Antipsychotic Drugs and Risk of Hip Fracture in People Aged 60 and Older in Norway

Marit S. Bakken, MD, PhD,† Jan Schjøtt, MD, PhD,‡§¶ Anders Engeland, MSc, PhD,*** Lars B. Engesæter, MD, PhD,‡†† and Sabine Ruths, MD, PhD*‡‡*

OBJECTIVES: To examine associations between exposure to various subgroups of antipsychotic drugs and risk of hip fracture in older adults.

DESIGN: Nationwide cohort study.

SETTING: Norway, 2005–2010.

PARTICIPANTS: Everyone living in Norway born before 1945 (N = 906,422).

MEASUREMENTS: Information was obtained on all prescriptions of antipsychotic drugs dispensed from 2004 to 2010 (Norwegian Prescription Database) and data on all primary hip fractures from 2005 to 2010 (Norwegian Hip Fracture Registry). Incidence rates of hip fracture during person-time exposed and unexposed to antipsychotic drugs were compared by calculating the standardized incidence ratio (SIR).

RESULTS: Thirty-nine thousand nine hundred thirty-eight (4.4%) participants experienced a primary hip fracture. Greater risk of hip fracture was associated with exposure to any antipsychotic (SIR = 2.1, 95% confidence interval (CI) = 1.9–2.1), first-generation antipsychotics (SIR = 2.0, 95% CI = 1.8–2.2), second-generation antipsychotics (SIR = 2.2, 95% CI = 1.9–2.4), prolactin-sparing antipsychotics (SIR = 2.4, 95% CI = 1.8–3.1) and prolactin-elevating antipsychotics (SIR = 2.0, 95% CI = 1.9–2.2).

CONCLUSION: In people aged 60 and older in Norway, those who took an antipsychotic drug had twice the risk of sustaining a hip fracture during exposure than during nonexposure. Although confounding by indication, comorbidity, or other drugs used cannot be excluded, this association is relevant for clinical practice because hip fracture and antipsychotic drug use are prevalent in vulnerable older individuals. Clinical studies examining mechanisms or causality of the observed association between antipsychotic drug use and excess risk of hip fracture are needed. **J Am Geriatr Soc 64:1203–1209, 2016.**

Key words: antipsychotics; hip fractures; aged; pharmacoepidemiology; population registers

Hip fractures are highly prevalent in older people, with implications for morbidity and mortality.[1,2] Numerous factors (e.g., medical conditions, drug use, lifestyle) affect the risk of hip fracture. Most hip fractures result from a combination of low bone mineral density and a fall,[3] and low bone mineral density and falls are both multifactorial in origin. Use of psychotropic drugs (antidepressant, anxiolytic, hypnotic, antipsychotic drugs) is an independent, and potentially modifiable, risk factor for falls in older people.[4] Their effects on bone metabolism differ; whereas antidepressants with serotonergic properties negatively affect bone metabolism,[5–7] there is no evidence that anxiolytics or hypnotics do, and the results are conflicting regarding antipsychotics.[8,9]

Schizophrenia and other psychotic disorders and symptoms are the main indications for treatment with antipsychotic drugs,[10] often involving long-term drug treatment.[11] Off-label prescribing is widespread, especially for behavioral and psychiatric symptoms of dementia in nursing home residents such as agitation and restlessness.[12–14] Treatment effects are limited in these conditions, severe adverse effects are common,[12] and antipsychotic drugs can be withdrawn from most residents without adversely affecting their behavior.[14] Antipsychotics are prescribed to 4% to 10% of community-dwelling people aged 70 and older[15,16] and 20% to 50% of nursing home

From the *Department of Global Public Health and Primary Care, Faculty of Medicine and Dentistry, University of Bergen; †Kavli Research Centre for Geriatrics and Dementia, Haraldsplass Deaconess Hospital; ‡Department of Clinical Science, Faculty of Medicine and Dentistry, University of Bergen; §Section of Clinical Pharmacology, Laboratory of Clinical Biochemistry; ¶Regional Medicines Information and Pharmacovigilance Centre, Haukeland University Hospital, Bergen; **Department of Pharmacoepidemiology, Norwegian Institute of Public Health, Oslo; ††Norwegian Arthroplasty Registry, Department of Orthopaedics and Department of Clinical Medicine, Haukeland University Hospital; and ‡‡Research Unit for General Practice, Uni Research Health, Bergen, Norway.

Address correspondence to Marit S. Bakken, Department of Global Public Health and Primary Care, University of Bergen, PB 7804, N-5018 Bergen, Norway. E-mail: marit.bakken@uib.no

DOI: 10.1111/jgs.14162

0002-8614/16/$15.00

residents worldwide.[17–20] Whereas prescription rates of antipsychotics for community-dwelling people are stable, they are declining in nursing homes; prescription rates in Norway are in the lowest parts of the range.[16,21]

Observational studies have shown associations between antipsychotic drug use and hip fracture; which subgroup is associated with the greatest excess risk is unclear,[8,13,22,23] as are the mechanisms involved.

