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Current Utilization of Antipsychotic Agents for Schizophrenia: Combination and High-Dose Therapies

Supporting Informed Decisions

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment in respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report.

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1 INTRODUCTION

Optimizing drug-related health outcomes and cost-effective use of drugs by identifying and promoting optimal drug prescribing and use is a goal of the Canadian Agency for Drugs and Technologies in Health (CADTH). Where possible, CADTH builds on existing applicable Canadian and international initiatives and research. CADTH's goals are achieved through three main approaches:

- identifying evidence-based optimal use in prescribing and use of specific drugs
- identifying gaps in clinical practice, then proposing evidence-based interventions to address these gaps
- supporting the implementation of these interventions.

Direction and advice are provided to CADTH through various channels, including the following:

- the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) Advisory Committee (CAC) and the Advisory Committee on Pharmaceuticals (ACP); including representatives from the federal, provincial, and territorial health ministries and related health organizations
- the COMPUS Expert Review Committee (CERC)
- stakeholder feedback.

Note: In 2010, the CAC and ACP were replaced by the Drug Policy Advisory Committee (DPAC), the DPAC Optimal Use Working Group (OUWG), and the Formulary Working Group.

1.1 COMPUS Expert Review Committee

CERC consists of eight Core Members appointed to serve for all topics under consideration during their term of office, and three or more Specialist Experts appointed to provide their expertise in recommending optimal use for one or more specific topics. For topics in the area of mental health, four specialists were appointed as Specialist Experts. Two of the Core Members are Public Members who bring a lay perspective to the committee. The remaining six Core Members hold qualifications as physicians, pharmacists, or health economists, or have other relevant qualifications, with expertise in one or more areas such as, but not limited to, family practice, internal medicine, institutional or community clinical pharmacy, pharmacoeconomics, clinical epidemiology, drug utilization, methodology, effecting behaviour change (through health professional and/or patient and/or policy interventions), and critical appraisal. The Core Members, including Public Members, are appointed by the CADTH Board of Directors.

The mandate of CERC is advisory in nature, and consists of providing recommendations and advice to CADTH on assigned topics that relate to the identification, evaluation, and promotion of optimal practices in the prescribing and use of drugs across Canada. The overall perspective used by CERC members in producing recommendations is that of public health care policy-makers in pursuit of optimizing the health of Canadians within the available health care system resources.

2 ISSUE

CAC and ACP have identified atypical antipsychotic (AAP) agents for schizophrenia — used in high-dose or in combination therapy — as being a priority topic for optimal practice initiatives based on the following criteria:

- large deviations from optimal utilization (overuse or underuse)
- size of patient populations
- impact on health outcomes and cost-effectiveness
- benefit to multiple jurisdictions
- measurable outcomes
- potential to effect change in prescribing and use.

2.1 Schizophrenia

Schizophrenia is a mental illness that requires lifelong treatment[1] and is associated with symptoms that include hallucinations, delusions, cognitive impairment, disorganized thoughts, social withdrawal, and amotivation.[2] Its worldwide prevalence is 0.5% to 1.5%,[3] and in Canada it affects about 1% of the population,[2] or about 234,305 (95% CI, 136,201 to 333,402) people (2004 data).[4] Schizophrenia is a chronic or recurrent illness and patients are at an increased risk for numerous other medical illnesses, and risks for suicide and substance abuse, homelessness, and unemployment.[5]

The total financial burden of schizophrenia in Canada was estimated to be $6.85 billion in 2004.[6] The annual direct health care and non-health care costs were estimated at $2.02 billion (2004 dollars); acute (23%) and non-acute (38%) hospital care accounted for the majority of these costs.[6] Diagnostic criteria for schizophrenia are currently based on the latest revisions of either the World Health Organization International Statistical Classification of Diseases and Related Health Problems (ICD-10) or the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV).[3]

2.1.1 Management of schizophrenia

Antipsychotic drugs form the cornerstone of treatment for schizophrenia,[2] as they target the characteristic symptoms of the disease.[3] These symptoms can be positive or negative in nature.[3] Positive symptoms reflect a distortion or abundance of normal functions and negative symptoms reflect a loss or restriction of normal functions.[7] Positive symptoms include hallucinations and delusions, while negative symptoms include affective flattening, loss of interest, and alogia (lack of speech).[7] The underlying principles in place for the administration of pharmacotherapy include the individualization of medication (the tailoring of treatment for each patient, which includes consideration of patient preferences), simple medication regimens, appropriate dosing, attention to side effect profiles, regular evaluation of responses in general (including adverse events),[5] and short- and long-term clinical efficacy, safety, and tolerability.[1]

Although there have been important developments in this area during the last 40 years, about one-third of persons with schizophrenia have a poor response to antipsychotic drugs.[8] Surveys of prescribing practices in the United Kingdom showed that the use of doses higher than those usually recommended is common, when antipsychotic agents are used either alone or in combination with another antipsychotic drugs.[8] Also, although combination therapy with two antipsychotic agents is not recommended in current clinical management guidelines,[5] with

the exception of combination therapy with clozapine,[8] it appears this practice is not uncommon.[8,9] Two longitudinal studies from the United States reported that 9.5% to 22.0% of patients with schizophrenia received two antipsychotic agents concurrently.[10,11] The proportion of patients treated with more than one AAP (antipsychotic polypharmacy) increased from 3.3% in 1999 to 13.7% in 2004.[10] Data from British Columbia indicate that the rate of antipsychotic polypharmacy increased between 1996, when an estimated 28% of patients discharged from hospital were on polypharmacy, compared with 45% in 2000. For patients using clozapine, the rate of polypharmacy increased from 22% in 1996 to 53% in 2000.[12] Reasons identified for this increasing prevalence include the use of as-required (PRN) medication, the gradual switch (bridging) from one antipsychotic to another one, as well as the combination of two antipsychotic drugs to achieve greater therapeutic response when there has been an unsatisfactory response to a single antipsychotic.[8] Overall prevalence rates of antipsychotic polypharmacy range from 4% to 58%,[9] and rates up to 69%[12] have been reported, depending on the treatment setting and patient population.

2.1.2 Technology description — antipsychotic drugs

Most existing antipsychotic therapies fall into one of two classes. The typical antipsychotic agents (also known as conventional antipsychotic agents or neuroleptics) are of the first-generation antipsychotic drug class. AAP agents are of the second-generation antipsychotic drug class.

Eight AAP agents are currently available in Canada: aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, and asenapine (Table 1). (Asenapine was not approved in Canada at the time this analysis was conducted.)

Table 1: Atypical and Typical Antipsychotic Drugs Available in Canada in 2009

Atypical Antipsychotic Drugs	Typical Antipsychotic Drugs
aripiprazole	chlorpromazine
asenapine*	fluphenazine
clozapine	haloperidol
olanzapine	loxapine
paliperidone	molindone
quetiapine	perphenazine
risperidone	pimozide
ziprasidone	thioridazine
	thiothixene
	trifluperazine

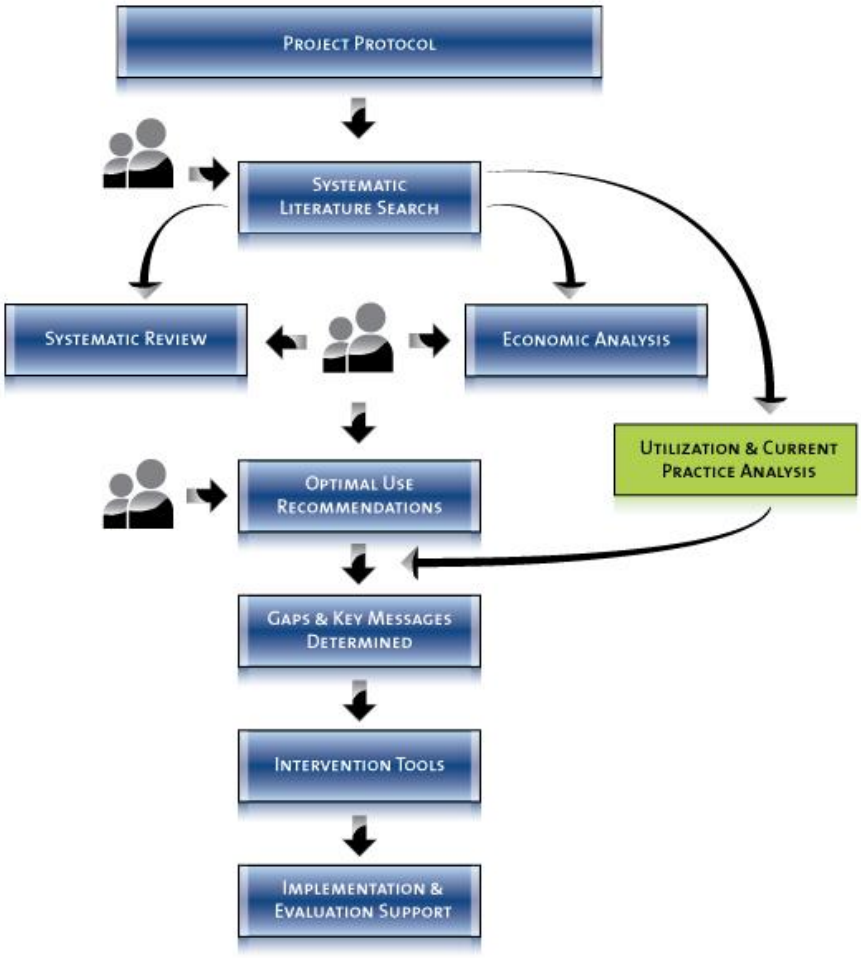
* Not approved in Canada at the time of analysis.

