

Atypical Antipsychotics and Parkinsonism

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Background: Atypical antipsychotic agents are thought to be less likely than older typical agents to produce parkinsonism. This has not been well documented. We compared the risk of development of incident parkinsonism among older adults dispensed atypical relative to typical antipsychotics.

Methods: Retrospective cohort study of all adults 66 years and older in Ontario. We used Cox proportional hazards models to study the association between the type, potency, and dose of antipsychotic dispensed and the development of parkinsonism during 1 year of follow-up.

Results: All 25 769 older adults prescribed antipsychotics were observed for 11 573 person-years, and 449 events of parkinsonism were identified. Relative to individuals dispensed an atypical antipsychotic, those dispensed a typical agent were 30% more likely (adjusted hazard ratio [HR], 1.30; 95% confidence interval [CI], 1.04-1.58)

and those exposed to neither agent were 60% less likely (HR, 0.40; 95% CI, 0.29-0.43) to experience development of parkinsonism. Furthermore, those dispensed lower-potency typical agents were no different (HR, 0.75; 95% CI, 0.48-1.15), and those dispensed higher-potency typical antipsychotics were at close to a 50% greater risk (HR, 1.44; 95% CI, 1.13-1.84) of development of parkinsonism relative to atypical antipsychotics. Relative to those dispensed a high-dose atypical antipsychotic, those dispensed a typical antipsychotic were at similar risk for parkinsonism (Wald $\chi^2=0.14$, $P=.7$).

Conclusions: The risk of development of parkinsonism associated with the use of high-dose atypical antipsychotics was similar to that associated with the use of typical antipsychotics. Caution should be used when prescribing atypical antipsychotic therapy at high doses.

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ANTIPSYCHOTIC DRUG THERAPY is widely used for the management of behavioral and psychological symptoms associated with dementia. One of the most important adverse drug events associated with the use of antipsychotics consists of extrapyramidal symptoms, of which parkinsonism is the most common. The newer atypical antipsychotics are thought to be less likely than the older typical antipsychotics to produce parkinsonism,¹ although this has not been well documented. Randomized controlled trials evaluating the use of atypical antipsychotics in this context provide little information on the link between these drugs and the development of parkinsonian features.² Only 5 trials were identified.³⁻⁷ Of these, 4 evaluated risperidone; 1, olanzapine; and none, quetiapine fumarate. Despite antipsychotics often being prescribed for long periods and adverse event rates generally increasing over time, these trials were short (range, 6-12 weeks). A better understanding of the risks of antipsychotic-induced parkinsonism associated with different types, potencies, and doses is needed.

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We studied a large cohort of older adults with dementia to determine whether there is an association between drug exposure and the subsequent development of parkinsonism for the atypical relative to the typical antipsychotic. This study explores the risks associated with different potencies and doses of these agents. As a secondary objective, we compared these rates with those of a group not exposed to antipsychotic drug therapy.

METHODS

DATA SOURCES

We conducted a population-based retrospective cohort study using Ontario administrative health care data.

COHORT DEFINITION

The cohort was drawn from all Ontario residents 66 years and older between April 1, 1997, and March 31, 2001. To ensure a homogeneous population, we restricted our sample to those with dementia without evidence of schizophrenia or a major depressive disorder. Antipsychotic therapy is likely used differently for those with psychiatric disorders. In-

dividuals were followed up to determine whether incident parkinsonism developed (ie, a diagnosis of Parkinson disease or the initiation of antiparkinsonian drug therapy). We compared those exposed to either type of antipsychotic with a group exposed to neither agent and those exposed to atypical vs typical antipsychotics (by potency and dose).

INCLUSION CRITERIA

Our cohort included individuals with evidence of dementia and no exposure to antipsychotics in the previous year. Individuals were identified as having dementia if they received a diagnosis (*International Classification of Diseases, Ninth Revision [ICD-9]* codes 290 or 331) in the 5 years before the index date from a hospital discharge or a physician service claim, or if they were dispensed donepezil in the year before the index date. Donepezil was the only drug therapy for the management of Alzheimer disease covered under the Ontario Drug Benefit plan program in the study period.

