

Atypical Antipsychotic Use for the Behavioural and Psychological Symptoms of Dementia in the Elderly

Final Report: Environmental Scan and Local/Historical Context

May 26th, 2015

Executive Summary

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

In Canada, atypical antipsychotics (aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) are available in various formulations, including oral tablet or capsule, oral solution, oral disintegrating tablet, intramuscular depot injection and intramuscular injection. Atypical antipsychotics are indicated for the management of psychiatric disorders including schizophrenia, bipolar disorder and/or depression. Only risperidone is indicated for the symptomatic management of aggression and psychotic symptoms in patients with severe dementia of the Alzheimer type. Risperidone, olanzapine and quetiapine are available as generic formulations.

In Ontario, most atypical antipsychotics are available as a general benefit on the Ontario Drug Benefit formulary (exception: Abilify Maintena, Zyprexa Intramuscular; clozapine-available through Special Drugs Program). Although “Therapeutic Notes” are available for five atypical antipsychotics, only two products (aripiprazole and lurasidone) specify in the “Therapeutic Notes” that these should not be used in the elderly for management of dementia or dementia-related behavioural problems. Across Canada, with the exception of Prince Edward Island, at least two atypical antipsychotics (usually quetiapine and risperidone) are available as general benefit. Many of the newer brand-name atypical antipsychotics are restricted via a special authorization program in most jurisdictions.

Part B: Guidelines for the management of patients with behavioural and psychological symptoms of dementia (BPSD)

Five guidelines/consensus statements were reviewed including Canadian Consensus Conference on the Diagnosis and Treatment of Dementia, NICE (National Institute for Health and Care Excellence), EFNS-ENS guidelines, and American Psychiatric Association guideline. These guidelines/consensus statements indicate that antipsychotics may be beneficial in treating BPSD, although their use may be associated with serious adverse effects. In general, antipsychotics should only be used for severe symptoms where there is risk of harm to the patient and/or others. As well, some guidelines specify that antipsychotics are only indicated when the patient has not responded to other treatments or when other treatments are not appropriate, or in conjunction with non-pharmacologic treatments.

Part C: Impact of different drug reimbursement schemes for atypical antipsychotics in the elderly

There is a lack of literature investigating various reimbursement schemes for atypical antipsychotics in the elderly for the management of BPSD.

Part D: Rapid Review of Selected Topics

Initiatives to reduce antipsychotic use in the elderly: In response to concerns about the use of antipsychotics in elderly patients with dementia, in particular those patients residing in long-term care facilities, various organizations have engaged in initiatives to reduce inappropriate use of these drugs. A

reduction in the rate of antipsychotic prescribing in dementia from 15-30% has been recommended.

Quetiapine for insomnia: The use of quetiapine for insomnia has been evaluated in limited studies, of which only one was a randomized controlled trial. It is unknown whether quetiapine's sedative effects are sustained in the long-term and what adverse effects are associated with quetiapine used in low dosages. There are no studies evaluating the use of quetiapine for insomnia in the elderly. As well, there are no trials comparing quetiapine to other active comparators (e.g., benzodiazepines, zopiclone).

Health Canada and Food and Drug Administration (FDA) warnings and advisories: Health Canada issued an advisory in 2005 regarding increased mortality associated with the use of atypical antipsychotic drugs in elderly patients with dementia. An advisory was issued by Health Canada in February 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). The US 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. A similar "Black Box" warning was required in 2008 for manufacturers of conventional antipsychotic drugs.

Table of Contents

Exhibits.....	5
Acknowledgments.....	6
Introduction	7
Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally.....	8
Availability and Costs of Atypical Antipsychotics in Canada.....	8
Common Drug Review	11
Product listing in Ontario.....	11
Public Plan Listings in Canada	12
Restriction Criteria	13
Selected International Jurisdictions.....	14
Part B: Guidelines for the management of behavioural and psychological symptoms of dementia	20
Part C: Impact of different drug reimbursement schemes for atypical antipsychotics.....	22
Part D: Rapid Review of Selected Topics.....	23
Initiatives to Reduce Antipsychotic Use in the Elderly	23
Antipsychotic Safety in the Elderly: Non-RCT evidence.....	28
Quetiapine for Insomnia	29
Health Canada and Food and Drug Administration (FDA) Alerts and Warnings	30
Discussion.....	31
Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally.....	31
Availability in Canada.....	31
Public Plan Listing in Ontario	31
Public Plan Listing in Canada.....	31
Selected International Jurisdictions.....	31
Part B: Guidelines for the treatment of behavioural and psychological symptoms of dementia	32
Part C: Impact of different drug reimbursement schemes for atypical antipsychotics in the elderly for management of BPSD	32
Part D: Rapid Reviews of Selected Topics	32
Health Equity.....	32
Conclusion.....	33

Reference List.....	Error! Bookmark not defined.
Appendix 1: Public drug plan benefit listings of typical antipsychotics.....	43
Appendix 2: Therapeutic Notes for Atypical Antipsychotics on the Ontario Drug Benefit formulary.....	44
Appendix 3: Webpages for Provincial Drug Formularies	45
Appendix 4: Restriction Criteria for Atypical Antipsychotics in Canada	46
Appendix 5: Interview Questions.....	51
Appendix 6: Tiered cost-sharing options	52

Exhibits

Exhibit 1: Atypical antipsychotics available in Canada.....	9
Exhibit 2: Summary of Common Drug Review recommendations for atypical antipsychotics	11
Exhibit 3: Public plan listings in Canada for atypical antipsychotics.....	12
Exhibit 4: Summary of interviews with representative from public drug program	13
Exhibit 5: Listing of atypical antipsychotics for select plans in the United States	15
Exhibit 6: Atypical Antipsychotic Medications (Australia)	17
Exhibit 7: Atypical Antipsychotic Medications (New Zealand).....	18
Exhibit 8: Atypical Antipsychotic Medications (Scotland).....	19
Exhibit 9: Examples of Canadian programs and initiatives to reduce antipsychotic use in patients with dementia	24

Acknowledgments

This review was funded by grants from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Health System Research Fund and Drug Innovation Fund. The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES, CIHI, or the Ontario MOHLTC is intended or should be inferred.

A special thank you to all of the provincial and territorial representatives in Canada from the respective Ministries of Health as well as the representative from the Non-Insured Health Benefits for First Nations and Inuit (NIHB) who participated in the telephone survey.

Introduction

With the increase in the aging population, there are 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 2031.¹ Dementia causes progressive disability and is a predictor of mortality.² The pharmacological treatment of dementia focuses on cognitive deterioration with memory loss and the management of behavioural and psychological symptoms of dementia (BPSD). The neuropsychiatric symptoms occur in approximately 90% of patients with dementia and present a challenge for clinicians and caregivers.³⁻⁵ Disruptive behavioral symptoms are associated with increased risks of cognitive decline (hazard ratio 1.45, 95% confidence interval, 1.03-2.03), functional decline (1.66, 95% CI, 1.17-2.36) and institutionalization (1.47, 95% CI, 1.10-1.97).⁶ BPSD comprises 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.^{6,7} 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%).⁸

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.⁹ Pharmacologic treatment options should be utilized when non-pharmacologic approaches have proven ineffective.¹⁰ A number of different agents have been used for the management of BPSD including anticonvulsants, antidepressants, benzodiazepines, cholinesterase inhibitors and antipsychotics.^{11,12} Antipsychotics are the class of drugs most studied, usually in trials lasting 6 to 12 weeks, for this condition.¹³⁻¹⁵

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.^{14,16,17} Atypical antipsychotics have become the standard of care in the treatment of BPSD due to potential advantages over typical antipsychotics, such as a lower incidence of extrapyramidal symptoms and tardive dyskinesia. However, although atypical antipsychotics have a lower propensity to cause extrapyramidal symptoms, they are associated with various metabolic effects such as weight gain, diabetes, obesity, dyslipidemia and metabolic syndrome, although the risk of metabolic sequelae in the elderly is still unknown.^{18,19} 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.²⁰

In addition, despite the use of these drugs in the management of patients with BPSD, the safety of antipsychotics has been questioned.^{21;22} Health Canada and other regulatory agencies around the world issued warnings about the increased harm, including increased mortality, to elderly patients prescribed antipsychotics.^{18;23-25} Although many of the initial studies indicated a higher rate of mortality with atypical antipsychotics compared to typical antipsychotics²⁶, other studies and meta-analyses have shown that typical antipsychotics are also associated with an increased risk of death.²⁷⁻²⁹

The objectives of this report are:

- **Part A:** To summarize coverage of atypical antipsychotics through public drug programs in Ontario and across Canada, as well as in select international jurisdictions
- **Part B:** To summarize the guidelines for management of elderly patients with behavioural and psychological symptoms of dementia
- **Part C:** To review the evidence relating to the impact of different drug reimbursement schemes for atypical antipsychotics on patient access and/or utilization and costs
- **Part D:** To provide rapid reviews on selected topics

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

Availability and Costs of Atypical Antipsychotics in Canada

In Canada, there are nine atypical antipsychotics commercially available: aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone. All of these drugs are available as oral formulations (e.g., tablet, sublingual tablet, oral disintegrating tablet, solution, capsule). Three drugs are available as injectable 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 behavior in patients with severe dementia. Clozapine, olanzapine, quetiapine and risperidone (oral dosage forms only) are available as generic formulations. Exhibit 1 outlines the dosage forms and costs (based on wholesale costs) for atypical antipsychotics.

Exhibit 1: Atypical antipsychotics available in Canada

Drug Name	Brand name	Manufacturer	Availability	Dosage form	Indication	Generic available	Monthly cost*	Date available
Aripiprazole	Abilify	Bristol-Myers Squibb	2, 5, 10, 15, 20, 30mg	Oral tablet	SCHZ, BPD, depression	No	124.01	Sep 2009
	Abilify	Otsuka Pharmaceutical	300mg/vial 400mg/vial	IM depot	SCHZ	No	481.27 [†]	Mar 2014
Asenapine	Saphris	Merck Canada	5, 10mg	Sublingual tablet	SCHZ, BPD	No	85.80	Dec 2011
Clozapine	Clozaril	Novartis	25, 50*, 100, 200mg*	Oral tablet	SCHZ	Yes	238.01 [†]	Dec 1991
Lurasidone	Latuda	Sunovion Pharmaceuticals	20, 40, 60, 80, 120mg	Oral tablet	SCHZ, BPD	No	122.40	Sep 2012
Olanzapine	Zyprexa	Eli Lilly	2.5, 5, 7.5, 10, 15, 20mg	Oral tablet	SCHZ, BPD	Yes	215.66	Dec 1997
	Generic	Various	2.5, 5, 7.5, 10, 15, 20mg				53.92	Apr 2008
	Zyprexa Zydis	Eli Lilly	5, 10, 15, 20mg	ODT	SCHZ, BPD	Yes	214.29	Jan 2004
	Generic	Various	5, 10, 15, 20mg				53.57	Oct 2009
	Zyprexa Intra-muscular	Eli Lilly	10mg/vial	IM injection	SCHZ, BPD	No	Not applicable	Jan 2004
Paliperidone	Invega	Janssen	3, 6, 9mg	ER tablets	SCHZ	No	167.10	Oct 2007
	Invega Sustenna	Janssen	50/0.5mL, 75mg/0.75mL, 100mg/mL, 150mg/1.5mL	IM depot	SCHZ	No	476.87	Jul 2010
Quetiapine	Seroquel	AstraZeneca	25, 100, 200, 300mg	Oral tablet	SCHZ, BPD	Yes	124.74	Dec 1997
	Generic	Various	25, 100, 150, 200, 300mg				29.66	Sep 2008
	Seroquel	AstraZeneca	50, 150, 200, 300, 400mg	ER tablets	SCHZ, BPD, depression	Yes	157.20	Sep 2007
	Generic	Various	50, 150, 200, 300, 400mg				62.88	Mar 2013

Drug Name	Brand name	Manufacturer	Availability	Dosage form	Indication	Generic available	Monthly cost*	Date available
Risperidone	Risperdal	Janssen	0.25, 0.5, 1, 2, 3, 4mg	Oral tablet	SCHZ, BPD, dementia	Yes	159.57	Dec 1993
	Generic	Various	0.25, 0.5, 1, 2, 3, 4mg				36.43	Jul 2006
	Risperdal	Janssen	1 mg/mL	Oral solution	SCHZ, BPD, dementia	Yes	169.92	Mar 1998
	Generic	Various	1 mg/mL				57.62	Jul 2006
	Risperdal M-tab	Janssen	0.5, 1, 2, 3, 4mg	ODT	SCHZ, BPD, dementia	Yes	122.55	Jul 2003
	Generic	Various	0.5, 1, 2, 3, 4mg				61.28	Dec 2011
	Risperdal Consta	Janssen	12.5, 25, 37.5, 50mg	IM depot	SCHZ, BPD	No	326.34	Oct 2007
Ziprasidone	Zeldox	Pfizer	20, 40, 60, 80mg	Oral capsule	SCHZ, BPD	No	121.40	Jan 2008

SCHZ: schizophrenia; BPD: bipolar disorder; IM: intramuscular; ODT: oral disintegrating tablets; ER: extended release

*Based on costs obtained from the Ontario Drug Benefit Formulary (Accessed: Jan 2, 2015), using lowest recommended dose for schizophrenia as per product monograph

†† Based on costs obtained from McKesson (Accessed: Jan 2, 201

Summary

- Atypical antipsychotics are available in various formulations, including oral tablet or capsule, oral solution, oral disintegrating tablet, intramuscular depot injection and intramuscular injection.
- Only risperidone (oral formulations) is indicated for the symptomatic management of aggression and psychotic symptoms in patients with severe dementia of the Alzheimer type.
- Risperidone, olanzapine and quetiapine are available as generic formulations.

