IMPACT OF A RESTRICTIVE DRUG ACCESS PROGRAM ON THE RISK OF CARDIOVASCULAR ENCOUNTERS IN CHILDREN EXPOSED TO ADHD MEDICATIONS

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ABSTRACT

Background
ADHD medications increase clinical encounters for cardiovascular symptoms. Uncertain are the roles of differences in ADHD medications and restrictive practices by drug programs.

Methods
We conducted two nested case-control studies. The first was nested within a cohort of children de novo users of methylphenidate, amphetamines or atomoxetine and the second case-control study was nested within a subcohort of de novo amphetamine or atomoxetine users with no cardiovascular events prior to the first dispensing of either drug. The outcome for both studies was the composite of physician visits, emergency room visits or hospitalizations for cardiovascular reasons. Cases were matched on sex, age and date of entry within the cohorts, with up to 10 controls. Patients with an active dispensation of ADHD medications at the index date (and up to 90 days previously) were considered exposed. Conditional logistic regression was used to calculate odd ratios (OR).

Results
The full cohort comprised 38,495 patients. Among these patients, 3595 (9.3%) had no prior cardiovascular events (the subcohort). In the full cohort, an association was demonstrated with exposure to amphetamine and atomoxetine (but not methylphenidate) and the cardiovascular encounter outcomes. When the sub-cohort was analyzed the associations with amphetamine or atomoxetine were no longer evident.

Conclusion
Reimbursement policies need to be considered when conducting observational studies. Had the analysis been conducted without consideration of these policies the results would have incorrectly identified amphetamine and atomoxetine as important risk factors for cardiovascular encounters.

Key Words: *ADHD, methylphenidate, amphetamine, atomoxetine, reimbursement policy, cardiovascular events*

Attention deficit hyperactivity disorder (ADHD) is the most common neurobehavioral disorder in children. Amongst community-based samples of school-aged children in the United States, prevalence rates are 4% to 12%, with similar results for Canadian children.[1,2] About two-thirds of the children diagnosed with ADHD receive a pharmacological treatment, either methyl-phenidate, amphetamines or atomoxetine.[3,4] These drugs can increase systolic and diastolic blood

pressure (on average 1– 4 mm Hg) and heart rate (on average 3– 8 beats per minute), both in children and adults.[5-10] Such side-effects may be predictors of future cardiovascular events.[11]

Several studies have examined the potential association between ADHD medication and cardiovascular events in children. ADHD medications have been shown to increase the risk of physician office and emergency room visits for cardiovascular symptoms.[12] Gould *et al.* have linked exposure to ADHD medications to higher risk of sudden cardiac death;[13] but, such results have not been observed by others.[12,14-17]

Access to these three drugs can vary depending upon the restrictive practices that are imposed in different jurisdictions. Therefore, it is of interest to assess the impact of this variable, restrictive access, on the association between ADHD medications and cardiovascular encounters in children. The aim of this study is to assess the frequency of cardiovascular medical encounters amongst Canadian children exposed to these three different drugs using a nested case-control design.

METHODS

Data Sources

Quebec is the second most populated province in Canada, with more than 7.9 million inhabitants in 2010.[18] A unique identification number is assigned to every individual, and all diagnoses and health services provided are systematically recorded. Information was obtained from the Quebec physician's services and claims databases (i.e., *Régie de l'assurance maladie du Québec* [RAMQ] databases) and the Quebec hospitalisation databases (i.e., *Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière* [MED-ECHO] databases), which have previously been validated.[19-22] For this study we used 3 RAMQ databases (i.e., the Medical Services, the Pharmaceutical and the Demographic databases) and 2 from the MED-ECHO database (i.e. the Hospitalisation - Descriptions and Hospitalisation – Diagnoses databases). Patient records were linked across all databases by use of a unique identification number. The identification numbers were encrypted to protect patient confidentiality. Access to data was granted by the *Comission d'accès à l'information* and the protocol was approved by the *Centre hospitalier de l'Université de Montréal* and the *St. Joseph's Healthcare Hamilton* ethics' committees.

Study Design

A series of four independent case-control studies nested within a unique cohort were conducted.

