trazodone or antihistamines for insomnia

* Therapeutic Note section for all atypical antipsychotics be aligned to include: “There is limited efficacy of atypical antipsychotics for management of elderly patients with behavioural and/or psychological symptoms of dementia. As well, there are safety concerns, including increased morbidity and mortality, with these agents. Use of antipsychotics in people with dementia who develop behavioural and/or psychological symptoms should be limited to those who have not responded to other treatments (including non-pharmacological) or when other treatments are not appropriate.”

**No provincial jurisdiction has addressed the issue of inappropriate antipsychotic use in patients with dementia, other than PEI, which has all available atypical antipsychotics on Special Access only. Other provinces have some brand-name antipsychotics listed as Special Access only, but generic products (in particular, quetiapine and risperidone) available as general benefit