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Comparative risk of hip fractures in elderly nursing home patients with depression using paroxetine and other selective serotonin reuptake inhibitors

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Aim: To evaluate comparative safety of paroxetine and other selective serotonin reuptake inhibitors (SSRIs) for the risk of hip fractures. **Patients & methods:** A propensity score-matched retrospective cohort study was conducted using 2007–2010 Minimum Data Set linked Medicare data. Robust Cox proportional hazards model was used to evaluate the risk of hip fractures in depressed elderly nursing home residents. **Results:** Cox analysis did not find any significant difference in the risk of hip fractures for the paroxetine users (hazard ratio: 1.09; 95% CI: 0.91–1.32) when compared with other SSRIs. Results from the sensitivity analysis supported the main findings. **Conclusion:** There was no differential risk of hip fractures between paroxetine and other SSRIs. Future studies are needed to evaluate other anticholinergic effects of paroxetine.

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Keywords: comparative effectiveness • comparative risk • depression • elderly • hip fracture • Medicare • nursing home residents • paroxetine • selective serotonin reuptake inhibitors • SSRIs

Falls and fractures among elderly people constitute a major public health concern with an estimated cost of US\$19 billion [1]. Falls are the leading cause of accidental death and the seventh leading cause of death in persons more than 65 years of age [2]. More than 90% of hip fractures in elderly are caused by falls which can cause severe health problems including reduced quality of life and premature death [3]. Prevalence of hip fractures is estimated to be around 36–44% in nursing home residents [4,5]. Incidence of hip fractures is much higher in elderly nursing home residents than in community-dwelling elderly. Nursing home residents are at two-times higher risk of hip fractures than community-dwelling elderly patients [6–8]. Hip fractures are the major cause of hospitalization [9], morbidity, mortality and lack of ability to walk in nursing home patients [10,11,12].

Depression is a significant risk factor for hip fractures [13,14]. Selective serotonin reuptake inhibitors (SSRIs) are the first-line agent for the treatment of depression in older patients. These include paroxetine, escitalopram, fluoxetine and sertraline as the drugs of choice [15]. Various studies indicate that the use of SSRIs is associated with lower bone mineral density [16,17] and increased risk of hip and other fractures [18–20]. Various meta-analyses have examined association between the use of SSRIs and risk of fractures. Results from these meta-analyses indicate that patients getting SSRIs have 1.64–2.76 times higher risk of hip fractures than the others [18,20].

Previous studies have consistently found that anticholinergic medications are significantly associated with risk of hip fractures [21,22]. As per the past literature, paroxetine has higher affinity for musca-

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rinic cholinergic receptors than other SSRIs [23,24]. Owen *et al.* found that the muscarinic binding properties of paroxetine were similar to desipramine but much lower than amitriptyline and substantially higher than sertraline [23]. Thus, the propensity of anticholinergic side effects is expected to be higher in paroxetine than other SSRIs. Goodnick *et al.* reported that all SSRIs, except paroxetine are devoid of anticholinergic properties [25]. A recent review concluded that paroxetine is a muscarinic antagonist and has less favorable tolerability profile than escitalopram [24]. The 2015 American Geriatrics Society Updated Beers Criteria classifies paroxetine as a strong anticholinergic antidepressant and potentially inappropriate for use in elderly patients [26]. The Anticholinergic Drug Scale (ADS) also classifies paroxetine as a level 2 anticholinergic agent when compared with other SSRIs [27]. The strong anticholinergic nature of paroxetine could lead to higher risk of hip fractures than the other SSRIs.

Paroxetine, although considered potentially inappropriate, is commonly used in depressed elderly patients [28–30]. However, limited comparative data exist regarding the risk of hip fractures in elderly nursing home patients with depression who are prescribed paroxetine versus other SSRIs. In 1998, Lapane and colleagues evaluated risk of femur fractures with the use of SSRIs and tricyclic antidepressants. Their results show an increased risk of femur fractures with the use of paroxetine [31]. Recently, Vestergaard *et al.* conducted a case–control study in Danish population to examine risk of fractures among users of various antidepressants. They did not find any association between paroxetine use and risk of fractures [32]. However, more research is needed to evaluate the risk of hip fractures in elderly residents with cognitive issues such as depression, especially among those who reside in nursing homes, a setting with highly vulnerable population. This research is designed to evaluate the comparative risk of paroxetine and other SSRIs for hip fractures due to differential anticholinergic effects of antidepressants in elderly patients. The study findings can help to optimize antidepressant use by increasing the use of low-level anticholinergic antidepressants in depressed elderly nursing home residents. This research will test the hypothesis that elderly with depression receiving paroxetine are at a greater risk for hip fractures due to the anticholinergic effect than users of other SSRIs.

