Journal of Population Therapeutics and Clinical Pharmacology
INCORPORATING FETAL ALCOHOL RESEARCH
Journal de la thérapeutique des populations et de la pharmacologie clinique

Original Research
10.22374/1710-6222.24.3.2

INCREASE IN PSYCHOACTIVE DRUG PRESCRIPTIONS IN THE YEARS FOLLOWING AUTISM SPECTRUM DIAGNOSIS: A POPULATION-BASED COHORT STUDY

Caroline Croteau[1]; Laurent Mottron[2]; Nancy Presse[1]; Jean-Eric Tarride[3]; Marc Dorais [4]; Sylvie Perreault[1]

[1]Faculty of Pharmacy, University of Montreal, Montreal, Quebec, Canada.

[2]Rivière des Prairies Hospital, Montreal, Quebec, Canada.

[3]McMaster University, Hamilton, Ontario, Canada.

[4]StatSciences Inc., ND Ile-Perrot, Quebec, Canada.

Correspondence may be directed to: sylvie.perreault@umontreal.ca

Submitted: February 25, 2017. Accepted: July 27, 2017. Published: August 18, 2017.

Abstract

Background
Psychoactive medications are commonly prescribed to autistic individuals, but little is known about how their use changes after diagnosis.

Objectives
This study describes the use of psychoactive drugs in children and young adults newly diagnosed with autism spectrum, between the year before and up to 5 years after diagnosis.

Methods
Multivariable logistic regression was used to examine the relationship between the use of psychoactive drugs before the first diagnosis of autism spectrum condition (from 1998 to 2010), and the clinical and demographic characteristics, identified from public health care databases in Quebec. The types of drugs prescribed and psychoactive polypharmacy were evaluated over 5 years of follow-up. Generalized estimating equations (GEE) were used to examine the association of age and time with the use of psychoactive drugs.

Results
In our cohort of 2,989 individuals, diagnosis of another psychiatric disorder before autism spectrum strongly predicted psychoactive drug use. We observed that the proportion of users of psychoactive drugs

increased from 35.6% the year before, to 53.2% 5 years after the autism spectrum diagnosis. Psychoactive polypharmacy (≥2 psychoactive drug classes) also increased from 9% to 22% in that time. Age and time since diagnosis strongly associated with the types and combinations of psychoactive drugs prescribed.

Conclusion

Psychoactive drug use and polypharmacy increases substantially over time after autism spectrum disorder diagnosis in children.

Key Words: *autism spectrum disorder, psychoactive drugs, medication use, polypharmacy*

Autism is a lifelong developmental condition defined by qualitative and quantitative alterations in social communication and interaction, and by restricted and repetitive behaviour, interests or activities. It is identified as ''Autism spectrum disorder" (''ASD") in the DSM-5.[1] Autism is increasingly recognized as a public health issue. The prevalence of the autism spectrum is increasing and was most recently estimated at between 1 and 2% of children.[2] This rising trend could be in part due to evolving diagnostic criteria, combined with increased medical and public awareness of the disorder.[3,4] Autistic individuals frequently suffer from comorbid psychological disorders further impairing psychosocial functioning.[5] Autism has no cure. Current interventions mostly focus on improving adaptive abilities by a combination of behavioural, educational, medical, and allied health therapies.[6,7]

Support for the use of pharmacologic interventions in the autism spectrum is growing.[8,9] Although medication can be useful for addressing challenging behaviours sometimes associated with the autism spectrum,[5,9] it is unclear whether psychoactive drugs are useful to manage the core features of the disorder[7] or to improve quality of life.[10] Supporting evidence is also lacking for treatment of psychiatric comorbidity in the autism spectrum.[11] Nonetheless, autistic individuals commonly receive psychoactive drugs, often in combination, including antipsychotics, antidepressants, psychostimulants, anticonvulsants, mood stabilizers, anxiolytics and sedatives.[12] Although not indicated as per the Canadian product label, only 2 medications, risperidone and aripiprazole, are approved by the FDA for the treatment of aggression and irritability.[6,9] Moreover, little is known about the safety and efficacy of psychotropic polypharmacy.[13] A concern regarding psychotropic drug use in the autism spectrum is that it increases with age. Data from Medicaid and commercial health plans reported that 40–71% of autistic children and adolescents use psychotropic medication.[14–18] Parent surveys from registries[19,20] report use of psychotropic medications slightly lower (27–35%). Rates of drug use[14–16,18–20] and polypharmacy[14,15,18,19] increase with age, with 5% of autistic children receiving more psychotropic medication per year of age.[16] An increase in psychotropic drug use with age, from 70–81% over 4.5 years, was also reported for 286 autistic adolescents and youth.[21]

Another preoccupying factor is that rates of psychoactive drug use also vary greatly depending on country of origin. Studies from Western Europe suggest more conservative prescription practices. In a UK study based on The Health Improvement Network (THIN), only 29% of autistic individuals were prescribed psychotropic drugs.[22] A German study of autistic individuals using national health insurance data found that 33% used psychopharmacological treatments.[23] These varied rates raise questions about potential under- or over-prescription of psychoactive drugs in the autism spectrum.

Although studied in the United States and Europe, data on the use of psychoactive drugs in Canada is limited. In Quebec, 14.3% of families with young autistic children and over 50% of autistic adolescents file claims with the public drug insurance plan.[24] So far, studies documenting drug prescription practices in the autism spectrum are mostly cross-sectional and based on *prevalent* cases. Studies examining the use of psychoactive drugs over time among newly diagnosed individuals, also referred to as *incident* cases, may improve our understanding of current prescription practices for children at various developmental stages. Here, we used a population-based cohort design to study psychotropic drug-prescribing patterns after ''ASD" diagnosis, in a longitudinal fashion. Variations

in the use and combinations of psychoactive drugs were evaluated from the year before and up to 5 years after diagnosis, while accounting for age at diagnosis.