EXCLUSION CRITERIA

We excluded individuals with a history of Parkinson disease, defined as those dispensed drug therapy specific for Parkinson disease (ie, a combination of levodopa and carbidopa, ropinirole hydrochloride, pramipexole, pergolide mesylate, selegiline hydrochloride, tolcapone, or entacapone) in the previous year or a diagnosis of Parkinson disease (*ICD-9* code 332) or other movement disorders (*ICD-9* code 333) in the previous 5 years. We excluded those with brain tumor (*ICD-9* code 191, 192, or 198.3), as this condition may predispose to parkinsonism.

We excluded individuals receiving dialysis or palliative care, because these are potential contraindications to antipsychotic therapy, and those with schizophrenia or major depressive psychoses (*ICD-9* code 295, 296, 298, or 299).

Two separate drug exposure cohorts were identified on the basis of the date of first exposure to an oral atypical or typical antipsychotic during the accrual period (**Table 1**). The nonantipsychotic comparison group was selected from the remainder of older adults with dementia who had at least 1 drug dispensed but no previous exposure to antipsychotic therapy. We considered only control subjects who had a drug dispensed, because recent physician contact ensures additional homogeneity across cohorts. To include all potentially eligible controls and to balance the distribution across years, we randomly selected a unique set of controls, in a ratio of 1 person receiving an antipsychotic to 1.25 controls. The first claim for an oral antipsychotic defined the index date for the antipsychotic group; the first claim for nonantipsychotic therapy defined the index date for the comparison group.

The final cohort consisted of 57 838 older adults divided into the following 3 groups: 11 571 receiving an atypical antipsychotic, 14 198 receiving a typical antipsychotic, and 32 069 receiving neither agent (Table 1).

TYPE, POTENCY, AND DOSE

Antipsychotic-induced parkinsonism is thought to be associated with the type, potency, and dose of the therapy. The 2 drug types consist of the typical (eg, chlorpromazine hydrochloride and haloperidol) and the newer atypical therapies (eg, olanzapine, risperidone, and quetiapine). Antipsychotics classified in the lower-potency range are thought to produce less parkinsonism relative to those in the higher-potency range.⁸ All atypical antipsychotics were classified as lower-

potency agents (**Table 2**). The typical antipsychotics were classified as being in a lower- or a higher-potency group.

Adverse events are generally dose related. The Ontario Drug Benefit database provides information on the quantity of the drug (eg, number of tablets dispensed), the days supplied, and the drug identification number. The drug identification number was linked to a database containing details about each drug, including the strength. This information was combined to compute the daily dose. For example, a patient dispensed 30 days' supply of 0.5-mg tablets of haloperidol and given 60 tablets would be deemed to receive 1 mg/d of haloperidol.

Each antipsychotic was classified into a dose category using the approach outlined by Barron et al¹⁰ (Table 2). We defined *low dose* as 25% or less of the maximum recommended dose; *medium dose*, between the low and the maximum recommended doses; and *high dose*, the maximum recommended dose or higher. We used the Centers for Medicare & Medicaid Services guidelines to identify the maximum recommended dose for an older adult.⁹ Flupentixol, periciazine, and pimozide did not have doses defined by the Centers for Medicare & Medicaid Services and were classified using the British National Formulary.¹¹

Therapy for older adults is often initiated with a lower dose and titrated upward. We identified individuals who were dispensed a high dose at some point during the study. Individuals were excluded if it was not possible to calculate their dose (n=933).