It is thought that antipsychotic drugs have their antipsychotic effect by occupying dopaminergic receptors in the brain, although a contribution from serotonergic effects cannot be excluded.[24] All antipsychotics have prolactin-elevating potential, primarily associated with dopaminergic D_2 receptor occupancy in the pituitary and the drugs' ability to penetrate the blood–brain barrier.[25] First-generation antipsychotics (FGAs) have high affinity for dopaminergic receptors, whereas dopaminergic affinity varies among second-generation antipsychotics (SGAs). The latter also show variable binding to serotonergic (5-hydroxytryptamine; 5-HT), adrenergic, histaminergic, and muscarinic receptors.[26] Serotonin levels and serotonergic neurotransmission may influence prolactin secretion.[27] Thus, SGAs could be associated with greater prolactin secretion, although antidopaminergic activity varies within this subgroup of antipsychotics.

Antipsychotic drugs probably affect bone tissue indirectly through prolactin-induced hypogonadism. Recent studies suggest that they may also directly affect bone homeostasis.[8,9,27–30] An example is risperidone, which is thought to affect bone formation and resorption through its ability to block 5-HT_{2B} and α1-adrenoceptors.[31]

Aims of the Study

The aim of the study was to examine associations between exposure to various subgroups of antipsychotic drugs and the risk of hip fracture in older people. The subgroups were FGAs or SGAs and prolactin-sparing or prolactin-elevating antipsychotics. If associations were found, the goal was to estimate the attributable risk of hip fracture.

METHODS

This was a nationwide study based on merged data from the Norwegian Prescription Database,[32] the Norwegian Hip Fracture Registry,[33] and the Central Population Registry.[34] The study lasted from January 1, 2005, to December 31, 2010.

Data Sources

The Norwegian Prescription Database, starting from January 2004, contains detailed information on all prescription drugs purchased at all pharmacies in Norway.[32] The data extracted for this study comprise all prescriptions of antipsychotics (Anatomical Therapeutic Chemical (ATC) system code[10] N05A) dispensed from January 2004 (prescriptions dispensed during 2004 necessary to identify current drug users when the study period started) until December 2010 according to each item's generic name, ATC code, and defined daily dose (DDD).[10] The Norwegian Prescription Database lacks individual information on medication dispensed to people staying in the hospital (~12,000 at any time) and in nursing homes (~40,000 at any time).

The Norwegian Hip Fracture Registry, starting from January 2005, contains national data (injury, fracture, surgery) on people who undergo surgery for hip fracture at all 55 hospitals in Norway performing such surgery.[33] For the purpose of this study, the date of first (primary) hip fracture registered for the period January 2005 until December 2010 was extracted. Even though hip fractures occurring during a hospital or nursing home stay are included in the Norwegian Hip Fracture Registry, these groups could not be identified in the dataset.

The Central Population Registry contains demographic information on the entire population of Norway. The data extracted for this study comprise birth year, sex and date of death or emigration if applicable.

The variables selected from these three registries were linked using the unique 11-digit personal identity number assigned after 1960 to everyone living in Norway.

Study Population

The study population included everyone born before 1945 and living in Norway on January 1, 2005. All individuals in this cohort were followed until the day of any first hip fracture, emigration or death, or the end of the study period on December 31, 2010.

Medications Studied

The following medications were included in this study: ATC code N05A, antipsychotics:

N05AA, phenothiazines with aliphatic side-chain (chlorpromazine, levomepromazine)
N05AB, phenothiazines with piperazine structure (dixyrazine, fluphenazine, perphenazine, prochlorperazine, trifluoperazine)
N05AC, phenothiazines with piperidine structure (thioridazine, pipotiazine)
N05AD, butyrophenone derivatives (haloperidol, melperone)
N05AE, indole derivatives (sertindole, ziprasidone)
N05AF, thioxanthene derivatives (flupenthixol, chlorprothixene, zuclopenthixol)
N05AG, diphenylbutylpiperidine derivatives (pimozide, penfluridol)
N05AH, diazepines, oxazepines, thiazepines, oxepines (clozapine, olanzapine, quetiapine)
N05AL, benzamides (sulpiride, tiapride amisulpride)
N05AX, others (risperidone, aripiprazole)

Although lithium is classified as N05A in the ATC system (N05AN01), its main indication as a mood stabilizer differs from that of all other N05A drugs, and it was excluded.[35]

For the purpose of subgroup analysis, the antipsychotic drugs were classified according to generation (first, second)[36] and prolactin effects (high or intermediate risk of increasing prolactin levels (prolactin elevating), low risk of increasing prolactin levels (prolactin sparing).[9,27,36,37] (See Table 1 for details.)

