Population-based studies on risk of fracture in patients with neurological disorders

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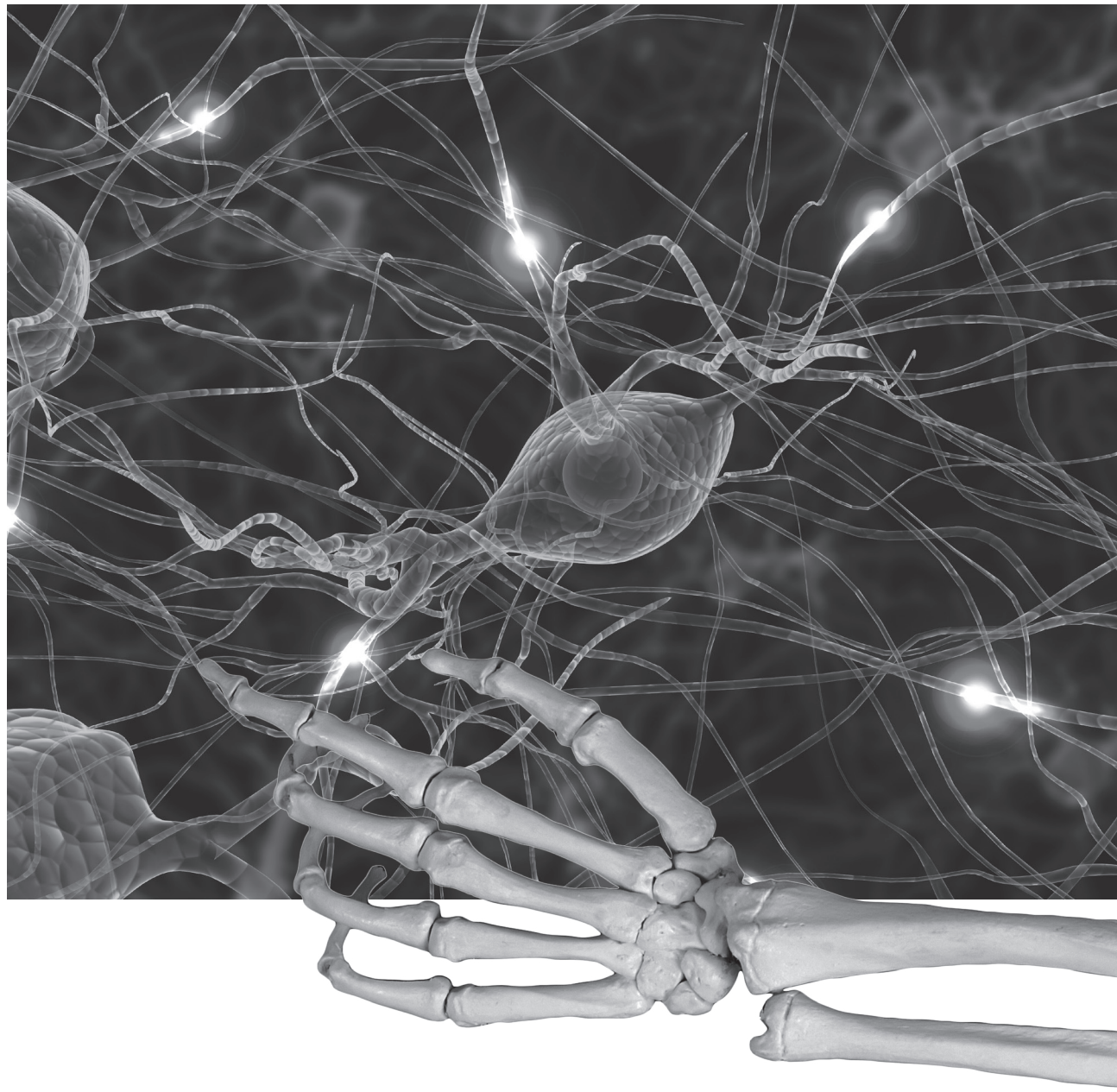
Life is not merely to be alive, but to be well
Marcus Valerius Martial (Roman Empire 40 - 104 AD)



Abbreviations

5-HT	5-hydroxytryptamine
5-HTT	5-hydroxytryptamine transporter
AHR	Adjusted Hazard Ratio
AOR	Adjusted Odds Ratio
BMD	Bone mineral density
CI	Confidence Interval
CMT	Charcot-Marie-Tooth disease
CPRD	Clinical Practice Research Datalink (formerly named GPRD)
GBS	Guillain-Barré Syndrome
GC	Glucocorticosteroid
GPRD	General Practice Research Database
H2RA	Histamine H_2-receptor antagonist
ICD	International Classification of Diseases
MD	Muscular dystropy
MG	Myasthenia Gravis
MS	Multiple sclerosis
PD	Parkinson's disease
PPI	Proton pump inhibitor
RLS	Record Linkage System
SSRI	Selective serotonin reuptake-inhibitor
TCA	Tricyclic antidepressants
WHO	World Health Organization

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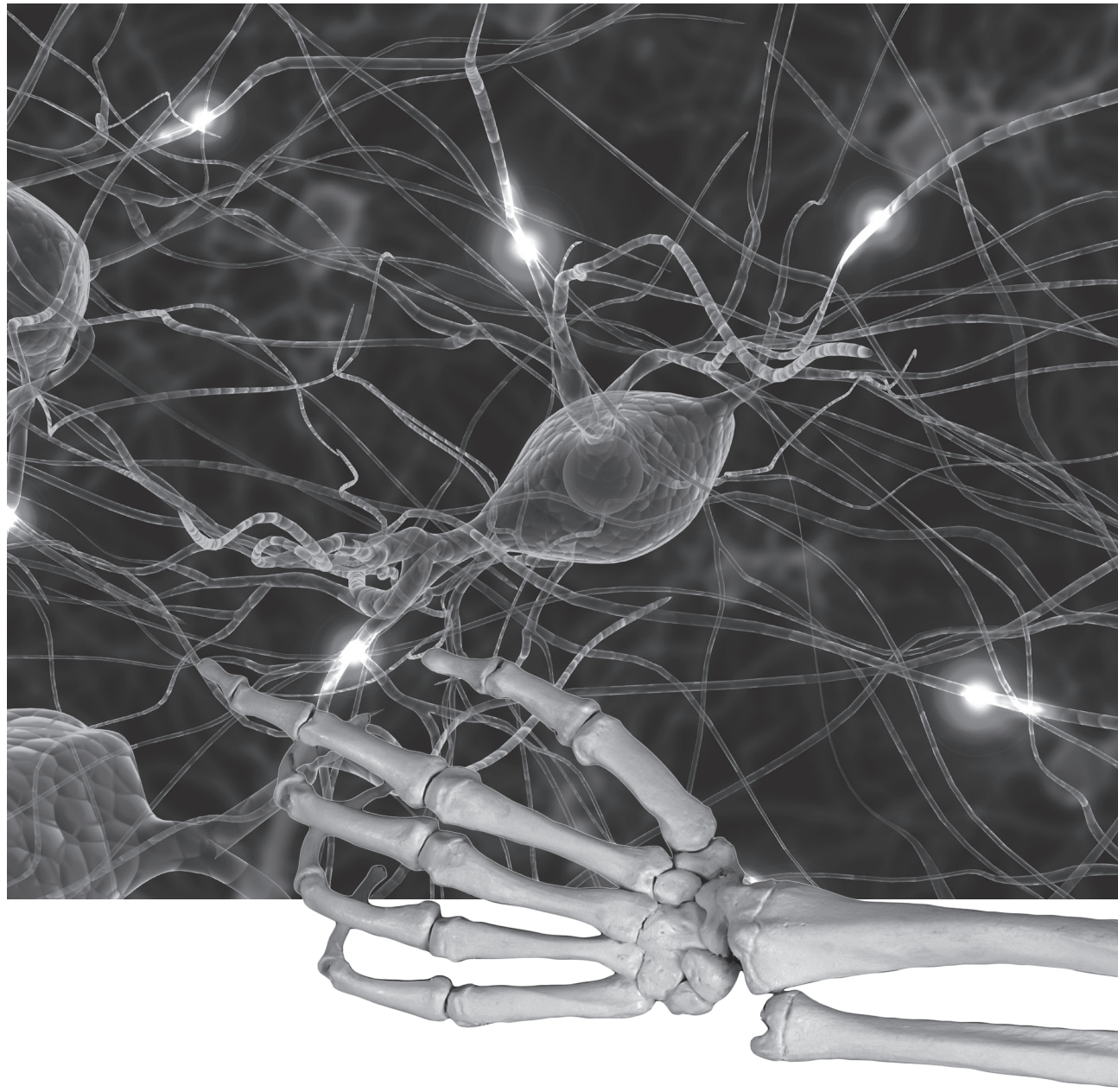
Chapter 1

Introduction



Burden of neurological disorders and fractures

Neurological disorders contributed 6.3% to the global burden of disease and contributed to 11.7% of all deaths in 2005, according to the World Health Organization (WHO) [1]. There is a large heterogeneity between different types of neurological disorders, but they can roughly be divided into central neurological disorders, like stroke and Parkinson's disease (PD) and other (peripheral) neurological disorders, like myasthenia gravis (MG) and muscular dystrophy (MD). Furthermore, 2.7 million incident osteoporotic fractures occurred in 2006 in Europe [2]. In the United Kingdom, over 300.000 patients are admitted to the hospital with fragility fractures each year [3]. Of all osteoporotic fractures, hip fractures usually have the largest impact on someone's life. About 20-24% patients die in the year after a hip fracture and 33% become totally dependent or need residential care [4,5]. Additionally, the direct costs from osteoporotic fractures were estimated at 38.7 billion in 2010 for Europe alone [2].

Patients with neurological disorders may be at an increased risk of fracture because they possess many risk factors for fractures. The disease, the comorbidities and concomitant treatment may increase the risk for fractures, like the use of glucocorticoids (GCs), psychotropic drugs (eg. antidepressants and antipsychotics) and proton pump inhibitors (PPIs) [6-10]. Thus, it may be necessary to determine which patient characteristics are associated with an increased fracture risk in order to improve a neurological patient's quality of life and to reduce fracture-related costs. Moreover, to prevent future fractures it may also be important to understand the mechanisms through which associated treatment of patients with neurological disorders, like GCs, antidepressants, antipsychotics and PPIs increases the risk of fracture (eg. through a fall-related effect, or via bone fragility).

Falls and bone fragility

A risk factor for fracture may increase the risk of fracture via an increased risk of falls and/or via an increased bone fragility [11-13]. Falls associated with fractures are multi-factorial in origin. There are the traditional risk factors for increasing the risk of falls (such as age-associated changes in strength and balance, visual impairment, dementia, psychotropic medications and footwear), changing the nature of the fall descent (such as taller height), impact of the fall (such as falling on the stairs) and bone strength [14].

The association between bone strength and an increased risk of fracture may need some further explanation. Reduced bone mineral density and the microarchitecture of the bone are two main components, which determine bone strength [15]. Cellular mechanisms are responsible for the adaptation of bone during life to maintain bone strength. This is a continuous process of modeling (construction) by osteoblasts and remodeling (reconstruction) by osteoclasts [16]. A full cycle of remodeling may take up to 4 months. Resorption probably continues for about 2 weeks, while formation can continue for 4 months until the new bone structural unit is completely created [17]. Additionally, micro-damage repair is carried out by new bone multicellular units and requires the participation of osteocytes, which are the resident cells of bone derived from osteoblasts during the process of bone formation [12]. This process may be affected by multiple factors. Firstly, bone mineral density may be reduced by increased remodeling of bone and may ultimately lead to osteoporosis [16]. Secondly, bone microarchitecture may be altered, for example as a consequence of a decreased density of osteocytes [12]. Both osteoporosis and reduced quality of bone microarchitecture have been associated with an increased risk of fracture [12,13].

The association of risk factors for fracture, falls and changes in bone mineral density and bone strength in patients with neurological disorders will be discussed in detail in the next paragraphs.

General risk factors for fractures

General risk factors for fracture include age, gender, smoking, use of glucocorticoids (GCs), alcohol use, low body mass index, rheumatoid arthritis, reduced bone mineral density, history of previous fractures, having a parent who fractured a hip and secondary osteoporosis (for example chronic malnutrition) (Table 1) [18]. These risk factors have been adopted in a general clinical risk score for fracture risk prediction named FRAX, which calculates a patient's long-term fracture probability [18].

Table 1: General risk factors for fractures used in FRAX [18]

Age
Gender
Smoking
Use of glucocorticoids
Alcohol use
Low body mass index
Rheumatoid arthritis
Reduced bone mineral density
History of previous fractures
Having a parent who fractured a hip
Secondary osteoporosis

The association of some of these risk factors with falling and/or bone fragility needs further attention. With increasing age, bone remodeling is faster than bone modeling and elderly are more likely to fall due to decreased muscle strength, balance and gait [16,19,20]. Postmenopausal woman have reduced amounts of estrogen, which increases the risk of osteoporosis in this patient group [21]. Cigarettes have direct toxic effects on osteoblasts/osteoclasts activity, and indirectly increase bone fragility via an increase in cortisol levels and a decrease in vitamin D levels with a subsequent decrease in calcium absorption. This results in a 5-10% reduction of bone mineral density in post-menopausal women as compared with non-smokers [22]. Increased cortisol levels inhibit bone formation and increase bone resorption. Moreover, it alters secretion of gonadotropin and growth hormones, cytokines and growth factors influencing bone. This results in reduced bone mineral density and reduced

quality of bone microarchitecture. This is also the case in patients treated with GCs and patients with Cushing's syndrome. About 30-67% of the patients with Cushing's syndrome develop a fracture [23]. Additionally, lower vitamin D levels decrease bone formation, because vitamin D enhances maturation of osteoblasts. Moreover, vitamin D together with calcium and phosphate help to mineralize the matrix secreted by the osteoblasts [24]. Alcohol consumption has been associated with 6% to 24% of the reported falls with fracture in elderly. Moreover, alcohol has been associated with direct negative effects on bone, but also increases the risk for bone fragility through concomitant reduction in body mass index, poor nutrition and reduced vitamin D levels [25,26]. Rheumatoid arthritis (RA) is a systemic inflammatory disease, which may cause local joint deformations and osteoporosis. Moreover, RA is often treated with GCs and is associated with immobility [27]. Reduced bone mineral density has been observed in patients subject to immobility, inactivity or bed-rest, especially in the load-bearing regions like legs, hip and pelvis [28]. This is regulated by osteocytes, which increase the amount of sclerostin and subsequently increase the amounts of urinary calcium and bone resorption markers present in serum [29].

Specific risk factors for fracture in patients with neurological disorders

Beside the general risk factors for fracture, some more specific risk factors have been observed among patients with neurological disorders (Table 2). These risk factors can again be divided into fall-related and bone fragility related risk factors.

Table 2: Specific risk factors for fractures in patients with neurological disorders

Impaired vision
Neurogenic osteoporosis
Low vitamin D levels
Immobility
High homocysteine levels
Psychiatric comorbidities (eg. depression, schizophrenia, anxiety)
Psychotropic drug use (antidepressants, antipsychotics, anxiolytics/hypnotics, anticonvulsants)

Patients with neurological disorders have an increased risk of falls. Gait disturbances and muscle weakness increase the risk of falls and are common among patients with PD, MG, MD, Charcot-Marie-Tooth disease (CMT), Guillain-Barré Syndrome (GBS) and after stroke [30-35]. Additionally, impaired vision is common as a result of a stroke or as a result of ocular MG, which further increases the risk for falls and subsequent fractures [20,34,36]. In MG antibodies reduce the number of acetylcholine receptors at the post-synaptic region of the neuromuscular junction [37]. Especially ocular muscles are susceptible, because they have a relative low number of acetylcholine receptors and have smaller motor units [38].

On the other hand, patients with neurological disorders have an increased risk of bone fragility. Reduced bone mineral density has been observed in patients who suffered a stroke [39], multiple sclerosis (MS) [40] and PD [41]. This can be explained via different mechanisms. One possible explanation is the presence of neurogenic osteoporosis [42]. It is suggested that neurogenic osteoporosis is a condition in which increased activity of the sympathic nervous system contributes to bone loss [42]. The neural connection between brain and bone is regulated centrally by several neurotransmitters, including serotonin, acetylcholine, norepinephrine and leptin. It has been suggested that interference in this regulation by for example an increased activity of the symphatic nervous system in stroke and depression may contribute to bone loss [42]. For example, noradrenergic activation of the beta-2 receptor leads to production of RANK ligand by osteoblasts. RANK ligand stimulates the formation of osteoclasts, which leads to a decrease of bone mineral density (BMD) [43]. Consequently, administration of beta-2 agonists in rats decreased BMD and strength, whereas administration of a beta-blocker had opposite effects [44,45]. Moreover, an 1.5-fold increased risk of hip/femur fracture was observed in patients using high doses (>1600 µg albuterol equivalents per day) of inhaled beta-2 agonists as compared with population-based control patients [46]. A similar mechanism may play a role in other neurological disorders. Other explanations for bone

fragility in patients with neurological disorders are the presence of low vitamin D levels, which have been observed in PD [41], stroke [47] and MS [48]. Immobility is common for patients shortly after onset of GBS and after stroke [49,50] and patients with other neurological disorders may also become immobile in their latest phase of the disorder [51]. When bedridden, bone mineral density decreases and bone structures change, which may result in bone fragility [28,52]. The risk of fracture has been found to higher in disabled MS patients compared with MS patients with a low disability score [53]. Furthermore, high levels of homocysteine have been observed in ischemic stroke patients [54]. Homocysteine may interfere with bone collagen cross-links, thereby increasing bone fragility [55]. Lastly, deformations of hand and feet in CMT patients are a direct result of their disease, which results in osteoporosis at these specific sites [56].

Fracture risk has been previously determined in patients after stroke, in PD and in some forms of MD compared with control patients. To provide a quick overview, the results of several, but not all, observational studies that studied fracture risk in patients with neurological disorders, are presented in Table 3.

Stroke has been associated with a 1.5- to 4-times higher risk of hip fractures [57,58]. However, information about the time course of increased risk of hip/femur fracture during the first year after stroke is scarce. Most studies that investigated fracture risk in relation to time after stroke adjusted for a limited number of confounders (age and sex) and did not distinguish between hemorrhagic and ischemic stroke. PD has been associated with a 2.4-fold increased risk in non-spine fractures in men and 2.6-fold increased risk of hip-fractures in women [59,60], although fracture risk has only been determined in small numbers of PD patients. Additionally, fracture risk has been determined in large patient groups treated with antiparkinson medication, but these cohorts were diluted with patients treated for restless legs syndrome [61,62]. Lastly, fracture risk was increased in patients with Duchenne MD and

Table 3: Risk of fracture with stroke, Parkinson's disease and muscular dystrophy

Type of neurological disorder	Setting	Mean age (years)	Fracture type	Fractures in exposure group (n)	Fracture risk compared with control patients without disease
Stroke					
Dennis [57]	Hospital, UK	73	Hip	26	RR 1.4 (95% CI, 0.9 – 2.1)
Ramnemark [58]	Hospital, Sweden	76	Hip	70	RR 2.1 – 3.8[a]
Parkinson's disease					
Schneider [59]	Community, US	78	Hip	11	HR 2.6 (95% CI, 1.4 – 4.6)
Fink [60]	Community, US	75	Non-Spine	7	HR 2.4 (95% CI, 1.1 – 5.0)
Vestergaard [61]	Community, Denmark (patients with parkinsonism)	43	Any	599	OR 1.2 (95% CI, 1.0 – 1.4)
			Hip	Unknown	OR 1.6 (95% CI, 1.2 – 2.1)
Muscular dystrophy					
Vestergaard [65]	Community, Denmark (combined Duchenne and Becker MD patients)	24	Any	Unknown	RR 1.8 (95% CI, 1.3 – 2.5)

a) Risk of hip fracture decreased with increasing age; No confidence interval was presented.