More than 90% of individuals continued to receive the same-potency antipsychotics. Therefore we assigned the potency on the basis of their index claim. Switching occurred between dose ranges within the potency groups. When a person discontinued antipsychotic therapy, he or she was followed up for 30 days from the expiration of the last claim for the development of parkinsonism. For those switching from a low to a higher dose, we ascribed any events that occurred to the higher dose. For those switching from a high to a lower dose, we continued to assign events to the higher dose for 1 week after the switch to allow for a residual high-dose effect during the transition period. We summarized the time that subjects spent on each dose using person-years.

ADVERSE EVENT

We identified incident parkinsonism as a new Parkinson disease diagnosis or the dispensing of an antiparkinsonian drug.

FOLLOW-UP

The antipsychotic drug group was followed up for evidence of parkinsonism during their period of continuous drug use for up to 1 year after their index claim. Patients were censored if they died. Adults in the antipsychotic group were censored if they discontinued the therapy or switched the type (ie, from a typical to an atypical antipsychotic or vice versa). These changes may have been made to manage drug-induced parkinsonism. By censoring, our measure of parkinsonism is conservative. In addition, individuals in the comparison group were censored if they were dispensed an antipsychotic.

COVARIATES

The age and sex of all individuals were identified. Nursing home residence was identified from the Ontario Drug Benefit database (using data from the year before the index date), as antipsychotic therapy is common in this setting. We included the year that the index antipsychotic was dispensed because prescribing patterns changed over time.

Comorbidity was measured using the Charlson index¹² and the number of distinct drug therapies dispensed in the year be-

Table 1. Characteristics of the Study Subjects*

Characteristic	Atypical Antipsychotic Group (n = 11 571)	Typical Antipsychotic Group (n = 14 198)	Comparison Group (n = 32 069)
Age, mean ± SD, y	82.74 ± 7.05	82.97 ± 7.14	81.54 ± 7.73
Age range, y			
66-75	1540 (13.3)	1865 (13.1)	6475 (20.2)
76-84	5173 (44.7)	6138 (43.2)	13 765 (42.9)
≥85	4858 (42.0)	6195 (43.6)	11 829 (36.9)
Female	7691 (66.5)	9061 (63.8)	21 562 (67.2)
Months since dementia diagnosis, mean ± SD	26.1 ± 27.0	25.6 ± 25.1	29.4 ± 24.9
Nursing home residence	5649 (48.8)	7369 (51.9)	10 106 (31.5)
Index year			
1997-1998	628 (5.4)	5717 (40.3)	7892 (24.6)
1998-1999	1664 (14.4)	4639 (32.7)	7810 (24.4)
1999-2000	3771 (32.1)	2619 (18.4)	7868 (24.5)
2000-2001	5562 (48.1)	1223 (8.6)	8499 (26.5)
Comorbidity by Charlson index score			
Mean ± SD score	1.01 ± 1.5	1.17 ± 1.6	0.96 ± 1.45
0	6177 (53.4)	6812 (48.0)	17 658 (55.1)
1	2345 (20.3)	3043 (21.4)	6320 (19.7)
≥2	3049 (26.4)	4343 (30.6)	8091 (25.2)
Total No. of drugs			
Mean ± SD No. of drugs	11.09 ± 6.86	10.75 ± 6.93	9.10 ± 6.36
1-5	2390 (20.7)	3390 (23.9)	10 637 (33.2)
6-10	3987 (34.5)	4731 (33.3)	10 719 (33.4)
11-15	2686 (23.2)	3068 (21.6)	6010 (18.7)
≥16	2508 (21.7)	3009 (21.2)	4703 (14.7)
Central nervous system medication use			
Barbiturates†	9 (0.1)	21 (0.1)	45 (0.1)
Benzodiazepines‡	5712 (49.4)	6993 (49.3)	10 168 (31.7)
Anticonvulsants§	574 (5.0)	745 (5.2)	1797 (5.6)
Antidepressants	4680 (40.4)	4578 (32.2)	7707 (24.0)
Antimanic agent (lithium carbonate)	51 (0.4)	55 (0.4)	81 (0.3)
Miscellaneous anxiolytics, sedatives, and hypnotics¶	155 (1.3)	376 (2.6)	434 (1.4)
Drug therapies and diseases associated with development of parkinsonism#	109 (0.9)	150 (1.10)	546 (1.7)
History of stroke	1070 (9.2)	1419 (10.0)	3037 (9.5)

*Includes all adults 66 years and older in Ontario with dementia and no history of parkinsonism who were newly dispensed drugs in one of the study groups, April 1, 1997, through March 31, 2001. The comparison group received no antipsychotics. Unless otherwise indicated, data are expressed as number (percentage) of subjects.

