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Antidepressant medication use and objectively measured physical activity and sedentary behaviors in adults: a cross-sectional analysis of a nationally representative sample of Canadian adults.

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Abstract

Background: Antidepressant medication is one of the most prescribed medications among Canadians. This medication class has been previously associated with adverse effects. To date, far too little attention has been paid to physical activity (PA) and sedentary behaviors (SB) in adults using antidepressant medication. The study aims to compare objectively measured time in PA and SB behaviors in a population-based sample of adults using antidepressant medication compared to a group of adults not using any psychotropic medication, and to investigate whether these behaviors differ according to four antidepressant classes.

Methods: We used representative data from the Canadian Health Measures Survey (2007–2013). Medication use was documented during an in-house visit. PA and SB were measured by accelerometer. We included 7680 participants aged 18 to 79 years. A set of weighted analyses of covariance with adjustments for sex, age, body-mass index, income, education level, season, smoking and marital status was conducted to compare mean differences in PA and SB variables between adults using antidepressants and controls.

Results: The cross-sectional weighted prevalence of antidepressant use was 9.3%. Adults using antidepressants completed significantly fewer minutes of moderate to vigorous PA and steps daily compared to adults without psychotropic medication. Daily time spent in light PA and SB were not significantly different between both groups. Sensitivity analyses controlling for self-reported mental and physical health showed no significant difference except smaller time spent in moderate to vigorous PA in adults using SSRI antidepressants than control.

Conclusion: Due to host of negative side effects associated with antidepressant usage and the present findings demonstrating lower levels of MVPA in those taking SSRIs, care providers should promote physical activity when prescribing this class of antidepressants.

Introduction

Antidepressant medications represent one of the most prescribed medications in Canada, and are among the top five prescription medications used in Canadians from 15 to 64 years. Data from nationally representative samples show that antidepressant use was reported by 8% and 17% of adults aged 45 to 64 for men and women, respectively (Rotermann et al., 2014). Moreover, the prevalence of antidepressant prescriptions increased between 2006 and 2012 in primary care (from 9.2% to 12.8%). However, the incidence of prescription did not rise during the same period (Morkem et al., 2015). These different patterns suggested a more prolonged antidepressant use in Canadians adults.

Antidepressant users represent a heterogeneous population including individuals with depressive or other disorders. Antidepressants are an evidence-based pharmacological treatment primarily used for the first-line treatment of major depressive disorder (Kennedy et al., 2016). Different antidepressant classes are prescribed based on patient and medication characteristics. However, adults using antidepressants do not represent only patients with a depressive disorder. For instance, fluoxetine can be prescribed in adults with obsessive-compulsive disorder or panic disorder. Furthermore, recent investigations showed an important prevalence of antidepressant prescriptions for off-label uses (i.e., prescriptions for indications that have not been approved by health authorities; Carton et al., 2015) in non-psychiatric settings (Deferio et al., 2018; Skånland & Cieślar-Pobuda, 2019; Wong et al., 2017). Off-label prescriptions represented 15 to 30% of antidepressant prescriptions in primary care in a Canadian study (Wong et al., 2017). Tricyclic antidepressants were the most prescribed antidepressant class among antidepressant off-label prescriptions. The most common antidepressant off-label indications were anxiety, insomnia, chronic pain or migraine, eating disorders and smoking cessation (Deferio et al., 2018; Skånland & Cieślar-Pobuda, 2019; Wong et al., 2016). Overall, almost half the antidepressant prescriptions were for other disorders than depressive disorder (Wong et al., 2016).

