ORIGINAL RESEARCH ARTICLE

Drugs Aging 2010; 27 (10): 815-829
1170-229X/10/0010-0815/$49.95/0

Risk of Falls and Fractures in Older Adults Using Antipsychotic Agents

A Propensity-Matched Retrospective Cohort Study

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Abstract

Background: Antipsychotics, especially atypical agents, are widely used in the elderly population to treat behavioural and psychiatric symptoms. Very few studies have compared the risk of falls and fractures among older adults using typical and atypical agents and none of the studies have evaluated differential risk across antipsychotic classes.

Objective: To examine the risk of falls and fractures associated with atypical antipsychotic use and typical antipsychotic use in community-dwelling older adults in the US.

Methods: The study involved a retrospective population-based cohort design matched on propensity scores involving older adults (aged ≥50 years) using atypical or typical antipsychotic agents in the IMS LifeLink™ Health Plan Claims Database. Patients taking atypical antipsychotics were matched with patients taking typical antipsychotics using the Greedy 5 → 1 matching technique. The study evaluated the relative risk of hospitalization/emergency room (ER) visits due to falls/fractures in a 1-year follow-up period, and patients treated with atypical antipsychotics were compared with those treated with typical antipsychotics using the Cox proportional-hazards regression model stratified on matched pairs. The covariates adjusted for in the regression model included duration of therapy and exposure to other psychotropic medications that increase the risk of falls and fractures.

Results: From July 2000 to December 2007, 11 160 (5580 atypical and 5580 typical) users of antipsychotics were obtained after matching on propensity scores. A total of 825 cases of falls/fractures with at least one hospitalization/ER visit following the use of antipsychotic agents were identified. The number of cases with falls/fractures was 450 in atypical antipsychotic users and 375 in typical antipsychotic users. Cox regression model analysis revealed no statistically significant difference between atypical users and typical users with respect to risk of falls/fractures (hazard ratio [HR] 1.01; 95% CI 0.83, 1.22). However, duration of therapy with any antipsychotic medication for >90 days was significantly (HR 1.81; CI 1.35, 2.43) associated with increased risk of falls/fractures compared with <30 days of treatment.

Conclusions: No statistically significant difference was found between atypical antipsychotic agents and typical antipsychotic agents with regards to the likelihood of falls/fractures in a large cohort of older adults. However, there is a need to be cautious while prescribing atypical and typical antipsychotics in older adults for long periods of time.

Introduction

Antipsychotics, especially atypical agents, are widely used in the elderly population to treat behavioural and psychiatric symptoms. The conditions for which these agents are used include depression, dementia, obsessive-compulsive disorder, personality disorders and post-traumatic stress disorder, despite the fact that the US FDA has approved use of atypical antipsychotics only in the treatment of schizophrenia and bipolar disorder.[1] In recent years, utilization of atypical antipsychotic agents in the elderly has significantly increased in the US, from 15% of antipsychotic use in 1996–8 to 73% in 2002–4.[2] This shift in utilization has been attributed to extensive off-label use, the perception that atypical antipsychotics are safer than typical agents, and promotion by pharmaceutical companies.[3]

Like other psychotropic agents such as benzodiazepines and antidepressants, antipsychotic drugs have been linked to increased risk of falls and fractures in the elderly residing in nursing homes and in community dwellings.[4,5] Researchers found that outpatient prescription of antipsychotics was three times higher in the group of patients hospitalized due to femur fracture than in a matched control group of patients with hospitalization due to acute myocardial infarction or pneumonia.[6] The high rate of falls and fractures in the former group has been attributed to the adverse effects of antipsychotic agents. Hyperprolactinaemia and sedation are the most common adverse effects associated with antipsychotics.[7,8] Extrapyramidal symptoms (EPS), tardive dyskinesia (TD) and elevated prolactin levels due to antipsychotic use also contribute to falls and fractures.[9]

Falls and fractures among older people constitute a major public health concern with substantial medical and economic consequences. Falls are the leading cause of accidental death and the seventh leading cause of death in persons aged >65 years.[10] More than 90% of hip fractures in the elderly are caused by falls, which can cause severe health problems, reduced quality of life, and premature death.[11] Few epidemiological studies[12-17] have examined the risk of falls and fractures among users of antipsychotics. Studies that have focused on all psychotropic drugs reported an association between the use of antipsychotic agents and risk of fractures and falls.[18-25] Almost all previously published studies in elderly patients found that antipsychotic use (both typical and atypical) increased the risk of falls and fractures when compared with nonuse. Very few studies have compared the risk of falls and fractures among older adults using typical and atypical agents, and none of the studies have confirmed differential risk across antipsychotic classes. With increased use of antipsychotic agents in older adults, it is important to confirm a relative advantage of one class of antipsychotic over the other. Therefore, a propensity-matched retrospective cohort study was conducted to compare the effect of atypical antipsychotic agents and typical antipsychotic agents on the risk of hospitalization or emergency room (ER) visits due to falls or fractures in community-dwelling older adults.

Methods

Data Source

The present study analysed data from the IMS LifeLink™ Health Plan Claims (also known as PharMetrics) Database. Medical claims records were obtained from 94 different managed care organizations in the US, encompassing more than

60 million unique patients. The database included patients' enrolment data and pharmacy, medical and institutional claims. Pharmacy data contained claims for each drug prescription, and included the date of dispensing, the quantity dispensed and the length of the supply. Provider and facility claims included the date of service, diagnoses codes (International Classification of Diseases, 9th revision, Clinical Modification [ICD-9-CM] codes)[26] and codes relating to procedures, which were based on the American Medical Association (AMA) Current Procedure Terminology (CPT-4) codes and the Center for Medicare and Medicaid Services [CMS] Health Care Common Procedure Coding System (HCPCS) codes.

All claims in the database included a unique encrypted identifier for each patient. This identifier can be used to construct a longitudinal history of medical care utilization for each patient. Compared with records from single-plan databases, records in the IMS LifeLink™ Health Plan Claims Database are representative of the national, commercially insured population.[27] The standard extract from the Health Plan Claims Database consists of two files: a claims detail file and an eligibility file. The claims detail file contains claim-specific elements and carries a number of the output variables. The eligibility file is a patient-level file. It contains the enrolment information for the specific individuals included in the claims detail file meeting the requestor's criteria. Only health plans submitting data for all members are included in the database; this ensures complete data capture and representative samples. Because they were obtained from a number of different sources, the data were subjected to a series of quality checks to ensure a standardized format. Demographic information such as the patient's year of birth, geographic region, age and enrolment details were also provided in the database. The data are also longitudinal, with a mean member enrolment time of 2 years. The IMS LifeLink™ Health Plan Claims Database adheres to all *Health Insurance Portability and Accountability Act* requirements. This study was approved by the University of Houston Committee for the Protection of Human Subjects, under Exempt Category.