Common Drug Review

The Common Drug Review (CDR) is a single process for reviewing new drugs and providing listing recommendations to participating publicly funded federal, provincial and territorial drug benefit plans in Canada; it was established in September 2003. No review was completed for clozapine, olanzapine, quetiapine or risperidone, as these products were available prior to 2003. For the newer agents that were reviewed by the CDR, a summary of recommendations is found in Exhibit 2. Note that these products are not indicated for behavioural and psychological symptoms of dementia, and thus no review for this indication was completed.

Exhibit 2: Summary of Common Drug Review recommendations for atypical antipsychotics

Product	Review #1	Review #2	Review #3
Aripiprazole	Abilify (2011) Schizophrenia and related disorders <i>List with criteria</i>	Abilify (2014) Depression <i>Do not list</i>	Abilify Maintena (2014) Schizophrenia <i>Active submission</i>
Asenapine	Saphris (2012) Schizophrenia <i>Do not list</i>	Saphris (2012) Bipolar disorder <i>List with criteria</i>	NA
Paliperidone	Invega (2008) Schizophrenia <i>Do not list</i>	Invega Sustenna (2011) Schizophrenia <i>Do not list</i>	NA
Lurasidone	Latuda (2013) Schizophrenia <i>List with criteria</i>	NA	NA
Ziprasidone	Zeldox (2008) Schizophrenia <i>List with criteria</i>	NA	NA

NA: Not applicable

Product listing in Ontario

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) are available as a general benefit on the Ontario Drug Benefit formulary. Typical antipsychotics are available as General Benefit (see Appendix 1).

Therapeutic Notes are used with five of the atypical antipsychotics (see Appendix 2). Therapeutic notes are intended to promote cost-effective prescribing, although these notes have a limited impact on physician prescribing.³⁰ In particular, aripiprazole and lurasidone specify that these products are not indicated for the treatment of dementia or dementia-related behavioural problems in the elderly.

Summary

- In Ontario, most atypical antipsychotics are available as a general benefit on the Ontario Drug Benefit formulary (exception: Abilify Maintena, Zyprexa Intramuscular, clozapine-available through Special Drugs Program).
- Only two products (aripiprazole and lurasidone) specify in the “Therapeutic Notes” that these should not be used in the elderly for management of dementia or dementia-related behavioural problems despite all atypical antipsychotics (with the exception of risperidone) not indicated in the elderly for dementia.

Public Plan Listings in Canada

Part 1: Listing Status

In order to determine the listing of atypical antipsychotics across Canada, the relevant webpages of the provincial drug formularies were searched (See Appendix 3). In Canada, atypical antipsychotics are available either as a general benefit or as a restricted benefit. The restricted benefit is enforced (e.g., prescriber is required to provide information, often in writing, regarding justification for use of atypical antipsychotics). Typical antipsychotics are listed as General Benefit in Canada (see Appendix 1). A summary of the various listings is found in Exhibit 3.

Exhibit 3: 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	No	No	No	No	No	No	No	No	No	No	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	No	No	No	No	No	No	No	No	No	No	No
Paliperidone	Invega	Ben	Ben	No	No	Ben	No	No	No	No	No	No	No
	Invega Sustenna	Res	Res	Res	No	Ben	Res	Res	Res	No	Res	No	Res
Quetiapine	Seroquel XR, Generic	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	No	No	No	Ben
	Seroquel, Generic	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Res	Ben	Ben	Ben
Risperidone	Risperdal Consta	Res	Res	Res	No	Ben	Res	Res	Res	Res	Res	Res	Res
	Risperdal, Generic	Ben	Ben	Ben	Ben	Ben	Ben	Ben	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

Restriction Criteria

In order for patients to be eligible for publically funded atypical antipsychotics, various jurisdictions use restriction criteria as part of the special authorization process (see Appendix 4). Note that the restriction criteria for these agents are for the management of schizophrenia and related psychotic disorders and/or bipolar disorder. These restriction criteria for these agents do not include the management of behavioural and psychological symptoms of dementia in the elderly (with the exception of risperidone oral in Prince Edward Island).

Part 2: Telephone Interview with Public Drug Program Representatives

A representative from each public drug program invited to participate in a 30 minute telephone interview (see Appendix 5) to gather further information about formulary listing of atypical antipsychotics (in particular for use in the elderly). Exhibit 4 summarizes the information obtained in the interviews.

Exhibit 4: Summary of interviews with representative from public drug program

Province	Listing	What was the basis for listing/change in listing?
British Columbia	Restricted, General listing	Restricted atypical antipsychotics (e.g., aripiprazole, asenapine, olanzapine, ziprasidone) are excluded for the treatment of symptoms related to dementia, including psychosis. Olanzapine is restricted as other options are available and there was some suggestion that there was inappropriate use of this agent in the elderly.
Saskatchewan	Restricted, General listing	Restricted atypical antipsychotics (e.g., aripiprazole, asenapine, olanzapine) are only indicated for treatment of schizophrenia and bipolar disorders. An academic detailing program targeting physicians as well as long-term care sites (specifically front-line workers) has been developed for the management of BPSD.
Manitoba	General listing	Covered atypical antipsychotics are readily available for all indications. Asenapine, lurasidone, paliperidone are currently not covered.
Ontario	General listing	All atypical antipsychotics are funded by the Ontario Public Drug Programs; therapeutic notes are used with five of the antipsychotics
Nova Scotia	Restricted, General listing	Restricted atypical antipsychotics (e.g., aripiprazole, asenapine, olanzapine, ziprasidone) are indicated for treatment of schizophrenia or bipolar disorder, and only after failure of other antipsychotic agents. Other available agents (with the exception of lurasidone and paliperidone) are not restricted by age, indication or previous drug use.
Prince Edward Island	Restricted	All atypical antipsychotics are restricted (requiring prior authorization). Only risperidone is approved for use in the elderly with strict criteria regarding dosage (maximum 2 mg/day). As well, a trial of conventional neuroleptics must be used before approval of an atypical antipsychotic.
Newfoundland	Restricted, General listing	Restricted atypical antipsychotics (e.g., aripiprazole, asenapine, olanzapine, ziprasidone) are indicated for treatment of schizophrenia or bipolar disorder, and only after failure of other antipsychotic agents. Other available agents (with the exception of lurasidone and paliperidone) are not restricted by age, indication or previous drug use.

Province	Listing	What was the basis for listing/change in listing?
NIHB	Restricted, General listing	Restricted atypical antipsychotics (e.g., aripiprazole, ziprasidone) are indicated for the treatment of schizophrenia or bipolar disorder, and only after intolerance or lack of response to another antipsychotic agent. Other available agents (with the exception of asenapine, lurasidone, paliperidone) are not restricted by age, indication or previous drug use.
Yukon, New Brunswick	Restricted, General listing	Restricted atypical antipsychotics (e.g., aripiprazole, asenapine) are indicated for treatment of schizophrenia or bipolar disorder, and only after failure of other antipsychotic agents. Other available agents (with the exception of lurasidone and paliperidone) are not restricted by age, indication or previous drug use.

Summary

- In most provinces (with the exception of Prince Edward Island), at least two atypical antipsychotics (namely quetiapine and risperidone) are available as general benefit. It should be noted that quetiapine and risperidone are available as generic formulations.
- Although olanzapine is available as a generic formulation, its use is restricted (to schizophrenia or bipolar disorder) in 6 of 12 jurisdictions.
- Restriction criteria for those atypical antipsychotics that require special authorization are limited to use for the treatment of schizophrenia and/or bipolar disorder. These drugs are not approved for use in behavior or psychological symptoms of dementia.

Selected International Jurisdictions

United States

As a measure to control ever-increasing costs associated with healthcare, the use of a preferred drug list (“formulary”) has been implemented in some jurisdictions. For example a preferred drug list is a list of medications that the provider will cover the cost for without the need to request a prior authorization. The preferred drugs are usually medications that are available generically or are the result of price negotiations between the pharmaceutical company and the provider. For example, in Illinois (Medicaid), the preferred brand name atypical antipsychotic is Latuda (lurasidone). Other brand name atypical antipsychotics such as Abilify, Saphris and Invega, are non-preferred.

A tiered co-payment system is a combination of cost-sharing and a preferred drug list.³¹ Three-tier structures commonly assign generic medications the lowest copay, formulary brand medications a somewhat higher copay, and non-formulary brand medications the highest copay. Three-tier copays provide consumers with more choice than in a closed formulary (where tier three drugs would not be covered at all) and attempt to reduce the number of prior authorizations that are needed for drug approval.³² In a five-tier system, tier 1 includes preferred generic drugs, tier 2 non-preferred generic drugs, tier 3 preferred brand drugs, tier 4 non-preferred brand drugs and tier 5 specialty drugs (e.g., injectables) (see Appendix 5 for examples of copayments with tiered formulary systems). (Exhibit 5)

Exhibit 5: Listing of atypical antipsychotics for select plans in the United States

Drug Plan	Abilify	Saphis	Latuda	Zyprexa	Invega	Seroquel	Risperdal	Zeldox
AETNA Preferred List (3-Tier system) (www.aetna.com)	Tier 3	Tier 3	Tier 3	Tier 3 (Tier 1 G)	Tier 3	Tier 3 (Tier 1 G)	Tier 3 (Tier 1 G)	Tier 3 (Tier 1 G)
Amerigroup Medication Formulary (Medicaid markets in Florida, Louisiana, Maryland, Nevada, New Jersey and Washington) (www.Providers.amerigroup.com)	Non- preferred	Non- preferred	Non- preferred	Preferred	Non- preferred	Preferred	Preferred	Preferred
Blue Cross Blue Shield of South Carolina Preferred Drug List (www.southcarolinablues.com)	Non- preferred	Non- preferred	Non- preferred	Preferred	Non- preferred	Preferred	Preferred	Non- preferred
Blue Cross Blue Shield of Texas Standard Preferred Drug List (October 2014) (www.bcbstx.com)	Non- preferred	Non- preferred	Non- preferred	Preferred	Non- preferred	Preferred	Preferred	Non- preferred
Connecticut Medicaid Preferred Drug List (www.ctdssmap.com)	Preferred	Preferred	Preferred	Preferred	Preferred	Preferred	Preferred	Preferred
Idaho Medicaid Preferred Drug List (www.healthandwelfare.idaho.gov)	Preferred	Non- preferred	Preferred	Preferred	Non- preferred	Preferred	Preferred	Preferred
Illinois Medicaid Preferred Drug List* http://www2.illinois.gov/hfs/sitecollectiondocuments/pdl.pdf	Non- preferred	Non- preferred	Preferred	Preferred	Non- preferred	Preferred	Preferred	Preferred
Kaiser Permanente 2014 Medicare Part D Comprehensive Formulary (5-tier system) (www.healthy.kaiserpermanente.org)	Tier 3	Tier 4	Tier 4	Tier 4 (Tier 2 G)	Tier 4	Tier 4 (Tier 2 G)	Tier 4 (Tier 2 G)	Tier 2
Kentucky Preferred Drug List 2014 (www.15subsidiz.magellanmedicaid.com)	Preferred	Preferred	Preferred	Preferred (G)	Non- preferred	Preferred (G)	Preferred (G)	Preferred
Oregon Fee-for-Service Enforceable Physical Health Preferred Drug List 2014 (http://www.oregon.gov/oha/healthplan/pages/tools_prov/pdl.aspx)	Non- preferred	Non- preferred	Non- preferred	Preferred (G)	Non- preferred	Preferred (G)	Preferred (G)	Preferred
Texas Medicaid Preferred Drug List (http://www.txvendordrug.com/pdl/)	Preferred	Preferred	Preferred	Preferred (G)	Non- preferred	Preferred (G)	Preferred (G)	Preferred

Drug Plan	Abilify	Saphis	Latuda	Zyprexa	Invega	Seroquel	Risperdal	Zeldox
WellCare Comprehensive Formulary (Medicare Advantage Plans) (covers New York, Connecticut, Florida, Georgia, Hawaii and others) (5-tier system) (https://www.wellcare.com/medicare_formulary/new_york)	Tier 4	Tier 4	Tier 4	Tier 2 (G)	Tier 5	Tier 2 (G)	Tier 4	Tier 4
Wellmark Prior authorization/Step therapy (http://www.wellmark.com/HealthAndWellness/DrugInformation/PharmacyHome.aspx)	Tier 3	Tier 4	Tier 4	Tier 1 (G)	Tier 4	Tier 1 (G)	Tier 1 (G)	Tier 1

*Prior authorization required for antipsychotic medications for long-term care residents

G: generic

Other Countries

Australia: In Australia, the Pharmaceutical Benefits Scheme (PBS) restricts some atypical antipsychotics to specific populations.³³ In 2008, the Royal Australian and New Zealand College of Psychiatrists and PHARMAC issued [Antipsychotics For Dementia: Best Practice Guide](#).³⁴ See Exhibit 6 for atypical antipsychotics available under PBS.