Becker MD [63,64]. However, only one study, which showed a 1.8-fold increased risk of fracture, determined fracture risk in Duchenne MD and Becker MD patients as compared with population-based control patients, but did not have the ability to statistically adjust for drug use and comorbidities associated with fracture [65].

Comorbidities of neurological disorders associated with an increased risk of fracture

Neurological disorders are associated with comorbidities, which increase the risk of fracture. For example, the risk of depression after diagnosis of PD is two-fold increased compared with control patients without PD, while social anxiety was diagnosed in 16% of PD patients as compared with 2% in the control group [66,67]. The 1-year prevalence of depression after stroke is about 36% [6] and the 5-year incidence rate of epilepsy after stroke is about 9.0% [68]. Schizophrenia has been associated with stroke as well [69]. Furthermore, 32% of MD patients develop a psychiatric disorder during life [7].

Depression itself may be associated with bone fragility through elevated cortisol and cytokine levels, reduced vitamin D levels as a consequence of reduced sun exposure, concomitant smoking and decreased activity [70,71]. Depression has also been associated with neurogenic osteoporosis [42]. Moreover, fatigue, which is associated with depression, may increase the risk of falls [70]. Schizophrenia has been associated with reduced bone mineral density, for which the underlying mechanism has not been fully elucidated. Low vitamin D levels may play a role, but also concomitant smoking, alcohol use, poor nutrition and reduced activity [72]. Epilepsy and seizures have been associated with falls [73]. Finally, treatment of these psychotropic comorbidities with anxiolytics, antidepressants, antipsychotics and anticonvulsants may increase disease control and may reduce risk of falls and bone fragility and therefore fracture. However, psychotropic treatment itself has also been associated with fracture risk (Table 4), which will be discussed in the next paragraph.

Concomitant treatment in neurological disorders associated with an increased risk of fracture

Treatment of neurological disorders and treatment of related comorbidities with GCs, dopaminergic drugs, antidepressants, anxiolytics/hypnotics, antipsychotics, anticonvulsants and PPIs may increase fracture risk as well.

GCs, which cause bone fragility are currently used to treat MD and MG [74,75]. In MD, treatment regimens with GCs are depending on type of MD. For Duchenne MD patients a dose of 0.75 milligram prednisolone per kilogram per day (mg/kg per day) is recommended. Consequently, for a boy who weighs 40 kg this means an average daily dose of 30 mg prednisolone per day [74]. For MG patients average daily dose may even be higher. Oral GC treatment is regularly started with 10 mg prednisolone per day and is quickly increased towards about 60 mg per day [76,77]. Once an effective clinical response is obtained (within about 10-12 weeks), this dose is slowly tapered down, towards 2.5 – 10 mg prednisolone equivalents each day or an equivalent dose on alternate days for maintenance [77]. Hence these patients are routinely exposed to an average daily dose exceeding 60 mg prednisolone, whereby after the initial 12 weeks, cumulative doses still exceed 1 gram per year [77]. Therefore, it has been hypothesized that MD and MG patients who are long term heavy users of GCs, are at an increased risk of fracture. Using the United Kingdom General Practice Research Database (GPRD), Van Staa et al. showed that use of GCs has been associated with a 1.3-fold increased risk of non-vertebral fracture in the general population, which increased towards 1.6-fold for patients with average daily doses of 7.5 mg per day or more. Similarly, the 2.6-fold increased risk observed for vertebral fractures, irrespective of average daily dose prescribed, increased towards a 5.2-fold increased risk for patients who were prescribed 7.5 mg or more prednisolone equivalents per day [8]. De Vries et al. further substantiated the risk of fracture and showed that intermittent use of high-dose oral GCs (daily dose ≥ 15 milligram and

cumulative exposure ≤ 1 gram) may result in a small increased risk of osteoporotic fracture, whereas patients who received several courses of high-dose GCs, which may be the case in MD and MG (daily dose ≥ 30 milligram and cumulative exposure >5 gram) had a substantially 3.6-fold increased risk of osteoporotic fracture, regardless of their underlying disorder [78]. Lastly, Bazelier and collegues showed that patients with the neurological disorder MS may have an additional increased risk of fracture when exposed to GCs. They reported that risk of osteoporotic fracture was 1.4-fold increased in patients with MS, whereas the risk of osteoporotic fracture was 1.9-fold increased for MS patients who were prescribed GCs in the previous 6 months. When the average daily dose was 7.5 mg per day or more, a 2.4-fold increased risk for osteoporotic fracture was observed [79]. In conclusion, patients with the neurological disorders MD and MG are regularly exposed to high average daily doses, which may exceed 30 milligrams of prednisolone equivalents per day and a cumulative exposure of 5 grams. Therefore these patients may be at an increased risk of fracture.

Dopamine agonists and levodopa, which are used in the treatment of PD, cause side effects like postural hypotension and slow mentation or confusion, which results in loss of protective reflexes during falling [80]. Additionally, levodopa use can induce hyperhomocysteinemia, which is associated with the onset of osteoporosis and subsequently increases the risk of fractures [55,81]. Fracture risk has been determined in large patient groups treated with dopaminergic drugs, but it remains unclear whether this risk can be attributed to PD or its treatment with dopaminergic drugs [61,62].

Neurological disorders have been associated with concomitant treatment with psychotropic drugs (antidepressants, anxiolytics/hypnotics, antipsychotics and anticonvulsants), which may cause falls and cause bone fragility. Antidepressants, anxiolytics/hypnotics, antipsychotics and anticonvulsants are often prescribed to treat respectively depression, anxiety, psychosis, and seizures. Tricyclic antidepressants and

anticonvulsants may also be used for the treatment of neuropathic pain [82].

Their risk of falls is increased through side effects like sedation, orthostatic hypotension, dizziness, visual disturbances and extrapyramidal symptoms [73,83,84]. On the other hand, antidepressants, antipsychotics and anticonvulsants may also increase the risk for bone fragility. Treatment with antidepressants with a high affinity to block the 5-hydroxytryptamine, (5-HT) re-uptake transporter system may affect bone metabolism and have a negative impact on bone micro-architecture and BMD, resulting in bone fragility [85,86]. Antipsychotics with a high affinity for dopamine D_2 receptors give rise to elevated prolactin levels, which has been associated with decreased bone mineral density [87]. Anticonvulsants may increase vitamin D catabolism, resulting in increased bone resorption [88].

Several epidemiological studies have reported increased risks of hip or femur fracture among users of antidepressants, antipsychotics, anxiolytics/hypnotics and anticonvulsants [73,89,90]. To provide a quick overview, the results of several, but not all, large epidemiological studies that investigated the risk of fracture in patients exposed to psychotropic drugs, are presented in Table 4.

As compared with control patients, risk of hip fracture was 2.4-fold increased for patients who used selective serotonin reuptake-inhibitors (SSRIs) and 2.2 and 1.5-fold increased for patients who used secondary and tertiary tricyclic antidepressants (TCAs) respectively [89]. Risk of hip/femur fracture was 1.3-fold increased among users of antipsychotics as compared with non-users [90]. Risk of any fracture was 2.0-fold increased among epilepsy patients who were currently treated with anticonvulsants as compared with untreated epilepsy patients and 1.1-fold increased for patients exposed to anxiolytics/hypnotics as compared with non-users [9,73].

Table 4: Risk of fracture with exposure to psychotropic drugs

Type of psychotropic drug	Subtype of drug	Setting	Mean age (years)	Fracture type	Fractures in exposure group (n)	Fracture risk compared with control patients without drug exposure
Antidepressants						
Liu [91]	SSRI	Community, Canada	>65	Hip	540	OR 2.4 (95% CI, 2.0 – 2.7)
	Secondary TCA				214	OR 2.2 (95% CI, 1.8 – 2.8)
	Tertiary TCA				739	OR 1.5 (95% CI, 1.3 – 1.7)
Vestergaard [9]	All	Community, Denmark	43	Any	18.511	OR 1.2 – 1.4[b]
	SSRI				14.958	OR 1.1 – 1.4[b]
	TCA				4.774	OR 1.1 – 1.3[b]
Antipsychotics						
Hugenholtz [92]	All	Community, UK	77	Hip	1.495	OR 1.3 (95% CI, 1.1 – 1.5)
Vestergaard [9]	All	Community, Denmark	43	Any	9.738	OR 1.1 – 1.2[b]
Anxiolytics/hypnotics						
Vestergaard [9]	All	Community, Denmark	43	Any	35.840	OR 1.1 (95% CI, 1.1 – 1.1)
Anticonvulsants						
Vestergaard [9]	All	Community, Denmark	43	Any	7.091	OR 1.4 (95% CI, 1.3 – 1.4)
Souverein [73]	All	Epilepsy community, UK	[c]	Any	945	OR 2.0 (95% CI, 1.5 – 2.7)

a) Risk of fracture not increased, except for use of high dose levodopa or high dose monoamine oxidase B inhibitor
b) Risk of fracture statistically significant increased, but risk vary with exposure to different average daily doses
c) 65% of the patients have an age below 60

Anxiolytics/hypnotics increase the risk for fracture through a fall-related mechanism [9], whilst no associations with negative effects on bone have been described. For antidepressants, antipsychotics and anticonvulsants it is not clear whether an increased risk of fracture is predominantly caused by an increased risk of falling or a higher fragility of bone. This could be tested indirectly when different durations of drug use are evaluated. When fracture risk is immediately increased after the start of drug use, this suggests that the cause may be fall-related. An effect on bone can only be observed after a few weeks, because one remodeling cycle of the bone may take up to 4 months [28].

Lastly, dysphagia affects a large number of particularly elderly patients and may be initiated by stroke and PD [91]. A substantial proportion of patients with dysphagia have concomitant acid-related disorders, which are managed with PPI therapy [91]. Recently, it has been reported that PPIs decrease calcium absorption in the stomach and therefore may reduce BMD and increase risk of fractures [92,93]. It has been hypothesized that patients with neurological disorders treated with PPIs may have reduced BMD as well and may be at an increased risk of fracture.

Several studies have evaluated the risk of fracture with use of PPIs, but they showed conflicting results with respect to the association with duration of use. Some observed increased risks of fracture with long-term PPI use [94,95], while others reported no trend between short and long-term PPI use [96,97].

Knowledge gap and objectives

Patients with neurological disorders may be at an increased risk of fracture via multiple causal pathways, including increases in the risk of falls and changes in bone mineral density and quality of bone microarchitecture. Risk of fracture may be increased by the disease itself, by comorbidities and by their treatment.

Firstly, treatment with antidepressants, antipsychotics and PPIs may cause an additional increase in fracture risk in patients with neurological disorders, but it is not clear which causal pathway (via falling or via bone fragility) contributes most. To have sufficient statistical power, this question should first be investigated in the general population before determination of an additional risk of fracture in patients with neurological disorders.

Secondly, fracture risk has never been determined in several forms of neurological disorders including MG, CMT, GBS and other forms of MD than Duchenne or Becker MD. Moreover, fracture risk has never been determined in a large cohort for PD patients and Duchenne and Becker MD patients compared with population-based control patients with the ability to adjust for a wide range of comorbidities and drug exposure. Furthermore, fracture risk has been determined in patients after stroke as compared with population-based control patients, but information about the time course in relation with fracture risk is scarce. Information about the time course in relation with fracture risk is also scarce for other neurological disorders.

Thirdly, information is scarce about the possible additional increase of fracture risk with concomitant use of GCs, dopaminergic drugs, antidepressants, antipsychotics, anxiolytics, anticonvulsants and PPIs in patients with neurological disorders.

Lastly, several clinical risk scores for fracture risk prediction are currently available, such as the Garvan calculator and FRAX [98,99]. But a limitation of these risk scores is that they do not take into account a wide range of neurological disorders as determinants. As far as we know, a specific risk score for patients with a neurological disorder is only available for patients with MS [100].

Therefore, the main objectives of this thesis are:

- to determine the risk of fracture in the general population exposed to PPIs, antidepressants and antipsychotics and to indirectly determine the causal pathway of fracture risk (Chapter 2)
- to determine fracture risk in patients after stroke, in patients with PD, MG, MD, CMT and GBS compared with population-based controls (Chapters 3 and 4)
    - to determine fracture risk in relation with time since diagnosis (Chapters 3 and 4)
    - to determine fracture risk in patients with neurological disorders with concomitant exposure to GCs, dopaminergic drugs, antidepressants, antipsychotics, anxiolytics / hypnotics, anticonvulsants and PPIs (Chapters 3 and 4).
- to develop a fracture risk prediction model for patients with neurological disorders (Chapter 3.3).

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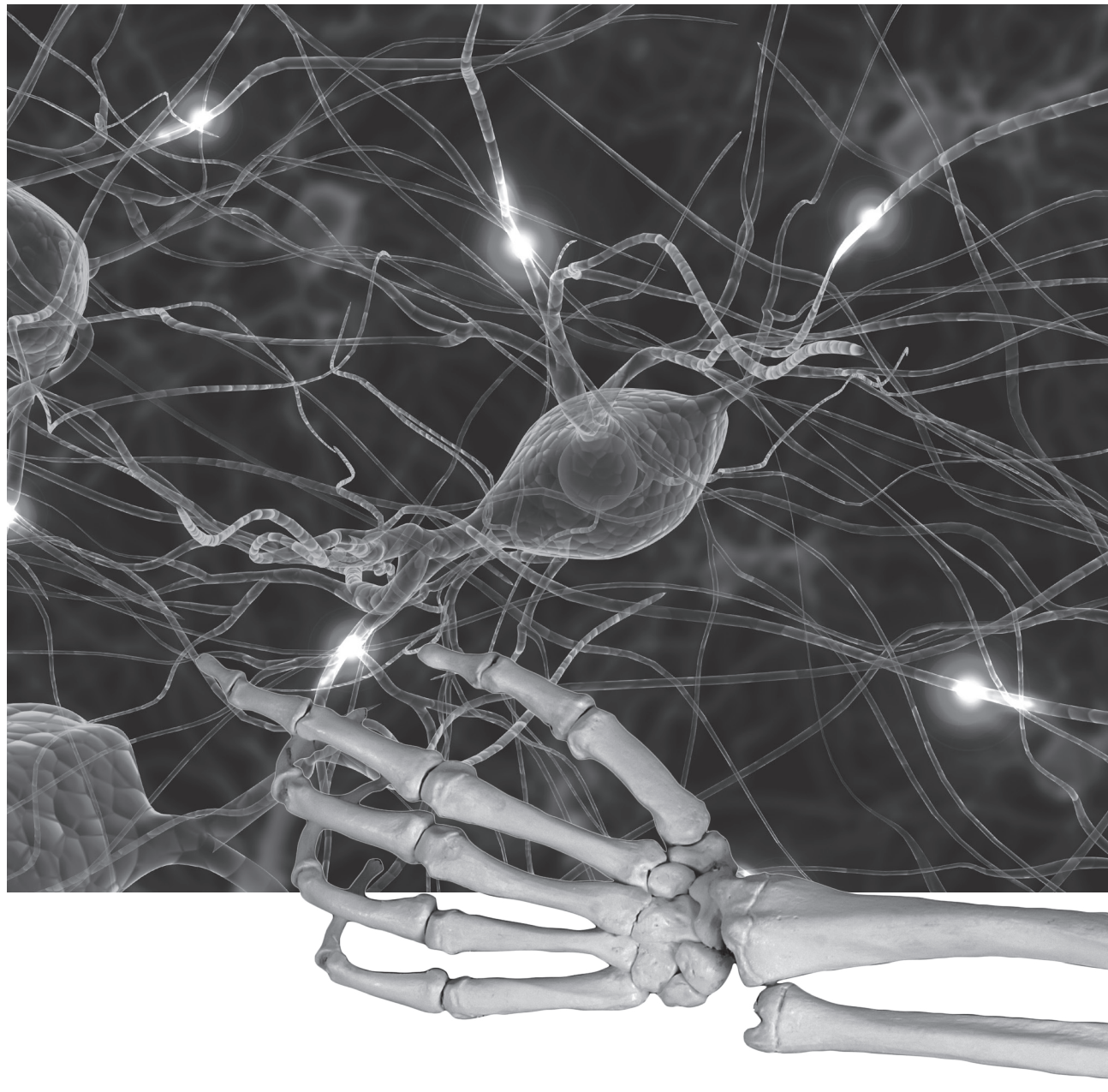
Chapter 2

Drug induced fracture risk



Chapter 2.1

Use of proton pump inhibitors and risk of hip/femur fracture: a population-based case-control study

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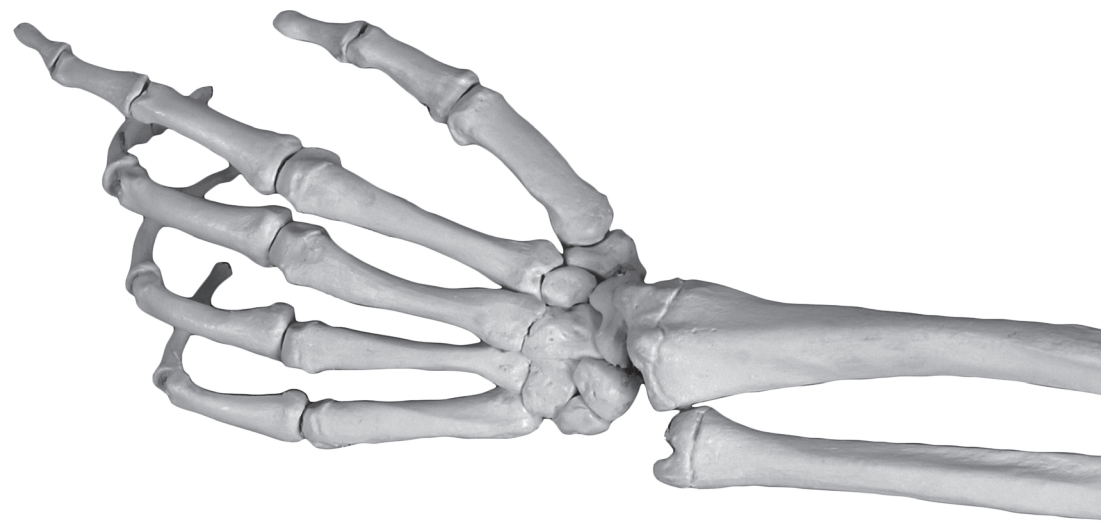


Abstract

Background: Previous studies evaluated the association between proton pump inhibitor (PPI) use and subsequent fracture risk, but they showed ambiguous results. To further test these conflicting results, the objective of this study was to evaluate the association between the use of PPIs and the risk of hip/femur fracture in a different study population.

Methods: A case-control study was conducted using data from the Dutch PHARMO record linkage system. The study population included 6,763 cases aged 18 years and older with a first hip/femur fracture during enrolment and 26,341 age, gender and region matched controls.

Results: Current users of PPIs had an increased risk of hip/femur fracture yielding an adjusted odds ratio (AOR) of 1.20 (95% confidence interval [CI], 1.04-1.40). Fracture risk attenuated with increasing durations of use, resulting in AORs of 1.26 (95% CI, 0.94 – 1.68) in the first 3 months, 1.31 (95% CI, 0.97 – 1.75) between 3 and 12 months, 1.18 (95% CI, 0.92 – 1.52) between 13 and 36 months and 1.09 (95% CI, 0.81 – 1.47) for use longer than 36 months.

Conclusion: Our findings show that there is probably no causal relationship between PPI use and hip fracture risk. The observed association may be the result of unmeasured distortions: although current use of PPIs was associated with a 1.2 fold increased risk of hip/femur fracture, the positive association was attenuated with longer durations of continuous use. Our findings do not support that discontinuation of PPIs decreases risk of hip fracture in elderly patients.

