Brief Communication

An Epidemiologic Study of Psychotropic Medication and Obesity-Related Chronic Illnesses in Older Psychiatric Patients

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Objective: Adverse effects from medication vary with age. Weight gain with several psychotropics is well known in adults but less information is available related to extent and complications of psychotropic-induced weight gain in older psychiatric patients. We determined the relative incidence of 2 obesity-related conditions (diabetes and hypertension) in older psychiatric patients receiving antipsychotics, antidepressants, and mood stabilizers.

Method: A population-based case–control study of all psychiatric patients aged 67 years or older in contact with either specialist services or primary care using administrative data from Nova Scotia.

Results: We identified incident cases of diabetes (n = 608) and of hypertension (n = 1056), as well as an equal number of control subjects for each condition. Amitryptiline, selective serotonin reuptake inhibitors (SSRIs), and olanzapine were associated with an increased risk of presenting with hypertension 6 months after initial prescription. By contrast, conventional antipsychotics were associated with a reduced incidence of hypertension. Olanzapine was also significantly associated with diabetes after 6 months (OR_{adj} = 2.58, 95% CI 1.12 to 5.92). The findings for SSRIs and olanzapine remained significant after adjusting for potential confounders such as sociodemographic characteristics, schizophrenia, beta blockers, thiazide diuretics, and corticosteroids.

Conclusions: Our results suggest that the association of psychotropics and 2 obesity-related conditions, hypertension and diabetes, applies to older psychiatric patients as well as younger populations. Within drug classes, there are drugs that have a greater association than others, and this may be a factor when choosing a specific agent.

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Clinical Implications

- Psychotropics are widely used in older patients to treat various psychiatric disturbances, and this is reflected in the disproportionately high use of these compounds in people aged 65 years or older. However, there are few studies of possible obesity-related side effects in this population.
- The results of this study suggest that the association of psychotropics and possible obesity-related conditions such as hypertension and diabetes applies to older psychiatric patients, as well as younger populations.
- Within drug classes, there are drugs that have a greater association than others, and this may be a factor when choosing a specific agent.

Limitations

- We relied on routine administrative data that may be subject to recording and ascertainment bias. We may therefore have underestimated the true incidence of diabetes and hypertension, and overestimated the association between certain psychotropic and possible obesity-related conditions.
- We do not know whether our results for older psychiatric patients are generalizable to other populations until further studies are undertaken in this area.
- As this was an epidemiologic study using administrative claims data, detailed clinical information or information on risk factors such as smoking, physical activity, diet, or family history was not available. We were also unable to evaluate the effect of treatment dose or compliance.

***Key Words*:** *seniors, obesity, psychotropics*

The growing prevalence of obesity and obesity-related disorders, such as type II diabetes and hypertension, is a major public health concern.[1–4] Aside from poor diet and sedentary lifestyle, antipsychotic agents, mood stabilizers, and several antidepressants can promote weight gain.[5–8] With 1 in 5 Canadians having a psychiatric disorder during their lifetime and the use of psychotherapeutic drugs as second only to cardiovascular drugs,[9] psychotropic medications may contribute to obesity and obesity-related disorders in Canada.

There is limited information on the longer-term effects of psychotropic-induced weight gain. Numerous controlled trials have reported short-term changes in glucose and cholesterol levels, although long-term consequences are less clear.[10] A large, noncommercial clinical trial in the United States indicated that olanzapine was associated with higher rates of discontinuation for weight gain or metabolic effects.[11]

Results from observational analyses of administrative databases are equivocal. A meta-analysis of 16 studies in patients with psychoses from the United States reported that clozapine and olanzapine showed an increased risk of diabetes, compared with conventional or no antipsychotics, but risperidone or quetiapine did not.[10] However, other epidemiologic studies found little difference between conventional and atypical antipsychotics in increasing the risk of diabetes.[12–14] One limiting factor of many US studies is that they are restricted to members of health care plans and therefore subject to selection bias.

There are still fewer data on people aged 65 years and older even though they are more likely to receive psychotropics than younger populations.[15,16] They may also differ in terms of obesity-related side-effects, as increasing age is independently associated with diabetes and hypertension.[14] This case–control study compares the proportion of older psychiatric patients taking psychotropics who developed 2 obesity-related conditions (diabetes and hypertension) with the proportion taking psychotropics who developed neither condition. We also investigated whether there were any differences between, and within, specific drug classes. We used the administrative databases of the provincial health care and pharmaceutical programs, which cover people aged 65 years and older in Nova Scotia.[17]

Abbreviations used in this article

DAD	Discharge Abstract Database
ICD	International Classification of Diseases
MHOIS	Mental Health Outpatient Data Information System
PHAC	Public Health Agency of Canada
SSRI	selective serotonin reuptake inhibitor