Exhibit 6: Atypical Antipsychotic Medications (Australia)

Product	Dosage form	Authority Required (streamlined)
Aripiprazole (Abilify)	Tablet	Schizophrenia
Asenapine (Saphris)	Tablet	Schizophrenia OR Treatment for up to 6 months of an episode of acute mania or mixed episodes associated with bipolar I disorder OR Maintenance treatment as monotherapy of bipolar I disorder
Clozapine	Tablet, oral liquid	Schizophrenia Patient must be non-responsive to other neuroleptic agents OR Patient must be intolerant of other neuroleptic agents
Lurasidone	Tablet	Not covered (rejected for schizophrenia in 2014) ³⁵
Olanzapine (generic)	Tablet, oral dissolving tablet, injection	Schizophrenia OR Maintenance treatment of bipolar I disorder
Paliperidone (Invega)	Long-acting injection, tablet	Schizophrenia
Quetiapine (Seroquel XR, generic)	Tablet, long-acting tablet	Schizophrenia OR Monotherapy for up to 6 months of an episode of acute mania associated with bipolar I disorder OR Maintenance treatment of bipolar I disorder
Risperidone (Risperdal, generic)	Tablet, oral disintegrating tablet, long-acting injection	Behavioural disturbances characterized by psychotic symptoms and aggression in patients with dementia where non-pharmacological methods have been unsuccessful OR Treatment under the supervision of a paediatrician or psychiatrist, in combination with non-pharmacological measures, of severe behavioural disturbances in a patient aged less than 18 years with autism. OR Schizophrenia OR Adjunctive therapy to mood stabilisers for up to 6 months, of an episode of acute mania associated with bipolar I disorder OR Maintenance treatment, in combination with lithium or sodium valproate, of treatment refractory bipolar I disorder
Ziprasidone	Capsule	Schizophrenia OR Monotherapy for up to 6 months, of an episode of acute mania or mixed episodes associated with bipolar I disorder

*New Zealand*³⁶: In New Zealand, the Pharmaceutical management Agency (PHARMAC) is the agency that decides which medicines, medical devices and related products are subsidized. Exhibit 7 outlines the funding of atypical antipsychotics. Note that in July 2014, only one generic brand is funded for quetiapine, risperidone and olanzapine. This is estimated to save approximately \$10 million over a 3-year period (July 2014-June 2017).

Exhibit 7: Atypical Antipsychotic Medications (New Zealand)

Product	Dosage form	Special authority
Aripiprazole (Abilify)	Tablet	Schizophrenia and an effective dose of risperidone or quetiapine has been trialled and has been discontinued because of unacceptable side effects or inadequate clinical response
Asenapine (Saphris)	Tablet	Not listed
Clozapine	Tablet	For hospital use
Lurasidone	Tablet	Not listed
Olanzapine (generic)	Tablet, oral dissolving tablet	Single source generic brand
Paliperidone (Invega)	Long-acting injection, tablet	Not listed
Quetiapine (generic)	Tablet, long-acting tablet	Single source generic brand
Risperidone (generic)	Tablet, oral liquid	Single source generic brand
	Oral disintegrating tablet	<p><i>Acute situations</i></p> <ol style="list-style-type: none"> 1. For a non-adherent patient on oral therapy with standard risperidone tablets or risperidone oral liquid; and 2. The patient is under direct supervision for administration of medicine. <p><i>Chronic situations</i></p> <ol style="list-style-type: none"> 1. The patient is unable to take standard risperidone tablets or oral liquid, or once stabilized refuses to take risperidone tablets or oral liquid; and 2. The patient is under direct supervision for administration of medicine.
Ziprasidone	Capsule	Ziprasidone is subsidized for patients suffering from schizophrenia or related psychoses after a trial of an effective dose of risperidone or quetiapine that has been discontinued, or is in the process of being discontinued, because of unacceptable side effects or inadequate response

Scotland:

In Scotland, atypical antipsychotics have been evaluated for use within NHS Scotland.³⁷ See Exhibit 8 for advice for atypical antipsychotics in Scotland.

Exhibit 8: Atypical Antipsychotic Medications (Scotland)

Product	Dosage form	Special authority
Aripiprazole (Abilify)	Tablet, long-acting injection, oral solution, orodispersible tablets	Schizophrenia or bipolar I disorder
Asenapine (Systrest)	Tablet	Not listed for treatment of bipolar I disorder
Lurasidone	Tablet	Schizophrenia
Olanzapine (Zyprexa, generic)	Tablet	Schizophrenia or bipolar disorder
Paliperidone (Invega)	Long-acting injection, tablet	Not listed (oral tablet)
Quetiapine (Seroquel, generic)	Tablet, long-acting tablet	Schizophrenia or bipolar disorder
Risperidone (generic)	Tablet, oral liquid, oral disintegrating tablet	Schizophrenia or bipolar disorder
Ziprasidone	Capsule	Not listed

Summary

- In the United States, most drug plans (in particular Medicaid-based plans) either cover only a selected atypical antipsychotics (i.e., preferred) or the atypical antipsychotics are listed on a tier structure. In general, those medications that are available as generic are considered “preferred”. Under some drug plans, use is restricted by age (i.e., not the young nor the elderly).
- In Australia, atypical antipsychotics are available under the “authority required-streamlined” system (similar to the Limited Use system in Ontario).
- New Zealand only has limited coverage for atypical antipsychotics. Some require special authorization (e.g., aripiprazole), whereas others that are available as generic formulation are single-sourced.

Part B: Guidelines for the management of behavioural and psychological symptoms of dementia

Various consensus recommendations and guidelines are available for the management of patients with BPSD, including the use of antipsychotic agents. In addition to these guidelines, the American Geriatric Society 2012 Beers consensus criteria for safe medication use in the elderly recommend avoiding antipsychotics to treat behavioral problems of dementia unless nonpharmacological options have failed and patient is a threat to self or others.³⁸

Canadian Consensus Conference on the Diagnosis and Treatment of Dementia: Pharmacological recommendations for the symptomatic treatment of dementia (2013)¹³

The fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia reviewed previous recommendations and revised where necessary, in light of new data from randomized controlled trials. One recommendation is related to the use of antipsychotics in management of BPSD.

Recommendation: Risperidone, olanzapine and aripiprazole can be used for severe agitation, aggression and psychosis where there is risk of harm to the patient and/or others. The potential benefit of all antipsychotics must be weighed against the significant risks such as cerebrovascular adverse events and mortality.

NICE (National Institute for Health and Care Excellence): Dementia-supporting people with dementia and their carers in health and social care (CG42)³⁹

This guideline, which was initially developed in 2006 and updated in 2012, is based on the best available evidence for the treatment and care of people with dementia. The recommendations related to the use of antipsychotic agents in patients with Alzheimer's disease are as follows:

Recommendation 1.7.2.1: People with dementia who develop non-cognitive symptoms or behaviour that challenges should be offered a pharmacological intervention in the first instance only if they are severely distressed or there is an immediate risk of harm to the person or others.

Recommendation 1.7.2.4: People with Alzheimer's disease, vascular dementia or mixed dementias with mild-to-moderate non-cognitive symptoms should not be prescribed antipsychotic drugs because of the possible increased risk of cerebrovascular adverse events and death

Recommendation 1.7.2.4: People with Alzheimer's disease, vascular dementia, mixed dementias or DLB with severe non-cognitive symptoms (psychosis and/or agitated behaviour causing significant distress) may be offered treatment with an antipsychotic drug after the following conditions have been met.

- There should be a full discussion with the person with dementia and/or carers about the possible benefits and risks of treatment. In particular, cerebrovascular risk factors should be assessed and the possible increased risk of stroke/transient ischaemic attack and possible adverse effects on cognition discussed.
- Changes in cognition should be assessed and recorded at regular intervals. Alternative

medication should be considered if necessary.

- Target symptoms should be identified, quantified and documented.
- Changes in target symptoms should be assessed and recorded at regular intervals.
- The effect of comorbid conditions, such as depression, should be considered.
- The choice of antipsychotic should be made after an individual risk–benefit analysis.
- The dose should be low initially and then titrated upwards.
- Treatment should be time limited and regularly reviewed (every 3 months or according to clinical need).

EFNS-ENS guidelines on the diagnosis and management of disorders associated with dementia⁴⁰

These guidelines consider dementias other than Alzheimer’s disease, including mixed dementia, dementia with Lewy bodies, vascular dementia, progressive supranuclear palsy and Parkinson’s disease dementia. Recommendations for the treatment of BPSD were made in these populations.

- Antipsychotic medications, conventional and atypical agents, may be utilized in clinical practice for aggression, psychosis and agitation as well selective serotonin re-uptake inhibitors for mood and behavioural disorders; however, there is little evidence to guide practice.

EFNS guidelines for the diagnosis and management of Alzheimer’s disease⁴¹

The European Federation of Neurological Societies guideline for the diagnosis and management of Alzheimer’s disease was revised in 2010. Recommendations for the use of antipsychotic agents for the management of patients with behavioural and psychological symptoms in dementia were made.

- Antipsychotics should only be used for moderate or severe BPSD symptoms causing significant distress which have either not responded to other treatments (like non-pharmacological measures or ChEIs) or when other treatments are not appropriate.
- Low dose of atypical agents should be used only after assessment of risk benefit and full discussion with patient (when capacity allows) and caregiver.
- Atypical agents have fewer side effects and do not confer a greater risk of stroke or mortality than conventional drugs.

American Psychiatric Association: Practice guideline for the treatment of patients with Alzheimer’s disease and other dementias¹⁰

The American Psychiatric Association Work Group on Alzheimer’s Disease and other Dementias developed guidelines for the treatment of patients with dementia, including Alzheimer’s disease. Recommendations for the use of antipsychotic agents were as follows:

- If the symptoms do cause significant distress or are associated with behavior that may place the patient or others at risk, treatment with low doses of antipsychotic medication is indicated in addition to nonpharmacological interventions. Treatment with an antipsychotic medication is also indicated if a patient is agitated or combative in the absence of psychosis, because antipsychotics have the most

support in the literature. However, the potential benefits of antipsychotic medications need to be weighed against the potential for increased mortality when they are used by individuals with dementia.

Summary

- There have been several guidelines/consensus recommendations published for the use of antipsychotics in the management of patients with BPSD.
- In general, a stepped care approach should be used in managing BPSD. Antipsychotics should only be used for severe symptoms where there is risk of harm to the patient and/or others. As well, some guidelines specify that antipsychotics are only indicated when the patient has not responded to other treatments or when other treatments are not appropriate, or in conjunction with non-pharmacologic treatments.

Part C: Impact of different drug reimbursement schemes for atypical antipsychotics

Methods

A literature search was conducted in Pubmed using the terms: antipsychotics AND (healthcare accessibility OR health policy OR reimbursement incentive OR national health programs OR cost sharing) and dementia. Bibliographies of identified articles were scanned for additional relevant articles.

Results

Only one study was identified through the literature search. This study reviewed Medicaid programs in the United States that used prior authorization for atypical antipsychotics and whether any changes were made to the criteria following the FDA safety warning in 2005 regarding atypical antipsychotics and increased mortality in older patients with dementia. Medicaid, which provides health insurance coverage for low-income Americans, uses prior authorization (PA) programs to control spending by requiring specific conditions be met before reimbursement is granted. Although these policies are primarily used as budget-control tools, these policies may have an important influence on clinical practice as well. Prior to the FDA advisory in 2005, of the fifty Medicaid programs, twenty-two (44%) had existing PA programs.⁴² One year after the advisory, twelve Medicaid programs changed their PA policies for atypical antipsychotics, although none directly addressed the FDA advisory. No program excluded behavioral symptoms or agitation of dementia as an indication.

Summary

- There is a lack of literature investigating various reimbursement schemes for atypical antipsychotics in the elderly for the management of BPSD.