Although antidepressant medications are effective to treat adults with major depressive disorders, antidepressant use could be (in)directly associated with lower and higher time spent in physical activity (PA) and sedentary behaviors, respectively. In a mice study, SSRI was related to a motor activity decrease (Marlatt et al., 2010). An increased risk of muscle injuries has been reported in adults with SSRI treatment (Labotz et al., 2006). Antidepressant use (i.e., antidepressants from tricyclic, SSRI and atypical categories) is associated with higher risk of cardiometabolic diseases and weight gain (Carvalho et al., 2016; Serretti & Mandelli, 2010), longitudinal risk of fractures, and gait disturbances in the elderly (Coupland et al., 2018). The weight gain associated with antidepressant use has been linked to a greater caloric intake and more time spent in sedentary behaviors (Jensen-Otsu & Austin, 2015). Moreover, adults with severe mental illness were less active compared to healthy adults. Among them, the antidepressant users were more inactive (Vancampfort et al., 2017). In this perspective, PA and sedentary behaviors could play a buffering effect between antidepressant use and adverse side effects (Bruins et al., 2014; Schuch et al., 2018).

PA and sedentary behaviors in adults using antidepressants have received little attention to date (Bernard & Carayol, 2015). Weekly self-reported time spent in PA was prospectively associated with a lower risk of antidepressant use in middle-aged Finnish adults (Lahti et al., 2013; Loponen et al., 2015; Stubbs et al., 2017; Waller et al., 2016). However, this association was not observed in adolescents (Kleppang et al., 2019). An increase of self-reported moderate-to-vigorous PA (MVPA) has been found as a behavioral marker of antidepressant treatment (Yun et al., 2020).

These studies suffered from several limitations. First, PA was self-reported although accelerometer data provide a more accurate quantification of the PA in daily life (Westerterp, 2009) and may exclude confounders such as recall bias commonly observed in adults with mood disorders (Morres et al., 2019). Second, previous findings about PA and sedentary behaviors in adults with major depressive disorder (Schuch et al., 2017) cannot be generalized to antidepressant users because 15 to 30% of antidepressant prescriptions may be for off-label indications and up to 45% of antidepressant prescriptions may be for other disorders than depressive disorder (Wong et al., 2016).

Third, no investigation examining PA in antidepressant users has been conducted in a nationally representative sample. Lastly, no information was available about PA and sedentary behavior patterns across antidepressant classes. In this perspective, Bernard and Carayol (2015) recommended the examination of PA and sedentary behaviors with objective measures in adults using antidepressant medications.

The aims of this study were: to describe PA and sedentary behaviors in a representative sample of Canadian adults using antidepressants, to compare objectively assessed daily time spent in PA and sedentary behaviors in a population-based sample of adults using antidepressant medication with adults without psychotropic use, and to investigate whether these behaviors differ according to four antidepressant classes. In the absence of any studies examining these accelerometer-measured behaviors, no a priori hypotheses were formulated.

Methods

Study setting and participants

This study used data collected by Statistics Canada during cycle 1, 2, and 3 (2007–2013) of the Canadian Health Measures Survey (CHMS). This national survey included people aged 6 to 79 years old and used a stratified three-stage sampling strategy (Tremblay & Gorber, 2007). Sociodemographic, general health and medication information were collected at participants' homes and direct physical measures were collected on a subsequent visit to a mobile examination center. All participants provided written informed consent. Ethics approval to conduct the survey was obtained from Health Canada's Research Ethics Board (Day et al., 2007). The current analyses included participants aged 18 to 79 years old with complete accelerometry and medication data. Pregnant women, participants with functional limitations and adults using any other psychotropic medication but not using antidepressants were excluded in our analyses. Controls did not use any psychotropic medication.

Measures

Sociodemographic and clinical characteristics

Age, level of education, household annual incomes, working status and body mass index were collected during the home interview. Self-reported diagnostic of mood disorders, level of mental health and subjective health were measured with three single-item questions. Smoking was established by urinary cotinine level measured during the mobile-examination clinic visit (Wong et al., 2013).