Introduction

Proton pump inhibitors (PPIs) are widely used to treat several gastrointestinal disorders, including peptic ulcer disease and gastroesophageal reflux [1]. It has been reported that use of PPIs decreases calcium absorption in the stomach [2,3], which increases the risk for hip fracture [4]. Conversely, PPIs may also reduce bone resorption through proton pump inhibition of osteoclastic cells [5-7], which may decrease the risk for a hip fracture.

To further investigate the clinical importance of these opposing effects, three large epidemiological studies have been conducted, using data from the UK General Practice Research Database (GPRD), the databases of the Danish national healthcare System and the Canadian Population Health Research Data Repository. All three studies found a positive association between the use of PPIs and risk of hip fracture [8,9,10]. In addition, the UK and the Canadian study reported that the risk of fracture further increased with longer cumulative durations of use [8,10]. Intriguingly, using data from the same GPRD, two other groups of researchers have reported different findings, which did not support a causal relationship between PPI use and fracture risk. In both GPRD studies the risk of hip fracture decreased with prolonged PPI use [11,12].

The discrepancies between the different "duration of use" analyses in the studies mentioned above are important, because "duration of use" analyses provide indirect evidence that may support a causal effect. Therefore, the objective of this study was to evaluate the association between the (duration of) use of PPIs and the risk of hip/femur fracture in a different study population.

Methods

Study design

The Dutch PHARMO Record Linkage System (RLS) was used to conduct a case-control study.

PHARMO RLS (http://www.pharmo.nl) includes the virtually complete pharmacy dispensing histories of community-dwelling residents in the Netherlands, which are linked to hospital admission records. Pharmacy data include information about the drug dispensed, the date of dispensing, the prescriber, the amount dispensed, the prescribed dosage regimen and the estimated duration of use. Hospital discharge records include detailed information on date of admission, discharge diagnoses and procedures. The version of the database used for this study, represents about 7% of the general Dutch population. Patients are included irrespective of their health insurance or socio-economic status. Moreover, validation studies have shown that the PHARMO RLS has a high level of data completeness and validity [13], especially with regards to recording of hip fractures [14,15].

A case-control analysis was conducted within PHARMO RLS between January 1, 1991 and December 31, 2002. Cases were 18 years or older and sustained a hip or femur fracture during the study period. The first hospital admission date for a hip/femur fracture defined the index date. The ICD codes 820-821 were used to identify hip/femur fractures. Up to four control patients were matched to each case by year of birth, gender and geographical region. The selected control patients were PHARMO RLS participants without any fracture during enrolment. Controls were assigned the same index date as their matched case.

Exposure assessment

Current users of PPIs or histamine H_2-receptor antagonists (H2RAs) were defined as patients who had received at least one PPI or H2RA dispensing within the 30 days before the index date. Recent, past and distant past users received their last dispensing in respectively the 31-91 days, 92-365 days or > 1 year before the index date.

For each current user, we calculated the average daily dose by division of the cumulative dose by the treatment time, using defined daily dosages (DDD).[16] One DDD is

equivalent to 20 mg orally administered omeprazole, 40 mg pantoprazole, 30 mg lansoprazole, 20 mg rabeprazole, 30 mg esomeprazole, 800 mg cimetidine, 300 mg ranitidine, 300 mg nizatidine, 150 mg roxatidine and 40 mg famotidine. The expected continuous duration of PPI or H2RA use was based on the prescribed drug supply and prescribed daily dose. In case of overlap between two dispensings (i.e. a repeat dispensing filled within the duration of use for a previous dispensing), or a repeat dispensing filled within 182 days after discontinuation of the previous period, this period was then extended. In case of missing data on daily dose, the median expected duration of use for the PPI or H2RA of interest, was used. Because acid suppressants may be prescribed for the treatment of gastrointestinal side effects of oral glucocorticoids, the main analysis was stratified to concomitant use of oral glucocorticoids (i.e. a prescription in the 6 months before the index date).

We adjusted our analyses for the use of anxiolytics/hypnotics within three months before, and antacids other than PPIs or H2RAs, hormone replacement therapy, beta-blockers, antidiabetics, antipsychotics, antidepressants, anticonvulsants, two or more non-steroidal anti-inflammatory drug dispensings, disease modifying antirheumatic drugs, average daily dose of oral corticosteroids in the six months before the index date. Furthermore, we adjusted our analyses for a history of diseases of the esophagus/stomach/duodenum, diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, anemia, mental disorders, endocrine disorders, congestive heart failure, cerebrovascular disease, and chronic obstructive pulmonary disease.

Sensitivity analyses

Two sensitivity analyses were conducted. In the first sensitivity analysis, we restricted cases and controls to those who had at least 1 year of follow-up time before the index date. In the second sensitivity analysis, we did not restrict our analyses to current PPI use only: in contrast

to the studies performed by Targownik et al. [10], de Vries et al. [11] and the current PHARMO study, Yang et al. did not take into account the timing of PPI exposure [8]. For example, in his study, patients who had stopped taking PPIs 10 years before the index date were considered to have the same increased risk of hip fracture as patients who were taking PPIs on the index date [8]. The underlying assumption of this study design, is that PPI-induced bone damage, is irreversible. Conversely, during the design of the current study, we assumed that bone damage caused by PPI intake probably is reversible, similar to detrimental effects on bone caused by other drugs, such as oral corticosteroids [17,18]. When reversibility of a side effect of a drug is assumed, the analyses should take into account the timing of exposure, which has been done in all our main analyses.

Statistical analysis

We used conditional logistic regression (SAS version 9.1.3, PHREG procedure; SAS Inc., Cary, NC, USA) to quantify the strength of the association between use of PPIs and H2RAs and risk of hip/femur fracture. Adjusted odds ratios (AORs) for hip/femur fracture were estimated by comparing PPI or H2RA use with no use. The analyses were stratified by class (PPI or H2RA), sex, continuous duration of use, average daily dose and concomitant use of oral corticosteroids. Backward elimination was used to establish the final model of confounders from the pivotal exposure analysis. In addition, smoothing spline regression plots were used to visualize the association between risk of hip/femur fracture and both timing and continuous duration of use [19].

Results

We identified 6,763 patients who sustained a hip/femur fracture and 26,341 controls (Table 1). Their mean age and gender were equally distributed among cases and controls. The average

time period of prescribing data before the index date was 4.1 years.

Table 2 shows that current use of both PPIs and H2RAs was significantly associated with an increased risk of hip/femur fracture, yielding AORs of 1.20 (95% confidence interval [CI], 1.04 - 1.40) and 1.19 (95% CI, 1.00-1.42) respectively. After discontinuing the use of acid suppressants for 1-3 months, a rapid drop towards baseline was observed for both PPIs and H2RAs. The risk of hip/femur fracture was statistically significantly higher among current users of PPIs and H2RAs compared to recent users. This association is also presented in Figure 1.

Table 2 also shows that longer durations of use attenuated the risk association. Current PPI users were at highest risk during the first year of continuous exposure, but this risk decreased over time. In addition, no increased risk of hip/femur fracture was observed among current users (8 cases and 29 exposed controls) with a duration of PPI use exceeding 7 years, yielding an AOR of 0.89 (95% CI, 0.34 – 2.01). The association between the duration of continuous PPI and H2RA use, and the risk of hip fracture is graphically illustrated in Figure 2.

Furthermore, the risk of hip/femur fracture was highest among those current users who received the highest daily dose of PPIs. The PPI use below an average daily dose of 1.00 DDD, resulted in an AOR of 1.21 (95% CI, 0.93 – 1.57) as shown in Table 3. This risk declined to an AOR of 1.12 (95% CI, 0.88 – 1.42) among users receiving a DDD between 1.00 and 1.75, but extended to a statistically significant increased risk among those who received more than 1.75 DDD, yielding an AOR of 1.35 (95% CI, 1.02 – 1.77). After comparing the results for average daily dose of PPIs with the average daily dose of H2RAs, no statistically significant differences were observed between both groups.

Table 4 shows the risk of hip fracture among current PPI users when stratifying according to concomitant use of oral glucocorticoids. Exposure to oral glucocorticoids

Table 1: Baseline characteristics of cases and controls

Characteristic	Cases (n=6,763)	(%)	Controls (n=26,341)	(%)	Crude OR (95% CI)[a]
Mean age (years)	75.7		75.3		
Numbers females	4,929	72.9	19,138	72.7	
Use 6 months before the index date					
Proton pump inhibitors	573	8.5	1,714	6.5	1.35 (1.22-1.49)
Histamine H_2-receptor antagonists	433	6.4	1,412	5.4	1.21 (1.08-1.35)
Other antacids	204	3.0	576	2.2	1.41 (1.20-1.66)
Oral glucocorticoids	366	5.4	918	3.5	1.59 (1.40-1.80)
Disease modifying antirheumatic drugs	115	1.7	202	0.8	2.27 (1.80-2.86)
Two or more non-steroidal anti-inflammatory drug dispensings	929	13.7	2584	9.8	1.46 (1.35-1.59)
Hospitalisation before index date					
Diseases of the esophagus, stomach and duodenum	118	1.7	248	0.9	1.86 (1.49-2.32)
Cardiovascular disease	359	5.3	1,289	4.9	1.10 (0.98-1.25)
Cerebrovascular disease	296	4.4	565	2.1	2.12 (1.84-2.45)

a: OR: odds ratio; CI: confidence interval.

Table 2: Use of PPIs or H2RAs and risk of hip fracture, by duration of use

	Cases (n=6,763)	(%)	Controls (n=26,341)	(%)	Crude OR (95% CI)[b]		Adjusted[a] OR (95% CI)[b]	
PPI use before								
Never	5,810	85.9	23,430	88.9	1.00		1.00	
Distant past use	305	4.5	907	3.4	1.38 (1.21-1.58)		1.24 (1.08-1.43)	
Past use	75	1.1	290	1.1	1.08 (0.83-1.39)		0.97 (0.74-1.26)	
Recent use	268	4.0	941	3.6	1.18 (1.03-1.36)		0.96 (0.83-1.12)	
Current use	305	4.5	773	2.9	1.62 (1.41-1.86)	[c]	1.20 (1.04-1.40)	[c]
Duration of use[d]								
≤3 months	71	1.0	177	0.7	1.63 (1.24-2.15)		1.26 (0.94-1.68)	
4-12 months	72	1.1	165	0.6	1.79 (1.36-2.38)		1.31 (0.97-1.75)	
13-36 months	94	1.4	251	1.0	1.55 (1.22-1.97)		1.18 (0.92-1.52)	
>36 months	68	1.0	180	0.7	1.54 (1.16-2.05)		1.09 (0.81-1.47)	
H2RA use before								
Never	5,624	83.2	22,545	85.6	1.00		1.00	
Distant past use	598	8.8	2,020	7.7	1.18 (1.07-1.30)		1.01 (0.90-1.12)	
Past use	108	1.6	364	1.4	1.21 (0.97-1.50)		1.03 (0.83-1.29)	
Recent use	237	3.5	892	3.4	1.06 (0.92-1.23)		0.91 (0.78-1.06)	
Current use	196	2.9	520	2.0	1.52 (1.28-1.80)	[e,f]	1.19 (1.00-1.42)	[e]
Duration of use[d]								
≤3 months	47	0.7	104	0.4	1.85 (1.30-2.62)		1.57 (1.10-2.24)	
4-12 months	43	0.6	116	0.4	1.51 (1.06-2.15)		1.14 (0.79-1.64)	
13-36 months	51	0.8	168	0.6	1.22 (0.89-1.68)		0.92 (0.67-1.28)	
>36 months	55	0.8	132	0.5	1.64 (1.19-2.25)		1.30 (0.94-1.81)	

a: Adjusted for use of other antacids, average daily dose of oral corticosteroids, anxiolytics/hypnotics, short or long acting benzodiazepines, hormone replacement therapy, anticonvulsants, antipsychotics, antidepressants, beta-blockers, antidiabetics, two ore more non-steroidal anti-inflammatory drug dispensings, disease modifying antirheumatic drugs, a history of digestive system disorders, anemia, mental disorders, cerebrovascular disease, congestive heart failure, endocrine disorders, rheumatoid arthritis, diabetes mellitus, chronic obstructive pulmonary disease and inflammatory bowel disease. Furthermore, the proton pump inhibitor (PPI) analysis was adjusted for the use of histamine H_2-receptor antagonists (H2RAs) and the H2RA analysis for the use of PPIs.
b: OR: odds ratio; CI: confidence interval.
c: Wald statistic: current PPI use statistically significantly different ($P<0.05$) from recent PPI use.
d: Duration of use: duration of continuous use with washout periods of ≤3 months.
e: Wald statistic: current H2RA use statistically significantly different ($P<0.05$) from recent H2RA use.
f: Wald statistic: current H2RA use statistically significantly different ($P<0.05$) from distant H2RA use.

Table 3: Use of PPIs or H2RAs and risk of hip fracture, by daily dose

Use before	PPI Adjusted[a] OR (95% CI)[b]	H2RA Adjusted[a] OR (95% CI)[b]
Never	1.00	1.00
Current use	1.20 (1.04-1.40)	1.19 (1.00-1.42)
Average daily dose, DDD[c]		
First time user	1.29 (0.79-2.09)	1.40 (0.78-2.51)
<1.00	1.21 (0.93-1.57)	0.93 (0.73-1.18)[d]
1.00-1.75	1.12 (0.88-1.42)	1.67 (1.21-2.31)[d]
>1.75	1.35 (1.02-1.77)	1.57 (0.89-2.77)

a: Adjusted for the same confounders listed in Table 2
b: OR: odds ratio; CI: confidence interval
c: DDD: defined daily dosage
d: Wald statistic: the risk of hip fracture is statistically significantly lower among current H2RA users with <1.00 DDD compared with current H2RA users with 1.00-1.75 DDD (P<0.05)

Table 4: Use of PPIs or H2RAs and risk of hip fracture, by exposure to oral corticosteroids

	Cases (n=6,763)	(%)	Controls (n=26,341)	(%)	Crude OR (95% CI)[b]	Adjusted[a] OR (95% CI)[b]
PPI use before						
Never	5,810	85.9	23,430	88.9	1.00	1.00
Current use	305	4.5	773	2.9	1.62 (1.41-1.86)	1.20 (1.04-1.40)
By oral corticosteroid use in the 6 months before[c]						
Unexposed	256	3.8	682	2.6	1.54 (1.33-1.79)[d]	1.19 (1.02-1.40)
<7.5 mg/day	21	0.3	47	0.2	1.86 (1.11-3.12)	1.31 (0.77-2.22)
7.5-15 mg/day	12	0.2	20	0.1	2.51 (1.21-5.18)	1.91 (0.90-4.07)
≥15 mg/day	13	0.2	14	0.1	3.67 (1.72-7.84)[d]	2.35 (1.07-5.20)
H2RA use before						
Never	5,624	83.2	22,545	85.6	1.00	1.00
Current use	196	2.9	520	2.0	1.52 (1.28-1.80)	1.19 (1.00-1.42)
By oral corticosteroid use in the 6 months before[c]						
Unexposed	165	2.4	468	1.8	1.42 (1.19-1.71)	1.18 (0.98-1.43)
<7.5 mg/day	16	0.2	24	0.1	2.64 (1.39-4.99)	1.73 (0.90-3.35)
7.5-15 mg/day	9	0.1	16	0.1	2.29 (1.01-5.19)	1.43 (0.61-3.38)
≥15 mg/day	5	0.1	6	0.0	3.59 (1.09-11.78)	2.34 (0.68-8.06)

a: Adjusted for same confounders listed in Table 2.
b: OR: odds ratio; CI: confidence interval.
c: Corticosteroids by prednisolone equivalents; data not shown for patients with only 1 oral steroid dispensing before the index date.
d: Wald statistic: the risk of hip fracture is statistically significantly higher among PPI users exposed to corticosteroids ≥15 mg/day compared with PPI users unexposed to corticosteroids (P<0.05)

Figure 1: Risk of hip/femur fracture and time between index date and most recent dispensing of acid suppressants.

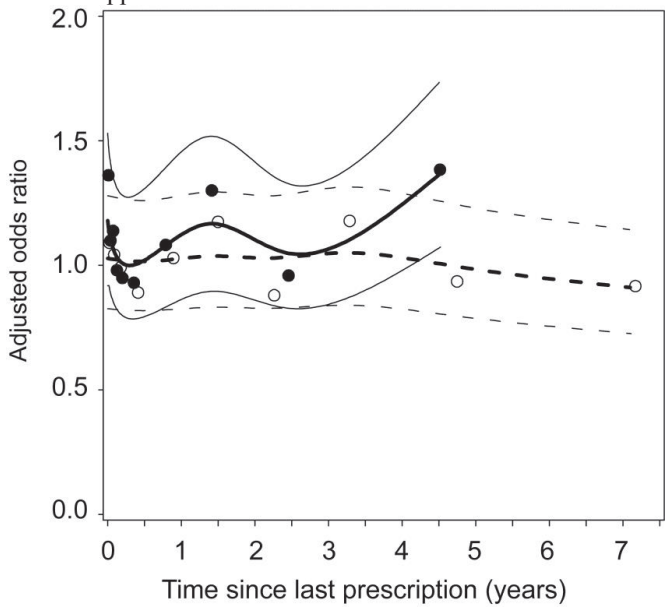
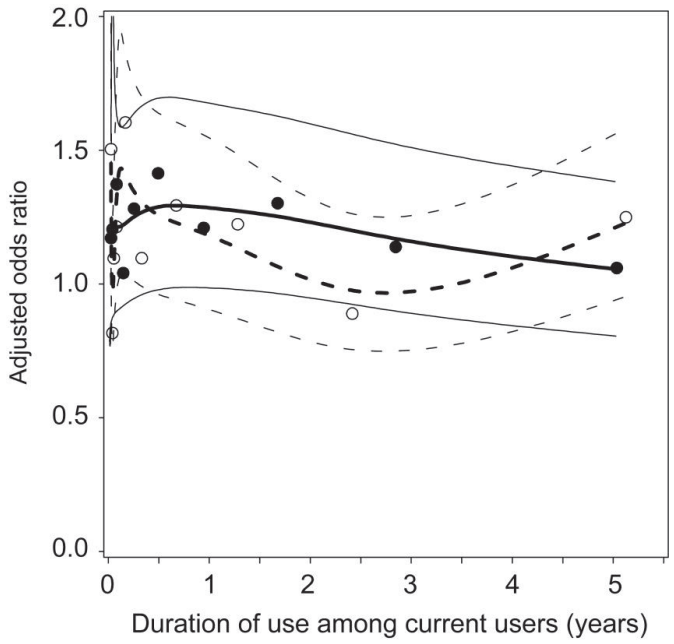


Figure 2: Risk of hip/femur fracture and continuous duration of PPI or H2RA use among current users.



Solid lines, solid circles: PPIs; Dashed lines, open circles: H2RAs (adjusted for same confounders as listed under Table 2).

increased fracture risk, while those who received 15 mg prednisolone equivalent/day or more were at highest risk (AOR of 2.35 [95% CI, 1.07 - 5.20]).

Stratification according to sex showed that risk of fracture was statistically significantly higher among current PPI users who were men, AOR 1.57 (95% CI, 1.16 - 2.12), compared to women AOR 1.12 (95% CI, 0.94 - 1.32) with a P-value <0.05. Although not statistically significant, we observed the same trend among current H2RA users.

In the first sensitivity analysis, we restricted cases and controls to those who had at least 1 year of follow-up time before the index date. Current users of PPIs or H2RAs had the following risks of hip/femur fracture: AORs 1.25 (95% CI, 1.07 - 1.47) for PPI users, and 1.12 (95% CI, 0.92 - 1.35) for H2RA users. This was not different from the findings in Table 2.