Study Design and Analysis

We assessed the potential effect of the following psychotropic drugs: high- and low-potency conventional neuroleptics (based on chlorpromazine equivalents),[18,19] olanzapine, quetiapine, risperidone, SSRIs, venlafaxine, amitryptiline, lithium, and other mood stabilizers. We identified cases and controls using the following datasets:

- The Seniors' Pharmacare database of claims by people aged 65 years and older including duration of each prescription
- The physician billings database of all fee-for-service claims including date of service, ICD-9 and ICD-10 diagnoses, and patient demographics
- The Canadian Institute of Health Information DAD of admissions, separation times, and diagnoses
- MHOIS of demographics, diagnoses, and care episodes

We defined cases as psychiatric patients who presented for the first time with 1 of the 2 obesity-related conditions of interest in either the DAD or physician billings databases for the study period (January 1, 2001, to December 31, 2003). We identified cases for each obesity-related condition separately using the following ICD-9 codes (or ICD-10 equivalents): diabetes (250) and hypertension (401). We checked for the absence of these diagnoses in the DAD or physician billings databases over the previous 5 years. We randomly selected a control psychiatric patient for each case, matched on age, sex, and previous health service use. The control subjects had not presented with the obesity-related condition of interest during the study period, or in the 5 years prior to the matched case's index diagnosis. Psychiatric patients were identified using criteria from PHAC for the surveillance of treated psychiatric disorder.[20,21] The PHAC definition consists of ICD-9 diagnoses from 290 to 319 inclusive, or ICD-10 equivalents. Case and control subjects had to have had at least one psychiatric record in DAD, physician billings or MHOIS from April 1, 1989, to December 31, 2003, and be eligible for the Senior Pharmacare Program on the study start date (January 1, 2001). They also had to be aged 67 years and older to allow a 2-year lead-in from initial eligibility, and therefore sufficient time for exposure to a psychotropic prescribed under the program.

We then compared the prescription rate for every psychotropic under investigation for case and control subjects. We included patients who had received 6 months or more of that particular medication prior to presentation for hypertension or diabetes. We used 6 months as studies of early-episode psychosis indicate that most

psychotropic-induced weight gain occurs within the first 6 months of starting medication.[22,23] We also conducted sensitivity analyses of changing this threshold to 3 months or more. We assessed the effects of potential confounders for the outcomes of interest including age (aged 80 years or older, marking the oldest 25% to 33% of the hypertensive or diabetic sample), sex, socioeconomic class (divided into quarters), schizophrenia, beta blockers, thiazide diuretics, and corticosteroids.[24,25] We used logistic regression to adjust for any potential confounder that we found to be associated with either outcome, as well as sex and age (the latter as a continuous variable).

The Capital Health Research Ethics Board approved this research.

Results

We identified 608 people with diabetes and 1056 people with hypertension, plus an equal number of control subjects for each condition.

Table 1 shows the results for diabetes. We found no statistically significant differences between the case and control subjects in terms of potential confounders with the exception of beta blockers, thiazide diuretics, and corticosteroids (Table 1). After adjusting for potential confounders, olanzapine was significantly associated with diabetes following 6 months of treatment (Table 1), and as soon as after 3 months of treatment (OR_{adj} = 2.38, 95% CI 1.12 to 5.07; P = 0.03).

Table 2 shows the results for hypertension. We found no statistically significant differences in the case and control subjects in terms of potential confounders with the exception of socioeconomic class, a diagnosis of schizophrenia, beta blockers, and thiazide diuretics (Table 2). Amitriptyline, SSRIs, and olanzapine were associated with an increased risk of presenting with hypertension after 6 months of use. Conventional neuroleptics were associated with a reduced risk of presenting for hypertension (Table 2). For psychotropics, SSRIs and olanzapine remained significantly associated with hypertension after adjusting for potential confounders (Table 2). On sensitivity analysis, the results for olanzapine and SSRIs were significant from 3 months onward (of use, respectively, OR_{adj} = 2.00, 95% CI 1.07 to 3.75; P = 0.03 and OR_{adj} = 1.34, 95% CI = 1.07 to 1.68; P = 0.01). Quetiapine was associated with a reduced risk of hypertension at 3 months (OR_{adj} = 0.40, 95% CI 0.17 to 0.93; P = 0.03).

Discussion

Antipsychotics are widely used in older patients to treat various psychiatric disturbances including delirium, dementia, schizophrenia, delusional disorder, and psychotic mood disorders. The frequency of their use is underlined by findings of a disproportionately high use of antipsychotics and benzodiazepines in geriatric patients, compared with those aged 65 years and younger. In spite of their use, there are few studies of side effects in this population. Available data on side effects are generally confined to nursing home residents and have not focused on obesity-related conditions.[15]

To our knowledge, this is the first population-based case–control study of the problem in this age group. We evaluated the effect of a wide range of psychotropics on diabetes and hypertension 6 months after prescription over a 3-year period. The prescription of some psychotropics was associated with increases in the treated incidence of hypertension and diabetes at a population level. Further, within drug classes, some medications showed an increased association with diabetes and hypertension in comparison with others (for example, olanzapine, compared with other atypical antipsychotics).

