Utilization of Antipsychotic Medications in the Youth Population of Manitoba: 1996-2011

by

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Abstract

Objectives: Serious safety concerns have been raised recently about the use of antipsychotic medications in young patients, particularly in regard to the second generation agents (SGAs), such as risperidone, olanzapine and quetiapine. This study aims to describe the utilization of antipsychotics in the youth population of the Canadian province of Manitoba (MB) over a period of 15 years and determine incidence of adverse events (i.e., diabetes, hypertension, and extrapyramidal syndromes - EPS) associated with antipsychotic therapies. An additional objective was to evaluate school enrolment and high school completion rates for young people receiving antipsychotic pharmacotherapy.

Methods: This population-based study was conducted using the databases from the Population Health Research Data Repository, housed at the Manitoba Centre of Health Policy. All young residents of MB (age ≤ 19 years), who received antipsychotic prescriptions between April 1, 1996 and March 31, 2011 were included in the study. Prevalence and incidence rates of antipsychotic use were calculated for this population. Cohorts (April 1, 1996 – March 31, 2010) were constructed to compare the incidence of adverse events for those prescribed risperidone, olanzapine or quetiapine therapy. Cox proportional hazards models were used for the analyses. School enrolment age and high school graduation rates were also calculated for this population. SAS® statistical software was used for the analyses.

Results: The prevalence of SGA use in the youth population of MB increased from 2.3 to 9 per 1,000 persons between 2001 and 2011, while the incidence increased from 1.2 to 2.7 per 1,000. Incidence rates were higher in males (0.8 to 1.5 per 1,000) than in females (0.3 to 1.1 per 1,000). The highest level of use was observed in the13-19 year group (49.4%). Risperidone was the most prescribed agent (65.2%) followed by quetiapine (19.6%) and olanzapine (7.4%). The most common diagnosis recorded in the study population was Attention Deficit Hyperactivity Disorder (56.8%) followed by Conduct Disorders (38%) and Mood Disorders (22.7%). Diabetes (2%) hypertension (2%) and EPS (1%) were reported for incident users. No meaningful comparisons could be conducted for diabetes because of the limited numbers of cases observed. The risk of hypertension was higher in olanzapine users compared to risperidone users (HR: 2.52, 95% CI: 1.20 – 5.29); however, there was no significant ($p < .05$) difference in risk of hypertension between risperidone and quetiapine users (HR: 1.50, 95% CI: 0.77 – 2.90). No significant difference was detected in the risk of EPS in patients prescribed risperidone and olanzapine (HR: 0.75, 95% CI: 0.42 – 1.34); however, those taking risperidone had a significantly higher risk of EPS compared to the quetiapine group (HR: 0.46, 95% CI: 0.26 – 0.82). School enrolment records showed that 82% of children

undergoing antipsychotic therapy enrolled to grade 1 at the age of 5-7 years, and 66% of all those attending high school had completed their education by the age of 17-19 years.

Conclusions: Increased utilization of SGAs was observed in the youth population of MB over the study period. Incidence of diabetes, hypertension and EPS were recorded following the first antipsychotic prescription in this population. Olanzapine therapy seemed to be associated with a higher risk of hypertension compared to risperidone users. Risperidone users seemed to be at higher risk of EPS than quetiapine users. School enrolment of SGAs users appeared to be comparable to those reported for the general population. High school completion rates may be lower than those of the general population.

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THIS THESIS IS DEDICATED TO

MY PARENTS

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List of Abbreviations

ABC - Aberrant Behavior Checklist

ADHD – Attention Deficit Hyperactivity Disorder

AE – Adverse Event

ASD – Autism Spectrum Disorder

BD – Bipolar Disorders

BPRS - Brief Psychiatric Rating Scale

CD – Conduct Disorder

CGI - Clinical Global Impression

CDRS - Children Depression Rating Scale

DIN – Drug Identification Number

DPIN - Drug Program Information Network

DSM – Diagnostic and Statistical Manual of Mental Disorders

EOS – Early Onset Schizophrenia

EPS - Extrapyramidal Syndromes

FGA – First Generation Antipsychotic

GAS - Global Assessment Scale

GP – General Practitioner

HAM-A - Hamilton Anxiety Rating Scale

HR – Hazard Ratio

ICD – International Classification of Disease

MB - Manitoba

MCHP – Manitoba Centre for Health Policy

ODD – Oppositional Defiant Disorder

PANSS - Positive And Negative Syndrome Scale

RAAP - Rating of Aggression Against People and/or Property

RCT – Randomized Controlled Trial

SCRPHIN – Scrambled Personal Health Identification Number

SGA – Second Generation Antipsychotic

VEOS – Very Early Onset Schizophrenia

YMRS - Young Mania Rating Scale

INTRODUCTION

Use of antipsychotic agents in children and adolescents

Antipsychotic medications, developed for the treatment of schizophrenia, can be broadly classified into first-generation agents (FGAs) and second-generation agents (SGAs). Chlorpromazine, the first of the FGAs, was discovered in 1950, and was followed by haloperidol in 1958. Chlorpromazine is a low potency D_2 receptor antagonist whereas haloperidol is a highly potent D_2 receptor antagonist that is 50 times more potent than chlorpromazine (Goodman & Gilman's, 2010, page: 427). The discovery of these drugs led to the development of other antipsychotics with varying chemical structures that were classified as phenothiazines (e.g., chlorpromazine, perphenazine), butyrophenones (e.g., haloperidol), thioxanthenes (flupenthixol, zuclopenthixol) and dibenzoxazepines (loxapine). These medications differ in potency, but share the common mechanism of dopamine D_2 receptor blockade, which has the favourable effect of controlling the positive symptoms of psychoses (e.g., delusions, hallucinations) (Goodman & Gilman's, 2010, page: 429 - 431). However, their pharmacological activity can potentially lead to undesirable effects such as extrapyramidal symptoms (EPS, pseudoparkinsonism, acute dystonic reactions, akathisia, tardive dyskinesia), cardiovascular events (e.g., postural hypotension, tachycardia, dizziness, arrhythmias), anticholinergic effects (e.g., constipation, xerostomia, blurred vision, urinary retention), and sedation (Jerrell et al.(a), 2008; Jerrell et al.(b), 2008; Correll et al., 2009; Caccia et al., 2011; Cohen et al., 2012). EPS are reported to be the most common adverse events associated with the use of FGAs,

and because of their severity resulted in low treatment compliance and highlighted the need for more tolerable antipsychotics.

The discovery of the first FGA and first SGA took place within the same decade. Clozapine, considered to be the first SGA, was discovered in 1958 and was not initially recognized as an antipsychotic agent (structurally similar to the tricyclic antidepressant imipramine) until later clinical trials confirmed it to be an effective antipsychotic, devoid of disabling neurological side effects (Hippius, 1989). Since clozapine lacked common side effects associated with "typical" antipsychotics (i.e., EPS), it was termed "atypical" (Hippius, 1989; Shen, 1999). Unfortunately, treatment with clozapine was found to result in agranulocytosis in some patients. Agranulocytosis, which is defined by an absolute neutrophil count lower than 0.5×10^9/L, is a life threatening condition that resulted in the death of 8 patients in 1974, and consequently to the withdrawal of clozapine from the European market (Hippius, 1989). Clozapine was not approved in North America until the 1990s, when its efficacy in treatment-resistant schizophrenia was demonstrated (Crilly, 2007). In Canada, clozapine was approved in 1991, but restricted to treatment-resistant schizophrenia, a condition generally defined as not responsive to treatment with at least two antipsychotics other than clozapine (Clozaril Product Monograph, Health Canada, 2013). In randomized, double-blind, comparative trials, the efficacy of clozapine was demonstrated to be superior to that of various antipsychotic agents in patients who had failed to respond to previous FGA or SGA treatment (Lerner et al, 2004; Wolff-Menzler et al, 2010). Other drugs (risperidone, olanzapine, ziprasidone, paliperidone, quetiapine and aripiprazole) were developed in the 1990s with the intent of reproducing clozapine efficacy without the risk of agranulocytosis.

SGAs have been studied in adult populations for the treatment of schizophrenia and bipolar disorder (Kando et al., 1997; Davies et al., 2004; Thomas et al., 2009; Citrome, 2012), and more recently in the elderly (> 65 years of age) for the control of behavioural disturbances in dementia (Lee et al., 2004; Tariot, 2004; Chan et al., 2011).

Children and adolescents have historically been excluded from clinical trials for ethical reasons. Consent to participate in the trial is one of the major issues that introduce challenges, as children cannot give their own consent and it has to come through parents. Ethical principles also define regulations imposed by government that restrict studies that involve risks for healthy subjects who cannot directly benefit by the participation in such studies (USFDA, 2011; Field et al., 2004): this is particularly important in children. Therefore, the safety and efficacy of antipsychotic drugs have not been systematically assessed in young populations; nevertheless, recent reports have demonstrated a widespread off-label utilization of SGAs in children and adolescents worldwide (Olfson et al, 2006; Correll et al, 2006; Thomson et al, 2007; Stachnik et al, 2007; Crystal et al, 2009; Rani et al.,2008; Chen et al,2009; Malone et al, 2009(b); Verdoux et al., 2010; Alessi-Severini et al., 2012; Ronsley et al., 2013; Olfson et al., 2012).

Diagnoses reported in pediatric populations treated with SGAs include schizophrenia, bipolar disorders (BD), autism and Attention Deficit-Hyperactivity Disorder (ADHD), as well as non-psychotic conditions such as anxiety and behavioural disorders including mood and conduct disorders (CD) (Olfson et al, 2006; Vitiello et al., 2009; Patten et al, 2012). However, most health agencies have not approved such indications in children and adolescents (Vitiello et al., 2009; Verdoux et al., 2010; Patten et al., 2012; Murphy et al., 2013). In particular, the Health Canada official product monographs of all antipsychotic

agents clearly states that "the safety and efficacy of these agents in children under the age of 18 have not been established"; the only exception is aripiprazole, which was approved in 2011 to the treatment of adolescents with schizophrenia (15-17 years of age) or with a manic or mixed episode of bipolar I disorder (13-17 years of age) (Health Canada, 2011). In the US, both risperidone and aripiprazole have been approved for the treatment of adolescents (13-17 years) with schizophrenia and of 10-17 year-olds with bipolar mania or mixed episodes. Risperidone is also approved in the US for the treatment of aggression associated with autism in children and adolescents (5-17 years).

The number of physician visits by children and adolescents that resulted on the prescription of an antipsychotic increased 6-fold in the US (from 201,000 to 1,224,000) between 1993 and 2002 (Olfson et al, 2006), while in the UK the overall prevalence increased almost 2-fold from (0.39 to 0.77 per 1,000) between 1992 and 2005 (Rani et al., 2008). Few population-based studies have been conducted in Canada on the utilization of antipsychotic medication in children and adolescents. A study conducted on children and adolescents in British Columbia (BC) reported a 3.8 fold increase (1.66 to 6.37 per 1,000 population) in the overall antipsychotic (both FGA and SGA) prescription prevalence between 1996 and 2011, whereas prescriptions for SGAs increased 18.1-fold (0.33 to 5.98 per 1,000 population) during the same period (Ronsley et al., 201). A study conducted in Manitoba (MB) using the Manitoba Population Health Research Data Repository (MPHRDR) determined that prevalence of antipsychotic use in the youth population (aged 18 years or younger) had increased 4 fold (from 1.9 per 1,000 to 7.4 per 1,000) between 1999 and 2008. The most common diagnoses associated with antipsychotic use are ADHD (5.2 per 1,000) and CDs (3.8 per 1,000); other diagnoses

include schizophrenia, autism, mood disorders and tics (Alessi-Severini et al, 2012). Another Canadian study used IMS Brogan databases to estimate the prescription of antipsychotics in the 17-year and younger age group. The most common reasons for SGA recommendations were for ADHD (17%), mood disorder (16%), CD (14%), and psychotic disorder (13%) (Pringsheim et al., 2011(b)). The majority of the recommendations identified were for SGAs (95%), with risperidone being the most common recommendation. The majority of recommendations were by psychiatrists (62%). Another study by Murphy et al. 2013, characterized antipsychotic prescriptions in low-income youth of the province of Nova Scotia. This study also showed that the use of SGAs had significantly increased in patients from 6 to 25 years of age. Most of the youth (66%) filling antipsychotic prescriptions had 2 or more psychiatric diagnosis. Psychotic disorders were the most common indication for the use of antipsychotics in this study; except for risperidone, which was more commonly prescribed for ADHD. Antipsychotic medications were more commonly prescribed by general practitioners (GP) (72%) followed by psychiatrists (16%) in this study. Moreover, the study highlighted that the age-and sex-adjusted rates of death were higher among those receiving an antipsychotic in comparison to the general population of Nova Scotia (Murphy et al., 2013).

Early onset schizophrenia

The onset of schizophrenia before the age of 18 years is defined as Early Onset Schizophrenia (EOS) (Helgeland et al., 2005; American Academy of Child and Adolescent Psychiatry, 2001). Very Early Onset Schizophrenia (VEOS), or Childhood Onset Schizophrenia (COS), has also been recognized in patients before the age of 13 years (Clemmemsen et al., 2012). EOS was not recognized in the diagnostic system

until the introduction of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III. In the DSM-II the category of childhood schizophrenia was not distinguished from autism, instead it was considered as a manifestation of autism. However, study by Kolvin (1971) clarified that schizophrenia in children had to be differentiated from autistic disorders. Since the introduction of the DSM-III, schizophrenia in children has been defined using the same criteria for adults based on the presence of positive (i.e., hallucinations, delusions, racing thoughts), negative (i.e., apathy, lack of emotion, poor or non-existent social functioning), and cognitive symptoms (i.e., disorganized thoughts, difficulty concentrating and/or following instructions, difficulty completing tasks, and memory problems) (Kolvin, 1971; Asarnow et al., 2004; Clemmemsen et al., 2012). The same diagnostic criteria are outlined in the current DSM-V, which requires that two or more characteristic symptoms (i.e., hallucinations, delusions, disorganized or catatonic behaviour, and/or negative symptoms) be present for at least one month (or less if successfully treated) (American Psychiatric Association, 2013).

While clinical research in children has been historically limited, things have started to change and several RCTs have recently been conducted to evaluate the safety and efficacy of SGAs in children and adolescents affected by schizophrenia (Kumra et al., 2008; Findling et al., 2008; Kryzhanovskaya et al., 2009; Haas et al., 2009; Findling et al., 2013 (a)). Please refer to Table 1 for details.

Table 1: Randomized controlled trials of SGAs in children and adolescent diagnosed with schizophrenia

Source	No. of patients/Age/ Length of study	Intervention	Results	Adverse events
Kumra et al., 2008	39/10-18 yrs/ 12 weeks	Clozapine (300 mg/day) olanzapine (up to 30mg/day)	Response criteria: 30% or more decrease in total BPRS score from baseline and a CGI scale of 1 (very much improved) or 2 (much improved). 66% patients in the clozapine-treated group met the response criteria whereas only 33% met response criteria in the olanzapine-treated patients.	Weight gain (13%) and metabolic abnormalities were major problems associated with both the treatments. 13% subject gained >7% of baseline body weight (clozapine: n=3; olanzapine: n=2) in the treated groups. 0.96% decrease in cholesterol level for clozapine and 7.43% increase in cholesterol level was observed in olanzapine group.
Findling et al., 2008	302/13-17 yrs/6weeks	Aripiprazole (10 or 30mg/day)	Treatment with 10 and 30mg/day resulted in significant improvement from baseline at the end of treatment on PANSS total score (-26.7 for 10mg/day, -28.6 for 30mg/day) in comparison to placebo (-21.2), on PANSS	Most common adverse events associated with aripiprazole were EPS (10mg: 13%; 30mg: 22%), somnolence (10mg: 11%; 30mg: 22%), and tremor (10mg: 2%; 30mg: 12%).

			positive symptom subscale, dose of 10mg/day improved the score by 7.6 while 30mg/day improved by 8.1 compared to placebo (-5.6). 10mg/day dose improved CGAS score by 14.7 while the 30mg/day improved it by 14.8 compared to placebo (9.8).	
Kryzhanovskaya et al., 2009	107/13-17 yrs/6 weeks	Olanzapine (2.5-20mg/day)	Olanzapine-treated adolescents had significantly greater improvement from baseline compared to the placebo-treated group in BPRS total score (Olz: -19.4 vs. placebo: -9.3; p =0.003), CGI-Severity of Illness (Olz: -1.1 vs. placebo: -0.5; p =0.004), PANSS total (Olz: -21.3 vs. placebo:-8.8; p =0.005), and PANSS positive scores (Olz: -6.6 vs. placebo: -2.7; p =0.002).	Significant increases in weight (Olz: 4.3 vs. placebo: 0.1 Kg), triglycerides (Olz: 41.6 vs. placebo: 4.4 mg/dl), uric acid (Olz: 32.7 vs. placebo: -5.7 μmol/L), most liver function tests, and prolactin (Olz: 8.8 vs. placebo: -3.3 μg/L) were observed during olanzapine treatment.
Haas et al., 2009	160/10-17 yrs/6	Risperidone (1-	Significant	Risperidone 4-6 mg/day had a

	weeks	3mg or 4-6mg/day)	improvements occurred in both risperidone groups versus placebo ($p < 0.001$) in PANSS total change scores (placebo, -8.9 [16.1]; risperidone 1-3 mg, -21.3 [19.6]; risperidone 4-6 mg, -21.2 [18.3]) and in clinical response rates (35%, 65%, 72%, respectively).	higher incidence of EPS (16% vs. 9%), dizziness (14% vs. 7%), and hypertonia (14% vs. 5%) than risperidone 1-3 mg/day.
Findling et al., 2013 (a)	283/13-17 yrs/ 32 weeks	Ziprasidone (40-160 mg/day); placebo	During 6 weeks of RCT period ziprasidone (-14.16 ± 0.78) was comparable to placebo (-12.35 ± 1.05) on BPRS-A scale.	The most common treatment emergent adverse events were somnolence, EPS.

*****The rating scales used in above trials are described in Appendix 1.

Bipolar disorders

Bipolar disorders (BD) are characterized by depressive and maniac episodes, and child-onset and adolescent-onset BD sometimes have more severe prognoses than adult-onset BD; generally because of longer delays in the initiation of treatment (Leverich et al., 2007). Bipolar illness in children is not identified before many years of psychopathology due to the lack of characteristic episodes seen in adult BD. Another reason that prevents early identification of BD in children is the presence of overlapping symptoms with other childhood psychotic disorders such as ADHD or major depressive disorders (Leverich et al., 2007).

According to the World Health Organization's (WHO) Global Burden of Disease study (Gore et al., 2011), BD was the fourth leading cause of disability among adolescents (15 to 19 years) worldwide, accounting for 5% of total disability in this age range (Gore et al., 2011). In recent years, there has been progress in the pharmacological treatment of BD and several RCTs have been conducted in BD children and adolescents using SGA monotherapy or combination therapy SGAs and mood stabilizers (Delbello et al., 2006; Tohen et al., 2007; Haas et al., 2009; Pavuluri et al., 2010; Findling et al., 2013 (b); Pathak et al., 2013). Findings from these RCTs are described in Table 2.