In the second sensitivity analysis, we lumped current, recent and past PPI use categories, and stratified them by cumulative duration of use, similar to the methodology of Yang et al.[8] There was still an inverse relationship between duration of PPI use and hip fracture, with a slightly decreased magnitude: AORs were 1.13 (95% CI, 1.02 - 1.25) for patients using PPIs up to 1 year, 1.21 (95% CI, 0.98 - 1.50) for 1-2 years, 1.03 (95% CI, 0.78 - 1.35) for 2-3 years and 0.96 (95% CI, 0.78 - 1.20) for PPI exposure exceeding 3 years. There was no association between H2RA users and hip fracture (data not shown).

Discussion

We found that current PPI use was associated with a 1.2-fold increased risk of hip/femur fracture. Higher daily dosages (>1.75 DDD), male gender, and use of oral corticosteroids further increased the risk. The highest increase of risk was observed within the year after initiation of acid suppressants, and attenuated with prolonged use. This finding, does not

support a causal effect of PPIs on bone, but suggests the presence of unmeasured distortion, such as selection bias and/or residual confounding.

The key finding of this study is that the increased risk of hip/femur fracture among current acid suppressant users is probably not causal. As far as we know, PPIs and H2RAs do not increase the risk of falling. Therefore, if a causal relationship exists, fracture risk should increase only after long-term exposure (at least 6-12 months to alter bone mineral density). However, the smoothing spline regression plots (Figure 2) did not provide evidence for a duration of use effect. Furthermore, acid suppression in the stomach caused by PPIs is significant greater and lasts longer compared with H2Ras [1,20]. Thus, if impaired calcium absorption caused by acid suppression is associated with an increased risk of fracture, this should be most abundant with PPI use. Nevertheless, prolonged H2RA use (instead of PPI use) of >36 months yielded a higher AOR of 1.30 (95% CI, 0.94 - 1.81) compared to PPI use with an AOR of 1.09 (95% CI, 0.81 - 1.47). These results support the alternative hypothesis that the observed association is flawed due to unknown distortion, instead of an increased fracture risk caused by impaired calcium absorption. Consequently, these results do not support the hypothesis that acid suppression is associated with an increased risk of fracture.

Clinical studies showed conflicting results regarding calcium uptake and osteoclastic pump inhibition in users of PPIs [21]. When studying calcium uptake along with a meal, Graziani et al. and Hardy et al. found that calcium uptake was decreased in hypochlorhydric subjects [3,22], whereas other studies did not observe any effect [23-25]. Only during fasting conditions calcium uptake was decreased among patients using PPIs [2,22] and among achlorhydric patients [23,26]. Furthermore, some in vitro [6,7] and in vivo [5] studies suggested that PPIs could inhibit the osteoclastic proton pump and thereby reduce bone resorption. Conversely, short-term omeprazole treatment did not alter osteoclast or osteoblast function in pediatric users [27]. Moreover, no significant differences were observed in BMD

among postmenopausal women using acid-suppressants (PPIs and H2RA), while in men even lower cross-sectional bone masses were observed [28]. In addition, the most recent study performed by Targownik et al. showed that both chronic PPI use and high daily doses of PPIs were not associated with osteoporosis or accelerated BMD loss [29].

Several observational studies that investigated the association between duration of acid suppressant use and fracture risk found discrepant results as well [8,10-12]. Both Yang et al. and Targownik et al. found that fracture risk increased with longer durations of PPI use [8,10]. In contrast, members of our group found results which are similar to the present study (i.e. PPI use for a duration ≤1 year is associated with the highest fracture risk) using the same database as Yang et al. [11]. Moreover, our sensitivity analysis, in which we resembled the definitions of Yang et al., did not support a duration of use effect. Additionally, Kaye et al. who also used the GPRD database did not find any association between the number of PPI prescriptions and hip fracture [12]. The reasons for these discrepancies remain unclear.

There are alternative explanations for the small, overall 1.2-fold increased risk among current users of acid suppressants. These include the inability of the current and previous studies, to measure (or only partially measure) alcohol consumption, smoking history and low body mass index. All these factors are associated with an increased risk of fracture [30-32]. Besides, PPIs are often used for the eradication of Helicobacter Pylori [33], which may be associated with an increased risk of osteoporosis [34]. In addition, PPIs are associated with the onset of Clostridium difficile [35], which may be an alternative explanation for the increased risk of fracture. Finally, celiac disease, which is associated with the onset of reflux esophagitis [36], has recently been associated with an increased risk of both osteoporosis and fracture [37]. Nevertheless, we were unable to fully adjust for these three potential confounders, because PHARMO RLS has missing data of diagnoses determined outside the hospital.

Our study has several strengths. As we used a population-based design, our study represents the entire population of the Netherlands. It has a large study size and the average period of follow-up exceeded 4 years. Furthermore, written dosage instructions allowed us to discriminate between different average daily doses of PPIs and H2RAs and concomitant use of average daily dosages of oral glucocorticoids. The main limitation of our study is the inability to adjust for residual confounding. No information was present in the PHARMO RLS about low body mass index, alcohol consumption, smoking, celiac disease, Clostridium difficile and Helicobacter Pylori eradication. These potential confounders could have overestimated the observed increased fracture risk. Conversely, no information was present about the use of over-the-counter (OTC) drugs like calcium and vitamin D supplements, which decrease this risk [4,38]. Yet, according to our knowledge, the trend observed in the spline showing the recency of use (Figure 1) would be similar, even after adjustments for these potential confounders. In addition, although not confirmed by clinical trials, current literature suggests that non-steroidal anti-inflammatory drugs inhibit bone formation [39]. For this reason our analyses were adjusted for the use of these drugs in the six months before the index date. Finally, data collection for this study ended on the 31st of December 2002. Addition of more recent data would probably identify more long-term PPI users, which would add more power to the duration of use results.

In conclusion, our findings show that there is probably no causal relationship between PPI use and hip fracture risk. The observed association may be the result of unmeasured distortions: although current use of PPIs was associated with a 1.2 fold increased risk of hip/femur fracture, the positive association was attenuated with longer durations of continuous use. Our findings do not support that discontinuation of PPIs decreases risk of hip fracture in elderly patients.

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Chapter 2.2

Use of antidepressants and the risk of fracture of the hip or femur

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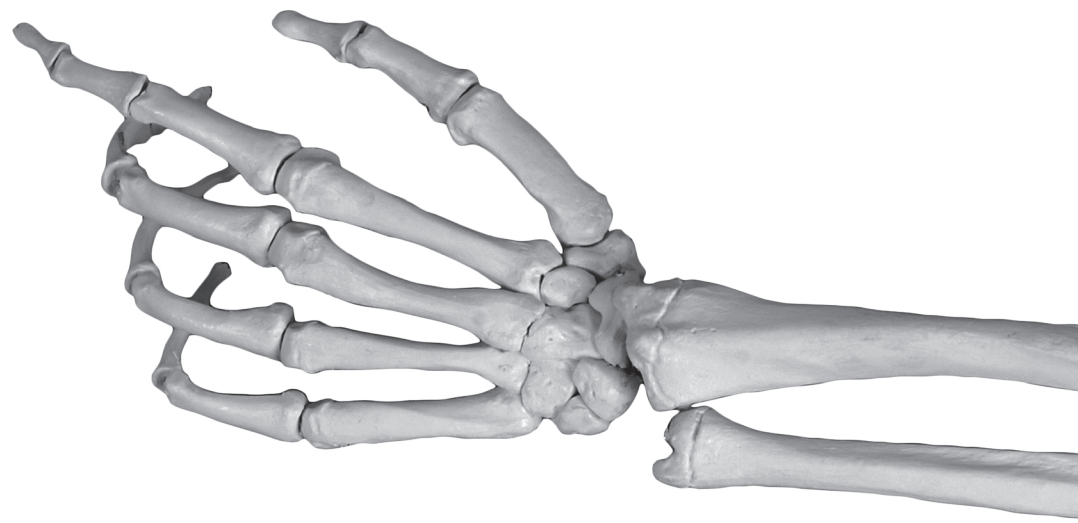


Abstract

Introduction: Antidepressants are known to have serious side effects. We examined the association between the use of antidepressants and the risk of hip/femur fractures with a special focus on the relation with the degree of 5-hydroxytryptamine transporter (5-HTT) inhibition and the duration of use.

Methods: A case–control study was conducted within the Dutch PHARMO-RLS database. Cases (*n*=6,763) were adult patients with a first hip/femur fracture during the study period. For each case, four controls (*n*=26,341) were matched by age, gender and geographic region.

Results: The risk of hip/femur fracture increased with current use of SSRIs (adjusted odds ratio (AOR) 2.35 [95% confidence interval (CI), 1.94 – 2.84]) and TCAs (AOR 1.76 [95% CI, 1.45 – 2.15]). The risk of hip/femur fracture declined rapidly after discontinuation of use. The risk of hip/femur fracture increased as the degree of 5-HTT inhibition of all antidepressants increased from AOR 1.64 [95% CI, 1.14 – 2.35] for drugs with low 5-HTT inhibition to AOR 2.31 [95% CI, 1.94 – 2.76] for those with high 5-HTT inhibiting properties.

Conclusion: Current use of both SSRIs and TCAs increase hip/femur fracture risk. Further studies are needed to elucidate the mechanistic pathways and the relation with the underlying pathophysiology. Until then, the elevated fracture risk should be considered when prescribing antidepressants.

Introduction

Depression is one of the most important mental health problems especially in the elderly and is associated with a poor natural history, reduced quality of life, increased utilization of medical health services and high mortality [1–4]. Although depression can be treated effectively with tricyclic antidepressants (TCAs), many users experience cardiovascular (e.g. orthostatic hypotension) and anticholinergic side effects (e.g. visual disturbances), which both may increase the risk of falling and thereby of fractures. The newer generation of antidepressants, including the selective serotonin re-uptake inhibitors (SSRIs), are considered as effective as the TCAs but with less bothersome side effects. Its use has increased over the last decade [5–7]. Some studies investigating the risk of falls with antidepressants have reported no significant difference in risk for SSRIs and TCAs [8,9].

Falls increase the risk of fracture, especially of the hip or femur in the elderly [10], with significant consequences for the individual and healthcare providers in terms of the impact on long-term morbidity, mortality and healthcare costs [11–14]. Several epidemiological studies have reported an increased risk of fracture with antidepressant use [9,15–17]. One explanation is that the increased fracture risk is mediated simply by falling [8].

Another explanation lies in the potential for antidepressants to affect the micro-architecture of bone. Functional serotonin (5-hydroxytryptamine, 5-HT) receptors and transporter systems have been localized on osteoblasts, osteoclasts and osteocytes [18–22] and 5-HT stimulates proliferation of osteoblast precursor cells in vitro [23]. Thus, drugs that block 5-HT re-uptake could affect bone metabolism and have a negative impact on bone micro-architecture. This has been illustrated by a recent case–control study conducted in Denmark, which reported an increased risk of fractures with an increased degree of blocking of the serotonin system [24].

The aim of this study was to examine the association between the use of antidepressants

and the risk of hip/femur fractures, with a special focus on the relation with the degree of 5-hydroxytryptamine transporter (5-HTT) inhibition afforded by different antidepressants and the duration of use.

Materials and methods

Study design

We conducted a case–control study within the Dutch PHARMO Record Linkage System (RLS) (www.pharmo.nl). The database includes the demographic details and complete medication histories for about one million community-dwelling residents in The Netherlands representing some 7% of the general population. Data are linked to hospital discharge records as well as several other health registries, including pathology, clinical laboratory findings and general practitioner data [25]. Almost every individual in The Netherlands is registered with a single community pharmacy, independent of prescriber and irrespective of their health insurance or socio-economic status. Pharmacy records have a high degree of completeness with regards to dispensed drugs [26,27]. Pharmacy data include information about the drug dispensed, the date of dispensing, the prescriber, the amount dispensed, the prescribed dosage regimen and the estimated duration of use. Hospital discharge records include detailed information on date of admission, discharge diagnoses and procedures. Validation studies on PHARMO RLS have confirmed a high level of data completeness and validity [28–30]. During data collection, the privacy and confidentiality of patients is maintained and complies with the Dutch Data Protection Act.

Study population

Data were collected for the period 1 January 1991 to 31 December 2002. Cases were patients aged 18 years and older with a record for a first fracture of the hip or femur during the study

period. The date of hospital admission was used to define the index date. Each case was matched by year of birth, sex and geographical region to up to four control patients without any evidence of ever having sustained a fracture. The index date for each control was the same as the date of fracture for the matched case.

Exposure assessment

Exposure to antidepressants was determined by reviewing prescription information before the index date. Current users were defined as individuals who had received a prescription for a TCA, an SSRI or other antidepressant within a 30-day period before the index date. Recent users were individuals whose most recent prescription was issued 31–90 days before the index date, and past users were those whose most recent prescription had been issued more than 3 months (>90 days) before the index date. Patients with a history of using more than one type of antidepressant before the index date were classified as appropriate, e.g. a current user of an SSRI may also qualify as a current user of a TCA. The average daily dose was calculated by dividing the cumulative exposure by the total treatment time. Dose equivalencies of antidepressants were applied from the WHO defined daily dose (DDD) [31] and were expressed as paroxetine equivalents (SSRIs) or amitriptyline equivalents (TCAs). The extent of 5-HTT inhibition was determined for each antidepressant with reference to Goodman and Gilman's 'The Pharmacological Basis of Therapeutics' [32] (Table 1).

Table 1: Drugs grouped according to the degree of serotonin transporter inhibition [31]

Degree of serotonin transporter inhibition (inhibition constant in nM)			
Low (>10)	Intermediate (>1 ≤10)	High (≤1)	Not classified
Desipramine	Imipramine	Clomipramine	Opipramol
Nortriptyline	Amitriptyline	Fluoxetine	Dosulepin
Doxepine	Fluvoxamine	Paroxetine	Moclobemide
Maprotiline	Venlafaxine	Sertraline	
Mianserine	Citalopram		
Trazodone			
Nefadozone			
Mirtazapine			

For each prescription, the expected duration of use (in days) was based on how the drug was supplied and the prescribed daily dose. If there were missing data on the total drug supply or written dosage instruction, the expected duration of use (based on the median duration for a prescription from patients of similar age and sex) was taken. When repeat prescriptions were issued, the expected duration of use period was extended according to the expected duration of the repeat prescription. In the event of overlap between two prescriptions (i.e. a repeat prescription given before the expected end date of a previous prescription), the 'overlap' days were added to the theoretical end date of the repeat prescription. If the gap between any consecutive prescriptions was 6 months or less, exposure was deemed to be continuous.

Potential confounders

The records of cases and controls were assessed for potential confounding variables, including use within the 3 months before the index date of a benzodiazepine; use within the 6 months before the index date of an antipsychotic (other than lithium), lithium, an anti-Parkinson drug, anticonvulsant, oral or inhaled glucocorticoid, bronchodilator, hormone replacement therapy, a disease-modifying anti-rheumatic drug (DMARD), anti-arrhythmic, thiazide diuretic, beta-blocker, drug for diabetes, metoclopramide, morphine/opiate or two or more prescriptions for an non-steroidal anti-inflammatory drug (NSAID); and a history at any time of hospitalisation for cardiovascular disease, malignant neoplasm, inflammatory bowel disease, rheumatoid disease, obstructive airway disease, impaired renal function, mental disorder or cerebrovascular disease. We have chosen a different time window for benzodiazepines, because in The Netherlands, benzodiazepines are dispensed for periods up to 1 month and other drugs for periods up to 3 months.

Statistical analysis

Conditional logistic regression analysis was used to estimate the risk of hip/femur fracture associated with the use of TCAs, SSRIs and the various confounding variables (SAS version 9.1.3, PHREG procedure) and were expressed as odds ratios (OR) with corresponding 95% confidence intervals (CI). Adjusted odds ratios (AOR) for hip/femur fracture were estimated by comparing antidepressant use with no use using conditional logistic regression analysis. Final regression models were determined by stepwise backward elimination using a significance level of 0.05. We stratified the study population to assess the risk with current use by age and sex.

Further analyses were conducted to evaluate the risk of fracture associated with current exposure to antidepressants versus no use grouping current users according to the daily dose of antidepressant prescribed and according to the degree of 5-HTT inhibition expected. Smoothing spline regression plots (SAS version 9.1.3) were used to visualize the longitudinal relationship between the risk of fracture and (a) the time between the index date and last dispensing of an antidepressant (recency of use) and (b) the duration of continuous use. The population attributable risk (PAR) was estimated using the following formula:

$$\text{PAR\%} = \frac{\text{Pe (OR -1)}}{\text{1 + Pe (OR -1)}} \text{ x 100.}$$

The prevalence (Pe) of antidepressant use was derived from national prescribing figures in 2003, www.gipdatabank.nl.

Results

We identified 6,763 patients who suffered a hip/femur fracture. These cases were matched to 26,341 controls. The mean age of cases and controls was 75 years and 73% were female (Table 2). The mean period of time with prescription information before the index date was 4.1 years. Prescriptions for paroxetine accounted for 50% of the prescriptions issued for an SSRI (25,131/50,287). Most of the other SSRI prescriptions were for fluoxetine (23.4%) or

fluvoxamine (20.3%). Amitriptyline (46.6%) and clomipramine (23.1%) accounted for the majority of TCA prescriptions (n=59,836).

Table 2 shows that compared with controls, cases were significantly more likely to have used a benzodiazepine in the previous 3 months and/or an antidepressant, an antipsychotic, anticonvulsant, oral glucocorticoid, opiate or drug for Parkinson's disease within the previous 6 months. In addition, cases were significantly more likely than controls to have a history of cerebrovascular disease or malignant neoplasm.

Table 2: Baseline characteristics of the study population

	Cases (n=6,763)	(%)	Controls (n=26,341)	(%)	Crude odds ratio (95% CI)
Mean age in years	75.7		75.3		
Age					
18 to 49 years	452	6.7	1,808	6.9	
50 to 69 years	1,061	15.7	4,239	16.1	
≥70 years	5,250	77.6	20,294	77.0	
Number of females	4,929	72.9	19,138	72.7	
Drug use before the index date					
TCAs	256	3.8	591	2.2	1.75 (1.51–2.04)
SSRIs	315	4.7	582	2.2	2.20 (1.91–2.54)
Antipsychotics[a]	412	6.1	921	3.5	1.79 (1.58–2.02)
Anticonvulsants[a]	242	3.6	431	1.6	2.23 (1.90–2.61)
Benzodiazepines[b]	967	14.3	2,751	10.4	1.44 (1.33–1.56)
Oral glucocorticosteroids[a]	366	5.4	918	3.5	1.59 (1.40–1.80)
Thiazide diuretics[a]	146	2.2	557	2.1	1.01 (0.84–1.21)
Opiates[a]	253	3.7	455	1.7	2.24 (1.92–2.63)
Anti-Parkinson drugs[a]	397	5.9	833	3.2	1.94 (1.71–2.19)
≥2 NSAID dispensings[a]	929	13.7	2,584	9.8	1.46 (1.35–1.59)
Hospitalization before the index date					
Cardiovascular disease	359	5.3	1,289	4.9	1.10 (0.98–1.25)
Cerebrovascular disease	296	4.4	565	2.1	2.12 (1.84–2.45)
Malignant neoplasms	341	5.0	1,021	3.9	1.54 (1.37–1.74)

[a]Within the 6 months before the index date
[b]Within the 3 months before the index date

Table 3 provides crude and adjusted risk estimates for hip/femur fracture associated with antidepressant use according to recency of use, and the results of analyses amongst current users stratified by sex and age. Compared with individuals who had never used the antidepressant in question, the risk of hip/femur fracture increased with current use of SSRIs (crude OR 2.88 [95% CI, 2.40 – 3.46]) and TCAs (crude OR 2.22 [95% CI, 1.84 – 2.68]).