3 OBJECTIVE

The objective of this report is to identify current utilization and expenditure on combinations and high doses of atypical antipsychotic agents for adolescents and adults with schizophrenia, in public and private drug plans in Canada.

4 PROJECT OVERVIEW

Once a topic is selected, CADTH undertakes activities related to key areas in the procedure. The CAC and ACP provide advice and guidance around topic identification. The OUWG, formed after topic identification, provides advice and guidance throughout the process, through to supporting intervention and evaluation tools. CERC provides expert advice and recommendations on the topic area relating to the identification, evaluation, and promotion of optimal prescribing and use of drugs. A broad range of stakeholders are invited to provide feedback at key stages in the CADTH process.



This report represents the Current Utilization Analysis related to the prescribing and use of combinations and high doses of atypical antipsychotic agents for the treatment of schizophrenia.

5 METHODS

5.1 Analysis Design

Expenditure on antipsychotic drugs in 2009 was obtained and reported for public and private drug plans in Canada.

A five-year, retrospective, cross-sectional, time-series analysis on the utilization of antipsychotic drugs and related expenditures was then conducted. Results were presented separately for all patients using antipsychotic agents and a subset of patients classified with an inferred diagnosis of schizophrenia based on an algorithm developed by IMS Brogan Inc. (Appendix 3).

Utilization of antipsychotic drugs and related expenditures were examined using aggregate-level and patient-level administrative claims data provided by IMS Brogan Inc. Total utilization and expenditure on atypical and typical antipsychotic drugs that were available on Canadian public and private drug plan formularies during our analysis period were captured. There were seven atypical and 10 typical antipsychotic drugs available in Canada in 2009 (Table 1).

5.2 Data Sources

Aggregate- and patient-level data were obtained from IMS Brogan Inc. The IMS Brogan Inc. database is the largest source of drug payment information (i.e., administrative claims data) in Canada.[13] IMS Brogan Inc. databases comply with federal and provincial privacy legislation.[13] Patient-level data provided by IMS Brogan Inc. are protected by means of anonymous identifiers to ensure patient confidentiality.

5.2.1 Aggregate-level data

Aggregate-level data from public drug plans in Canada were available for nine of the 10 provinces (i.e., British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Québec, New Brunswick, Nova Scotia, and Newfoundland and Labrador) and the Non-Insured Health Benefits (NIHB) program. In addition, 67% of private-payer claims in Canada were captured.[13] Aggregate-level data were not available for publicly funded programs in Prince Edward Island, Northwest Territories, Yukon Territory, and Nunavut Territory because data from these programs are not provided to IMS Brogan Inc.

5.2.2 Patient-level data

Patient-level data for antipsychotic agent use was available for the Ontario Drug Benefits Program and 67% of private-payer claims in Canada.[13] Patient-level data refer to information from an individual patient's pharmacy claims; such data permit more analytical flexibility, since summary statistics can be estimated for various subgroups of interest (e.g., patients using combinations of specific drugs).

5.3 Statistical Analysis

5.3.1 Aggregate-level analysis

Aggregate-level data were employed to determine the total expenditure on atypical and typical antipsychotic agents for public (i.e., British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Québec, New Brunswick, Nova Scotia, Newfoundland and Labrador, and NIHB) and private drug plans in Canada between January 1, 2009 and December 31, 2009.

5.3.2 Patient-level analysis

Patient-level data were used to conduct a retrospective, cross-sectional, time-series analysis of standard-dose monotherapies (atypical or typical), high-dose atypical monotherapies, and combination therapies (any combination of typical and/or atypical antipsychotic agents) used by patients identified in the Ontario Public Drug Programs and private drug plans in Canada (i.e., 34% of all prescription claims in Canada) between January 1, 2005 and December 31, 2009. As part of the analysis, each "active month of therapy" (i.e., each month that claims for antipsychotic drugs were found) was classified as a type of therapy and subcategory as shown in Table 2. Clozapine (both monotherapy and combinations with other antipsychotic agents) was analyzed separately from other atypical antipsychotic agents.

Table 2: Types of Therapy and Subcategories	
Type of Therapy	**Subcategory**
Standard-Dose Monotherapy	Standard-dose oral non-clozapine atypical antipsychotic monotherapy
	Standard-dose injectable atypical antipsychotic monotherapy
	Standard-dose clozapine monotherapy
	Standard-dose (or high-dose) typical antipsychotic monotherapy*
High-Dose Atypical Monotherapy	High-dose oral non-clozapine atypical antipsychotic monotherapy
	High-dose injectable atypical antipsychotic monotherapy
	High-dose clozapine monotherapy
Combination Therapy	Dual combination therapy with non-clozapine atypical antipsychotic agents
	Dual combination therapy with typical antipsychotic agents
	Dual combination therapy with a non-clozapine atypical antipsychotic and typical antipsychotic agents
	Dual combination therapy with an oral non-clozapine atypical antipsychotic and injectable non-clozapine atypical antipsychotic agents
	Dual combination therapy with clozapine and a non-clozapine atypical antipsychotic agent
	Dual combination therapy with clozapine and an injectable non-clozapine atypical antipsychotic agent
	Dual combination therapy with clozapine and a typical antipsychotic agent
	Patients using ≥ 3 antipsychotic agents

* Typical antipsychotic agents were excluded from the dosage analysis due to the inherent variability in the dosing intervals of typical "depot" antipsychotic agents.

Each active month was classified according to one of the aforementioned types of therapy and subcategories based on patients' drug claims histories. Results were aggregated for all patients in the analysis and reported as annual totals. In addition, the mean cost per active month was calculated for each subcategory (Appendices 4 to 7).

The following example illustrates how results were calculated and reported.

> *Assume that two patients claimed antipsychotic drugs in 2005. The first patient claimed "dual combination therapy with typical antipsychotics" for four months and "high-dose clozapine monotherapy" for two months. The second patient claimed "standard-dose clozapine monotherapy" for 12 months. Therefore, the total number of active months in 2005 was 18 active months. The total number of active months on combination therapy and high-dose atypical monotherapy was six. In other words, 33.3% (6/18) of active months in 2005 were for combination therapy and high-dose atypical monotherapy.*

Patients were considered to fall in one of the subcategories for high-dose atypical monotherapy if there was at least one claim within the respective active month with a calculated average daily dose (mg/day) exceeding the recommended daily dose (Appendix 3). This definition of high-dose therapy was developed based on information provided in the Compendium of Pharmaceuticals and Specialties or the Food and Drug Administration product monographs, and in consultation with Canadian psychiatrists. Of note, the average daily dose was not presented since patients contributing to the estimated active months of high-dose therapy varied with respect to the specific agents used and the duration of use. Combination therapy was defined as the use of two or more antipsychotic drugs. To be classified as high-

dose atypical monotherapy or combination therapy, patients must have used the strategy for ≥ 30 days.

IMS Brogan Inc. data does not contain the prescription's indication (the physician's prescribing intent). To identify patients with schizophrenia, an IMS Brogan Inc. algorithm was used to classify patients by indication based on an inferred diagnosis according to their drug claims histories (Appendix 3).