Study Design

A retrospective propensity score-matched cohort study was utilized to compare atypical antipsychotic users with typical users with respect to risk of falls and fractures. The study involved analysis of claims detail and enrolment data files. The study sample included all older adults aged ≥50 years who were taking antipsychotic medication any time between July 2000 and December 2007. Figure 1 outlines the development of the treatment and comparison groups. The index date was identified as the day of the first prescription of antipsychotics. Patients were excluded from the study if they had any filled prescriptions of atypical or typical antipsychotics any time in the 6 months before the index date (baseline period). Inclusion in the cohort required patients to have been continuously eligible month by month without any gap for 6 months before and at least 6 months after the index date. Thus, patients were followed for a minimum time period of 6 months and for a maximum of 1 year (follow-period).[28] Patients were lost to follow-up if they lost their continuous insurance eligibility. Patients with a minimum eligibility of 6 months in the follow-up period were included in the study because recent studies have revealed a short-term (180 days) mortality risk due to adverse events with the use of typical and atypical antipsychotics in older adults.[29,30]

Exposures and Outcome Definitions

Antipsychotic treatment exposure was measured using prescription claims data. The atypical antipsychotic cohort involved users of clozapine, olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole. The typical antipsychotic cohort involved users of loxapine, fluphenazine, trifluprom azine, chlorprothixene, haloperidol, chlorpromazine, thioridazine, prochlorperazine, promazine, trifluperazine, thiothexene, molindone, perphenazine, acetophenazine, mesoridazine, paliperidone, pimozide and perphenazine/amitriptyline. Patients receiving typical antipsychotics were matched on propensity score with patients taking atypical antipsychotics.

The primary outcome measure was the occurrence of hospitalization or ER visit due to a fall or

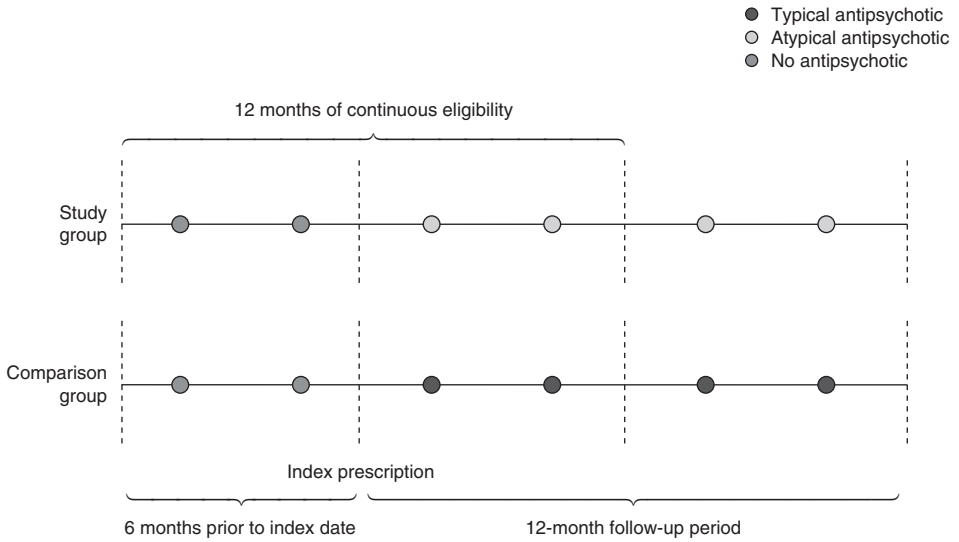

Fig. 1. Definitions used to identify and construct the treatment and comparison groups.

femur fracture within 1 year after the index date. The occurrence of a fall or femur fracture was identified using hospital or ER visit claims, based on the ICD-9-CM codes.[26] The ICD-9-CM uses E codes (E880–E888) to signify accidental falls. The ICD-9-CM codes for femur fractures were selected on the basis of the clinical classification of medical conditions provided by the Agency for Healthcare Research and Quality (AHRQ).[31] Patients were followed until hospitalization or ER visit due to falls and femur fractures or the end of the follow-up period or until the end of their continuous eligibility any time after 6 months from the index date. The maximum follow-up time was 1 year. Patients were censored if they (i) lost their continuous eligibility before 1 year, (ii) reached the end date of the follow-up period or (iii) switched from one class of antipsychotic medications to another.

Cohort Matching

The strength of observational studies lies in their ability to estimate treatment effects in real-world settings. Observational studies are useful for determining causal relationship but are criticized for the absence of randomized assignment of treatment, which could lead to bias in the results due to uncontrolled confounding by unmeasured, unknown or inadequately measured covariates.[32] In order to make causal inferences, random allocation of treatment to subjects is necessary. As antipsychotic use was not randomly assigned in the study population, potential confounding and selection bias was addressed by matching the two groups on propensity score.[29] The rationale for using a propensity score-matching technique was to minimize differences between the two groups so that they differed on only one variable (i.e. assignment to one treatment group vs another).[33]

Variables were selected on the basis of previously published studies and guidance provided on the selection of variables for propensity score estimation.[34] More than 60 covariates, identified from an examination of published literature and expert opinions collected from experienced clinicians and researchers working in the psychiatric discipline, were included in the propensity score estimation. Propensity scores were calculated from the large number of baseline characteristics (6 months before the index date), which included clinical characteristics (co-morbidities and co-medications), sociodemographics, year of cohort

entry and provider specialty. Severity of illness was also considered to be one of the important predictors of treatment allocation and was measured as all-cause hospitalization in the 6 months before the index date.[35]

The logistic regression model was developed using all controlled baseline characteristics. Using the resulting predicted probabilities from the logistic model, patients taking atypical antipsychotics were matched with patients taking typical antipsychotics using the Greedy 5 → 1 matching technique.[36] This technique reduces the matched-pair bias caused by incomplete and inexact matching.[36] The 5 → 1 Digit Match indicates that cases are first matched to controls on the first 5 digits of the propensity score. Those that do not match are then matched on 4 digits. This process is continued down to a 1-digit match. If more than one control is found that matches a case, the control is selected at random.[36]

Statistical Analysis

Differences between the two groups with respect to all the covariates used to calculate the propensity score were evaluated using a chi-squared (χ^2) test for categorical variables and t-test for continuous variables before and after matching. The goodness of fit of matched pairs was estimated by calculating the percentage reduction in bias in the group difference in covariates before and after matching that remained significant after matching.[37] Survival analysis was then performed on the matched cohort to assess the risk of falls/fractures in patients taking atypical versus typical antipsychotics. Kaplan-Meier survival plots were created to depict unadjusted relationships between atypical antipsychotic use versus typical antipsychotic use and time to hospitalization/ER visit due to a fall/fracture. Pairwise log-rank tests were used to compare survival curves for statistical difference. The Cox proportional-hazards regression model stratified on matched pairs was used to obtain hazard ratios (HRs) for the risk of hospitalization/ER visit due to a fall/fracture in atypical versus typical agent users. The stratified Cox proportional-hazard model was applied using the STRATA option of PROC PHREG to account for matched-pair design.[38,39] To address possible residual confounding even after matching, baseline covariates that remained significant were adjusted for in the final model. The use of other psychotropic medications during the follow-up period such as antidepressants, antiepileptics, anti-anxiety medications, sedatives and hypnotics, which are also associated with a risk of falls/fractures,[18] was adjusted for in the Cox model to obtain unconfounded results. Another important covariate included in the model was duration of therapy, measured as 'the duration of time from the initiation to discontinuation of therapy, with a maximum allowable gap of 30 days'.[40] The duration of therapy was categorized as <30, 30–90 and >90 days.[41] The proportional hazards assumption for the model was checked by including an interaction term between the independent variable and log of time. A p-value of 0.05 was used to calculate confidence intervals for the HR estimates. SAS version 9.1 was used for the analysis (SAS Institute Inc., Cary, NC, USA).