METHODS

Data Sources and Study Sample

Data were obtained from the *Régie de l'assurance maladie du Québec* (RAMQ), which administers public health services for all residents of Quebec, Canada. Demographic data on RAMQ beneficiaries include age, sex, demographic region and date of death. The RAMQ databases document claims for medical services (outpatient, inpatient and emergency room visits), pharmaceutical services, and ICD-9 (International Classification of Diseases: 9th revision) diagnostic and procedure codes.[25–27] The data provided by RAMQ for this study spans from January 1993 to December 2010.

Autistic individuals were identified from the medical services database by an algorithm requiring ≥2 diagnostic codes for ''ASD," defined as ICD-9 code 299.X (excluding 299.2), recorded in the 12 years between January 1998 and December 2010 (Figure 1). We included diagnostic codes repeated at least twice to reduce the risk of misclassification.[18,28] The cohort entry date was defined as the date of the first recorded

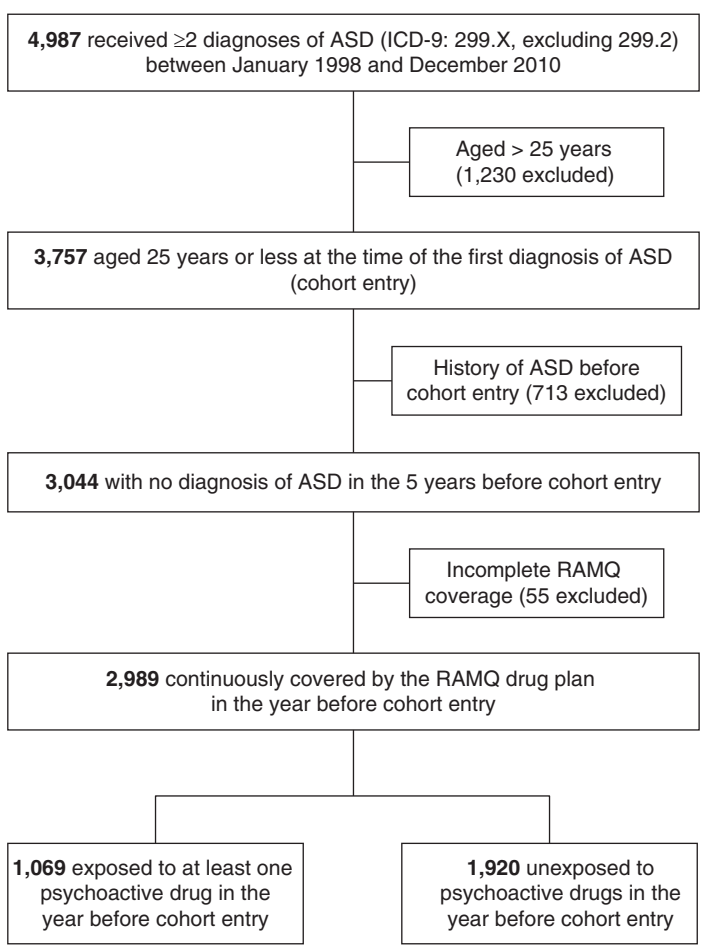

FIG. 1 Flowchart of sample selection for the analysis of psychoactive medication use in incident cases of autism spectrum disorder (ASD) among individuals covered by the RAMQ public drug insurance plan.

''ASD" diagnostic code. Prevalent cases (individuals diagnosed in the 5 years before cohort entry) and those aged ≥ 26 years at cohort entry were excluded to ensure the study sample only contained incident cases involving children and youth. Individuals not covered by the RAMQ drug insurance plan for the entire year preceding cohort entry were also excluded. Individuals were followed for 5 years after cohort entry, or until death, disenrollment of the RAMQ drug plan, or end of the study period (December 2010).

Psychoactive Medication Use

We further identified individuals receiving at least one psychoactive drug within the year preceding and the 5 years following cohort entry. Use of psychoactive drugs was defined as ≥1 psychoactive drug claim in a given year. We determined the psychoactive drug class for the year preceding and the 5 years following cohort entry. Drug classes were categorized according to the American Hospital Formulary System[29] and included anticonvulsants, antipsychotics, antidepressants, anxiolytics and attention-deficit hyperactivity disorder (ADHD) drugs (stimulants and atomoxetine). The most commonly prescribed molecule for each drug class was identified for the study period.

Demographic and Clinical Characteristics

We recorded gender, age at diagnosis, demographic region, the number of visits to a general practitioner or specialist (pediatrician, neurologist, psychiatrist), number of hospitalizations during the year before cohort entry and length of hospital stay. We also documented the types of non-autistic neuropsychiatric disorders diagnosed within the year preceding cohort entry (ICD-9 295-298; 300-319; 345). These disorders included schizophrenia (ICD-9 295), mood disorders (ICD-9 296; 311), anxiety disorders (ICD-9 300), conduct disorders (ICD-9 312-313), ADHD (ICD-9 314), delays in development (ICD-9 315), intellectual disability (ICD-9 317-319) and epilepsy (ICD-9 345). The characteristics were presented for the entire cohort and stratified by the use / no use of psychoactive drugs within the year preceding the cohort entry. This stratification was employed to separate individuals with a more severe health condition (users of psychoactive drugs) from the others (non-users).

Data Analysis

We stratified the entire cohort by psychoactive drug users and non-users and age subgroup (1–5, 6–12, 13–17, and 18–25 years old). Values are presented as percentage, mean ± standard deviation (SD) or median with first quartile (Q1) and third quartile (Q3). Comparisons of demographic and clinical characteristics between users and non-users of psychoactive drugs within the year before cohort entry were done using the Pearson Chi-Square test (or Fisher Exact test if small number of observations) for categorical variables and t-test (or Wilcoxon Mann-Whitney test if non-normal distribution) for continuous variables. A multivariable logistic regression analysis was performed to identify determinants associated with psychoactive drug use in the year preceding ''ASD" diagnosis for the entire cohort. Determinants included gender, calendar year, demographic region of diagnosis, other neurologic and psychiatric conditions, epilepsy, consultation with a medical specialist and hospitalization the year before diagnosis.