†Includes amobarbital sodium, butobarbital sodium, pentobarbital sodium, phenobarbital, and secobarbital sodium.

‡Includes alprazolam, bromazepam, chlordiazepoxide hydrochloride, clonazepam, clorazepate dipotassium, diazepam, flurazepam hydrochloride, lorazepam, nitrazepam, oxazepam, temazepam, and triazolam.

§Includes carbamazepine, clobazam, divalproex sodium, ethosuximide, gabapentin, lamotrigine, methsuximide, phenytoin sodium, primidone, topiramate, valproate sodium, valproic acid, and vigabatrin.

||Includes amitriptyline hydrochloride, amoxapine, bupropion hydrochloride, citalopram, clomipramine hydrochloride, desipramine hydrochloride, doxepin hydrochloride, fluoxetine hydrochloride, fluvoxamine maleate, imipramine hydrochloride, isocarboxazid, maprotiline hydrochloride, moclobemide, nefazodone, nortriptyline hydrochloride, paroxetine, phenelzine sulfate, protriptyline hydrochloride, sertraline hydrochloride, tranylcypromine sulfate, trazodone hydrochloride, trimipramine maleate, tryptophan, and venlafaxine hydrochloride.

¶Includes chloral hydrate.

#Includes methyl dopa, metoclopramide hydrochloride, reserpine, and tetrabenazine.

fore the index date.¹³ This drug-based comorbidity measure has been used in other studies.¹⁴ We identified the dispensing of central nervous system therapies using the American Hospital Association formulary¹⁵ (eg, benzodiazepines and antidepressants) because these therapies may be used in addition to antipsychotics to manage behavioral and psychological symptoms associated with dementia (Table 1).

We identified concomitant use of drug therapy associated with the development of parkinsonism using a list outlined by Weiner and Lang,¹⁶ restricted to those available through the Ontario Drug Benefit (ie, methyl dopa, metoclopramide hydrochloride, and reserpine). Use of these drugs was identified during the follow-up. Finally, we identified any diagnosis of stroke (within 5 years before the index date), because stroke can be associated with parkinsonism.

STATISTICAL ANALYSES

Comparability of Groups

We examined the distribution of all baseline covariates across our groups to ensure that there were no obvious differences.

Incident Parkinsonism

We conducted time-to-event analyses for the development of incident parkinsonism using Cox proportional hazards models. All analyses controlled for age, sex, age-sex interactions, nursing home residence, index year of study, comorbidity scores, concurrent central nervous system medication use, drug therapy

Table 2. Classification of Antipsychotics Into 3 Dosage Ranges*

Antipsychotic	Dosage, mg/d		
	Low	Medium	High
Atypical antipsychotics†			
Lower potency			
Olanzapine	2.5	2.6-9	10
Risperidone	0.5	0.6-1.9	2
Quetiapine fumarate	50	51-199	200
Typical antipsychotics‡			
Lower potency			
Periciazine§	2.5	2.6-9	10
Thioridazine hydrochloride	18.75	18.76-74	75
Chlorpromazine hydrochloride	18.75	18.76-74	75
Mesoridazine besylate	6.25	6.26-24	25
Pimozide§	0.5	0.6-1	2
Higher potency			
Flupentixol	0.5	0.6-1	2
Fluphenazine, hydrochloride	1	2-3	4
Haloperidol	1	2-3	4
Loxapine succinate	2.5	2.6-9	10
Perphenazine	2	3-7	8
Thiothixene	1.75	1.76-6	7
Trifluoperazine hydrochloride	2	3-7	8

*For all antipsychotics, the low dose was defined as being less than or equal to 25% of the high-dose threshold, and the medium dose was the range between the low and high doses. Unless otherwise indicated, the high dose was based on the highest recommended dose in the "Interpretive Guidelines for Long-term Care Facilities."¹⁹

†Clozapine was not included in the atypical antipsychotic group because it is a restricted-use drug and was not available from the Ontario Drug Benefit Plan.