Antidepressant Medication

During the home visit, an interviewer asked participants to collect every medication container present in their house, collected all drug identification numbers from medication containers, then he asked when was the last time they used every medication. Current medication use was defined as any medication taken by the respondent during the previous seven days. Up to fifteen medications were recorded for each respondent. Each drug identification number was recorded according to Anatomical Therapeutic Chemical classification (ATC; Bosak et al., 2018; Bowring et al., 2017). For our analyses, psychotropic drugs from the following groups were considered: N05A antipsychotics, N05B anxiolytics, N05C hypnotics and sedatives, and N06A antidepressants. Four antidepressant medication classes were also coded: Serotonin-Norepinephrine Reuptake Inhibitors (SNRI; N06AX16/AA22, N06AX17/AA24, N06AX21, N06AX23), Selective Serotonin Reuptake Inhibitor (SSRI; N06AB), Tricyclic (N06AA [except N06AA22 AND N06AA24]) and other antidepressants (N06AF, N06AG, N06AX01-12 [or N07BA02], 13–15, 18, 19, 22, 24, 25; Laugesen et al., 2013).

Physical Activity and Sedentary Behaviors

PA and sedentary behaviors were objectively measured with Actical accelerometers (Phillips-Respironics). The Actical records time-stamped acceleration in three dimensions, thereby indicating physical activity intensity. This accelerometer has been validated to measure physical activity in adults (Heil, 2006). Participants wore the Actical over their right hip on an elasticized belt during their waking hours for seven consecutive days. To be included in the analysis, participants needed at least four valid days of data defined as at least 10 hours of wear time (Colley et al., 2011). Time spent daily in PA at different intensity levels was categorized with validated count per minute (cpm) thresholds for

adults: sedentary (<100 cpm), light (100 to 1,534 cpm) and moderate to vigorous intensity (≥1535 cpm; Colley & Tremblay, 2011). The Actical also measured steps per day. Participants with extreme counts (i.e. >20,000 cpm) were excluded from analyses (Colley et al., 2010).

Data Analysis

Student t tests and chi squares were performed to compare antidepressant users and controls on PA and sedentary behavior variables as well as sociodemographic, anthropometric and health variables. Four weighted analyses of covariance regression models (ANCOVA) incorporating age, sex, body mass index, accelerometer wear time, data collection season, work and marital status, smoking, education level, and income were carried out. The four dependent variables were: average time performing MVPA and light PA (LPA), average daily steps, and daily time spent in sedentary behaviors. To account for the complex, multistage probability sampling design, weights (i.e., activity monitor subsample weights combining cycles 1, 2, and 3) and bootstraps provided by Statistics Canada were used in analyses. Since the number of minutes of MVPA was not normally distributed, Poisson models were carried out for this variable. All analyses were performed during 2018 and 2019, using the "*survey"* package in R version 3.4.

Sensitivity Analyses

To examine the possible effect of antidepressants combined with another psychotropic medication, a set of sensitivity analyses was performed. The ANCOVAs were carried out including only adults using another psychotropic with antidepressants, then we reran models including participants using only an antidepressant medication. Based on reviewer suggestions, a second set of sensitivity analyses has been carried out. All models have been performed with self-reported levels of mental and physical health as covariates.

Results

Data from 7680 participants were included in analysis. The weighted prevalence of antidepressant medication use was 9.3% in adults 18- to 79-year-olds. Among these, 1.1% used

tricyclic antidepressants, 1.7% used other antidepressants, 2.4% used SNRI, and 5.0% used SSRI. Moreover, 6.6% used only antidepressant medications and 2.9% used antidepressants along with at least another psychotropic medication. Unadjusted antidepressant users and control characteristics are provided in Table 1. Descriptive findings for adults reporting tricyclics, other antidepressants, SNRI or SSRI use; and antidepressant use combined with or without another psychotropic medication are presented in online supplements in Table S1, S2, and S3, respectively. Description of means, standard deviation and medians of LPA, MVPA, steps per day and time spent in sedentary behaviors are described in Table 2.

The weighted ANCOVAs revealed that antidepressant users spent significantly less time in MVPA (d = -0.02, p =0.03) and performed a lower daily number of steps (d = -0.01, p = 0.05) in comparison to adults not using any psychotropic medication. Among antidepressant users, SSRI use was associated with significant lower time spent in MVPA (d = -0.13, p = 0.01) and daily steps (d = -0.10, p = 0.05). Adults classified as “other antidepressant users” had significantly lower daily steps (d = -0.20, p = 0.03) than the control group. No significant differences were found in adults using either SNRI or tricyclic antidepressants. No significant differences were observed for daily time spent in sedentary behaviors, except for adults using “other” antidepressant medications (d = 0.18, p = 0.04). All details about statistical results are available in online supplements.