Cohort Selection

A cohort of 66,105 incident users of ADHD medication was provided to us by RAMQ. Eligible patients had to have been dispensed any formulation of either methylphenidate, amphetamines or atomoxetine between January 1st 2001 and October 31st 2010 and be covered by the RAMQ drug insurance plan at least 1 year prior to and at least 30 days following the date of the first dispensation of any of the 3 study drugs (hereby defined as the date of entry within the cohort). From this cohort, we selected individuals who were below 19 years of age at the date of entry into the cohort. Patients were excluded if they had any of the study outcomes prior to entry into the cohort. Selected patients remained in the cohort until their date of death or their last day of continuous adherence to the RAMQ drug insurance plan.

Case Definition

Three physicians (ML, MD and JLL) determined by consensus a list of ICD-9 and ICD-10 diagnostic codes which could be linked to potential cardiovascular side-effects due to exposure to the study drugs. A detailed description of this list is available in Appendix 1. *A priori*, each of the four nested case-control studies examined as an outcome a distinct type of medical encounter for at least one of the pre-specified diagnostic codes: 1) an outpatient visit with a cardiologist, an internist or a paediatrician (hereby defined as a cardiovascular outpatient visit), 2) an emergency room visit, 3) a hospitalisation and 4) a composite of any of the 3 types of medical encounters (hereby defined as the composite outcome).

A patient's case status was assessed independently within each nested case-control study and a patient could be defined as a case in several of the analyses. The date of the first physician service claim in an outpatient setting or in an emergency room setting with one of the pre-specified diagnostic codes was defined as the index date of the case in each respective nested case-control study. The date of the first day of a hospitalisation with one of the pre-specified diagnostic codes was defined as the index date of the case in the hospitalisation case-control study. Within the composite medical encounter nested case-control study, the earliest date of any of the 3 events was defined as the index date of the case.

Controls

Within each nested case-control study, each eligible case was randomly matched on the case's age, sex and the date of entry within the cohort (± 30 days of the case's date of entry within the cohort) to up to 10 controls. If less than 10 controls could be matched to an individual case, all potential controls were selected. The case's index date served as the matched control's index date. Eligible controls had to be continuously covered by the RAMQ drug insurance plan from the control's date of entry within the cohort up to the control's index date.

Exposure Status

We examined the exposure status of cases and controls to 3 drugs (methylphenidate, amphetamines, and atomoxetine). In order to consider delays in access to care, we created 3 time windows of exposure for each of the 3 drugs: 1) active dispensing at the time of the index date (Figure 1A), 2) the last medication dispensing occurred within 30 days prior to the index date (Figure 1B) and 3) the last medication dispensing occurred within 90 days prior to the index date (Figure 1C). Patients who were exposed to more than 1 drug were analysed as exposed to each drug separately.

Creation of sub-cohorts of amphetamine users without prior cardiovascular events and atomoxetine users without prior cardiovascular events. Both amphetamines and atomoxetine reimbursement are restricted within the RAMQ drug insurance plan.[23] Reimbursement of amphetamines is conditional to patients in whom methylphenidate is contraindicated or produced a side-effect or did not adequately control ADHD symptoms. Reimbursement of atomoxetine is conditional to patients in whom both methylphenidates and amphetamines are contraindicated or produced side-effects or did not adequately control ADHD symptoms.

Initiation of amphetamines or atomoxetine in many patients may therefore be due to adverse cardiovascular effects on the previous drug(s). Inclusion of these patients in a study could cause a detection bias and a susceptibility bias. In an attempt to control for these potential biases, we created two distinct sub-cohorts, a sub-cohort of amphetamines users without prior cardiovascular encounters (hereby defined as AMPHE-NOPCV) and a sub-cohort of atomoxetine users without prior cardiovascular events (hereby defined as ATOMOX-NOPCV) in order to re-examine the outcomes within incident users of both these drugs. Figure 2 shows the potential pathways by which patients may be included within both sub-cohorts. Patients who received amphetamine without prior evidence of cardiovascular encounters at the time of their first dispensation of amphetamine were included within the AMPHE-NOPCV (Figure 2A). Patients who received atomoxetine without prior evidence of cardiovascular events of the time of their first dispensation of atomoxetine were included within the ATOMOX-NOPCV (Figure 2B). This method was used to better control for the detection and susceptibility biases.