Psychoactive polypharmacy was evaluated by calculating the proportion of children who received at least 2 concomitant classes of psychoactive drugs during a minimal period of 90 days for the year prior the cohort entry and over the 5 years of follow-up. The 90-day overlap period was retained since the most stringent definition.[30] Sensitivity analyses were done using minimal concomitant periods of 30 and 60 days. Moreover, the analysis with a minimal period of 90 days was replicated for each age group. A gap of 15 days was permitted between the last day of medication supply and the next fill date (gap of 7 days for the minimal period of 30 days) to account for imperfect adherence and short inpatient stays. The most common combinations of drug classes in each age group were identified. Trends over time and age group were assessed by a generalized estimating equation (GEE), accounting for gender and calendar year of autism spectrum diagnosis.

Proportions of individuals using psychoactive drugs in the year before the cohort entry and for each of the 5 years following were evaluated overall and for each drug class, according to the age group. Trends over time and age group were assessed by

a GEE, accounting for gender and calendar year of ''ASD" diagnosis.

P-values less than 0.05 were considered statistically significant. Analyses were performed using the Statistical Analysis System Software (version 9.4; SAS Institute, Cary, North Carolina). The study was approved by the Research and Ethics Committee of the University of Montreal.

RESULTS

Demographic and Clinical Characteristics

We identified 2,989 incident cases of ''ASD", among which 1,069 were psychoactive drug users (Figure 1). The median time between the first and second diagnosis needed to be included in the cohort was 3.3 months. Table 1 presents the demographic and clinical characteristics according to the age group and use/non-use of psychoactive drugs. Overall, the median age at first diagnosis was 6 years (Q1:3, Q3:12), 80.2% were males, and 80.6% had consulted a medical specialist in the year before diagnosis. Psychoactive drug users were twice as likely to visit specialists as non-users. Hospitalizations were rare and of short duration, although adolescents and young adults were hospitalized for longer periods than children. Among the 2,989 ''ASD" cases, 56.1% of children had been diagnosed with another neuropsychiatric disorder in the year before the cohort entry. Psychoactive drug users consistently presented more neuropsychiatric disorders than non-users. The most frequent disorders were developmental delay for the 1 to 5-year-olds, ADHD for the 6 to 12-year-olds, and anxiety disorders for the adolescents and young adults. Epilepsy and intellectual disability were noticeably more frequent in the older group, especially in psychoactive drug users.

Predictors of Psychoactive Medication Use Before the Cohort Entry

Analyses concerning the determinants of use of psychoactive drugs in the year prior to cohort entry are presented in Table 2. All neuropsychiatric disorders evaluated, with the exception of delays in development, were associated with a greater probability to receive psychoactive medication. Although not statistically significant, visits to a specialist and hospitalization before cohort entry presented the same trend. Predictors by age group were also explored. However, the limited number of observations for each age category introduced some instability in the logistic regression model (data not shown).

Psychoactive Medication Use Over Time

The proportion of psychoactive drug use increased from the year prior to cohort entry (35.6%) to the 5th year of follow-up (53.2%) (Table 3). In the year prior to cohort entry, medication use was below 7% in the 1–5 age group for every psychoactive drug class, but at the 5th year of follow-up antipsychotics and ADHD medication use reached 17.5% and 21.8%, respectively. In the 6–12 age group, antipsychotics and ADHD medication use were more common in the year prior, ADHD drugs use remained stable during follow-up, whereas antipsychotic use increased to almost one-third of individuals at the 5th year. Among the 13–17, the use of the various drug classes was common at the year prior, with several classes increasing substantially during follow-up. With the exception of ADHD medications, all drug classes were frequently prescribed in the 18-25 group in the year prior and were maintained in the following years. Proportions of ADHD drug use increased in the 1–5 group during the 5 years following cohort entry, were highest in the 6–12, but decreased in the older age groups. Anxiolytic use remained relatively stable in all age groups, whereas proportions use of antipsychotics, anticonvulsants and antidepressants steadily increased across all age groups. Time (from the year prior to the 5th year of follow-up) and age group were significantly associated with the use of the different psychoactive classes ($p<0.05$), even after adjusting for potential calendar year trends; however, time did not significantly influence prescriptions of anxiolytic medication ($p=0.31$). Results remained consistent when medication class trends were stratified by gender (data not shown). Use of ADHD drugs was higher in males ($p<0.0001$). Gender also impacted the use of anticonvulsants and anxiolytics.

Methylphenidate was the most prescribed ADHD drug (79.7%). Atypical antipsychotics were the most frequently prescribed antipsychotic (~85% of prescriptions), with risperidone being the most common (43.5%). Valproic acid was the most common

TABLE 1 Demographic and Clinical Characteristics of Incident Cases Of ASD at Cohort Entry (n=2,989).

Age group	All patients			1 – 5 years		
User of psychoact. drugs †	**All**	**Yes**	**No**	**All**	**Yes**	**No**
	(n =2,989)	(n=1,069)	(n=1,920)	(n=1,371)	(n=173)	(n=1,198)
Male — %	80.2	80.0	80.3	80.7	81.5	80.6
Urban — %	91.4	89.5	92.5	93.3	91.9	93.5
Number of visits in the year before cohort entry — mean ± SD						
General practitioner	1.4 ± 2.2	1.3 ± 2.2	1.4 ± 2.2	1.7 ± 2.5	1.9 ± 2.8	1.6 ± 2.4
Specialist	4.9 ± 7.8	6.7 ± 10.3	4.0 ± 5.8*	5.1 ± 6.2	8.0 ± 8.0	4.7 ± 5.8*
Hospitalizations in the year before cohort entry						
Mean number ± SD	0.2 ± 0.6	0.3 ± 0.8	0.2 ± 0.5*	0.2 ± 0.6	0.5 ± 0.9	0.2 ± 0.5*
Length of stay (days) — median	1.3	3.3	1.0	1.0	1.8	1.0
(Q1 – Q3)	(1.0 – 5.5)	(1.0 – 16.0)	(1.0 – 2.0)*	(1.0 – 2.0)	(1.0 – 4.0)	(1.0 – 2.0)*
Other neuropsychiatric disorders in the year before cohort entry — %	56.1	73.5	46.5*	52.4	71.7	49.8*
Schizophrenia	3.2	7.1	1.0*	0.2	0.6	0.1
Mood disorders	3.9	8.4	1.3*	0.2	0.6	0.2
Anxiety disorders	12.5	23.5	6.4*	4.5	10.4	3.6*
Conduct disorders	10.6	18.2	6.4*	6.9	15.0	5.7*
ADHD	14.5	26.3	7.9*	9.7	22.5	7.9*
Delays in development	22.4	18.2	24.6*	32.6	36.4	32.1
Intellectual disability	4.7	8.0	2.8*	3.1	5.8	2.8*
Epilepsy	4.1	9.9	0.9*	3.0	17.3	0.9*