Table 1. Comparison of Number of Hip Fractures During Exposed and Unexposed Person-Time 7 in the Population of Norway Born Before 1945 and Exposed to Any Antipsychotic Drug (Except Lithium) from 2005 to 2010

	1.0 DDD		0.5 DDD		0.25 DDD	
Cohort	n	SIR (95% CI)	n	SIR (95% CI)	n	SIR (95% CI)
Total	387	2.1 (1.9–2.3)	670	2.1 (1.9–2.2)	1,065	2.0 (1.9–2.1)
Female	300	2.1 (1.9–2.3)	512	2.0 (1.8–2.2)	809	1.9 (1.8–2.0)
Male	87	2.2 (1.8–2.7)	158	2.3 (2.0–2.7)	256	2.4 (2.1–2.7)

DDD = defined daily dose; SIR = standardized incidence ratio; CI = confidence interval.

Exposure

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.[10] Prescribed daily dose (PDD) and actual drug consumption vary within a population. The Norwegian Prescription Database does not include information on whether or when purchasers consumed the dispensed drugs. Thus, assumptions had to be made about drug exposure. For any antipsychotics, calculations were performed for 0.25, 0.5, and 1.0 DDDs, respectively. The average DDD is probably closest to 0.25 in this study population.[38,39] Quite similar results were found when calculating standardized incidence ratios (SIRs) for 0.25 and 0.5 DDDs (Table 1); to avoid misclassifying antipsychotic drug nonusers as users, 0.5 was chosen as the best proxy for medication exposure for all subgroup analysis. It was assumed that people started using the drugs on the day they were purchased and that they continued using them on the consecutive days corresponding to the number of 0.5 DDDs prescribed. An individual could possibly switch between exposure and nonexposure one or more times during the 6-year period.

Overall and recently started use of antipsychotic drugs was investigated. Overall use was defined as any exposure to antipsychotics within the study period, including all exposure periods. Recently started use was defined as the first 14 days of exposure to the drug in question after a 360-day washout period.

Statistical Analysis

Incidence of primary hip fracture during the person-days exposed and unexposed to antipsychotics in the study period was compared by calculating the SIR.[40] Standardization was indirect and accounted for sex, birth cohort, and time period (divided into 2-month intervals). The magnitude of two different estimates (e.g., the SIRs for FGAs and SGAs or the SIRs for women and men) cannot be directly compared. A SIR greater than 1 indicates greater risk of hip fracture associated with antipsychotic drug exposure.

For SIR values based on fewer than 100 observed primary hip fractures in exposed people, exact 95% confidence intervals (CI) were calculated assuming a Poisson distribution of the observed number of hip fractures (O) in exposed people, estimating the mean using the expected number of hip fractures in the exposed people. When the observed numbers of hip fractures in exposed people exceeded 100, 95% CIs were approximated using the following formula: (SIR · exp $(-1.96\sqrt{O})$, SIR• exp $(1.96\sqrt{O})$).

To calculate the attributable risk of exposure to antipsychotic drugs on hip fracture, the observed number of fractures minus the expected number of fractures during the number of person-days exposed to antipsychotic drugs was divided by the observed number of fractures in the study population.

Ethics and Approval

The Regional Committee for Medical and Health Research Ethics (138/07) and the Norwegian Data Inspectorate (08/00133) approved the study. The Norwegian Directorate of Health granted an exemption from the duty of confidentiality (08/1843).

RESULTS

The study population comprised 906,422 people with a mean age of 72.8 ± 8.9 on January 1, 2005 (56% women). Mean follow-up was 5.2 ± 1.6 years; 218,775 people died (53% women), and 4,949 emigrated (44% women).

Eight percent of the study population was exposed to an antipsychotic drug during the study period; 66% were women (Table 2). For both sexes, drug use was most prevalent in individuals born from 1920 to 1924 and 1925 to 1929 (data not shown). Of users of antipsychotic drugs, 62% purchased more than one prescription (71% of those who experienced a hip fracture).

During the study period, 39,938 individuals (4.4%) experienced a primary hip fracture; 72% of hip fractures occurred among women. Mean age at the time of fracture was 83.

Most fractures in people exposed to antipsychotics occurred in those born from 1925 to 1934 (39%) and 1915 to 1924 (33%).

Table 1 shows that the associations between overall use of any antipsychotic drug and hip fracture were stable at the population level when SIRs were calculated for the number of days corresponding to 1.0, 0.5, or 0.25 DDDs. In women, the SIRs decreased with increasing estimated time of exposure. The opposite was true in men, but the differences between the sexes were small.