Results

Matching Process and Patient Characteristics

A total of 39 587 new users of antipsychotic agents between July 2000 and December 2007 were identified after application of the inclusion and exclusion criteria. Of these new users, 26 991 patients were taking typical antipsychotic agents and 12 596 patients were taking atypical antipsychotic agents.

Figure 2 shows the distribution of propensity scores for 38 906 new users of typical (26 758) and atypical (12 148) antipsychotic agents; the propensity score could not be calculated for 681 patients in the cohort because of missing baseline covariate information. The distribution of propensity scores for the two groups before matching revealed good discrimination between atypical antipsychotic users and typical antipsychotic users (figure 2a). This underscores the importance of analytical approaches such as matching to reduce the influence of subjects with extreme propensity scores, thereby avoiding comparing incomparable

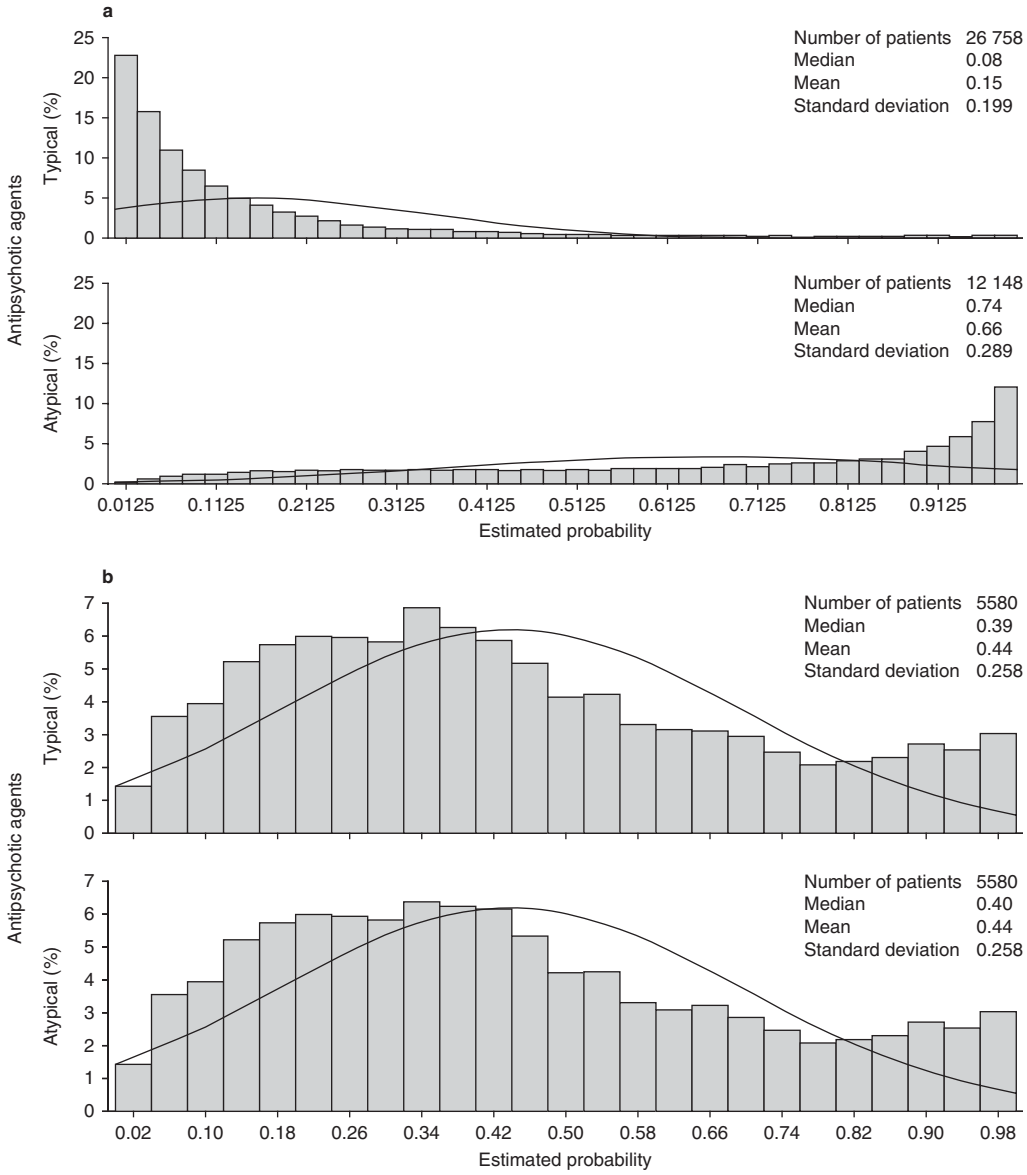

Fig. 2. Distribution of propensity scores in (**a**) 38 906 patients in the cohort with complete information before matching (propensity scores could not be calculated for 681 patients because of missing baseline covariates information) and (**b**) 11 160 patients after matching (data source: IMS LifeLink™ Health Plan Claims Database,1999–2003). The curved lines are normality curves indicating the distributions of propensity scores.

groups.[42] Figure 2b shows the distribution of the propensity scores of the two groups after matching. The statistics and distribution suggest that the two matched groups were similar in nature and hence comparable.