Age group	6 – 12 years			13 – 17 years			18 – 25 years		
	All	**Yes**	**No**	**All**	**Yes**	**No**	**All**	**Yes**	**No**
User of psychoact. drugs †	(*n*=931)	(*n*=455)	(*n*=476)	(*n*=346)	(*n*=201)	(*n*=145)	(*n*=341)	(*n*=240)	(*n*=101)
	81.4	81.3	81.5	79.8	79.1	80.7	75.4	77.1	71.3
Male — %	89.6	88.1	91.0	91.0	89.6	93.1	89.4	90.4	87.1
Urban — %									
Number of visits in the year before cohort entry — mean ± SD	1.1 ± 2.0	1.1 ± 2.1	1.1 ± 2.0	0.9 ± 1.7	0.9 ± 1.8	0.8 ± 1.5	1.5 ± 2.1	1.7 ± 2.3	1.0 ± 1.6*
Hospitalizations in the year before cohort entry	5.4 ± 10.2	7.6 ± 12.7	3.3 ± 6.6*	4.1 ± 6.6	5.6 ± 8.0	2.0 ± 2.9*	4.0 ± 6.8	5.0 ± 7.8	1.5 ± 2.5*
Mean number ± SD									
Length of stay (days) — median	0.2 ± 0.5	0.2 ± 0.6	0.1 ± 0.4*	0.2 ± 0.7	0.3 ± 0.8	0.1 ± 0.3*	0.4 ± 0.9	0.5 ± 1.1	0.1 ± 0.3*
(Q1 – Q3)	1.0 (1.0 – 4.5)	1.4 (1.0 – 12.5)	1.0 (1.0 – 1.0)*	8.5 (1.8 – 28.3)	8.5 (1.0 – 28.0)	8.5 (8.0 – 46.0)	8.0 (2.7 – 23.5)	10.0 (3.0 – 23.5)	4.5 (1.0 – 19.5)
Other neuropsychiatric disorders in the year before cohort entry — %	58.7	76.7	41.4*	41.4*	77.6	41.4*	57.8	66.3	38.6*
Schizophrenia	0.4	0.9	0.0	6.9	9.0	4.1	19.1	22.1	11.9*
Mood disorders	1.6	2.9	0.4*	10.1	11.4	8.3	18.2	22.1	8.9*
Anxiety disorders	13.6	19.3	8.2*	24.3	30.9	15.2*	29.9	34.6	18.8*
Conduct disorders	17.1	25.3	9.2*	14.2	19.9	6.2*	4.7	5.8	2.0
ADHD	24.8	40.2	10.1*	16.2	24.9	4.1*	3.5	3.8	3.0
Delays in development	18.5	21.3	15.8*	11.9	13.9	9.0	2.4	2.9	1.0
Intellectual disability	3.2	4.6	1.9*	4.6	7.0	1.4*	15.0	17.1	9.9
Epilepsy	3.7	6.4	1.1*	5.8	10.0	0.0*	8.2	11.3	1.0*

Q1 = first quartile; Q3 = third quartile; SD = standard deviation.
*† Use of psychoactive drugs in the year prior to cohort entry; * $p < 0.05$ between users and non-users of psychoactive drugs.*

TABLE 2 Determinants of Psychoactive Drug Use in the Year Prior to Cohort Entry

	OR (95% CI)
Determinants at cohort entry	
Male	1.08 (0.87-1.34)
Schizophrenia	**4.64 (2.64-8.16)**
Mood disorders	**3.70 (2.23-6.12)**
Anxiety disorders	**3.80 (2.94-4.92)**
Conduct disorders	**2.59 (1.98-3.39)**
ADHD	**4.94 (3.92-6.24)**
Delays in development	0.74 (0.59-1.92)
Intellectual disability	**2.69 (1.80-4.01)**
Epilepsy	**15.73 (9.19-26.91)**
Visit to a specialist (by additional visit)	1.16 (0.91-1.47)
Hospitalization in the year before cohort entry	1.27 (0.99-1.62)

OR = odds ratio; CI = confidence interval.
Other socio-demographic variables and cohort entry were not significantly associated with drug prescriptions and were thus removed from the model; Statistically significant ($p < 0.05$) results in are shown in bold.

anticonvulsant prescribed (36.6%). The most frequently used antidepressants were selective serotonin reuptake inhibitors (SSRIs;~50% of prescriptions), with citalopram (18.2%) being the most common. Lorazepam (38.3%) was the most commonly prescribed anxiolytic.

Polypharmacy

Polypharmacy, defined as the concomitant use of 2 different drug classes for an overlapping period of 90 days, increased during the study follow-up period from 9% to 22% (p<0.0001; Figure 2A). Sensitivity analyses using periods of 30 and 60 days presents similar trends. Psychoactive polypharmacy increased steadily throughout follow-up in children (age groups: 1–5 and 6–12) but seemed to stabilize after 3 years in adolescents (13–17) and young adults (18–25) (Figure 2B). Age and time but not gender significantly affected polypharmacy (p<0.0001). In the 2 youngest groups (1–5 and 6–12), the use of an antipsychotic and ADHD drugs was the most common combination during follow-up. In the 13–17 group, the most common combination was an antipsychotic and anticonvulsant drug in the first years following diagnosis, replaced with an antipsychotic and antidepressant over time. In young adults (18–25), the most common drug combination was antipsychotics and anticonvulsants throughout follow-up, closely followed by the antipsychotic and antidepressant combination.