Table 3 compares the incidence of hip fracture during overall exposed person-time (number of days corresponding to the 0.5 DDDs prescribed) with the incidence of hip fracture during overall unexposed person-time. The risk of hip fracture was greater in people exposed to any antipsychotic drug (SIR = 2.1, 95% CI = 1.9–2.1). Generally, the

Table 2. People in Norway Born Before 1945 Exposed to Any Antipsychotic Drug (Except Lithium) from 2005 to 2010 (Exposed Person-Days 0.5 Defined Daily Doses)

	All	First Generation[a]	Second Generation[b]	Prolactin Elevating[c]	Prolactin Sparing[d]
Cohort			n (%)		
Total (n = 906,422)	72,580 (8.0)	63,990 (7.1)	13,786 (1.5)	70,504 (7.8)	3,874 (0.4)
Women (n = 506,568)	47,934 (9.5)	42,433 (8.4)	8,875 (1.8)	46,756 (9.2)	2,330 (0.5)
Men (n = 399,854)	24,646 (6.2)	21,557 (5.4)	4,911 (1.2)	23,748 (5.9)	1,544 (0.4)

Individuals may have received more than one antipsychotic drug.

[a]Chlorpromazine, levomepromazine, dixyrazine, fluphenazine, perphenazine, prochlorperazine, trifluoperazine, thioridazine, pipotiazine, haloperidol, melperone, flupenthixol, chlorprothixene, zuclopenthixol, pimozide, penfluridol, tiapride.

[b]Sertindole, ziprasidone, clozapine, olanzapine, quetiapine, sulpiride, amisulpride, risperidone, aripiprazole.

[c]Chlorpromazine, levomepromazine, perphenazine, prochlorperazine, haloperidol, ziprasidone, flupenthixol, chlorprothixene, zuclopenthixol, olanzapine, sulpiride, amisulpride, risperidone.

[d]Clozapine, quetiapine, aripiprazole.

Table 3. Comparison of Number of Hip Fractures During Exposed and Unexposed Person-Time in the Population of Norway Born Before 1945 and Exposed to Various Antipsychotic Drug Subgroups from 2005 to 2010 (Exposed Person-Days 0.5 Defined Daily Doses)

	Any		First Generation[a]		Second Generation[b]		Prolactin Elevating[c]		Prolactin Sparing[d]	
Cohort	n	SIR (95% CI)	n	SIR (95% CI)	n	SIR (95% CI)	n	SIR (95% CI)	n	SIR (95% CI)
Total	670	2.1 (1.9–2.2)	386	2.0 (1.8–2.2)	308	2.2 (1.9–2.4)	606	2.0 (1.9–2.2)	58	2.4 (1.8–3.1)
Women	512	2.0 (1.8–2.2)	295	2.0 (1.7–2.2)	233	2.1 (1.8–2.3)	462	2.0 (1.8–2.1)	46	2.4 (1.8–3.3)
Men	158	2.3 (2.0–2.7)	91	2.2 (1.8–2.8)	75	2.6 (2.0–3.2)	144	2.3 (2.0–2.7)	12	2.4 (1.2–4.1)
Birth cohort										
1935–1944	174	3.3 (2.8–3.8)	108	3.4 (2.8–4.1)	81	3.2 (2.6–4.0)	153	3.2 (2.7–3.7)	17	3.4 (2.0–5.4)
1925–1934	262	2.1 (1.9–2.4)	134	1.8 (1.5–2.2)	135	2.4 (2.1–2.9)	238	2.1 (1.8–2.4)	24	2.6 (1.6–3.8)
1915–1924	220	1.6 (1.4–1.9)	137	1.7 (1.5–2.0)	85	1.5 (1.2–1.9)	202	1.6 (1.4–1.9)	16	1.8 (1.0–3.0)
1915	14	1.2 (0.6–1.9)	7	1.0 (0.4–2.0)	7	1.4 (0.6–2.9)	13	1.4 (0.2–5.1)	1	1.6 (0.0–8.7)
Attributable risk		0.9%		0.5%		0.3%		0.8%		0.1%

Any antipsychotic drug (Anatomical Therapeutic Chemical code N05A) except lithium.

Individuals may have purchased first- and second-generation antipsychotics, so combined n was higher than for any antipsychotic drug.

Prolactin-elevating and -sparing antipsychotics were selected antipsychotics, so combined n was lower than for any antipsychotic drug

[a]Chlorpromazine, levomepromazine, dixyrazine, fluphenazine, perphenazine, prochlorperazine, trifluoperazine, thioridazine, pipotiazine, haloperidol, melperone, flupenthixol, chlorprothixene, zuclopenthixol, pimozide, penfluridol, tiapride.

[b]Sertindole, ziprasidone, clozapine, olanzapine, quetiapine, sulpiride, amisulpride, risperidone, aripiprazole.

[c]Chlorpromazine, levomepromazine, perphenazine, prochlorperazine, haloperidol, ziprasidone, flupenthixol, chlorprothixene, zuclopenthixol, olanzapine, sulpiride, amisulpride, risperidone.

[d]Clozapine, quetiapine, aripiprazole.