Table 2: Randomized controlled trials of SGAs in children and adolescent diagnosed with Bipolar Disorder

Source	No. of patients/ Age/Length of study	Intervention	Results	Adverse events
Delbello et al., 2006	50/12-18 yrs/ 28 days	Quetiapine: 400-600 mg/day; Divalproex: 80-120 μg/ml	Change in YMRS score between the two treatment groups was 3.3 (statistically non significant; 95% CI: -3.5 to 10.1). Similarly CDRS and PANSS-P score differences among the two treatment groups were, 1.6 and 3.5 respectively, statistically non-significant. However, each treatment group improved YMRS, CDRS and PANSS-P scores significantly at the end of study from their baseline values.	Safety profile of both quetiapine and divalproex were found to be similar. Most common side effects were sedation (quetiapine:15 vs divalproex:9), dizziness (quetiapine:9 vs divalproex:9) and gastrointestinal upset (quitiapine:6 vs divalproex:7).
Tohen et al., 2007	161/13-17 yrs/3 weeks	Olanzapine (2.5-20mg/day); placebo	Significant improvement in YMRS was observed with patients receiving olanzapine. Significantly greater proportion of patients treated with olanzapine met the response and remission criteria compared to placebo (44.8% vs. 18.5% and 35.2% vs. 11.2% respectively).	Olanzapine was associated with significant weight gains (7 % increase over baseline). Olanzapine was also associated with significant changes in prolactin, fasting glucose, fasting total cholesterol, uric acid and hepatic enzymes.
Haas et al., 2009	169/10-17 yrs/3 weeks	Risperidone (0.5-2.5 or 3-6 mg/day)	Significant improvement in YMRS was observed with risperidone (mean change: -	Adverse effects associated with the higher dose of risperidone were

			18.5±9.7 for the 0.5-2.5mg/day dose; -16.5±10.3 for the 3-6mg/day dose) treatment in comparison to placebo (mean change: -9.1±11.0).	EPS (25%), prolactin level elevation (males: +23%; females: +49%) and weight gain (10%).
Pavuluri et al., 2010	66/8-18 yrs/ 6 weeks	Risperidone: 0.5-2.5 mg/day; Divalproex: 60-120 μg/ml	In comparison to divalproex, risperidone had significantly better response rate (78.1 % vs. 45.5 %) and remission rate (62.5% vs. 33.3 %) on YMRS.	Subject retention was significantly higher in the risperidone group (dropout: 24%) in comparison to divalproex (dropout: 48%). Increased irritability was the cause for dropout in the divalproex group.
Findling et al., 2013 (b)	296/10-17 yrs/ 30 weeks	Aripiprazole (10 or 30mg/day); placebo	Discontinuation rates due to lack of efficacy were significantly lower in both aripiprazole doses (10mg/day: 22.7%, 30 mg/day: 14.1%) in comparison to placebo (48.4%). Both aripiprazole doses were significantly superior to placebo regarding response rates (10mg: 58.7%; 30mg: 64.8%; placebo: 29.7%), CGA-F (10mg: 22.1; 30 mg: 24.3; placebo: 13.4) and CGI-Bipolar severity of overall (10mg: -2.3; 30 mg: -2.5; placebo: -1.7) at endpoint in all analyses	Commonly reported adverse events included headache (24-27%), somnolence (28%), and EPS (13-25%).
Pathak et al.,	277/ 10-17 yrs/	Quetiapine (400 or	Both doses (400mg: -14.25,	Mean change in body weight

2013	3 weeks	600 mg/day); placebo	600mg: -15.60) of quetiapine significantly improved the YMRS score over placebo (-9.04).	with quetiapine was 1.7 kg in comparison to placebo (0.4 kg).

*****The rating scales used in above trials are described in Appendix 1.

Autism

Autism and related Pervasive Developmental Disorders (PDD), also known as Autism Spectrum Disorder (ASD) are characterized by a lack of social and communication skills, lack of interests, and repetitive/stereotyped patterns of behaviour. Children with autism often display irritability aggression and disruptive behaviours including tantrums and self-injurious behaviour. According to the DSM-V, individuals with ASD show symptoms from early childhood even if sometimes those symptoms are not recognized until later. While educational and behavioural interventions are often considered for the core symptoms of autism, irritability and aggression associated with autism are often treated with SGAs (McDougle et al., 2008). Among the SGAs, risperidone and aripiprazole are the most thoroughly investigated agents for this condition in pediatric populations, and have demonstrated efficacy in several RCTs (Masi et al., 2001; Malone et al., 2002 (a); McCracken et al., 2002; Shea et al., 2004; Anderson et al., 2007; Marcus et al., 2009; Owen et al., 2009). The Food and Drug Administration (FDA) in the US has approved risperidone (2007) and aripiprazole (2009) for the treatment of irritability associated with autism in children and adolescents. Please refer to Table 3 for details.

Table 3: Randomized controlled trials of SGAs in children and adolescent diagnosed with Autism

Source	No. of patients/ Age/Length of study	Intervention	Results	Adverse events
Masi et al., 2001	24/ 3.6-6.6 yrs/ 16 weeks	Risperidone (0.5 mg/day)	Risperidone monotherapy resulted in a 21% improvement in CPRS and 14% in CARS total scores from baseline. CGAS improved by over 25% with risperidone therapy.	Out of 24, 13 children were free of any side effects. Only 3 had a weight gain over 10%.
McCracken et al., 2002	101/5-17 yrs/8 weeks	Risperidone (0.5-3.5 mg/day); placebo	56.9% reduction in the irritability score in comparison to 14.1% decrease in the placebo group.	Risperidone therapy was associated with an average weight gain of 2.7±2.9 kg, as compared with 0.8±2.2 kg with placebo ($P<0.001$).
Shea et al., 2004	80/ 5-12 yrs/ 8 weeks	Risperidone (0.01-0.06 mg/kg/day)	At the dose of 0.04 mg/kg/day risperidone-treated patients showed a 64% improvement over baseline in the irritability score compared to placebo (31%). 87% children on children showed	Most frequent adverse events were somnolence (72.5% vs. 7.7%), weight gain (2.7 vs. 1.0 kg) compared to placebo.

			global improvement in their condition compared to placebo (40%).	
Owen et al., 2009	98/6-17 yrs/ 8 weeks	Aripiprazole (5, 10 or 15 mg/day); placebo	Aripiprazole significantly improved ABC irritability subscale (aripiprazole -12.9 vs placebo -5.0) score and CGI-I (aripiprazole 2.2 vs placebo 3.6).	Aripiprazole was associated with EPS (14.9%) and weight gain (2kgs).
Marcus et al., 2009	218/6-17 yrs/8 weeks	Aripiprazole (5, 10 or 15 mg/day); placebo	All aripiprazole doses produced a significantly greater improvement than placebo in mean ABC Irritability subscale scores (5 mg/day, -12.4; 10 mg/day, -13.2; 15 mg/day, -14.4; versus placebo, -8.4; all $p < .05$)	Sedation was the most common adverse event leading to discontinuation (placebo 7.7%, aripiprazole 5 mg/day 9.4%, 10 mg/day 13.6%, and 15 mg/day 7.4%).
Findling et al., 2014	85/6 – 17 yrs/15 months	Aripiprazole (2-15 mg/day); placebo	Time for the relapse of irritability associated with AD was not significantly different between aripiprazole and placebo groups. At 16 weeks Kaplan-Meier relapse rate HR for	During phase I (single blind stabilization, 13-26 weeks), the most common adverse events of aripiprazole in comparison to placebo were weight gain (25.2%), somnolence (14.8%)

	aripiprazole and placebo was 0.57.	and vomiting (14.2%). During phase II (double-blind randomization, 16 weeks), adverse events in aripiprazole group were respiratory tract infections (10.3%), movement disorder (5.1%).

*****The rating scales used in above trials are described in Appendix 1.

Attention deficit hyperactivity disorder and disruptive behavioural disorders

Literature reviews have reported highly variable prevalence of ADHD worldwide, ranging from values as low as 1% to as high as 20% among school-age children (Faraone et al., 2003; Polanczyk et al., 2007). Individuals with ADHD often suffer from comorbid conditions such as oppositional defiant disorder (ODD) and conduct disorder (CD), major depressive disorder, anxiety disorders, bipolar disorder and tic disorders. Almost 50% of children diagnosed with ADHD meet the criteria for either ODD or CD; however, almost 100% of children under the age of 12 years who meet the criteria for ODD or CD, also meet the criteria for ADHD (Pliszka et al, 2003). ADHD is generally treated with stimulants; however, children with ADHD/CD and severe aggressive outbursts are normally treated with stimulants and SGAs. Several RCTs evaluating the efficacy and safety of SGAs in ADHD are summarized in Table 4.

Table 4: Randomized controlled trials of SGAs in children and adolescent diagnosed with ADHD

Source	No. of patients/Age/ Length of study	Intervention	Results	Adverse events
Findling et al., 2000	20/ 5-15 yrs/10 weeks	Risperidone 1.5-3 mg/day	At 10 weeks, the RAAP score difference from baseline for risperidone users (-1.65 ± 0.40) was significantly lower than that for the placebo group (-0.16 ± 0.54). CGI-S score difference from baseline was significantly lower in risperidone group (-2.58 ± 0.49) than placebo (-0.08 ± 0.66).	Risperidone was well tolerated as none of the users developed EPS.
Snyder et al., 2002	110/5-12 yrs/6 weeks	Risperidone 0.02 to 0.06 mg/kg per day	The risperidone-treated group showed significant ($p < .001$) reduction in mean scores on the conduct problem subscale (from 33.4 at baseline to 17.6 at end point; 47.3% reduction) compared to the placebo-treated subjects (mean baseline of 32.6 to 25.8 at end point; 20.9% reduction). CGI scale ratings of improvement	EPS were reported in 7 (13.2%) subjects in the risperidone group

			showed highly significant gains for risperidone (32%) over placebo (10%).	
Connor et al., 2008	19/12-17 yrs/ 7 weeks	Quetiapine (200-600mg/day)	Quetiapine was superior to placebo in all clinician assessed (CGI ≤ 2) measures and on the parent assessed quality of life rating scales (quetiapine treatment resulted in improvement of 11.3 units vs. a decline of 4 units with placebo)	One patient developed akathesia
Holzer et al., 2013	11/10-18 yrs/10-weeks	Atomoxetine and olanzapine	Combination therapy reduced the symptoms of ADHD by 33% on the ADHD rating scale and modified overt aggression scale; 73% patient responded to the therapy for ADHD and 55% responded for aggression.	Olanzapine treatment was associated with significant weight gain on an average of 3.9 kgs.

*****The rating scales used in above trials are described in Appendix 1.

Safety

RCTs have significantly improved our understanding of the efficacy of SGAs in young populations; however, RCTs (particularly in children) may not be the best source to evaluate safety issues of these agents. Most pediatric trials are small (in terms of length of study and number of subjects) and designed to address efficacy; as a consequence, (because they are often underpowered from a statistical perspective) they can rarely detect anticipated or unanticipated safety outcomes. Moreover, RCT populations often do not mirror the age, sex, and race distribution of the target patient population. The primary reasons for RCTs being underpowered include cost and difficulty in recruiting study subjects. However, observational studies usually sample from a much broader population and the assessment of safety in terms of detecting adverse events can be more effectively conducted (Hannan 2008).

Recent reviews have raised concerns regarding the use of SGAs in youth populations as they have been linked to metabolic and neurological side effects such as excessive weight gain and abnormalities in lipid and glucose metabolism, and EPS (Pringsheim et al., 2011(a); Pringsheim et al., 2011(c); Ho et al., 2011; Seida et al., 2012; Ben, 2012). The youth population may be more susceptible to SGA-related adverse events than adults because of pharmacokinetic differences (Correll et al., 2009). The age related pharmacokinetic differences include differences in absorption, distribution, metabolism and elimination of drug substances. For example, gastric pH, gastric emptying time, immaturity of secretion and activity of bile and pancreatic fluid impacts the absorption, while membrane permeability, plasma protein binding and total body water content affects both absorption and distribution of drugs. Further, differences in biochemical

characteristics (expression of CYP enzymes) in children affect metabolism and immaturity of glomerular filteration impacts the elimination of drugs in pediatric population (Fernandez et al., 2011). The risk of weight gain, increased BMI, and abnormal lipid levels in the youth population are greatest with olanzapine followed by clozapine and quetiapine (Correll et al, 2009). These adverse events predispose the youth population to future cardiometabolic risks such as diabetes, dyslipidemia and hypertension (Correll et al, 2009). Even though the risk of EPS is reduced with SGAs, it is not completely eliminated (Cohen et al, 2012; Caccia et al, 2011); the risk of neurological side effects is greatest with risperidone, followed by olanzapine and aripiprazole (Correll et al, 2009). Some of the observational studies highlighting adverse events associated with SGAs are summarized in Table 5.

Table 5: Observational studies of adverse events associated with SGAs

Study	Population/Design/Treatment	Assessment	Relevant Results	Conclusion
McIntyre et al., 2008	N= 8640 Mean Age: 10.4±3.6 years Retrospective cohort study evaluating Medicaid medical and pharmacy claims (Jan 1996 to Dec. 2005) 4140 children and adolescents prescribed 1 of 5 SGA (aripiprazole, ziprasidone, quetiapine, risperidone or olanzapine) or 2 FGAs (haloperidol, fluphenazine) compared to randomly selected 4500 children not treated with antipsychotic medication.	Incidence/Prevalence of obesity, type 2 diabetes mellitus, dyslipidemia, hypertension, CV events and orthostatic hypotension were measured. Multiple logistic regression was performed.	Adolescents in the treated cohort had higher incidence of obesity (OR 1.34; CI:1.09-1.66), type 2 diabetes mellitus (OR 1.52; CI:1.08-2.13), dyslipidemia (OR 2.08; CI:1.41-3.03), hypertension (OR 2.78; CI:1.69-4.55) and orthostatic hypotension (OR 1.47; CI:1.11-1.92). Patients exposed to multiple antipsychotics were at significantly higher risk for obesity, type 2 diabetes mellitus and dyslipidemia. Incidence of CV events was higher in patients on FGAs or multiple antipsychotics. Orthostatic hypotension was more prevalent in patients on SSRIs and mood	In comparison to untreated, treated adolescents were at higher risk of metabolic and CV adverse events.

			stabilizer compared to non-treated group.	
Panagiotopoulos et al., 2009	N=432 Mean age: SGA treated=13.7 ±2.7 years; SGA naive=13.9 ±2.8 years Drugs used: risperidone, quetiapine, olanzapine, clonazepam Retrospective chart-review conducted on all child and adolescent psychiatry emergency admissions over 2.5 years. Data included age, sex, psychiatric diagnosis, medications, height, weight, fasting glucose, and lipid profile.	BMI, fasting glucose, lipid profile (TC, triglycerides, TG, LDL, HDL)	The mean BMI was higher in the SGA-treated (n = 68), compared with the SGA-naive group (n = 99) (mean difference 0.81; 95% CI 0.46 to 1.16). In the SGA-treated group, 31% were obese and 26% were overweight, compared with 15% and 8%, respectively, in the SGA-naive group ($p < 0.01$). In the SGA-treated group (n = 65), 21.5% had type 2 diabetes, compared with 7.5% in the SGA-naive group (n = 80) ($p = 0.01$). SGA treated patients had higher TC (43.9 vs. 28.8), triglycerides (15.6 vs 6.6) and LDL (29.6 vs. 16.4) in comparison to SGA-naïve patients.	Youth treated with SGAs had significantly higher rates of obesity and glucose intolerance than SGA-naive youth. These data emphasize the need for consistent metabolic monitoring of youth with psychiatric disorders who are prescribed SGAs.
Moreno et al. , 2010	N=90 Mean age: 14.9± 3 years Drugs used: risperidone,	Weight and metabolic differences (TC, LDL,	Baseline weight and metabolic indices were not significantly	There were early weight gain and metabolic

	olanzapine, quetiapine Weight and metabolic differences among diagnostic groups before and three months after starting treatment with SGAs were compared in a naturalistic cohort of children and adolescents (14.9 +/- 3.0 years) diagnosed with bipolar disorder (n = 31), other psychotic disorders (n = 29), and other nonpsychotic disorders (n = 30), with no (35.6%) or very little (6.6 +/- 9.0 days) previous exposure to antipsychotics.	triglycerides, fasting glucose, T4)	different among diagnoses. Three months after starting treatment with SGAs, more than 70% patients had significant weight gain, BMI increased in all diagnostic groups (54.2 %, $p < 0.001$ for all comparisons). Increase in TC (156.6± 27.9 mg/dl), LDL cholesterol (86.7± 24.1 mg/dl) in the SGA group in comparison to baseline. SGA use was associated with decrease in free T4 by 0.4 ng/dl.	changes across diagnoses in youth treated with SGAs compared to the respective baseline values.
Andrade et al., 2011	N=9636 Age: 5-18 years Drugs used: risperidone, olanzapine, quetiapine, aripiprazole, clozapine, ziprasidone Retrospective cohort study on children who initiated SGA therapy between Jan 2001 and Dec 2008.	Outcome= incident diabetes. Use of SGAs and risk of was assessed. Incident rates were calculated with 95% CI. Multivariate Poisson distribution was used to estimate strength of association between SGA use and onset of DM. Propensity	Crude incidence rate of DM for SGA exposed cohort was 3.23 cases per 1,000 person-years (CI 1.67-5.65), compared to 0.76 cases per 1,000 person-yrs (CI 0.49-1.12) among non-users and 1.86 cases per 1,000 person-yrs (CI: 1.12-2.90) among antidepressants users.	SGA exposed children had 4-fold higher rate of diabetes in comparison to unexposed children. However, in comparison to children exposed to antidepressant medications there was no

		score method was used to match SGA users to non-user group and antidepressant user (2 comparison groups).	Unadjusted incidence rate ratio of diabetes among SGA users was 4.24 (CI: 1.95-8.72) in comparison to non-users. In comparison to antidepressant users unadjusted incident rate ratio of diabetes among SGA users was 1.74 (CI:0.77-3.78).	statistically significant increase in diabetes rates in SGA-exposed children.
Pringsheim et al., 2011(b)	N=4,40,776 Age: 1-18 years Population based study evaluating IMS and Canadian Disease and Therapeutic Index database (2005-2009)	Prescribed drug frequency, reason for recommendation of drug and duration of use of antipsychotics, psychostimulants and selective SSRIs were measured using descriptive statistics	Antipsychotic drug recommendations for children increased by 114%. The majority of recommendations were for SGAs and ADHD was the most common cause for SGA recommendation. The median duration for the use of risperidone was 90 days (age 1 -6 yrs), 180 days (age 7-12 yrs) and 200 days among children 13-18 years old. Psychostimulant and SSRIs drug prescriptions increased by 36% and 44% respectively.	There has been disproportionate increase in off-label use of antipsychotics from 2005 to 2009, despite the lack of approval for pediatric use by Health Canada.
Alessi-Severini	Age: 18 years or younger	Antipsychotic	Prevalence of SGAs	Extensive off-

et al., 2011	Population based study using Administrative health database of Manitoba health and Statistics Canada census (1999-2008)	prescribing in children and adolescents	increased from 1.9 per 1,000 to 7.4 per 1,000. Male to female antipsychotic use ratio increased from 1.9 to 2.7. The total number of prescriptions also increased significantly. More than 70% prescriptions were written by GP and most common diagnosis was ADHD and conduct disorders.	label use of SGAs among youth population of MB has been observed for aggressive behaviour across a range of diagnosis.
Ronsley et al., 2013	Age: 18 years or younger Population based study using Administrative database of British Columbia Ministry of Health (1996-2011)	Prevalence of antipsychotic prescription for children by age, sex, antipsychotic type, primary diagnosis and prescribers	Overall antipsychotic prescription prevalence increased from 1.66 to 6.37 per 1,000 population. SGA prescriptions increased 18 fold. The highest increase in all antipsychotic prescription was observed in males aged 13-18 yrs (3.3-14.4 per 1,000 population). The most common diagnosis associated with all antipsychotic prescription were depressive disorders	Extensive off-label use of antipsychotics has been observed in BC children and the prescriptions were not only from psychiatrists but also from GP and pediatricians.