DISCUSSION

This cohort study examined changes in the use of psychoactive drugs over time in newly diagnosed cases of ‘’ASD” as provided by Quebec Healthcare database. Overall, 35.8% of our cohort had already received at least one psychoactive drug in the year preceding diagnosis. The use of psychoactive drugs increased to 53.2% after 5 years with an individual’s age and time since diagnosis strongly influencing the type and combinations of drugs prescribed. This increase in prescriptions was especially noticeable in children.

Psychoactive drug use in autistic children has been mostly investigated by cross-sectional studies examining prevalent cases in a particular time period. Here, we followed a cohort of incident cases for up to 5 years and found that several medications are increasingly prescribed from the time of diagnosis, as children

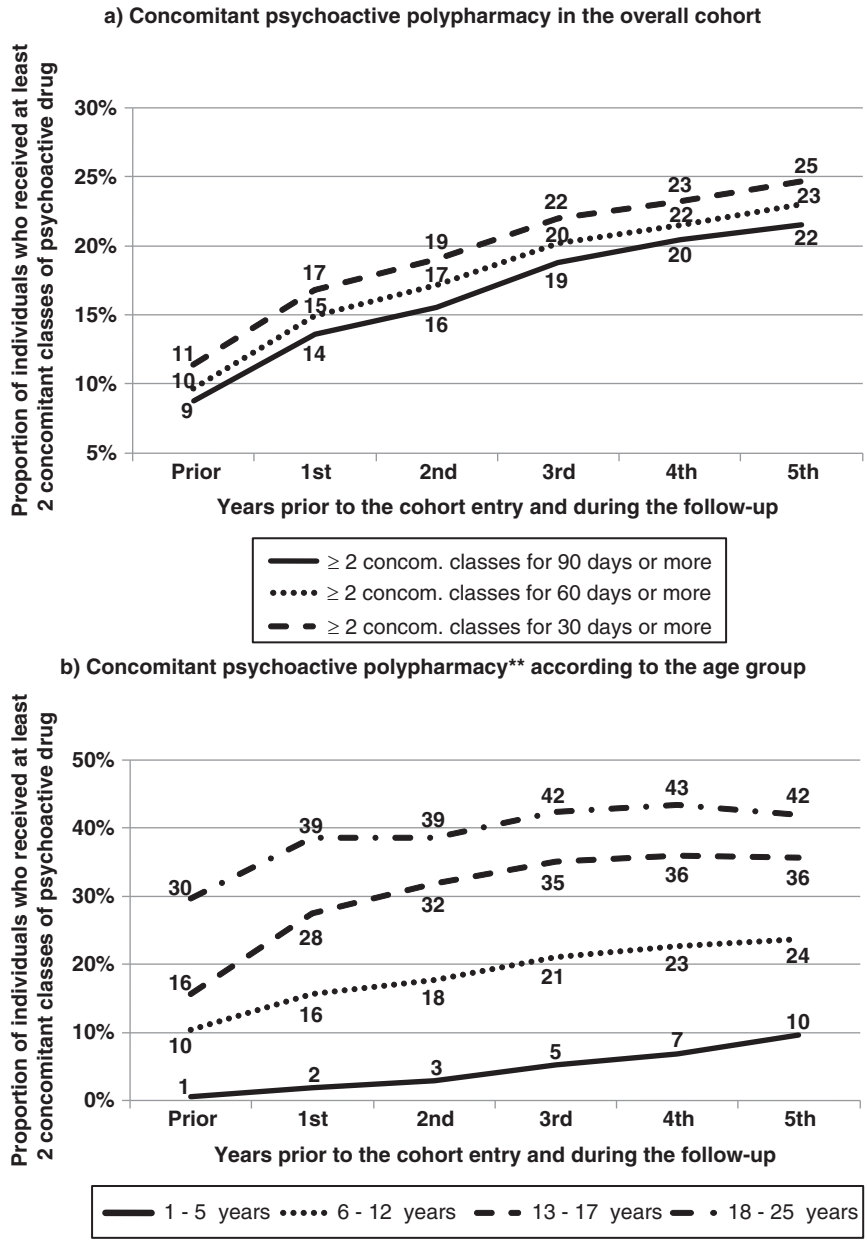

FIG 2. The proportion of use of psychoactive polypharmacy in the year prior to the cohort entry and over 5 years of follow-up. a) Gaps of up to 15 days between the last day of medication supply and the next fill date permitted; For 30-day polypharmacy period up to a 7-day gap in the polypharmacy regimen allowed. b) ** Percentage of individuals who received at least 2 concomitant classes for a minimum period of 90 days. Gaps of up to 15 days between the last day of medication supply and the next fill date permitted.

TABLE 3 Proportion of Individuals Using Psychoactive Drugs in the Year Prior to Cohort Entry and at Each Year of the Follow-Up