SIR = standardized incidence ratio; CI = confidence interval.

observed excess risk was higher in exposed men (SIR = 2.3, 95% CI = 2.0–2.7) than in exposed women (SIR = 2.0, 95% CI = 1.8–2.2). The risk decreased with increasing age. There were too few hip fractures in people born before 1915 to yield representative results.

Subgroups of Antipsychotics

Greater risk of hip fracture was associated with exposure to any antipsychotic (SIR = 2.1, 95% confidence interval (CI) = 1.9–2.1), first-generation antipsychotics (SIR = 2.0, 95% CI = 1.8–2.2), second-generation antipsychotics (SIR = 2.2, 95% CI = 1.9–2.4), prolactin-sparing antipsychotics (clozapine, quetiapine, aripiprazole) (SIR = 2.4, 95% CI = 1.8–3.1) and prolactin-elevating antipsychotics (e.g., chlorpromazine, haloperidol, olanzapine, risperidone) (SIR = 2.0, 95% CI = 1.9–2.2). The percentage of hip fractures attributable to exposure to any antipsychotic drug at the population level was an estimated 0.9% (Table 3).

Recently Started Drug Use

Subanalysis for recently started antipsychotic drug use revealed that 48 individuals fractured their hips during the first 14 days of exposure to any antipsychotic drug after a 360-day washout period (whole population: SIR = 1.8, 95% CI = 1.3–2.4; women: SIR = 1.7, 95% CI = 1.2–2.3; men: SIR = 2.2, 95% CI = 1.2–3.8). Within all subgroups, except for antipsychotics with low risk of increasing prolactin levels (n = 4 with nonsignificant results), the excess risk of hip fracture was higher in exposed men than in exposed women (not shown).

DISCUSSION

Older people in Norway had a twice the risk of sustaining a hip fracture during antipsychotic drug exposure than during nonexposure. Previous case–control studies showed similar associations between antipsychotic drug use and risk of hip fracture based on data from 1987 to 2002 (primarily including FGAs)[23,41,42] and 2005 to 2008 (including FGAs and SGAs).[13] After adjusting for possible confounders such as psychiatric diagnoses[41] and concomitant drug use,[13] an association between antipsychotic agents and higher risk of hip fracture was still evident.

FGAs and SGAs

Although SGAs have fewer adverse side effects than FGAs in terms of sedation and parkinsonism, these drugs are associated with greater risks of cerebrovascular and cardiovascular events and mortality;[14] in the last decade, associations have also been found with hip fractures.[13,42,43] The current results suggest that SGAs are not necessarily safer than FGAs with regard to hip fracture. In a large self-controlled case series[13] that included 8,234 individuals with hip fracture, greater risk of hospitalization for hip fracture was identified with short- and long-term (>12 weeks) use of FGAs and SGAs. The risk associated with SGAs was highest during the first week after initiation and declined with prolonged use (albeit still significantly elevated), whereas the risk associated with FGAs persisted at the same level.[13] Firm conclusions about whether FGAs or SGAs affect the risk of hip fracture more cannot yet be drawn; randomized controlled trials are lacking, and previous observational studies generally included few SGA users.[23,41–43]

Potential Effects on Bone Tissue

Antipsychotic drug use is an established risk factor for falls. Furthermore, all antipsychotics have some prolactin-elevating potential, which may affect bone metabolism. Hyperprolactinemia is a commonly reported adverse side effect, and it has been proposed that prolactin-sparing antipsychotics should be preferred for people at high risk of sustaining a hip fracture.[44] In support of this suggestion, the incidence of hip fracture was three times as great in individuals treated with antipsychotics and experiencing high prolactin levels.[43] The current study showed twice the risk of hip fracture associated with using antipsychotics with high or intermediate risk of increasing prolactin levels but an even higher excess risk associated with using antipsychotics with a low risk of increasing prolactin levels. These results suggest that other qualities of the drugs could be important. It has been suggested that blockade of 5-HT_{2B} and α1-adrenoceptors may affect osteoblast proliferation and differentiation when using the SGA risperidone,[31] and recent preclinical studies have shown direct serotonergic effects on bone homeostasis.[28–30] To the knowledge of the authors of the current study, no clinical studies have investigated the associations between serotonergic and adrenergic effects on bone tissue of antipsychotics and risk of hip fracture.

Complex effects on transmitters and respective receptors, including dopamine, serotonin, and adrenergic pathways; indirect effects through prolactin and sex hormones; and metabolic (fat and sugar metabolism), sedative, and cardiovascular side effects (e.g., postural hypotension and arrhythmias) of the various antipsychotics probably influence the risk of hip fracture. A clear dose–response relationship is lacking for many proposed mechanisms of action of antipsychotic drugs on bone metabolism, and even prolactin-elevating effects are not always dose dependent.[27] Thus, a complex interplay between direct and indirect effects of the drugs may affect the risk of falls and hip fracture. The design of the current study does not allow for conclusions to be reached on mechanisms (changes in bone, bone mineral density, falls, or other factors) or causality (the use of antipsychotic drugs or their indication (psychosis)).