			(12.8%), hyperkinetic syndrome of childhood (11.7%) and neurotic disorders (11.1%). 38.6% antipsychotic prescriptions came from psychiatrists followed by GP (34.3%) and pediatricians (15.6%).	
Bobo et al., 2013	Age: 6- 24 years Retrospective cohort study of Tennessee Medicaid program	Comparison of risk of type 2 diabetes among recent initiators of antipsychotic drugs vs. propensity-score matched controls who recently initiated another psychotropic drug	Antipsychotics had higher risk of type 2 diabetes than the control (HR:3.03, CI: 1.73 – 5.32). The risk of type 2 diabetes increased with cumulative dose. Similar trend was observed when the cohort was restricted to the children aged 6-17 yrs. The risk of type 2 diabetes especially increased with atypical antipsychotics (HR: 2.89, CI: 1.64 – 5.10). Most commonly prescribed antipsychotic was risperidone (37%) for which risk of type 2	Antipsychotics prescription increases the risk of type 2 diabetes among children and youth population and the risk is further escalated with cumulative dose.

	diabetes was 2-fold higher than the control (HR: 2.20, CI: 1.14 – 4.26)

BMI=Body mass Index; TC= Total cholesterol; LDL= low-density lipoprotein; T4= Thyroxin; CV= Cardiovascular; OR= Odds ratio; DM= Diabetes mellitus; CI=confidence interval, HR= hazard ratio

Education and antipsychotic use

Schooling is an important aspect of the development of young people, and any kind of psychologic disturbance in children and adolescents can be expected to negatively impact school performance (years of schooling completed, qualifications achieved or class grade obtained). Intervention with SGAs has been shown to improve children's well-being (Masi et al., 2011), indirectly suggesting a positive impact on successful learning including school performance. However, direct evidence is lacking and the impact of adverse medication-related events needs to be assessed (Kubiszyn et al, 2012; Chalita et al, 2012). To date no studies have been conducted on the impact of antipsychotic therapy on school performance in children.

STUDY OBJECTIVES

Objectives of this study were

1) To determine the utilization of antipsychotic agents (both FGAs and SGAs), which includes evaluation of

- prevalence of prescribed antipsychotic use in the youth population of MB between April 1, 1996 and March 31, 2011;
- incidence rate of prescribed antipsychotic use in the youth population of MB between April 1,1996 and March 31, 2011, stratified by sex and age group (0-6, 7-12, 13-19 years);

2) To describe the characteristics of the cohort of incident users in terms of diagnoses (i.e., schizophrenia, autism, ADHD, conduct disorders, mood disorders, tics).

3) To report on the specialty of antipsychotic prescribers (i.e., initiators of pharmacotherapy) involved in the treatment of the target population.

4) To compare rates of adverse events (i.e., diabetes, hypertension, EPS) in appropriately defined cohorts of new users of each SGA (risperidone vs. olanzapine and risperidone vs. quetiapine).

5) To determine school enrolment and high school completion rates among young people that have been prescribed antipsychotic medications.

METHODS

Data source

Data for this study were obtained from the administrative health care databases located in the Manitoba Population Health Research Data Repository housed at the Manitoba Centre for Health Policy (MCHP). The Repository is a comprehensive collection of administrative, registry, survey, and other data primarily relating to the residents of MB. The administrative health database hold records for almost all individual contacts with the provincial health care system, including physicians, hospitals, personal care homes, home care, and pharmaceutical prescriptions of all registered individuals. Information about an individual is modified to remove potentially identifying data in a way that minimizes the likelihood that an individual's identity can be determined by any reasonably foreseeable method. All registered individuals are assigned Scrambled Personal Health Identification Number (SCRPHIN), which is a unique 9-digit number to protect privacy (Fransoo et al., 2008; Brownell et al, 2006). At MCHP, data are suppressed (not revealed or published) when the number of persons or events involved is five or less. This process of suppressing data is conducted to avoid potential identification of individuals residing in areas of low-density population.

Education data were also accessed. Education databases, also housed at MCHP, contain de-identified records for MB students in schools from Nursery level to Grade 12; these records facilitate longitudinal population-based studies involving educational outcomes. Information provided includes the numbers of students who graduated or withdrew from school, whether they have dropped out entirely or have moved to another

school or jurisdiction (Brownell et al., 2006). The Population Registry facilitates determination of mortality and whether a student is a resident of Manitoba. Each student is identified by the unique Manitoba Education and Training Number (METNMBR) that facilitates tracking a child's progress from Kindergarten to Grade 12; subsequent linkage with the SCRPHIN helps build histories across multiple data files.

A list of databases of the Manitoba Population Health Research Data Repository is provided in Table 6.

Table 6. Databases and variables

Databases	Variables accessed
Manitoba Health Insurance Registry	SCRPHIN, Date of birth, Postal code
Hospital abstracts	SCRPHIN, Admission date, Discharge date, Length of stay, Diagnosis
Medical Services	SCRPHIN, Date of service, Pattern of practice code, Diagnosis
Drug Program Information Network (DPIN)	SCRPHIN, DIN, Date provided, Days Supplied on Rx, Prescriber specialty
Emergency Care	SCRPHIN, Date of admission, Date of disposition
Statistics Canada Census	Population of Manitoba
Vital Statistics	SCRPHIN, Date of death, Cause of death
Manitoba Education Citizenship and Youth (MECY)	SCRPHIN, METNMBR, Graduation flag, Graduation code, Total credits

These databases are described as follows:

- Manitoba Health Insurance Registry: a longitudinal population-based registry

maintained by Manitoba Health of all individuals who have been registered with Manitoba Health at some point since 1970. The registry includes individual-level demographics, family composition information, residential postal codes and data fields for registration (birth, entry into province, and migration in/out of province).

- Hospital abstracts: hospital forms/computerized records that contain summaries of demographic and clinical information (e.g., sex, postal code, diagnoses and procedure codes) completed at the point of discharge from the hospital.
- Medical Services data: claims for physician visits in offices, hospitals and outpatient departments; fee-for-service components for tests performed in offices and hospitals; as well as information about physicians' specialities.
- Drug Program Information Network (DPIN): prescription drug database that connects Manitoba Health and all pharmacies in MB. The DPIN system generates complete drug profiles for all MB residents (including registered First Nations), regardless of insurance coverage.
- Emergency Care: records of emergency department visits in Winnipeg. Data files include admission, discharge and transfer as well as records of E-triage.
- Statistics Canada: records on the population of Canada based on census conducted every five years.
- Vital Statistics: data derived from administrative mortality data and include information on date and cause of death.

- Manitoba Education Citizenship and Youth: education data maintained by Manitoba Education provide information on enrolment, courses, marks, standard tests, assessments,

graduation status, level of funding, and demographics for MB students from Kindergarten to Grade 12.

Study design

This was a population-based study of children and adolescents (age 0-19 years) of the province of MB over a 15-year period (April 1, 1996 – March 31, 2011).

The study was divided into three sections:

1) Utilization phase where prevalence and incidence of use was determined over the time period of April 1, 1996 – March 31, 2011. Description of the study cohort in terms of demographics and diagnoses (related to treatment (i.e., psychotic disorders, mood disorders, attention deficit hyperactivity disorders, conduct disorders) and possible SGA-induced adverse events (i.e. diabetes, cardiovascular, movement disorders).
2) Adverse events assessment: comparison of incidence rates of diabetes, hypertension and movement disorders between users of ripseridone, olanzapine and quetiapine in appropriately selected cohorts.
3) Assessment of school enrolment and graduation rates.

1) Utilization

Prevalence of use of antipsychotics was measured as number of users per 1,000 persons per year during the study period. Prevalent users were defined as any individual with at least one prescription of an antipsychotic drug in each year of the study period.

From the prevalent cohort, a group of new users (incident users) of antipsychotics, defined as individuals with no antipsychotic prescription in the year prior to first prescription, were selected. Incidence rates were calculated as number of new users per 1,000 persons per year. Stratification by sex and age group (0-6, 7-12, 13-19 years) was conducted.

The incident user cohort was described in terms of demographics and diagnoses. Specialties of the prescribers of the first antipsychotic prescription (therapy initiators) were also reported.

2) Adverse events assessment

The cohort of incident users was selected for the assessment of adverse events (i.e., diabetes, hypertension and EPS). Because of the negligible utilization of FGAs only SGA-users were included in the retrospective open cohort study design. Subjects were allowed to enter the cohort at any moment (open cohort design) during the defined study period (i.e., April 1, 1996 to March 31, 2010) and were followed longitudinally from cohort entry (index date) until one of the following events occurred: diagnosis of diabetes, hypertension, or EPS; discontinuation of therapy (i.e., failure to refill the prescription within 30 days or switch to another agent), death, moving out of province/ loss of coverage, end of cohort entry (i.e., March 31, 2010). The end of the study period was March 31, 2011 however; recruitment of the incident users was stopped in March 31, 2010 to allow 1-year follow-up for those who entered the cohort in March, 2010. For each comparison, individuals with a pre-existing diagnosis of diabetes, hypertension or EPS, respectively, were excluded (please refer to the section entitled “Study Population”

for more details regarding inclusion and exclusion criteria).

Rates of adverse events were compared among users of risperidone, olanzapine and quetiapine. Risperidone, which had been identified as the most commonly prescribed agent in this population (Alessi-Severini et al, 2012), was used as the reference. Comparisons were conducted using Cox proportional hazard models to calculate Hazard Ratios (HR) in the following groups: risperidone vs. olanzapine and risperidone vs. quetiapine.

3) Linkage with the education database

Incident users were linked to the education databases. High school completion/graduation is frequently used as an outcome variable for children's level of educational attainment. Attainment of Grade 12 by a certain age, such as 17 years old, provides a similar measure (MCHP Concept: High School Completion / Graduation and Grade 12 Attainment, 2013). Criteria used to identify high school completion/graduation in MB are as follows:

1. The "Year End Status" variable (or Graduation Flag) on the student's high school marks data.
2. Achieving a required total number of high school credits. The minimum number of credits is between 28 and 30, depending on the year of high school completion/graduation.
3. Earning four or more grade 12-course credits, regardless of how many credits in total the student had earned during high school.

However, it is possible that some of these students transferred to a First Nations school as

no enrolment data are available to identify these cases. According to MCHP, between 2-3 % of all school-aged children in Manitoba are in a First Nations school (MCHP Concept: High School Completion / Graduation and Grade 12 Attainment, 2013). Grade 1 enrolment was measured by the first enrolment record of the student.

Study population

According to Statistics Canada, the general youth population of MB ranged from 327,796 to 327, 551, between 1996 – 2011. From the data available in the Manitoba Population Health Research Data Repository the total user population, who were prescribed at least one antipsychotic agent between April 1, 1996 and March 31, 2011, included 23,888 youths (age ≤ 19 years). Among them, 8,284 persons were identified as incident users of antipsychotics (FGAs and SGAs), which means that they had no history of antipsychotic use in the one year prior to cohort entry. The incident cohort of 8,284 patients was selected on the basis of the following inclusion and exclusion criteria:

Inclusion criteria

1) Age ≤ 19 years at the date of their first antipsychotic prescription.

2) No history of antipsychotic use in the year prior to cohort entry (open cohort design that allowed multiple starts).

Exclusion criteria:

Subjects who spent more than 25% of the year prior to cohort entry in hospital were excluded from the study (as the DPIN database does not include information on

prescriptions administered in hospitals).

Additional exclusion criteria were applied for the analysis of each of the adverse events (i.e., diagnosis of diabetes, hypertension or EPS); individuals with a pre-existing condition of diabetes, hypertension, or EPS, defined by a diagnostic code or a prescription of a medication to treat the condition, were excluded from the corresponding analysis (see flow chart in Appendix II - Cohort definition for each analysis).

Follow-up

All subjects included in the study were followed up for one year after receiving their first antipsychotic prescription (index date). As the DPIN database does not contain records of medications administered in the hospital, subjects admitted to a hospital for 30 days or longer were censored unless the reason for hospitalization was an event of interest. Subjects who switched from one antipsychotic agent to another and subjects who failed to refill an antipsychotic prescription for 30 days or longer were also censored. Subjects who moved out of the province were censored at the end of their coverage information available in the registry database.

Outcomes

There was a defined outcome for each analysis (see Table 7 for details and specific codes used). In the diabetes analysis, the outcome was defined as a diagnosis of diabetes either in hospital or in their medical records and/or dispensation of an antidiabetic agent. For the hypertension analyses, the outcome was defined as a diagnosis of hypertension and/or dispensation of antihypertension drugs. A diagnosis of movement disorder and/or

dispensation of antiparkinson agents were considered to be the outcome in the EPS comparison.

Table 7. Definition of outcomes

Outcome of Interest	Medical records	Hospital abstracts
Diabetes	ICD9-249,250	ICD9- 249, 250 ICD10- E10-E14
Hypertension	ICD9- 401-405	ICD9- 401-405 ICD10- I1-I15
EPS	ICD9- 332, 333, 781	ICD9- 332, 333, 781 ICD10- G20-G26

Covariates

Baseline characteristics of the antipsychotic incident users were evaluated. Age and sex of each individual was retrieved from the Manitoba Health's population registry. Data on dispensation of any antipsychotic medication in the year prior to the cohort entry date were obtained from the DPIN database. Data on the number of comorbid conditions were obtained from both hospital abstracts and medical services databases. Data were accessed in the year prior to the index date, starting from April 1, 1995, to identify comorbid conditions for each person in the cohort. As an overall measure of comorbidity, Aggregated Diagnostic Groups (ADGs, formerly known as Ambulatory Diagnostic Groups) were assigned to the patients based on five clinical and utilization criteria: duration of the condition, severity of the condition, diagnostic certainty, etiology of the condition and specialty care involvement. A patient can be assigned 0 to 32 ADGs, based

on the diagnoses in an ADG. ADGs are part of Johns Hopkins Adjusted Clinical Group® (ACG®) case-mix system (Starfield et al., 1991, Reid et al., 2001; MCHP Concept: Adjusted Clinical Groups® (ACG®) – Overview, 2014).

Statistical analysis

Effects of individual SGAs on the incidence of adverse events were compared to risperidone (reference SGA). Time-to-event analysis using Cox proportional hazards models was conducted to assess the hazard rate (HR). The HR is the limit of the number of events per unit time divided by the number of individuals at risk, as the time interval approaches zero, and can be expressed as follows:

$$h(t) = \lim_{\Delta t \to 0} \frac{\text{observed events in interval}[t, t + \Delta t]/N(t)}{\Delta t}$$

Where $N(t)$ is the number at risk at the beginning of an interval. A hazard is the probability that a patient fails between t and $t + \Delta t$, given that the patient has survived up to time t, divided by Δt, as Δt approaches zero

In other words, the hazard rate is the probability of the event of interest occurring for patients at risk who are yet to experience the event within a specified time period. For example, if the event of interest is diabetes then the hazard rate for diabetes at time t, h(t), is the probability of the patient to stay diabetes-free up to time t (Allison, 2010). The hazard rate for patient *i* can be expressed as follows.

$$h_i(t) = h_0(t)\exp\{ßZi\}$$

Where $h_0(t)$ is a baseline hazard rate, Z_i is the *i*th patient's covariate and ß is the risk or regression coefficient. Cox proportional hazards models allow for the estimation of risk by taking into account censoring and by adjusting for confounders.

Potential confounders such as age, sex, socio-economic status and co-morbid diseases (ADGs) were adjusted for in all analyses. Significance of the confounders was determined by t-test and chi-square test and p-value <0.05 was considered to represent significance. Adjustments were also made for the use of other medications in one year prior to the cohort entry.

Analyses were performed using SAS statistical software for Windows, version 9.3 (SAS® Institute, Cary, North Carolina) (see Appendix 3. Example of SAS codes and Appendix 4. Example of SAS outputs). All analyses were conducted from a remote access site of the Manitoba Centre for Health Policy located at the Faculty of Pharmacy, University of Manitoba.

Approvals

This population-based study was approved by the Health Research Ethics Board (HREB) (Ethics reference number H2012:150) of the University of Manitoba and the Health Information Privacy Committee (HIPC) (File Number 2012/2013-16). Additional approvals from the Ministry of Education and the Winnipeg Regional Health Authority (WRHA) were obtained to access education and emergency datasets, respectively. The study was conducted in full compliance with the Personal Health Information Act of Manitoba (PHIA). (Please refer Appendix 5. Approvals).

RESULTS

Prevalence

Twenty-three thousand and eight hundred and eighty eight (23,888) children and adolescents of age 0-19 years were prescribed antipsychotics in MB between 1996 and 2011. Out of these, 2,924 (12.24 %) were FGAs users and 20,964 (87.76 %) were SGAs users. The prevalence of antipsychotics use in the youth population of MB between 1996 and 2011 is presented in Figure 1.