Part D: Rapid Review of Selected Topics

Initiatives to Reduce Antipsychotic Use in the Elderly

Antipsychotics are often prescribed in the elderly to manage behavioural and psychological symptoms of dementia. Canadian data from 2006-7 indicate that approximately 38% of senior nursing home residents on public drug programs in Manitoba, New Brunswick and PEI had claims for antipsychotics, compared to only 2.6% of senior claimants living in the community. Similar results have been observed in Saskatchewan (30.6% in 2004) and Ontario (32.4% in 2003).^{43;44} Internationally, the prevalence of antipsychotic use in nursing homes ranged from 11% in Hong Kong, 27% in the United States, 34% in Switzerland and 38% in Finland.⁴⁵

In order to reduce the inappropriate prescription of antipsychotic medications to individuals with dementia, various interventions, including educational based and interdisciplinary interventions, have been used. A systematic review of 22 studies evaluated the effectiveness of some of these interventions.⁴⁶ Interventions were classified according to the Effective Practice and Organisation of Care (EPOC) taxonomy: professional (e.g., educational outreach), organizational (e.g., multidisciplinary teams), structural (e.g., changes in physical structure) and regulatory interventions. Of the eleven studies that were randomized or controlled in design, nine studies showed reductions in antipsychotic prescribing of between 12 and 20%. However, long-term sustainability of the interventions has not been well studied as most included trials had less than 12 months of followup.

Non-pharmacologic therapy including exercise therapy, use of quiet rooms (Namaste therapy), stimulating rooms (Snoezelen therapy) and music therapy have been utilized to allow for reduction of antipsychotic use.⁴⁷ Although music therapy and sensory stimulation were effective during treatment, no long-lasting effect was noted.

Other studies have looked at management of BPSD using non-pharmacologic therapies, but not necessarily measuring the effect on antipsychotic use. In a systematic review, training front-line staff to understand and manage BPSD can lead to significant symptom reduction; however, the utilization of antipsychotics was not assessed. Twelve of the twenty included studies resulted in significant symptom reductions, four studies found positive trends and four studies found no impact on symptoms.⁴⁸ Another systematic review of 162 trials concluded that psychoeducation for caregivers was effective treatment for management of neuropsychiatric symptoms, with long-lasting benefits.⁴⁹

Provincial and Regional Programs

In response to concerns about the use of antipsychotics in elderly patients with dementia, in particular those patients residing in long-term care facilities, various organizations, provincially, nationally and internationally, have engaged in initiatives to reduce inappropriate use of these drugs. In Canada, the Ministries of Health for [British Columbia](#) and [Alberta](#) have developed best practice guidelines for managing patients with behavioural and psychological symptoms of dementia residing in long-term care facilities, which includes guidelines for appropriate use of antipsychotics for management of BPSD.^{50;51}

Some examples of national, provincial and local programs are shown in Exhibit 9.

Other organizations have developed strategies/programs for management of patients with dementia, including initiatives for treatment of BPSD. Ontario's Ministry of Health and Long-Term Care has a [Strategy for Alzheimer Disease and Related Dementias](#) that is providing support for [Behavioural Supports](#) initiatives, staff training and funding the Alzheimer Society of Ontario to deliver a range of services to improve treatment and management of Alzheimer's disease.^{52;53} The Behavioural Supports Ontario (BSO) initiative provides enhanced service for older people with responsive behaviours linked to cognitive impairments and their caregivers. A program called "P.I.E.C.E.S.", which represents Physical, Intellectual, Emotional, Capabilities, Environment and Social, provides health-care providers with a framework to assess residents according to each of the areas highlighted. Staff are trained to provide person-centered, non-pharmacological approach to managing behavior associated with dementia. Although not specifically designed to reduce antipsychotic use in the elderly, one long-term care facility employing P.I.E.C.E.S. was able to discontinue antipsychotics in 25% of residents without any increase in behavioural symptoms or rise in use of physical restraints.⁵⁴ The Ontario College of Family Physicians provides a Continuing Medical Education program on Behavioural and Psychological symptoms of Dementia that includes information on medications used in the treatment of BPSD.⁵⁵

Although there are numerous organizations and provincial bodies with a dementia strategy, Canada is the only G7 nation without a national dementia strategy.⁵⁶

Exhibit 9: Examples of Canadian programs and initiatives to reduce antipsychotic use in patients with dementia

Program	Description of program
Canadian Foundation for Healthcare Improvement ⁵⁷	<ul style="list-style-type: none"> Fifteen teams from healthcare organizations across Canada are involved in a collaborate to tackle the inappropriate use of antipsychotic medications in long-term care (ongoing)

Program	Description of program
<p>British Columbia (Ministry of Health): Best Practice Guideline for Accommodating and Managing Behavioural and Psychological Symptoms of Dementia in Residential Care⁵⁸</p>	<ul style="list-style-type: none"> • Guideline includes an algorithm designed to support clinical assessment and care decisions of persons with BPSD. • Components include: adopting a person-centered approach, determining target behaviours in dementia, developing appropriate care plans, considerations for non-pharmacological and pharmacological interventions. • The guidelines recommend non-pharmacologic measures (e.g., environmental and behavioural modifications and psychosocial interventions) as first-line management for BPSD. • If the use of antipsychotic medications is deemed medically appropriate, it is recommended that on commencement of therapy, team reviews should be conducted weekly, every 2 weeks and then monthly.
<p>British Columbia (Vancouver Coastal Health): Atypical Antipsychotic Agents-guideline for use as part of the management strategy of behavioural and psychological symptoms of dementia (BPSD)⁵⁹</p>	<ul style="list-style-type: none"> • To support clinicians in making informed decisions regarding use of atypical antipsychotic drugs in patients with dementia in acute or residential care • Recommendations include patient assessment, initial use of non-pharmacologic therapy, indication of drug therapy, involvement and documentation of informed consent, initiation, titration and monitoring of drug therapy. • Documentation of effectiveness is recommended by 8 weeks and review with purpose to discontinue by 3-6 months.
<p>Saskatchewan (RxFiles): academic detailing program⁶⁰</p>	<p>RxFiles Academic Detailing program is engaged in the Long-term Care Project to provide education to long-term care workers including managers, nurse educators and other health-care professionals, as well as engaging health care professionals to pursue an integrated approach to drug therapy in the elderly (not exclusive to use of antipsychotics)</p>

Program	Description of program
Alberta (Alberta Health Services): Seniors Health Strategic Clinical Network, Best practices in the management of behavioural and psychological symptoms of dementia in residents of long-term care facilities in Alberta ⁵¹	<ul style="list-style-type: none"> • Aging Brain Care is developing a project to support the appropriate use of antipsychotics in long-term care facilities. • Appropriate Use of Antipsychotics Toolkit for Care Teams is available that includes person-centred and non-pharmacologic approaches, care planning for responsive behaviours, prescribing antipsychotic medication, medication review requirements of antipsychotics and staff resources to support families. • One project targeted eleven long-term care homes to provide care for patients with depending on antipsychotic medications. In June 2013, a total of 248 residents were on antipsychotics without an appropriate diagnosis. By January 2014, this was reduced to 126.

Accreditation Canada's Qmentum program focuses on quality and safety throughout all aspects of an organization's services. Accreditation Canada accredits over 1,700 sites offering long-term care services across Canada.⁶¹ For surveys starting after January 01, 2015, the following safety standard will be measured⁶²:

Standard 12.7: The team assesses the appropriateness of anti-psychotic medication use among residents and makes improvements.

Guidelines

The team determines whether it is appropriately using anti-psychotics (i.e., they are being used to treat indicated conditions or if they are being used to manage responsive behaviours, they are only used when other options have failed), and uses the information to improve services.

Canadian Institute of Health Information (CIHI) has an indicator related to percentage of residents on antipsychotics without a diagnosis of psychosis ("Potentially Inappropriate Use of Antipsychotics in Long-Term Care). Quality indicators provide organizations with measures of quality across key domains, including physical and cognitive function, safety and quality of life.⁶³

Choosing Wisely is an initiative of the American Board of Internal Medicine (ABIM) Foundation that is helping providers and patients engage in conversations to reduce overuse of tests and procedures.⁶⁴ A similar campaign "Choosing Wisely Canada" has been developed in Canada.⁶⁵ The Canadian Geriatrics Society has provided a document "Five Things Physicians and Patients Should Question" that includes the following:

Don't use antipsychotics as first choice to treat behavioural and psychological symptoms of dementia.

People with dementia often exhibit aggression, resistance to care and other challenging or disruptive behaviours. In such instances, antipsychotic medicines are often prescribed, but they provide limited benefit and can cause serious harm, including premature death. Use of these drugs should be limited to cases where non-pharmacologic measures have failed and patients pose an imminent threat to themselves or others. Identifying and addressing causes of behaviour change can make drug treatment unnecessary.

International Programs

United Kingdom: A report that examined the use of antipsychotic medication for people with dementia in England was commissioned in 2009 by the Minister of State, Department of Health, National Health Service. The author concluded that there are significant issues in terms of quality of care and patient safety with regards to the use of these medications; these drugs have only a limited positive effect in treating symptoms but are also associated with significant harm. This report estimated that each year approximately 180,000 dementia patients were treated with antipsychotics; amongst them, only 20% gain some benefit whereas 1800 additional deaths and 1620 extra cerebrovascular adverse events were predicted. Eleven recommendations were made to help reduce the use of these drugs to the level where benefit will outweigh risk. These recommendations included national leadership to reduce the level of prescription of antipsychotic medication, audits, goals for the reduction of use of antipsychotic medication, further research into non-pharmacological methods of treating behavioural problems of dementia and development of educational programs for management of patients with BPSD. The report recommended a reduction in the rate of antipsychotic prescribing in dementia to a third of the 2009 level over a three-year period.⁶⁶

Since the time of the report, the government has made a commitment to reduce the inappropriate prescribing of antipsychotic medication for people with dementia. The [National Dementia and Antipsychotic Prescribing Audit](#) collects information from GP practices on the prescribing of antipsychotic drugs for people with dementia.⁶⁷ The report from 2012 provides the analysis over a 6-year period (2006 to 2011). The key findings of this report include:

- The number of people newly diagnosed each year with dementia in the participating practices has increased by 67.7 per cent in the last six years (from 2006 to 2011)
- There is a higher prevalence of diagnosed dementia in women (66.3 per cent) than in men
- The majority of people diagnosed with dementia are aged 65 years and above (94.7 per cent)
- There was a decrease of 10.25 percentage points in the number of people with dementia receiving prescriptions of antipsychotic medication for people with dementia from 17.05 per cent in 2006 to 6.80 per cent in 2011
- There has been a 51.8 per cent reduction in the number of people with dementia receiving a prescription of antipsychotic medication from 2008 to 2011.

United States: In the United States, the [Centres for Medicare and Medicaid Services](#) (CMS) National Partnership to Improve Dementia Care in Nursing Homes (formally known as the Initiative to Improve Behavioural Health and Reduce the Use of Antipsychotic Medications in Nursing Home Residents) was launched in 2012, in response to increased mortality associated with these agents and a study showing that a third of persons receiving antipsychotics in nursing homes had no diagnosis to support the use of the drug.^{68;69} As part of the partnership, CMS developed a national action plan that utilizes a multidimensional approach including public reporting, raising public awareness, regulatory oversight, technical assistance/training and research. The action plan is targeted at enhancing individualized, person-centered care approached for nursing home residents, particularly those with dementia-related behaviours. The goal in the first year was to reduce the national prevalence rate of antipsychotic medication use in long-stay nursing home residents by 15%. This was achieved between the end of 2011 and the end of 2013 (from 23.8% to 20.2% except for patients with schizophrenia, Tourette's or Huntington's disease). The goal for the end of 2015 is to reduce the use of antipsychotic medications by 25 percent and 30 percent by the end of 2016.

A [2012 report by the Office of Inspector General](#) of the US Department of Health & Human Services found that almost all of the nursing homes assessed (99%) failed to meet federal requirement for assessing and developing care plans for patients receiving antipsychotic drugs, including periodic assessments of patients taking these medications.⁷⁰

Summary: In response to concerns about the use of antipsychotics in elderly patients with dementia, in particular those patients residing in long-term care facilities, various organizations have engaged in initiatives to reduce inappropriate use of these drugs. A reduction in the rate of antipsychotic prescribing in dementia from 15-30% has been recommended.