After adjustment for other variables associated with fracture risk, the ORs remained significantly increased (AOR 2.35 [95% CI, 1.94 – 2.84] for SSRIs and 1.76 [95% CI, 1.45 – 2.15] for TCAs). Under the assumption that the risk of hip fracture amongst users of SSRIs/TCAs is similar in the period 1991–2002 and 2003, we estimated that the population attributable risk of hip fracture is 1.1% for current users of TCAs and 4.4% for current users of SSRIs. For SSRIs, there was some effect modification by sex (AOR 2.50 [95% CI, 2.03 – 3.08] for females and 1.72 [95% CI, 1.08 – 2.74] for males) and age (AOR 2.00 [95% CI, 1.21 – 3.29] for SSRI users aged 18–69 years and 2.39 [95% CI, 1.94 – 2.94] for SSRI users aged ≥70 years).

Figure 1a shows a clear association between the time since the last dispensing of an SSRI and the risk of hip/femur fracture. The risk of hip/femur fracture, which was increased in current users, declined rapidly after discontinuation of use. A similar trend was observed for users of TCAs (Fig. 1b). The risk of hip/femur fracture was increased during the first few months of continuous use of SSRIs, peaking at about 8 months, and remained elevated after about 1.5 years of continuous use (Fig. 2a). Short-term exposure to TCAs showed a rapid increase in hip/femur fracture risk that declined after 1 year of exposure (Fig. 2b).

Table 4 presents the results of analysis amongst current users according to the average daily dose of antidepressant used. Compared with individuals who had never used an SSRI, medium and high dose SSRI users had a greater risk of fracture than low dose users, although the differences were not statistically significant. There was no evidence to suggest a dose–response relationship for the risk of hip/femur fracture with TCA use.

Table 3: Use of SSRIs and TCAs and the risk of hip/femur fracture

	Cases (n=6,763)	Controls (n=26,341)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Exposure to SSRIs				
Never exposed	6,174	25,041	1.00	1.00
Past use (>90 days before the index date)	303	820	1.52 (1.33–1.75)	1.23 (1.07–1.42)
Recent use (31–90 days before the index date)	86	193	1.87 (1.45–2.42)	1.48 (1.14–1.93)
Current use (1–30 days before the index date)	200	287	2.88 (2.40–3.46)	2.35 (1.94–2.84)
By gender				
Males	33	59	2.30 (1.48–3.59)	1.72 (1.08–2.74)
Females	167	228	3.02 (2.46–3.70)	2.50 (2.03–3.08)
By age				
Age 18–69 years	33	44	3.07 (1.95–4.82)	2.00 (1.21–3.29)
Age ≥70 years	167	243	2.84 (2.32–3.48)	2.39 (1.94–2.94)
Exposure to TCAs				
Never exposed	6,175	24,864	1.00	1.00
Past use (>90 days before the index date)	360	978	1.52 (1.34–1.72)	1.14 (1.00–1.30)
Recent use (31–90 days before the index date)	56	176	1.32 (0.97–1.79)	0.98 (0.72–1.34)
Current use (1–30 days before the index date)	172	323	2.22 (1.84–2.68)	1.76 (1.45–2.15)
By gender				
Males	29	43	2.85 (1.76–4.62)	2.19 (1.31–3.67)
Females	143	280	2.11 (1.72–2.60)	1.69 (1.36–2.09)
By age				
Age 18–69 years	31	60	2.18 (1.40–3.40)	1.31 (0.80–2.14)
Age ≥70 years	141	263	2.22 (1.80–2.74)	1.81 (1.46–2.25)

[a]SSRI use was adjusted for (a) current use of an antidepressant other than SSRI, (b) use in the past 3 months of a benzodiazepine; (c) use in the past 6 months of oral corticosteroids, hormone replacement therapy, antipsychotics, beta-blockers, opioids, anticonvulsants, drugs for diabetes, more than two dispensings of an NSAID, DMARDs and metoclopramide and (d) a history of malignant neoplasms, mental disorders, cerebrovascular diseases, obstructive airway diseases or inflammatory bowel diseases. TCA use was adjusted for current use of an antidepressant other than TCA and other potential confounders as listed above (b)–(d) for SSRI use

Table 4: Current use of SSRIs and TCAs and the risk of hip/femur fracture by average daily dose

Average daily dose (DDD)	Cases	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)[c]
Current SSRI use[a]				
One prescription before the index date	16	30	2.15 (1.17–3.96)	1.72 (0.92–3.21)
Low (<0.5)	22	47	1.88 (1.13–3.13)	1.50 (0.89–2.53)
Medium (0.5–1.0)	77	95	3.40 (2.51–4.62)	2.77 (2.03–3.80)
High (>1.0)	85	115	3.08 (2.31–4.09)	2.49 (1.86–3.34)
Current TCA use[b]				
One prescription before the index date	12	21	2.39 (1.17–4.86)	1.95 (0.94–4.06)
Low (<0.5)	95	186	2.13 (1.66–2.74)	1.73 (1.33–2.24)
Medium (0.5–1.0)	53	91	2.41 (1.71–3.38)	1.82 (1.28–2.58)
High (>1.0)	12	25	1.99 (1.00–3.97)	1.35 (0.66–2.79)

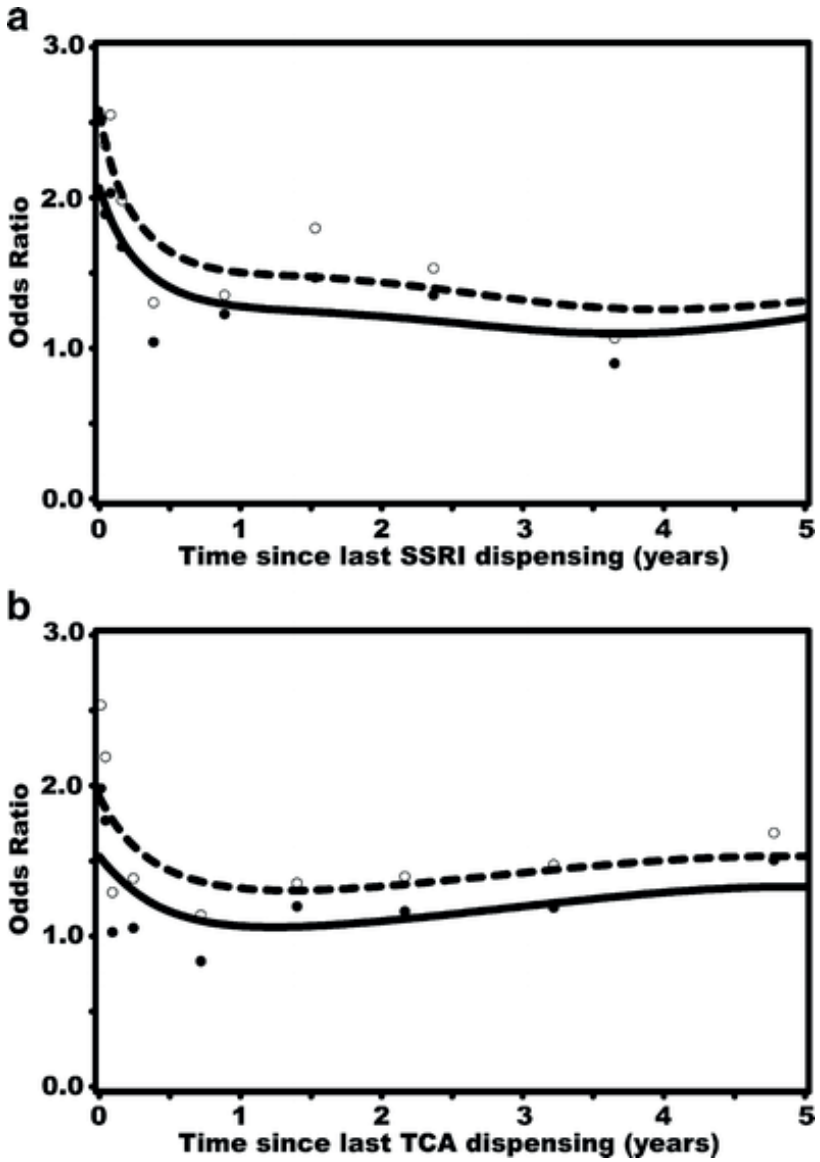
[a]Referent: never exposed to SSRIs
[b]Referent: never exposed to TCAs
[c]Adjustments were made for the confounders listed in the footnote of Table 3

Table 5: Risk of hip/femur fracture by degree of serotonin (5-HT) transporter inhibition

	Cases (n=6,763)	Controls (n=26,341)	Adjusted OR (95% CI)[a]
Never exposed	5,677	23,698	1.00
Past use (>90 days before the index date)	506	1,514	1.19 (1.76–2.29)
Recent use (31–90 days before the index date)	158	404	1.32 (1.09–1.61)
Current use (1–30 days before the index date)	422	725	2.01 (1.76–1.29)
Low 5-HT transporter inhibition	46	102	1.64 (1.14–2.35)
Medium 5-HT transporter inhibition	132	241	1.92 (1.53–2.40)
High 5-HT transporter inhibition	234	358	2.31 (1.94–2.76)
Not classified	10	24	1.44 (0.67–3.04)

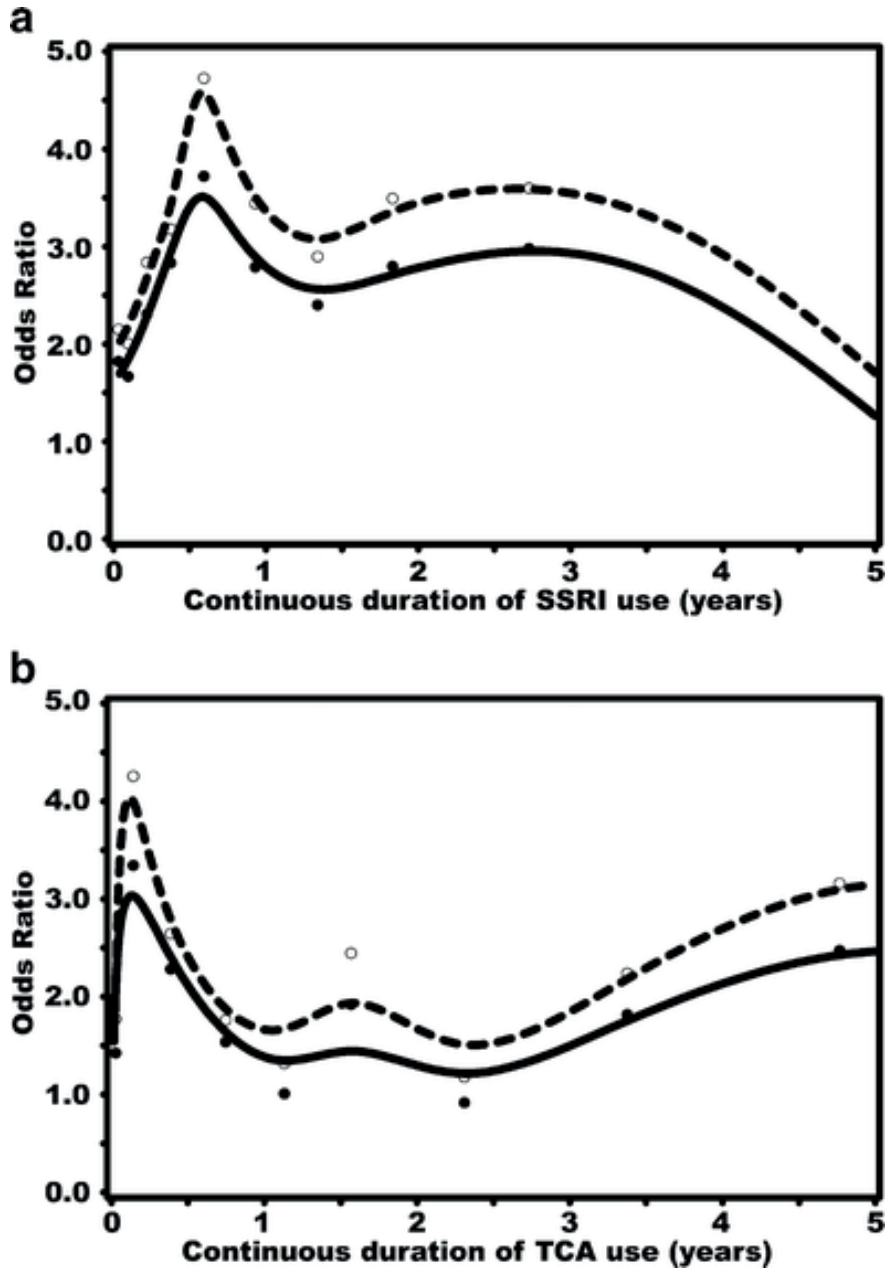
[a]Adjustments were made for the confounders listed in the footnote of Table 3

Figure 1: Recency of SSRI (a) and TCA (b) use before the index date and risk of hip/femur fracture.



Dashed lines and open dots: crude ORs with 95% CI; solid lines and solid dots: adjusted ORs with 95% CI. Adjustments were made for the same confounders as in Table 3.

Figure 2: Recency of SSRI (a) and TCA (b) duration of continuous use amongst current users before the index date and risk of hip/femur fracture.



Dashed lines and open dots: crude ORs with 95% CI; solid lines and solid dots: adjusted ORs with 95% CI. Adjustments were made for the same confounders as in Table 3.

Table 5 presents the results of analyses amongst all antidepressant users, where current users were grouped according to the degree of 5-HTT inhibition afforded by the different drugs. The risk of hip/femur fracture increased as the degree of 5-HTT inhibition increased from AOR 1.64 [95% CI, 1.14 – 2.35] for drugs with low 5-HTT inhibition to AOR 2.31 [95% CI, 1.94 – 2.76] for those with high 5-HTT inhibiting properties. Users of antidepressants with stronger anticholinergic properties, or a strong potential to induce orthostatic hypotension, did not have higher risks of hip fracture compared to users of antidepressants with weaker properties (data not shown).

Discussion

This study has demonstrated an increased risk hip/femur fracture for current users of SSRIs and TCAs. For both SSRIs and TCAs, the increased risk declined rapidly about 6 months after discontinuation of use. Fracture risk associated with SSRIs and TCAs was the greatest during the first few months of use and an elevated risk persisted with continuous use of SSRIs. We found some evidence for a dose effect with SSRIs but not TCAs. Furthermore, we found evidence to suggest that the risk of fracture was greater amongst people using antidepressants with a higher degree of 5-HTT inhibition.

The magnitude of increased fracture risk with antidepressant use described here is in line with findings from other epidemiological studies [9,15–17,24]. Those studies that compared risk with SSRIs and TCAs [9,15,16] similarly reported no difference in risk. There is also evidence to support our observation of an increased risk during the initial period of exposure [15,16]. Richards et al. [17] investigated fracture risk with SSRIs and reported a dose effect and a sustained elevation in risk with prolonged use. Vestergaard et al. reported a dose-dependent increase in fracture risk for sedating TCAs and most SSRIs. Furthermore, they also found an association between the increase in risk of any fracture and the inhibition of the

serotonin transporter system [24].

We observed a similar increase in fracture risk for users of SSRIs and TCAs. The explanation for that increased fracture risk may be related simply to an increase in the risk of falls associated with antidepressant use, especially as there is evidence to suggest that both SSRIs and TCAs are associated with an increased risk of fall. A large study of nursing home residents showed that, compared with non-users and after adjusting for potential confounders, the risk of falls was similar in new users of TCAs and SSRIs. The association was dose dependent and the increased risk persisted through the first 180 days of use and beyond [8]. TCAs are known to inhibit cardiovascular Na+, Ca2+ and K+ channels which can lead to life-threatening arrhythmias. SSRI use has been associated with an increased risk of syncope [33], postural hypotension and dizziness [34] during the early days of exposure, and both SSRIs and TCAs can affect sleep patterns [35,36], thereby increasing the risk of falls [37].

Another explanation for the increased fracture risk observed here is the effect of antidepressants on bone physiology. Functional 5-HT receptors are present in bone cells and 5-HT stimulates proliferation of osteoblast precursor cells in vitro [23]. There is emerging evidence from animal studies that 5-HT is involved in bone remodeling and can alter bone mineral density (BMD) [18–20,22]. Indeed, recent findings have shown that SSRIs decrease BMD in animal models [38] and humans [17,39–41]. Such studies that compared BMD changes with different antidepressants reported no association between TCA use and BMD [39,40]. In a recent study of osteoporotic fractures, it was observed that the use of SSRIs (but not TCAs) in older women was independently associated with an increased rate of hip bone loss (0.82% reduction per year) [41], although there was limited information on dose and duration of use.

To explore the possibility that fracture risk may be directly related to inhibition of the 5-HTT system, we grouped together the antidepressants used according to the degree of 5-HTT

inhibition afforded. It was apparent that the risk of hip/femur fracture increased as the degree of 5-HTT inhibition increased. Whilst none of the risk estimates was significantly different, a clear trend was evident and this supports the possibility that stronger inhibition of the 5-HTT system on the bone could cause a greater disruption of the balance between osteoblasts and osteoclasts and hence have a greater detrimental effect on bone micro-architecture.

Drug-induced changes in bone micro-architecture can be rapid. Analysis of the micro-architecture of femur bone in rats treated with 5-HT showed changes in trabecular bone volume and an increased femoral stiffness after just 3 months [10]. Other drug exposures had demonstrated similarly rapid effects on human bone, e.g. corticosteroids [42,43]. It is possible that a rapid change in bone micro-architecture affected by antidepressant use accounted for, or at least contributed to, the increased fracture risk during the early months of exposure.

We found that as the duration of treatment with TCAs increased, the risk of fracture declined, whereas the risk for fracture with continuation of SSRIs fell after the initial increase but remained somewhat elevated thereafter. It may be that with chronic administration of antidepressants, adaptive changes occur [44]. These may result in an adjustment to the cardiovascular effect of TCAs and SSRIs, explaining the decrease in fracture risk after a few months of use, whereas changes in bone physiology are not subject to adaptive changes, explaining the sustained fracture risk in SSRI users.

Limitations of our study include absence of potentially confounding data on body mass index (BMI), smoking status and exercise. In a US/Puerto Rican cohort study, it was likely that lack of adjustment for BMI, current smoking status, activities of daily living score, cognitive impairment and Rosow–Breslau physical impairment scale accounted for up to 30% of the increased risk of hip fractures amongst users of SSRIs [45]. We do not anticipate that missing data on these variables would have an important impact on our findings; therefore, as if our ORs were decreased by 30%, a positive association would remain. Another limitation lies in

the potential for confounding by indication, as depression itself is associated with an increased risk of falls and fractures [46]. There is also the possibility of a channeling effect whereby, for some frail patients with depression, an SSRI was prescribed instead of a TCA because of the more favorable side-effect profile anticipated. This could have overestimated the risk associated with SSRIs observed here. These unmeasured types of confounding as well as selection bias (e.g. healthy user bias), which can change over time, may be alternative explanations for our observed associations between fracture risk and duration of antidepressant use or discontinuation of antidepressants. In Figs. 1 and 2, data beyond 4 years are sparse, which makes extrapolation uncertain. Lastly, the PAR calculation showed that 4.4% of hip fractures in The Netherlands might be attributed to current use of SSRI; however, given the previous limitations and the susceptibility of our study for unmeasured distortions, this figure should be interpreted with great care.

One of the strengths of this study is size of the population available and the reliability of information on prescribing and hospitalizations. Furthermore, the longitudinal nature of recording has two advantages. First, to our knowledge, this is the only study where duration of use analysis has allowed speculation on the effects of antidepressants on bone. Second, this is the second study to evaluate the effect of 5-HTT inhibition on fracture risk estimates.

In summary, our findings demonstrate that both SSRIs and TCAs increase the risk of hip/femur fracture in current users and that the risk increases with the degree of 5-HTT inhibition afforded by different antidepressants. We did not find convincing evidence for a dose effect. The pathophysiology can be fall-related and/or bone-related. Further studies, including controlled prospective trials, are needed to evaluate the relative contribution of disease-related and treatment-related effects to the increased risk of falls and hip/femur fractures and to elucidate the pathophysiology. Until then, physicians prescribing antidepressants should consider the elevated risk for fractures in elderly, possibly frail, people

using antidepressants and value the rule: “start low, go slow.