We reproduced the four nested case-control studies within both of these sub-cohorts. The date of the first dispensation of amphetamines was used as the date of entry within the AMPHE-NOPCV. Identification of cases and selection of their matched controls within the sub-cohort of amphetamine users were conducted in the same manner as within the full study cohort. This methodology was also used within the ATOMOX-NOPCV.

FIG. 1A, 1B, 1C

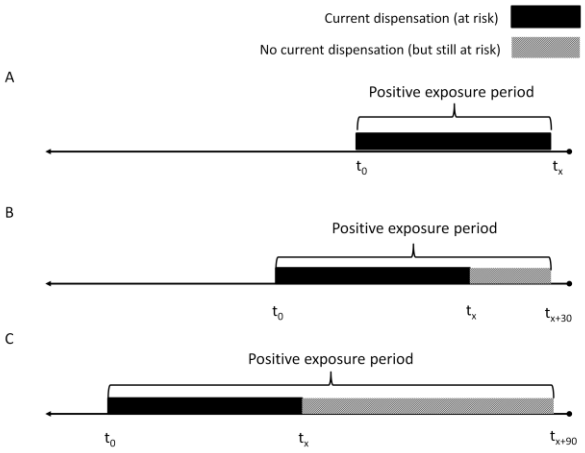
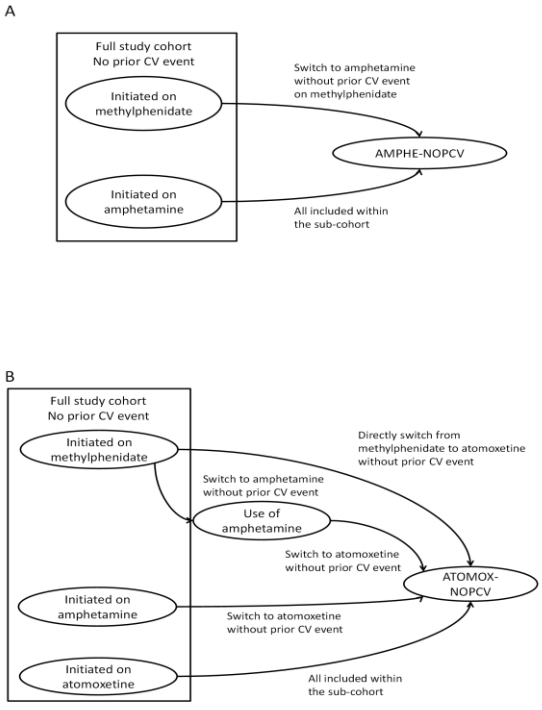


FIG. 2A, 2B



Statistical Analyses

Discrete data are presented as absolute and relative values (n [%]) while continuous data are presented as means and standard deviations (means [SD]). We used conditional logistic regressions to compute odds ratio and 95% confidence intervals (OR [95% CI]) within all nested case-control analyses (within the full study cohort analyses and within both sub-cohort analyses). Two-tailed p-values < 0.05 were considered to indicate statistical significance in all tests. Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Analysis of the Full Study Cohort

Of the 66,105 patients provided by RAMQ, a total of 38,495 patients (58.2%) were selected for inclusion within the full study cohort. Of the 27,610 patients excluded, 17,524 were of 19 years of age or more at the date of entry within the cohort, 9667 received at least one dispensation of at least 1 of the 3 drugs prior to the date of entry within the cohort and 419 had suffered at least 1 of the study outcomes prior to the date of entry within the cohort.

Table 1 summarizes the key demographic and drug-related characteristics of the patients included at the time of entry within the full study cohort. This cohort was comprised of 27,061 males (70.3%) and the mean age was 9.1 (3.0) years old. Most patients were initiated on methylphenidate (37,011 patients [96.1%]). Pharmaceutical treatments were predominately initiated by either a paediatrician (18,270 patients [47.5%]) or a general practitioner (14,162 patients [36.8%]).