Table I reports differences in baseline characteristics between the two groups before and after matching. The process used to match patients from the two groups produced a strong balance of baseline characteristics. After matching, a significant

Table I. Baseline characteristics of atypical antipsychotic users and typical antipsychotic users (data source: IMS LifeLink™ Health Plan Claims Database, 1999–2003)

Characteristics	Unmatched cohort (39 587 unmatched patients)			Matched cohort (11 160 matched patients)		
	atypical users (n = 12 596)	typical users (n = 26 991)	p-value	atypical users (n = 5580)	typical users (n = 5580)	p-value
Age [y (mean ± SD)]	70.77 (13.10)	65.60 (10.17)	<0.0001	69.84 (12.44)	69.43 (12.85)	0.09
Sex [n (%)]						
Male	4986 (39.58)	9 345 (34.62)	<0.0001	2164 (38.78)	2144 (38.42)	0.69
Female	7610 (60.42)	17 646 (65.38)		3416 (61.22)	3436 (61.58)	
Region [n (%)]						
West	1585 (12.58)	2 847 (10.55)	<0.0001	638 (11.43)	652 (11.68)	0.47
Midwest	5285 (41.96)	12 490 (46.27)		2349 (42.10)	2268 (40.65)	
South	3027 (24.03)	6 015 (22.29)		1389 (24.89)	1434 (25.70)	
East	2699 (21.43)	5 639 (20.89)		1204 (21.58)	1226 (21.97)	
Year of cohort entry [n (%)]						
2000	1106 (8.78)	3 485 (12.91)	<0.0001	543 (9.73)	537 (9.62)	0.55
2001	2878 (22.85)	7 785 (28.84)		1403 (25.14)	1359 (24.35)	
2002	2978 (23.64)	6 658 (24.67)		1334 (23.91)	1322 (23.69)	
2003	5132 (40.74)	8 927 (33.07)		2180 (39.07)	2261 (40.52)	
2004	242 (1.92)	59 (0.22)		64 (1.15)	45 (0.81)	
2005	99 (0.79)	36 (0.13)		22 (0.39)	25 (0.45)	
2006	97 (0.77)	25 (0.09)		22 (0.39)	20 (0.36)	
2007	64 (0.51)	16 (0.06)		12 (0.22)	11 (0.20)	
Provider specialty [n (%)]*						
Geriatrics/internal medicine	1635 (12.98)	3 929 (14.56)	<0.0001	823 (14.75)	856 (15.34)	<0.0001
General/family medicine	1249 (9.92)	2 478 (9.18)		631 (11.31)	639 (11.45)	
Psychiatry	2622 (20.82)	250 (0.93)		369 (6.61)	240 (4.30)	
Other	7090 (56.29)	20 334 (75.34)		3757 (67.33)	3845 (68.91)	
Hospitalization in past 6 months [n (%)]*						
Yes	4094 (32.50)	9 072 (33.61)	0.02	1558 (27.92)	1448 (25.95)	0.01
No	8502 (67.50)	17 919 (66.39)		4022 (72.08)	4132 (74.05)	
Medical history in past 6 months [n (%)]						
Hypertension	5304 (42.11)	11 041 (40.91)	0.02	2297 (41.16)	2341 (41.95)	0.39
Coronary heart disease	2007 (15.93)	4 127 (15.29)	0.09	888 (15.91)	925 (16.58)	0.34
Congestive heart failure	1398 (11.10)	1 973 (7.31)	<0.0001	582 (10.43)	591 (10.59)	0.78
Acute myocardial infarction	301 (2.39)	468 (1.73)	<0.0001	130 (2.33)	130 (2.33)	1.00
Cardiac arrhythmias	2032 (16.31)	3 595 (13.32)	<0.0001	848 (15.20)	870 (15.59)	0.56
Circulatory disorder	2355 (18.70)	5 156 (19.10)	0.33	994 (17.81)	1014 (18.17)	0.62
Thromboembolic disorder	382 (3.03)	1 001 (3.71)	0.0006	193 (3.46)	185 (3.32)	0.67
Diabetes mellitus	2169 (17.22)	4 845 (17.95)	0.07	1009 (18.08)	1032 (18.49)	0.57

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Table I. Contd

Characteristics	Unmatched cohort (39 587 unmatched patients)			Matched cohort (11 160 matched patients)		
	atypical users (n = 12 596)	typical users (n = 26 991)	p-value	atypical users (n = 5580)	typical users (n = 5580)	p-value
Cerebrovascular disease	1917 (15.22)	1 895 (7.02)	<0.0001	714 (12.80)	713 (12.78)	0.97
Hip/femur fracture	354 (2.81)	235 (0.87)	<0.0001	100 (1.79)	107 (1.92)	0.62
Chronic obstructive pulmonary disorder	1533 (12.17)	3 513 (13.02)	0.01	699 (12.53)	716 (12.83)	0.62
Falls	498 (3.95)	332 (1.23)	<0.0001	147 (2.63)	144 (2.58)	0.85
Thyroid disorder	1457 (11.57)	2 703 (10.01)	<0.0001	568 (10.18)	584 (10.47)	0.61
Renal failure	492 (3.91)	1 026 (3.80)	0.61	237 (4.25)	253 (4.53)	0.45
Other renal disorders	3122 (24.79)	6 490 (24.05)	0.10	1319 (23.64)	1313 (23.53)	0.89
Liver disorder	571 (4.53)	3 235 (11.99)	<0.0001	324 (5.81)	281 (5.04)	0.07
Gastric disorder	3463 (27.49)	11 489 (42.57)	<0.0001	1718 (30.79)	1669 (29.91)	0.31
Ulcers	592 (4.70)	941 (3.49)	<0.0001	240 (4.30)	259 (4.64)	0.38
Cancer (any type)*	1296 (10.29)	11 779 (43.64)	<0.0001	833 (14.93)	701 (12.56)	0.0003
Cataract	1201 (9.53)	2 457 (9.10)	0.16	551 (9.87)	553 (9.91)	0.94
Glaucoma	561 (5.25)	1 412 (5.23)	0.94	284 (5.09)	283 (5.07)	0.96
Anaemia	1517 (12.04)	4 193 (15.53)	<0.0001	699 (12.53)	718 (12.87)	0.58
Osteoporosis	630 (5.00)	1 189 (4.41)	0.008	262 (4.70)	273 (4.89)	0.62
Rheumatoid arthritis	185 (1.47)	622 (2.30)	<0.0001	86 (1.54)	103 (1.85)	0.21
Back pain	2350 (18.66)	5 610 (20.82)	<0.0001	1141 (20.45)	1153 (20.66)	0.77
Dyslipidaemia	2372 (18.83)	6 449 (23.99)	<0.0001	1113 (20.30)	1125 (20.30)	0.85
Obesity	234 (1.86)	658 (2.44)	0.0003	114 (2.04)	103 (1.85)	0.45
HIV infection	19 (0.15)	44 (0.16)	0.77	9 (0.16)	11 (0.20)	0.65
Pneumonia	844 (6.70)	1 802 (6.68)	0.92	372 (6.67)	399 (7.15)	0.31
Endocarditis	321 (2.55)	759 (2.81)	0.13	168 (3.01)	172 (3.08)	0.82
Suicide attempt	53 (0.42)	3 (0.01)	<0.0001	7 (0.13)	3 (0.05)	0.20
Alcohol and substance abuse disorder	676 (5.37)	361 (1.34)	<0.0001	198 (3.55)	178 (3.19)	0.29
Extrapyramidal symptoms	277 (2.20)	237 (0.88)	<0.0001	104 (1.86)	111 (1.99)	0.62
Parkinsonian disease	594 (4.72)	154 (0.57)	0.57	150 (2.69)	122 (2.19)	0.08
Psychotic disorder [n (%)]						
Dementia	3612 (28.68)	923 (3.42)	<0.0001	820 (14.70)	761 (13.64)	0.10
Schizophrenia*	1930 (15.32)	419 (1.55)	<0.0001	413 (7.40)	343 (6.15)	0.008
Anxiety disorder	2293 (18.20)	1 288 (4.77)	<0.0001	683 (12.24)	665 (11.92)	0.60
Conduct disorder	205 (1.63)	41 (0.15)	<0.0001	46 (0.82)	33 (0.59)	0.14
Mood disorder	5443 (43.21)	2 324 (8.61)	<0.0001	1495 (26.79)	1489 (26.68)	0.89
Other psychotic disorder	1496 (11.88)	1 962 (7.27)	<0.0001	477 (8.55)	468 (8.39)	0.75
Other drugs used in past 6 months [n (%)]						
Antihypertensive	6739 (53.50)	13 851 (51.32)	<0.0001	3048 (54.62)	3111 (55.75)	0.23