‡Prochlorperazine edisylate was not included in the typical antipsychotic group because it is primarily used as an antiemetic.

§The high dose was based on the initial daily dose recommended for the elderly in the British national formulary.

||The high dose is the maximum daily dose recommended for the elderly in the British national formulary.

pies associated with parkinsonism, and history of stroke. All covariates were treated as categorical.

First, we assessed whether there were differences in the risk of development of parkinsonism among the 3 study cohorts, using the atypical drug group as the reference. Next, we investigated the 2 antipsychotic cohorts for the effects of potency and dose on the development of parkinsonism using a Cox regression model, with dose as a time-dependent variable. We tested whether there were differences between the atypical and the typical lower-potency and higher-potency antipsychotic groups, using atypical antipsychotics as the reference, and between the high-dose atypical and higher-potency typical antipsychotic groups, using low-dose atypical antipsychotics as the reference, with respect to their association with the development of parkinsonism. We tested for dose-response effects separately within each type of antipsychotic. All analyses used the SAS UNIX Release 8.2.¹⁷ All tests were performed at the 5% level of significance and were 2 sided.

RESULTS

CHARACTERISTICS

Table 1 describes our cohort of 57 838 older adults with dementia. Among the 25 769 individuals dispensed an-

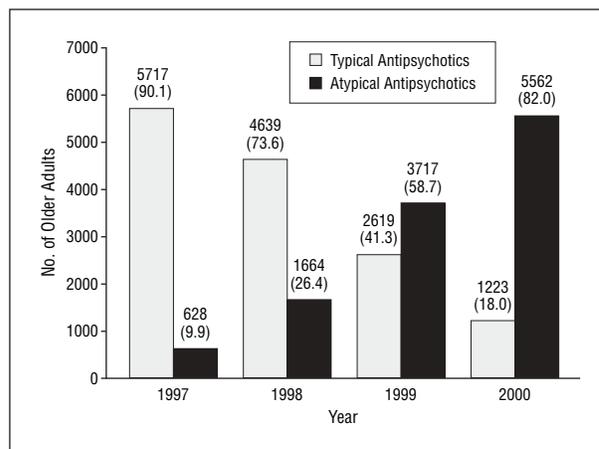


Figure 1. The number (percentage) of older adults dispensed an atypical or a typical antipsychotic by year, from 1997 to 2000. In 1997, typical antipsychotics were more frequently prescribed than were atypical antipsychotics, which had only become available through the Ontario Drug Benefit Plan that year. In 2000, this pattern was reversed, with the atypical antipsychotics being much more frequently dispensed.

typical therapy, 11 571 (45%) were dispensed an atypical and 14 198 (55%) a typical antipsychotic. Among the atypical antipsychotic group, 9237 (80%) were initially dispensed risperidone; 2131 (18%), olanzapine; and 203 (2%), quetiapine. Among those dispensed a typical antipsychotic, 7755 (55%) were dispensed haloperidol; 3167 (22%), loxapine succinate; and 1861 (13%), thioridazine hydrochloride. **Figure 1** illustrates that in 1997, typical antipsychotics were more frequently prescribed than atypical antipsychotics. This pattern reversed by the end of the study.

The characteristics of the antipsychotic groups as outlined in Table 1 are similar, although the control group was slightly younger and less likely to reside in a nursing home or to be dispensed benzodiazepines or antidepressants.