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.⁷¹ Use of antipsychotics in the elderly has been associated with increased risk of sedation, falls⁷², fractures⁷³⁻⁷⁵, cardiovascular events⁷⁶, renal injury,⁷⁷ and overall mortality.^{26;71;78}

A review 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)²⁶, leading to the issuance of a black box warning for the use of atypical antipsychotics for BPSD.^{23;79} A similar black box warning was issued for typical antipsychotics by the FDA in 2008 based on observational studies showing increased risk of mortality in older patients using typical antipsychotics compared to atypical antipsychotics.⁸⁰ Both atypical and conventional antipsychotics have been associated with higher rates of mortality than nonantipsychotic medications, except for anticonvulsants.⁸¹ The increased risk has been shown to persist for at least 6-12 months.^{78;81}

A recent study reviewed epidemiological evidence derived from 20 observational cohort studies. The authors concluded that the evidence for elevated mortality in typical antipsychotic users compared to atypical antipsychotic users is consistent across various populations. The average relative risk for typical

antipsychotics vs. atypical antipsychotics in the first six months after starting antipsychotic therapy was 1.4 (average risk difference=4.3%, ranging from 2.5% to 7.3%). Elderly using typical antipsychotics were at a higher risk for stroke, ventricular arrhythmia, myocardial infarction and hip fracture compared to atypical antipsychotics.⁷¹

Comparative safety within the antipsychotic drug class and measures of level of risk have largely been inconclusive due challenges with residual confounding and selection bias that is inherent in observational studies of this population.^{27;82} In general, there is conflicting evidence to support differences between atypical and typical antipsychotics, aside from extrapyramidal symptoms.⁸³⁻⁸⁸ Additionally, no evidence of within class differences have been found between antipsychotic products.^{89;90} Little evidence is available on the safety of newer atypical antipsychotics (aripiprazole, ziprasidone, paliperidone, asenapine, lurasidone) in this population.

Quetiapine for Insomnia

Quetiapine is labeled in Canada for the treatment of schizophrenia, bipolar disorder and/or major depressive disorder. However, it has been used off-label for other indications such as anxiety disorders, dementia, autism, delirium and insomnia.^{14;91} Estimates for use of atypical antipsychotics for insomnia (as the primary indication) have ranged from 5 to 12%.⁹² In British Columbia, 58% of prescriptions for quetiapine were for the 25 mg tablet, a dose recommendation for sleep, whereas the recommended dose range for approved indications is 150 to 800 mg/day.⁹³ Another study measured the use of quetiapine and other atypical antipsychotics in Canada as well as the most common diagnoses associated with quetiapine use. In this study, the top four diagnoses associated with quetiapine in 2012 were mood disorders, psychotic disorders, anxiety disorders and sleep disturbances.⁹⁴ A 10-fold increase in quetiapine recommendations for sleep disturbances were observed between 2005 and 2012.

Quetiapine, particularly at lower doses, has a strong affinity for antagonist at the histamine H1-receptors, similar to diphenhydramine, amitriptyline and doxepin. The sedative properties of quetiapine are believed to be related to the antagonism at this receptor site.

Quetiapine for management of outpatients with insomnia has been studied in a randomized, double-blind, placebo-controlled cross-over study. The effects of quetiapine on the polysomnographic sleep structure and subjective sleep quality of 14 healthy men (mean age 27 years old) was evaluated in a two-night study.⁹⁵ Compared with placebo, quetiapine improved sleep latency ($p<0.01$), total sleep time ($p<0.001$) and sleep efficiency ($p<0.001$). An open-label study evaluated quetiapine 25 mg in 18 adults with insomnia.⁹⁶ Improvement in sleep parameters was observed after two weeks. Total sleep time and sleep efficiency evaluated by polysomnography were improved at weeks 2 and 6 ($p=0.05$). A randomized, double-blind, placebo controlled clinical trial was conducted in 13 patients (mean age 46 years; range 25-62).⁹⁷ Although quetiapine increased total sleep time and decreased sleep latency in the quetiapine group compared to the placebo group, these results were not statistically significant. Reported adverse effects in the quetiapine group included dry lips, dry tongue and morning drowsiness.

Summary: The use of quetiapine for insomnia has been evaluated in limited studies. It is unknown whether quetiapine’s sedative effects are sustained in the long-term and what adverse effects are associated with quetiapine used in low dosages. There are no studies evaluating the use of quetiapine for insomnia in the elderly, in particular in patients with Alzheimer’s disease.⁹⁸ As well, there are no trials comparing quetiapine to other active comparators (e.g., benzodiazepines, zopiclone).

Health Canada and Food and Drug Administration (FDA) Alerts and Warnings

- Health Canada issued an advisory in 2005 regarding increased mortality associated with the use of atypical antipsychotic drugs in elderly patients with dementia.⁷⁹ Based on this advisory, manufacturers of atypical antipsychotic drugs were required to include a warning of the risk in the product monographs.
- 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).⁹⁹ The indication for risperidone is now limited to “severe dementia of the Alzheimer type”.
- In 2002, Health Canada issued an “Important Safety Information” on risperidone in elderly dementia patients regarding reports of strokes in this patient population.¹⁰⁰ An “Important Safety Information” bulletin was issued in 2004 for olanzapine. 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.¹⁰¹
- The US 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.²³ A similar “Black Box” warning was required in 2008 for manufacturers of conventional antipsychotic drugs.¹⁰²
- The effectiveness of the regulatory warnings has been evaluated in several studies. One study noted a decline in prescribing rate of antipsychotics after the FDA warnings; however, another trial concluded that although the rate of increase in new prescriptions for atypical antipsychotics declined, the overall prescription rate increased by 20% from 1512 per 100 000 elderly patients to 1813 per 100 000 patients.^{103;104} Another study conducted in France observed a 40% reduction in antipsychotic use from 14.2% in 2003 to 10.2% in 2011.¹⁰⁵ Although the French agency issued a warning in 2004, the decrease in antipsychotic use began prior to this time period. Similarly, use of conventional and atypical antipsychotics for patients with dementia declined significantly before implementation of the black box warning issued by the FDA in 2005. A study conducted in Germany also found that warnings of international drug authorities and manufacturers regarding adverse drug events associated with atypical antipsychotics in patients with dementia did not impact overall prescription behavior.¹⁰⁶

Discussion

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

Availability in Canada

- Atypical antipsychotics are available in various formulations, including oral tablet or capsule, oral solution, oral disintegrating tablet, intramuscular depot injection and intramuscular injection.
- Only risperidone (oral formulations) is indicated for the symptomatic management of aggression and psychotic symptoms in patients with severe dementia of the Alzheimer type.
- Risperidone, olanzapine and quetiapine are available as generic formulations.

Public Plan Listing in Ontario

- In Ontario, most atypical antipsychotics are available as a general benefit on the Ontario Drug Benefit formulary (exception: Abilify Maintena, Zyprexa Intramuscular, clozapine-available through Special Drugs Program).
- Only two products (aripiprazole and lurasidone) specify in the “Therapeutic Notes” that these should not be used in the elderly for management of dementia or dementia-related behavioural problems despite all atypical antipsychotics (with the exception of risperidone) not indicated in the elderly for dementia.

Public Plan Listing in Canada

- In most provinces (with the exception of Prince Edward Island), at least two atypical antipsychotics (namely quetiapine and risperidone) are available as general benefit.
- Although olanzapine is available as a generic formulation, its use is restricted (to schizophrenia or bipolar disorder) in 6 of 12 jurisdictions.
- Restriction criteria for those atypical antipsychotics that require special authorization are limited to use for the treatment of schizophrenia and/or bipolar disorder. These drugs are not approved for use in behavior or psychological symptoms of dementia.

Selected International Jurisdictions

- In the United States, most drug plans (in particular Medicaid-based plans) either cover only a selected atypical antipsychotics (i.e., preferred) or the atypical antipsychotics are listed on a tier structure. In general, those medications that are available as generic are considered “preferred”. Under some drug plans, use is restricted by age (i.e., not the young nor the elderly).
- In Australia, atypical antipsychotics are available under the “authority required-streamlined” system (similar to the Limited Use system in Ontario).
- New Zealand only has limited coverage for atypical antipsychotics. Some require special authorization (e.g., aripiprazole), whereas others that are available as generic formulation are single-sourced.

Part B: Guidelines for the treatment of behavioural and psychological symptoms of dementia

- Guidelines/consensus statements indicate that antipsychotics may be beneficial in treating BPSD, although their use may be associated with serious adverse effects.
- In general, antipsychotics should only be used for severe symptoms where there is risk of harm to the patient and/or others. As well, some guidelines specify that antipsychotics are only indicated when the patient has not responded to other treatments or when other treatments are not appropriate, or in conjunction with non-pharmacologic treatments.

Part C: Impact of different drug reimbursement schemes for atypical antipsychotics in the elderly for management of BPSD

- There is a lack of literature investigating various reimbursement schemes for atypical antipsychotics in the elderly for the management of BPSD.

Part D: Rapid Reviews of Selected Topics

- In response to concerns about the use of antipsychotics in elderly patients with dementia, in particular those patients residing in long-term care facilities, various organizations have engaged in initiatives to reduce inappropriate use of these drugs. A reduction in the rate of antipsychotic prescribing in dementia from 15-30% has been recommended.
- The use of quetiapine for insomnia has been evaluated in limited studies, of which only one was a randomized controlled trial. It is unknown whether quetiapine's sedative effects are sustained in the long-term and what adverse effects are associated with quetiapine used in low dosages. There are no studies evaluating the use of quetiapine for insomnia in the elderly. As well, there are no trials comparing quetiapine to other active comparators (e.g., benzodiazepines, zopiclone).
- 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.
- Similarly, the US 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. A similar "Black Box" warning was required in 2008 for manufacturers of conventional antipsychotic drugs.

Health Equity

In Ontario, typical and atypical antipsychotics are available on the Public Drug formulary as general benefits. No health equity issues were identified for Ontario. However, a study from British Columbia found that community-dwelling seniors with dementia (but not schizophrenia or bipolar disorder) and in

the lowest-income quintile, had higher odds of potentially inappropriate use, compared with highest-income seniors.¹⁰⁷

Conclusion

Atypical antipsychotics are available in Canada for the management of psychiatric disorders including schizophrenia, bipolar disorder and depression. Only risperidone is indicated for the symptomatic management of aggression and psychotic symptoms in patients with severe dementia of the Alzheimer type. Risperidone, olanzapine and quetiapine are available as generic formulations.

Most public drug plans in Canada require special authorization prior to funding brand-name atypical antipsychotics; restriction criteria limit the use of these drugs for the treatment of schizophrenia and/or bipolar disorder. In Ontario, most atypical antipsychotics are available as a general benefit on the Ontario Drug Benefit formulary.

In response to concerns about the use of antipsychotics in elderly patients with dementia, in particular those patients residing in long-term care facilities, various organizations have engaged in initiatives to reduce inappropriate use of these drugs. A reduction in the rate of antipsychotic prescribing in dementia from 15-30% has been recommended.

Reference List

- (1) Government of Canada. Dementia. http://healthycanadians.gc.ca/diseases-conditions-maladies-affections/disease-maladie/dementia-demence/index-eng.php?utm_source=vanity_url&utm_medium=canada.ca_dementia_en&utm_campaign=canada.ca . 2014.
- (2) Wolfson C, Wolfson D, Asgharian M, et al. A reevaluation of the duration of survival after the onset of dementia. *N Engl J Med* 2001; 344:1111-1116.
- (3) Ballard C, Creese B, Corbett A, Aarsland D. Atypical antipsychotics for the treatment of behavioral and psychological symptoms in dementia, with a particular focus on longer term outcomes and mortality. *Expert Opin Drug Saf* 2011; 10(1):35-43.
- (4) Rosdinom R, Zarina M, Zanariah M, et al. Behavioural and psychological symptoms of dementia, cognitive impairment and caregiver burden in patients with dementia. *Prev Med* 2013; 57 (suppl):S67-S69.
- (5) Levy K, Lanctot KL, Farber SB, Li A, Herrmann N. Does pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease relieve caregiver burden? *Drugs & aging* 2012; 29(3):167-179.
- (6) Scarmeas N, Brandt J, Blacker D, et al. Disruptive behavior as a predictor in Alzheimer disease. *Arch Neurol* 2007; 64:1755-1761.
- (7) Lopez O, Becker J, Chang Y, et al. The long-term effects of conventional and typical antipsychotics in patients with probable Alzheimer's disease. *The American journal of psychiatry* 2013; 170:1051-1058.
- (8) Alzheimer's Association. Types of Dementia. <http://www.alz.org/dementia/types-of-dementia.asp> . 2015.
- (9) Anon. Management of non-cognitive symptoms associated with dementia. *Drug Ther Bull* 2014; 52:114-118.
- (10) American Psychiatric Association. Practice guideline for the treatment of patients with Alzheimer's disease and other dementias. *The American journal of psychiatry* 2007; 164 (12 suppl):5-56.
- (11) Jeste D, Blazer D, Casey D, et al. ACNP White Paper: update on use of antipsychotic drugs in elderly persons with dementia. *Neuropsychopharm* 2008; 33:957-970.
- (12) Seitz DP, Adunuri N, Gill SS, Gruneir A, Herrmann N, Rochon P. Antidepressants for agitation and psychosis in dementia. *Cochrane Database Syst Rev* 2011;(2):CD008191.