Patients & methods

Data source

The current study used 2007–2010 Minimum Data Set linked Medicare data files from all the states in

the US to examine the comparative safety of paroxetine versus other SSRIs for the risk of hip fractures in a cohort of depressed elderly nursing home patients. The Medicare data including Medicare Provider Analysis and Review (MEDPAR) file (part A), carrier file (part B), prescription claims file (part D), Minimum Data Set (MDS) and master beneficiary summary file (MBSF) chronic condition segments were used in this research. The chronic condition (CC) segments of the MBSF contain information regarding the presence of 27 common or chronic conditions using inpatient and outpatient claims-based algorithms [33,34]. The cohort included Medicare beneficiaries with depression based on the MBSF CC segments and those with MDS assessments for 2007–2010. This study was approved by the University of Houston Committee for the Protection of Human Subjects under the exempt category.

Study design & sample

The present study used retrospective cohort design matched on propensity score to examine the risk of hip fractures associated with the use of paroxetine versus other SSRIs in elderly nursing home patients with depression. Development of study cohort is outlined in Figure 1. Index antidepressant use was defined as the first prescription of antidepressant after at least 1 year without any prescription fill date for any of the antidepressant medications. Patients were included in the study cohort if they: had nursing home stay anytime during the study period, were 65 years and older; received a depression diagnosis during the 1-year baseline period, initiated SSRIs between 1 January 2008 and 31 December 2009 and had continuous coverage for Medicare part A, B and D; and no health maintenance organization (HMO) during the 1-year baseline period. Patients with HMO coverage during the study period were excluded because predefined chronic condition indicators were only obtained from the claims files of fee-for-service beneficiaries and not from managed care organizations [35,36].

Exposures & outcome definitions

Exposure to paroxetine and other SSRIs was the primary exposure variable in this study. Use of paroxetine and other SSRIs was measured using Medicare part D claims data. Other SSRI users included elderly who were prescribed sertraline, citalopram, fluoxetine, fluvoxamine or citalopram. The National Drug Codes in the part D file were used to identify exposure to paroxetine and other SSRIs [37]. Time to hip fractures was the primary outcome variable of this study. It was measured using the CC indicator for hip fractures in

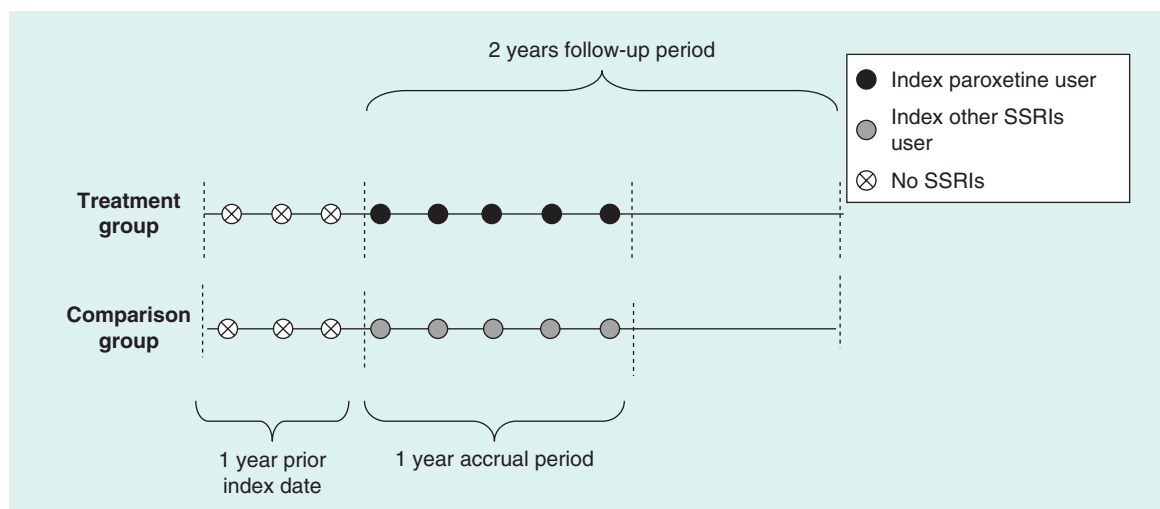


Figure 1. Cohort construction.
SSRI: Selective serotonin reuptake inhibitor.

the MBSF CC segments. The maximum follow-up period was 1 year. Study subjects were censored if they reached the end of the follow-up period; switched to a different antidepressant class or switched from paroxetine to other SSRIs or vice versa, had a gap of more than 15 days in the use of index antidepressant [38–40] or died, whichever occurred earlier.