Year(s) prior and following * the cohort entry	Prior	1st	2nd	3rd	4th	5th
	(*n*=2,989)	(*n*=2,654)	(*n*=2,189)	(*n*=1,827)	(*n*=1,498)	(*n*=1,227)
At least 1 psychoactive drug - %	35.6	44.9	46.1	49.8	52.2	53.2
By age group *						
At least 1 psychoactive drug - %						
1 – 5	12.6	20.5	24.6	30.0	35.5	37.8
6 – 12	48.9	57.6	55.1	57.0	56.5	56.2
13 – 17	58.1	70.2	69.3	72.1	73.5	75.7
18 – 25	70.4	80.1	76.6	77.7	76.3	77.1
Antipsychotics - %						
1 – 5	2.4	6.8	9.7	12.1	15.7	17.5
6 – 12	18.5	27.0	28.0	32.6	32.2	30.7
13 – 17	31.5	47.6	49.0	50.5	52.5	55.7
18 – 25	53.1	64.9	61.2	63.1	63.9	63.1
ADHD drugs - %						
1 – 5	4.6	10.0	13.9	17.5	19.3	21.8
6 – 12	37.7	39.4	34.9	33.6	32.4	31.3
13 – 17	27.8	24.9	21.5	18.8	16.0	8.6
18 – 25	8.2	7.3	5.9	5.1	5.0	5.0
Anticonvulsants - %						
1 – 5	2.6	3.5	3.5	4.6	4.6	6.2
6 – 12	5.9	6.9	7.6	9.7	11.1	13.7
13 – 17	11.9	17.5	20.7	25.0	26.5	25.7
18 – 25	29.9	34.8	36.4	36.9	38.4	38.6
Antidepressants - %						
1 – 5	0.3	1.7	2.9	3.8	4.9	7.6
6 – 12	5.6	8.6	9.2	11.3	10.7	11.7
13 – 17	13.9	24.6	24.3	26.9	24.3	30.0
18 – 25	26.7	33.5	27.3	30.2	28.8	30.1
Anxiolytics - %						
1 – 5	6.2	5.3	5.0	4.8	6.9	4.9
6 – 12	5.3	5.9	5.6	5.5	7.9	9.2
13 – 17	7.5	10.0	8.8	11.1	16.6	18.6
18 – 25	24.9	26.3	28.0	26.3	23.7	24.6

* *Age groups and years of follow-up were significantly associated with the proportion of use of all psychoactive drugs, excepted for the anxiolytics where the years of follow-up were not significantly associated with the proportion of use.*

grow up. We also report that many children already receive psychoactive drugs before they are diagnosed as ''ASD," especially those diagnosed at a later age. Neurodevelopmental disorders in the year before cohort entry strongly predicted future psychoactive drug use, which aligns with findings from other studies of clinical predictors of psychotropic medication use in autism.[14,18,19,31] Such disorders may reflect a previous misdiagnosis, a delay in obtaining a formal autism diagnosis or diagnostic substitution.[32]

Prescriptions of anticonvulsants, antidepressants and antipsychotics increased in the 5 years following cohort entry and in the years following diagnosis in each group. Previous studies show that age is positively correlated with medication use.[21,33] Behavioural problems associated with autism may evolve with age,[34,35] influencing the medications that are prescribed at various ages.[21] In our study, the most commonly prescribed drug class varied by age group, which supports this conclusion. This may also suggest that physicians are increasingly willing to prescribe particular classes of psychoactive drugs as patients age. The large increase in prescriptions of anticonvulsants in adolescents and young adults during follow-up may reflect efforts to address challenging behaviours in these age groups, despite the absence of seizures. Most autistic adults have no access to specialist services, which may explain their high rate of medication.[36] Difficulties in accessing adequate alternative treatments and services may be contributing to the increasing reliance on psychoactive medications as autistic children grow older.[21,36]

Polypharmacy was common in the years following diagnosis, with the most common combinations of drug classes varying by age group. The positive correlation between polypharmacy and age is consistent with previous studies.[14,15,18,19,21] Prescriptions in more than one drug class concomitantly increased in each age group in follow-up. This is worrisome because the risks of side effects increase if drugs are used concomitantly due to potential drug–drug interactions, additive adverse drug reactions, and 'medication cascade effects' (drugs used to treat the adverse effects of other drugs).[13]

Guidelines like those developed in the UK and the U.S. currently suggest a pathway for particular pharmacological treatments in the autism spectrum.[5,37–39] However, recommendations regarding the monitoring of patients treated with atypical antipsychotics vary[40] and guidelines regarding the treatment of associated co-morbidities are greatly needed.[11] Different countries report wide variations in psychopharmacological prescription patterns.[20] Contributing factors may include variations in clinical guidelines,[20] differential access to specialty health care,[41] and/or cultural beliefs.[42] Although direct comparison is limited due to the difference in methodology, in our study of incident cases, percentages of psychoactive medication use throughout follow-up (35.6–53.2%) is consistent with those reported in published North American studies based on prevalent cases, (40–71%).[14–18]

Many questions remain concerning the effects of long-term psychoactive drug use on overall health, especially in children. Antipsychotics are especially concerning. Sedation and metabolic abnormalities including weight gain, diabetes, and cardiovascular effects are clinically relevant adverse effects in youth using atypical antipsychotics.[43] Use of these drugs should be limited to individuals with severe impairment or risk of injury.[5,7] The high rate of antipsychotic prescriptions, especially risperidone, recorded in this study, suggests that this may not be the case.

Other psychoactive drug classes were also frequently prescribed. Most ADHD medications have not been studied in sufficient depth in autistic individuals, who incidentally may be more sensitive than non-autistic individuals to the side effects of these drugs.[37] Regarding antidepressants, the Cochrane collaboration found no evidence of benefit in an updated systematic review, but some evidence of harm regarding treatment of repetitive behaviours with SSRIs in autistic individuals.[44] Furthermore, a systematic review and meta-analysis study assessing the use of anticonvulsant medications for the treatment of behavioural symptoms in autism found no significant difference between medication and placebo.[45]

This study provides important data about the prescription of psychoactive medications for a large number of autistic individuals over many years of follow-up, enabling a longitudinal analysis of newly diagnosed cases. Compared to methods such as interviews or questionnaires, using computerized administrative databases in such research avoids recall bias, and allows capturing of drug history, medical services

and the natural evolution of the disease over a long period. Nonetheless, our population-based study has some limitations inherent to the analysis of administrative databases. First, the diagnoses of ''ASD" in the RAMQ database was not cross-validated and cannot identify all cases. The sampling methodology used for this study did not allow for prevalence calculations. A published study using 2010 data from the RAMQ based on ICD-9 code 299.X has reported the prevalence of ''ASD" to be 0.64% in children 2 to 12 years of age and 0.60% in adolescents.[46] The requirement of 2 or more diagnostic codes in our study would limits the potential for misclassification[28] which is however still possible. Additionally, timing of 1st ''ASD" diagnosis by a physician could be different from when this was documented in the RAMQ database, which could impact the identification of incident cases. Interestingly, the exclusion criteria used in this study yielded a young cohort of ''ASD" cases with a median age at first diagnosis of 6 years, which compares favourably with a published Medicaid study evaluating age of first diagnosis (64.9 months).[47] Furthermore, the codes used for the identification of other neuropsychiatric disorders in the year preceding the index date have also not been cross-validated. However, the classes of medications used during this same time period are in alignment with these diagnoses. Second, information regarding the entire 5 years of follow-up was available for only some individuals. Therefore, our results may not reflect the entire sample. However, we performed a sensitivity analysis to examine changes in the use of other medical services with universal coverage, such as hospitalization and doctor visits (data not shown) and found that these were consistent between the entire cohort and the subgroup of individuals covered by the RAMQ drug plan. Third, given the database reports filled prescriptions alone, drugs dispensed may not accurately reflect medications taken. Finally, this study excluded individuals with private medical insurance, which may introduce selection bias, as those individuals may use expensive non-drug therapeutic approaches more frequently, leading to differential drug use.