- (13) Herrmann N, Lanctot K, Hogan D. Pharmacological recommendations for the symptomatic treatment of dementia: the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia 2012. *Alzheimers Res Ther* 2013; 5 (Suppl 1):S5.
- (14) Maglione M, Maher AR, Hu J, Wang Z, Shanman R, Shekelle PG et al. Off-Label Use of Atypical Antipsychotics: An Update. Rockville MD: 2011.
- (15) Ballard C, Waite J. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. *Cochrane Database Syst Rev* 2006; 1:CD003476.
- (16) Depping AM, Komossa K, Kissling W, Leucht S. Second-generation antipsychotics for anxiety disorders. *Cochrane Database Syst Rev* 2010;(12).
- (17) Komossa K, Depping AM, Meyer M, Kissling W, Leucht S. Second-generation antipsychotics for obsessive compulsive disorder. *Cochrane Database Syst Rev* 2010;(12).
- (18) Gareri P, De FP, Manfredi VG, De SG. Use and safety of antipsychotics in behavioral disorders in elderly people with dementia. *J Clin Psychopharmacol* 2014; 34(1):109-123.
- (19) Guenette MD, Chintoh A, Remington G, Hahn M. Atypical antipsychotic-induced metabolic disturbances in the elderly. *Drugs & aging* 2014; 31(3):159-184.
- (20) Zheng L, Mack W, Dagerman K, et al. Metabolic changes associated with second-generation antipsychotic use in Alzheimer's disease patients: the CATIE-AD study. *The American journal of psychiatry* 2009; 166:583-590.
- (21) Ma H, Huang Y, Cong Z, et al. The efficacy and safety of atypical antipsychotics for the treatment of dementia: a meta-analysis of randomized placebo-controlled trials. *J Alzheim Dis* 2014; 42:915-937.
- (22) Rochon P, Normand S, Gomes T, et al. Antipsychotic therapy and short-term serious events in older adults with dementia. *Arch Intern Med* 2008; 168:1090-1096.
- (23) Food and Drug Administration. Public Health Advisory: deaths with antipsychotics in elderly with behavioural disturbances. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm053171.htm> . 2005.
- (24) Health Canada. Health Canada advises consumers about important safety information on atypical antipsychotic drugs and dementia. <http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2005/13696a-eng.php> . 2005.
- (25) Ray W, Chung C, Murray K, et al. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med* 2009; 360:225-235.
- (26) Schneider L, Dagerman K, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *N Engl J Med* 2005;

294:1934-1943.

- (27) Huybrechts KF, Gerhard T, Crystal S, Olfson M, Avorn J, Levin R et al. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. *BMJ* 2012; 344:e977.
- (28) Wang P, et al. Risk of death in elderly users of conventional vs atypical antipsychotic medications. *N Engl J Med* 2005; 353.
- (29) Langballe EM, Engdahl B, Nordeng H, Ballard C, Aarsland D, Selbaek G. Short- and long-term mortality risk associated with the use of antipsychotics among 26,940 dementia outpatients: a population-based study. *Am J Geriatr Psychiatry* 2014; 22(4):321-331.
- (30) Hildebrand A, Yao Z, Gomes T, Camacho X, Garg A, Juurlink D. Adherence to prescribing recommendations made on a provincial formulary. *Healthcare Policy* 2014; 9:20-30.
- (31) Ovsag K, Hyder S, Mousa S. Preferred drug lists: potential impact on healthcare economics. *Vascular health and risk management* 2008; 4:403-413.
- (32) Motheral B, Fairman K. Effect of a three-tier prescription copay on pharmaceutical and other medical utilization. *Med Care* 2001; 39:1293-1304.
- (33) Australian Government Department of Health. Pharmaceutical Benefits Scheme. Australian Government Department of Health [2013 Available from: URL:<http://www.pbs.gov.au/browse/body-system>
- (34) Best Practice Advocacy Centre New Zealand. Antipsychotics in dementia. <http://www.bpac.org.nz/a4d/welcome.asp> . 2008.
- (35) Pharmaceutical Benefits Scheme (PBS). Lurasidone hydrochloride, Summary document. <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-03/Lurasidone-hydrochloride> . 2014.
- (36) PHARMAC. PHARMAC: Pharmaceutical Management Agency for New Zealand. <http://www.pharmac.health.nz/> [2014
- (37) Scottish Medicines Consortium. SMC Advice Directory. https://www.scottishmedicines.org.uk/SMC_Advice/Advice_Directory/SMC_Advice_Directory 2015.
- (38) The American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers criteria for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society* 2012; 60:616-631.
- (39) NICE. Dementia: supporting people with dementia and their carers in health and social care (CG42). <https://www.nice.org.uk/guidance/cg42/chapter/1-guidance> . 2012.

- (40) Sorbi S, Hort J, Erkinjuntti T, et al. EFNS-ENS guidelines on the diagnosis and management of disorders associated with dementia. *European journal of neurology : the official journal of the European Federation of Neurological Societies* 2012; 19:1159-1179.
- (41) Hort J, O'Brien J, Gainotti G, et al. EFNS guidelines for the diagnosis and management of Alzheimer's disease. *European journal of neurology : the official journal of the European Federation of Neurological Societies* 2010; 17:1236-1248.
- (42) Polinski JM, Wang PS, Fischer MA. Medicaid's prior authorization program and access to atypical antipsychotic medications. *Health Aff (Millwood)* 2007; 26(3):750-760.
- (43) Rochon P, Stukel T, Bronskill S, et al. Variation in nursing home antipsychotic prescribing rates. *Arch Intern Med* 2007; 167:676-683.
- (44) Canadian Institute for Health Information. Antipsychotic use in seniors: an analysis focusing on drug claims, 2001 to 2007. <https://www.cihi.ca> . 2009.
- (45) Feng Z, Hirdes J, Smith T, et al. Use of physical restraints and antipsychotic medications in nursing homes: a cross-national study. *Int J Geriatr Psychiatry* 2009; 24:1110-1118.
- (46) Coon J, Abbott R, Rogers M, et al. Interventions to reduce inappropriate prescribing of antipsychotic medications in people with dementia resident in care homes: a systematic review. *JAMDA* 2014; 15:706-718.
- (47) Morley JE. Antipsychotics and dementia: a time for restraint? *J Am Med Dir Assoc* 2012; 13(9):761-763.
- (48) Spector A, Orrell M, Goyder J. A systematic review of staff training interventions to reduce the behavioural and psychological symptoms of dementia. *Ageing Res Rev* 2013; 12:354-364.
- (49) Livingston G, Johnston K, Katona C, et al. Systematic review of psychological approaches to the management of neuropsychiatric symptoms of dementia. *The American journal of psychiatry* 2005; 162:1996-2021.
- (50) HealthLinkBC. Dementia. <http://www.healthlinkbc.ca/healthtopics/content.asp?hwid=uf4984> . 2013.
- (51) Alberta Health Services. Appropriate use of antipsychotics toolkit for care teams. <http://www.albertahealthservices.ca/auatoolkit.asp> . 2015.
- (52) Ontario Ministry of Health and Long-term Care. Ontario's Strategy for Alzheimer disease and related dementias. <http://www.health.gov.on.ca/en/common/ministry/publications/reports/alz/summary.aspx> . 2015.

- (53) Brain Xchange. Behavioural Supports Ontario (BSO). <http://brainxchange.ca/Public/Resource-Centre-Topics-A-to-Z/Behavioural-Supports-Ontario.aspx> . 2015.
- (54) Winnipeg Health Region. About P.I.E.C.E.S. <http://www.wrha.mb.ca/wave/2012/01/about-pieces.php> . 2014.
- (55) Ontario College of Family Physicians. Behavioural and psychological symptoms of dementia: learning objectives. [http://ocfp.on.ca/cme/offerings/alzheimer-s-strategy-dementia/behavioural-and-psychological-symptoms-of-dementia-\(bpsd\)](http://ocfp.on.ca/cme/offerings/alzheimer-s-strategy-dementia/behavioural-and-psychological-symptoms-of-dementia-(bpsd)) . 2015.
- (56) Goodman L, The Canadian Press. National dementia strategy coming, health ministers say. <http://www.ctvnews.ca/health/national-dementia-strategy-coming-health-ministers-say-1.2034320> . 2014.
- (57) Canadian Foundation for Healthcare Improvement. CHFI supports projects to improve care for dementia patients: teams across Canada will tackle inappropriate antipsychotic medication use. <http://www.cfhi-fcass.ca/SearchResultsNews/2014/06/04/cfhi-supports-projects-to-improve-care-for-dementia-patients-teams-across-canada-will-tackle-inappropriate-antipsychotic-medication-use> . 2014.
- (58) British Columbia Ministry of Health. Best practice guideline for accommodating and managing behavioural and psychological symptoms of dementia in residential care. <http://www.health.gov.bc.ca/library/publications/year/2012/bpsd-guideline.pdf> . 2012.
- (59) Drouillard N, Mithani A, Chan P. Therapeutic approaches in the management of behavioral and psychological symptoms of dementia in the elderly. *BMC* 2013; 55:90-95.
- (60) RxFiles. Long-term care and residential care: evidence-based resources. <http://www.rxfiles.ca/rxfiles/Modules/ltc/ltc.aspx> . 2015.
- (61) Accreditation Canada. The value of long-term care accreditation. <http://www.accreditation.ca/sites/default/files/long-term-care-en.pdf> . 2013.
- (62) Accreditation Canada. Standards: Long-term Care Services. *Accreditation Canada* 2015.
- (63) Canadian Institute of Health Information (CIHI). Potentially inappropriate use of antipsychotics in long-term care. <http://indicatorlibrary.cihi.ca/display/HSPIL/Potentially+Inappropriate+Use+of+Antipsychotics+in+Long-Term+Care> . 2015.
- (64) Choosing Wisely. Ten things physicians and patients should questions. <http://www.choosingwisely.org/doctor-patient-lists/american-geriatrics-society/> . 2014.
- (65) Choosing Wisely Canada. Five things physicians and patients should question. <http://www.choosingwiselycanada.org/recommendations/geriatrics/> . 2014.

- (66) Banerjee S. the use of antipsychotic medication for people with dementia: time for action. <http://psychrights.org/research/digest/nlps/BanerjeeReportOnGeriatricNeurolepticUse.pdf> . 2009.
- (67) Health & Social Care Information Centre. National Dementia and Antipsychotic Prescribing Audit National Summary Report. <http://www.hscic.gov.uk/searchcatalogue?productid=7624&q=title%3a%22National+Dementia+and+Antipsychotic+Prescribing+Audits%22&sort=Most+recent&size=10&page=1#top> . 2012.
- (68) Chen Y, Briesacher B, Field T, et al. Unexplained variation across US nursing homes in antipsychotic prescribing rates. *Arch Intern Med* 2010; 170:89-95.
- (69) Centers for Medicare and Medicaid Services. Interim report on the CMS national partnership to improve dementia care in nursing homes: Q42011 - Q1 2014. <http://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Downloads/Survey-and-Cert-Letter-14-19.pdf> . 2014.
- (70) US Department of Health & Human Services. Nursing facility assessments and care plans for residents receiving atypical antipsychotic drugs. <https://oig.hhs.gov/oei/reports/oei-07-08-00151.asp> . 2012.
- (71) Jackson J, Schneeweiss S, VanderWeele T, Blacker D. Quantifying the Role of Adverse Events in the Mortality Difference between First and Second-Generation Antipsychotics in Older Adults: Systematic Review and Meta-Synthesis. *PLoS ONE* 2014; 9:e105376.
- (72) Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Archives of internal medicine* 2009; 169(21):1952-1960.
- (73) Fraser LA, Liu K, Naylor KL, Hwang YJ, Dixon SN, Shariff SZ et al. Falls and fractures with atypical antipsychotic medication use: a population-based cohort study. *JAMA internal medicine* 2015.
- (74) Rigler SK, Shireman TI, Cook ΓÇÉ Wiens GJ, Ellerbeck EF, Whittle JC, Mehr DR et al. Fracture risk in nursing home residents initiating antipsychotic medications. *Journal of the American Geriatrics Society* 2013; 61(5):715-722.
- (75) Pouwels S, Van Staa TP, Egberts ACG, Leufkens HGM, Cooper C, De Vries F. Antipsychotic use and the risk of hip/femur fracture: a population-based case ΓÇôcontrol study. *Osteoporosis international* 2009; 20(9):1499-1506.
- (76) Setoguchi S, Wang PS, Alan Brookhart M, Canning CF, Kaci L, Schneeweiss S. Potential causes of higher mortality in elderly users of conventional and atypical antipsychotic medications.

Journal of the American Geriatrics Society 2008; 56(9):1644-1650.