Cohort matching

Observational studies provide treatment estimates in real-world settings. However, selection bias is a common problem in these studies due to nonrandomization of patients to different treatment groups [41]. Lack of randomization leads to pretreatment differences rather than actual treatment effects in observational studies [42]. Propensity scoring is a common technique to control for selection bias in observational studies [43,44]. This technique was proposed by Rosenbaum and Rubin in 1983 [45], and is the conditional probability of assignment to a particular treatment given a vector of observed covariates [46]. Propensity score matching is commonly used to achieve balance between the two groups such that the matched groups differ only on treatment assignment and thereby suitable for the estimation of treatment effect. A large number of covariates were used for the calculation of propensity scores based on previously published literature, expert opinions of experienced clinicians and variable selection on the basis of their association with treatment and outcome [47–50]. These covariates included sociodemographic characteristics such as age, gender and race and clinical characteristics such as co-medications and illness history during the 1-year baseline period. Hip fracture at baseline was used as one of the covariates for the calculation of propensity scores. All the covari-

ates used in this study for the calculation of propensity scores are listed in [Table 1](#).

Propensity scores were calculated for each individual as a function of baseline covariates using logistic regression model. Nursing home patients taking paroxetine were matched with nursing home patients taking other SSRIs using GREEDY 5→1 matching technique. This technique matches cases to controls on the first 5 digits of the propensity score. Those who remain unmatched are then matched on 4 digits of the propensity score. This process is repeated until the subjects in both the treatment groups are matched on the 1 digit of the propensity score. A control is selected at random if more than one matched control is found for a case. The GREEDY 5→1 matching technique reduces matched-pair bias caused by incomplete and inexact matching [51].

Statistical analysis

The differences between the two groups were examined using χ^2 test for categorical variables and t -test for continuous variables, before and after matching. Survival analysis was conducted using matched cohort of paroxetine and other SSRI users to evaluate the risk of hip fractures. The Cox proportional-hazard model was utilized to evaluate the risk of hip fractures associated with paroxetine using other SSRIs as the reference category. An ID option of PROC PHREG in SAS 9.1 was used to run Robust Cox regression model [52]. Conventional Cox models assume independence of observations whereas the robust Cox regression model uses robust sandwich estimator to account for the clustering within matched pairs [53]. This model has been found to yield hazard ratios with minimal bias when compared with other propensity score-matched Cox models [54,55].

Table 1. Baseline characteristics of elderly patients with depression using paroxetine and other selective serotonin reuptake inhibitors[†].

Characteristics	Unmatched cohort (n = 57,571)		Matched cohort (n = 9240)		p-value
	Paroxetine users (n = 4620; %)	Other SSRI users (n = 52,951; %)	Paroxetine users (n = 4620; %)	Other SSRI users (n = 4620; %)	
Gender:					0.35
– Female	67.8	67.1	67.8	66.6	0.21
– Male	32.2	32.9	32.2	33.4	
Age in years:					0.95
– 65–84	56.1	56.1	56.1	57.1	0.33
– 85 and above	43.9	43.9	43.9	42.9	
Race:					0.08
– White	79.0	77.9	79.0	77.6	0.11
– Non-White	21.0	22.1	21.0	22.4	
Medical history in past 12 months:					
– CHF	51.9	54.3	51.9	55.4	0.002*
– Endocarditis	5.6	6.1	5.6	6.5	0.24
– Ischemic heart disease	67.2	68.2	67.2	67.9	0.14
– Acute myocardial infarction	9.0	9.9	9.0	9.8	0.04*
– Stroke/transient ischemic attack	31.2	34.7	31.2	29.1	<0.0001*
– Cardiac arrhythmia	32.2	33.5	32.2	33.0	0.07
– Circulatory disorder	36.2	38.2	36.2	37.7	0.01*
– Thromboembolic disorder	7.9	8.4	7.9	8.5	0.19
– Peripheral arterial disorder	13.7	14.5	13.7	14.4	0.13
– Hypertension	91.6	93.3	91.6	92.0	<0.0001*
– Diabetes mellitus	39.3	41.5	39.3	42.4	0.004*
– Hyperlipidemia	73.4	74.5	73.4	71.6	0.09
– Renal failure	19.2	22.1	19.2	27.4	<0.0001*
– Other renal disease	46.1	49.3	46.1	48.1	<0.0001*
– Fall and fracture	16.9	18.6	16.9	16.9	0.004*
– Osteoporosis	36.3	36.2	36.3	32.3	0.71
– Rheumatoid arthritis and osteoarthritis	68.4	71.2	68.4	60.2	<0.0001*
– Gout and other crystal arthropathies	4.1	4.2	4.1	3.8	0.75
– Back pain	24.0	23.1	24.0	20.6	0.19

[†]All medication use and diagnostic data are based on 1 year prior to the initiation of the SSRI medication.
 *p-value significant at 0.05.
 CHF: Congestive heart failure; SSRI: Selective serotonin reuptake inhibitor.

Table 1. Baseline characteristics of elderly patients with depression using paroxetine and other selective serotonin reuptake inhibitors[†] (cont.).