The sensitivity analyses compared adults not using any psychotropic medication to adults using antidepressants and no other psychotropic medication, and adults using antidepressants and at least one other psychotropic medication. Similar findings were found for MVPA (d = -0.10, p = 0.05) and daily steps (d = -0.10, p = 0.03) in adults using only antidepressant medication. Otherwise, no significant differences were found between adults using antidepressants and at least one other psychotropic medication for PA and sedentary behavior outcomes. In multivariate models adjusted for self-reported levels of mental and physical health, adults using SSRI had a significant lower daily time spent in MVPA (d = -0.01, p = 0.01). No other significant differences were found.

Discussion

This study compared objectively measured physical activity and sedentary behavior in adults using antidepressants with adults without psychotropic use in a nationally representative sample. To the best of our knowledge, this is the first study to examine this question with medication assessed during a home interview combined with accelerometer data in Canadians. Prevalence of antidepressant use in our sample of Canadian adults was in line with previous analyses of nationally representative data in Canada (Morkem et al., 2015) and the US (Pratt et al., 2017). Regarding sociodemographic characteristics, our antidepressant users group was comparable to the US adults using this medication (Jensen-Otsu & Austin, 2015). Our key findings were that adults with antidepressant treatment spent significantly fewer daily minutes in MVPA and performed fewer daily steps. However, it is very important to note that effect sizes were low. Thus, this difference may not be clinically significant. The differences were more marked for patients with SSRI or other antidepressant medications.

These results differ from Jensen-Otsu's investigation (2015) that did not identify a significant difference between antidepressant users and non-users for leisure PA. However, physical activity was assessed with a self-reported questionnaire. Even if no previous study assessed MVPA in antidepressant users, our findings can be compared to investigations including possible antidepressant users (e.g., adults with depressive disorders, anxiety, chronic pain or with sleep disorders; Wong et al., 2016). Thus, our findings were in accordance with previous studies that found lower objectively measured MVPA among adults with depressive disorders, chronic pain or other chronic diseases compared to healthy controls (Bernard et al., 2018; Farnsworth et al., 2015; Schuch et al., 2017). It has been suggested that antidepressant users reported more time in sedentary screen time activities (Jensen-Otsu & Austin, 2015). However, our results indicated that objectively measured time spent in sedentary behaviors was significantly higher only in adults using "other" antidepressant medications.

The fewer daily steps among antidepressant users are clinically relevant. The number of steps per day is a measure of total PA and differs from the measures of PA at defined levels of intensity (Tudor-Locke et al., 2011a). This outcome has been independently associated with numerous health outcomes (Newton et al., 2013; Tudor-Locke et al., 2018). Moreover, walking was the preferred PA in adults with depressive disorder (Burton et al., 2015; Busch et al., 2016), other mental disorders (Simonton et al., 2018), older adults and adults with chronic diseases (Wong et al., 2018).

The sensitivity analyses suggest that adults with “only” an antidepressant treatment had a significantly lower levels of PA. Nevertheless, no significant differences with controls were observed among adults combining an antidepressant with another psychotropic medication (i.e., antipsychotics, anxiolytics, hypnotics and sedatives). This suggests that other psychotropic treatments may have an antagonist effect with antidepressants and “compensate” the possible negative association between PA and antidepressant use (Bernard & Carayol, 2015). Moreover, in our sensitivity analysis controlling for self-reported mental and physical health, SSRI users performed significantly less daily minutes of MVPA than the control group. This is in line with the results from Marlatt et al. (2010) indicating a decrease in locomotor activity in mice using SSRI antidepressants. This result might suggest that the difference is attributed to a specific diagnosis for which the antidepressant was prescribed since this information were not available for this survey. It might also indicate a side effect from this specific type of medication. However, at this point causation cannot be inferred since the cross-sectional design of this study is not appropriate for this purpose and too little is known about the interaction between SSRIs and physical activity at a physiological level (Bernard & Carayol, 2015). These results and the fact that the difference appears even when our analysis is controlled for self-reported health reinforce the importance of the promotion of PA in SSRI users. It is important to note that in these sensitivity analyses, all of the other differences observed became non-significant. As reported in supplementary files (Tables S20-S35) the difference in MVPA and daily steps observed in antidepressant users, and the difference in daily steps in SSRI and other antidepressant users would be better explained by the self-reported physical health. Considering the major prevalence of depressive symptoms in adults with