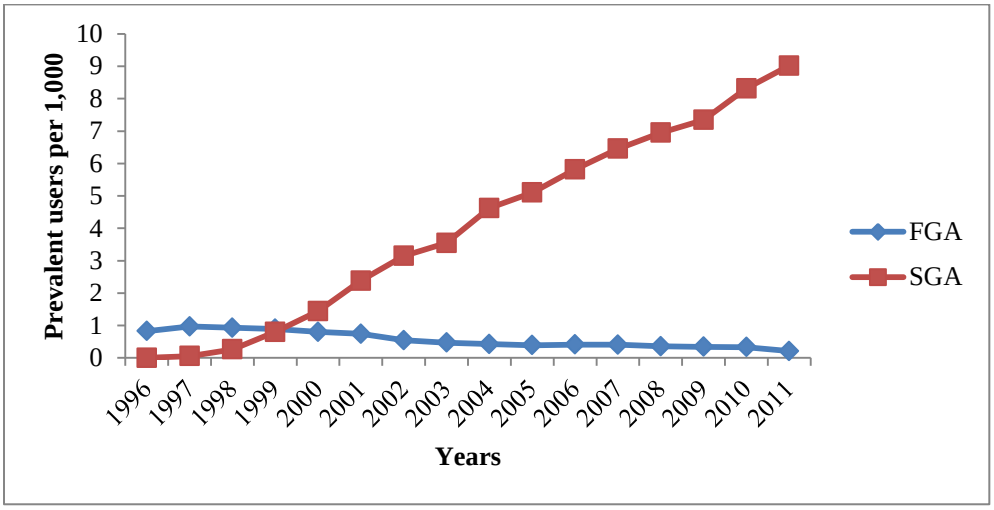

Figure 1: Prevalence of antipsychotics use (per 1,000 population). A 3-fold increase in SGA use was observed between 2001 and 2011

Incidence

Incident users for this study were defined as new users with no antipsychotic prescriptions in the year prior to cohort entry. After applying all the inclusion and exclusion criteria for incident users, a cohort of 8,284 users was selected. Out of these, 1,088 (13.13 %) were FGAs users and 7,196 (86.87 %) were SGAs users. The incidence

of antipsychotics use by sex in the youth population of Manitoba between 1996 and 2011 is depicted in Figure 2.

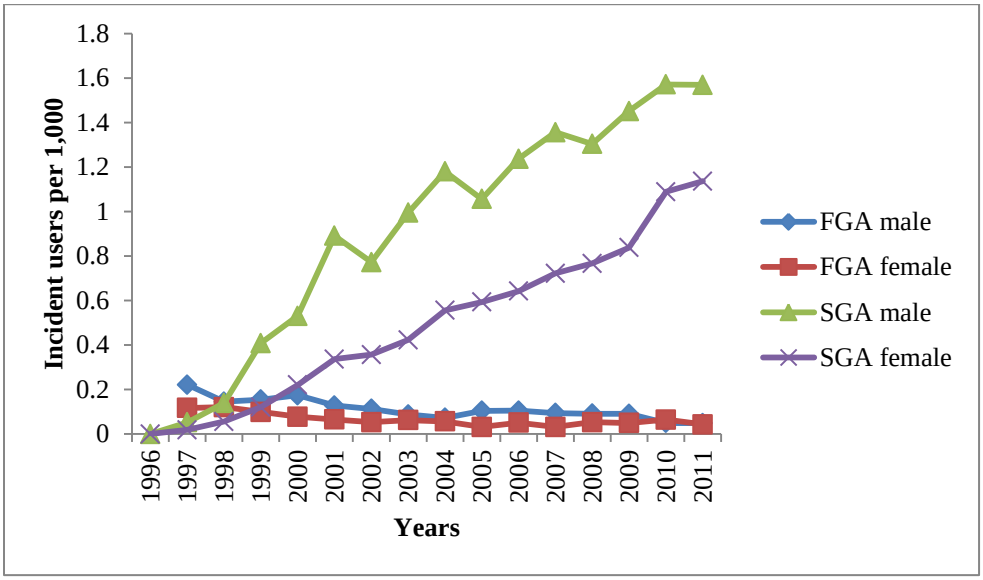

Figure 2: Incidence of antipsychotics use by gender (per 1,000 population) in the youth population. Incidence rate of SGA use was higher in males (0.8 to 1.5 per 1,000 between 2001 and 2011) compared to females (0.3 to 1.1 per 1,000 between 2001 and 2011)

Incidence of SGA use increased dramatically during the period 1996 to 2011 while the incidence of FGA use decreased. Incidence rate of SGA use was higher in males (0.8 to 1.5 per 1,000) between 2001 and 2011 compared to females (0.3 to 1.1 per 1,000) during the same time interval.

Among SGAs, risperidone (65.2%) was the most utilized drug followed by quetiapine (19.6%) and olanzapine (7.4%). Number of incident users of each SGA per year is presented in Figure 3. The highest level of SGA use was observed in the age group 13-19 years (49.4%).

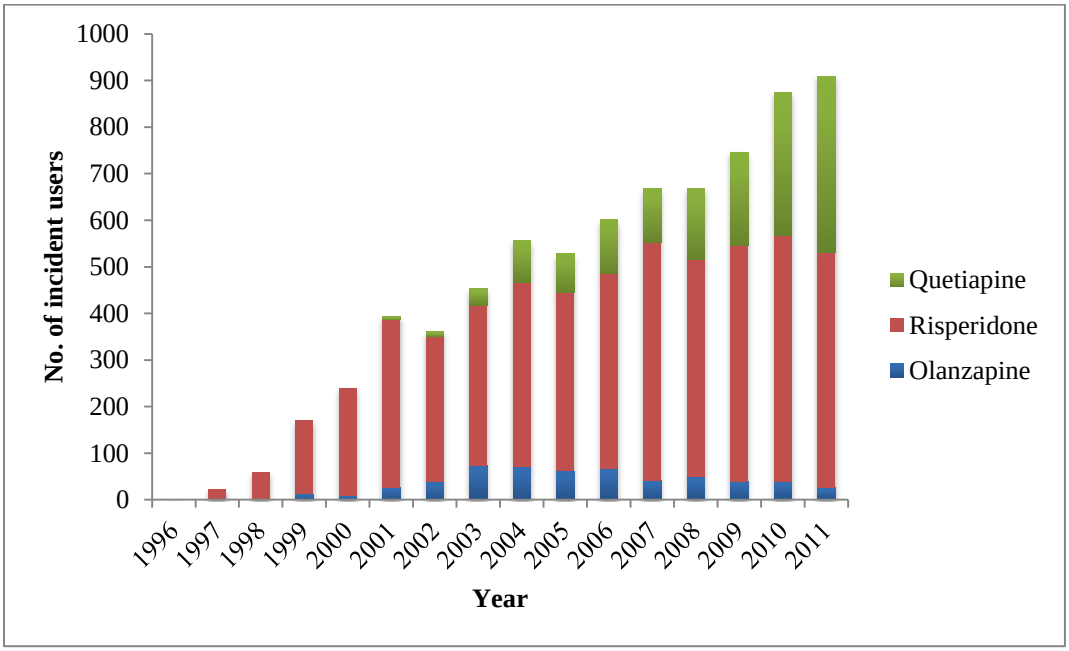

Figure 3: Incident users of each SGA per year. Risperidone was the most commonly prescribed agent to the youth population of MB

The most common diagnosis linked to antipsychotics users was ADHD (57%) followed by conduct disorders (38%) and mood disorders (24%); 39.4% of the first antipsychotic prescriptions were written by psychiatrists followed by pediatricians (38.5%) and general practitioners (20.3%). Diagnoses of diabetes (2%), hypertension (2%), EPS (1%), arrhythmias (0.9%) and hyperlipidemia (0.1%) were detected in this patient population after initiation of antipsychotic therapy. Please note that these are diagnoses linked to users at any point after initiation of therapy, they are not indicative of any causality. In particular the diagnosis of Type 1 and Type 2 diabetes could not be differentiated by the available codes; furthermore, the definition was very broad allowing for just one record in either medical or hospital file. These were reported only as descriptive information. Description of the cohort is presented in Table 8.

Table 8. Cohort description

Cohort (n=8,284)	
Gender (n, %)	
Males	5,344 (65%)
Females	2,940 (36%)
Age at cohort entry (n, %)	
0-6 years	961 (11.6%)
7-12 years	3,233 (39%)
13-19 years	4,096 (49.4%)
Overall Diagnosis of conditions (n, %)	
Schizophrenia	729 (8.8 %)
ADHD	4,716 (56.9 %)
Conduct disorders	3,167 (38.2 %)
Autism	1,088 (13.1 %)
Mood disorders	1,978 (23.9 %)
Tics	1,472 (17.8 %)
Diagnosis post 1st antipsychotic Rx (%)	
Diabetes	2 %
Hypertension	2 %
EPS	1 %
Arrhythmias	0.9 %
Hyperlipidemia	0.1 %
Prescribers of first Rx (%)	
Psychiatrist	39.4 %
Pediatrician	38.5 %
General Physician	20.3 %

Rates of adverse events (i.e., diabetes, hypertension, EPS) were compared among users of each SGA (i.e., risperidone vs. olanzapine, risperidone vs. quetiapine).

Diabetes

The description of the diabetes cohort is reported for information only. As previously explained, the impossibility of accurately discriminate between Type 1 and Type 2 diabetes made the comparisons not meaningful.

The diabetes cohort was selected by including individuals with no prior history of diabetes and/or antidiabetic prescription. Six thousand four hundred thirty eight (6,427) individuals were selected for the comparison of incidence of diabetes among users of

risperidone and olanzapine; 5,814 were started on risperidone and 613 on olanzapine. Similarly, for the comparison of diabetes among users of risperidone vs. quetiapine, seven thousand five hundred twenty three (7,523) individuals were selected out of which 5,814 were started on risperidone and 1,709 on quetiapine. Incidence of diabetes was evaluated at 365 days following first antipsychotic prescription; however, meaningful comparison among SGA users could not be achieved after all exclusion criteria were applied and covariates included in the model because of low counts. Baseline characteristics of risperidone vs. olanzapine groups and risperidone vs. quetiapine groups are presented in table 9 and table 10 respectively.

Table 9. Baseline characteristics of risperidone and olanzapine users – Diabetes

Characteristics	**Risperidone (n = 5,814)**	**Olanzapine (n = 613)**	**†p-value**
Age, years (mean ± SD)	11.39 ± 3.91	15.37 ± 3.53	<.0001
Age distribution (n,%)			
0-6	829 (14.26)	20 (3.26)	
7-12	2,938 (50.53)	101 (16.48)	
13-19	2,047 (35.21)	492 (80.26)	
Sex (male)	4,178 (71.86)	340 (55.46)	<.0001
Income			
Low	2,575 (44.29)	307 (50.08)	<.0003
Unknown	533 (9.17)	30 (4.89)	
*Year of cohort entry			
1999	256 (4.62)	10 (1.68)	
2000	411 (7.41)	31 (5.20)	
2001	360 (6.49)	44 (7.38)	
2002	392 (7.07)	86 (14.43)	
2003	429 (7.74)	78 (13.09)	
2004	433 (7.81)	67 (11.24)	
2005	468 (8.44)	70 (11.74)	
2006	561 (10.12)	46 (7.72)	
2007	518 (9.34)	55 (9.23)	
2008	568 (10.24)	39 (6.54)	

2009	589 (10.62)	43 (7.21)	
2010	560 (10.10)	27 (4.53)	
Frequency of GP visits (mean ± SD)	1.99 (4.44)	2.14 (4.28)	
Comorbidity (n, %)			
ADHD	3,304 (56.83)	152 (24.80)	<.0001
Autism	489 (8.41)	29 (4.73)	<.0001
Mood disorders	390 (6.71)	137 (22.35)	<.0001
Conduct disorders	1,983 (34.11)	109 (17.78)	<.0001
Anxiolytics	927 (15.94)	121 (19.74)	0.0156
Benzodiazepine	501 (8.62)	103 (16.80)	<.0001
Anticonvulsants	405 (6.97)	73 (11.91)	<.0001
Antidepressants	1,278 (21.98)	211 (34.42)	<.0001

*Year 1996 to 1998 were suppressed due to small cell size.
† Chi-sq test was used to assess the differences. p-value <0.05 represents significance.

Table 10. Baseline characteristics of risperidone and quetiapine users – Diabetes

Characteristics	**Risperidone (n = 5,814)**	**Quetiapine (n = 1,709)**	**†p-value**
Age, years (mean ± SD)	11.39 ± 3.91	15.29 ± 2.84	<.0001
Age distribution (n,%)			
0-6	829 (14.26)	44 (2.57)	
7-12	2,938 (50.53)	221 (12.93)	
13-19	2,047 (35.21)	1444 (84.49)	
Sex (male)	4,178 (71.86)	677 (39.61)	<.0001
Income			
Low	2,575 (44.29)	765 (48.26)	<.0001
Unknown	533 (9.17)	124 (13.95)	
*Year of cohort entry			
2001	360 (7.38)	15 (0.88)	
2002	392 (8.04)	44 (2.59)	
2003	429 (8.79)	110 (16.47)	
2004	433 (8.88)	95 (5.59)	
2005	468 (9.59)	132 (7.77)	
2006	561 (11.50)	125 (7.36)	
2007	518 (10.62)	180 (10.59)	
2008	568 (11.64)	233 (13.71)	
2009	589 (12.07)	351 (20.66)	

2010	560 (11.48)	414 (24.375	
Frequency of GP visits (mean ± SD)	1.99 (4.44)	1.71 (3.53)	
Comorbidity (n, %)			
ADHD	3,304 (56.83)	448 (26.21)	<.0001
Autism	489 (8.41)	54 (3.16)	<0.0001
Mood disorders	390 (6.71)	540 (31.60)	<.0001
Conduct disorders	1,983 (34.11)	291 (17.03)	<.0001
Anxiolytics	927 (15.94)	367 (21.47)	<0.0001
Benzodiazepine	501 (8.62)	297 (17.38)	<.0001
Anticonvulsants	405 (6.97)	159 (9.30)	<.0001
Antidepressants	1,278 (21.98)	720 (42.13)	<.0001

*Year 1996 to 2000 were suppressed due to small cell size.
† Chi-sq test was used to assess the differences. p-value <0.05 represents significance.

Hypertension

Risperidone vs. Olanzapine

Six thousand twenty one (6,021) individuals were included in the hypertension comparison: 5,436 were started on risperidone and 585 started on olanzapine. Individuals selected for this comparison had no history of hypertension diagnosis or prescription of an antihypertensive drug. The two groups (risperidone vs. olanzapine) differed significantly in the following characteristics: age (11.47 vs. 15.58 years), sex (male) (71.56 % vs. 54.70%), income (low: 83.19% vs. 91.61%; unknown: 16.81% vs. 8.39%), diagnosis of ADHD (54.86% vs. 21.71%), autism (8.26% vs. 4.79%), mood disorders (6.92% vs. 23.08%), conduct disorders (33.20% vs. 17.26%). Use of additional medications was also significantly different: anxiolytics (16.08% vs. 20.68%), benzodiazepines (8.63% vs. 16.75%), anticonvulsants (6.75% vs. 11.28%), antidepressants (21.71% vs. 33.85%). Baseline characteristics of the two groups (risperidone vs. olanzapine) are presented in Table 11.

Table 11. Baseline characteristics of risperidone and olanzapine users – Hypertension

Characteristics	**Risperidone (n = 5,436)**	**Olanzapine (n = 585)**	**†p-value**
Age, years (mean ± SD)	11.47 ± 3.93	15.58 ± 3.31	<.0001
Age distribution (n,%)			
0-6	758 (13.94)	12 (2.05)	
7-12	2,706 (49.78)	92 (15.73)	
13-19	1,972 (36.28)	481 (82.22)	
Sex (male)	3,890 (71.56)	320 (54.70)	<.0001
Income			
Low	2,430 (83.19)	295 (91.61)	<.0001
Unknown	491 (16.81)	27 (8.39)	
*Year of cohort entry			
1999	233 (4.49)	10 (1.76)	
2000	383 (7.39)	30 (5.28)	
2001	338 (6.52)	32 (7.39)	
2002	374 (7.21)	82 (14.44)	
2003	412 (7.95)	71 (12.50)	
2004	403 (7.77)	60 (10.56)	
2005	438 (8.45)	65 (11.44)	
2006	507 (9.78)	43 (7.57)	
2007	484 (9.34)	53 (9.33)	
2008	529 (10.20)	42 (7.39)	
2009	558 (10.76)	43 (7.57)	
2010	525 (10.13)	27 (4.75)	
Frequency of GP visits (mean ± SD)	1.90 (4.25)	2.04 (4.04)	
Comorbidity (n, %)			
ADHD	2,982 (54.86)	127 (21.71)	<.0001
Autism	449 (8.26)	28 (4.79)	0.0031
Mood disorders	376 (6.92)	135 (23.08)	<.0001
Conduct disorders	1,805 (33.20)	101 (17.26)	<.0001
Anxiolytics	874 (16.08)	121 (20.68)	0.0044
Benzodiazepine	469 (8.63)	98 (16.75)	<.0001
Anticonvulsants	367 (6.75)	66 (11.28)	<.0001
Antidepressants	1,180 (21.71)	198 (33.85)	<.0001

*Year 1996 to 1998 were suppressed due to small cell size.

† Chi-sq test was used to assess the differences. p-value <0.05 represents significance.

Number of events, mean duration of follow-up days, contributed person years of risperidone and olanzapine user groups are presented in Table 12.

Table 12. Incidence of hypertension in 365 days follow-up time, since treatment initiation: risperidone vs. olanzapine

Cohort	Events (N)	Duration of follow-up days (mean± SD)	Contributed person-years	Crude event rate per 100 p-y
Risperidone	92	226 ± 130	3,344.18	2.75
Olanzapine	9	194 ±1 37	313.59	2.87

Results of the unadjusted and adjusted (for variables listed in table 11) Cox model are presented in Table 13.

Table 13. Hazard ratios for risperidone vs. olanzapine – Hypertension

Group	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Risperidone vs. Olanzapine	1.04 (0.52 – 2.06)	2.52 (1.20 – 5.29)

Risperidone vs. Quetiapine

Seven thousand one hundred fourteen (7,114) individuals were included in the hypertension comparison. Out of these 5,436 were started on risperidone and 1,678 were started on quetiapine. Individuals selected for this comparison had no history of diagnosis of hypertension or prescription of an antihypertensive drug. The two groups (risperidone vs. quetiapine) differed significantly in the following characteristics: age (11.47 vs. 15.32 years), sex (male) (71.56 % vs. 39.15%), income (low: 83.19% vs. 87.56%; unknown: 16.81% vs. 13.44%), diagnosis of ADHD (54.86% vs. 24.61%), autism (8.26% vs. 3.10%), mood disorders (6.92% vs. 32.54%), conduct disorders (33.20% vs. 16.81%).

Use of additional medications was also significantly different in both the groups: anxiolytics (16.08% vs. 21.39%), benzodiazepines (8.63% vs. 17.40%), anticonvulsants (6.75% vs. 30.10%), antidepressants (21.71% vs. 41.95%). Baseline characteristics of the two groups (risperidone vs. quetiapine) are presented in Table 14.