The IMS Brogan Inc. algorithm was reviewed by psychiatrists serving on CERC. The psychiatrists expressed concern that the IMS Brogan Inc. algorithm may not capture all patients with schizophrenia, particularly elderly patients who may be misclassified as having dementia. Consequently, two patient subgroups were examined in the analysis to ensure the validity of findings:

- all patients who claimed antipsychotic drugs (6.1 Results)
- patients with schizophrenia, as per the IMS Brogan Inc. algorithm (6.2 Results).

6 RESULTS

6.1 Antipsychotic Drug Use for All Patients

6.1.1 All patients — publicly funded drug plans in Canada

Total expenditures on antipsychotic drugs in Canadian public drug plans are presented in Table 3. Annual expenditures in 2009 ranged from $5.3 million in Nova Scotia to $145.2 million in Ontario. Altogether, expenditure on antipsychotic drugs in 2009 by 11 public drug plans was $421.9 million.

Table 3: Total Expenditure on Antipsychotic Drugs in Public Drug Plans in 2009

Drug Plan	Expenditure ($)	Percentage*
British Columbia	69,262,770	16.4%
Alberta†	8,408,398	2.0%
Saskatchewan	13,720,585	3.3%
Manitoba	16,979,063	4.0%
Ontario	145,151,845	34.4%
Québec	134,085,938	31.8%
New Brunswick	11,401,421	2.7%
Nova Scotia	5,319,023	1.3%
Newfoundland and Labrador	5,703,368	1.4%
Non-Insured Health Benefits (NIHB)	11,886,523	2.8%
Total	**421,918,934**	**100.0%**

* Aggregate-level data were not available for publicly funded programs in Prince Edward Island, Northwest Territories, Yukon Territory, and Nunavut Territory because data from these programs are not provided to IMS Brogan Inc.
† Data represents 85% capture rate; social assistance data is not included.

6.1.2 All patients — Ontario Public Drug Programs

In December 2009, there were 108,819 active beneficiaries captured in the Ontario Public Drug Programs data set. Throughout 2009, patients using antipsychotic drugs claimed 1.3 million active months of antipsychotic therapy, for a total expenditure of $145.2 million (Appendix 4). Atypical antipsychotic strategies (either monotherapy or in combination with

other antipsychotic agents) represented > 90% of the active months and > 94% of the total expenditures. The majority of antipsychotic drugs claimed (85.2% of active months) were for patients using standard-dose monotherapy; atypical antipsychotic monotherapy represented 89% of active months and 96% of costs for all standard-dose monotherapies. For patients using combination therapy and high-dose atypical monotherapy, the active months were 12.5% and 2.3% respectively (Figure 1). Combinations involving one or more atypical antipsychotic agents represented > 88% of all combination therapy active months. There was considerable expenditure for patients using combination therapy ($41.8 million, > 88% of which was represented by combinations involving at least one atypical agent) and high-dose atypical monotherapy ($13.5 million); in total, these strategies accounted for $55.3 million or 38.1% of total expenditure on antipsychotic drugs in 2009 (Figure 2).

Figure 1: All Patients — Share of Active Months, Ontario Public Drug Programs, 2009

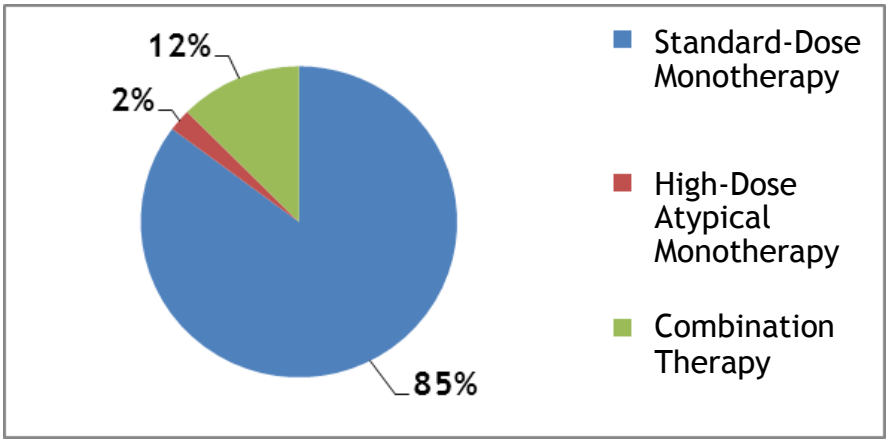
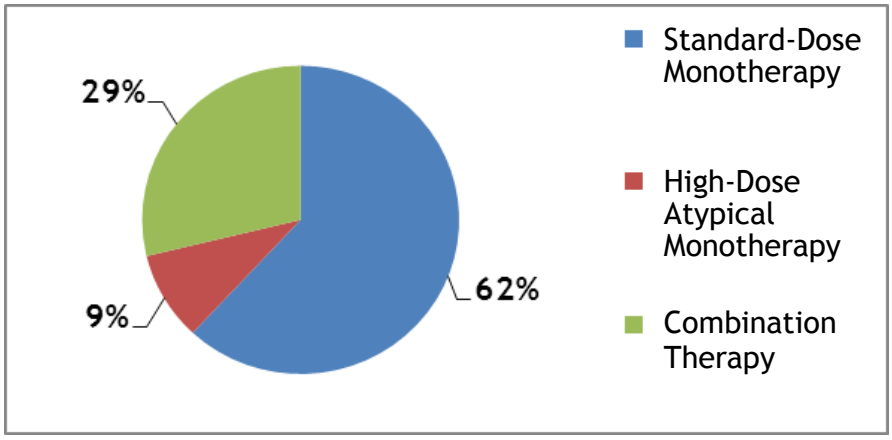


Figure 2: All Patients — Share of Expenditure, Ontario Public Drug Programs, 2009



The most widely used combination therapy was risperidone plus quetiapine (Table 4). Approximately 50% of the total expenditure and active months for patients using combination therapy were captured in the top five most widely used combination therapies.

Table 4: All Patients — Top Five Most Widely Used Combination Therapies, Ontario Public Drug Programs, 2009

Rank	Combination Therapies	Active Months	Expenditure ($)
1	risperidone plus quetiapine	28,909	4,018,885
2	olanzapine plus quetiapine	25,572	9,410,767
3	olanzapine plus risperidone	12,060	3,947,961
4	quetiapine plus haloperidol	5,513	686,305
5	olanzapine plus haloperidol	4,962	1,530,382

Among patients using high-dose atypical monotherapy, the most widely used antipsychotic drug was olanzapine (Table 5). Approximately 99% of the total expenditure and active months for patients using high-dose atypical monotherapy were captured in the top five most widely used high-dose atypical monotherapies.

Table 5: All Patients — Top Five Most Widely Used High-Dose Atypical Monotherapies, Ontario Public Drug Programs, 2009

Rank	Monotherapies	Active Months	Expenditure ($)
1	olanzapine	15,554	9,732,043
2	quetiapine	5,561	1,753,335
3	risperidone	4,869	817,348
4	injectable risperidone	3,206	1,195,070
5	paliperidone	26	7,306

Combination therapy and high-dose atypical monotherapy were 2.3 to 25 times more expensive than typical monotherapy and 0.8 to 8.3 times more expensive than atypical monotherapy, depending upon the subcategory of the type of therapy (Appendix 4). Compared with standard-dose atypical monotherapy, combinations involving at least one (non-clozapine) atypical antipsychotic agent were 2.4 to 8.3 times more costly, and high-dose (non-clozapine) atypical therapy was 4.3 to 5.5 times more costly. Overall, substantial growth in the share of active months for patients using combination therapy and high-dose atypical monotherapy was not observed between 2005 and 2009; the share was approximately 13.6% in 2005, increasing to 14.8% in 2009.

6.1.3 All patients — privately funded drug plans in Canada

In December 2009, there were 63,713 active beneficiaries captured in the private drug plans data set. Throughout 2009, patients using antipsychotic drugs claimed 695,600 active months of antipsychotic therapy, for a total expenditure of $62.3 million (Appendix 5). Atypical antipsychotic strategies (either alone or in combinations) represented more than 92% of active months, and > 98% of total expenditures on antipsychotic agents. The majority of antipsychotic drugs claimed (93.1% of active months) were for patients using standard-dose monotherapy; 6.0% and 0.9% of active months were for patients using combination therapy and high-dose atypical monotherapy respectively (Figure 3). Combinations involving one or more atypical antipsychotic agents represented more than 97% of all combination therapy active months. There was considerable expenditure on patients using combination therapy

($9.4 million; more than 91% of which was represented by combinations involving at least one atypical agent) and high-dose atypical monotherapy ($2.8 million); in total, these strategies accounted for $12.2 million or 19.6% of total expenditure on antipsychotic drugs in 2009 (Figure 4).