Characteristics	Unmatched cohort (n = 57,571)			Matched cohort (n = 9240)		
	Paroxetine users (n = 4620; %)	Other SSRI users (n = 52,951; %)	p-value	Paroxetine users (n = 4620; %)	Other SSRI users (n = 4620; %)	p-value
Medical history in past 12 months (cont.):						
– Parkinson	3.5	3.8	0.38	3.5	3.5	0.96
– Extrapyrarnidal syndrome	2.4	2.5	0.88	2.4	2.1	0.26
– Fibromyalgia	1.8	1.9	0.44	1.8	1.8	0.75
Psychotic disorder:						
– Anxiety	12.6	10.8	0.0002*	12.6	11.3	0.07
– Mood disorder	21.7	24.3	<0.0001*	21.7	21.9	0.80
– Migraine	0.5	0.5	0.95	0.5	0.5	0.88
– Schizophrenia	5.3	6.2	0.02*	5.3	6.1	0.11
– Bipolar disorder	1.0	1.0	0.78	1.0	1.0	0.92
– Insomnia	2.7	2.6	0.79	2.7	2.6	0.75
– Dementia	37.3	42.5	<0.0001*	37.3	14.1	0.59
– Other psychiatric disorders	13.8	12.7	0.02*	13.8	36.8	0.76
– Liver disorder	8.7	8.4	0.38	8.7	8.6	0.77
– Gastric disorder	50.7	50.8	0.92	50.7	41.7	<0.0001*
– Ulcers	10.5	11.4	0.08	10.5	11.1	0.38
– Cancer	20.6	20.9	0.58	20.6	21.2	0.46
– Dysphagia	8.8	10.8	<0.0001*	8.8	8.7	0.85
– Anemia	72.1	75.4	<0.0001*	72.1	72.0	0.84
– Asthma	16.2	15.0	0.03*	16.2	16.8	0.43
– Chronic obstructive pulmonary disease	42.7	41.2	0.05	42.7	51.4	<0.0001*
– Pneumonia	15.0	15.7	0.20	15.0	17.4	0.002*
– Benign prostatic hyperplasia	16.1	16.8	0.27	16.1	18.9	0.001*
– Hypothyroidism	27.3	28.8	0.03*	27.3	26.8	0.54
– Cataract	77.4	78.8	0.02*	77.4	76.5	0.30
– Glaucoma	24.1	25.6	0.02*	24.1	24.2	0.92
– Obesity	4.7	5.1	0.26	4.7	5.4	0.13
– Alcohol	3.2	3.3	0.58	3.2	3.6	0.25

[†]All medication use and diagnostic data are based on 1 year prior to the initiation of the SSRI medication.
 *p-value significant at 0.05.
 CHF: Congestive heart failure; SSRI: Selective serotonin reuptake inhibitor.

Table 1. Baseline characteristics of elderly patients with depression using paroxetine and other selective serotonin reuptake inhibitors* (cont.).

Characteristics	Unmatched cohort (n = 57,571)			Matched cohort (n = 9240)		
	Paroxetine users (n = 4620; %)	Other SSRI users (n = 52,951; %)	p-value	Paroxetine users (n = 4620; %)	Other SSRI users (n = 4620; %)	p-value
Other drugs used in past 12 months:						
- Anti-infective agents	71.0	71.5	0.39	71.0	70.6	0.68
- Endocrine and metabolic drugs	61.2	61.7	0.46	61.2	61.6	0.64
- Cardiovascular agents	83.4	85.5	0.0001*	83.4	82.9	0.54
- Anti-hyperlipidemic drugs	39.6	42.1	0.0008*	39.6	39.5	0.95
- Respiratory agents	32.2	31.7	0.46	32.2	35.1	0.003*
- Antihistamines and other cold remedies	20.5	19.7	0.18	20.5	18.9	0.05
- Gastrointestinal agents	22.9	22.7	0.68	22.9	20.3	0.002*
- Genitourinary products	12.1	12.3	0.67	12.1	11.9	0.70
- Antianxiety agents	4.9	4.2	0.03*	4.9	4.4	0.30
- Antipsychotics	12.8	13.4	0.26	12.8	12.5	0.66
- Hypnotics	10.8	10.7	0.87	10.8	11.5	0.29
- Stimulants/anti-obesity/anorexiant	3.3	3.1	0.36	3.3	3.0	0.31
- Other psychotherapeutic agents	7.3	9.4	<0.0001*	7.3	7.5	0.84
- Anticonvulsants	13.4	14.2	0.12	13.4	14.1	0.32
- Antiparkinsonian	5.4	6.0	0.06	5.4	6.1	0.11
- Analgesics and anti-inflammatories	54.7	54.9	0.84	54.7	52.8	0.07
- Musculoskeletal agents	22.4	23.3	0.19	22.4	22.7	0.78
- Nutritional products	26.5	28.1	0.02*	26.5	27.8	0.17
- Hematological agents	32.7	33.9	0.10	32.7	33.1	0.66
- Topical products	45.7	46.5	0.27	45.7	45.5	0.85
- Central acetylcholinesterase inhibitors	12.3	14.9	<0.0001*	12.3	13.4	0.11
- Alcohol- and drug-dependence agents	0.4	0.6	0.11	0.4	0.6	0.15
- Antineoplastic agents	5.5	5.5	0.97	5.5	4.8	0.13

*All medication use and diagnostic data are based on 1 year prior to the initiation of the SSRI medication.