Table 14. Baseline characteristics of risperidone and quetiapine users – Hypertension

Characteristics	**Risperidone (n = 5,436)**	**Quetiapine (n = 1678)**	**†p-value**
Age, years (mean ± SD)	11.47 ± 3.93	15.32 ± 2.81	<.0001
Age distribution (n,%)			
0-6	758 (13.94)	42 (2.50)	
7-12	2,706 (49.78)	212 (12.63)	
13-19	1,972 (36.28)	1424 (84.86)	
Sex (male)	3,890 (71.56)	657 (39.15)	<.0001
Income			
Low	2,430 (83.19)	747 (87.56)	0.0179
Unknown	491 (16.81)	116 (13.44)	
*Year of cohort entry			
2001	338 (7.40)	14 (0.84)	
2002	374 (8.19)	42 (2.52)	
2003	412 (9.02)	109 (6.53)	
2004	403 (8.82)	90 (540)	
2005	438 (9.59)	130 (7.79)	
2006	507 (11.10)	120 (7.19)	
2007	484 (10.60)	181 (10.85)	
2008	529 (11.58)	226 (13.55)	
2009	558 (12.22)	344 (20.62)	
2010	525 (11.49)	412 (24.70)	
Frequency of GP visits (mean ± SD)	1.90 (4.25)	1.63 (3.33)	
Comorbidity (n, %)			
ADHD	2,982 (54.86)	413 (24.61)	<.0001
Autism	449 (8.26)	52 (3.10)	<.0001
Mood disorders	376 (6.92)	546 (32.54)	<.0001
Conduct disorders	1,805 (33.20)	282 (16.81)	<.0001

Anxiolytics	874 (16.08)	359 (21.39)	<.0001
Benzodiazepine	469 (8.63)	292 (17.40)	<.0001
Anticonvulsants	367 (6.75)	158 (30.10)	0.0003
Antidepressants	1,180 (21.71)	704 (41.95)	<.0001

*Year 1996 to 2000 were suppressed due to small cell size.
† Chi-sq test was used to assess the differences. p-value <0.05 represents significance.

Number of events, mean duration of follow-up days, contributed person-years of risperidone and quetiapine user groups are presented in Table 15.

Table 15. Incidence of hypertension in 365 days follow-up time, since treatment initiation: risperidone vs. quetiapine

Cohort	**Events (N)**	**Duration of follow-up days (mean± SD)**	**Contributed person-years**	**Crude event rate per 100 p-y**
Risperidone	92	227 ± 130	3,329.13	2.76
Quetiapine	13	163 ± 132	750.25	1.73

Results of the unadjusted and adjusted (for variables listed in table 14) Cox model are presented in Table 16.

Table 16. Hazard ratios for risperidone vs. quetiapine – Hypertension

Group	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)**
Risperidone vs. Quetiapine	0.64 (0.36 – 1.14)	1.50 (0.77 – 2.90)

Extrapyramidal Symptoms

Risperidone vs. Olanzapine

Six thousand four hundred thirty eight (6,438) individuals were selected for EPS comparison; 5,821were started on risperidone and 617 on olanzapine. Individuals selected for this comparison had no history of EPS diagnosis or prescription of an

antiparkinsons agent. Significant differences were observed between the two groups (risperidone vs. olanzapine): age (11.37 vs. 15.35 years), sex (male) (72.17% vs. 55.75%), income (low: 82.69% vs. 91.47%; unknown: 17.31% vs. 8.53%), diagnosis of ADHD (57.19% vs. 24.31%), autism (8.25% vs. 4.38%), mood disorders (6.56% vs. 22.53%), conduct disorders (34.08% vs. 17.83%). Use of additional medications was also significantly different: EPS inducing agents (metoclopramide, tetrabenazine, reserpine, methyldopa, amiodarone, valproate, lithium) (4.31% vs. 7.46%), anxiolytics (15.70% vs. 20.10%), benzodiazepines (8.21% vs. 16.53%), anticonvulsants (6.68% vs. 11.51%), antidepressants (21.51% vs. 34.04%). The baseline characteristics of the two groups (risperidone vs. olanzapine) are presented in Table 17.

Table 17. Baseline characteristics of risperidone and olanzapine users – EPS

Characteristics	**Risperidone (n = 5,821)**	**Olanzapine (n = 617)**	**†p-value**
Age, years (mean ± SD)	11.37 ± 3.90	15.35 ± 3.52	<.0001
Age distribution (n,%)			
0-6	835 (14.34)	19 (3.08)	
7-12	2,954 (50.75)	105 (17.02)	
13-19	2,032 (34.91)	493 (79.90)	
Sex (male)	4,201(72.17)	344 (55.75)	<.0001
Income			
Low	2,575(82.69)	311 (91.47)	<.0001
Unknown	539 (17.31)	29 (8.53)	
***Year of cohort entry**			
1999	253 (4.54)	9 (1.50)	
2000	409 (7.34)	29 (4.82)	
2001	358 (6.42)	43 (7.14)	
2002	392 (7.03)	88 (14.62)	
2003	433 (7.77)	80 (13.29)	
2004	438 (7.86)	68 (11.30)	
2005	471 (8.45)	71 (11.79)	

2006	568 (10.19)	46 (7.64)	
2007	519 (9.31)	55 (9.14)	
2008	551 (10.30)	42 (6.98)	
2009	593 (10.63)	44 (7.31)	
2010	564 (10.11)	25 (4.49)	
Frequency of GP visits (mean ± SD)	2.03 (4.52)	2.15 (4.27)	
Comorbidity (n, %)			
ADHD	3,329 (57.19)	150 (24.31)	<.0001
Autism	480 (8.25)	27 (4.38)	0.0007
Mood disorders	382 (6.56)	139 (22.53)	<.0001
Conduct disorders	1,984 (34.08)	110 (17.83)	<.0001
Anxiolytics	914 (15.70)	124 (20.10)	0.0048
EPS inducing agents	251 (4.31)	46 (7.46)	0.0004
Benzodiazepines	478 (8.21)	102 (16.53)	<.0001
Anticonvulsants	389 (6.68)	71 (11.51)	<.0001
Antidepressants	1,252 (21.51)	210 (34.04)	<.0001

*Year 1996 to 1998 were suppressed due to small cell size.
† Chi-sq test was used to assess the differences. p-value <0.05 represents significance.

Contributed person-years and crude event rate per 100 person-years were measured based on the number of events and mean duration of follow-up days. Contributed person-years is the sum of the time each person was observed, totalled for all persons. This represents the total time the population was at risk of and being observed for the outcome.

Number of events, mean duration of follow-up days, contributed person-years of risperidone and olanzapine user groups are presented in Table 18.

Table 18. Incidence of EPS in 365 days follow-up time, since treatment initiation – risperidone vs. olanzapine

Cohort	Events (N)	Duration of follow-up days (mean± SD)	Contributed person-years	Crude event rate per 100 p-y
Risperidone	70	226 ± 131	3,597.42	1.95
Olanzapine	16	193 ± 137	324.66	4.92

Results of the unadjusted and adjusted Cox model are presented in Table 19.

Table 19. Hazard ratios for risperidone vs. olanzapine – EPS

Group	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Risperidone vs. Olanzapine	2.41 (1.40 – 4.15)	0.75 (0.42 – 1.34)

Risperidone vs. Quetiapine

Seven thousand five hundred fifty nine (7,559) individuals were included in the EPS comparison. Out of these, 5,821 were started on risperidone and 1,738 were started on quetiapine. Individuals selected for this comparison had no history of diagnosis of EPS or prescription of an antiparkinsons agent. The two groups differed significantly in the following characteristics: age (11.37 vs. 15.29 years), sex (male) (72.17% vs. 38.95%), income (low: 82.69% vs. 85.76%; unknown: 17.31% vs. 14.24%), diagnosis of ADHD (57.19% vs. 26.06%), autism (8.25% vs. 3.05%), mood disorders (6.56% vs. 31.47%), conduct disorders (34.08% vs. 17.38%). Additional medications use was also significantly different: anxiolytics (15.70% vs. 21.63%), benzodiazepines (8.21% vs. 17.26%), anticonvulsants (6.68% vs. 9.32%), antidepressants (21.51% vs. 42.29%).

Baseline characteristics of the two groups (risperidone vs. quetiapine) are presented in Table 20.

Table 20. Baseline characteristics of risperidone and quetiapine users – EPS

Characteristics	Risperidone (n = 5,821)	Quetiapine (n = 1,738)	ŧp-value
Age, years (mean ± SD)	11.37 ± 3.90	15.29 ± 2.83	<.0001
Age distribution (n,%)			
0-6	835 (14.34)	44 (2.53)	
7-12	2,954 (50.75)	225 (12.95)	
13-19	2,032 (34.91)	1,469 (84.52)	
Sex (male)	4,201 (72.17)	677 (38.95)	<.0001
Income			
Low	2,575 (82.69)	771 (85.76)	0.0293
Unknown	539 (17.31)	128 (14.24)	
***Year of cohort entry**			
2001	358 (7.29)	15 (0.87)	
2002	392 (7.98)	44 (2.54)	
2003	433 (8.81)	109 (6.30)	
2004	438 (8.91)	96 (5.55)	
2005	471 (9.58)	134 (7.75)	
2006	568 (11.56)	131 (7.58)	
2007	519 (10.56)	189 (10.93)	
2008	578 (11.76)	236 (13.65)	
2009	593 (12.07)	354 (20.47)	
2010	564 (11.48)	421 (24.35)	
Frequency of GP visits (mean ± SD)	2.03 (4.52)	1.77 (3.66)	
Comorbidity (n, %)			
ADHD	3,329 (57.19)	453 (26.06)	<.0001
Autism	480 (8.25)	53 (3.05)	<.0001
Mood disorders	3,82(6.56)	457 (31.47)	<.0001
Conduct disorders	1,984 (34.08)	302 (17.38)	<.0001
EPS inducing agents	251 (4.31)	74 (4.26)	0.9221
Anxiolytics	914 (15.70)	376 (21.63)	<.0001
Benzodiazepine	478 (8.21)	300 (17.26)	<.0001
Anticonvulsants	389 (6.68)	162 (9.32)	0.0002
Antidepressants	1252 (21.51)	735 (42.29)	<.0001

*Year 1996 to 2000 were suppressed due to small cell size.

ŧ Chi-sq test was used to assess the differences. p-value <0.05 represents significance.

Number of events, mean duration of follow-up days, contributed person-years of risperidone and quetiapine user groups are presented in Table 21.

Table 21. Incidence of EPS in 365 days follow-up time, since treatment initiation – risperidone vs. quetiapine

Cohort	Events (N)	Duration of follow-up days (mean± SD)	Contributed person-years	Crude event rate per 100 p-y
Risperidone	68	228 ± 130	3599.27	1.89
Quetiapine	19	164 ± 132	778.66	2.44

Results of the unadjusted and adjusted (for variables listed in table 20) Cox model are presented in Table 22.

Table 22. Hazard ratios for risperidone vs. quetiapine – EPS

Group	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Risperidone vs. Quetiapine	1.17 (0.70 – 1.95)	0.46 (0.26 – 0.82)

Education

The general level of school enrolment was assessed by looking at the age of school enrolment at grade 1. The enrolment data comprise of variables such as enrolment date, birthdate, and current grade. Each student is identified by unique METNMBR. Purpose of this number is to keep record of child's progress and this number remains the same from Kindergarten to Grade 12. In our study we found that around 82% of incident users get enrolled in grade 1 at the age 5 – 7 years. No enrolment data was available for students attending First Nations schools (approximately 3%). For some students first enrolment record was not available for grade 1.

High school graduation was assessed by looking at the last or most recent school enrolment record available for each individual in the cohort during the study period 1996 to 2011.

In this study we looked at the cohort of an age-specific group of 17-19 years of age, to determine whether they completed high school within that time, considering that some students will take longer to complete high school. Students who move out of the province are not included in the calculation of high school completion.

Education records include a "year–end status" variable, which indicates status of the student at the end of each academic year whether a student has graduated, transferred, left school. Theoretically, graduates could be identified through this year–end status variable. However, not all graduates were identified by this variable as prior to 2009/10, some schools did not use this variable consistently. To compensate for this, for those Grade 12 students without "graduation" as their year–end status, the number of credits obtained by the student throughout high school, was counted (28 credits up to 2007/2008, 29 credits up to 2008/2009 and 30 credits as of 2010/2011). Students who had accumulated the required number of credits for graduation were considered "graduates."

Our cohort comprises of children and adolescents of age 0 to 19 years therefore, to estimate the number of high school graduates, an age specific group was formed in which adolescents of age 17-19 years were grouped together. The high school graduation was determined by looking at the most recent enrolment record and year-end status of each student. Out of 8,284 incident users, 1,824 users were of age group 17-19 years. Total of 1,209 students from total 1,824, (approximately 66%) of age group 17-19 years had confirmed graduation status by end of study (i.e., March 31, 2011). No confirmed

graduation date was available for the remaining students at the end of the study; however, it can be assumed that the graduation status could in fact be higher than our estimates.

DISCUSSION

Study design

Observational studies have some advantages over RCTs. They are less expensive and easier to conduct than RCTs. Observational studies usually apply to a broader population and can follow longitudinally many individuals for a long period of time as compared to RCT, hence, they can provide assessment of drug use in the real world setting. Observational studies are important when there are ethical limitations to RCTs, for example, when assessments of potential risk factors are made on child and adolescent populations (Hannan, 2008). Furthermore, it is unethical to conduct placebo-controlled trials where sufficient data can be obtained from observational studies using historical records (e.g., mortality analysis in cancer therapy). RCTs may be inadequate in cases where the outcome of an intervention is determined by activities of the care providers, such as surgery or physiotherapy. In these cases observational studies are often preferable (Thadhani, 2006).

The largest drawback of observational studies is selection bias that occurs when study participants are not representative of the population at risk of the outcome. Therefore, careful designs are required for the results of observational studies to be considered reliable.

The incident user design used in this study reduces selection biases, especially when secondary data sources such as health care databases are used. Theoretically, the incident-user design articulates the causal questions about benefit or harm of an intervention, as this design captures all events occurred after the start of the therapy (Johnson et al, 2013). For the incident user design it is important to include details of prescriptions that can be

used to define potential confounders. Administrative prescription records can provide a detailed measure of medications used thereby, it facilitates the identification of those who were prescribed any medication for the first time. Furthermore, prescription details (e.g., date of prescription, drug prescribed, prescribers) can be linked to other files such as hospital abstracts, health registries to ascertain potential confounders (Ray, 2003). The incident user design also works particularly well for evaluation of short-term adverse events that occur early after pharmacotherapy initiation (Ray, 2003). Nevertheless, it is recognized that observational studies can always carry a risk for potential unmeasured confounders (Hannan, 2008).

Selection of the cohort

This retrospective cohort study was conducted on children and adolescents (≤ 19 years) living in Manitoba, who were initiated on antipsychotic therapy during the period April 1, 1996 to March 31, 2010. As DPIN data records commenced in 1995, choosing this time period facilitated the selection of incident users of antipsychotics without a history of antipsychotic use in the year prior to cohort entry. The one-year pre-selection window may identify users of newly marketed drug as their first-ever use (i.e., truly treatment naïve) whereas, for users of older drugs, this window may identify patients starting a new episode of therapy (Johnson et al., 2013). In this study, recruitment of the incident users was stopped in March 31, 2010 to allow 1-year follow-up for those who entered the cohort in March, 2010.

The DPIN database allows the study of the prescription history of virtually the entire (over 90%) population of the province as it records drug use of all the residents of MB,

without restrictions of age and health coverage (Kozyrskyj et al.1998). However, DPIN does not include information on medications administered in hospitals; therefore, in order to avoid misclassification bias, patients who had been hospitalized for more than 25% of the year prior to cohort entry, were excluded. Furthermore, subjects admitted to a hospital for longer than 30 days during the study period would have been censored, unless the hospitalizations were related to the outcomes of interest, (i.e., diagnosis of diabetes, hypertension or EPS); however, none of hospitalizations recorded in this category were associated with the outcomes of interest. Subjects who switched from one agent to another during the study period were also censored.

The cohort selected for the study comprised 8,284 incident users. From this cohort three sub-cohorts were formed for the comparison of diagnoses of diabetes, hypertension and EPS events. Exclusion criteria for pre-existing diagnoses and exposure to medications were applied for all the three diagnoses.

The evaluations of school enrolment and high school graduation were done on the baseline cohort of incident users.

Confounding

A number of steps were taken to control for possible confounders. Age, sex, area of residence, income and comorbidities were adjusted to control for possible selection bias. The overall comorbidity burden was determined by the Aggregated Diagnostic Groups (ADG) which is a part of the 'The Johns Hopkins ACG(r) Case-Mix System, version 10'. The ADG system reflects the overall health status of the individual; this method was developed to include all available ICD-9 and ICD-10 diagnosis codes assigned to a patient. Diagnosis of every patient was further grouped into one of 32 different ADG. For this study, individuals were assigned to one of the 32 different ADGs by aggregating the diagnoses recorded in the medical services and hospital abstracts databases, prior to the cohort entry according to methods previously used (Brownell et al., 2012).

During the study period, risperidone, olanzapine and quetiapine were identified as the most utilized SGAs as these agents have been the longest on the Canadian market (since 1993, 1997 and 2001, respectively). To account for the change in prescribing trend with the introduction of newer agents, adjustments were made in the analyses for the variable "index year".

Despite all adjustments, no clinical parameters were available to determine how well patients responded to therapy or how their everyday life was improved because of therapy (in our datasets no linkage to clinical test results or medical charts was possible); this is a limitation common to similar studies utilizing administrative databases. There are also some important confounders (e.g., lifestyle factors such as lack of physical activity

or unhealthy diet) that can affect hypertension and diabetes outcomes and that cannot be measured through administrative data.

Utilization of antipsychotic agents

In the present study we found that the prevalence of antipsychotic use among children and adolescents increased almost nine-fold between 1999 and 2011, whereas, the prevalence of FGAs decreased during the same period in this population. Among incident users almost 87% were on SGAs while only 13% were on FGAs. The increase in SGA and the concomitant decrease in FGA use can be explained by the marketing of the SGAs as safer agents in comparison to FGAs. FGAs have never been widely used in the pediatric population because of their well-known toxicity particularly in terms of movement disorders (e.g., EPS), which can be particularly devastating in children, while SGAs have certainly been reported as safer in this perspective.

Our results are consistent with a previous study done on MB youth population, which determined a four-fold increase in antipsychotic prescription from 1999 to 2008 (Alessi-Severini et al., 2012). However, our results looked at the utilization after 2008 and found that there was a significant increase in utilization of SGAs between 2008 and 2011 in this population. A recent study done on the youth population of BC, also documented a significant increase in SGA prescriptions during the 1996 to 2011 time period (Ronsley et al., 2013). It is evident from these studies that the utilization of antipsychotics has gone up in recent years, despite the safety concerns raised in recent years (Pringsheim et al., 2011(a); Pringsheim et al., 2011(c); Ho et al., 2011; Seida et al., 2012; Ben, 2012) and the lack of Health Canada approved indications in children.

Stratification by sex revealed that males had higher incidence rates of use in comparison to females. Several other studies have reported that males receive more prescriptions of antipsychotics than females (Ronsley et al., 2013; Olfson et al., 2006; Alessi-Severini et al., 2012).