PARKINSONISM BY ANTIPSYCHOTIC TYPE

During the study, 25 769 older adults prescribed antipsychotic drug therapy were observed for a total of 11 573 person-years, and 449 events of parkinsonism were identified.

Table 3 documents that relative to older adults dispensed atypical antipsychotics, development of incident parkinsonism was 30% more likely in those dispensed typical agents (adjusted hazard ratio [HR], 1.30; 95% confidence interval [CI], 1.04-1.58) and 60% less likely in those exposed to neither therapy (HR, 0.40; 95% CI, 0.29-0.43).

POTENCY AND DOSE

All atypical antipsychotics were classified in the lower-potency group. Of the 14 198 older adults dispensed typical antipsychotics, most (11 736 [83%]) were dispensed a higher-potency drug.

As outlined in Table 3, relative to those dispensed atypical antipsychotics (all lower potency), those dispensed

Table 3. Antipsychotic-Induced Incident Parkinsonism Among Older Adults Dispensed Atypical or Typical Antipsychotics

Study Cohort [Person-Years]	No. of Events (Event Rate ± SE)*	Adjusted HR (95% CI)	Potency [Person-Years]	No. of Events (Event Rate ± SE)*	Adjusted HR (95% CI)	Dose [Person-Years]	No. of Events (Event Rate ± SE)*	Adjusted HR (95% CI)	P Value for Trend
Nonantipsychotic comparison group (n = 32 069) [28 268]	360 (1.27 ± 0.07)	0.40 (0.29-0.43)	NA	NA	NA	NA	NA	NA	NA
Atypical antipsychotic group (n = 11 571) [6250]	221 (3.54 ± 0.23)	1.00 (Reference)	Lower (n = 11 571) [6250]	221 (3.54 ± 0.23)	1.00 (Reference)	Low [2537]	70 (2.76 ± 0.33)	1.00 (Reference)	<.001
						Medium [2946]	104 (3.53 ± 0.34)	1.26 (0.93-1.72)	
						High [746]	47 (6.30 ± 0.89)	2.07 (1.42-3.02)	
Typical antipsychotic group (n = 14 198) [5341]	228 (4.27 ± 0.28)	1.30 (1.04-1.58)	Lower (n = 2462) [1054]	26 (2.47 ± 0.48)	0.75 (0.48-1.15)	Low [288]	6 (2.08 ± 0.84)	0.83 (0.35-1.95)	.80
						Medium [609]	17 (2.79 ± 0.67)	1.14 (0.65-1.99)	
						High [154]	3 (1.95 ± 1.11)	0.69 (0.21-2.23)	
						Low [1824]	69 (3.78 ± 0.45)	1.51 (1.04-2.20)	
						Medium [1832]	97 (5.30 ± 0.52)	2.16 (1.51-3.08)	
High [617]	36 (5.84 ± 0.94)	2.23 (1.43-3.46)	.06						
Higher (n = 11 736) [4286]	202 (4.71 ± 0.32)	1.44 (1.13-1.84)							

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable.

*The event rate is the number of antipsychotic-induced parkinsonism events per 100 person-years of follow-up.

lower-potency typical antipsychotics were no different (HR, 0.75; 95% CI, 0.48-1.15) and those dispensed higher-potency typical antipsychotics were at close to a 50% greater risk (HR, 1.44; 95% CI, 1.13-1.84) of development of parkinsonism. In the typical antipsychotic group, the combined parkinsonism event rate in the lower-potency group was 2.47 per 100 person-years (SE, 0.48); in the higher-potency group, it was 4.71 per 100 person-years (SE, 0.32).