CONCLUSION

This study shows that among newly diagnosed autistic children and youth, prescriptions of psychoactive medication and polypharmacy increases over time, and an individual's age and the time since diagnosis strongly influences the types and combinations of drugs used. This increase over time is potentially concerning, especially if such medications are used to manage the core features of the autism spectrum or to replace other, potentially inaccessible treatments and services. Further research is needed to understand why clinicians prescribe psychoactive drugs with increasing frequency in the years following an autism spectrum diagnosis. Real-life, long-term efficacy and safety data on the use of these medications, in combination with or in comparison to other non-pharmacological treatment modalities, is urgently needed.

ACKNOWLEDGEMENTS

We thank collaborators from the *Régie de l'assurance maladie du Québec* for assistance with the data. We are grateful to the *Commission d'accès à l'information* du Québec for authorizing the study. Drs. Perreault and Mottron have a National Research Award from the *Fonds de recherche du Québec-Santé*. Dr. Presse has a postdoctoral fellowship from the Canadian Institutes for Health Research. Mr. Dorais served as the statistical expert for this research.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

DISCLOSURE

Drs. Perreault, Mottron, Tarride, Presse, and Mr. Dorais report no biomedical financial interests or potential conflicts of interest. Ms. Croteau is employed by Pfizer Canada and has direct ownership of stock from Pfizer Inc. This manuscript was prepared as part of Ms Croteau's studies towards a PhD degree from University of Montreal.

REFERENCES

1. American Psychiatric Association. Autism Spectrum Disorder. In: Diagnostic and statistical manual of mental disorders. 5th ed., ed. Arlington, VA. American Psychiatric Publishing 2013:50–59.
2. Autism and Developmental Disabilities Monitoring Network. Surveillance Year 2010. Prevalence of autism

spectrum disorders among children aged 8 years - Autism and Developmental Disabilities Monitoring Network 11 Sites, United States, 2010. Morb Mortal Wkly Rept Surveillance summaries/CDC 2014;63(SS02):1–21.
3. Ouellette-Kuntz H, Coo H, Lam M et al. The changing prevalence of autism in 3 regions of Canada. J Autism Dev Disord 2014;44(1):120–36.
4. Taylor B, Jick H, MacLaughlin D. Prevalence and incidence rates of autism in the UK: time trend from 2004-2010 in children aged 8 years. BMJ Open 2013;3(10): e003219.
5. National Institute for Health and Care Excellence. Autism: the management and support of children and young people on the autism spectrum. (Clinical guideline 170) 2013.
6. Kendall T, Megnin-Viggars O, Gould N, et al. Management of autism in children and young people: summary of NICE and SCIE guidance. BMJ 2013;347:f4865.
7. Quality AfHRa. Therapies for children with autism spectrum disorders. Comparative Effectiveness Review: Houston, TX: John M. Eisenberg Center for Clinical Decisions and Communications Science; 2014.
8. Siegel M, Beaulieu A. Psychotropic medications in children and adolescents with autism spectrum disorders: a systematic review and synthesis for evidence-based practice. J Autism Dev Disord 2012;42:1592–605.
9. Volkmar F, Siegel M, Woodbury-Smith M et al. Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. J Am Acad Child Adolesc Psychiatr 2014;53(2):237–57.
10. Moyal WN, Lord C, Walkup JT. Quality of life in children and adolescents with autism spectrum disorders: what is known about the effects of pharmacotherapy? Pediatr Drugs 2014;16:1230–38.
11. American Academy of Child and Adolescent Psychiatry. Policy Statement on Comorbidity Treatment in Autism Spectrum Disorders and Intellectual Disabilities. Available at: http://www.aacap.org/aacap/Policy_Statements/2013/Comorbidity_Treatment_in_Autism_Spectrum_Disorders_and_Intellectual_Disabilities.aspx. Accessed 16 Apr 2016.
12. Huffman LC, Sutcliffe TL, Tanner ISD, Feldman HM. Management of symptoms in children with autism spectrum disorders: a comprehensive review of pharmacologic and complementary-alternative medicine treatments. J Dev Behav Pediatr 2011;32:56–68.
13. Jureidini J, Tonkin A, Jureidini E. Combination pharmacotherapy for psychiatric disorders in children and adolescents: prevalence, efficacy, risks and research needs. Pediatr Drugs 2013;15:377–91.
14. Mandell DS, Morales KH, Marcus SC, et al. Psychotropic medication use among Medicaid-enrolled children with autism spectrum disorders. Pediatrics 2008;121(3):e441–8.
15. Logan SL, Nicholas JS, Carpenter LA, et al. High prescription drug use and associated costs among Medicaid-eligible children with autism spectrum disorders identified by a population-based surveillance network. Ann Epidemiol 2012;22(1):1–8.
16. Cidav Z, Lawer L, Marcus SC, Mandell DS. Age-related variation in health service use and associated expenditures among children with autism. J Autism Dev Disord 2013;43:924–31.
17. Schubart JR, Camacho F, Leslie D. Psychotropic medication trends among children and adolescents with autism spectrum disorder in the Medicaid program. Autism 2013;18(6):631–37.
18. Spencer D, Marshall J, Post B, et al. Psychotropic medication use and polypharmacy in children with autism spectrum disorders. Pediatrics 2013;132(5):833–40.
19. Coury DL, Anagnostou E, Manning-Courtney P, et al. Use of psychotropic medication in children and adolescents with autism spectrum disorder. Pediatrics 2012;130(2):S69–76.
20. Rosenberg RE, Mandell DS, Farmer JE, et al. Psychotropic medication use among children with autism spectrum disorders enrolled in a National Registry, 2007-2008. J Autism Dev Disord 2010;40:324–51.
21. Esbensen AJ, Greenberg JA, Seltzer MM, Aman MG. A Longitudinal investigation of psychotropic and non-psychotropic medication use among adolescents and adults with autism spectrum disorders. J Autism Dev Disord 2009;39:1339–49.
22. Murray ML, Hsia Y, Glaser K et al. Pharmacological treatments prescribed to people with autism spectrum disorder (ASD) in primary health care. Psychopharmacology 2014;231:1011–21.
23. Bachmann CJ, Manthey T, Kamp-Becker, Glaeske G, Hoffmann F. Psychopharmacological treatment in children and adolescents with autism spectrum disorders in Germany. Res Dev Disabil 2013;34:2551–63.
24. Turgeon M, Tremblay E, Déry N, Guay H. L'usage des médicaments chez les enfants et adolescents ayant reçu un diagnostic de trouble du spectre de l'autisme couverts par le régime public d'assurance médicaments du Québec. Neuropsychiatr Enfance Adolesc 2014;62(2):119–26.