Age and Sex

Generally, the excess risk of hip fracture during antipsychotic drug exposure was most prominent in the youngest birth cohorts. Prescriptions for nursing homes residents are not included in the Norwegian Prescription Database, leading to systematic misclassification of approximately 40,000 people at any time as drug nonusers. Thus, the estimated associations between antipsychotic drug use and hip fractures in the oldest birth cohorts are probably conservative. Exposure to antipsychotic drugs was associated with a higher excess risk of hip fracture in men than in women. Because clinical information was lacking, it is not known whether antipsychotic drug use affecting, for example, fall risk and bone metabolism differently in men than in women or if confounders are differently distributed in men and women caused this difference. Thus, these results should be interpreted with caution. Nevertheless, a previous study that adjusted for comorbidities identified similar trends.[42]

Recently Started Drug Use

The risk of hip fracture was higher in drug users who had started recently. Other studies[13,23] have found that antipsychotic drug initiation is associated with greater risk of fracture, but the mechanisms involved are unknown. Orthostatic hypotension is the most frequent vascular side effect of antipsychotic drugs, affecting approximately 40% of users.[45] This could be a problem in older adults at high risk of falling. Orthostatic hypotension is a particular concern during the early stages of antipsychotic treatment, and the development of tachyphylaxis, a sudden decrease in drug response, reduces the risk. Orthostatic hypotension is associated with the blockade of peripheral α1-adrenoceptors.[46]

The current results suggest that men who have recently initiated an antipsychotic drug are at higher risk than women who are new users, but the numbers are small and should be interpreted with caution.

Methodological Considerations

The national health registries provided a unique opportunity to link complete data on antipsychotic drugs purchased by a nationwide unselected community-dwelling

older population with all primary hip fractures registered in Norway. The 6-year follow-up period revealed large numbers of cases, and the design prevented selection and information bias. The conservative definition of exposed person-days, not allowing for nonadherence (treatment gaps), yielded conservative risk estimates.

The sparse amount of clinical information available is the most important limitation of the study. SIRs were adjusted for major confounders (age and sex), but confounding by indication, by participant clinical characteristics, and by other medication use cannot be excluded. The health registries in Norway include neither complete and validated diagnostic information nor data on falls, bone mineral density, body mass index, or lifestyle factors such as alcohol and smoking. Thus, it is unknown whether people purchasing prescriptions for antipsychotics were actually diagnosed with psychosis or not. Low-dosage antipsychotics are also prescribed for behavioral and psychiatric symptoms in people with dementia and for pain.[14] Confounding by indication may affect the results, because psychoses, other clinical conditions, and antipsychotic drug use itself may increase the risk of falls and fractures through altered activity level, psychomotor function, and bone mineral density. In a large case–control study in the United Kingdom,[41] the positive associations between antipsychotic drug use and risk of hip fractures remained when adjusting for mental disorders, lifestyle factors, and concomitant drug use—indicating that the antipsychotic drug use itself affects fracture risk.

It is unknown whether purchased antipsychotic drugs were actually consumed, but the large proportion redeeming more than one prescription supports assumed adherence. Widespread nonadherence (misclassification of nonexposed person-time as exposed person time) would possibly have led to overestimation of the association between antipsychotics and hip fracture. Several strategies (strict definition of exposure and time-varying exposure) were applied to minimize, but could not exclude, misclassification. Information on other medication use is available from the Norwegian Prescription Database, but with the time-varying exposure used in the analysis, matching exposure periods for other medications was not possible. The time-varying exposure is a major strength of the study, because fixed exposure would have led to extensive and unmeasurable misclassification, yielding unreliable results.

The Norwegian Hip Fracture Registry includes 90% of all hip fracture operations in Norway,[33] with somewhat lower completeness during the first 3 years. It was assumed that underreporting was not systematically biased because of individual factors related to exposure (antipsychotic drug use) or outcome (hip fracture), which could have affected the results of the study.

Organizational factors in the healthcare system (mainly public in Norway), substance availability, treatment traditions, and prescribing patterns must be considered in transferring these results to other countries.

In conclusion, the results of this study support the hypothesis that antipsychotics are a risk factor for hip fracture. No evidence was found that SGAs and prolactin-sparing antipsychotics were safer than FGAs and prolactin-elevating antipsychotics with regard to hip fracture. This large registry-based study with limited clinical information does not allow for conclusions on mechanisms (effect on bone quality or falling) or causality of the observed association between antipsychotic drug use and hip fracture, and confounding by indication, comorbidity, other drugs used, lifestyle factors, or a combination of these cannot be excluded. Thus, clinical studies are needed to further explore these questions, although the observed association between antipsychotic drug use and hip fracture is relevant for clinical practice because both factors are prevalent in vulnerable older individuals.