In this study, risperidone was consistently the most utilized SGA during the time period, which is also documented in other Canadian studies (Pringsheim et al., 2011 (b); Alessi-Severini et al., 2012).

The use of olanzapine was found to be lower than the use of quetiapine. Although quetiapine was used only among 19.6% of the users, a closer look at the trends of SGA use from 2004 onwards demonstrates that the use of quetiapine has increased remarkably while olanzapine use decreased. This preference for quetiapine over olanzapine could be due to reports of worrisome weight gain among olanzapine users (Panagiotopoulos et al., 2009; Vitiello et al., 2009; Moreno et al., 2010). While olanzapine has shown efficacy in early onset schizophrenia and pediatric bipolar disorders, treatment with olanzapine was consistently found to be associated with weight gain, dyslipidemia and also EPS (Maloney et al., 2010). Olanzapine, despite having an approved indication in the US since 2009 for the treatment of schizophrenia or manic/mixed episodes in bipolar I disorders in adolescents of age 13-17 years, does not seem to be the preferred medication as first choice in this population (Maloney et al., 2010).

Emergency department data were included in our dataset. Unfortunately, this database did not prove to be useful as reasons for emergency room visits were not recorded. In addition, data for the first four years of this study were missing as the database records

started from 1999/00. Due to these limitations, emergency care data could not be used in this study.

Prescribers

The majority of antipsychotic prescriptions were initiated by psychiatrists followed by pediatricians and GP. This finding is consistent with another Canadian study, which reported 62% of recommendations by psychiatrist followed by paediatrician and GP (17% each) (Pringsheim et al., 2011(b)). Previous study (Alessi-Severini et al. 2012) has shown GPs to be the most prevalent prescribers. In light of our current findings it could be suggested that specialists initiate therapy in children and follow-up prescriptions are written by GPs.

Incidence of Adverse Events

In this study we found that a number of individuals had records of diagnoses of diabetes (2%), hypertension (2%), EPS (1%), arrhythmias (0.9%) and hyperlipidemia (0.1%) identified after their first prescriptions of an SGA. Among all these diagnoses, we had very few cases of arrhythmias and hyperlipidemia and it was not possible to conduct analyses specifically on these diagnoses. These diagnoses were made among the users of all SGAs however, for the comparison study was done among the users of risperiodone, olanzapine and quetiapine. Exclusion criteria were applied for pre-existing diagnoses and prescriptions, also, adjustments were made for the potential confounders.

As explained in the Methods and Results, challenges were encountered in defining the diagnosis of diabetes, therefore the initial percentage of 2% is not reflective of the true

incidence of Type 2 diabetes in this population; furthermore, after applying all exclusion criteria and adjustments for covariates, it was not possible to run meaningful comparisons.

Almost 65.2% of users started on risperidone, which was considered the reference drug for the comparison analyses.

The youth population of MB comprises 27% of the total population of MB (327,551 out of 1,208,268 in 2011). Even though the incidence of antipsychotic use was high during the study period, the overall number of persons selected into each cohort (diabetes, hypertension and EPS) was relatively small and number of cases quite low, limiting the opportunity for meaningful comparisons through stratification.

Diabetes cohort

Type-2 diabetes was earlier thought to be associated with adulthood; however, it has recently been accepted as a significant health problem in childhood. Factors responsible for early onset of type-2 diabetes in children include obesity, hypertension, dyslipidemia, genetic predisposition and poverty. Recent studies have associated antipsychotic therapy with clinically significant diabetes (Nielsen et al., 2010; Andrade et al., 2011; Jerrell et al., 2012; Bobo et al., 2013). In one study the use of antidepressants, antipsychotics (SGA) and a combination of the two, has reported 1.3 to 2 times greater risk of diabetes (Jerrell et al., 2012). Another study aimed at investigating the association between antipsychotic therapy and diabetes development among schizophrenia patients, found that FGAs, olanzapine and clozapine treatments were important factors associated with diabetes onset within 3 months of therapy initiation, whereas aripiprazole was associated

with lower diabetes incidence (Nielsen et al., 2010). A retrospective cohort study conducted on a population of over 9,000 children and adolescents showed an increased incidence of diabetes within the first year of initiation of antipsychotic therapy, compared to children who were not on antipsychotic therapy (Andrade et al., 2011). Different effects of SGAs on weight gain and insulin resistance have been suggested to influence the risk of diabetes. Such effects include antagonism of 5-HT receptor resulting in inhibition of insulin release and increase in insulin resistance causing impairment of glucose utilization (Liebzeit et al., 2001; Mir et al., 2001; Schwenkreis et al., 2004). Furthermore, SGAs can influence the function of β-cells through α_2 adrenergic receptor activation (Schwenkreis et al., 2004).

The aim of our study was to look at the diagnosis of type-2 diabetes; however, the ICD-9-CM code that identifies type-2 diabetes is specified by the fifth digit (thus only detectable in hospital claims, not physician visit claims). Therefore, in this study the diagnosis of diabetes was identified by looking at ICD-9 code (250) for diabetes mellitus. To select specific cases of type 2 diabetes, individuals with prescription of insulin were excluded from the study and the cases with prescription of oral antidiabetic agent, following antipsychotic treatment, were attributed to antipsychotic therapy; however, this reduced significantly the numbers of events and, after applying exclusion criteria and covariate adjustments, because of the low counts, and cell suppression, no meaningful comparisons were possible. Please note that, as explained in the Methods, the initial assessment of diabetes prevalence in this population was just a broad assessment of total diagnoses of any type of diabetes from either medical or hospital records at any time during the time period of the study.

Hypertension cohort

Onset of cardiovascular events including hypertension has been associated with SGA use in young patients (Jerrell et al., 2008; Correll et al., 2009; Jerrell et al., 2011). The incidence of hypertension and other cardiovascular events have been linked to other comorbid conditions such as obesity, abnormal lipid levels and type-2 diabetes. It has also been observed that the odds of developing incident hypertension are significantly higher among adolescents 13 years or older and that the incidence was unrelated to the type of antipsychotic used (McIntyre et al., 2008). In our study we observed that the crude event rate per-100 person years for risperidone users was 2.75 while for olanzapine and quetiapine it was 2.87 and 1.73 respectively. When the risk of hypertension in the risperidone group was compared against the one treated with olanzapine, the unadjusted Cox model did not show any difference between the two groups (HR:1.04, 95% CI: 0.52 – 2.06). However, the adjusted model showed that olanzapine was associated with higher risk of hypertension than risperidone (HR:2.52, 95% CI: 1.20 – 5.29).

The risk of hypertension in risperidone and quetiapine group was not significantly different in both unadjusted (HR: 0.64, 95% CI: 0.36 – 1.14) and adjusted (HR: 1.50, 95% CI: 0.77 – 2.90) Cox models. Other studies have shown that olanzapine is associated with higher risk of metabolic disorders, which include increased body weight and dyslipidemia, in comparison to risperidone and quetiapine (McIntyre et al., 2008; Correll et al., 2009). As these factors are directly related to cardiovascular adverse events, olanzapine treatment group would be expected to be associated with a higher risk of hypertension than risperidone and quetiapine, which is consistent with our finding; however, McIntyre et al. had previously attempted to distinguish the incidence of

hypertension among users of different antipsychotics and their results indicated that the risk of hypertension was independent of the antipsychotic received (McIntyre et al., 2008). It is important to note that specific adjustments due to medications that can affect blood pressure (e.g., stimulants) were not conducted; however, adjustments for a diagnosis of ADHD and adjustments for co-morbid factors (ADGs) were performed, as risperidone was the most used medication for ADHD confounding would have made risperidone treatment show a higher risk, which was not the case in our study.

EPS cohort

At the time of introduction to the market, SGAs were claimed to be devoid of EPS; however, in our study we have reported occurrence of EPS in all treatment groups. In the unadjusted Cox model, risk of incidence of EPS in olanzapine was higher than in the risperidone group (HR: 2.41, 95% CI: 1.40 – 4.15). However, in the adjusted model, significance was lost (HR: 0.75, 95% CI: 0.42 – 1.34). Comparison between the risperidone and quetiapine group showed no significant difference in the risk of EPS for the unadjusted model (HR: 1.17, 95% CI: 0.70 – 1.95); however, in the adjusted model quetiapine had a significantly lower risk of EPS than risperidone group (HR: 0.46, 95% CI: 0.26 – 0.82). The incidence of EPS is directly related with the affinity of the antipsychotic for dopamine D_2 receptor. Risperidone has a higher affinity for D_2 receptor than olanzapine and quetiapine, with quetiapine having least affinity for D_2 receptor (Seeman, 2006). This suggests that risperidone should be associated with higher risk of EPS than olanzapine or quetiapine. A meta-analysis of RCTs on risperidone suggests that in comparison to placebo risperidone has significantly higher odds ratio for EPS in children (Pringsheim et al.(a), 2011). In this regard our result is consistent with other

studies lower risk with quetiapine and olanzapine with only quetiapine being statistically significant.

Education

According to Manitoba Education, children are required to attend school from the time they reach compulsory school age (7 years of age, or will be reaching 7 years of age by December 31 in a given calendar year) until they attain the age of 18 (Manitoba Education). In our study we have found that among incident users of antipsychotics, about 82% of individuals started their Grade 1 when they were of 5 – 7 years of age. However, no enrolment data was available for students attending First Nations schools (approximately 3%) also, for some students first enrolment record was not available for grade 1. In the general population of age 5-7 years, Grade 1 enrolment was approximately 88.6 % in 2011 (Manitoba Health population report, 2011; Manitoba Education enrolment record, 2010). It appears that the antipsychotic user population started school on time.

Studies looking at educational outcomes in children and adolescents treated with psychopharmacotherapy are limited. A population-based birth-cohort (children born in 1990) study conducted at MCHP determined that the health status had a small but statistically significant role in explaining progress and performance in school (Fransoo et al., 2008). However, socio-economic status and demographic variables affected educational outcomes in several studies (Brownell et al., 2004; Fransoo et al., 2008; Brownell et al., 2010). As per Manitoba Health, the graduation rate in the general population is 83.5% (June 2011). One aim of this study was to evaluate the education

status in the cohort of antipsychotic users during the study duration. A graduation rate of 66% has been confirmed in this population; however, this finding is probably an underestimation of the real rate because of missing data. This finding is also limited to a specific cohort of students. Further longitudinal studies following the entire history of medication use and school performance are warranted to determine accurate graduation rates.

Strengths

This population-based study was conducted using the comprehensive administrative health database of MB. The DPIN database captures more than 90% of all prescriptions filled in the community by MB residents (including registered First Nations) without limitations due to age and type of drug coverage; it is in fact one of the few databases in Canada which include prescription information for children and adolescents.

Prescription data can be linked to patients' diagnoses reported in hospital and medical records and can be linked also to education data allowing for the opportunity to measure educational outcomes in children and adolescents.

Since, this study was conducted on the entire youth population of a Canadian province results are free from sampling errors and can likely be considered representative of the general youth population of Canada.

Limitations

As with any observational study based on administrative data, this study was not devoid of limitations. We did not evaluate the effect of dose of antipsychotics on incidence of adverse events. We did not measure the direct benefit of antipsychotic therapy, or assess the quality of life of young users of antipsychotic medications, and the lack of clinical detail also hampered the opportunity to adjust for channelling bias. It needs to be mentioned also that prescription information provided by administrative databases are dispensation records and there is no assurance that the medications prescribed are actually consumed by patients. In addition, as explained in the Methods section,

diagnoses are linked to users' medical history and their records appear at different times during study period, therefore they cannot directly be attributed to a specific prescription; as a result, no inference can be made about reason for prescribing. Prevalence of diagnoses cannot be compared to that of other reports as wide variability is expected (Bobo et al., 2013). Lastly, it is recognized that the possibility of unmeasured confounders is always an intrinsic limitation of observational studies.

CONCLUSION

In this study we have found that the utilization of SGAs in the youth population of Manitoba increased between 1996 and 2011, despite the fact that most of these agents are not approved by Health Canada for the indications and the age-groups they are being prescribed. This indicates an extensive off-label use of antipsychotics among children and adolescents. In line with several other studies, we also identified diagnoses of diabetes, hypertension and EPS in this population after initiation of antipsychotic therapy. This study was conducted on a relatively small population; therefore comparisons of incidence of adverse events was limited to hypertension and EPS in users of risperidone, olanzapine and quetiapine . It is also important to mention that the adverse events were observed in all the groups, therefore, no therapy is without risk and it is important that clinicians monitor carefully children treated with antipsychotics to avoid the development of serious adverse events. Finally, young users of antipsychotics seem to be enrolling in school according to patterns similar to those of the general population, while graduation rates might be lower than those of the general population. Additional studies, which will include clinical outcomes and assessment of quality of life parameters, are needed to confirm our results.

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Appendix 1. Rating scales

Positive and negative syndrome scale (PANSS)

PANSS is a 30-item, 7-point severity scale to assess positive and negative symptoms in schizophrenia and general psychopathology. It is more rigorous scale as compared to other rating scales. The PANSS assessment is derived from behavioral information collected from a number of sources including: a clinical interview, observations during the interview and reports by primary care or hospital staff or family members. It helps in the assessment of negative, positive, depressive, general features of schizophrenia and enables profiling of syndromes. These scales are helpful in identifying the disease state and response of the patients to the therapy (Kay et al, 1987).

Brief Psychiatric Rating Scale (BPRS)

The BPRS is well established and well known rating scale in psychiatry. It scores 16 symptom such as somatic concern, anxiety, depressive mood, hostility and hallucinations rated from 0 (not present) to 6 (extremely severe) or 1 to 7. BPRS can be used to rate severity of a number of different symptoms and treatment response; however, it does not focus on the negative symptoms. This scale was developed essentially for schizophrenia but also includes symptoms of depression (Mullins et al, 1985).

The Brief Psychiatric Rating Scale for Children (BPRS-C) is not a child version of the well-known 18-item BPRS clinical rating form that has often been applied in the study of severely disturbed adult psychiatric patients. The BPRS-C was developed to provide a descriptive profile of symptoms applicable to a broad range of child and adolescent psychiatric disorders.

The BPRS-C consists of 21 items that are rated on 7-point scales of severity (not present, very mild, mild, moderate, moderately severe, severe, extremely severe). This rating scale structure and specific content was derived from a factor analysis of the 63 items of the Children's Psychiatric Rating Scale. The BPRS-C focuses on symptomatic status which is usually obtained from other clinician ratings forms such as the Children's Global Assessment Scale (Lachar et al, 2001; Hughes et al., 2001).

Global Assessment Scale (GAS)

GAS is a rating scale for evaluating the overall functioning of a subject during a specified time period on a continuum from psychological or psychiatric sickness to health. The scale values range from 1, which represents the hypothetically sickest individual, to 100, the hypothetically healthiest. The scale is divided into ten equal intervals, such as 1-10, 11-20 and so on till 90-100. The vast majority of individuals in treatment will be rated between 1 and 70. Most outpatients will be rated in between 31 to 70, and most inpatients between 1 and 40. GAS is relatively simple (can be used with minimal training) and reliable (less variability), hence it useful in a wide variety of clinical and research settings (Endicott et al., 1976).

Clinical Global Impression (CGI)

CGI is the most widely used brief assessment tool in psychiatry, the CGI is a 3-item observer-rated scale that measures illness severity (CGIS), global improvement or change (CGIC) and therapeutic response. The illness severity and improvement sections of the instrument are used more frequently than the therapeutic response section in both clinical and research settings. The concept of improvement in CGI scale refers to the clinical improvement in patient’s current condition from the condition at the start of the therapy.

It is a 7 point scale from 1 (‘normal’, not ill) to 7 (extremely ill). It is a readily understood practical measurement tool that can easily be used by a clinician in a busy clinical setting (Guy, 1976).

Young Mania Rating Scale (YMRS)

YMRS is used to assess disease severity in patients already diagnosed with mania. This is an 11-item scale intended to be used by a trained clinician who assigns a severity rating for each item based on personal interview (Young et al.,1978; Youngstrom et al., 2002).

Hamilton Anxiety Rating Scale (HAM-A)

HAM-A consists of 14 items each defined by a series of symptoms (anxiety, tension, depressed mood, palpitations, breathing difficulties, sleep disturbances, restlessness and other physical symptoms). It was one of the first rating scales developed to measure the severity of anxiety symptomatology. This is a widely used scale and an accepted outcome measure in clinical trials.

Children Depression Rating Scale (CDRS)

CDRS is derived from the HAM-depression. It is a 16-items scale used to determine the severity of depression in children 6-12 years of age. A score of 15 on CDRS is equivalent to a score of 0 on HAM-depression. Assessment is based on interviews of child, parents and school teacher.

Aberrant Behavior Checklist (ABC)

ABC is 58-item third party informant rating scale developed for institutionalized low functioning adolescents and adults. 58-items are divided into 5 sub-groups. Its applicability to children or community residents is unknown (Johannes, 1991).

Rating of Aggression Against People and/or Property (RAAP)

RAAP scale is a global rating scale of aggression that is completed by a clinician. It is scored from 1 (no aggression) to 5 (intolerable behaviour).