Of the 11 571 older adults dispensed an atypical antipsychotic, 2720 (24%) were dispensed a high dose at some time during the study. This group accounted for only 746 person-years of follow-up. There was a positive dose-related association between the use of atypical antipsychotics and the development of incident parkinsonism (Table 3). Relative to those dispensed a low-dose antipsychotic, those dispensed a high-dose agent were more than twice as likely to experience development of parkinsonism (HR, 2.07; 95% CI, 1.42-3.02). The parkinsonism event rate in the low-dose atypical group was 2.76 per 100 person-years (SE, 0.33); in the high-dose group, 6.30 per 100 person-years (SE, 0.89).

Of those dispensed a lower- or a higher-potency typical antipsychotic, 3481 (25%) were dispensed a high-dose agent at some time during the 1-year follow-up. There was a dose-related trend in the higher-potency typical antipsychotic group for the development of incident parkinsonism ($P = .06$). Of those dispensed a higher-potency antipsychotic, the event rate was 3.78 per 100 person-years (SE, 0.45) in the low-dose group and 5.84 per 100 person-years (SE, 0.94) in the high-dose group ($P = .06$).

Figure 2 illustrates the overall risk of development of parkinsonism for the atypical and typical antipsychot-

ics with respect to potency (lower and high) and dose (low, medium, and high). Relative to those dispensed a high-dose atypical antipsychotic, those dispensed a typical agent were at a similar risk for parkinsonism (Wald $\chi^2 = 0.14$; $P = .7$).

COMMENT

Our findings demonstrate that when the potency and dose of antipsychotics are considered, atypical antipsychotics are not necessarily safer than typical antipsychotics in relation to the development of parkinsonism. We found a dose-related association between the use of atypical antipsychotics and the development of incident parkinsonism. At high doses, individuals were more than twice as likely to experience development of parkinsonism relative to those dispensed a drug at a low dose. These findings suggest that parkinsonism is more common than previously suspected when higher doses of what have been considered the safer atypical antipsychotics are dispensed. These findings are important, given that a quarter of older adults in our study were dispensed a high-dose agent.

We demonstrate that older adults dispensed a high-dose atypical antipsychotic have a similar risk of development of parkinsonism as those dispensed a higher-potency typical antipsychotic. Clinicians who would not prescribe a typical antipsychotic to older adults because of safety concerns may also need to rethink the use of atypical antipsychotics when they are prescribed at high doses. It is important to analyze comparative drug studies across similar levels of potency and dose. Our find-

ings underscore the importance of prescribing the atypical antipsychotics at lower doses to minimize the risk of parkinsonism.

Our findings are consistent with biological evidence and data reported in a meta-analysis. From a biological perspective, the atypical and typical antipsychotics overlap in their affinity for receptors (ie, blockade of dopaminergic receptors in the striatum) that can produce parkinsonism. There is also support for the overlap of adverse events in a meta-analysis conducted by Leucht et al¹⁸ of randomized controlled trials to compare the atypical antipsychotics with the lower-potency typical antipsychotics for the management of schizophrenia. They found no evidence that atypical antipsychotics were less likely to produce extrapyramidal effects relative to the typical agents.

Our study suggests that the overall rate of development of parkinsonism was almost 3 times higher in those dispensed an atypical agent relative to those dispensed neither agent. Our results are consistent with work by Avorn et al,¹ who found that parkinsonian signs documented by results of a clinical examination were more than 3 times as likely in older adults who took lower-potency typical antipsychotic therapy compared with those not prescribed any psychoactive medication. Furthermore, parkinsonian signs were more than 6-fold higher in those dispensed high doses of a higher-potency typical antipsychotic.

IMPORTANCE IN CLINICAL PRACTICE

Our findings are important because atypical antipsychotics are increasingly being dispensed to older adults with dementia. In a 4-year period, the dispensing of atypical antipsychotics has moved from accounting for less than 10% to accounting for more than 80% of all antipsychotics dispensed. Bronskill et al¹⁹ demonstrate that among older adults with no previous exposure to antipsychotics, 24% were dispensed antipsychotics within 1 year of their nursing home admission.