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	atypical users (n = 12 596)	typical users (n = 26 991)	p-value	atypical users (n = 5580)	typical users (n = 5580)	p-value
Antianginal	1103 (8.76)	2 007 (7.44)	<0.0001	524 (9.39)	558 (10.00)	0.27
Antiarrhythmic	215 (1.71)	462 (1.71)	0.97	117 (2.10)	113 (2.03)	0.78
Other cardiovascular drug	4121 (32.72)	7 979 (29.56)	<0.0001	1851 (33.17)	1905 (34.14)	0.27
Antihyperglycaemic	1804 (14.32)	4 099 (15.19)	0.02	886 (15.88)	920 (16.49)	0.38
Antihyperlipidaemic	2963 (23.52)	7 062 (26.16)	<0.0001	1450 (25.99)	1464 (26.24)	0.76
Anti-obesity	399 (3.17)	275 (1.02)	<0.0001	134 (2.40)	133 (2.38)	0.95
Analgesic	5339 (42.39)	17 564 (65.07)	<0.0001	2747 (49.23)	2749 (49.27)	0.96
Estrogen (hormone replacement therapy)	1711 (13.58)	5 446 (20.18)	<0.0001	864 (15.48)	893 (16.00)	0.45
Antihistamine	2347 (18.63)	6 950 (25.75)	<0.0001	1224 (21.94)	1258 (22.54)	0.43
Anti-gastric[a]	1610 (12.78)	4 694 (17.39)	<0.0001	787 (14.10)	803 (14.39)	0.66
Anticoagulant	910 (7.22)	2 406 (8.91)	<0.0001	459 (8.23)	464 (8.32)	0.86
Other haematological agent	949 (7.53)	1 197 (4.43)	<0.0001	418 (7.49)	424 (7.60)	0.82
Haematopoietic agent	626 (4.97)	1 279 (4.74)	0.31	269 (4.82)	301 (5.39)	0.16
Corticosteroid	1147 (9.11)	5 877 (21.77)	<0.0001	658 (11.79)	636 (11.40)	0.51
Vitamin D	34 (0.27)	110 (0.41)	0.03	15 (0.27)	20 (0.36)	0.39
Bronchodilator	1580 (12.54)	3 673 (13.61)	0.003	772 (13.84)	834 (14.95)	0.09
Antifungal	12 (0.10)	53 (0.20)	0.02	8 (0.14)	9 (0.16)	0.80
Anti-infective agent	4582 (36.38)	14 680 (54.39)	<0.0001	2334 (41.82)	2341 (41.95)	0.98
Urinary anti-infective agent	328 (2.60)	676 (2.50)	0.55	136 (2.44)	165 (2.96)	0.09
Anti-cancer	346 (2.75)	2 391 (8.86)	<0.0001	194 (3.48)	164 (2.94)	0.10
Anti-ulcer	3766 (29.90)	9 959 (36.90)	<0.0001	1880 (33.69)	1956 (35.05)	0.12
Alcohol drug dependency	23 (0.18)	6 (0.02)	<0.0001	4 (0.07)	5 (0.09)	1.00
Ophthalmic	1457 (11.57)	2 766 (10.25)	<0.0001	624 (11.18)	649 (11.63)	0.45
Thyroid agent	2055 (16.31)	3 674 (13.61)	<0.0001	857 (15.36)	868 (15.56)	0.77
Hypnotic	1964 (15.59)	3 157 (11.70)	<0.0001	828 (14.84)	823 (14.75)	0.89
Anticholinergic	1233 (9.79)	4 061 (15.05)	<0.0001	563 (10.09)	534 (9.57)	0.35
Smoking deterrent	61 (0.64)	215 (0.80)	0.09	35 (0.63)	35 (0.63)	1.00
Endocrine and metabolic agents	1089 (8.65)	2 365 (8.76)	0.70	488 (8.75)	509 (9.12)	0.48
Antidepressant[*]	7794 (61.88)	7 234 (26.80)	<0.0001	2898 (51.94)	3073 (55.07)	0.0009
Anti-anxiety drug	4141 (32.88)	6 624 (24.54)	<0.0001	1669 (29.91)	1734 (31.08)	0.18
Antiepileptic	3213 (25.51)	2 509 (9.30)	<0.0001	1102 (19.75)	1155 (20.70)	0.21
Lithium	725 (5.76)	141 (0.52)	<0.0001	151 (2.71)	126 (2.26)	0.12

a Includes peripheral opioid receptor antagonists, gastrointestinal adsorbents, inflammatory bowel agents, antiflatulents, gastrointestinal stimulants and other miscellaneous agents.

[*] Threshold for statistical significance set at p = 0.05 for both cohorts.

Table II. Selected characteristics of the matched cohort for risk of falls/fractures (data source: IMS LifeLink™ Health Plan Claims Database, 1999–2003)

Characteristic	Atypical antipsychotic users (n = 5580)	Typical antipsychotic users (n = 5580)
Follow-up [days (mean ± SD)]	332.31 ± 63.90	334.69 ± 61.48
Time to event [days (mean ± SD)]	279.70 ± 114.62	288.02 ± 114.73
Hospitalization/ER visits due to a fall/fracture [n (%)]*	450 (8.06)	375 (6.72)
Duration of therapy [n (%)]*		
<30 days	2089 (37.44)	4498 (80.61)
30–90 days	1084 (19.43)	470 (8.42)
>90 days	2407 (43.14)	612 (10.97)
Use of other drugs during the follow-up period [n (%)]		
Antidepressant	3302 (59.18)	3107 (55.68)
Anti-anxiety drug	1887 (33.82)	1892 (33.91)
Antiepileptic	1412 (25.30)	1272 (22.80)
Hypnotic	972 (17.42)	1002 (17.96)

ER = emergency room; * Threshold for statistical significance set at p = 0.05.

difference was still found between the two groups with respect to provider specialty, all-cause hospitalization, diagnosis of schizophrenia, diagnosis of cancer and use of antidepressants in the 6 months before the initiation of treatment. However, the percentage reduction in bias calculated, based on $(1-D_i)/D_j \times 100\%$, where D_i and D_j are group differences in covariate means after matching and before matching, respectively,[37] was more than 90% for all covariates that remained statistically significant after matching.