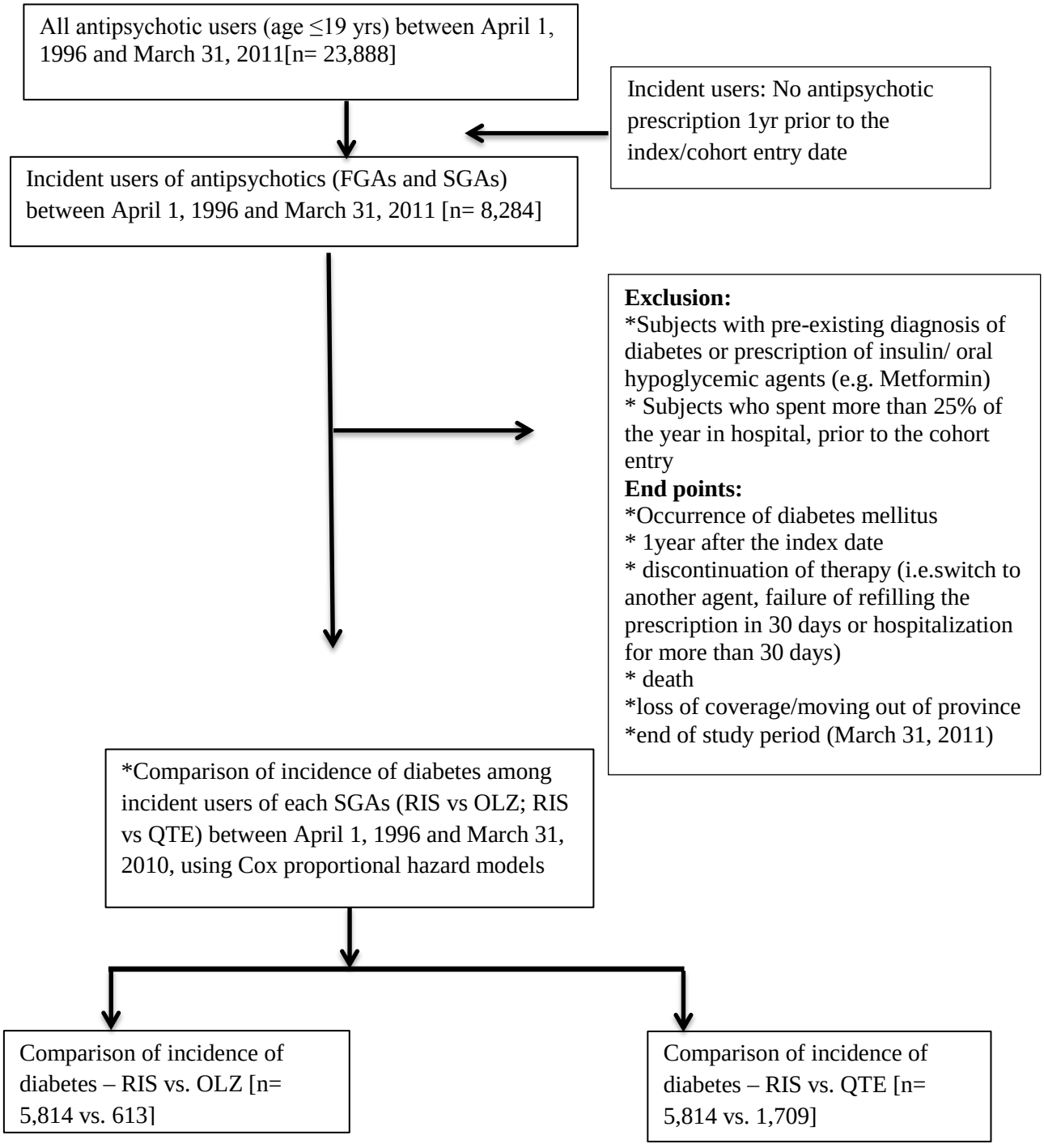
Example of items of rating scales is as follows:

Rating Scales	Items
PANSS- positive scales	P1 Delusions. P2 Conceptual disorganisation. P3 Hallucinatory behaviour. P4 Excitement. P5 Grandiosity. P6 Suspiciousness/persecution. P7 Hostility
BPRS	1. Somatic concern. 2. Anxiety: psychic. 3. Emotional withdrawal. 4. Conceptual disorganisation (incoherence) 5. Self-depreciation and guilt feelings. 6. Anxiety: somatic. 7. Specific movement disturbances. 8. Exaggerated self-esteem. 9. Depressive mood. 10. Hostility. 11. Suspiciousness. 12. Hallucinations. 13. Motor retardation.

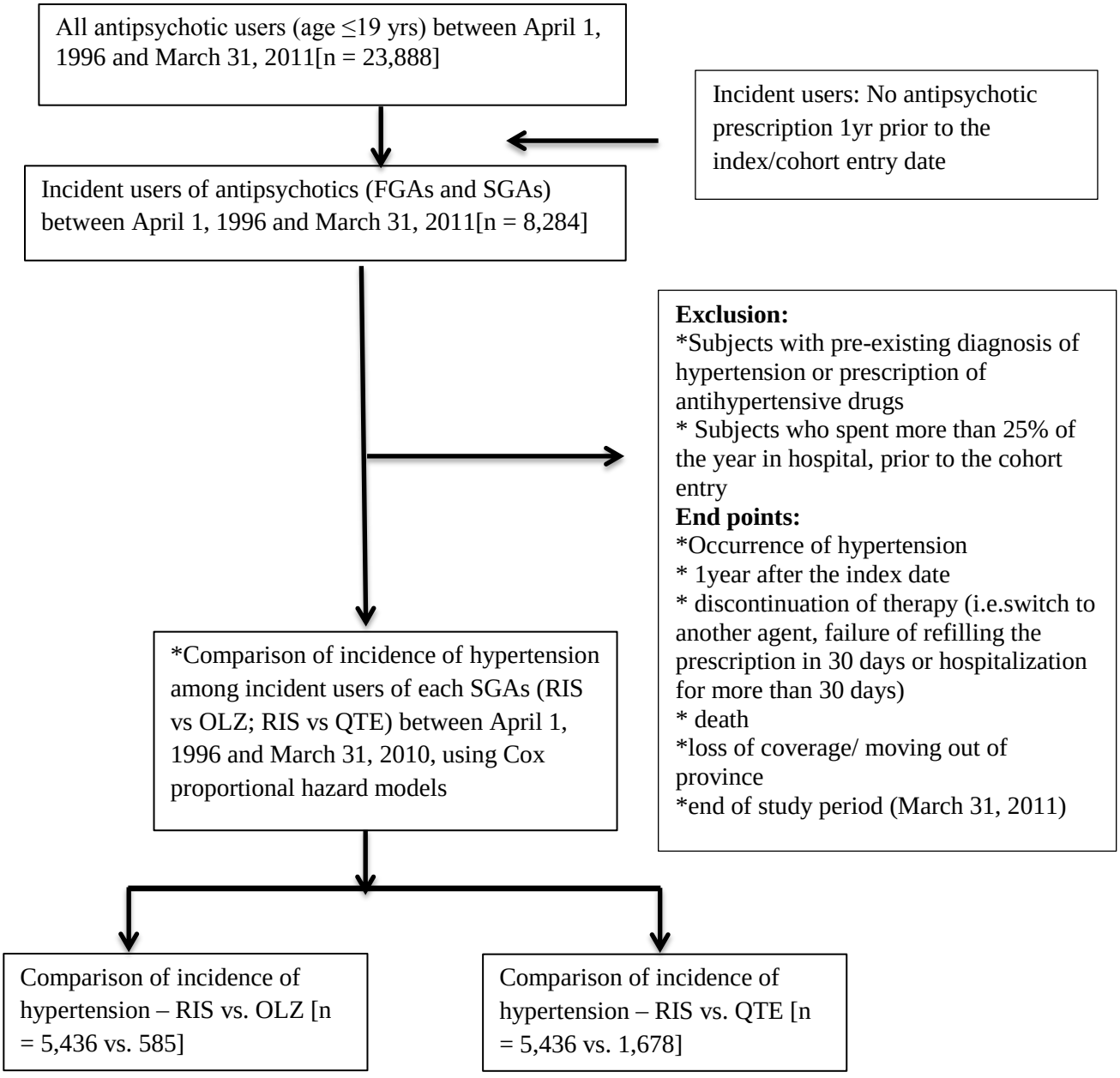
	14. Uncooperativeness. 15. Unusual thought content. 16. Blunted or inappropriate affect
YMRS	1. Elevated mood 2. Increased motor activity and energy 3. Sexual interest 4. Sleep 5. Irritability 6. Speech (rate and amount) 7. Language and thought disorder 8. Content 9. Disruptive-aggressive behaviour 10. Appearance 11. Insight
HAM-A	Item 6: Depressed Mood Unknown. 0= Natural mood. 1=When it is doubtful whether the patient is more despondent or sad than usual. Eg. the patient vaguely indicates to be more depressed than usual. 2=When the patient is more clearly concerned with unpleasant experiences, although he/she is still without helplessness or hopelessness. 3= The patient shows clear nonverbal signs of depression and/or hopelessness. 4= The patient remarks on despondency and helplessness or the patient cannot be distracted from non-verbal signs of depression that dominate the interview.

Appendix 2. Cohort definition

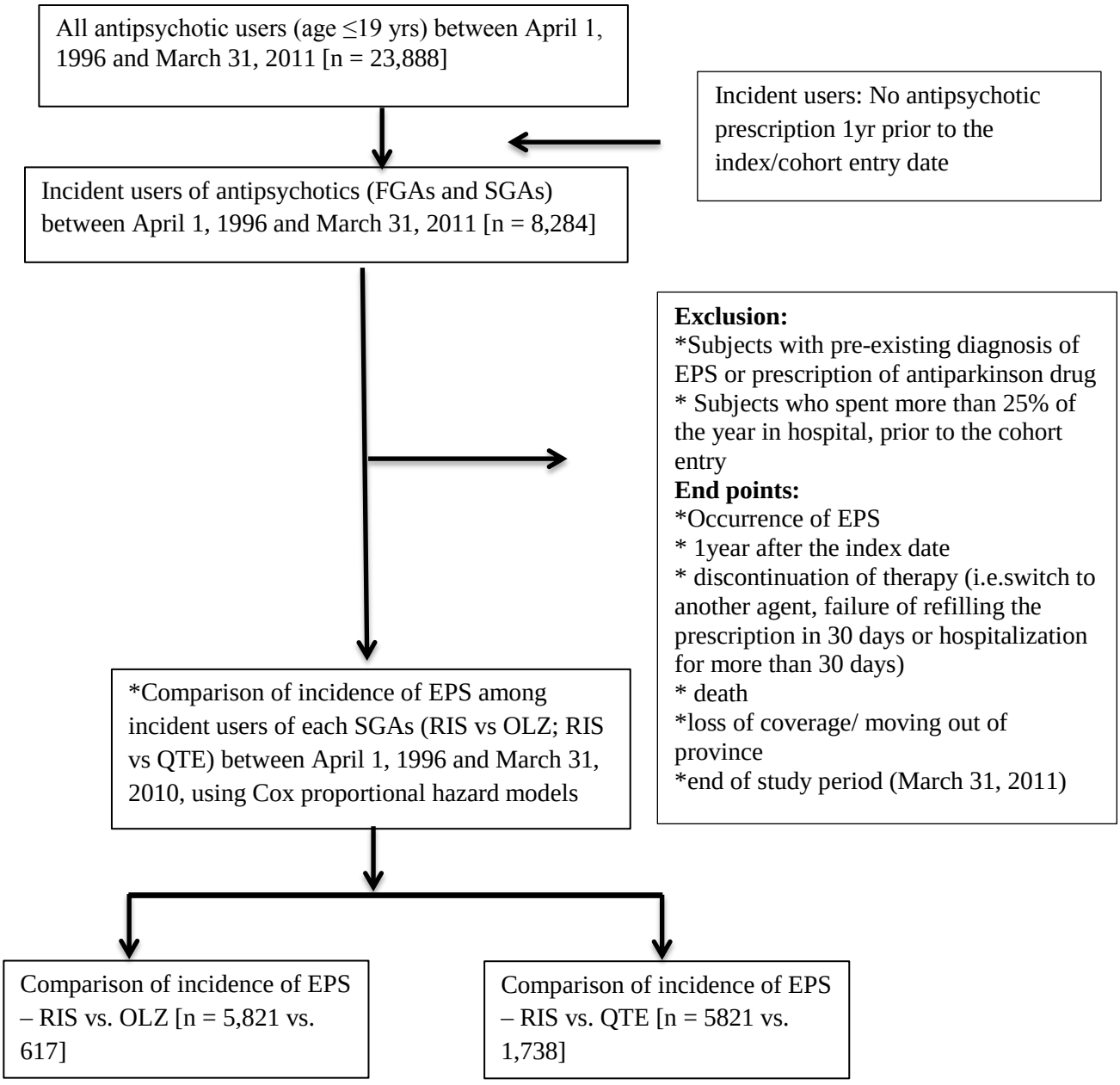
Diabetes



Hypertension



EPS


All antipsychotic users (age ≤19 yrs) between April 1, 1996 and March 31, 2011 [n = 23,888]
Incident users: No antipsychotic prescription 1yr prior to the index/cohort entry date
Incident users of antipsychotics (FGAs and SGAs) between April 1, 1996 and March 31, 2011 [n = 8,284]
Exclusion:
*Subjects with pre-existing diagnosis of EPS or prescription of antiparkinson drug
* Subjects who spent more than 25% of the year in hospital, prior to the cohort entry
End points:
*Occurrence of EPS
* 1year after the index date
* discontinuation of therapy (i.e.switch to another agent, failure of refilling the prescription in 30 days or hospitalization for more than 30 days)
* death
*loss of coverage/ moving out of province
*end of study period (March 31, 2011)
*Comparison of incidence of EPS among incident users of each SGAs (RIS vs OLZ; RIS vs QTE) between April 1, 1996 and March 31, 2010, using Cox proportional hazard models
Comparison of incidence of EPS – RIS vs. OLZ [n = 5,821 vs. 617]
Comparison of incidence of EPS – RIS vs. QTE [n = 5821 vs. 1,738]

Appendix 3. Example SAS code:

Cox proportional hazard ratio

```
proc sort data=eps_cohort1; by scrphin;run;
data table_cox;
merge eps_endpoints1 eps_cohort1 (in=in1);
if in1;
by scrphin;
studyperiod=studyperiod/365.25;
status=0;
if eps in ('rx', 'hsp', 'med', 'dth')then status=1;
run;
proc sql;
create table py as
select scrphin, sum(studyperiod*365.25) as py, status,
atypical
from table_cox
group by atypical;
run;

proc freq data= table_cox; table status*atypical;run;

data ptimes;
set table_cox;
daysfu=endpoint-secondgendate;
run;
proc means data=ptimes; class atypical; var daysfu; run;

*End point=365 days;

data data;
set table_cox;
studyperiod=endpoint-secondgendate;
if studyperiod le 365 then flag_period=365;
run;
data data36;
set data;
if flag_period=365 and status=1 then status365=1;
if status365=. then status365=0;
studyperiod365=studyperiod;
run;
title 'unadjusted cox ph for eps within 365 days';
proc phreg data=data36;
class atypical (ref= '0');
model studyperiod365*status365(0)=atypical/risklimits;
run;
title 'adjusted cox ph for eps within 365 days';
proc phreg data=data36;
class atypical (ref= '0')sex (ref= '1') ;
model studyperiod365*status365(0) = atypical age sex inc
totalperphin incidentyear adg_index
 benzo_flag anticonv_flag antidep_flag anxio_flag epsind_flag
d_296 d_299 d_312 d_314  /risklimits;run;
```

Appendix 4. Example SAS output

unadjusted cox ph for eps within 365 days 524
10:46 Friday, February 7, 2014

The PHREG Procedure

Model Information

Data Set	WORK.DATA36
Dependent Variable	studyperiod365
Censoring Variable	status365
Censoring Value(s)	0
Ties Handling	BRESLOW

Number of Observations Read	6517
Number of Observations Used	6510

Class Level Information

Class	Value	Design Variables
atypical	0	0
	1	1

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
6510	86	6424	98.68

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	1458.016	1449.680
AIC	1458.016	1451.680
SBC	1458.016	1454.135

unadjusted cox ph for eps within 365 days

525

10:46 Friday, February 7,

2014

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	8.3353	1	0.0039
Score	10.7542	1	0.0010
Wald	10.0980	1	0.0015

Type 3 Tests

Wald

Effect	DF	Chi-Square	Pr > ChiSq
atypical	1	10.0980	0.0015

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Label
atypical	1	1	0.88080	0.27718	10.0980	0.0015	2.413	1.401	4.154	atypical 1

The PHREG Procedure

Model Information

Data Set	WORK.DATA36
Dependent Variable	studyperiod365
Censoring Variable	status365
Censoring Value(s)	0
Ties Handling	BRESLOW

Number of Observations Read	6517
Number of Observations Used	6510

Class Level Information

Class	Value	Design Variables

atypical	0	0
	1	1
SEX	1	0
	2	1

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
6510	86	6424	98.68

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	1458.016	1332.965
AIC	1458.016	1364.965
SBC	1458.016	1404.234

adjusted cox ph for eps within 365 days

527

10:46 Friday, February 7, 2014

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	125.0507	16	<.0001
Score	134.5784	16	<.0001
Wald	109.4765	16	<.0001

Type 3 Tests

Effect	DF	Wald Chi-Square	Pr > ChiSq
atypical	1	0.9302	0.3348
age	1	33.1536	<.0001
SEX	1	0.0814	0.7753
inc	1	0.0082	0.9280
totalperphin	1	0.0536	0.8168
incidentyear	1	1.5453	0.2138
adg_index	1	0.9306	0.3347
benzo_flag	1	15.5429	<.0001
anticonv_flag	1	5.0239	0.0250
antidep_flag	1	3.9112	0.0480
anxio_flag	1	5.4539	0.0195
epsind_flag	1	2.0544	0.1518
d_296	1	0.8813	0.3479
d_299	1	1.0199	0.3125
d_312	1	0.0067	0.9347
d_314	1	7.3079	0.0069

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits
atypical	1	1	-0.28303	0.29345	0.9302	0.3348	0.753	0.424 1.339
age		1	0.24103	0.04186	33.1536	<.0001	1.273	1.172 1.381
SEX	2	1	0.06634	0.23246	0.0814	0.7753	1.069	0.678 1.685
inc		1	0.01584	0.17529	0.0082	0.9280	1.016	0.721 1.432
totalperphin		1	0.00609	0.02631	0.0536	0.8168	1.006	0.956 1.059
incidentyear		1	0.03971	0.03194	1.5453	0.2138	1.041	0.977 1.108
adg_index		1	-0.50530	0.52381	0.9306	0.3347	0.603	0.216 1.684
benzo_flag		1	1.42602	0.36171	15.5429	<.0001	4.162	2.048 8.457
anticonv_flag		1	-1.04231	0.46502	5.0239	0.0250	0.353	0.142 0.877
antidep_flag		1	-0.51916	0.26251	3.9112	0.0480	0.595	0.356 0.995
anxio_flag		1	-0.86624	0.37093	5.4539	0.0195	0.421	0.203 0.870
epsind_flag		1	0.65487	0.45689	2.0544	0.1518	1.925	0.786 4.713
d_296		1	0.13330	0.14199	0.8813	0.3479	1.143	0.865 1.509
d_299		1	0.19130	0.18942	1.0199	0.3125	1.211	0.835 1.755

adjusted cox ph for eps within 365 days

528

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits
d_312	1	0.01438	0.17562	0.0067	0.9347	1.014	0.719 1.431
d_314	1	-0.61603	0.22788	7.3079	0.0069	0.540	0.346 0.844

Analysis of Maximum Likelihood Estimates

Parameter		Label
atypical	1	atypical 1
age		
SEX	2	Sex of patient 2
inc		
totalperphin		
incidentyear		
adg_index		
benzo_flag		Benzodiazepines
anticonv_flag		anticonvulsants
antidep_flag		antidepressants
anxio_flag		anxiolytics
epsind_flag		EPS inducing agents
d_296		Mood disorders
d_299		Autism
d_312		Conduct disorders
d_314		ADHD

Appendix – 5. Approvals

Pledge of confidentiality – The Personal Health Information Act

Research Ethics Board approval – Reference Number H2012:150

Health Information Privacy Committee approval – File Number 2012/2013-16

Manitoba Centre for Health Policy approval – Project Number 2012-044

Manitoba Education

WRHA approval for Emergency care

UNIVERSITY OF MANITOBA

Pledge # 102-3324

PLEDGE OF CONFIDENTIALITY
PERSONAL HEALTH INFORMATION

I acknowledge that I have successfully completed ***The Personal Health Information Act*** (PHIA) training offered by the University. I have read and understood the University of Manitoba ("the University") policy on security and confidentiality of personal health information as described in The FIPPA and PHIA Policy, which is in accordance with ***The Personal Health Information Act.***

I have read and understood the University procedures on security and confidentiality of personal health information as described in The FIPPA and PHIA Procedures, including procedures relating to collection, access, use, disclosure, retention and storage, and destruction of personal health information. I have successfully completed the PHIA training offered by the University.