A total of 1344 patients (3.5%) were identified as cases for the composite outcome within the full study cohort and were matched to 12,311 controls (an average of 9.2 controls per case). Of the 1344 patients identified as cases, 1009 (75.0%) were identified as cases for the cardiovascular outpatient visit outcome, 308 (22.9%) were identified as cases for the emergency room visit outcome and 194 (14.4%) were identified as cases for the hospitalization outcome. Sum of cases within each individual outcome (cardiovascular outpatient visit, emergency room visit and hospitalization) is greater than the number of cases for the composite outcome since 167 patients encountered more than 1 type of medical encounters. Table 2 presents the results of the conditional logistic regressions conducted within the full study cohort.

TABLE 1 Patient characteristics at the time of entry within the full cohort

Characteristics	Child cohort N=38,495
Age, years (SD)	9.1 (3.0)
Male sex n (%)	27,061 (70.3%)
Medication dispensed at the date of entry within the cohort* n (%)	
Methylphenidate	37,011 (96.1%)
Amphetamine	876 (2.3%)
Atomoxetine	613 (1.6%)
Specialty of the physician initiating the anti-ADHD drug† n (%)	
General Practitioner	14,162 (36.8%)
Cardiologist	12 (0.0%)
Internal medicine	15 (0.0%)
Neurologist	1,448 (3.8%)
Pediatrician	18,270 (47.5%)
Psychiatrist	4,170 (10.8%)
Other specialty	306 (0.8%)
Specialty missing	118 (0.3%)

*Sum of all patients is over 38,495 because 5 patients were dispensed 2 types of drugs.
†Sum of all patients is over 38,495 because 6 patients were prescribed drugs by 2 physicians of different specialty.

TABLE 2 Results of the conditional logistic regressions within the full cohort

	Outpatient visit	Emergency room visit	Hospitalization	Composite outcome
Number of cases	1009	308	194	1344
Number of control	9388	2725	1762	12,311
Time windows				
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Methylphenidate				
Current exposure	0.91 (0.78 – 1.05)	1.05 (0.78 – 1.42)	0.97 (0.68 – 1.40)	0.94 (0.82 – 1.07)
Within 30 days	0.99 (0.86 – 1.15)	1.01 (0.76 – 1.36)	0.75 (0.53 – 1.07)	0.99 (0.87 – 1.12)
Within 90 days	0.95 (0.81 – 1.10)	1.02 (0.77 – 1.36)	0.93 (0.66 – 1.31)	0.98 (0.86 – 1.12)
Amphetamine				
Current exposure	1.26 (0.89 – 1.78)	1.24 (0.63 – 2.46)	1.50 (0.74 – 3.03)	1.26 (0.93 – 1.70)
Within 30 days	**1.43 (1.06 – 1.94)**	1.11 (0.58 – 2.13)	1.41 (0.72 – 2.75)	**1.33 (1.02 – 1.74)**
Within 90 days	**1.52 (1.14 – 2.01)**	0.96 (0.50 – 1.85)	1.31 (0.68 – 2.56)	**1.35 (1.05 – 1.75)**
Atomoxetine				
Current exposure	**2.80 (2.07 – 3.78)**	1.91 (0.93 – 3.91)	**3.25 (1.74 – 6.06)**	**2.37 (1.82 – 3.10)**
Within 30 days	**2.84 (2.15 – 3.74)**	1.78 (0.91 – 3.50)	**3.33 (1.86 – 5.97)**	**2.30 (1.79 – 2.96)**
Within 90 days	**2.83 (2.17 – 3.69)**	**1.88 (1.01 – 3.51)**	**2.98 (1.67 – 5.32)**	**2.33 (1.82 – 2.97)**

Current exposure, The patient is in possession of an active dispensation at the time of the event; Within 30 days, The patient is in possession of an active dispensation at the time of the event or the patient's last dispensation ended within 30 days of the event; Within 90 days, The patient is in possession of an active dispensation at the time of the event or the patient's last dispensation ended within 90 days of the event.

Exposure to Methylphenidate within the Full Study Cohort

Methylphenidate use did not increase the odds of any of the 4 examined outcomes.