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Chapter 2.3

Antipsychotic use and the risk of hip/femur fracture: a population-based case-control study

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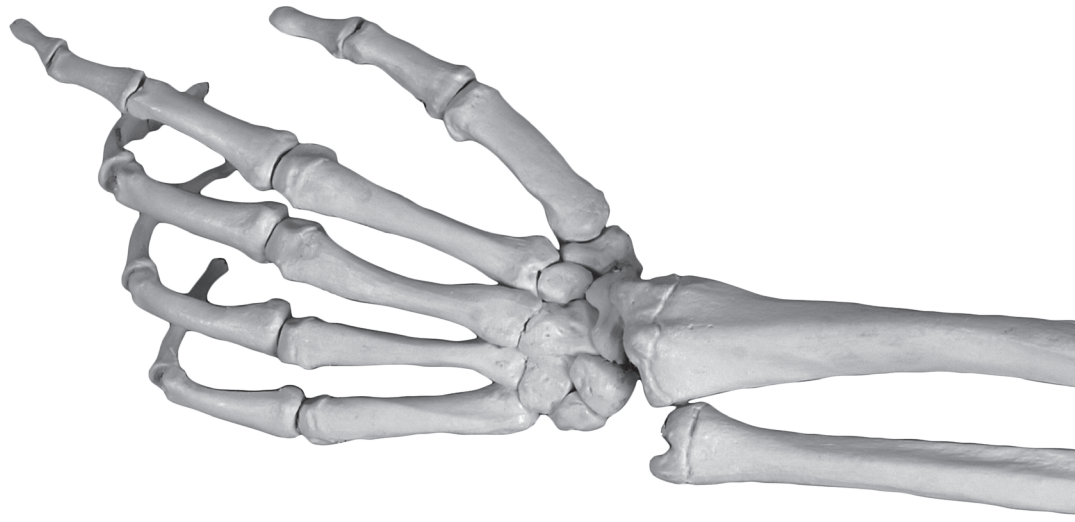


Abstract

Objective: To assess the risk of hip/femur fracture associated with antipsychotic use, with particular reference to any difference in risk with conventional versus atypical antipsychotics, dose and pharmacological properties.

Methods: A case-control study was conducted using data from the PHARMO Record Linkage System amongst individuals aged 18 years and older between 1991 and 2002. Cases had a record of a hip or femur fracture, while controls had no evidence of ever having sustained any fracture.

Results: Most cases were elderly (77.6% aged $\geq$ 70 years). We found an increased risk for hip/femur fracture associated with the use of antipsychotic drugs. The risk for current users (adjusted odds ratio [AOR] 1.68 [95% confidence interval (CI), 1.43 - 1.99]) was significantly greater than with past use (AOR 1.33 [95% CI, 1.14 - 1.56]). Current use of conventional antipsychotics (AOR 1.76 [95% CI, 1.48 - 2.08]) but not atypical antipsychotics (AOR 0.83 [95% CI, 0.42 - 1.65]) was associated with an increased risk. We did not find evidence for a dose effect.

Conclusion: The use of conventional, but not atypical antipsychotics, seems to be associated with an increased risk of hip/femur fracture, possibly related to the pharmacological properties of conventional antipsychotics. However, the numbers of atypical antipsychotic users were small, and therefore this observation needs further attention in other study populations.

Introduction

Antipsychotics are common in the treatment of schizophrenia, affective disorders, organic psychosis and dementia [1, 2]. The side effects associated with antipsychotic use include sedation, extrapyramidal symptoms (EPS) and orthostatic hypertension, all of which may increase the risk of falls, especially during the initial period of exposure [3]. Conventional antipsychotics (e.g. haloperidol, chlorpromazine) and the atypical antipsychotic risperidone at high-dose have a high affinity for dopamine D_2 receptors [4]. This pharmacological property is clearly associated with the risk of EPS but also gives rise to elevated prolactin levels [5, 6]. In contrast, most atypical antipsychotics like clozapine, olanzapine, quetiapine, and low-dose risperidone have a higher affinity for the 5-hydroxytryptamine-2A ($5\text{-}HT_{2A}$) receptor than for dopamine D_2 receptors [4]. Blocking of the $5\text{-}HT_{2A}$ receptor has been associated with lowered prolactin levels. In contrary, the stimulating of $5\text{-}HT_{2\,A}$ receptors has been linked to increased prolactin levels [7]. The latter is the case when using a selective serotonin reuptake inhibitor (SSRI).

Elevated serum prolactin may reduce bone mineral density (BMD) in the long-term [6, 8, 9]. O'Keane et al. [10] found that the BMD of patients using prolactin-raising antipsychotics was significantly lower than that of users of antipsychotics without prolactin-raising properties. In line with these results are the findings that patients using SSRI's also experience a lower BMD [11] and have an increased risk of fracture [12].

Several epidemiological studies have reported an increased risk of hip or femur fracture amongst users of antipsychotics [13-19]. One study found a relationship between dose and use of antipsychotics, regardless of timing of exposure, although this was not reported for current users [17], Liperoti et al. found no difference in fracture risk between conventional and atypical antipsychotics [15], whereas Howard et al. found an increased risk for individuals using prolactin-raising antipsychotics [13]. In addition, there is some evidence to suggest that

men using antipsychotics have a greater risk of fracture than women [13].

The aims of this study were to evaluate the association between the use of antipsychotics and the risk of fracture of the hip or femur for men and women, to derive risk estimates separately for conventional and atypical antipsychotics, and to investigate the risk associated with dose and pharmacological properties.

Methods

Setting and study design

We conducted a case-control study within the Dutch PHARMO Record Linkage System (RLS) (www.pharmo.nl). The database includes the demographic details and complete medication histories for about one million community-dwelling residents in the Netherlands representing some 7% of the general population. Data are available from 1986 onwards and are linked to hospital discharge records as well as several other health registries, including pathology, clinical laboratory findings and general practitioner data. Almost every individual in the Netherlands is registered with a single community pharmacy, independent of prescriber and irrespective of his or her health insurance or socioeconomic status. Pharmacy records have a high degree of completeness with regard to dispensed drugs [20]. Pharmacy data include information about the drug dispensed, the date of dispensing, the prescriber, the amount dispensed, the prescribed dosage regimen and the estimated duration of use. Hospital discharge records include detailed information on date of admission, discharge diagnoses and procedures. Validation studies on PHARMO RLS have confirmed a high level of data completeness and validity with regards to fractures [21]; PHARMO has been used more often to address risk factors of hip/femur fracture risk [22-24].

Study population

Data were collected for the period 1 January 1991 to 31 December 2002. Cases were patients aged 18 years and older with a record for a first fracture of the hip or femur during the study period. The date of hospital admission was used to define the index date. Each case was matched by year of birth, sex and geographical region to up to four control patients without any evidence of ever having sustained a fracture during data collection. The controls were assigned the same index date as the corresponding case.

Exposure assessment

Exposure to antipsychotics (Anatomical and Therapeutic Chemical [ATC] category N05A excluding lithium [25]) was determined by reviewing dispensing information before the index date. 'Current' users were patients who had been dispensed at least one antipsychotic within the 30-day period before the index date. 'Recent' users were those who had been dispensed an antipsychotic between 31 days and 182 days before the index date. 'Past' users were patients who had one or more dispensings for an antipsychotic but who had stopped treatment more than 182 days before the index date.

For each current user the average daily dose was estimated by dividing the total amount of antipsychotics dispensed by the treatment time. Average daily doses were expressed in haloperidol equivalents using defined daily dosages [25]. The duration of continuous use was calculated using the expected duration of use (in days) for each dispensing (the dispensed amount of the drug divided by the recorded dosage instruction). The total exposure period was defined as the sum of the total expected durations of use from all dispensings. If the period between two antipsychotic dispensings exceeded 6 months this was considered a gap in treatment. Drugs dispensed before the gap were not included when calculating the period of continuous use.

Antipsychotic drugs were classified as atypical (quetiapine, clozapine, risperidone,

olanzapine) or conventional (pipamperone, haloperidol, zuclopenthixol, thioridazine, levomepromazine and 'others') (Table 1). The most recently dispensed antipsychotic was used to define the type. When more than one dispensing was issued all dispensings were taken into account.

Amongst current users we assessed the sedative, extrapyramidal, prolactin-raising and orthostatic hypotensive pharmacological properties of the antipsychotic dispensed as determined by an extensive review of the literature [1, 4, 6, 26-32] (Table 1).

Table 1: Categorization of antipsychotic drugs and side effect profiles

Group	Generic name	Sedative properties	EPS[a] properties	Prolactin properties	OH[b] properties
Atypical	Clozapine	High	Low	Non-Raising	High
	Olanzapine	Medium	Low	Non-Raising	Medium
	Quetiapine	Medium	Low	Non-Raising	Medium
	Risperidone	Medium	Medium	-	Medium
	Risperidone ≤ 4mg/day	-	-	Non-Raising	-
	Risperidone > 4mg/day	-	-	Raising	-
Conventional	Haloperidol	Low	High	Raising	Low
	Levomepromazine	High	Medium	Raising	Medium
	Pipamperone	High	Low	Raising	Medium
	Thioridazine	High	Low	Raising	High
	Zuclopenthixol	Medium	Medium	Raising	High
Other conventional	Benperidol	High	Low	Raising	Low
	Bromperidol	Low	High	Raising	Low
	Chlorpromazine	High	Medium	Raising	High
	Chlorprothixene	Medium	Medium	Raising	High
	Droperidol	Medium	Medium	Raising	Medium
	Flupentixol	Low	Medium	Raising	Medium
	Fluphenazine	Low	High	Raising	Medium
	Fluspirilene	Low	Medium	Raising	Medium
	Penfluridol	High	Medium	Raising	Low
	Perazine	High	Low	Raising	High
	Periciazine	High	Medium	Raising	Medium
	Perphenazine	Medium	Medium	Raising	Low
	Pimozide	Low	Medium	Raising	Low
	Prochlorperazine	Medium	High	Raising	Medium
	Sulpiride	Low	Medium	Raising	Low
	Tiapride	Low	Low	Raising	Low
	Trifluoperazine	Low	High	Raising	Low

a) EPS: Extropyramidal symptoms
b) OH: Orthostatic hypotension

If more than one antipsychotic had been prescribed before the index date, we selected the drug

with the most severe side effect profile.

Potential confounders

The records of cases and controls were reviewed for evidence of potential confounders that have been associated with fracture risk [33, 34]. These included a recent history (in the previous year) of anemia, mental disorders, impaired renal function, injuries, and skin or subcutaneous diseases and a history at any time of malignant neoplasm, endocrine disorder, cardiovascular disease, cerebrovascular disease, obstructive airway disease, inflammatory bowel disease, musculoskeletal or connective tissue disease, rheumatoid arthritis, polymyalgia rheumatica or ankylosing spondylitis. Other potential confounders included a dispensing within 3 months before the index date of a benzodiazepine or a prescription within the previous 6 months for the any of the following: eye drops, bronchodilators, inhaled or oral corticosteroids, statins, hormone replacement therapy, lithium, antidepressants, beta-blockers, opioids, anti-arrythmics, anticonvulsants, thiazide diuretics, renin-angiotensin-aldosterone system (RAAS) inhibitors, thyroid and anti-thyroid hormones, drugs for diabetes, disease-modifying anti-rheumatic drugs (DMARDs), metoclopramide, $5HT_3$ antagonists and two or more prescriptions for a non-steroidal anti-inflammatory drug (NSAID).

Statistical Analysis

Odds ratios (ORs) were derived for the risk of hip/femur fracture associated with the use of antipsychotics and the various potential confounding variables. Adjusted odds ratios (AORs) for hip/femur fracture were estimated by comparing antipsychotic use with no use determined by conditional logistic regression analysis. Final regression models were determined by stepwise backward elimination using a significance level of 0.05. Significant differences between categories were determined with the Wald statistic option of the PHREG procedure of

SAS 9.1.

Analyses were conducted to evaluate the risk of fracture associated with current exposure to antipsychotics versus no use, grouping current users according to the daily dose of antipsychotic prescribed, whether the antipsychotic prescribed was conventional or atypical and according to the severity of expected side effects. We also stratified the study population to assess the risk with current use by age and sex.

Results

Table 2 shows the baseline characteristics of cases and controls. We identified 6,763 cases with a fracture of the hip or femur and 26,341 matched controls. Almost three-quarters (73%) of the study population was female.

Table 2: Characteristics of cases and controls

Characteristic	Cases (n=6,763)	(%)	Controls (n=26,341)	(%)
Age (years)				
18-49	452	6.7	1,808	6.9
50-69	1,061	15.7	4,239	16.1
≥ 70	5,250	77.6	20,294	77.0
Number of females	4,929	72.9	19,138	72.7
Medical history				
Rheumatoid arthritis	353	5.2	1,108	4.2
Cardiovascular disease	359	5.3	1,289	4.9
Malignant neoplasm	391	5.8	1,021	3.9
Inflammatory bowel disease	361	5.3	921	3.5
Cerebrovascular disease	296	4.4	565	2.1
Drug use in 6 months before index date				
Oral glucocorticoids	366	5.4	918	3.5
DMARDs	115	1.7	202	0.8
Antidepressants	643	9.5	1,343	5.1
Anxiolytics	1,170	17.3	3,451	13.1
Anticonvulsants	494	7.3	938	3.6
Lithium	18	0.3	34	0.1
Hormone replacement therapy	77	1.1	347	1.3
Bisphosphonates	261	3.9	616	2.3

The mean duration of follow-up before the index date was 5.8 years for cases and 5.7 years for controls. The median age was 79 years for cases and controls. The median duration of use for

current users was 30 days (determined from 94% of current users).

The use of antipsychotic drugs by cases and controls and the results of conditional logistic regression analysis are presented in Table 3. Antipsychotic drug use was significantly higher amongst cases compared with controls, with a trend towards increased risk of hip/femur fracture with recency of use. Current use of antipsychotics was associated with a significantly increased risk of hip/femur fracture compared with no use (AOR 1.68 [95% CI, 1.43 - 1.99]) and the risk associated with current use was significantly greater than that associated with past use (AOR 1.33 [95% CI, 1.14 - 1.56]). When current use was defined by daily dose, the risk estimates for fracture did not demonstrate a dose-response relationship. Further stratified analyses suggested that the risk of hip/femur fracture for current users of antipsychotics was greater for men (AOR 1.93 [95% CI, 1.28 - 2.90]) than for women (AOR 1.63 [95% CI, 1.36 - 1.96]), although not significantly so. Similarly, risk was increased for individuals aged ≥ 70 years (AOR 1.74 [95% CI, 1.46 - 2.06]), but not for younger patients (AOR 0.95 [95% CI, 0.48 - 1.87]).

Figure 1 presents ORs for hip/femur fracture with duration of continuous use before the index date amongst current users. There was a marked increase in fracture risk during the first 8 months of continuous antipsychotic use (AOR 2.83 [95% CI, 1.75 - 4.57]) and evidence to suggest a second period of increased risk as the duration of continuous use approached 2 years.

The current use of atypical antipsychotics did not appear to increase the risk of hip/femur fracture (AOR 0.83 [95% CI, 0.42 - 1.65]) (Table 4). The risk associated with current use of conventional antipsychotics (AOR 1.76 [95% CI, 1.48 - 2.08]) was increased, however, and was significantly greater than with the use of atypical antipsychotics (p=0.038).

Table 5 presents the ORs for hip/femur fracture according to the pharmacological profile of the antipsychotic in current use. The use of antipsychotics with high prolactin-raising properties(i.e. most conventional antipsychotics and risperidone > 4mg/day) was

Table 3: Risk of hip/femur fracture with antipsychotic use versus no use, including risk estimates (derived by conditional logistic regression analysis) for current use overall and by daily dose, and for current use by sex and age-group.

Antipsychotic use[a]	Cases (n= 6,763)	Controls (n= 26,341)	Crude OR (95% CI)	Adjusted OR (95% CI)[b]
No use	6,105	24,770	1.00	1.00
Past use	249	653	1.57 (1.35 - 1.83)	1.33 (1.14 - 1.56)[c]
Recent use	172	425	1.63 (1.36 - 1.96)	1.38 (1.15 - 1.66)
Current use	237	493	2.00 (1.70 - 2.35)	1.68 (1.43 - 1.99)[c]
By average daily dose, mg/day[d]				
First time users	71	150	1.98 (1.48 - 2.63)	1.60 (1.19 - 2.15)
<0.8	60	122	2.04 (1.49 - 2.79)	1.79 (1.30 - 2.47)
0.8-1.9	60	126	2.01 (1.47 - 2.75)	1.66 (1.20 - 2.30)
≥ 2	46	95	1.96 (1.37 - 2.80)	1.71 (1.19 - 2.46)
By gender				
Females	193	419	1.90 (1.59 - 2.27)	1.63 (1.36 - 1.96)
Males	44	74	2.53 (1.72 - 3.72)	1.93 (1.28 - 2.90)
By age category				
Ages 18-69 years	15	35	1.78 (0.97 - 3.28)	0.95 (0.48 - 1.87)
Ages ≥ 70 years	222	458	2.00 (1.69 - 2.37)	1.74 (1.46 - 2.06)

a) For current, recent and past users the last antipsychotic was dispensed respectively within 30, between 31 – 182 and more than 182 days prior to the index date.
b) Adjusted for a history of malignant neoplasm, anaemia, endocrine disorders, skin or subcutaneous disease, cerebrovascular disease, obstructive airway disease, musculoskeletal or connective tissue disease, use of benzodiazepines, inhaled or oral glucocorticoids, statins, antidepressants, beta-blockers, opioids, anticonvulsants, RAAS-inhibitors, drugs for diabetics, DMARDs, metoclopramide and two or more NSAID dispensing.
c) Significant difference between current and past use of antipsychotics (p=0.036 after Wald test).
d) Haloperidol equivalents.