Risk of Falls/Fractures

Table II shows selected characteristics of the matched cohort. A total of 825 cases of falls/fractures requiring hospitalization/ER visits following the use of antipsychotic agents were identified. The number of fall/fracture cases was 450 (72.138 per 1000 person-years) in atypical antipsychotic users and 375 (86.831 per 1000 person-years) in typical antipsychotic users. The mean ± SD duration of follow-up for atypical users was 332.31 ± 63.90 days and for typical users it was 334.69 ± 61.48 days. The mean ± SD time to event observed was 279.70 ± 114.62 days for atypical users and 288.02 ± 114.73 days for typical users. Figure 3 shows Kaplan-Meier survival curves that demonstrate the unadjusted association between antipsychotic use and risk of falls/fractures, with atypical antipsychotic users being at higher risk than typical antipsychotic users (p = 0.0042 by log-rank test).

Table III presents results from the Cox proportional hazard model. This model was adjusted for duration of therapy and other psychotropic drugs likely to induce falls and fractures. Baseline

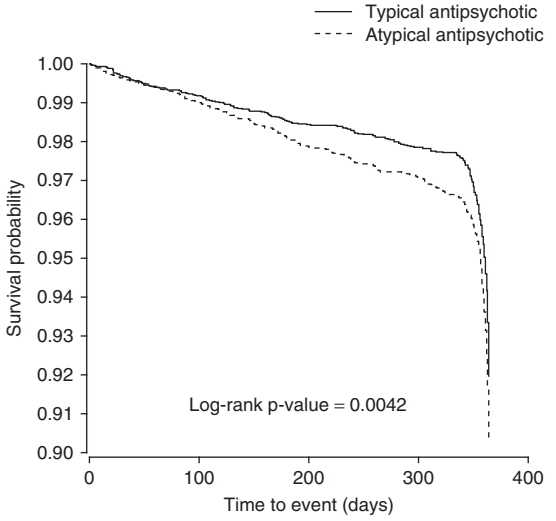

Fig. 3. Kaplan-Meier plot of crude association between users of different antipsychotics and risk of falls and fracture (data source: IMS LifeLink™ Health Plan Claims Database, 1999–2003).

Table III. Cox proportional hazard model for risk of falls/fracture among antipsychotic users (data source: IMS LifeLink™ Health Plan Claims Database, 1999–2003)

Variables	Hazard ratio	95% CI	p-Value
Antipsychotic drug class			
Typical	1.00	Reference	
Atypical	1.01	0.83, 1.22	0.3829
Duration of therapy*			
<30 days	1.00	Reference	
30–90 days	1.40	0.98, 2.01	0.1542
>90 days*	1.81	1.35, 2.43	0.0004
Other psychotropic drugs used during follow-up*			
Antidepressant	1.08	0.78, 1.50	0.6210
Anti-anxiety drug*	1.47	1.16, 1.88	0.0016
Antiepileptic*	1.43	1.09, 1.87	0.0084
Hypnotic	1.30	0.94, 1.78	0.1060
Baseline characteristics that remained significant after matching			
*Provider specialty**			
Geriatrics/internal medicine	1.00	Reference	
General/family medicine	0.83	0.53, 1.31	0.4366
Psychiatry*	0.35	0.20, 0.64	0.0005
Other*	0.67	0.48, 0.94	0.0236
*Hospitalization in past 6 months**			
No	1.00	Reference	
Yes*	1.56	1.20, 2.01	0.0006
Medical history in past 6 months			
Schizophrenia	0.68	0.43, 1.07	0.0964
Cancer	1.23	0.87, 1.74	0.2219
Other drugs used in past 6 months			
Antidepressant	1.08	0.78, 1.50	0.6210

* Threshold for statistical significance set at p = 0.05.

characteristics that remained significant after matching were also adjusted for in this model. There was no statistically significant difference (HR 1.01; 95% CI 0.83, 1.22) between propensity score-matched atypical and typical antipsychotic users with respect to risk of falls/fractures. However, duration of therapy of >90 days was significantly (HR 1.81; 95% CI 1.35, 2.43) associated with increased risk of falls and fractures compared with duration of therapy of <30 days. Duration of therapy of 30–90 days was not statistically significant. The other factors likely to have influenced risk of falls/fractures were psychotropic drugs such as anti-anxiety medications (HR 1.47; 95% CI 1.16, 1.88) and antiepileptics (HR 1.43; 95% CI 1.09, 1.87); hospitalization in the 6 months prior to the index date (HR 1.56; 95% CI 1.20, 2.01); and psychiatrist provider (HR 0.35; 95% CI 0.20, 0.64) or any other provider (HR 0.67; 95% CI 0.48, 0.94).

Discussion

Although antipsychotic use has shown to be associated with risk of falls and fractures, the differential risk between atypical and typical antipsychotics has remained unaddressed. This study found that no significant difference exists between users of atypical and typical antipsychotics with respect to risk of falls/fractures after controlling for duration of use and other psychotropic drugs in propensity score-matched cohorts based on the multivariate Cox-proportional hazard model. In contrast to the previous study stating that use of conventional antipsychotics but not atypical antipsychotics is associated with increased risk of fractures,[15] this study did not find any significant difference between the two groups. A subanalysis conducted to examine falls and fractures separately revealed similar findings (results not shown). The current study finding might be attributable to head-to-head comparison of the two treatment groups using a propensity score matched-cohort design and adjusting for potential confounders such as duration of therapy and exposure to other psychotropic drugs. The main advantage of matching on propensity score is that it eliminates incomparable subjects in both exposed groups and thus provides more precise and unbiased estimates of true treatment effects.[42,43] The results of the current study suggest that no significant difference exists between typical and atypical antipsychotic use with respect to risk of falls/fractures.

The non-significant findings with respect to falls and fractures can be attributed to the underlying pharmacology of the antipsychotic agents. Conventional antipsychotic agents have a high affinity for dopamine D_2 receptors and thus have a high propensity to cause EPS, TD and elevated prolactin levels.[44] Atypical antipsychotic agents

have the ability to interact with both serotonin 5-HT_{2A} receptors and D_2 receptors and thus have a lower propensity to cause EPS and TD and a transient increase in prolactin levels. However, there are data suggesting a risk of developing EPS during treatment with atypical antipsychotic agents. A recent meta-analysis has shown that treatment with atypical antipsychotic agents is not associated with significantly fewer EPS.[45] All antipsychotics have a strong affinity for D_2 receptors. Atypical antipsychotics also have serotonergic and histaminergic receptor-blocking properties, leading to a possible increased risk of sedation and orthostatic hypotension.[46] Hyperprolactinaemia and loss of bone mineral density are also associated with both atypical and typical antipsychotic agents.[9] Thus, the pharmacological consequences of typical and atypical antipsychotic agents seem to be similar with respect to the adverse events of falls and fractures.