Exposure to Amphetamines within the Full Study Cohort

Current exposure to amphetamines did not increase the odds of any of the four outcomes examined but patients whose last dispensation of amphetamines ended within 30 days or within 90 days of the index date showed higher odds of cardiovascular outpatient visits (OR=1.43 95%CI: 1.06 – 1.94 and OR=1.52 95%CI 1.14 – 2.01, respectively) (Table 2). These higher odds were also observed in the analysis for the composite outcome (OR=1.33 95%CI: 1.02 – 1.74 and OR=1.35 95%CI 1.05 – 1.75, respectively).

Exposure to Atomoxetine within the Full Study Cohort

As reported in Table 2, exposure to atomoxetine greatly increases the odds of cardiovascular outpatient visits, hospitalisations, and the composite outcome. Patients exposed to atomoxetine whose last dispensation ended within 90 days of the index date also showed higher odds of emergency room visits (OR=1.88 95%CI 1.01 – 3.51).

Analysis of the Sub-cohort of Amphetamine users without Prior Cardiovascular Events

We identified 5143 patients (13.4%) who received at least one dispensation of amphetamines. Among these patients, 5008 (97.4%) did not have any of the outcomes of interest prior to the first dispensation of amphetamines, and were therefore included in the AMPHE-NOPCV. The majority of these patients were male (3686 patients [73.6%])

and their average age was 10.3 (3.0) years old. A total of 109 patients (2.1%) were identified as cases for the composite outcome. Of the 109 patients identified as cases, 93 (85.3%) were identified as cases for the cardiovascular outpatient visit outcome, 12 (11.0%) were identified as cases for the emergency room visit outcome and 12 (11.0%) were identified as cases for the hospitalization outcome.

Table 3 shows the results of the conditional logistic regressions conducted within the AMPHE-NOPCV. In opposition to the observed increases in odds of events in patients exposed to amphetamine within the full study cohort, no statistically significant increase was observed within the AMPHE-NOPCV.

TABLE 3 Results of the conditional logistic regressions within the sub-cohort of amphetamines users without prior cardiovascular events

	Outpatient visit	**Visit to ER**	**Hospitalization**	**Composite outcome**
Number of cases	93	12	12	109
Number of control	709	95	93	836
Time windows				
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Amphetamine				
Current exposure	**0.52 (0.32 – 0.84)**	4.71 (0.98 – 22.66)	0.82 (0.20 – 3.35)	0.82 (0.53 – 1.25)
Within 30 days	0.68 (0.42 – 1.11)	6.99 (0.84 – 58.14)	0.98 (0.24 – 4.10)	1.00 (0.64 – 1.58)
Within 90 days	0.84 (0.50 – 1.41)	6.86 (0.82 – 57.37)	1.49 (0.34 – 6.51)	1.11 (0.68 – 1.81)

Current exposure, The patient is in possession of an active dispensation at the time of the event; Within 30 days, The patient is in possession of an active dispensation at the time of the event or the patient's last dispensation ended within 30 days of the event; Within 90 days, The patient is in possession of an active dispensation at the time of the event or the patient's last dispensation ended within 90 days of the event.

TABLE 4 Results of the conditional logistic regressions within the sub-cohort of atomoxetine users without prior cardiovascular events.

	Outpatient visit	**Visit to ER**	**Hospitalization**	**Composite outcome**
Number of cases	109	20	22	128
Number of control	695	108	145	815
Time windows				
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Atomoxetine				
Current exposure	0.82 (0.52 – 1.28)	0.81 (0.27 – 2.46)	0.91 (0.36 – 2.27)	1.10 (0.73 – 1.67)*
Within 30 days	0.91 (0.58 – 1.45)	0.56 (0.17 – 1.82)	1.52 (0.55 – 4.15)	1.22 (0.79 – 1.89)
Within 90 days	1.01 (0.62 – 1.64)	0.73 (0.20 – 2.68)	1.30 (0.44 – 3.80)	1.20 (0.76 – 1.91)

Current exposure, The patient is in possession of an active dispensation at the time of the event; Within 30 days, The patient is in possession of an active dispensation at the time of the event or the patient's last dispensation ended within 30 days of the event; Within 90 days, The patient is in possession of an active dispensation at the time of the event or the patient's last dispensation ended within 90 days of the event. The "Composite outcome" represents an independent analysis where the outcome is the first occurrence of any of the three independent outcomes. Furthermore, controls for each individual study were resampled and therefore patients identified as cases within one of the individual outcomes may have distinct controls in the "Composite outcome". Therefore, results of the "Composite outcome" must be regarded as in independent analysis and not an average result of the three results obtained in the individual studies.*Results of the "Composite outcome" are not necessarily within the range of results obtained for the three individual outcomes and must be regarded as an independent result.