*p-value significant at 0.05.

CHF: Congestive heart failure; SSRI: Selective serotonin reuptake inhibitor.

The Cox proportional-hazard model is based on proportional hazards (PH) assumption. This assumption was checked using the interaction term between SSRIs treatment and log of time to hip fractures. Additionally, Schoenfeld test was conducted to confirm the PH assumption. The PH assumption was met based on the diagnostic tests performed, thus robust Cox regression was performed to estimate the risk of hip fractures across the two treatment groups. An *a priori* level of 0.05 was used to check the statistical significance in this study.

Sensitivity analysis

Sensitivity analysis was conducted to confirm the robustness of the study findings. In the sensitivity analysis, patients were excluded if they did not have at least one MDS assessment at baseline. Both MDS

assessment and chronic condition indicator was used to ascertain diagnosis of hip fractures during the 1-year follow-up.

Results

Patient selection & matching

The process used for the identification of the elderly patients with depression who initiated treatment with paroxetine or other SSRIs is presented in [Figure 2](#). Analysis of 2007–2010 MDS linked Medicare data yielded 57,571 new users of SSRIs between January 2008 and December 2009 after applying inclusion and exclusion criteria. Out of these, 4620 (8.02%) received paroxetine and 52,951 received other SSRIs (91.98%). Results from the propensity score matching revealed 4620 patients in each of the two treatment groups. [Table 1](#) reports differences in baseline