Figure 3: All Patients — Share of Active Months, Privately Funded Drug Plans, 2009

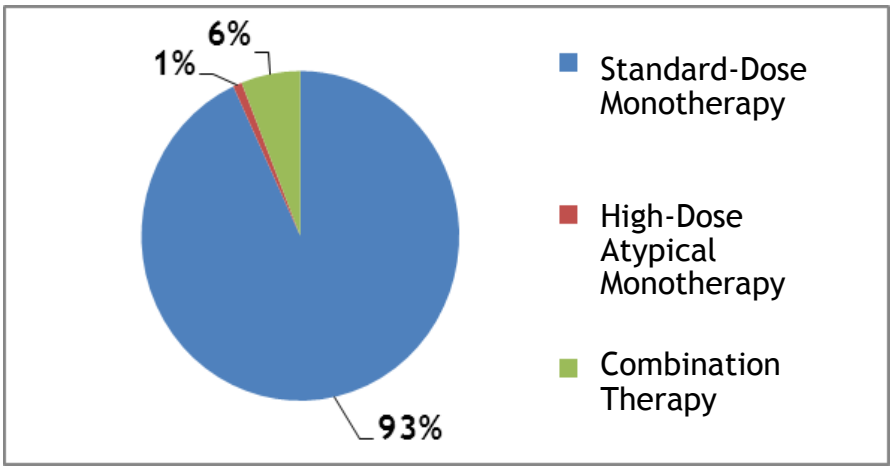
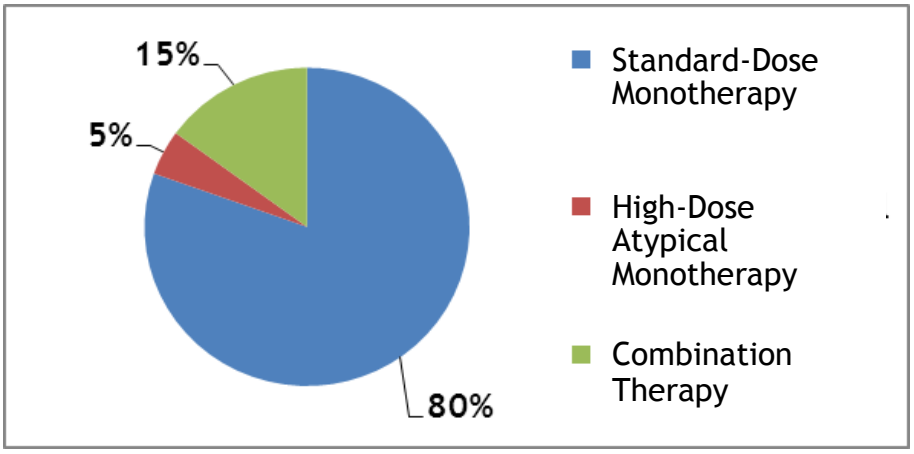


Figure 4: All Patients — Share of Expenditure, Privately Funded Drug Plans, 2009



The most widely used combination therapy was risperidone plus quetiapine (Table 6). Greater than 50% of total expenditure and active months for patients using combination therapy were captured in the top five most widely used combination therapies.

Table 6: All Patients — Top Five Most Widely Used Combination Therapies, Privately Funded Drug Plans, 2009			
Rank	**Combination Therapies**	**Active Months**	**Expenditure ($)**
1	risperidone plus quetiapine	11,404	1,582,301
2	olanzapine plus quetiapine	6,019	1,967,782
3	olanzapine plus risperidone	2,214	588,880
4	quetiapine plus methotrimeprazine	1,662	204,037
5	ziprasidone plus quetiapine	1,390	396,493

Among patients using high-dose atypical monotherapy, the most widely used drug was olanzapine (Table 7). Approximately 99% of total expenditure and active months for patients using high-dose atypical monotherapy were captured in the top five most widely used high-dose atypical monotherapies.

Table 7: All Patients — Top Five Most Widely Used High-Dose Atypical Monotherapies, Privately Funded Drug Plans, 2009			
Rank	**Monotherapies**	**Active Months**	**Expenditure ($)**
1	olanzapine	2,362	1,450,292
2	quetiapine	2,165	870,821
3	risperidone	930	191,909
4	injectable risperidone	645	241,907
5	ziprasidone	169	68,234

Combination therapy and high-dose atypical monotherapy were 2.3 to 51.4 times more expensive than typical monotherapy and 0.5 to 10.7 times more expensive than atypical monotherapy, depending upon the subcategory of the type of therapy (Appendix 5). Compared with standard-dose atypical monotherapy, combinations involving at least one (non-clozapine) atypical antipsychotic agent were 2.0 to 7.1 times more costly, and high-dose (non-clozapine) atypical therapy was 4.7 to 5.7 times more costly. Overall, substantial growth in the share of active months for patients using combination therapy and high-dose atypical monotherapy was not observed between 2005 and 2009; the share remained at approximately 7.0% throughout the entire period.

6.2 Antipsychotic Drug Use for Schizophrenia Patients

The following section provides results for patients inferred to have schizophrenia using the indications algorithm developed by IMS Brogan Inc. (Appendix 3).

6.2.1 Schizophrenia patients — Ontario Public Drug Programs

In December 2009, there were 25,107 active beneficiaries with an inferred diagnosis of schizophrenia as captured in the Ontario Public Drug Programs data set. Throughout 2009, patients with schizophrenia who were using antipsychotic drugs claimed 290,000 active months of antipsychotic therapy, for a total expenditure of $50.8 million (Appendix 6). Atypical antipsychotic strategies (either monotherapy or in combination with other antipsychotic agents) represented > 84% of active months and > 93% of the total expenditure. The majority of antipsychotic drugs claimed (77.4% of active months) were for standard-dose monotherapy; 18.6% and 4.0% of active months were for patients using combination therapy and high-dose atypical monotherapy respectively (Figure 5). Combinations involving one or

more atypical antipsychotic agents represented more than 85% of all combination therapy active months. There was considerable expenditure for patients using combination therapy ($15.6 million; more than 88% of which was represented by combinations involving at least one atypical agent) and high-dose atypical monotherapy ($5.7 million); in total, these strategies accounted for $21.3 million or 42% of the total expenditure on antipsychotic agents in 2009 (Figure 6).

Figure 5: Patients with an Inferred Diagnosis of Schizophrenia — Share of Active Months, Ontario Public Drug Programs, 2009