The major strength of the current study is the control of potential confounders in propensity score-matched cohorts. Duration of therapy is an important confounder in studies evaluating association between exposure and outcome.[47] Vitry et al.[21] illustrated that long-term use of psychotropic medications in the elderly leads to increased risk of falls, but these investigators did not evaluate individual classes of psychotropic medications. With respect to antipsychotic medications, a statistically significant association was found between duration of therapy and risk of falls and fractures. The risk of falls and fractures increased for those taking antipsychotics for >90 days. Previous studies have found that longer duration of treatment is associated with decreasing bone mineral density and hyperprolactinaemia, leading to weaker bones.[12,14] The findings of the current study suggest that duration of antipsychotic use is a significant predictor of falls and fractures in older adults and there is a need to monitor those using antipsychotic agents on a long-term basis.

Bivariate analyses revealed a significant difference in the duration of therapy between the two groups. Atypical antipsychotics were found to be more frequently prescribed for a longer period of time than typical antipsychotics (table II). In fact, the multivariate analysis found significant effects of atypical use on falls and fractures if duration was not controlled for (results not shown). These findings suggest that duration of antipsychotic use plays a more important role than the nature of antipsychotic use. Concomitant psychotropic use is a significant health concern in the elderly population because of the cumulative risk associated with use of these drugs. A previous study has reported significantly increased prescription of CNS drugs in elderly patients who have had a fall.[48] Thus, concurrent use of other psychotropic medications was also controlled for in the multivariate analysis. Consistent with past literature, a significant association was found between risk of falls/fractures and the use of antiepileptic and anti-anxiety agents.[19,22,49] This study reinforces the need to manage psychotropic use to reduce patient harm resulting from falls.[50] Consistent with previous studies, all-cause hospitalization in the previous 6 months was found to be an important predictor of risk of hospitalization/ER visits for falls and fractures, and the importance of this outcome as a measure of severity of illness was thus confirmed.[35] Provider specialty was also found to be a significant variable in the regression model, indicating that the type of provider is an important predictor of risk of adverse events.

The limitations of this study should also be considered while interpreting the results. The use of computer-recorded information to capture data did not allow us to ascertain whether the subjects actually used their dispensed medicines. The diseases and outcome measurements were based on diagnostic data in medical claims. Incomplete records submitted by providers together with inaccurate demographic information and clinical detail in the ICD-9-CM system may limit the accuracy of administrative data.[28] Additionally, use of ICD-9-CM E-codes to ascertain injurious falls leading to hospitalization/ER visits could have been underutilized. The population evaluated in this study comprised community-dwelling older adults, and the results may not be generalizable to other settings. The claims captured only dispensing data and not actual usage; consequently there may have been issues concerning temporality of usage and adverse outcome. The dose-response relation-

ship was not examined, because of the complexity of the study design and the possibility of changes in dose over time.[29] Variables included in the propensity score were limited to those available in the data source and those used in the previous literature; there is a possibility that some unmeasured confounder might have affected the results. Finally, not all eligible patients available in the treatment group could be matched, which may also limit the generalizability of the results.

The study design and analytical approach were strengths of this study. There is a possibility that patients in the two treatment groups differed in terms of disease severity or that patients were preselected to receive one therapy over the other because of some unobservable characteristics, which can lead to selection bias. However, matching based on propensity score can diminish the effect of selection bias. Propensity scores coupled with temporal details can be useful for addressing causality between exposure and outcome.[28] Only new users of antipsychotics were included in the study cohort to address the issue of prevalence bias. Although randomization of exposure did not take place, this study used a large sample of population-based, retrospective data and applied a pseudorandomization technique of propensity score matching to strengthen the study findings.

Conclusions

In this retrospective analysis, the use of atypical antipsychotic agents was not associated with risk of falls/fractures when compared with use of typical antipsychotic agents in community-dwelling older adults. However, longer duration of treatment was found to be associated with an increase in risk of falls/fractures. These findings suggest that there is a need to be cautious when prescribing antipsychotic agents to older adults for long periods of time. Regular follow-up of patients and constant monitoring can be instrumental in minimizing the risk of falls and fractures associated with long-term use of antipsychotics. Future studies are needed to evaluate the comparative safety of individual antipsychotic treatments in older adults.

Acknowledgements

The authors have no conflicts of interest that are directly relevant to the content of this study. No funding was received for this study. The statements, findings, conclusions, views and opinions contained and expressed in this article are based in part on data obtained under license from the following IMS Health Incorporated information service(s): IMS LifeLink™ Health Plan Claims Database (1999–2003), IMS Health Incorporated. All rights reserved. The statements, findings, conclusions, views and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.

References

1. Research Activities. Outcomes/effectiveness research: evidence is lacking to support many off-label uses of atypical antipsychotic drugs. 2007 Feb [online]. Available from URL: http://www.ahrq.gov/research/feb07/0207RA18.htm [Accessed 2009 Apr 16]
2. Jano E, Chen H, Johnson ML, et al. Antipsychotic utilization and expenditure trends among elderly persons. Psychiatr Serv 2007 Nov; 58 (11): 1400
3. Aparasu RR, Bhatara V, Gupta S. U.S. national trends in the use of antipsychotics during office visits, 1998-2002. Ann Clin Psychiatry 2005; 17 (3): 147-52
4. Cumming RG. Epidemiology of medication-related falls and fractures in the elderly. Drugs Aging 1998 Jan; 12 (1): 43-53
5. Hartikainen S, Lonnroos E, Louhivuori K. Medication as a risk factor for falls: critical systematic review. J Gerontol 2007; 62A (10): 1172-81
6. French DD, Campbell R, Spehar A, et al. Outpatient medications and hip fractures in the US: a national veterans study. Drugs Aging 2006; 22 (10): 877-85
7. Busche C, Shaw M, Peveler RC. A review of the association between antipsychotic use and hyperprolactinaemia. J Psychopharmacol 2008 Mar; 22 (2 Suppl.): 46-55
8. Miller DD. Atypical antipsychotics: sleep, sedation and efficacy. J Clin Psychiatry 2004; 6 Suppl. 2: 3-7
9. Naidoo U, Goff DC, Klibanski A. Hyperprolactinemia and bone mineral density: the potential impact of antipsychotic agents. Psychoneuroendocrinology 2003; 28: 97-108
10. Akyol AD. Falls in the elderly: what can be done? Int Nurs Rev 2007; 54: 191-6
11. Hayes WC, Myers ER, Morris JN, et al. Impact near the hip dominates fracture risk in elderly nursing home residents who fall. Calcif Tissue Int 1993; 52: 192-8
12. Hugenholtz GW, Heerdink ER, Staa TP, et al. Risk of hip/femur fractures in patients using antipsychotics. Bone 2005; 37: 864-70
13. Liperoti R, Onder G, Lapane KL, et al. Conventional or atypical antipsychotics and the risk of femur fracture among elderly patients: results of a case-control study. J Clin Psychiatr 2007; 68: 929-34
14. Pouwels S, Staa TP, Egberts ACG. Antipsychotic use and the risk of hip/femur fracture: a population-based case-control study. Osteoporosis Int 2009 Sep; 20 (9): 1499-506