25. World Health Organization International classification of diseases. Manual of the international statistical classification of diseases, injuries, and cause of death. 9th revision. Geneva, Switzerland: World Health Organization, 1977. PHS 80-1260.
26. Régie de l'Assurance Maladie du Québec. Rapport annuel de gestion 2005-2006. Governement of Quebec, 2006.
27. Wilchesky M, Tamblyn RM, Huang A. Validation of diagnostic codes within medical services claims. J Clin Epidemiol 2004;57(2):131–41.
28. Burke JP, Jain A, Yang W et al. Does a claim diagnosis of autism mean a true case? Autism 2014;18(3):321–30.
29. American Society of Health Systems Pharmacist. AHFS Drug Information. Bethesda, MD: American Society of Health-System Pharmacists; 2013.
30. Chen H, Patel A, Sherer J, Aparasu R. The definition and prevalence of pediatric psychotropic polypharmacy. Psychiatr Serv 2011;62(12): 1450–55.
31. Downs J, Hotopf M, Ford T, et al. Clinical predictors of antipsychotic use in children and adolescents with autism spectrum disorders: a historical open cohort study using electronic health records. Eur Child Adolesc Psychiatr 2016;25(6):649–58.
32. King M, Bearman P. Diagnostic change and the increased prevalence of autism. Int J Epidemiol 2009;38(5):1224–34.
33. Aman MG, Lam KSL, Van Bourgondien ME. Medication patterns in patients with autism: temporal, regional, and demographic influences. J Child Adolesc Psychopharmacol 2005;15(1):116–26.
34. Fecteau S, Mottron L, Berthiaume C, Burack JA. Developmental changes of autistic symptoms. Autism 2003;7(3):255–68.
35. Shattuck PT, Seltzer MM, Greenberg JS et al. Change in autism symptoms and maladaptive behaviours in adolescents and adults with an autism spectrum disorder. J Autism Dev Disord 2007;37(9):1735–47.
36. Howlin P, Moss P. Adults with autism spectrum disorders. Can J Psychiatry 2012;57(5):275–83.
37. Mahajan R, Pilar Berna M, Panzer R, et al. Clinical practice pathways for evaluation and medication choice for attention-deficit/hyperactivity disorder symptoms in autism spectrum disorders. Pediatrics 2012;130(suppl 2):S125–38.
38. Ameis SH, Corbett-Dick P, Cole L, Correll CU. Decision making and antipsychotic medication treatment for youth with autism spectrum disorders: applying guidelines in the real world. J Clin Psychiatr 2013;74(10):1022–24.
39. McGuire K, Fung LK, Hagopian L, et al. Irritability and problem behavior in autism spectrum disorder: A Practice pathway for pediatric primary care. Pediatrics 2016;137(S2):e20152851L.
40. Baribeau DA, Anagnostou E. An update on medication management of behavioral disorders in autism. Curr Psychiatr Rep 2014;16(3):437.
41. Hsia Y, Wong AYS, Murphy DGM, Simonoff E, Buitelaar JK, Wong ICK. Psychopharmacological prescriptions for people with autism spectrum disorder (ASD): a multinational study. Psychopharmacology 2014;231(6): 999–1009.
42. Zito JM, Safer DJ, de Jong-van den Berg LTW et al. A three-country comparison of psychotropic medication prevalence in youth. Child Adolesc Psychiatr Ment Health 2008;2(1):26.
43. Caccia S. Safety and pharmacokinetics of atypical antipsychotics in children and adolescents. Pediatr Drugs 2013;15:217–33.
44. Williams KB, Brignell A, Randall M, Silove N, Hazell P. Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD) (Review). Cochrane Database of Systematic Reviews 2013;Issue 8. Art. No. CD004677.
45. Hirota T, Veenstra-Vanderweele J, Hollander E, Kishi T. Antiepileptic medications in autism spectrum disorder : a systematic review and meta-analysis. J Autism Dev Disord 2014;44:948–57.
46. Institut national d'excellence en santé et en services sociaux. Portrait de l'usage des médicaments chez les enfants et les adolescents ayant reçu un diagnostic de trouble du spectre de l'autisme couverts par le régime public d'assurance médicaments. Portrait d'usage rédigé par Mélanie Turgeon, Éric Tremblay, Nicole Déry et Hélène Guay. Québec, Qc : INESSS; 2013.
47. Mandell DS, Morales KH, Xie M, Lawer LJ, Stahmer AC, Marcus SC. Age of diagnosis among Medicaid-enrolled children with autism, 2001-2004. Psychiatr Serv 2010;61(8):822–29.