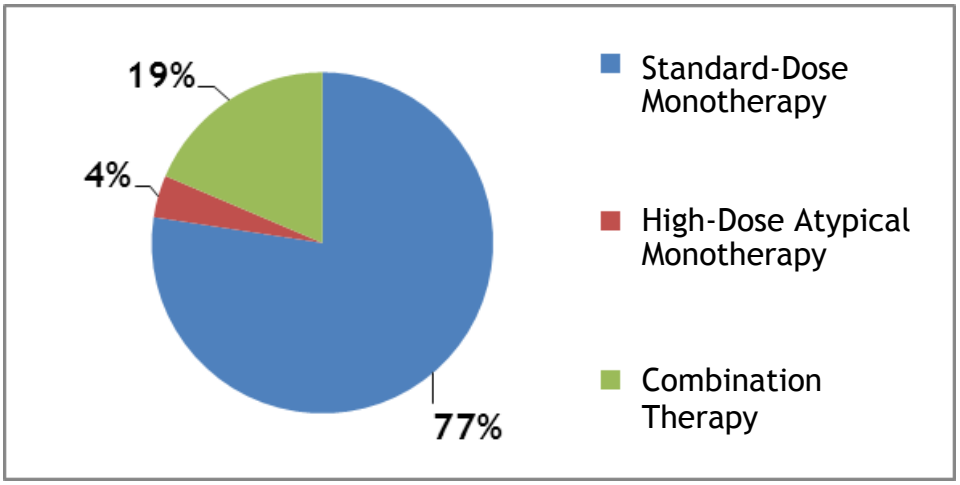
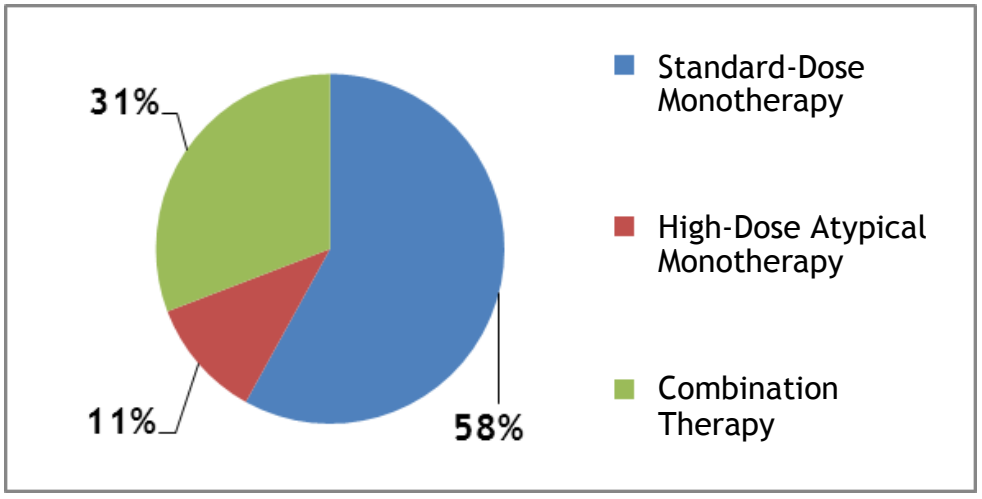


Figure 6: Patients with an Inferred Diagnosis of Schizophrenia — Share of Expenditure, Ontario Public Drug Programs, 2009



The most widely used combination therapy was risperidone plus quetiapine (Table 8). Approximately 40% to 45% of total expenditure and active months for patients using combination therapy were captured in the top five most widely used combination therapies.

Table 8: Patients with an Inferred Diagnosis of Schizophrenia — Top Five Most Widely Used Combination Therapies, Ontario Public Drug Programs, 2009			
Rank	**Combination Therapies**	**Active Months**	**Expenditure ($)**
1	risperidone plus quetiapine	7,970	1,353,668
2	olanzapine plus quetiapine	6,638	2,888,520
3	olanzapine plus risperidone	4,589	1,663,520
4	olanzapine plus haloperidol	2,059	727,584
5	quetiapine plus haloperidol	1,623	219,456

Among patients using high-dose atypical monotherapy, the most widely used drug was olanzapine (Table 9). All expenditure and active months for patients using high-dose atypical monotherapy were captured in the top five most widely used high-dose atypical monotherapies.

Table 9: Patients with an Inferred Diagnosis of Schizophrenia — Top Five Most Widely Used High-Dose Atypical Monotherapies, Ontario Public Drug Programs, 2009			
Rank	**Monotherapies**	**Active Months**	**Expenditure ($)**
1	olanzapine	6,727	4,254,810
2	risperidone	2,384	408,564
3	quetiapine	1,607	498,025
4	injectable risperidone	882	491,904
5	paliperidone	8	2,437

Combination therapy and high-dose atypical monotherapy were 1.0 to 10.4 times more expensive than typical monotherapy and 0.5 to 5.3 times more expensive than atypical monotherapy, depending upon the subcategory of the type of therapy (Appendix 6). Compared with standard-dose atypical monotherapy, combinations involving at least one (non-clozapine) atypical antipsychotic agent were 1.6 to 5.3 times more costly, and high-dose (non-clozapine) atypical therapy was 3.4 to 4.0 times more costly. Overall, substantial growth in the share of active months for patients using combination therapy and high-dose atypical monotherapy was not observed between 2005 and 2009; the share remained at approximately 23% throughout the entire period.

6.2.2 Schizophrenia patients — privately funded drug plans in Canada

In December 2009, there were 18,629 active beneficiaries captured in the private drug plans data set with an inferred diagnosis of schizophrenia using the IMS Brogan Inc. algorithm. Throughout 2009, patients with schizophrenia who were using antipsychotic drugs claimed 204,000 active months of antipsychotic therapy, for a total expenditure of $19.9 million (Appendix 7). Atypical antipsychotic strategies (either monotherapy or in combination with other antipsychotic agents) represented > 89% of active months and > 97% of the total expenditure. The majority of antipsychotic drugs claimed (92.7% of active months) were for standard-dose monotherapy; 6.3% and 1.0% of active months were for patients using combination therapy and high-dose atypical monotherapy respectively (Figure 7). Combinations involving one or more atypical antipsychotic agents represented more than 91% of all combination therapy active months. There was considerable expenditure for patients using combination therapy ($2.9 million; more than 91% of which was represented by combinations involving at least one atypical agent) and high-dose atypical monotherapy

($855,000); in total, these strategies accounted for $3.8 million or 18.9% of the total expenditure on antipsychotic agents in 2009 (Figure 8).

Figure 7: Patients with an Inferred Diagnosis of Schizophrenia — Share of Active Months, Privately Funded Drug Plans, 2009

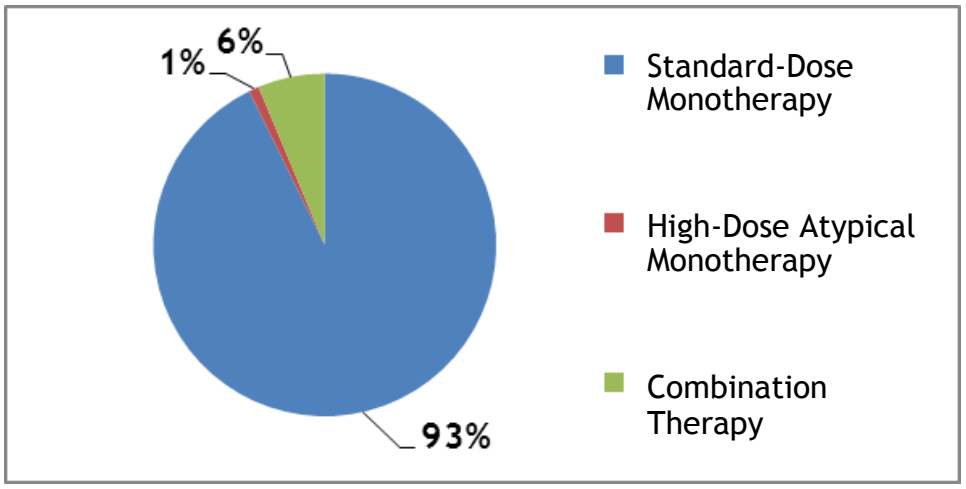
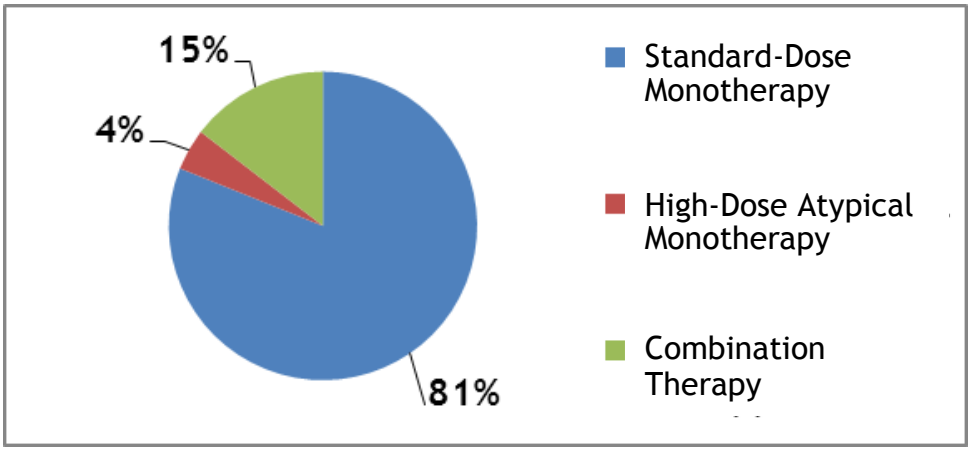


Figure 8: Patients with an Inferred Diagnosis of Schizophrenia — Share of Expenditure, Privately Funded Drug Plans, 2009



The most widely used combination therapy was risperidone plus quetiapine (Table 10). Approximately 50% of total expenditure and active months for patients using combination therapy were captured in the top five most widely used combination therapies.