Table 4: Risk of hip/femur fracture with current antipsychotic use according to class and type of antipsychotic

Antipsychotic use[a]	Cases (n= 6,763)	Controls (n= 26,341)	Crude OR (95% CI)	Adjusted OR (95% CI)[b]
No use	6,105	24,770	1.00	1.00
Past use	249	653	1.57 (1.35 - 1.83)	1.33 (1.14 - 1.56)
Recent use	172	425	1.63 (1.36 - 1.96)	1.38 (1.15 - 1.66)
Current use	237	493	2.00 (1.70 - 2.35)	1.68 (1.43 - 1.99)
Conventional antipsychotics[c]	227	453	2.08 (1.78 – 2.48)	1.76 (1.48 - 2.08)[d]
Pipamperone	70	165	1.71 (1.29 - 2.28)	1.54 (1.15 - 2.06)
Haloperidol	75	106	2.87 (2.13 - 3.86)	2.33 (1.72 - 3.18)
Zuclopenthixol	38	56	2.78 (1.83 - 4.21)	2.44 (1.59 - 3.75)
Thioridazine	7	17	1.59 (0.64 - 3.93)	1.51 (0.60 - 3.78)
Levomepromazine	8	27	1.01 (0.45 - 2.28)	0.80 (0.35 - 1.82)
Others	34	96	1.39 (0.93 - 2.07)	1.19 (0.79 - 1.78)
Atypical antipsychotics[c]	11	44	0.95 (0.48 - 1.86)	0.83 (0.42 - 1.65)[d]
Risperidone	8	32	0.95 (0.43 - 2.10)	0.84 (0.38 - 1.88)
Quetiapine, olanzapine, clozapine	3	12	0.93 (0.26 - 3.34)	0.83 (0.23 - 3.02)

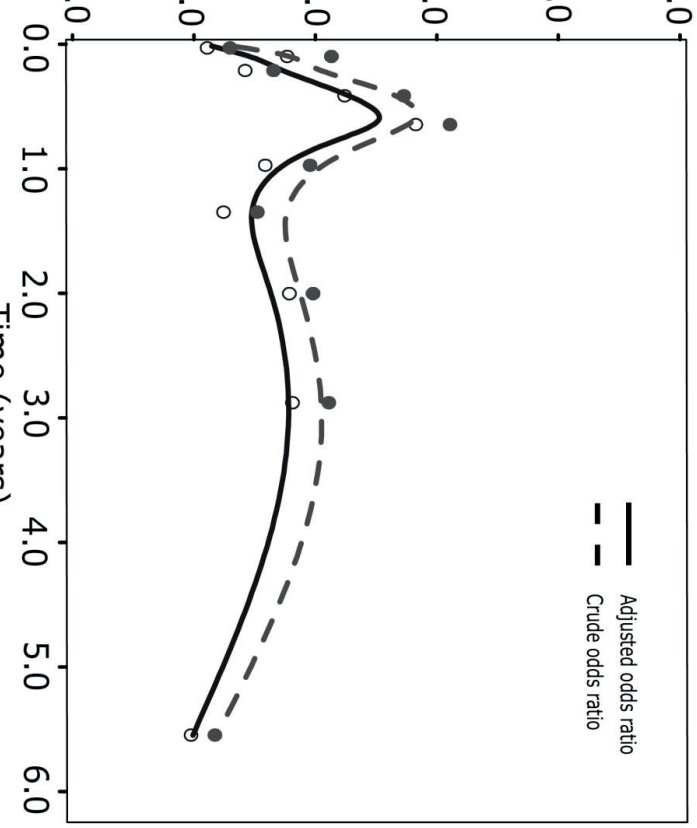
a) If more than one antipsychotic had been dispensed before the index date, then all dispensings were taken into account. For current, recent and past users the last antipsychotic was dispensed respectively within 30, between 31 – 182 and more than 182 days prior to the index date.
b) In both the crude as is the adjusted analysis also adjusted for other antipsychotics
c) Adjusted for confounders as presented in Table 3
d) Significant difference between conventional antipsychotics and atypical antipsychotics (p=0.038 after Wald test).

Table 5: Risk of hip/femur fracture with current antipsychotic use according to the pharmacological properties

Antipsychotic use[a]	Cases (n= 6,763)	Controls (n= 26,341)	Crude OR (95% CI)	Adjusted OR (95% CI)[b]
No use	6,105	24,770	1.00	1.00
Past use	249	653	1.57 (1.35 - 1.83)	1.33 (1.14 - 1.56)
Recent use	172	425	1.63 (1.36 - 1.96)	1.38 (1.15 - 1.66)
Current use	237	493	2.00 (1.70 - 2.35)	1.68 (1.43 - 1.99)
Sedative properties				
Low	89	144	2.54 (1.95 - 3.31)	2.09 (1.59 - 2.74)
Medium	53	125	1.78 (1.28 - 2.47)	1.50 (1.07 - 2.10)
High	95	224	1.75 (1.37 - 2.24)	1.51 (1.17 - 1.94)
EPS properties				
Low	80	191	1.73 (1.33 - 2.26)	1.55 (1.18 - 2.04)
Medium	74	163	1.90 (1.44 - 2.51)	1.58 (1.18 - 2.10)
High	83	139	2.46 (1.87 - 3.24)	1.97 (1.49 - 2.61)
Prolactin properties				
Non-raising	10	39	1.06 (0.52 - 2.12)	0.91 (0.45 - 1.85)
Raising	227	454	2.08 (1.76 - 2.45)	1.75 (1.48 - 2.08)
Orthostatic hypotensive properties				
Low	97	157	2.55 (1.98 - 3.29)	2.08 (1.60 - 2.71)
Medium	92	257	1.49 (1.17 - 1.90)	1.27 (0.99 - 1.64)
High	48	79	2.50 (1.74 - 3.59)	2.19 (1.51 - 3.18)

a) When more than one antipsychotic was dispensed simultaneously before the index date, then the antipsychotic with the most severe side-effect was selected. For current, recent and past users the last antipsychotic was dispensed respectively within 30, between 31 – 182 and more than 182 days prior to the index date.
b) Adjusted for confounders as presented in Table 3

Figure 1: The risk of hip/femur fracture with duration of continuous antipsychotic use (years) before the index date amongst current users



associated with an increased risk of hip/femur fracture (AOR 1.75 [95% CI, 1.48 - 2.08]), whereas antipsychotics with low prolactin-raising properties (i.e. most atypical antipsychotics including risperidone $\leq$ 4 mg/day) were not associated with an increased risk of fracture (AOR 0.91 [95% CI, 0.45 - 1.85)]. After comparison of both groups no significant difference was observed. Analysis stratifying current use according to the EPS properties of the antipsychotics suggested a trend towards increased risk with increasing EPS (AOR 1.55 [95% CI, 1.18 - 2.04] for low EPS and AOR 1.97 [95% CI, 1.49 - 2.61] for high EPS), but this trend did not reach statistical significance. There was no apparent association between the degree of potential orthostatic hypotensive or sedative side effects and the risk of hip/femur fracture.

Discussion

The findings of this study have demonstrated an increased risk of hip/femur fracture with the use of antipsychotics. The risk was highest for current users, especially the most elderly. The use of conventional antipsychotics appeared to account for the increased risk and there was evidence for an increased risk with prolactin-raising antipsychotics and those with greater potential to affect the extrapyramidal system. We did not find evidence to support an association between the average daily dose of antipsychotic and the risk of hip/femur fracture.

Our findings confirm an association described in other epidemiological studies on the risk of hip/femur fracture with the use of antipsychotics [13-19]. The 1.7-fold increased risk of fracture amongst current users and declining risk after discontinuation of use agrees with the findings of others**.** Hugenholtz et al. [18] reported a 1.3-fold increased adjusted risk of fracture amongst current users who had been using antipsychotics long-term, and produced a plot similar to ours for risk with cumulative days of treatment (Figure 1). Ray et al. [16] reported a doubling of risk amongst current users (OR 2.0 [95% CI 1.6 - 2.6]), although that risk estimate may have been reduced with adjustment for more potential confounding variables.

In agreement with other recent studies, we did not find an association between the average daily dose of antipsychotic and the risk of hip/femur fracture for current users [17, 18]. Vestergaard et al. [17] described a dose-response relationship for all users of antipsychotics before the index date but the association was not apparent for current users and the elapsed time between the last dispensing and the index date could have been as much as 4 years. Although we found a higher fracture risk for men currently using antipsychotics, the difference between the sexes was not significant. A greater fracture risk for men using antipsychotics has been reported before [13], however, which could reflect the effects of antipsychotic use and physiological processes promoting bone loss [9].

The association between the risk of hip/femur fracture and the EPS and prolactin-

raising properties of the antipsychotic prescribed could explain the shape of curve derived by plotting the OR for fracture risk against the duration of antipsychotic use (Figure 1). The symptoms associated with extrapyramidal effects often start soon after the initiation of treatment and may be transient [35]. In addition, the sedative and orthostatic hypotensive side effects of antipsychotics often occur immediately after the start of treatment. The second period of increased risk after several months of use may reflect the effects of long-term hyperprolactinaemia on bone density. Indeed, Hugenholtz et al. [18] found an increased risk only amongst long-term users of antipsychotics and attributed this to the prolactin-raising properties of antipsychotics. We did not find an association between the sedative and orthostatic hypotensive side effects and fracture risk in our analyses.

One of the strengths of our study is the size of the study population (6,763 cases and 26,341 controls) and that it is representative for the general population of the Netherlands, although the absolute number of users of atypical antipsychotics was low. All prescribing information was collected routinely and we do not expect our findings to be biased with regards to exposure status. Also, as fractures invariably result in hospitalization, we are confident that cases, controls and index dates were identified reliably. Nevertheless, given the observational nature of this study, the results should be interpreted with knowledge of its limitations. First, cases and controls were not matched on the period of observation available in the database and the results could be affected by information bias. However, the exclusion of patients with less than one year of follow-up did not affect the results substantially. Second, information about relevant diagnoses and co-morbidities may have been recorded upon hospitalization for a fracture and it is likely that the information available for cases was more complete and up-to-date than that available for controls. It could be argued that we did not consider the use of bisphosphonates as a potential confounder. However, there should be a priori evidence, that a confounder is associated both with antipsychotic exposure and hip

fracture risk. As far as we know, there is no clear evidence that antipsychotic users are more likely to be exposed to bisphosphonates, compared to non-users. Moreover, in a case-control study the use of bisphosphonates may act as an intermediate variable between exposure and outcome, rather than a confounder. This is supported by the positive association between bisphosphonate use and hip fracture (crude OR: 1.71 [95% CI, 1.47 - 1.99], Table 2). Another potential limitation is the unavailability of data on smoking and alcohol consumption for a population that may include individuals with high levels of nicotine and/or alcohol consumption. Both are well known risk factors of fracture risk [36,37]. The possibility remains, therefore, that missing data on alcohol and smoking habit could (partially) explain the positive association between antipsychotic use and fracture risk.

Finally, the comparison between conventional and atypical antipsychotics should be interpreted with caution, because the analyses in the group of atypical antipsychotic users are based on a limited number of patients. Furthermore, atypical antipsychotics were introduced later into clinical use than typical antipsychotics, which may have led to different fracture risk profiles. Further studies are required to confirm these results. The same applies for the results regarding the prolactin raising properties.

Confounding by indication is an alternative explanation for the observed association between use of antipsychotics and risk of hip fracture. The PHARMO database does not contain routinely collected information on, for example, cognitive disorders and mental illnesses for the majority of their patients. Schizophrenia has been associated with perturbations in bone metabolism [10]. However, a study among >3,600 Finnish institutionalized elderly (mean age 83 years), showed that only 4% were diagnosed with schizophrenia, whereas 58% suffered from dementia, and 16% suffered from depression. A substantial number (41%) of patients with dementia or depression were prescribed antipsychotics. Furthermore, of 11%-30% of all patients who had behavioral problems such as

wandering, being physically or verbally abusive, or who resisted care, 48%-64% were prescribed an antipsychotic at least once a year [38]. Jeste et al. confirmed that antipsychotics are often prescribed off-label for behavioral disturbances associated with dementia [39]. Because dementia [40, 41] and depression [42] are risk factors for fractures, they may be an alternative explanation for the positive association between antipsychotic use and risk of hip/femur fracture. This hypothesis is in line with the findings of Bolton et al. who investigated antipsychotic use and the risk of fractures, but found no increased risk among both conventional and atypical antipsychotic users. In this study the results were adjusted for a wide range of confounders including dementia, schizophrenia and depression [43].

In conclusion, our findings support an increased risk for fracture of the hip or femur for individuals prescribed antipsychotics. There was a difference in fracture risk with the use of atypical versus conventional antipsychotics, wherein patients using conventional antipsychotic drugs had an increased risk of hip/femur fracture. However, it should be noted that the numbers of atypical antipsychotic users were small, and that this observation needs further attention in other study populations. We did not find a relationship between average daily dose of antipsychotic and fracture risk. Whilst the possibility remains that the underlying disease or behaviour caused any increased risk of hip/femur fractures, our findings may provide important information for prescribers, especially those managing elderly and vulnerable patients.

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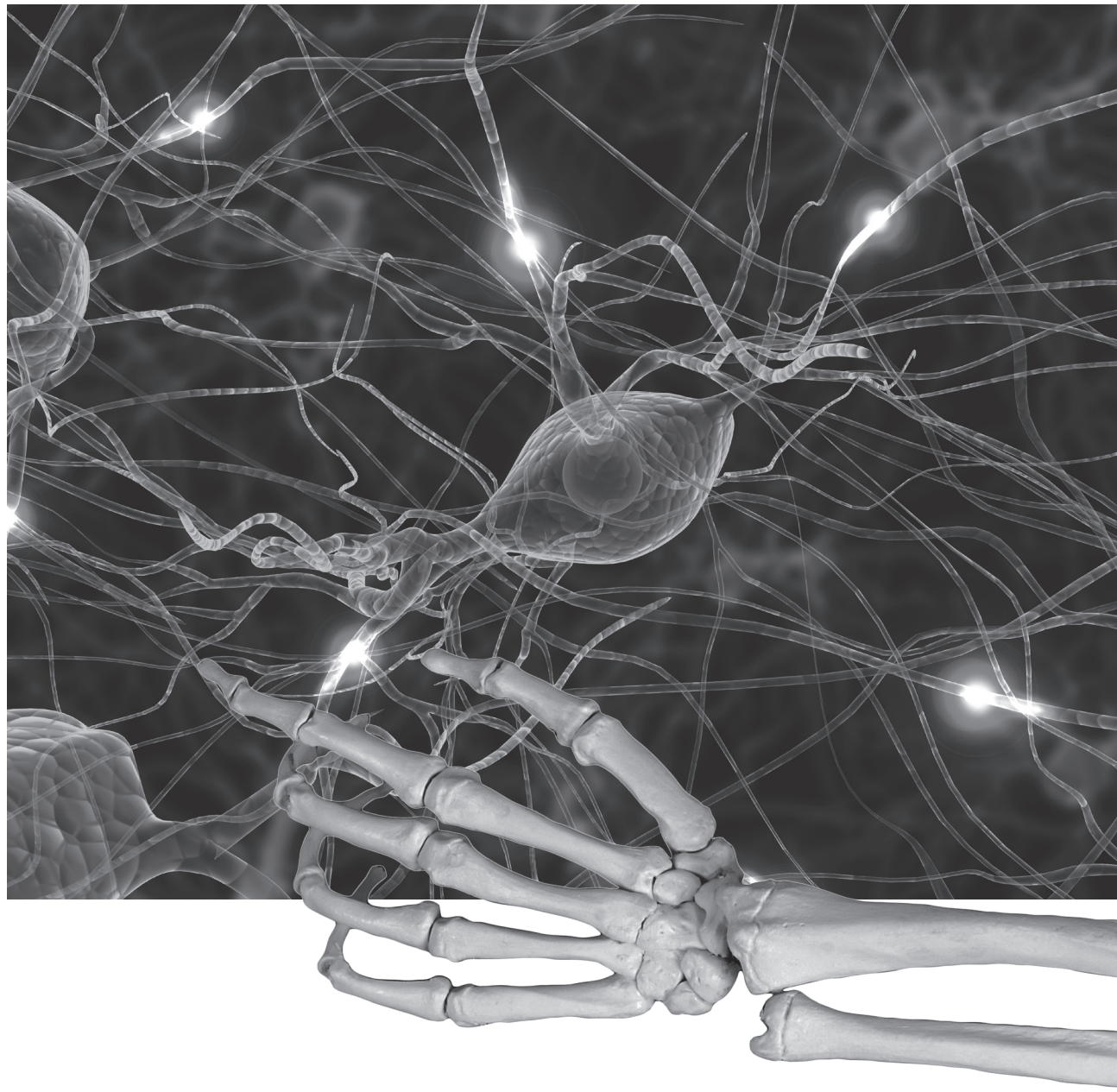
Chapter 3

Central neurological disorders and risk of fracture



Chapter 3.1

Risk of hip/femur fracture after stroke: a population-based case-control study

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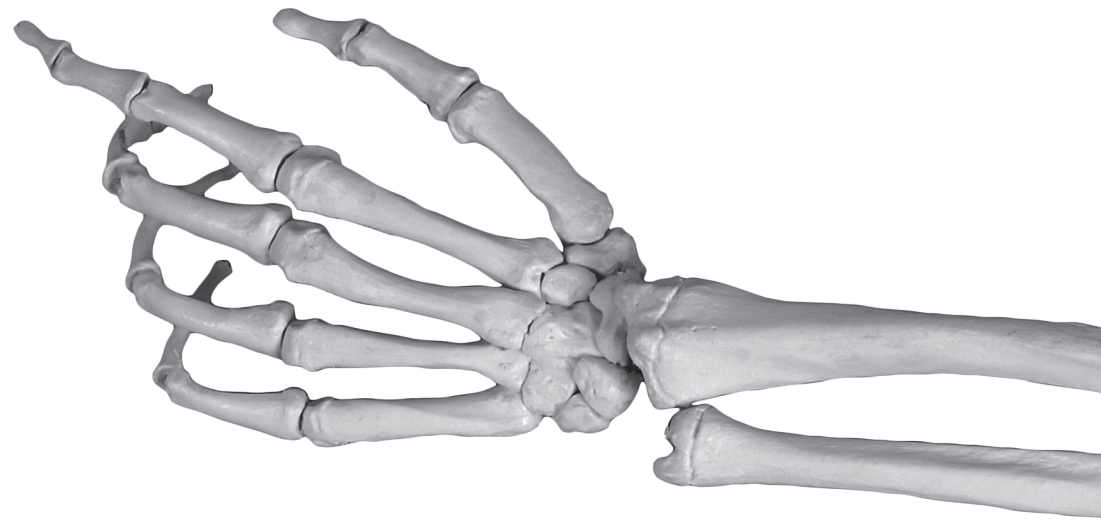


Abstract

Introduction: Stroke increases the risk of hip/femur fracture, as seen in several studies, although the time course of this increased risk remains unclear. Therefore our purpose is to evaluate this risk and investigate the time-course of any elevated risk.

Methods: We conducted a case-control study using the Dutch PHARMO Record Linkage System database. Cases (n=6,763) were patients with a first hip/femur fracture; controls were matched by age, sex and region. Odds ratios (ORs) for the risk of hip/femur fracture were derived using conditional logistic regression analysis, adjusted for disease and drug history.

Results: An increased risk of hip/femur fracture was observed in patients who experienced a stroke at any time before the index date (adjusted OR [AOR] 1.96 [95% confidence interval (CI), 1.65 - 2.33]). The fracture risk was highest among patients who sustained a stroke within 3 months before the index date (AOR 3.35 [95% CI, 1.87 - 5.97]) and among female patients (AOR 2.12 [95% CI, 1.73 - 2.59]). The risk further increased among patients younger than 71 years (AOR 5.12 [95% CI, 3.00 - 8.75]). Patients who had experienced a haemorrhagic stroke tended to be at a higher hip/femur fracture risk compared with those who had experienced an ischaemic stroke.

Conclusions: Stroke is associated with a 2.0-fold increase in the risk of hip/femur fracture. The risk was highest among patients younger than 71 years, female and those whose stroke was more recent. Fall prevention programmes, bone mineral density measurements and use of bisphosphonates may be necessary to reduce the occurrence of hip/femur fractures during and after stroke rehabilitation.

Introduction

Stroke is a major cause of death and long-term disability in most industrialized populations. More than half of all strokes occur in people over 75 years of age and there is a trend towards increasing stroke incidence, especially in the elderly population because the population is living longer [1].

Osteoporosis has been recognized as a serious complication after stroke [2,3]. Stroke has been associated with a 1.5 to 4 times higher risk of hip fractures [4,5], and there is an increasing prevalence of hip/femur fractures among stroke survivors [6]. Several long-term, prospective studies investigated bone mineral density (BMD) after stroke [2]. Those studies reported non-uniform patterns of changes in BMD with significant bone loss on the paretic side, with a rapid onset after stroke, especially in patients with the most severe functional deficits.

Information about the time course of increased risk of hip/femur fracture during the first year after stroke is scarce. Most studies [4,6,7], but not all [8], that investigated fracture risk in relation to time after stroke, adjusted for a limited number of confounders (age and sex) and did not distinguish between haemorrhagic and ischaemic stroke. The objective of this study, therefore, was to evaluate the association between stroke and the risk of hip/femur fracture, and to identify any impact of stroke type and recency of stroke on that risk.