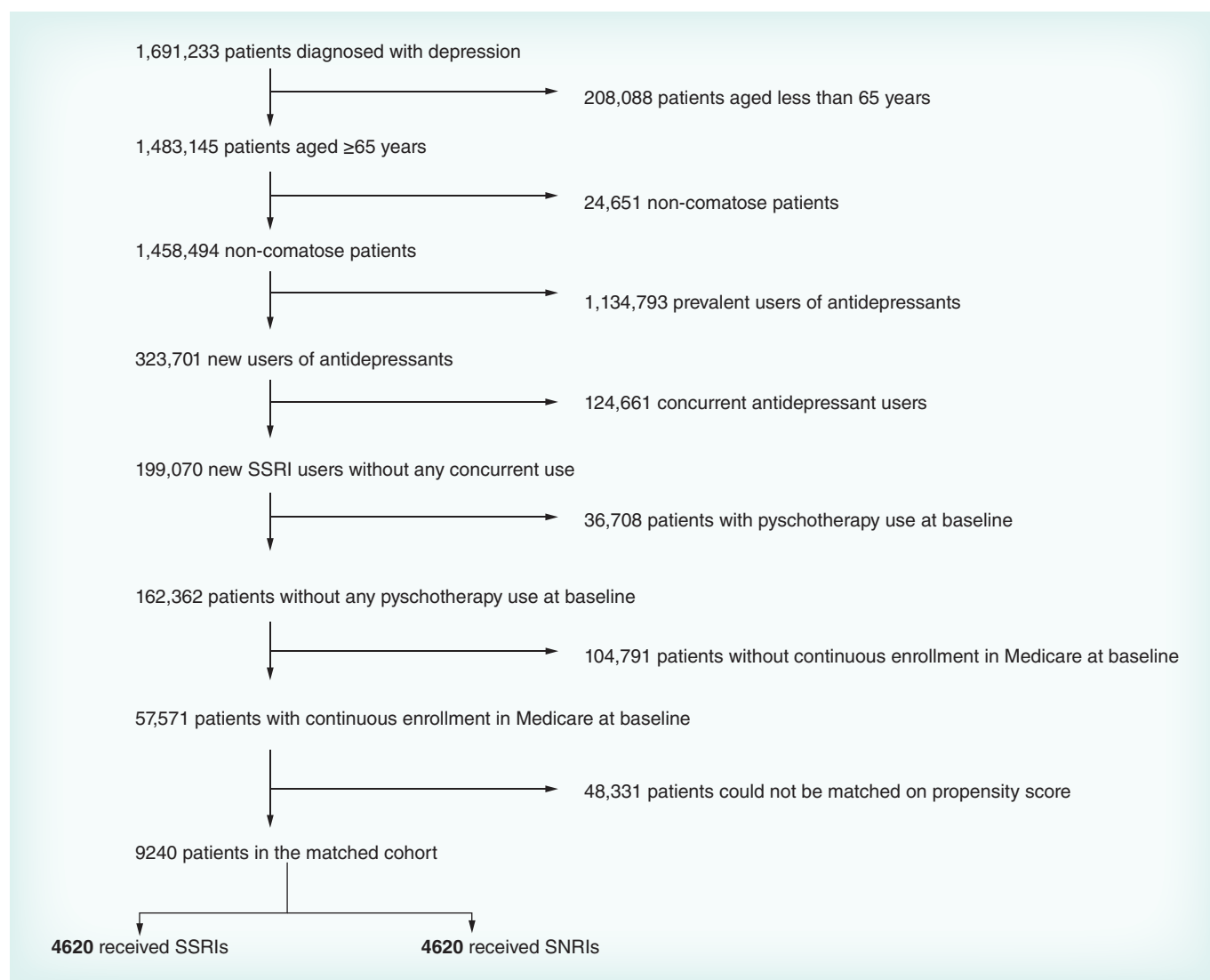


Figure 2. Identification of elderly patients with depression using paroxetine and other selective serotonin reuptake inhibitors. SNRI: Serotonin–norepinephrine reuptake inhibitor; SSRI: Selective serotonin reuptake inhibitor.

characteristics between paroxetine and other SSRIs before and after matching. After matching, both the treatment groups were similar in terms of distribution of the baseline characteristics and fairly comparable. Figure 3 presents distribution of propensity scores after matching. This figure indicates a fair balance in the majority of the pretreatment characteristics between the two treatment groups.

Risk of hip fractures

A total of 430 cases of hip fractures were observed in the matched cohort during the follow-up period. Out of these, 213 (4.6%) cases were in paroxetine group and 217 (4.7%) were in other SSRIs group. Figure 4 presents risk of hip fracture among elderly patients with depression who used paroxetine or other SSRI antidepressants. The graph demonstrates that there was no difference in the risk of hip fracture between the two treatment groups. The results from the Schoenfeld test indicated that the proportional hazards assumption was met ($p = 0.81$). Table 2 presents results from the robust Cox proportional hazard model for the risk of hip fractures between users of paroxetine and other SSRIs. The robust Cox proportional hazard model did not find any significant difference in risk of hip fractures between paroxetine

users (hazard ratio [HR]: 1.09; 95% CI: 0.91–1.32) when compared with the other SSRI users.

Sensitivity analysis

Results of the sensitivity analysis were consistent with the findings of the main study (Table 2). The sensitivity analysis showed no difference in the risk of hip fractures based on MDS criterion between patients who initiated treatment with paroxetine (HR: 1.19; 95% CI: 0.91–1.56) and those who initiated treatment with other SSRIs.

Discussion

Past literature indicates strong association between the use of SSRIs and risk of fractures due to antidepressant's affinity for serotonin [18,20]. Paroxetine has higher serotonergic potential than other SSRIs which can lead to higher risk of hip fractures [19]. Additionally, paroxetine is a strong anticholinergic and thus, might carry a higher risk of hip fractures than other SSRIs. However, no previous study has directly compared the safety of paroxetine with other SSRIs for the risk of hip fractures in depressed elderly nursing home residents. The current propensity score–matched retrospective cohort study indicates that paroxetine does not differ significantly from other SSRIs regarding the risk of hip