Table 10: Patients with an Inferred Diagnosis of Schizophrenia — Top Five Most Widely Used Combination Therapies, Privately Funded Drug Plans, 2009			
Rank	**Combination Therapies**	**Active Months**	**Expenditure ($)**
1	risperidone plus quetiapine	3,245	480,027
2	olanzapine plus quetiapine	1,387	450,015
3	olanzapine plus risperidone	830	239,302
4	olanzapine plus haloperidol	396	113,885
5	quetiapine plus haloperidol	388	61,244

Among patients using high-dose atypical monotherapy, the most widely used drug was olanzapine (Table 11). Approximately 99% of total expenditure and active months for patients using high-dose atypical monotherapy were captured in the top five most widely used high-dose atypical monotherapies.

Table 11: All Patients — Top Five Most Widely Used High-Dose Atypical Monotherapies, Privately Funded Drug Plans, 2009			
Rank	**Monotherapies**	**Active Months**	**Expenditure ($)**
1	olanzapine	784	455,871
2	quetiapine	498	188,759
3	risperidone	393	97,081
4	injectable risperidone	218	98,612
5	ziprasidone	27	10,931

Combination therapy and high-dose atypical monotherapy were 2.4 to 40.1 times more expensive than typical monotherapy and 0.5 to 8.2 times more expensive than atypical monotherapy, depending upon the subcategory of the type of therapy (Appendix 7). Compared with standard-dose atypical monotherapy, combinations involving at least one (non-clozapine) atypical antipsychotic agent were 1.8 to 6.9 times more costly, and high-dose atypical (non-clozapine) therapy was about five times more costly. Overall, substantial growth in the share of active months for patients using combination therapy and high-dose atypical monotherapy was not observed between 2005 and 2009; the share was approximately 8.7% in 2005, decreasing to 7.3% in 2009.

7 DISCUSSION

7.1 Summary of Main Findings

Annual expenditures on antipsychotic agents in Canada by 11 publicly funded drug plans in 2009 were approximately $421.9 million, while $62.3 million was spent by privately funded drug plans. These estimates are conservative since they do not capture expenditures in special drug programs, out-of-pocket expenditures by patients for antipsychotic agents, and data not submitted to IMS Brogan Inc. (e.g., Prince Edward Island, Northwest Territories, Yukon Territory, Nunavut Territory, and a number of privately funded drug plans).

The majority of antipsychotic agent utilization — 85% to 93% of active months — was for standard-dose monotherapy. Yet there was considerable expenditure for patients using combination therapy and high-dose atypical monotherapy, despite these strategies not being recommended in most current clinical practice guidelines.[5,8,9,12] It is estimated that

combination therapy and high-dose atypical monotherapy accounted for 20% to 38% of total expenditures on antipsychotic agents in 2009. From the analysis of the subset of patients with an inferred diagnosis of schizophrenia, we found that 77% to 93% of active months were for standard-dose monotherapy. Combination therapy and high-dose atypical monotherapy accounted for 19% to 42% of total antipsychotic agent expenditures for patients with an inferred diagnosis of schizophrenia in 2009.

The vast majority of combination use involved at least one atypical antipsychotic agent. In both patient populations and data sets, the most widely used combination therapy (based on active months of therapy) was risperidone plus quetiapine; accounting for roughly 20% to 30% of active months for all combination therapies. Olanzapine plus quetiapine and olanzapine plus risperidone were the second and third most widely used combination therapies. Differences in results between patient populations and data sets started to emerge at the fourth and fifth ranked combination therapies. Overall, the top five most widely used combination therapies accounted for roughly 50% of total expenditures for all combination therapies.

In both patient populations and data sets, the most widely used high-dose atypical monotherapies (based on active months of therapy) were olanzapine, quetiapine, and risperidone. One exception existed for patients with schizophrenia in the Ontario Public Drug Programs, where risperidone was the second most utilized high-dose atypical monotherapy. Overall, high-dose olanzapine monotherapy accounted for roughly 40% to 60% of active months for all high-dose atypical monotherapies. Of note, a generic version of olanzapine was approved in Canada in June 2007,[14] and as such, expenditure data in this report should be interpreted accordingly.

An interesting finding in this analysis was that in the Ontario Public Drug Programs data set for all patients, utilization of combination therapy and high-dose atypical monotherapy, as measured by the percentage of active months, was largely stable between 2005 (13.6%) and 2009 (14.8%). During this same time, expenditures for combination therapy and high-dose atypical monotherapy increased considerably from 32.9% to 38.1%. This finding implies that there may have been a shift to more expensive antipsychotic drugs (e.g., ziprasidone), or average daily doses may have increased over time. Additionally, in the privately funded drug plans data set for all patients, both active months and expenditure for combination therapy and high-dose atypical monotherapy were largely stable between 2005 and 2009. Possible explanations for this may be the composition of the patient populations within each drug plan or the fee caps that some privately funded drug plans employ to limit annual expenditures per beneficiary.

Overall, the percentage of active months for combination therapy and high-dose atypical monotherapy was considerably higher for patients in the Ontario Public Drug Programs than in the privately funded drug plans. This finding may, in part, be attributable to the composition of the patient populations within each drug plan. Publicly funded drug plans typically provide benefits to individuals older than 65 or those with low incomes; as such, this population is likely older and more economically disadvantaged compared with the private-payer population. Patient age may be correlated with the use of combination therapy and high-dose atypical monotherapy as older patients may have tried and not been adequately controlled on standard-dose monotherapy. Income may be correlated with the severity of schizophrenia as greater severity may increase the probability of underemployment. Both factors may act to increase the likelihood of receiving reimbursement from a publicly funded drug plan and may

explain the disproportionately higher utilization of combination therapy and high-dose atypical monotherapy by patients in the Ontario Public Drug Programs.

7.2 Strengths and Limitations

There are a number of strengths of this study. First, this is the first Canadian report to provide insight into health care expenditures on antipsychotic drugs at the national level, including an analysis of utilization by the type of therapy (i.e., standard-dose monotherapy versus high-dose atypical monotherapy versus combination therapy), type of patient (i.e., all patients versus patients with an inferred diagnosis of schizophrenia), and type of drug plan (i.e., Ontario Public Drug Programs versus privately funded drug plans). Second, analyses presented in this report were generated using the IMS Brogan Inc. database, which is the largest source of drug payment information (i.e., administrative claims data) in Canada.[13] Third, the definition of high-dose therapy used in the analyses was based on information provided in the Compendium of Pharmaceuticals and Specialties or Food and Drug Administration product monographs, and in consultation with Canadian psychiatrists.

Despite its strengths, this analysis has certain limitations that warrant discussion.

- Aggregate-level data for estimates of utilization, and related expenditures, for some drug plans were not submitted to IMS Brogan Inc. and are therefore not included in the analysis.
- Patients paying out of pocket for antipsychotic agents are not included in this analysis.
- Costs of antipsychotic drugs may vary across drug plans and may change over time. Of note, changes to generic drug policies in public drug plans across Canada since 2009 may have had an impact on the daily cost of antipsychotic drugs.
- Variations in drug plan policies (e.g., patient deductibles) may have a minor impact on comparisons of expenditure data between drug plan data sets.
- In Ontario, clozapine is covered through the Ontario Special Drugs Program. In jurisdictions where clozapine is formulary listed, patterns of high-dose or combination AAP use may differ from that of Ontario.
- Patient-level data were available only for the Ontario Public Drug Programs and privately funded drug plans; thus, utilization of antipsychotic agents by type of therapy was not estimable for other publicly funded drug plans in Canada.
- IMS Brogan Inc. data does not contain data on indication for therapy. To identify patients with schizophrenia, an IMS Brogan Inc. algorithm was used to classify patients by indication based on an inferred diagnosis according to drug claims histories.
- Patient-level data provide information on the number of antipsychotic agents claimed by beneficiaries, not on actual patterns of use (e.g., intermittent use) or wastage.
- An active month for a patient using a combination therapy and a high-dose of one or more antipsychotic drugs, simultaneously, was only classified to combination therapy to avoid double counting.
- Although therapy duration had to be at least 30 days to be captured in the analysis of active months, the patient-level analysis is limited in its ability to differentiate between short-term use of combination therapy and high-dose atypical monotherapy, such as during relapses or while titrating doses, and for chronic use.