- (77) Hwang YJ, Dixon SN, Reiss JP, Wald R, Parikh CR, Gandhi S et al. Atypical antipsychotic drugs and the risk for acute kidney injury and other adverse outcomes in older adults: a population-based cohort study. *Annals of Internal Medicine* 2014; 161(4):242-248.
- (78) Gill S, Bronskill S, Normand S, et al. Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med* 2007; 146:775-786.
- (79) Health Canada. Atypical antipsychotic drugs and dementia: advisories, warnings and recalls for health professionals. <http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2005/14307a-eng.php> . 2005.
- (80) Schneeweiss S, Setoguchi S, Brookhart A, et al. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *CMAJ* 2007; 176:627-632.
- (81) Kales H, Valenstein M, Kim H, et al. Mortality risk in patients with dementia treated with antipsychotics versus other psychiatric medications. *The American journal of psychiatry* 2007; 164:1568-76.
- (82) Pratt N, Roughead E, Salter A, Ryan P. Choice of observational study design impacts on measurement of antipsychotic risks in the elderly: a systematic review. *BMC medical research methodology* 2012; 12:72.
- (83) Hien LT, Cumming RG, Cameron ID, Chen JS, Lord SR, March LM et al. Atypical antipsychotic medications and risk of falls in residents of aged care facilities. *Journal of the American Geriatrics Society* 2005; 53(8):1290-1295.
- (84) Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *New England Journal of Medicine* 2005; 353(22):2335-2341.
- (85) Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. *New England Journal of Medicine* 2009; 360(3):225-235.
- (86) Gill SS, Rochon PA, Herrmann N, Lee PE, Sykora K, Gunraj N et al. Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. *Bmj* 2005; 330(7489):445.
- (87) Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C, Wang PS. Comparative safety of conventional and atypical antipsychotic medications: risk of death in British Columbia seniors. *Effective health care research report* 2007;(2).
- (88) Jackson JW, Schneeweiss S, VanderWeele TJ, Blacker D. Quantifying the Role of Adverse Events in the Mortality Difference between First and Second-Generation Antipsychotics in

Older Adults: Systematic Review and Meta-Synthesis. *PLoS one* 2014; 9(8):e105376.

- (89) Finkel S, Kozma C, Long S, Greenspan A, Mahmoud R, Baser O et al. Risperidone treatment in elderly patients with dementia: relative risk of cerebrovascular events versus other antipsychotics. *International psychogeriatrics* 2005; 17(04):617-629.
- (90) Huybrechts KF, Gerhard T, Crystal S, Olfson M, Avorn J, Levin R et al. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. *Bmj* 2012; 344.
- (91) Anderson S, vande Griend J. Quetiapine for insomnia: a review of the literature. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists* 2014; 71:394-402.
- (92) Hermes E, Semyak M, Rosenheck R. Use of second-generation antipsychotic agents for sleep and sedation: a provider survey. *Sleep* 2013; 36:597-600.
- (93) University of British Columbia. Is use of quetiapine for sleep evidence-based? http://www.ti.ubc.ca/sites/ti.ubc.ca/files/79_0.pdf . 2010.
- (94) Pringsheim T, Gardner D. Dispensed prescriptions for quetiapine and other second-generation antipsychotics in Canada from 2005 to 2012: a descriptive study. *CMAJ Open* 2014; 2:E225.
- (95) Cohrs S, Rodenbeck A, Guan Z, et al. Sleep-promoting properties of quetiapine in healthy subjects. *Psychopharmacology* 2004; 184:421-429.
- (96) Wiegand M, Landry F, Bruckner T, et al. quetiapine in primary insomnia: a pilot study. *Psychopharmacology* 2008; 196:337-338.
- (97) Tassniyom K, Paholpak S, Tassniyom S, et al. Quetiapine for primary insomnia: a double-blind, randomized controlled trial. *J Med Assoc Thai* 93, 729-734. 2010.

Ref Type: Online Source

- (98) McCleery J, Cohen D, Sharpley A. Pharmacotherapies for sleep disturbances in Alzheimer's disease. *Cochrane Database Syst Rev* 2014; 3:CD009178.
- (99) Healthy Canadians. Risperidone-restriction of the dementia indication. <http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2015/43797a-eng.php> . 2015.
- (100) Health Canada. Updated safety information for Risperdal (risperidone) in elderly dementia patients, announced in Canada. <http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2002/14164a-eng.php> . 2002.
- (101) Health Canada. Health Canada Endorsed Important Safety Information on Zyprexa (olanzapine). <http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2004/14300a-eng.php> . 2004.

- (102) US Food and Drug Administration. Information for Healthcare Professionals: conventional antipsychotics. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm> . 2008.
- (103) Kales H, Zivin K, Kim H, et al. Trends in antipsychotic use in dementia 1999-2007. *Arch Gen Psychiatry* 2011; 68:190-197.
- (104) Valiyeva E, Herrmann N, Rochon P, et al. Effect of regulatory warnings on antipsychotic prescription rates among elderly patients with dementia: a population-based time-series analysis. *CMAJ* 2008; 179.
- (105) Gallini A, Andrieu S, Donohue JM, Oumouhou N, Lapeyre-Mestre M, Gardette V. Trends in use of antipsychotics in elderly patients with dementia: Impact of national safety warnings. *Eur Neuropsychopharmacol* 2014; 24(1):95-104.
- (106) Schulze J, van den Bussche H, Glaeske G, Kaduszkiewicz H, Wiese B, Hoffmann F. Impact of safety warnings on antipsychotic prescriptions in dementia: nothing has changed but the years and the substances. *Eur Neuropsychopharmacol* 2013; 23(9):1034-1042.
- (107) Puyat JH, Law MR, Wong ST, Sutherland JM, Morgan SG. The essential and potentially inappropriate use of antipsychotics across income groups: an analysis of linked administrative data. *Can J Psychiatry* 2012; 57(8):488-495.
- (108) New Brunswick Department of Health. New Brunswick Prescription Drug Program Formulary. <http://www.gnb.ca/0212/nbpdpformulary-e.asp> 2013
- (109) Nova Scotia Pharmacare. Nova Scotia Formulary. <http://novascotia.ca/dhw/pharmacare/formulary.asp> 2013
- (110) PEI Pharmacare. Formulary. <http://healthpei.ca/formulary> 2013
- (111) Newfoundland and Labrador Department of Health and Community Services. Newfoundland and Labrador Interchangeable Drug Products Formulary. <http://www.health.gov.nl.ca/health/nlmdp/fmlsearch.asp> 2013

Appendix 1: Public drug plan benefit listings of typical antipsychotics

Drug	Brand name	BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL	YK	NIHB/ NU/ NW
Chlorpromazine	Generic	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben
Flupentixol	Fluanxol (inj)	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben
	tablet	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben
Fluphenazine	Generic (inj)	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben
	Generic tablet	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben
Haloperidol	Generic	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben
Loxapine	Generic	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben
Methotrimeprazine	Generic	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben
Pericyazine	Neuleptil	Ben	Ben	Ben	Ben	Ben	Ben	Ben	No	Ben	Ben	Ben	Ben
Perphenazine	Generic	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben
Pimozide	Orap	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben
Pipotiazine	Piportil L4	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	No	Ben
Prochlorperazine	Generic	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben
Thiothixene	Navane	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben
Trifluoperazine	Generic	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben
Zuclopenthixol	Clopixol	Ben	Ben	Res	No	No	Ben	No	No	No	Ben	Ben	No

NO=not listed

RES=restricted listing

BEN=unrestricted listing

Appendix 2: Therapeutic Notes for Atypical Antipsychotics on the Ontario Drug Benefit formulary

Antipsychotic (Brand)	Therapeutic Note
Aripiprazole (Abilify)	<p>Notes: For the treatment of schizophrenia and related psychotic disorders after failure, intolerance or contraindication to at least one less expensive antipsychotic alternative.</p> <p>Not indicated for the treatment of dementia or dementia-related behavioral problems in the elderly</p>
Asenapine (Saphris)	<p>For the acute treatment of manic or mixed episodes associated with bipolar I disorder as either:</p> <p>Monotherapy, after a trial of lithium or divalproex sodium has failed, and trials of less expensive atypical antipsychotic agents have failed due to intolerance or lack of response;</p> <p>OR</p> <p>Co-therapy with lithium or divalproex sodium, after trials of less expensive atypical antipsychotic agents have failed due to intolerance or lack of response</p>
Lurasidone (Latuda)	<p>For the management of the manifestations of schizophrenia after failure, intolerance or contraindication to at least one less expensive antipsychotic alternative.</p> <p>Not indicated for the treatment of dementia or dementia-related behavioral problems in the elderly</p>
Paliperidone (Invega Sustenna), Risperidone (Risperdal Consta)	<p>For the treatment of schizophrenia or schizoaffective disorders in patients who have:</p> <p>A history of non-adherence; AND one of the following:</p> <p>(a) Inadequate control or significant side-effects from two or more formulary oral antipsychotic medications, including at least one atypical agent; OR</p> <p>(b) Inadequate control or significant side-effects from one or more conventional depot antipsychotic agents</p>

Appendix 3: Webpages for Provincial Drug Formularies

Province	Webpage for Drug Formulary
British Columbia	http://www.health.gov.bc.ca/pharmacare/benefitslookup/faces/Search.jsp
Alberta	https://idbl.ab.bluecross.ca/
Saskatchewan	http://formulary.drugplan.health.gov.sk.ca/
Manitoba	http://web6.gov.mb.ca/eFormulary/
Ontario	https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp
Quebec	http://www.ramq.gouv.qc.ca/en/regie/legal-publications/Pages/list-medications.aspx
New Brunswick	http://www.gnb.ca/0212/nbpdpformulary-e.asp
Nova Scotia	http://novascotia.ca/dhw/pharmacare/formulary.asp
Prince Edward Island	http://healthpei.ca/formulary
Newfoundland	http://www.health.gov.nl.ca/health/nlpdp/fmlsearch.asp
Yukon Territories	https://apps.gov.yk.ca/pls/apex40p/f?p=161:9000:4324580815029961:::~:
NIHB (Non-insured Health Benefits) Program	http://www.hc-sc.gc.ca/fniah-spnia/nihb-ssna/provide-fournir/pharma-prod/med-list/index-eng.php

Appendix 4: Restriction Criteria for Atypical Antipsychotics in Canada

Province	Criteria
Alberta	
Asenapine	<p>"For the acute treatment of manic or mixed episodes associated with bipolar I disorder as co-therapy with lithium or divalproex sodium."</p> <p>"For the acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy, after a trial of lithium or divalproex sodium has failed due to intolerance or lack of response, or the presence of a contraindication to lithium or divalproex sodium as defined by the product monographs."</p> <p>"Special authorization coverage may be granted for 24 months."</p> <p>These products are eligible for auto-renewal.</p>
British Columbia	
Aripiprazole	<p>Patient specific diagnosis identified as Schizophrenia or other psychosis (not dementia related)</p> <p>AND</p> <p>Treatment failure or intolerance to at least one other specified anti-psychotic agent.</p> <p>Patients who meet Schizophrenia diagnosis criteria requirements for aripiprazole automatically receive coverage for olanzapine and ziprasidone.</p>
Asenapine	<p>Diagnosis of Bipolar I disorder</p> <p>AND</p> <p>Treatment failure or intolerance to lithium, carbamazepine or divalproex sodium</p> <p>AND</p> <p>Treatment failure to at least one other anti-psychotic agent.</p>
Olanzapine	<p>1. Patient specific diagnosis identified as Schizophrenia or other psychosis (not dementia related)</p> <p>AND</p> <p>Treatment failure or intolerance to at least one other specified anti-psychotic agent</p> <p>AND/OR</p> <p>2. Diagnosis of Bipolar I disorder</p> <p>AND</p> <p>Treatment failure or intolerance to lithium, carbamazepine or divalproex sodium</p>
Paliperidone Sustena	<p>Management of the manifestations of schizophrenia or related psychotic disorders in:</p> <p>Patients who have tried oral paliperidone or risperidone</p> <p>PLUS</p> <p>at least one other antipsychotic agent</p> <p>PLUS</p> <p>continue to be inadequately controlled at maximally-tolerated dose</p> <p>OR</p> <p>Patients who are currently receiving a conventional depot antipsychotic</p> <p>PLUS</p> <p>experiencing significant side effects such as extrapyramidal symptoms or tardive dyskinesia</p> <p>OR</p> <p>Patients with a history of non-adherence to antipsychotic medications resulting in important negative outcomes such as repeated hospitalizations</p> <p>Patients who meet criteria for paliperidone palmitate automatically receive coverage of risperidone microspheres</p>