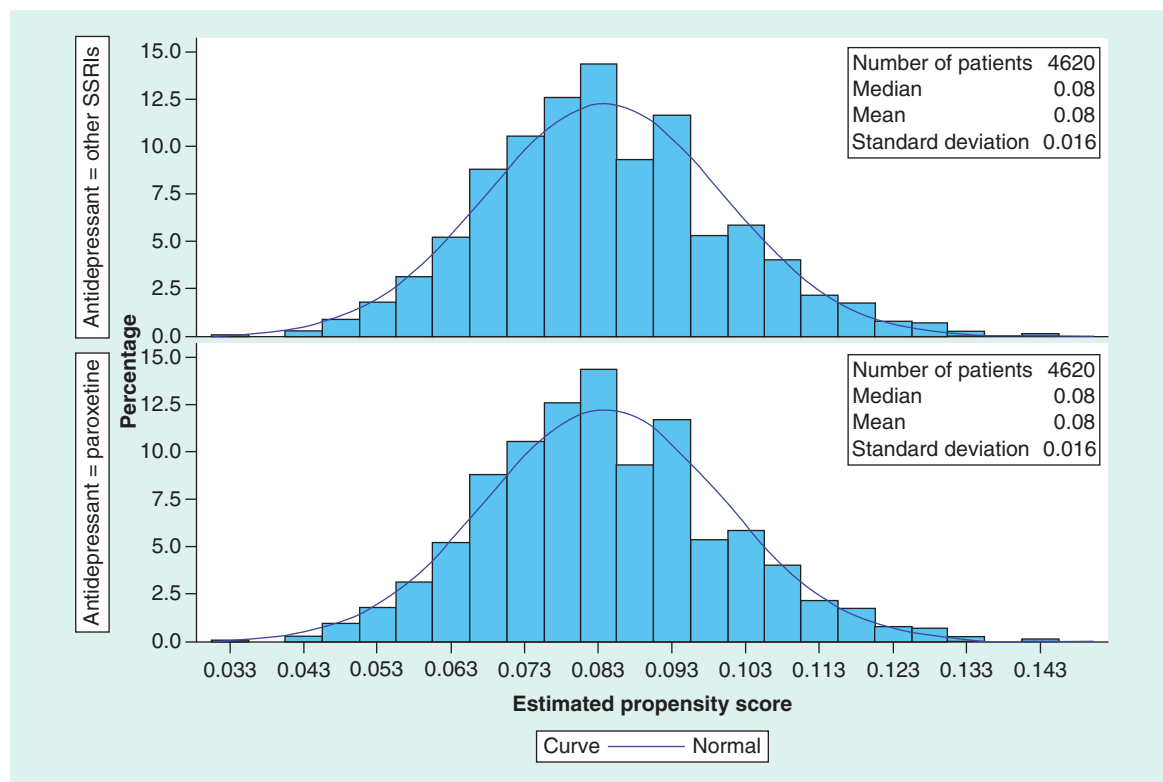


Figure 3. Distribution of propensity scores among the users of paroxetine and other selective serotonin reuptake inhibitors.
 SSRI: Selective serotonin reuptake inhibitor.

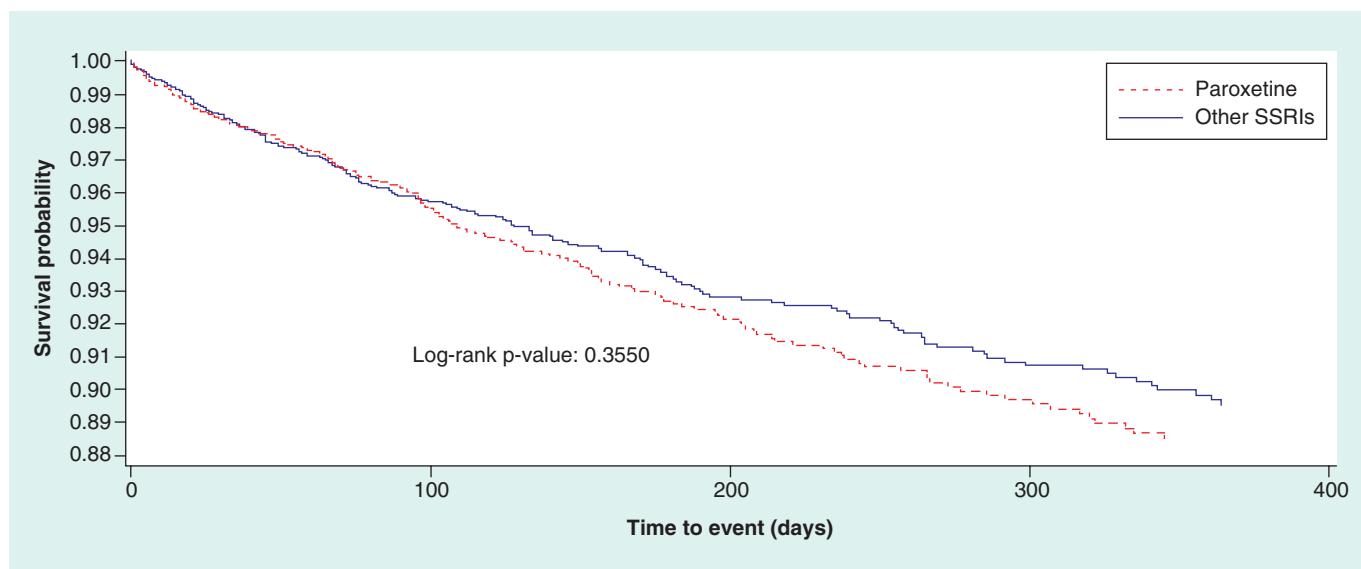


Figure 4. Kaplan–Meier curve for the risk of hip fracture for users of paroxetine and other selective serotonin reuptake inhibitors. SSRI: Selective serotonin reuptake inhibitor.

fractures. Vestergaard *et al.* also did not find any significant relationship between paroxetine use and risk of fractures based on a case–control design [32].

The pharmacological differences in paroxetine and other SSRIs at the receptor level could lead to a differential risk of hip fractures. However, results from the present study suggest that pharmacological differences between paroxetine and other SSRIs do not translate into clinically significant difference for the risk of hip fractures in elderly nursing home residents with depression. The study findings do not indicate absence of risk of hip fractures with the use of SSRIs. In fact, these findings suggests that paroxetine and other SSRIs carry similar risk for hip fractures. Future studies are needed to better understand the similarity in the safety profile of paroxetine when compared with other SSRIs, in spite of paroxetine having strong anticholinergic properties and strong affinity for serotonin receptors.