7.3 Results in Relation to Previous Studies

The British Columbia Mental Health and Addictions Research Institute reported on a study designed to determine the "proportion of patients treated with persistent antipsychotic

polypharmacy in an outpatient population."[15] Among the patients who were recruited for the study between October 20, 2005 and October 6, 2006, 164 were diagnosed with schizophrenia, 83 with schizoaffective disorder, 49 with major depression, 77 with bipolar disorder, and 30 with psychosis not otherwise specified. The primary finding of this study was that 26% of all qualified outpatients were treated with persistent antipsychotic polypharmacy. When diagnosis was considered, those with schizophrenia had a persistent polypharmacy prevalence rate of 32%. This study also reported significantly higher rates of excessive antipsychotic dosing (defined as a daily dose 1.5 times or greater than the defined daily dose) among patients who used combination therapy versus monotherapy. While our results appear to be conservative in light of the findings from British Columbia, it is difficult to make direct comparisons between the two studies due to important differences in methodology. These include a different unit of analysis (i.e., active months versus proportion of patients) and the definition of polypharmacy/combination therapy.

Studies on the prevalence of combination antipsychotic therapy in countries other than Canada have reported variable findings, although our findings are generally within the range of estimates reported.[10-12] Unlike these previous studies, we did not detect a substantial increase in the prevalence of combination therapy over time. Apart from jurisdictional differences in drug utilization, one possible reason for this is that we studied the period between 2005 and 2009, while other studies assessed utilization patterns from the mid-to-late 1990s to as far as 2004.

8 CONCLUSION

In many drug plans in Canada, antipsychotic agents are among the top classes of drugs in terms of total expenditures. Within Canada, annual expenditures on antipsychotic agents by 11 publicly funded drug plans in 2009 were approximately $421.9 million, while $62.3 million was spent by privately funded drug plans. Although the majority of antipsychotic agent utilization is for patients using standard-dose monotherapy, there is considerable expenditure on combination therapy and high-dose atypical monotherapy. It is estimated that combination therapy and high-dose atypical monotherapy accounted for 20% to 38% of expenditures on antipsychotic agents in 2009. The utilization of combination therapy and high-dose atypical monotherapy, as measured by active months, was largely stable between 2005 and 2009. Given the lack of evidence to support the efficacy and safety of combination therapy and high-dose atypical monotherapy,[16-18] further research is required to better understand the underlying reasons for why these strategies are employed. Optimizing the prescribing of these strategies may result in better health outcomes for patients with schizophrenia and also yield savings that could be applied to other areas of mental health care.

APPENDIX 1: EXPERT COMMITTEE AND CONTRIBUTORS

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Conflicts of Interest

Dr. Mike Evans has received grant support from AstraZeneca Canada Inc. to offset the cost of Mini-Med School, an educational program for the public.

Dr. Scott Klarenbach is a member of a research group funded by an unrestricted grant from Amgen Canada Inc. and Merck Frosst Canada Ltd. to the Alberta Kidney Disease Network.

Dr. Richard Williams has received funding for educational lectures from Eli Lilly and funding for conferences from Pfizer. He has received compensation for consulting services from Bristol-Myers Squibb Canada. He has received compensation for consulting services and research funding from Organon Canada Ltd., Janssen-Ortho Inc., Pfizer, Eli Lilly, and AstraZeneca Canada. He has received research funding from Obecure, Sanofi-aventis Canada, and Solvay.

Dr. Gary Remington has received financial support for his research from Novartis Canada, Medicure, and Merck KGaA (Germany). He is also involved in a Phase I Clinical Trial with Neurocrine Biosciences.

Dr. Heather Milliken has received funding for educational lectures and compensation for consulting services from Pfizer and Janssen-Ortho Inc. She has also received research funding from Janssen-Ortho Inc. and Eli Lilly.

APPENDIX 2: ABBREVIATIONS

AAP	atypical antipsychotic
ACP	Advisory Committee on Pharmaceuticals
CAC	COMPUS Advisory Committee
CADTH	Canadian Agency for Drugs and Technologies in Health
CERC	COMPUS Expert Review Committee
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
DPAC	Drug Policy Advisory Committee
DSM-IV	American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition
ICD-10	World Health Organization International Statistical Classification of Diseases and Related Health Problems
NIHB	Non-Insured Health Benefits program
OUWG	Optimal Use Working Group

APPENDIX 3: DEFINITIONS

Defining High-Dose Therapy

Patients were classified as using high-dose therapy if the patient had at least one claim within the respective month with a calculated average daily dose (mg/day) that exceeds the recommended dose. These definitions for high dose are based on information provided in the Compendium of Pharmaceuticals and Specialties or the Food and Drug Administration product monographs, and in consultation with Canadian psychiatrists.

Table A1: Definition of "High Dose" in CADTH Utilization Study

Generic Name	Trade Name	Dose Range	Definition of "High Dose"*	Manufacturer
aripiprazole	Abilify	10 mg to 15 mg/day	> 30 mg/day	Bristol-Myers Squibb
asenapine†	Saphris	10 mg/day (5 mg twice daily)	> 10 mg/day	Schering-Plough
clozapine	Clozaril	300 mg to 600 mg/day	> 600 mg/day‡	Novartis
olanzapine	Zyprexa, Zypexa Zydis	5 mg to 10 mg/day	> 20 mg/day	Eli Lilly
paliperidone	Invega	6 mg to 12 mg/day	> 12 mg/day	Janssen-Ortho
paliperidone injection§	Invega Sustenna	39 mg to 234 mg/month	> 234 mg/month	Janssen-Ortho
quetiapine	Seroquel	300 mg to 800 mg/day	> 800 mg/day	AstraZeneca
quetiapine	Seroquel XR	400 mg to 800 mg/day	> 800 mg/day	AstraZeneca
risperidone	Risperdal, Risperdal M-Tab	4 mg to 6 mg/day	> 6 mg/day¶	Janssen-Ortho
risperidone injection‡	Risperdal Consta	25 mg to 50 mg/ 2 weeks	> 50 mg/2 weeks	Janssen-Ortho

* Based on maximum recommended doses according to the product monograph, unless otherwise indicated.
† Not approved in Canada at the time of analysis.
‡ Based on expert opinion. Maximum recommended dose according to product monograph is 900 mg per day.
§ Long-acting injectable agent.
¶ Based on expert opinion. Maximum recommended dose according to product monograph is 16 mg per day.

Defining Patients with Schizophrenia

IMS Brogan Inc. data does not contain the prescription's indication (the physician's prescribing intent). However, IMS Brogan Inc.'s Rx Dynamics team, in collaboration with internal experts (e.g., clinical analysts, medical doctors) and external users, developed an algorithm to classify patients by indications based on "inferred diagnosis," according to their drug claims histories.

Table A2: Algorithm to Identify Patients in IMS Brogan Inc. Database with Schizophrenia	
Inferred Diagnosis	**Criteria for Inferred Diagnosis**
ADHD	Patients with recent claims (within 2 years) for methylphenidate, dextroamphetamine, dexmethylphenidate hydrochloride, are classified under ADHD. New psychostimulants indicated for ADHD will be added to this list as they enter the market.
Bipolar Disorder	Claimants must have a previous claim (within 2 years) for one of these drugs: lithium, valproic acid, carbamazepine, or divalproex sodium.
Depression	Patients with a history of taking antidepressants before starting any antipsychotic agents are classed in this group. A minimum of 2 years of history is searched on every patient, and the antidepressants must pre-date the first antipsychotic agent by at least 30 days.
Schizophrenia	Claimants younger than 65 and without previous bipolar disorder, depression, or ADHD inferred diagnosis.
Dementia	Patients older than 65, commencing an antipsychotic agent, with no record of having taken drugs for bipolar disorder or prior antipsychotic treatment.

ADHD = attention-deficit hyperactivity disorder.

The IMS Brogan Inc. algorithm was reviewed by psychiatrists serving on our expert review committee (CERC). The psychiatrists expressed concern that the IMS Brogan Inc. algorithm may not capture all patients with schizophrenia, particularly elderly patients who may be misclassified as having dementia. Consequently, two patient subgroupings were examined in the analysis to ensure the validity of findings:

- all patients who claimed antipsychotic drugs (6.1 Results)
- patients with schizophrenia, as per the IMS Brogan Inc. algorithm (6.2 Results).