Province	Criteria
Risperdal Consta	<p>Management of the manifestations of schizophrenia or related psychotic disorders in:</p> <p>Patients who have tried oral risperidone or paliperidone</p> <p>PLUS</p> <p>at least one other antipsychotic agent</p> <p>PLUS</p> <p>continue to be inadequately controlled at maximally-tolerated doses</p> <p>OR</p> <p>Patients who are currently receiving a conventional depot antipsychotic</p> <p>PLUS</p> <p>experiencing significant side effects such as extrapyramidal symptoms or tardive dyskinesia</p> <p>OR</p> <p>Patients with a history of non-adherence to antipsychotic medications resulting in important negative outcomes such as repeated hospitalizations</p> <p>Patients who meet criteria for risperidone microspheres automatically receive coverage of paliperidone palmitate</p>
Ziprasidone	<p>Patient specific diagnosis identified as schizophrenia or other psychosis (not dementia related)</p> <p>AND</p> <p>Treatment failure or intolerance to at least one other specified anti-psychotic agent.</p> <p>Patients who meet Schizophrenia diagnosis criteria requirements for ziprasidone automatically receive coverage for olanzapine and aripiprazole.</p>
Saskatchewan	
Aripiprazole	For the treatment of schizophrenia and schizoaffective disorders
Asenapine	<p>(a) For the treatment of patients with bipolar disorder in combination with lithium or divalproex after trials of less expensive atypical antipsychotic agents (i.e. risperidone and quetiapine) have failed due to intolerance or lack of response.</p> <p>(b) For the treatment of bipolar disorder as monotherapy for patients who have failed lithium or divalproex AND have failed trials of less expensive atypical antipsychotic agents (i.e. risperidone and quetiapine) due to intolerance or lack of response.</p>
Clozapine	For treatment of schizophrenia in patients who are either treatment resistant or treatment intolerant and have no other medical contraindications.
Olanzapine	<p>For treatment of: (a) Schizophrenia.</p> <p>(b) Other psychotic conditions where there has been:</p> <p>Treatment failure to other atypical anti-psychotic agents.</p> <p>Intolerance to other atypical anti-psychotic agents.</p> <p>(c) Patients with acute mania of bi-polar affective disorder for an additional 4 weeks following hospital discharge, and:</p> <p>(d) For maintenance treatment of bipolar disorder in patients who are unresponsive to other first line agents (lithium, divalproex and lamotrigine).</p>
Paliperidone (Invega Sustenna) Risperidone (Risperdal Consta)	For the treatment of patients exhibiting a compliance problem with an oral antipsychotic and in whom the administration of a conventional injectable extended action antipsychotic is ineffective or poorly tolerated
New Brunswick¹⁰⁸	
Asenapine	<p>For the acute treatment of manic or mixed episodes associated with bipolar I disorder as either:</p> <ul style="list-style-type: none"> • Monotherapy, after a trial of lithium or divalproex sodium has failed, and trials of less expensive atypical antipsychotic agents have failed due to intolerance or lack of response • Co-therapy with lithium or divalproex sodium, after trials of less expensive atypical antipsychotic agents have failed due to intolerance or lack of response.

Province	Criteria
Aripiprazole, Lurasidone	For the treatment of schizophrenia and related psychotic disorders (not dementia related) in patients with a history of failure, intolerance, or contraindication to at least one less expensive antipsychotic agent.
Olanzapine	For the acute and maintenance treatment of schizophrenia and related psychotic disorders. For the acute treatment of manic or mixed episodes in bipolar I disorder in patients with intolerance or a history of failure to one other atypical antipsychotic. For maintenance treatment in patients with bipolar disorder who are currently stabilized on olanzapine. Clinical Note: <ul style="list-style-type: none"> • Advice from a psychiatrist is suggested prior to starting therapy. Claim Note: <ul style="list-style-type: none"> • Prescriptions written by New Brunswick psychiatrists do not require special authorization. Subsequent refills ordered by other practitioners will not require special authorization.
Invega Sustena, Risperdal Consta	For the treatment of schizophrenia in patients: a. for whom compliance with an oral antipsychotic presents problems, OR b. who are currently receiving a typical depot antipsychotic and experiencing significant side effects (EPS or TD) or lack of efficacy.
Risperidone (oral disintegrating tablets)	a. For the treatment of schizophrenia and related psychotic disorders. b. For use in severe dementia for the short-term symptomatic management of inappropriate behaviour due to aggression and/or psychosis. c. For the acute management of manic episodes associated with Bipolar 1 disorder. Clinical Note: <ul style="list-style-type: none"> • Requests will be considered for patients who have difficulty swallowing oral tablets. Claim Note: <ul style="list-style-type: none"> • Prescriptions written by New Brunswick psychiatrists do not require special authorization. Subsequent refills ordered by other practitioners will not require special authorization.
Nova Scotia¹⁰⁹	
Aripiprazole, Lurasidone	For the treatment of schizophrenia and schizoaffective disorders in patients who have a contraindication to quetiapine and risperidone, or have failed a trial of quetiapine and risperidone due to intolerance or lack of response
Asenapine	For the acute treatment of manic or mixed episodes associated with bipolar I disorder as either: · monotherapy, after a trial of lithium or divalproex sodium has failed, and trials of less expensive atypical antipsychotic agents have failed due to intolerance or lack of response · co-therapy with lithium or divalproex sodium, after trials of less expensive atypical antipsychotic agents have failed due to intolerance or lack of response
Olanzapine	a. For the treatment of schizophrenia and related psychotic disorders upon the written request of a psychiatrist, either first line or upon failure of other antipsychotic agents b. For the acute treatment of manic or mixed episodes in bipolar I disorder in patients with intolerance or a history of failure to one other atypical antipsychotic c. For maintenance therapy in patients with bipolar disease who are currently stabilized on olanzapine
Invega Sustena, Risperdal Consta	a. For patients having problems with compliance on an oral antipsychotic or b. For patients who are currently receiving a conventional depot antipsychotic and are experiencing significant side effects (EPS or TD) or lack of efficacy
Ziprasidone	For the treatment of schizophrenia and schizoaffective disorder
PEI¹¹⁰	
Aripiprazole, Ziprasidone	For the treatment of schizophrenia and schizoaffective disorders in patients who have a contraindication to a trial of at least TWO less expensive antipsychotic because of intolerance or lack of response

Province	Criteria
Asenapine	For the acute treatment of manic or mixed episodes associated with bipolar I disorder as either: <ul style="list-style-type: none"> • Monotherapy, after a trial of lithium or divalproex sodium has failed, and trials of less expensive atypical antipsychotic agents have failed due to intolerance or lack of response. • Co-therapy with lithium or divalproex sodium, after trials of less expensive atypical antipsychotic agents have failed due to intolerance or lack of response.
Quetiapine	<u>Nursing Home Program, Seniors Drug Program and Catastrophic Drug Program</u> For the treatment of patients with schizophrenia and related psychotic disorders and the acute treatment of manic or mixed episodes in bipolar disorder upon written request or recommendation of a psychiatrist or geriatrician.
Risperidone	<u>Seniors drug program</u> a) Dosages up to a maximum of 2mg daily (1mg twice daily) may be provided for the symptomatic management of inappropriate behaviour due to aggression and/or psychosis with dementia in patients who have failed or are intolerant to a trial of conventional neuroleptics upon written request or recommendation of a psychiatrist or geriatrician. (b) For the treatment of patients with schizophrenia and related psychotic disorders and the acute treatment of manic or mixed episodes in bipolar disorder upon written request or recommendation of a psychiatrist or geriatrician. <u>Nursing home program</u> a) Dosages up to a maximum of 2mg daily (1mg twice daily) may be provided without a Special Authorization for the symptomatic management of inappropriate behaviour due to aggression and/or psychosis with dementia in patients who have failed or are intolerant to a trial of conventional neuroleptics. (b) Dosages of more than 2mg daily will be considered upon written request or recommendation of a psychiatrist or geriatrician.
Olanzapine	<u>Nursing Home Program, Seniors Drug Program and Catastrophic Drug Program</u> For the treatment of patients with schizophrenia and related psychotic disorders and the acute treatment of manic or mixed episodes in bipolar disorder upon written request or recommendation of a psychiatrist or geriatrician.
Yukon	
Aripiprazole, Lurasidone	For treatment of schizophrenia & related disorders in patients who have failed other, less expensive antipsychotic agents because of intolerance or lack of response, and on recommendation of a psychiatrist. Specialists consult to be provided.
Asenapine	For the treatment of manic or mixed episodes associated with bipolar I disorder. As co-therapy with lithium or divalproex, after sufficient trials of less expensive antipsychotic agents have failed due to intolerance or lack of response. OR as monotherapy, after sufficient trials of lithium or divalproex have failed AND trials of less expensive atypical antipsychotic agents have failed.
Risperdal Consta	Treatment of schizophrenia and related disorders on recommendation of Psychiatrist. Consult to be provided. For patients who have tried oral risperidone AND at least one other antipsychotic agent AND continue to be inadequately controlled at maximally tolerated dose OR for patients who are currently on a conventional depot antipsychotic AND experiencing significant side effects such as extrapyramidal symptoms or tardive dyskinesia OR patients with a history of non-adherence to antipsychotic medications resulting in important negative outcomes such as repeated hospitalizations
Newfoundland ¹¹¹	
Aripiprazole	For the treatment of schizophrenia and schizoaffective disorders in patients who have a contraindication to a trial of at least TWO less expensive antipsychotic agents, or who failed a trial of at least TWO less expensive antipsychotic agents because of intolerance or lack of response.
Asenapine	For the acute treatment of manic or mixed episodes associated with bipolar I disorder as either: Monotherapy, after a trial of lithium or divalproex sodium has failed, and trials of at least TWO less expensive atypical antipsychotic agents have failed due to intolerance or lack of response Co-therapy with lithium or divalproex sodium, after trials of at least TWO less expensive atypical antipsychotic agents have failed due to intolerance or lack of response

Province	Criteria
Olanzapine	<p><i>Schizophrenia and other psychotic disorders:</i> For patients with the following diagnosis, following failure or intolerance to an adequate trial* of risperidone <i>and</i> quetiapine:</p> <ul style="list-style-type: none"> Schizophrenia Schizoaffective disorder Schizophreniform disorder Psychosis NOS *An adequate trial is defined as: <i>risperidone:</i> 1-6mg for a period of no less than 4 weeks at a maximally tolerated dose within this range; <i>quetiapine:</i> 400-800mg for a period of no less than 4 weeks at a maximally tolerated dose within this range. <i>Bipolar Disorder:</i> <p>For the treatment of an acute manic or mixed episode of bipolar I disorder following failure or intolerance to another atypical antipsychotic.</p> <p>For continuation therapy for the treatment of bipolar I disorder, maintenance therapy, in those patients who have previously been approved through the Department for bipolar I, acute, mania or mixed phase. Coverage will be considered to a MAXIMUM daily dose of 30mg.</p>
Risperidone Oral Disintegrating Tablet	For the treatment of schizophrenia or schizoaffective disorder in patients where there are compliance issues or in patients who cannot swallow other listed benefit oral formulations of risperidone.
Risperdal Consta, Invega Sustenna	For the management of the manifestations of schizophrenia and related psychotic disorders in patients: with documented compliance issues with an oral antipsychotic OR who are currently receiving a conventional depot antipsychotic and are experiencing significant side effects (EPS or TD) or lack of efficacy.
Ziprasidone	<p>For the treatment of schizophrenia and schizoaffective disorders:</p> <ul style="list-style-type: none"> a. in patients who have not achieved a satisfactory response from an adequate trial (*an adequate trial is defined as a trial of the selected medication for a period of no less than 4 weeks at a maximally tolerated dose) of at least one other antipsychotic agent, OR b. in situations for which the clinician has not been able to implement an adequate trial of another antipsychotic medication due to the development of intolerable adverse effects.
NIHB	
Aripiprazole, Ziprasidone	For the treatment of schizophrenia and schizoaffective disorders in patients who have a. Intolerance or lack of response to an adequate trial of another antipsychotic agent; OR b. A contraindication to another antipsychotic agent
Asenapine	<p>For the acute treatment of manic or mixed episodes associated with bipolar I disorder as either:</p> <ul style="list-style-type: none"> - Monotherapy, after a trial of lithium or divalproex sodium has failed or is contraindicated, and trials of two atypical antipsychotic agents have failed due to intolerance or lack of response <p>OR- Co-therapy with lithium or divalproex sodium, after trials of two atypical antipsychotic agents have failed due to intolerance or lack of response.</p>

Appendix 5: Interview Questions

How long have you listed atypical antipsychotics on your provincial formulary? How are they listed (e.g., restricted, general benefit)?
Why did you decide to list atypical antipsychotics this way?
What was the basis for this listing (e.g., quantity limits, general listing)?
Do you have any studies comparing usage/costs before and after implementation of this listing?
Why are certain atypical antipsychotics NOT funded?
Do you restrict prescribing to certain specialties (or are certain specialties exempt from restrictions)?
Do you have any special restrictions regarding the use of atypical antipsychotics in the elderly?

Appendix 6: Tiered cost-sharing options

Prescription Drug Plan	Tier 1 (generic)	Tier 2 (preferred brand)	Tier 3 (non-preferred brand)	Tier 4 (specialty)
Plan A	\$5	\$28	\$55	25%
Plan B	\$2	\$20	\$40	N/A
Plan C	\$10	\$25	50%	25%
Plan D	\$4	\$17	75%	25%

Adapted from:

<http://www.cancer.org/treatment/findingandpayingfortreatment/managinginsuranceissues/medicare/medicarepartd/medicare-part-d-formularies-and-drug-coverage>