Analysis of the Sub-cohort of Atomoxetine users without Prior Cardiovascular Events

A total of 3707 patients (9.6%) received at least one dispensation of atomoxetine within the full study cohort. Among these patients, 3595 patients (97.0%) did not have outcomes of interest before the first dispensation of atomoxetine, and were therefore included in the ATOMOX-NOPCV. This sub-cohort comprised of 2671 males (74.3%) and the mean age was 10.7 (3.0) years old. A total of 128 patients (3.5%) were identified as cases for the composite outcome. Of these, 109 (85.1%) were identified as cases for the cardiovascular outpatient visit outcome, 20 (15.6%) were identified as cases for the emergency room visit outcome, and 22 (17.2%) were identified as cases for the hospitalization outcome.

Similar to the results observed within the AMPHE-NOPCV, no association was observed between any of the time windows examined and the odds of medical encounters for any of the pre-specified diagnostic codes within the ATOMOX-NOPCV (Table 4).

DISCUSSION

Given the cardiac effects of the pharmacological treatments currently given to children and the high number of potential users,[5-11] increased risk of cardiovascular events in children is of concern to the general public and to healthcare practitioners. Although several studies have previously examined the risk of cardiovascular events in children exposed to methylphenidate, amphetamines and atomoxetine,[12-17] none have been conducted in the context of a restrictive drug access policy such as the one currently in place in Quebec, Canada.

Descriptive analyses of our study population showed that 70% of children in our cohort were boys and, as expected, due to the restrictive drug access policies, the vast majority of children were initiated on a methylphenidate treatment regimen. Our high male to female ratio is similar to those observed in other jurisdictions and reflects the higher prevalence of and treatment for ADHD in male patients.[15,17,24] Based upon the results of the conditional logistic regressions within the full study cohort, exposure to amphetamines or to atomoxetine would seem to greatly increase the odds of medical encounters for any of the pre-specified diagnostic codes. These results are contradictory to previously published results that did not find any association between the use of amphetamines or atomoxetine and the risk of cardiovascular events.[12,14-17]

However, as mentioned above, restrictive access policies currently in place may grant access to amphetamines and atomoxetine to patients who developed a cardiovascular event while treated with the first line drug (i.e. methylphenidate). Inclusion of these patients within the analyses of the full study cohort may have biased the results. Patients with prior cardiovascular events and their parents may seek out medical services more actively and physicians may follow them more rigorously; both behaviours would lead to detection biases. The analyses conducted within the full study cohort may also be affected by a susceptibility bias. The restrictive access policy will tend to switch patients with predisposition to the cardiogenic effects of these drugs from methylphenidate to either amphetamines or atomoxetine. Due to this predisposition, patients exposed to the second line drugs will present higher baseline risk of events than those remaining on methylphenidate.

In an attempt to control for these biases we conducted secondary analyses of the measures of association within the AMPHE-NOPCV and ATOMOX-NOPCV sub-cohorts. The measures of association previously observed as an increase in odds within the full study cohort decreased and became non-statistically significant. Although we had hypothesized the effects of these two biases, one may argue that this lack of association may actually be due to the lower number of cases which limited the statistical power of the sub-cohorts. Although we cannot rule out this option, our results are concordant with the results from other groups who have not observed any increase in the risk of cardiovascular events among patients exposed to any of the study drugs when restrictive access practices were not implemented.