Due to the limitations of the IMS Brogan Inc. algorithm, the results for patients with schizophrenia should be interpreted with caution. Of note, it may be possible to draw inferences about the utilization of antipsychotic agents by patients with schizophrenia based on the utilization trends observed for all patients reported in the first section of the results.

APPENDIX 4: COST OF THERAPIES COMPARED USING ONTARIO PUBLIC DRUG PROGRAM DATA, ALL PATIENTS

All Patients — Expenditure, Active Months, and Mean Cost per Active Month, Ontario Public Drug Programs, 2009					
Type of Therapy	**Expenditure**	**Active Months**	**Mean Cost per Active Month**	**Ratio of Mean Cost per Month Relative to Typical Monotherapy**	**Ratio of Mean Cost per Month Relative to Atypical Monotherapy**
> 3 Molecules	$4,291,087	10,522	$408	14.3	4.7
Atypical + Typical Dual Therapy	$13,094,088	62,098	$211	7.4	2.4
Atypical Dual Therapy	$17,772,695	67,706	$263	9.2	3.0
Standard-Dose Atypical Monotherapy	$81,900,092	945,387	$87	3.0	1.0
High-Dose Atypical Monotherapy	$12,310,032	26,010	$473	16.6	5.5
Standard-Dose Clozapine Monotherapy*	$7,561	40	$189	6.6	2.2
High-Dose Clozapine Monotherapy*	$903	3	$301	10.6	3.5
Injectable Atypical + Oral Atypical Dual Therapy	$5,527,817	7,655	$722	25.4	8.3
Injectable Atypical + Typical Dual Therapy	$532,631	904	$589	20.7	6.8
Standard-Dose Injectable Atypical Monotherapy	$4,776,922	14,663	$326	11.5	3.8
High-Dose Injectable Atypical Monotherapy	$1,195,070	3,206	$373	13.1	4.3
Typical Dual Therapy	$554,284	8,361	$66	2.3	0.8
Typical Monotherapy (any dose)	$3,188,663	112,157	$28	1.0	0.3
Total	**$145,151,845**	**1,258,712**	**$115**	**4.1**	**1.3**

* Small sample sizes. Results should be interpreted with caution.

APPENDIX 5: COST OF THERAPIES COMPARED USING PRIVATELY FUNDED DRUG PLANS DATA, ALL PATIENTS

All Patients — Expenditure, Active Months, and Mean Cost per Active Month; Privately Funded Drug Plans, 2009					
Type of Therapy	**Expenditure**	**Active Months**	**Mean Cost per Active Month**	**Ratio of Mean Cost per Month Relative to Typical Monotherapy**	**Ratio of Mean Cost per Month Relative to Atypical Monotherapy**
> 3 Molecules	$778,395	1,878	$414	24.9	5.2
Atypical + Typical Dual Therapy	$2,109,319	13,230	$159	9.6	2.0
Atypical Dual Therapy	$5,378,459	23,620	$228	13.7	2.8
Standard-Dose Atypical Monotherapy	$47,334,352	588,435	$80	4.8	1.0
High-Dose Atypical Monotherapy	$2,589,666	5,653	$458	27.5	5.7
Clozapine + Atypical Dual Therapy	$193,247	485	$398	23.9	5.0
Clozapine + Typical Dual Therapy	$124,661	299	$417	25.0	5.2
Standard-Dose Clozapine Monotherapy	$1,086,849	3,738	$291	17.4	3.6
High-Dose Clozapine Monotherapy*	$27,597	37	$746	44.7	9.3
Injectable Atypical + Clozapine Therapy*	$23,154	27	$858	51.4	10.7
Injectable Atypical + Oral Atypical Dual Therapy	$614,179	1,077	$570	34.2	7.1
Injectable Atypical + Typical Dual Therapy	$61,789	127	$487	29.2	6.0
Standard-Dose Injectable Atypical Monotherapy	$882,570	5,442	$162	9.7	2.0
High-Dose Injectable Atypical Monotherapy	$241,907	645	$375	22.5	4.7
Typical Dual Therapy	$45,468	1,194	$38	2.3	0.5
Typical Monotherapy (any dose)	$828,439	49,691	$17	1.0	0.2
Total	**$62,320,053**	**695,578**	**$90**	**5.4**	**1.1**

* Small sample sizes. Results should be interpreted with caution.

APPENDIX 6: COST OF THERAPIES COMPARED USING ONTARIO PUBLIC DRUG PROGRAMS DATA, PATIENTS WITH SCHIZOPHRENIA

Patients with Inferred Diagnosis of Schizophrenia — Expenditure, Active Months, and Mean Cost per Active Month, Ontario Public Drug Programs, 2009					
Type of Therapy	**Expenditure**	**Active Months**	**Mean Cost per Active Month**	**Ratio of Mean Cost per Month Relative to Typical Monotherapy**	**Ratio of Mean Cost per Month Relative to Atypical Monotherapy**
> 3 Molecules	$1,634,933	3,923	$417	5.8	3.0
Atypical + Typical Dual Therapy	$5,235,318	22,947	$228	3.2	1.6
Atypical Dual Therapy	$6,054,009	19,610	$309	4.3	2.2
Standard-Dose Atypical Monotherapy	$25,434,067	180,344	$141	2.0	1.0
High-Dose Atypical Monotherapy	$5,163,836	10,726	$481	6.7	3.4
Standard-Dose Clozapine Monotherapy	$3,713	11	$338*	4.7	2.4
High-Dose Clozapine Monotherapy	NA	NA	NA	NA	NA
Injectable Atypical + Oral Atypical Dual Therapy	$2,203,679	2,928	$753	10.4	5.3
Injectable Atypical + Typical Dual Therapy	$219,382	359	$611	8.5	4.3
Standard-Dose Injectable Atypical Monotherapy	$2,608,662	5,183	$503	7.0	3.6
High-Dose Injectable Atypical Monotherapy	$491,904	882	$558	7.7	4.0
Typical Dual Therapy	$296,867	4,119	$72	1.0	0.5
Typical Monotherapy (any dose)	$1,413,156	38,969	$36	0.5	0.3
Total	**$50,759,525**	**290,001**	**$175**	**2.4**	**1.2**

NA = not applicable.
* Small sample sizes. Results should be interpreted with caution.

APPENDIX 7: COST OF THERAPIES COMPARED USING PRIVATELY FUNDED DRUG PLANS DATA, PATIENTS WITH SCHIZOPHRENIA

Patients with Inferred Diagnosis of Schizophrenia — Expenditure, Active Months, and Mean Cost per Active Month; Privately Funded Drug Plans, 2009					
Type of Therapy	**Expenditure**	**Active Months**	**Mean Cost per Active Month**	**Ratio of Mean Cost per Month Relative to Typical Monotherapy**	**Ratio of Mean Cost per Month Relative to Atypical Monotherapy**
> 3 Molecules	$234,343	608	$385	21.0	4.3
Atypical + Typical Dual Therapy	$752,352	4,532	$166	9.0	1.8
Atypical Dual Therapy	$1,397,477	6,257	$223	12.2	2.5
Standard-Dose Atypical Monotherapy	$14,732,429	164,076	$90	4.9	1.0
High-Dose Atypical Monotherapy	$756,473	1,711	$442	24.1	4.9
Clozapine + Atypical Dual Therapy	$126,708	314	$404	22.0	4.5
Clozapine + Typical Dual Therapy	$39,417	121	$326	17.8	3.6
Standard-Dose Clozapine Monotherapy	$593,137	1,902	$312	17.0	3.5
High-Dose Clozapine Monotherapy	$11,770	16	$736*	40.1	8.2
Injectable Atypical + Clozapine Therapy	$3,180	2	$1,590*	86.7	17.7
Injectable Atypical + Oral Atypical Dual Therapy	$282,923	455	$622	33.9	6.9
Injectable Atypical + Typical Dual Therapy	$41,455	68	$610	33.2	6.8
Standard-Dose Injectable Atypical Monotherapy	$414,908	1,147	$362	19.7	4.0
High-Dose Injectable Atypical Monotherapy	$98,612	218	$452	24.7	5.0
Typical Dual Therapy	$23,109	534	$43	2.4	0.5
Typical Monotherapy (any dose)	$405,509	22,104	$18	1.0	0.2
Total	**$19,913,803**	**204,065**	**$98**	**5.3**	**1.1**

* Small sample sizes. Results should be interpreted with caution.

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