15. Landi F, Onder G, Cesari M, et al. Psychotropic medications and risk of falls among community-dwelling frail older people: an observational study. J Gerontol 2005; 60A (5): 622-6
16. Hein LTT, Cumming RG, Cameron ID, et al. Atypical antipsychotic medications and risk of falls in residents of aged care facilities. J Am Geriatr Soc 2005; 53: 1290-5
17. Katz IR, Rupnow M, Kozma C, et al. Risperidone and falls in ambulatory nursing home residents with dementia and psychosis or agitation: secondary analysis of a double-blind placebo-controlled trial. Am J Geriatr Psychiatry 2004; 12: 499-508
18. Takkouche B, Montes-Martinez A, Gill SS, et al. Psychotropic medications and the risk of fracture: a meta-analysis. Drug Saf 2007; 30 (2): 171-84
19. Ray WA, Griffin MR, Schaffner W, et al. Psychotropic drug use and risk of hip fractures. N Engl J Med 1987; 316 (7): 363-9
20. Mustard CA, Mayer T. Case-control study of exposure to medication and the risk of injurious falls requiring hospitalization among nursing home residents. Am J Epidemiol 1997; 145: 738-45
21. Vitry AI, Hoile AP, Andrew LG, et al. The risk of falls and fractures associated with persistent use of psychotropic medications in elderly people. Arch Gerontol Geriatr 2010; 50 (3): e1-4
22. Bolton JM, Metge C, Lix L, et al. Fracture risk from psychotropic medications: a population-based analysis. J Clin Psychopharmacol 2008; 28 (4): 384-91
23. Vestergaard P, Rejnmark L, Mosekilde L. Anxiolytics, sedatives, antidepressants, neuroleptics and the risk of fracture. Osteoporosis Int 2006; 17: 807-16
24. Thapa PB, Gideon P, Fought RL, et al. Psychotropic drugs and risk of recurrent falls in ambulatory nursing home residents. Am J Epidemiol 1995; 142 (2): 202-11
25. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis, 1. Psychotropic drugs. J Am Geriatr Soc 1999; 47: 30-9
26. World Health Organization. ICD-9: international statistical classification of diseases and related health problems. 9th rev. Geneva: World Health Organization, 1978
27. PharMetrics® Integrated Database. Data assets. IMS [online]. Available from URL: http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=6d7660b6f5aa0210VgnVCM100000ed152ca2RCRD&vgnextchannel=bc42650204850210VgnVCM100000ed152ca2RCRD&vgnextfmt=default [Accessed 2009 Oct 24]
28. Valuck RJ, Libby AM, Sills MR, et al. Antidepressant treatment and risk of suicide attempt by adolescents with major depressive disorder: a propensity-adjusted retrospective cohort study. CNS Drugs 2004; 18 (15): 1119-32
29. Gill SS, Bronskill SE, Normand SLT, et al. Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med 2007; 146: 775-86
30. Schneeweiss S, Setoguchi S, Brookhart A, et al. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. CMAJ 2007; 176 (5): 627-32
31. Elixhauser A, Steiner CA, Whittington CA, et al. Clinical classifications for health policy research: hospital inpatient statistics, 1995. Healthcare Cost and Utilization project, HCUP-3 research note. Rockville (MD): Agency for Healthcare Research and Quality, 2000. AHCPR Pub. No. 98-0049
32. Grobee DE. Confounding and indication for treatment in evaluation of drug treatment for hypertension. BMJ 1997; 315: 1151-4
33. Baser O. Too much ado about propensity score models? Comparing methods of propensity score matching. Value Health 2006; 9 (6): 377-85
34. Brookhart MA, Schneeweiss S, Rothman KJ, et al. Variable selection for propensity score models. Am J Epidemiol 2006; 163 (12): 1149-56
35. Aparasu RR, Jano E, Johnson ML, et al. Hospitalization risk associated with typical and atypical antipsychotic use in community-dwelling elderly patients. Am J Geriatr Pharmacother 2008; 6: 198-204
36. Parson LS. Reducing bias in a propensity score matched-pair sample using greedy matching techniques [online]. Available from URL: http://www2.sas.com/proceedings/sugi26/p214-26.pdf [Accessed 2009 Mar 30]
37. Feng WW, Jun Y, Plaines D, et al. A method/macro based on propensity score and Mahalanobis distance to reduce bias in treatment comparison in observational study [online]. Available from URL: http://www.lexjansen.com/pharmasug/2006/publichealthresearch/pr05.pdf [Accessed 2009 Apr 7]
38. Alexander MT, Kufera JA. Butting heads on matched cohort analysis using SAS software [online]. Available from URL: http://www.nesug.org/proceedings/nesug07/sa/sa01.pdf [Accessed 2009 May 1]
39. Austin PC. Type I error rates, coverage of confidence intervals, and variance estimation in propensity-score matched analysis. Int J Biostat 2009; 5 (1): 1-21
40. Leslie RS. Calculating medication compliance, adherence, and persistence in administrative pharmacy claims database [online]. Available from URL: http://www.wuss.org/proceedings08/08WUSS%20Proceedings/papers/anl/anl09.pdf [Accessed 2009 Apr 12]
41. Wang PS, Schneeweiss S, Setoguchi S, et al. Ventricular arrhythmias and cerebrovascular events in the elderly using conventional and atypical antipsychotic medications. J Clin Psychopharmacol 2007; 27 (6): 707-10
42. Dehejia RH, Wahba S. Propensity score-matching for non-experimental causal studies. Rev Econ Stat 2002; 84 (1): 151-61
43. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983; 70 (1): 41-55
44. Meltzer HY, Matsubara S, Lee JC. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin-2 pKi values. Am Soc Pharmacol Exp Ther 1989; 251 (1): 238-46
45. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009; 373: 31-41
46. Burns MJ. The pharmacology and toxicology of atypical antipsychotic agents. J Toxicol Clin Toxicol 2001; 39: 1-14

47. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis. I: psychotropic drugs. J Am Geriatr Soc 1999 Jan; 47 (1): 30-9

48. French DD, Campbell R, Spehar A, et al. Drugs and falls in community-dwelling older people: a national veterans study. Clin Ther 2006; 28 (4): 619-30

49. Cooper JW. Falls and fractures in nursing home patients receiving psychotropic drugs. Int J Geriatr Psychiatry 1994; 9: 975-80

50. 2010 National patient safety goals [online]. Available from URL: http://www.jointcommission.org/patientsafety/nationalpatientsafetygoals/ [Accessed 2010 Feb 22]

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