In consideration of my association (including as a student, if applicable), appointment, employment, or contract with the University ("my relationship"), and as an integral part of the terms and conditions of my relationship, I hereby agree, pledge and undertake that I will not at any time, during my relationship with the University, access or use personal health information, or reveal or disclose to any persons within or outside the University, any personal health information except as may be required in the course of my duties and responsibilities, in accordance with applicable laws, and pursuant to University and departmental policies governing proper release of the information.

I understand that my obligations concerning the protection of confidentiality relate to all personal health information in the custody or under the control of the University that I may gain access to, directly or indirectly, as a result of my relationship.

I understand that the obligations outlined above will continue after my relationship with the University ends.

I understand that unauthorized use or disclosure of personal health information may result in disciplinary action being taken, and/or legal action at the discretion of the University.

Sarita Jha
Name of Individual Making Pledge (Print)

[redacted]
Signature of Individual Making Pledge

Pharmacy
Faculty/Department/Program/Office/Unit/Site

Oct 05, 2011
Date Signed

Administrative Use only

[redacted]
Access & Privacy Office
University of Manitoba

Oct 7/11
Date Signed

Return to: Access & Privacy University of Manitoba 233 Elizabeth Dafoe Library Winnipeg, Manitoba R3T 2N2

UNIVERSITY OF MANITOBA | BANNATYNE CAMPUS
Research Ethics Boards

P126 - 770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Tel: (204) 789-3255
Fax: (204) 789-3414

APPROVAL FORM

Principal Investigator: Ms. S. Jha
Supervisor: Dr. S. Alessi-Severini

Ethics Reference Number: H2012:150
Date of Approval: May 24, 2012
Date of Expiry: May 24, 2013

Protocol Title: Use of Antipsychotic Medications in the Youth Population of Manitoba: Safety and Effectiveness (Linked to H2006:145)

The following is/are approved for use:

- **Proposal submitted April 9, 2012**
- **Data Capture Sheet, Version dated May 22, 2012**

The above underwent delegated review and was **approved as submitted** on May 24, 2012 by Dr. John Arnett, Ph.D., C. Psych., Health Research Ethics Board, Bannatyne Campus, University of Manitoba on behalf of the committee per your submission dated April 9, 2012 and May 22, 2012. The Research Ethics Board is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement, and the applicable laws and regulations of Manitoba. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the *Food and Drug Regulations of Canada.*

This approval is valid for one year only. A study status report must be submitted annually and must accompany your request for re-approval. Any significant changes of the protocol and informed consent form should be reported to the Chair for consideration in advance of implementation of such changes. The REB must be notified regarding discontinuation or study closure.

This approval is for the ethics of human use only. For the logistics of performing the study, approval must be sought form the relevant institution, if required.

Sincerely yours,

John Arnett, Ph.D., C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Ethics Reference Number on all correspondence.
Inquiries should be directed to REB Secretary
Telephone: (204) 789-3255 / Fax: (204) 789-3414

UNIVERSITY OF MANITOBA | BANNATYNE CAMPUS
Research Ethics Board

P126 - 770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Telephone 204-789-3255
Fax 204-789-3414

HEALTH RESEARCH ETHICS BOARD (HREB)

CERTIFICATE OF ANNUAL APPROVAL

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Ms. S. Jha	U of M/Pharmacy	HS15294(H2012:150)
HREB MEETING DATE (If applicable):	**APPROVAL DATE:** May 20, 2014	**EXPIRY DATE:** May 24, 2015
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable): Dr. S. Alessi-Severini		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
N/A	Use of Antipsychotic Medications in the Youth Population of Manitoba: Safety and Effectiveness (Linked to H2006:145)
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: U of M Internal Funds	

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
April 29, 2014	May 1, 2014

REVIEW CATEGORY OF ANNUAL REVIEW: **Full Board Review** ☐ **Delegated Review** ☒

THE FOLLOWING AMENDMENT(S) and DOCUMENTS ARE APPROVED FOR USE:

Document Name(if applicable)	Version(if applicable)	Date

Annual approval

*Annual approval implies that the most recent **HREB approved** versions of the protocol, Investigator Brochures, advertisements, letters of initial contact or questionnaires, and recruitment methods, etc. are approved.*

Consent and Assent Form(s):

CERTIFICATION

The University of Manitoba (UM) Health Research Board (HREB) has reviewed the annual study status report for the research study/project named on this ***Certificate of Annual Approval*** as per the category of review listed above and was found to be acceptable on ethical grounds for research involving human participants. Annual approval was granted by the Chair or Acting Chair, UM HREB, per the response to the conditions of approval outlined during the initial review (full board or delegated) of the annual study status report.

HREB ATTESTATION

The University of Manitoba (UM) Health Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

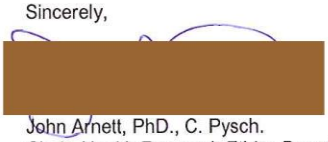
QUALITY ASSURANCE

The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of annual approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the REB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the REB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,



John Arnett, PhD., C. Pysch.
Chair, Health Research Ethics Board
Bannatyne Campus

Manitoba

Health
Health Information Privacy Committee
4043 – 300 Carlton Street
Winnipeg, MB R3B 3M9
T 204-786-7204 **F** 204-944-1911
www.manitoba.ca

October 2, 2012

Sarita Jha
University of Manitoba
164-Apotex Centre
750 McDermot Avenue
Winnipeg, MB R3E 0T5

File No. 2012/2013 – 16

Dear Sarita:

Re: Use of Antipsychotic Medications in the Youth Population of Manitoba: Safety & Effectiveness

Thank you for providing clarification for the above named project. The Health Information Privacy Committee has now ***approved*** your request for data for this project.

Any significant changes to the proposed study design should be reported to the Chair/HIPC for consideration in advance of their implementation. Also, please be reminded that *all manuscripts and presentation materials resulting from this study must be submitted for review at least 30 days prior to being submitted for publication or presentation.*

Please note that a Researcher Agreement will need to be completed before work on this project can commence. This will be initiated by the MCHP. If you have any questions or concerns, please do not hesitate to contact Lisa LaBine, Committee Coordinator at 204-786-7204.

Yours truly,

[redacted]

For:

D. Biehl, MD, FRCP
Chair, Health Information Privacy Committee

Please quote the file number on all correspondence

c.c. D. Malazdrewicz
S. Alessi-Severini

Manitoba
spirited energy

UNIVERSITY OF MANITOBA | Faculty of Medicine
Community Health Sciences

Manitoba Centre for Health Policy
408-727 McDermot Avenue
Winnipeg, Manitoba
Canada, R3E 3P5
Telephone (204) 789-3819
Fax (204) 789-3910
info@cpe.umanitoba.ca

October 24, 2012

Sarita Jha
Faculty of Pharmacy
164 Apotex Centre
750 McDermot Avenue
Winnipeg, MB R3E 0T5

Dear Sarita:

Re: "Use of Antipsychotic Medications In The Youth Population Of Manitoba: Safety And Effectiveness"
MCHP project number: "2012-044"

Enclosed is a copy for your records of the fully executed Researcher Agreement, representing approval to proceed with the above research project at the Manitoba Centre for Health Policy (MCHP) using Manitoba Health data. It is important that the requirements outlined in this agreement be shared with all members of your project team, specifically Section 5 obligations respecting use and disclosure and Section 6 regarding reports, monitoring and enforcement. It is also important that all correspondence with MCHP relating to this project reference the MCHP project number.

We look forward to facilitating access to the Population Health Research Data Repository for your project. To proceed, please contact Charles Burchill (Manager, Program and Analysis System) at charles_burchill@cpe.umanitoba.ca. Sophie Buternowsky, Senior grants Accountant, at MCHP will be contacting you regarding invoicing for your project.

If any changes are made to the original approved study protocol, they must be submitted to the Health Research Ethics Board for approval and the data providers. A copy of the submissions and approvals must also be sent to MCHP.

We would be glad to assist you in meeting ongoing project requirements for maintaining access to the data, as outlined at our website:
http://umanitoba.ca/faculties/medicine/units/community_health_sciences/departmental_units/mchp/resources/access.html

Should you have any questions, please do not hesitate to contact me at (204) 975-7770.

Sincerely,

[redacted]

Jo-Anne Baribeau
Repository Access Coordinator

Manitoba Centre for Health Policy

umanitoba.ca/medicine/units/mchp/

UNIVERSITY OF MANITOBA | Faculty of Pharmacy

Apotex Centre
750 McDermot Avenue
Winnipeg, Manitoba
Canada R3E 0T5
Telephone (204) 474-9306
Fax (204) 474-7617

July 18, 2012

Dr. Gerald Farthing
Deputy Minister
Manitoba Education
Room 156 Legislative Building
450 Broadway Avenue
Winnipeg, Manitoba R3C 0V8

Dear Dr. Farthing

Re Project: **"Use of antipsychotic medications in the youth population of Manitoba: Safety and Effectiveness"**

Recent reports on the use of antipsychotic medications in Canada suggest a significant increase in off-label prescribing to children and adolescents. The rise in prescriptions for antipsychotic agents started in the late 1990s with the introduction of second-generation agents (SGAs), (e.g. risperidone, olanzapine, quetiapine) as they appeared to have better safety profiles compared to the conventional first-generation agents (FGAs), (e.g. haloperidol and phenothiazines) especially in terms of movement disorders. A recent study (Alessi-Severini et al, 2012) on youth population of Manitoba suggests that prevalence of use of antipsychotic medications in young females increased significantly over the period of 1999 to 2008 this increase in prevalence among young males were found to be much higher during the same period . Although SGAs show a lower risk for movement disorders, long-term use of SGAs is associated with a higher risk of metabolic adverse events. SGAs are approved in Canada for the treatment of schizophrenia and bipolar disorder in adults; however, the most common diagnoses linked to the use of these agents in children were attention-deficit hyperactivity disorder (ADHD) and conduct disorders. As more reports on serious adverse events become available, it is important to evaluate the safety and effectiveness of antipsychotics in children and adolescents. Furthermore, the effect of antipsychotics on the academic performance of children is unknown. As education plays a crucial role in the development and wellbeing of children, it is very important to evaluate how antipsychotic therapy affects their academic performance.

This population-based study will determine rates of adverse events (e. g. cardiovascular events, metabolic disturbances, extrapyramidal symptoms) in the entire youth population of the province of Manitoba treated with antipsychotic medications.
Effectiveness of SGAs treatment will be determined by longitudinal evaluation of indicators such as hospitalizations rates, use of the health care system (e.g. physicians' visits, emergency room visits), and schooling records (such as continuity of enrolment, grades and drop-out rates). This study will give insight into the effect of antipsychotic medications on the academic performance of young patients.

Approval by the Health Research Ethics Board (HREB) has been received (H2012:150).
This project has also been submitted for approval by the Manitoba Health Information Privacy Committee (HIPC). Copies of these approvals will be on file at the Manitoba Centre for Health Policy (MCHP). If you require a copy, please let me know. As well, all of the data analyses will be conducted at MCHP remote access site at the Faculty of Pharmacy (University of Manitoba).

As required, I seek your permission for the access and use of the Education data housed in the Manitoba Population Health Research Data Repository at MCHP. For use of your data, you or your designate will receive early drafts of papers at which time I welcome your input in ensuring that aspects of your program are accurately represented and confidentiality is maintained. If it is of interest, I will be happy to provide you with briefings on the outcomes of this project prior to its public release.

This project, as most projects publicly funded and undertaken by university researchers, assumes the right to publish results obtained as part of the research, subject to established safeguards for the protection of privacy or confidentiality of personal data.

In compliance with the Manitoba Personal Health Information Act (PHIA) section 24(4) I agree:

- not to publish the personal health information and/or personal information requested in a form that could reasonably be expected to identify the individuals concerned;
- to use the personal health information and/or personal information requested solely for the purposes of this approved research project; and
- to ensure that the research project contains reasonable safeguards to protect the confidentiality and security of the personal health information and/or personal information and procedures to remove all identifying information at the earliest opportunity consistent with the purposes of the project.

The above conditions specified in the PHIA with respect to personal health information will also be adhered to with respect to personal information in the Education datasets. As required, access to data is only permitted upon approval of the specific project from you or your appointee. I now officially seek your approval for use of these data for the project "Use of antipsychotic medications in the youth population of Manitoba: Safety and Effectiveness" (Protocol Synopsis attached). If you are in agreement with this request, I would be most appreciative if you would sign and date below indicating your approval, and return a copy to MCHP at your earliest convenience.

I look forward to working with you and providing you with important policy relevant research.

Yours sincerely

[redacted]

Sarita Jha
Graduate Student, Faculty of Pharmacy
University of Manitoba
Email: jhas@cc.umanitoba.ca

cc: Dr. Wenda Dickens, Early Childhood Education Unit, Manitoba Education
Deborah Malazdrewicz, Executive Director, Health Information Management, Manitoba Health
MCHP, Repository Access Coordinator

Enclosed: Protocol Synopsis

I approve the access and use of the Manitoba Education data located in the Population Health Research Data Repository at MCHP for the project entitled, "Use of antipsychotic medications in the youth population of Manitoba: Safety and Effectiveness."

[redacted] Aug 28/12

Dr. Gerald Farthing, Deputy Minister — Date
Manitoba Education

UNIVERSITY OF MANITOBA | Faculty of Pharmacy

Apotex Centre
750 McDermot Avenue
Winnipeg, Manitoba
Canada R3E 0T5
Telephone (204) 474-9306
Fax (204) 474-7617

July 18, 2012

Michael Moffatt, MD, MSc, FRCPC
Chair, WRHA Research Review Committee
Winnipeg Regional Health Authority
4th Floor, 650 Main St.
Winnipeg MB R3B 1E2

Dear Dr. Moffatt,

Re Project: **"Use of antipsychotic medications in the youth population of Manitoba: Safety and Effectiveness"**

Recent reports on the use of antipsychotic medications in Canada suggest a significant increase in off-label prescribing to children and adolescents. The rise in prescriptions for antipsychotic agents started in the late 1990s with the introduction of second-generation agents (SGAs), (e.g. risperidone, olanzapine, quetiapine) as they appeared to have better safety profiles compared to the conventional first-generation agents (FGAs), (e.g. haloperidol and phenothiazines) especially in terms of movement disorders. A recent study (Alessi-Severini et al, 2012) on youth population of Manitoba suggests that prevalence of use of antipsychotic medications in young females increased significantly over the period of 1999 to 2008 this increase in prevalence among young males were found to be much higher during the same period . Although SGAs show a lower risk for movement disorders, long-term use of SGAs is associated with a higher risk of metabolic adverse events. SGAs are approved in Canada for the treatment of schizophrenia and bipolar disorder in adults; however, the most common diagnoses linked to the use of these agents in children were attention-deficit hyperactivity disorder (ADHD) and conduct disorders. As more reports on serious adverse events become available, it is important to evaluate the safety and effectiveness of antipsychotics in children and adolescents. Furthermore, the effect of antipsychotics on the academic performance of children is unknown. As education plays a crucial role in the development and wellbeing of children, it is very important to evaluate how antipsychotic therapy affects their academic performance.

This population-based study will determine rates of adverse events (e. g. cardiovascular events, metabolic disturbances, extrapyramidal symptoms) in the entire youth population of the province of Manitoba treated with antipsychotic medications.

Effectiveness of SGAs treatment will be determined by longitudinal evaluation of indicators such as hospitalizations rates, use of the health care system (e.g. physicians' visits, emergency room visits), and schooling records (such as continuity of enrolment, grades and drop-out rates). This study will give insight into the effect of antipsychotic medications on the academic performance of young patients.

This project is being lead by Sarita Jha, Graduate Student from Faculty of Pharmacy, University of Manitoba.
This project has received approval by University of Manitoba Health Research Ethics Board (HREB) ((H2012:150). This project has been submitted for approval to the Manitoba Health Information and Privacy Committee (HIPC). Copies of these approvals will be sent to you and will also be on file at the Manitoba Centre for Health Policy (MCHP) prior to any data access. All data access and analysis will be conducted at MCHP remote access site at the Faculty of Pharmacy (University of Manitoba).

As required in the Data Sharing Agreement between the University of Manitoba and the Winnipeg Regional Health Authority (WRHA), I seek your permission for the access and use of the WRHA data detailed in the attached HIPC application which is housed in the Population Health Research Data Repository at MCHP. For use of your data, you or your designate will receive early drafts of papers at which time we welcome your input in ensuring that aspects of your program are accurately represented and confidentiality is maintained. If it is of interest, we will be happy to provide you with briefings on the outcomes of this project prior to its public release.

This project, as most projects publicly funded and undertaken by university researchers, assumes the right to publish results obtained as part of the research, subject to established safeguards for the protection of privacy or confidentiality of personal data.

In compliance with the Manitoba Personal Health Information Act (PHIA) section 24(4) - we agree as follows:

- not to publish the personal health information and/or personal information requested in a form that could reasonably be expected to identify the individuals concerned;
- to use the personal health information and/or personal information requested solely for the purposes of the approved research project; and
- to ensure that the research project contains reasonable safeguards to protect the confidentiality and security of the personal health information and/or personal information and procedures to remove all identifying information at the earliest opportunity consistent with the purposes of the project.

As required, access to data is only permitted upon approval of the specific project from you or your appointee. This letter is to seek your approval for use of these data for the project "Use of antipsychotic medications in the youth population of Manitoba: Safety and Effectiveness" (Protocol Synopsis attached).

If you are in agreement with this request, please sign and date below indicating your approval, and return a copy to MCHP at your earliest convenience.

Thank you.

Yours sincerely

[redacted]

Sarita Jha
Graduate Student, Faculty of Pharmacy
University of Manitoba
Email: jhas@cc.umanitoba.ca

cc: Landis Esposito, Privacy Officer, Winnipeg Regional Health Authority
Deborah Malazdrewicz, Executive Director, Health Information Management, Manitoba Health
Jo-Anne Baribeau, MCHP Repository Access Coordinator

encls: Protocol Synopsis and HIPC application,

I approve the access and use of the "Emergency Care- ADT and E-triage [WRHA]" Data located in the Population Health Research Data Repository housed at MCHP for the project entitled, "Use of antipsychotic medications in the youth population of Manitoba: Safety and Effectiveness."

[redacted] Aug 7, 2012

Dr. Michael Moffatt, Executive Director — Date
Research and Applied Learning Division
Winnipeg Regional Health Authority