ACKNOWLEDGMENTS

David Breuer edited the manuscript for English language.

The Western Norway Regional Health Authority provided a PhD grant for Marit Stordal Bakken.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Author Contributions: Ruths, Engesæter, Engeland, Schjøtt, Bakken: study concept and design. Engeland, Engesæter, Ruths: acquisition of data. Bakken, Engeland, Ruths, Schjøtt, Engesæter: analysis and interpretation of data. Bakken: drafting the manuscript. Ruths, Schjøtt, Engeland, Engesæter: critically revision of manuscript for important intellectual content. Engeland, Bakken: statistical analysis. Anders Engeland had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Ruths: study supervision.

Sponsor's Role: None.

REFERENCES

1. Leibson CL, Tosteson AN, Gabriel SE et al. Mortality, disability, and nursing home use for persons with and without hip fracture: A population-based study. J Am Geriatr Soc 2002;50:1644–1650.
2. Frihagen F, Waaler GM, Madsen JE et al. The cost of hemiarthroplasty compared to that of internal fixation for femoral neck fractures. 2-year results involving 222 patients based on a randomized controlled trial. Acta Orthop 2010;81:446–452.
3. Cumming RG, Nevitt MC, Cummings SR. Epidemiology of hip fractures. Epidemiol Rev 1997;19:244–257.
4. 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;47:30–39.
5. Bolton JM, Targownik LE, Leung S et al. Risk of low bone mineral density associated with psychotropic medications and mental disorders in postmenopausal women. J Clin Psychopharmacol 2011;31:56–60.
6. Bliziotes M. Update in serotonin and bone. J Clin Endocrinol Metab 2010;95:4124–4132.
7. Tsapakis EM, Gamie Z, Tran GT et al. The adverse skeletal effects of selective serotonin reuptake inhibitors. Eur Psychiatry 2011;27:159–169.
8. Brown MJ, Mezuk B. Brains, bones, and aging: psychotropic medications and bone health among older adults. Curr Osteoporos Rep 2012;10:303–311.
9. Graham SM, Howgate D, Anderson W et al. Risk of osteoporosis and fracture incidence in patients on antipsychotic medication. Expert Opin Drug Saf 2011;10:575–602.
10. World Health Organization Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index [on-line]. Available at http://www.whocc.no/atc_ddd_index/ Accessed June 16, 2014.
11. Harrow M, Jobe TH. Does long-term treatment of schizophrenia with antipsychotic medications facilitate recovery? Schizophr Bull 2013;39:962–965.