When comparing our data with other findings, one limitation is that most studies have included both younger and older ages, and have not been restricted to people aged 65 years and older. Although, there is general agreement that certain classes of psychotropics are associated with weight gain and possible obesity-related disorder, there are conflicting data for comparisons within classes. For instance, some studies have found that olanzapine is associated with a greater risk of developing diabetes, compared with other antipsychotics,[10,11,26,27] while others have not.[12–14]

This disparity in results in the general population may be due to the presence of other drugs that may increase diabetes risk, and differences in patient populations, analytical methods, or the identification of diabetes and hypertension.[11,14] We therefore do not know whether our results necessarily apply to other populations.

There are several limitations to this study. We have no information on risk factors such as physical activity or family history. We probably underestimated the true incidence of hypertension and diabetes as we only counted recognized cases, and up to one-third of diabetes in North America is undiagnosed.[10] The number of patients on some medications was too small to allow analysis (for example, clozapine), or might have been underpowered for accurate determination of the risks of diabetes or hypertension during treatment with those drugs. The concurrent prescription of other psychotropics might have confounded the results of our analyses of hypertension. However, this would not explain our findings for diabetes where only one psychotropic was associated with the outcome of interest. It is also possible that increasing awareness of the association between particular medications, such as olanzapine and the metabolic syndrome, might have led to ascertainment bias. However, this would have applied more toward the end of the study period.

Table 1 Variables associated with diabetes

Variable	Cases *n* = 608	Control subjects *n* = 607	OR (95% CI)	*P*	Adjusted OR[a] (95% CI)	*P*
Age, >80 years	196	195	1.00 (0.99–1.02)	0.90		
Sex, male	193	193	1.00 (0.78–1.27)	0.98		
Quarterly income						
$49 562[b]	194	179				
$40 184–$49 561	129	150	0.79 (0.58–1.08)	0.14		
$33 776–$40 183	146	120	1.12 (0.82–1.54)	0.06		
$0–$33 775	139	158	0.81 (0.60–1.10)	0.21		
Schizophrenia	36	27	1.35 (0.81–2.26)	0.25		
Beta blockers	167	132	1.77 (1.05–1.36)	0.02		
Corticosteriods	52	30	2.86 (1.13–1.80)	0.01	1.78 (1.11–2.84)	0.02
Thiazide diuretics	140	82	2.58 (1.42–1.92)	<0.001	1.90 (1.40–2.56)	<0.001
Olanzapine	20	8	2.55 (1.11–5.82)	0.03	2.58 (1.12–5.92)	0.03
Risperidone	26	28	0.92 (0.54–1.60)	0.78		
Quetiapine	9	11	0.72 (0.29–1.81)	0.49		
Low-potency conventional antipsychotics[c]	21	14	2.14 (0.96–4.78)	0.06		
High-potency conventional antipsychotics[d]	30	25	1.21 (0.70–2.08)	0.50		
SSRIs	122	105	1.20 (0.90–1.60)	0.22		
Venlafaxine	29	26	1.12 (0.65–1.92)	0.68		
Amitriptyline	39	41	0.95 (0.60–1.49)	0.81		
Lithium	15	18	0.83 (0.41–1.66)	0.59		
Other mood stabilizers	33	35	0.94 (0.58–1.53)	0.80		

[a] Adjusted for age (as a continuous variable), sex, beta blockers, thiazide diuretics, corticosteroids, and olanzapine

[b] Reference category

[c] Chlorpromazine, thioridazine, and methotrimeprazine

[d] Fluphenazine, haloperidol, droperidol, thiothixene, flupentixol, fluphenazine, trifluoperazine, perphenazine, pimozide, pipotiazine, periciazine, and zuclopenthixol

Lastly, we did not evaluate the effect of treatment dose or adherence in this analysis. However, we focused on psychiatric patients where doses are higher than those for nonpsychiatric reasons. Further, the potential for psychotropic-induced obesity for many drugs is not directly related to dose.

In conclusion, our results suggest that the association of psychotropics and obesity-related conditions applies to older patients as well as younger populations. Within drug classes, some medications have a greater association than others, and this may help clinicians choose an agent. These findings are particularly relevant as people aged 65 years or older are more likely than other age groups to be prescribed psychotropics.