Our study has several strengths. First, we received data from RAMQ on all patients covered by the RAMQ drug insurance plan who met our selection criteria. As such, we could analyse the

odds of cardiovascular events within the total child population covered by this public drug insurance plan who initiated at least 1 of the 3 study drugs. Second, we used a nested case-control design within a cohort of incident users. This design allowed the comparison of cases and controls with similar characteristics at initiation of pharmaceutical treatments.[25,26] As mentioned above, this design did not adequately control for potential detection and susceptibility biases among amphetamines or atomoxetine users due to the restrictive drug access policies in Quebec, Canada. To further strengthen our study, we reproduced all our analyses within two additional sub-cohorts in an attempt to control for these issues (Figure 2). Third, we examined several time windows to assess different risk profiles and pharmacological effects of the study drugs. Although onset of cardiac symptoms with these drugs may be rapid, the longer time windows were examined to account for delays between the onset of symptoms and the time required for a patient to get access to a specialist; a potential problem especially in milder cases.

However, this study has some limitations. First, we only had data on dispensations given to patients and/or their parents and cannot confirm whether these patients actually took the drugs. This can introduce non-differential misclassification of exposure, which would tend to bias results towards no association. Second, identification of cases was entirely based upon information contained within the medico-administrative databases; medical records could not be reviewed to confirm the presence or absence of the reported diagnoses. Despite this limit, a recent validation study determined that the reliability between diagnostic codes present within the Quebec medico-administrative databases and medical patient files is high.[19,20] Third, in order to encompass more possibilities, we decided to conduct several statistical analyses to take into account multiple combinations of exposure and outcomes. We did not apply corrections for multiple comparisons, so chances of type 1 error are increased.

CONCLUSION

This study emphasizes the importance of taking in consideration the drug reimbursement policies within any pharmacoepidemiological study using medico-administrative data. Had we not considered these policies, we would have incorrectly identified amphetamines and atomoxetine as an important risk factor for cardiovascular encounters. Our final results do not suggest that exposure either to methylphenidate, amphetamines or atomoxetine increases the risk of cardiovascular encounters in children, and are concordant with results observed by others.

Acknowledgement

Funding for the study was provided by the Canadian Institutes of Health Research grant #103529 (CIHR Catalyst Grant: Post Market Drug Safety and Effectiveness).

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APPENDIX 1

The ICD-9 codes used to designate a cardiovascular encounter are:
401.x – 405.x (Hypertensive diseases),
410.x – 414.x (Ischemic heart disease),
420.x – 429.x (Other forms of heart disease),
430.x (Subarachnoid hemorrhage),
431.x (Intracerebral hemorrhage),
432.x (Other and unspecified intracranial hemorrhage),
433.x (Occlusion and stenosis of precerebral arteries),
434.x (Occlusion of cerebral arteries),
435.x excluding
435.2 (Transient cerebral ischemia excluding subclavian steal syndrome),
436.x (Acute, but ill-defined, cerebrovascular disease),
437.1 (Other generalized ischemic cerebrovascular disease),
437.2 (Hypertensive encephalopathy),
437.3 (Cerebral aneurysm, nonruptured),
437.6 (Nonpyogenic thrombosis of intracranial venous sinus),
437.8 (Other cerebrovascular disease),
437.9 (Unspecified cerebrovascular disease),
441.0 (Dissection of aorta),
444.x (Arterial embolism and thrombosis),
785.0 (Tachycardia, unspecified),
785.1 (Palpitations),
785.2 (Undiagnosed cardiac murmurs),
785.3 (Other abnormal heart sounds),
785.5 (Shock without mention of trauma),
785.9 (Other symptoms involving cardiovascular system)
798.x (Sudden death, case unknown)

The ICD-10 codes used to designate a cardiovascular encounter are:
B33.2 (Viral carditis),
G45.0 (Vertebro-basilar artery syndrome),
G45.1 (Carotid artery syndrome [hemispheric]),
G45.2 (Multiple and bilateral precerebral artery syndromes),
G45.8 (Other transient cerebral ischaemic attacks and related syndrome),
G45.9 (Transient cerebral ischaemic attack, unspecified),
G46.0 (Middle cerebral artery syndrome),
G46.1 (Anterior cerebral artery syndrome),
G46.2 (Posterior cerebral artery syndrome),
G46.4 (Cerebellar stroke syndrome),
G46.5 (Pure motor lacunar syndrome),
G46.6 (Pure sensory lacunar syndrome),
G46.7 (Other lacunar syndrome),
I10.x (Essential [primary] hypertension),
I11.x (Hypertensive heart disease),
I12.x (Hypertensive renal disease),
I13.x (Hypertensive heart and renal disease),