physical diseases, antidepressant prescriptions are recommended to treat it (Olver & Hopwood, 2013). Moreover, it has been demonstrated that physical diseases were associated to less daily time spent in PA (Bernard et al., 2018; Bernard et al., 2018; Hains-Monfette et al., 2019).

This study set out with the aim of comparing physical activity and sedentary behavior outcomes between users of four classes of antidepressants and controls. Findings suggested that adults using SSRI or “other” antidepressants had significantly lower PA levels. Antidepressants belonging to the “other” category were mainly the Monoamine Oxidase Inhibitor (MOAI) class. These are recommended for adults with treatment-resistant major depressive disorder and atypical depression, but also adults with bipolar depression and older individuals with major depressive disorder as a second or third treatment attempt (Shulman et al., 2013). Consequently, these results may be partly explained by the fact that adults with MOAI treatment have more severe mental disorder symptoms and also higher risk of morbidity (Nelson & Spyker, 2017). Therefore, care providers may strengthen PA assessment and promotion in patients with SSRI and MOAI.

This is the first time that data from representative national samples of adults has been used to examine objectively measured PA and sedentary behaviors in antidepressant users. Thus, our findings are generalizable to the Canadian population. Additionally, the ATC information collected during a home interview decrease the risk of misclassification reported in previous studies using administrative data. Some limitations need to be considered when interpreting our results. First, the cross-sectional design precludes causal inferences. Therefore, it is impossible to establish a causality relation between PA and sedentary behaviors, and antidepressant use. Second, detailed information about mental disorder diagnostics was not available in CHMS data. Thus, our statistical models were not adjusted for these important variables. Third, the CHMS dataset contained no information about antidepressants dose, treatment duration or adherence (Bulloch & Patten, 2010). These parameters may affect PA and sedentary behaviors in CHMS participants. Fourth, our analyses were not controlled for non-psychotropic medication. Since use of prescribed medication (e.g., diuretics, anticoagulants, lipid-regulating agents) is linked to less PA (Fernandez-Navarro et al., 2018; Silva et

al., 2012; Stamatakis et al., 2009) and antidepressant users are more at risk to use other medications (Sundbom & Hedborg, 2019), there might have been interactions between non-psychotropic medication and PA. Fifth, the time spent in sedentary behaviors or LPA could be underestimated because the accelerometer data were not collected with a 24h wear protocol (Matthews et al., 2012; Tudor-Locke et al., 2011b). Sixth, due to the large number of statistical analyses, the risk of type 1 is inflated. Finally, the Actical accelerometer might not be the best instrument to distinguish sedentary behaviors from LPA compared to other more recent devices (Duncan et al., 2018).

In conclusion, adults using SSRI have lower levels of MVPA than adults that do not use any psychotropics. First line care providers should systematically assess PA and sedentary behaviors (Romain et al., 2018), and particularly brisk walking behaviors, with their patients when they receive an antidepressant prescription and help them make a plan to achieve an adequate number of steps and MVPA time daily. To help them achieve this goal, they may use guides such as *The Exercise and Depression Toolkit* (Exercise and Depression Toolkit - UBC, 2019; Glowacki et al., 2019), effective behavior change techniques (Bernard et al., 2015), or include kinesiologists in their interdisciplinary teams to specifically assess and suggest physical activity to patients (Busch et al., 2016). Future prospective cohort studies should monitor the device-measured PA and sedentary patterns in naive SSRI users before and after treatment begins. The assessment of these behaviors should be performed with more specific devices, such as the Genactive and activPAL accelerometers (Sellers et al., 2016).

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