Given the association between the use of antipsychotics and the development of parkinsonism, it is important to go back to the basic principles of prescribing.²⁰ Specifically, before starting antipsychotic therapy, one should explore nonpharmacologic approaches. If drug therapy is required, choose a drug in the class with the fewest adverse events, use the lowest dose required to achieve the desired effect, and reevaluate the ongoing need for the therapy. Finally, consider new signs of parkinsonism to be a potential adverse event before commencing antiparkinsonian drug therapy to avoid initiating a “prescribing cascade.”²¹

LIMITATIONS

This is a cohort study that uses administrative data and is potentially vulnerable to confounding. We have taken steps to minimize those issues by carefully selecting the cohorts, identifying key covariates, and adjusting for potential risk factors associated with the outcome. Specifically, by restricting the cohort to dementia, we obtained inception cohorts that were comparable on measured co-

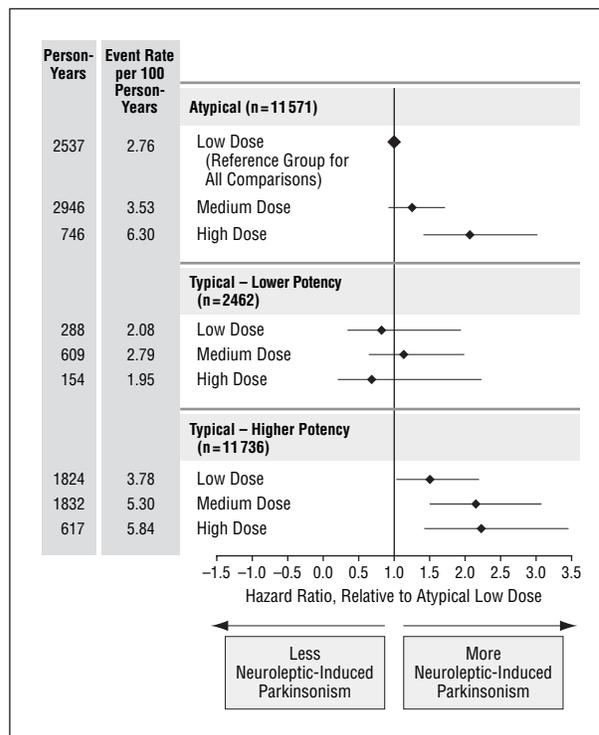


Figure 2. Hazard ratios (and 95% confidence intervals) for the development of parkinsonism, accounting for the type (atypical or typical), potency (lower or higher), and dose (low, medium, or high) of the antipsychotic dispensed. Low-dose atypical antipsychotics constituted the reference group for the comparisons. The overlap of the confidence intervals for the high-dose atypical antipsychotics and the high-dose, higher-potency typical antipsychotics suggests that the advantage of the atypical antipsychotics in terms of the risk of development of incident parkinsonism is lost when higher doses of atypical antipsychotics are dispensed.

variates at baseline. Furthermore, our analyses controlled for key variables that might capture selection biases, including age, sex, and comorbidity.

Our data likely underestimate the true amount of parkinsonism associated with the use of antipsychotics. We identified only parkinsonism severe enough to lead to a diagnosis or the initiation of drug therapy. Parkinsonian signs are frequently identified on clinical examination²² but may not lead a physician to indicate a diagnosis of parkinsonism or to initiate drug treatment. Furthermore, most of the individuals dispensed an atypical antipsychotic in our cohort were dispensed risperidone. Therefore, our results may not be generalizable to all types of atypical antipsychotics. Finally, some of the parkinsonism identified in our study may have been the result of underlying Parkinson disease that was unrelated to or exacerbated by antipsychotic drug therapy.

CONCLUSIONS

We demonstrate a dose-related increased risk of parkinsonism among older adults dispensed atypical antipsychotics. The risk of development of parkinsonism was similar among those dispensed a high-dose atypical antipsychotic and those dispensed a higher-potency typical antipsychotic. Caution should be used, particularly when prescribing a high-dose atypical antipsychotic.

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