I15.x (Secondary hypertension),
I20.x (Angina pectoris),
I21.x (Acute myocardial infarction),
I23.x (Certain current complications following acute myocardial infarction),
I24.x (Other acute ischaemic heart diseases),
I25.0 (Atherosclerotic cardiovascular disease, so described),
I25.1 (Atherosclerotic heart disease),
I25.3 (Aneurysm of heart),
I25.4 (Coronary artery aneurysm),
I25.5 (Ischaemic cardiomyopathy),
I25.6 (Silent myocardial ischaemia),
I25.8 (Other forms of chronic ischaemic heart disease),
I25.9 (Chronic ischaemic heart disease, unspecified),
I30.x (Acute pericarditis),
I31.x (Other diseases of pericardium),
I32.x (Pericarditis in diseases classified elsewhere),
I33.x (Acute and subacute endocarditis),
I34.x (Nonrheumatic mitral valve disorders),
I35.x (Nonrheumatic aortic valve disorders),
I36.x (Nonrheumatic tricuspid valve disorders),
I37.x (Pulmonary valve disorders),
I38 (Endocarditis, valve unspecified),
I39.x (Endocarditis and heart valve disorders in diseases classified elsewhere),
I40.x (Acute myocarditis),
I41.x (Myocarditis in diseases classified elsewhere),
I42.x (Cardiomyopathy),
I43.x (Cardiomyopathy in diseases classified elsewhere),
I44.x (Atrioventricular and left bundle-branch block),
I45.x (Other conduction disorders),
I46.x (Cardiac arrest),
I47.x (Paroxysmal tachycardia),
I48 (Atrial fibrillation and flutter),
I49.x (Other cardiac arrhythmias),
I50.x (Heart failure),
I51.x (Complications and ill-defined descriptions of heart disease),
I52.0 (Other heart disorders in bacterial diseases classified elsewhere),
I52.8 (Other heart disorders in other diseases classified elsewhere),
I60.x (Subarachnoid haemorrhage),
I61.x (Intracerebral haemorrhage),
I62.x (Other nontraumatic intracranial haemorrhage),
I63.x (Cerebral infarction),
I64 (Stroke, not specified as haemorrhage or infarction),
I65.x (Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction), I66.x (Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction), I67.0 (Dissection cerebral arteries, nonruptured),
I67.1 (Cerebral aneurysm, nonruptured),
I67.2 (Cerebral atherosclerosis),
I67.3 (Progressive vascular leukoencephalopathy),
I67.4 (Hypertensive encephalopathy),

I67.6 (Nonpyogenic thrombosis of intracranial venous system),
I67.7 (Cerebral arteritis, not elsewhere classified),
I67.8 (Other specified cerebrovascular diseases),
I67.9 (Cerebrovascular disease, unspecified),
I68.x (Cerebrovascular disorders in diseases classified elsewhere),
I69.x (Sequelae of cerebrovascular disease),
I70.x (Atherosclerosis),
I71.x (Aortic aneurysm and dissection),
I72.x (Other aneurysm and dissection),
I73.8 (Other specified peripheral vascular diseases),
I73.9 (Peripheral vascular disease, unspecified),
I74.x (Arterial embolism and thrombosis),
I79.0 (Aneurysm of aorta in diseases classified),
I79.2 (Peripheral angiopathy in diseases classified elsewhere),
I97.1 (Other functional disturbances following cardiac surgery),
I98.1 (Cardiovascular disorders in other infectious and parasitic diseases classified elsewhere),
I98.8 (Other specified disorders of circulatory system in diseases classified elsewhere), R00.x (Abnormalities of heart beat),
R01.x (Cardiac murmurs and other cardiac sounds),
R57.0 (Cardiogenic shock),
R57.1 (Hypovolaemic shock),
R57.8 (Other shock),
R57.9 (Shock, unspecified),
R96.x (Other sudden death, cause unknown),
R98 (Unattended death).