12. Maher AR, Maglione M, Bagley S et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: A systematic review and meta-analysis. JAMA 2011;306:1359–1369.
13. Pratt N, Roughead EE, Ramsay E et al. Risk of hospitalization for hip fracture and pneumonia associated with antipsychotic prescribing in the elderly: A self-controlled case-series analysis in an Australian health care claims database. Drug Saf 2011;34:567–575.
14. Declercq T, Petrovic M, Azermai M et al. Withdrawal versus continuation of chronic antipsychotic drugs for behavioural and psychological symptoms in older people with dementia. Cochrane Database Syst Rev 2013;3:CD007726.
15. Desplenter F, Caenen C, Meelberghs J et al. Change in psychotropic drug use among community-dwelling people aged 75 years and older in Finland: repeated cross-sectional population studies. Int Psychogeriatr 2011;23:1278–1284.
16. Norwegian Institute of Public Health. The Norwegian Prescription Database 2009–2013 (Legemiddelstatstikk 2014:2; Reseptregisteret 2009–2013). Oslo, Norway: Norwegian Institute of Public Health, 2014.
17. Jung HY, Meucci M, Unruh MA et al. Antipsychotic use in nursing home residents admitted with hip fracture. J Am Geriatr Soc 2013;61:101–106.
18. dervan PuttenMJ, Wetzels RB, Bor H et al. Antipsychotic drug prescription rates among Dutch nursing homes: The influence of patient characteristics and the dementia special care unit. Aging Ment Health 2014;18:828–832.
19. Vu M, Hogan DB, Patten SB et al. A comprehensive profile of the sociodemographic, psychosocial and health characteristics of Ontario home care clients with dementia. Chronic Dis In Can 2014;34:132–144.
20. Nurminen J, Puustinen J, Kukola M et al. The use of chemical restraints for older long-term hospital patients: A case report from Finland. J Elder Abuse Negl 2009;21:89–104.
21. Ruths S, Sorensen PH, Kirkevold O et al. Trends in psychotropic drug prescribing in Norwegian nursing homes from 1997 to 2009: A comparison of six cohorts. Int J Geriatr Psychiatry 2013;28:868–876.
22. Pratt N, Roughead EE, Salter A et al. Choice of observational study design impacts on measurement of antipsychotic risks in the elderly: A systematic review. BMC Med Res Meth 2012;12:72.
23. Rigler SK, Shireman TI, Cook-Wiens GJ et al. Fracture risk in nursing home residents initiating antipsychotic medications. J Am Geriatr Soc 2013;61:715–722.
24. Stone JM, Davis JM, Leucht S et al. Cortical dopamine D2/D3 receptors are a common site of action for antipsychotic drugs-an original patient data meta-analysis of the SPECT and PET in vivo receptor imaging literature. Schizophr Bull 2009;35:789–797.
25. Arakawa R, Okumura M, Ito H et al. Positron emission tomography measurement of dopamine D(2) receptor occupancy in the pituitary and cerebral cortex: Relation to antipsychotic-induced hyperprolactinemia. J Clin Psychiatry 2010;71:1131–1137.
26. Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: Insights from receptor-binding profiles. Mol Psychiatry 2008;13:27–35.
27. Peuskens J, Pani L, Detraux J et al. The effects of novel and newly approved antipsychotics on serum prolactin levels: A comprehensive review. CNS Drugs 2014;28:605–624.
28. Collet C, Schiltz C, Geoffroy V et al. The serotonin 5-HT2B receptor controls bone mass via osteoblast recruitment and proliferation. FASEB J 2008;22:418–427.
29. Li X, Ma Y, Wu X et al. Serotonin acts as a novel regulator of interleukin-6 secretion in osteocytes through the activation of the 5-HT(2B) receptor and the ERK1/2 signalling pathway. Biochem Biophys Res Commun 2013;441:809–814.
30. Chabbi-Achengli Y, Launay JM, Maroteaux L et al. Serotonin 2B receptor (5-HT2B R) signals through prostacyclin and PPAR-ss/delta in osteoblasts. PLoS ONE 2013;8:e75783.
31. Calarge CA, Ivins SD, Motyl KJ et al. Possible mechanisms for the skeletal effects of antipsychotics in children and adolescents. Adv Psychopharmacol 2013;3:278–293.
32. Furu K. Establishment of the nationwide Norwegian Prescription Database. Nor J Epidemiol 2008;18:129–136.
33. Gjertsen JE, Engesaeter LB, Furnes O et al. The Norwegian Hip Fracture Register: Experiences after the first 2 years and 15,576 reported operations. Acta Orthop 2008;79:583–593.
34. The Norwegian Central Population Register [on-line]. Available at http://www.folkeregistret.no/ Accessed July 11, 2015.
35. Kjosavik SR, Hunskaar S, Aarsland D et al. Initial prescription of antipsychotics and antidepressants in general practice and specialist care in Norway. Acta Psychiatr Scand 2011;123:459–465.
36. Besnard I, Auclair V, Callery G et al. Antipsychotic-drug-induced hyperprolactinemia: Physiopathology, clinical features and guidance. Encephale 2014;40:86–94.
37. Bushe C, Shaw M, Peveler RC. A review of the association between antipsychotic use and hyperprolactinaemia. J Psychopharmacol 2008;22(2 Suppl):46–55.
38. Lesen E, Petzold M, Andersson K et al. To what extent does the indicator "concurrent use of three or more psychotropic drugs" capture use of potentially inappropriate psychotropics among the elderly? Eur J Clin Pharmacol 2009;65:635–642.
39. Rikala M, Hartikainen S, Sulkava R et al. Validity of the Finnish Prescription Register for measuring psychotropic drug exposures among elderly Finns: A population-based intervention study. Drugs Aging 2010;27:337–349.
40. Engeland A, Skurtveit S, Morland J. Risk of road traffic accidents associated with the prescription of drugs: A registry-based cohort study. Ann Epidemiol 2007;17:597–602.
41. Hugenholtz GW, Heerdink ER, van Staa TP et al. Risk of hip/femur fractures in patients using antipsychotics. Bone 2005;37:864–870.
42. Pouwels S, van Staa TP, Egberts AC et al. Antipsychotic use and the risk of hip/femur fracture: A population-based case-control study. Osteoporos Int 2009;20:1499–1506.
43. Howard L, Kirkwood G, Leese M. Risk of hip fracture in patients with a history of schizophrenia. Br J Psychiatry 2007;190:129–134.
44. Montejo AL. Prolactin awareness: An essential consideration for physical health in schizophrenia. Eur Neuropsychopharmacol 2008;18(Suppl 2):S108–S114.
45. Mackin P. Cardiac side effects of psychiatric drugs. Hum Psychopharmacol 2008;23(Suppl 1):3–14.
46. Leung JY, Barr AM, Procyshyn RM et al. Cardiovascular side-effects of antipsychotic drugs: The role of the autonomic nervous system. Pharmacol Ther 2012;135:113–122.