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Table 2 Variables associated with hypertension

Variable	Cases *n* = 1056	Control subjects *n* = 1055	OR (95% CI)	*P*	Adjusted OR[a] (95% CI)	*P*
Age, >80 years	255	254	1.00 (0.99–1.01)	0.93		
Sex, male	397	397	1.00 (0.84–1.19)	0.99		
Quarterly income						
$49 562[b]	331	343				
$40 184–$49 561	254	191	1.38 (1.08–1.75)	<0.001	1.39 (1.09–1.78)	0.01
$33 776–$40 183	217	236	0.95 (0.75–1.21)	0.23	0.95 (0.75–1.21)	0.68
$0–$33 775	254	285	0.92 (0.74–1.16)	0.09	0.96 (0.76–1.21)	0.71
Schizophrenia	53	82	0.63 (0.44–0.90)	0.01	0.58 (0.40–0.85)	0.01
Beta blockers	200	112	1.97 (1.53–2.52)	<0.001	1.88 (1.46–2.42)	<0.001
Corticosteriods	48	51	0.94 (0.63–1.40)	0.75		
Thiazide diuretics	110	49	2.39 (1.69–3.38)	0.001	2.28 (1.60–3.25)	<0.001
Olanzapine	26	13	2.02 (1.03–3.96)	0.04	2.39 (1.17–4.88)	0.02
Risperidone	42	57	0.73 (0.48–1.09)	0.12		
Quetiapine	9	18	0.54 (0.21–1.35)	0.18		
Low-potency conventional antipsychotics[c]	32	48	0.61 (0.38–0.99)	0.04		
High-potency conventional antipsychotics[d]	48	73	0.64 (0.44–0.93)	0.02		
SSRIs	190	144	1.39 (1.10–1.76)	0.01	1.33 (1.04–1.69)	0.02
Venlafaxine	35	25	1.41 (0.84–2.38)	0.19		
Amitriptyline	60	39	1.57 (1.04–2.37)	0.03		
Lithium	23	16	1.45 (0.76–2.75)	0.26		
Other mood stabilizers	49	53	0.92 (0.62–1.37)	0.68		

[a] Adjusted for age (as a continuous variable), sex, socioeconomic class, schizophrenia, beta blockers, thiazide diuretics, SSRIs, amitriptyline, low- and high-potency conventional antipsychotics, and olanzapine

[b] Reference category

[c] Chlorpromazine, thioridazine, and methotrimeprazine

[d] Fluphenazine, haloperidol, droperidol, thiothixene, flupentixol, fluphenazine, trifluoperazine, perphenazine, pimozide, pipotiazine, periciazine, and zuclopenthixol

population surveys. Although this research is based on data obtained from the PHRU, the observations and opinions expressed are those of the authors and do not represent those of PHRU.

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Résumé : Une étude épidémiologique des médicaments psychotropes et des maladies chroniques liées à l'obésité chez les patients psychiatriques âgés

Objectif : Les effets indésirables de la médication varient avec l'âge. La prise de poids qu'entraînent plusieurs psychotropes est bien connue chez les adultes, mais il y a moins d'information relativement à la portée et aux complications de la prise de poids induite par les psychotropes chez les patients psychiatriques âgés. Nous avons déterminé l'incidence relative de 2 affections liées à l'obésité (diabète et hypertension) chez des patients psychiatriques âgés recevant des antipsychotiques, des antidépresseurs et des régulateurs de l'humeur.

Méthode : Une étude cas-témoin dans la population de tous les patients psychiatriques de 67 ans et plus en contact avec des services spécialisés ou des soins primaires utilisant les données administratives de la Nouvelle-Écosse.

Résultats : Nous avons identifié cas incidents de diabète (n = 608) et d'hypertension (n = 1056), ainsi qu'un nombre égal de témoins pour chaque affection. L'amitryptiline, les inhibiteurs spécifiques du recaptage de la sérotonine (ISRS), et l'olanzapine étaient associés à un risque accru de présentation d'hypertension, 6 mois après la prescription initiale. Au contraire, les antipsychotiques conventionnels étaient associés à une incidence réduite d'hypertension. L'olanzapine était aussi significativement associée au diabète après 6 mois (OR_{adj} = 2,58, 95 % IC 1,12 à 5,92). Les résultats des ISRS et de l'olanzapine demeuraient significatifs après ajustement pour tenir compte des facteurs de confusion potentiels comme les caractéristiques sociodémographiques, la schizophrénie, les bêtabloquants, les diurétiques thiazidiques, et les corticostéroïdes.

Conclusions : Nos résultats suggèrent que l'association des psychotropes et des 2 affections liées à l'obésité, le diabète et l'hypertension, s'applique aux patients psychiatriques âgés de même qu'aux populations plus jeunes. Parmi les classes de médicaments, certains médicaments ont une association plus marquée que d'autres, ce qui peut constituer un facteur lorsqu'on choisit un agent spécifique.