Although paroxetine and other SSRIs are similar for the risk of hip fractures, these newer antidepressant

agents are not same. Therefore, the prescribers need to weigh the risk–benefit ratio along with patient characteristics such as age, gender, physical conditions, illness and medication history when prescribing these antidepressants to the more vulnerable population such as elderly patients residing in nursing homes. Previous research indicates frequent use of paroxetine in nursing homes for the treatment of depression in elderly patients [28–30]. In the present study of the new SSRI users, around 8% of the patients initiated treatment with paroxetine. With an aging population and concerns of inappropriate medication use, there is a pressing need to optimize medication use and pharmaceutical care of elderly patients residing in nursing homes.

The present study had several strengths. Use of MDS-linked Medicare claims data provided actual practice data involving large sample size and long follow-up period. Prescription claims such as Medicare part D claims are valid and reliable sources for gathering medication-related information [56,57]. Using new-user cohorts for paroxetine and other SSRIs helped to

Table 2. Cox proportional hazard model for risk of hip fracture in the elderly with depression taking paroxetine and other selective serotonin reuptake inhibitors.

Variables	Hazard ratio	95% CI	p-value
PS matched Cox proportional hazard model			
Paroxetine (n = 4620)	1.09	0.91–1.32	0.35
Other SSRIs (n = 4620)	1.00	Reference	
Sensitivity analysis			
Paroxetine (n = 2084)	1.19	0.91–1.56	0.20
Other SSRIs (n = 2084)	1.00	Reference	

SSRI: Selective serotonin reuptake inhibitor.

minimize prevalence bias. Class-specific analyses using propensity score matching technique helped to control for the indication and selection bias. However, this study has some limitations. The diseases and outcome measurements were based on diagnostic data in medical claims. Exposure to SSRIs was ascertained using pharmacy claims. The claims capture only dispensing data and not the actual use by patients. Central anticholinergic effects may be dose-dependent and may involve selective muscarinic receptor antagonism in the central nervous system. However, doses of paroxetine, other SSRIs and co-medications were not accounted in the present study as dose information is not captured well in claims databases. Also, drug-related anticholinergic burden was not accounted. However, other anticholinergic drugs used at baseline were included as covariates in the calculation of propensity scores. The present study used Medicare claims, which is secondary data and thus has limitations due to miscoding and undercoding [58]. Propensity score-matched cohort was used to compare the risk of hip fractures between the two treatment groups. Propensity scores control for observed confounding due to measured confounders. There is a chance for unobserved confounding due to unmeasured confounders in the present study. However, sensitivity analysis was conducted and it supported the study findings. Lastly, this study might have limited generalizability as the study population was limited to elderly nursing home residents. Future studies need to replicate the study findings in other settings.

Conclusion

This retrospective cohort study evaluated comparative safety of paroxetine and other SSRIs in elderly nursing home residents with depression; the study did not find any statistically significant difference in the risk of hip fractures between the two treatment groups. The findings were consistent in the sensitivity analysis using a different cohort definition. Future studies are needed to evaluate other anticholinergic effects of paroxetine to optimize pharmaceutical care of elderly patients residing in nursing homes.

Future perspective

Evidence-based medicine emphasizes on scientific evidence along with clinician expertise and patient preferences. The comparative evaluation of safety and effectiveness of new and existing treatments is essential to establish strong empirical evidence base for an informed decision-making. The results of the present study revealed that use of paroxetine is not associated with increased risk of hip fractures when compared with the use of other SSRIs in depressed elderly nursing home patients. However, future studies are needed to evaluate other anticholinergic effects of paroxetine. The stewardship for such safety research lies with academia as pharmaceutical industry traditionally focuses on comparative effectiveness once the drug is approved by regulatory agencies. With widespread use of approved agents in different populations and indications, there is a constant need to evaluate the safety of medications. The pharmacoepidemiological studies provide real world data to evaluate comparative safety and effectiveness. The concerns of bias are limited for safety studies when compared to effectiveness studies. Therefore, comparative safety research provides the needed balance to optimize medication use in vulnerable populations.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors obtained approval from the University of Houston Committee for the Protection of Human Subjects under the exempt category. This study involved use of existing de-identified databases and thus informed consent was not required.

Executive summary

- Paroxetine is a strong anticholinergic antidepressant with high serotonergic potential than other selective serotonin reuptake inhibitors (SSRIs). Thus, paroxetine can increase the risk of hip fractures compared to other SSRIs in elderly patients.
- The present study used propensity score-matched retrospective cohort study design and 2007–2010 Minimum Data Set linked Medicare data to compare the risk of hip fractures in new users of paroxetine and other SSRIs.
- The findings from this study reveal no differential risk of hip fractures between the two treatment groups. Results from the sensitivity analysis corroborated the main findings.
- Future studies need to replicate the study findings in other clinical settings and also evaluate other anticholinergic effects of paroxetine.

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