Methods

Study design

A case-control study was conducted using the PHARMO Record Linkage System (RLS) database (www.pharmo.nl). PHARMO RLS is a database that contains the pharmacy dispensing data of about one million community-dwelling Dutch residents. These data are linked to a nationwide hospital discharge register [9]. In the Netherlands, pharmacies maintain

a virtually complete register of dispensed medications that have been prescribed by specialists and general practitioners. Patients are included irrespective of health insurance or socioeconomic status, and represent about 7% of the general population. Several independent validation studies have shown that the PHARMO RLS database has a high level of completeness and validity [10,11].

Cases and control subjects

Cases were patients aged 18 years or older who had sustained a hip/femur fracture during the study period (1 January 1991 to 31 December 2002). Each case was matched with up to four control patients by year of birth, sex and region of residence. Control patients were those registered on the database without evidence of having sustained any type of fracture at any time during enrolment. Among cases, the date of hospital admission for first hip/femur fracture was defined as the index date. Each control was assigned the index date of the matched case.

Stroke definition

For each patient, the history of stroke before the index date was determined. Stroke was defined according to the International Classification of Diseases (ICD) codes 430–436, excluding 435. Types of stroke included: haemorrhagic (ICD-9: 430, 431 and 432), ischaemic (ICD-9: 433 and 434) and unspecified (ICD-9: 436). The recency of stroke was determined by calculating the time between the index date and the most recent hospital admission for stroke before the index date.

Statistical analysis

Conditional logistic regression was used to estimate odds ratios (ORs) for fracture risk (SAS version 9.1.3, PHREG procedure). Using backward elimination, adjustments were made for the

following potential risk factors that have been associated with an increase or decrease in fracture risk: use of benzodiazepines in the three months before the index date; use of bronchodilators, inhaled corticosteroids, oral corticosteroids, antipsychotics, lithium, antidepressants, beta-blockers, opioids, anticonvulsants, thiazide diuretics, renin-angiotensin-aldosterone system (RAAS) inhibitors, anti-thyroid hormones, thyroid hormones, two or more dispensings of a non-steroidal anti-inflammatory drug, disease modifying anti-rheumatic drugs, nitrates, antidiabetics, calcium channel blockers, bisphosphonates, hormone replacement therapy (HRT), digoxin and other anti-arrythmics within the six months before the index date. In addition, a hospital diagnosis of anemia, mental disorder, impaired renal functioning, skin or subcutaneous disease, any serious injury within the year before the index date, or a diagnosis of malignant neoplasm, endocrine disorder, cardiovascular disease, obstructive airways disease, inflammatory bowel disease, musculoskeletal and connective tissue diseases or rheumatoid arthritis at any time before the index date were considered as potential confounding factors.

Smoothing spline regression plots (SAS version 9.1.3) were used to visualize the longitudinal relationship between the risk of fracture and the recency of stroke. This method has been advocated as an alternative to categorical analysis [12].Spline regression lines were calculated using the GPLOT procedure of SAS similar to the method described by De Vries et al.[13].

Results

Baseline characteristics of the study subjects are shown in Table 1. We identified 6,763 patients who sustained a hip/femur fracture and matched these cases with 26,341 controls. The mean age of cases and controls was 75 years and the majority (73%) were female. Among cases, 225 (3.3%) had a history of stroke, compared with 407 (1.5%) control patients. The majority of hip/femur fractures occurred among subjects aged 50 years or older. The mean

period of time between stroke and index date was 2.2 years. The use of bisphosphonates did not differ between patients having a history of stroke (2.3%) and patients without a history of stroke (2.1%) in the control population. Further baseline characteristics are described in other studies using the same PHARMO RLS dataset [14-15].

Table 1: Baseline characteristics

Characteristics	Cases (n = 6,763)	(%)	Controls (n = 26,341)	(%)
Mean age (years)	75.7		75.3	
Number females, %	4,929	72.9	19,138	72.7
Disease history (ever)				
Cardiovascular disease	359	5.3	1,289	4.9
Cerebrovascular disease	296	4.4	565	2.1
Medication use within the six months before the index date				
Thiazide diuretics	816	12.1	2,970	11.3
RAAS inhibitors	963	14.2	3,280	12.5
Beta blockers	914	13.5	3,850	14.6
Calcium channel blockers	718	10.6	2,560	9.7
Nitrates	639	9.4	2,405	9.1
Antidiabetics	748	11.1	2,207	8.4
Anti-arrythmics and digoxin	526	7.8	1,793	6.8
Bisphosphonates	216	3.2	532	2.0
Hormone replacement therapy	77	1.1	347	1.3
Oral corticosteroids	366	5.4	918	3.5

Hip/femur fracture risk was increased among patients who had suffered a stroke at any time before the index date, yielding an unadjusted OR of 2.22 (95% confidence interval [CI], 1.88 - 2.62) (Table 2). After adjustment the OR was decreased by 12%, yielding an adjusted OR (AOR) of 1.96 (95% CI, 1.65 - 2.33).

The hip/femur fracture risk was highest shortly after the stroke occurred (<3 months before the index), yielding an AOR of 3.35 (95% CI, 1.87 - 5.97). This risk was attenuated with a longer time since stroke exposure: stroke occurrence between 3 and 12 months before the index resulted into an AOR of 1.98 (95% CI, 1.33 - 2.94). Figure 1 shows that hip/femur fracture risk remained largely steady when the time since most recent stroke exceeded one year, except for the time point after 4 years. However, strokes occurring between one and three

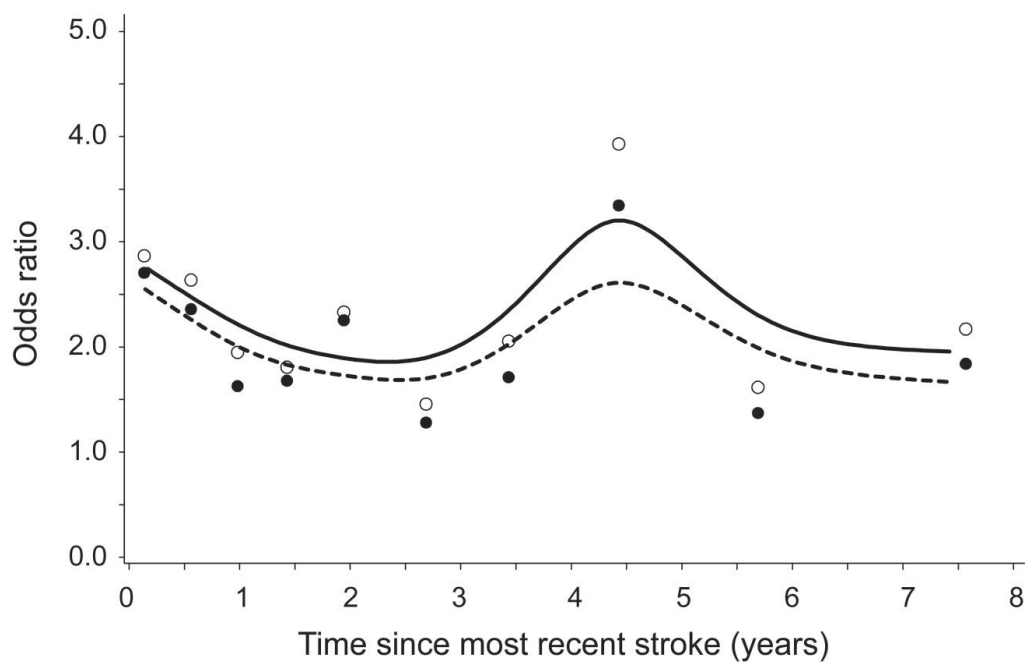
years before the index date did not result in a higher fracture risk (AOR 1.73 [95% CI, 1.28 - 2.33]) when compared with a longer time since stroke (AOR 1.94 [95% CI, 1.49 - 2.53]).

Table 2: Risk of hip/femur fracture and type of stroke

	Cases (n=6,763)	Controls (n=26,341)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Never suffered from stroke	6,538	25,934	1.00	1.00
Ever suffered from stroke	225	407	2.22 (1.88 - 2.62)	1.96 (1.65 - 2.33)
Haemorrhagic stroke[b]	35	66	2.14 (1.41 - 3.22)	1.94 (1.27 - 2.96)
Ischaemic stroke[c]	93	182	2.06 (1.60 - 2.65)	1.85 (1.42 - 2.39)
Undefined stroke[d]	97	159	2.44 (1.89 - 3.15)	2.10 (1.61 - 2.73)

a) Adjusted for: the use of benzodiazepines with the three months before the index date; use of inhaled corticosteroids, oral corticosteroids, antipsychotics, antidepressants, beta-blockers, opioids, anticonvulsants, two or more dispensings of a non-steroidal anti-inflammatory drug, disease modifying anti-rheumatic drugs, nitrates, antidiabetics, calcium channel blockers, bisphosphonates, HRT, anti-arrythmics (excluding digoxin) within the six months before the index date; a diagnosis of anaemia, mental disorder, skin or subcutaneous disease within the year before the index date; a diagnosis of malignant neoplasm, endocrine disorder, obstructive airways disease, inflammatory bowel disease, or musculoskeletal and connective tissue diseases at any time before the index date.
b) ICD-9: 430, 431 & 432
c) ICD-9: 433, 434
d ICD-9: 436

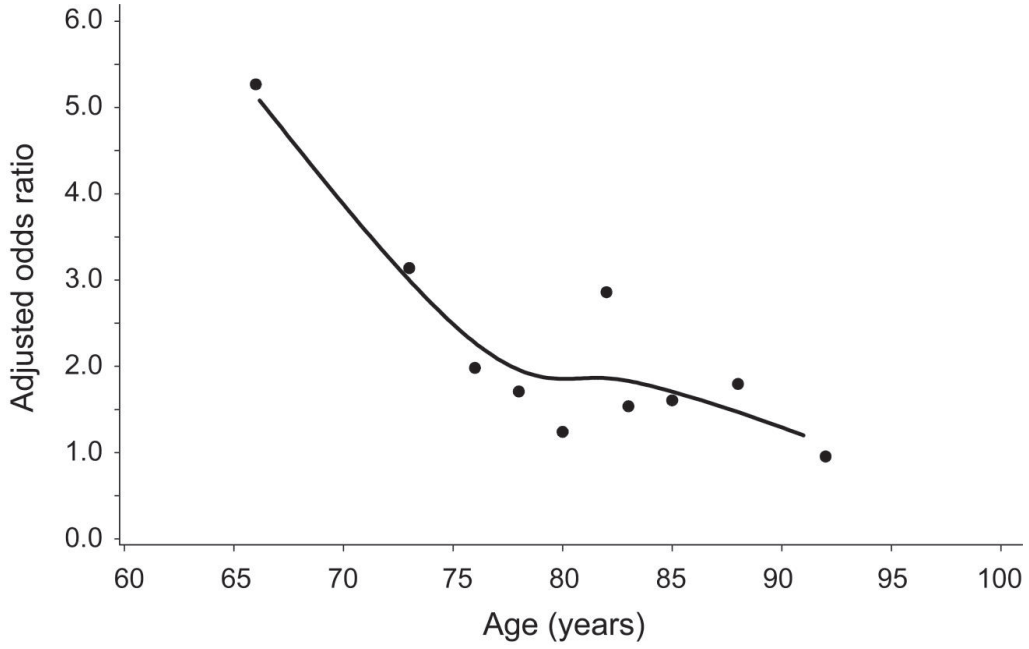
Figure 1: Smoothed spline visualization of the relationship between recency of stroke and risk (adjusted) of hip/femur fracture.



Solid line, hollow dots: unadjusted odds ratios. Dashed line, solid dots: adjusted odds ratios.

Table 2 shows that patients with haemorrhagic stroke tended to be at higher risk of hip/femur fracture (AOR 1.94 [95% CI, 1.27 - 2.96]) compared with patients who had an ischaemic stroke (AOR 1.85 [95% CI, 1.42 - 2.39]). However, the difference did not reach statistical significance. For patients who had sustained a haemorrhagic stroke, our data showed that the risk of hip/femur fracture was highest when the event occurred recently (within the year before index date, AOR 3.02 [95% CI, 1.30 - 7.00]). This risk was attenuated when the haemorrhagic stroke occurred between one and three years before the index date (AOR 2.00 [95% CI, 1.02 - 3.91]). After more than three years, the fracture risk was no longer significantly increased (AOR 1.41 [95% CI, 0.69 - 2.89]).

Figure 2: Smoothed spline visualization of the relationship between age and the risk (adjusted) of hip/femur fracture after stroke.



Hip/femur fracture risk after stroke declined with increasing age (Figure 2). The youngest stroke survivors (≤70 years) were at highest risk, yielding an AOR of 5.12 (95% CI,

3.00 - 8.75) (Table 3). Subjects aged between 71 and 80 years showed a two-fold increase in risk of hip/femur fracture (AOR 2.07 [95% CI, 1.57 - 2.73]) after stroke. The oldest patients (>80 years old) showed the smallest excess risk (AOR 1.51 [95% CI, 1.18-1.94]) after stroke. We observed a similar trend among patients who had a hospital diagnosis or a dispensing within the 3 months prior to the index date. The results show an AOR of 5.90 (95% CI, 2.42 - 14.38) for the youngest stroke survivors (≤70 years), AOR of 2.13 [95% CI, 1.45 - 3.10] for subjects aged between 71 and 80 years and an AOR of 1.73 [95% CI, 1.23 - 2.45] for the oldest patients (>80 years old). When we stratified patients younger than 71 years by recency of stroke, the risk of hip/femur fracture appeared to be increased 23-fold within the year after a stroke (AOR 23.17 [95% CI, 4.93 - 108.79]; 12 cases and 2 controls) (data not shown). Female survivors of stroke had a higher risk of hip/femur fracture (AOR 2.12 [95% CI, 1.73 - 2.59]) compared with males (AOR 1.63 [95% CI, 1.17-2.28]).

Table 3: Risk of hip/femur fracture and strokes stratified by sex and age

	Cases (n=6,763)	Controls (n=26,341)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Never suffered from stroke	6,538	25,934	1.00	1.00
Ever suffered from stroke	225	407	2.22 (1.88 - 2.62)	1.96 (1.65 - 2.33)
By gender				
Males	57	126	1.82 (1.32 - 2.51)	1.63 (1.17 - 2.28)
Females	168	281	2.40 (1.97 - 2.91)	2.12 (1.73 - 2.59)
By age				
18 – 70 years	41	28	6.31 (3.83 - 10.39)	5.12 (3.00 - 8.75)
71 – 80 years	91	152	2.44 (1.87 - 3.18)	2.07 (1.57 - 2.73)
> 80 yrs	93	227	1.61 (1.26 - 2.06)	1.51 (1.18 - 1.94)

a) See table 2 for adjustments.

Discussion

In this study, we found that stroke was associated with a 2.0-fold increased risk of hip/femur fracture. A shorter time period between stroke and index date, a younger age and being female further increased the risk of hip/femur fracture.

Our findings of an increased risk of hip/femur fracture shortly after stroke, which

attenuated when the stroke had occurred 3-12 months ago, extend results from other epidemiological studies. A retrospective study among 273,288 Swedish stroke patients reported a rapid drop in fracture risk within the first year after stroke [7]. After the first year, the risk remained slightly elevated, which is similar to our findings. The same study reported that women aged 50-54 years at the time of stroke had a 12-fold risk of hip fracture in the first year post stroke. This could contribute to our finding of a 23-fold increased risk for stroke patients less than 70 years of age. Patients aged 70 or older are more likely to have other risk factors for hip fracture, and it is likely that the relative contribution of stroke to the overall risk of hip fracture decreases with age. A study by Ramnemark et al. reported that stroke patients had an incidence of hip fracture that was 2-4 times higher than the reference population [5]. Subsequently, they found that the incidence of hip fracture increased with age, while the prevalence of previous strokes among patients with fracture increased significantly over time [6]. A nationwide Danish case-control study reported a 1.8-fold increased risk of hip fracture within the 3 years after a stroke [8]. In line with our results, they found that this risk was attenuated as the time since stroke increased. Therefore the four-fold increased risk of hip fracture, 4.5 years after stroke in Figure 1, is probably an outlier of the trend, as described by the smoothing spline method.

An increased risk of falling and a decreased femoral BMD in the year after a stroke have been reported [2, 16, 17]. Falls in elderly people are common; 28-35% of people aged ≥ 65 years fall at least once over a one-year time period. It has been estimated that 1% of these falls result in a hip fracture [18]. In a follow-up study among 1,139 Swedish patients admitted for acute stroke, Ramnemark et al. reported that 84% of all fractures after stroke were caused by falls and that hip fracture was the most frequent fracture [5]. Additionally, in a survey in the United Kingdom that included 108 stroke patients, Forster and Young found that 46% fell at least once while in hospital and 73% fell within the six months after hospital discharge. A total

of 270 falls have been reported after hospital discharge of which 145 (54%) were reported in the first eight weeks after hospital discharge, whereas 125 (46%) were reported in the eight-week to six-month period [19]. In an observational study by Mackintosh, 92% of the subjects who had recurrent falls within six months after discharge from stroke rehabilitation had fallen at least once whilst being in the hospital or during stroke rehabilitation [16]. The increased risk of falling shortly after stroke supports our findings of highest risk of fracture in the first 3 months after stroke.

Our finding of a rapid increase in hip/femur fracture risk is in line with data from longitudinal studies, which report substantially higher rates of BMD loss within the first six months after stroke (4-10% BMD loss of the femoral region); this attenuated to 1-3% for the second half of the year [20-24]. Loss of BMD was most obvious in paralyzed extremities such as the femoral neck and the proximal humerus as a result of decreased mobility. Jørgensen et al. also found that less disabled patients, with functional ambulation category (FAC) scores of 2-6, had only a 3% decrease in BMD at the femoral neck [25]. Conversely, in healthy elderly patients, annual rates of loss of total BMD have been estimated at 0.5-1.0% [2]. Femoral neck BMD loss in osteoporotic patients has been reported to be around 0.4% per year and to increase significantly with age [26].

The strengths of our study include its reasonable sample size, the duration of follow-up available to study the associations between stroke and risk of hip/femur fracture and its external validity (ie PHARMO is representative for the total Dutch population) [9]. Linkage with the Dutch National Hospitalization Registry assured routine collection of hospitalizations for stroke. Moreover, we were able to distinguish between fracture risk among patients with ischaemic and haemorrhagic stroke types.

Our study had some limitations. First, patients were included irrespective of whether their stroke was associated with hemiplegia or not. Kanis et al. found a significant increase in

relative risk of 2.42 in hemiplegic stroke patients. Stroke without hemiplegia was associated with a much lower (insignificant) increase in risk (RR 1.51) [27]. In the PHARMO database, the types of stroke diagnosis (ischaemic, haemorrhagic or unspecified) have not been internally validated. However, a similar distribution of stroke diagnoses was reported in a clinical study performed by Potter et al. in the United Kingdom [28]. They included patients obtained from 5 hospitals in England who were admitted with a clinical diagnosis of suspected stroke in the years 2004-2008. The proportions of haemorrhagic, ischaemic and unspecified stroke were 15%, 56% and 27% respectively, compared to 16%, 45% and 39% for the control patients in our study. We have not been able to assess whether risk of mortality after hip fracture risk was different between patients with and without stroke. Finally, we were not able to adjust for confounders such as body mass index and smoking.

In conclusion, after adjustment for general risk factors of fracture risk, patients with stroke had a 2.0-fold increased risk of hip/femur fracture. The risk was greatest in those who were younger than 71 years, female and who had recently sustained a stroke. Our findings imply that it is important to conduct fracture risk assessment immediately after a patient is hospitalized for stroke. Severity of stroke (ie the degree of paresis or immobility), being female and age < 70 years are important risk factors to take into account. Fall prevention programmes, BMD measurements and use of bisphosphonates may be necessary to minimize hip fractures in the elderly during and after stroke rehabilitation.

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Chapter 3.2

Risk of fracture in patients with Parkinson's disease

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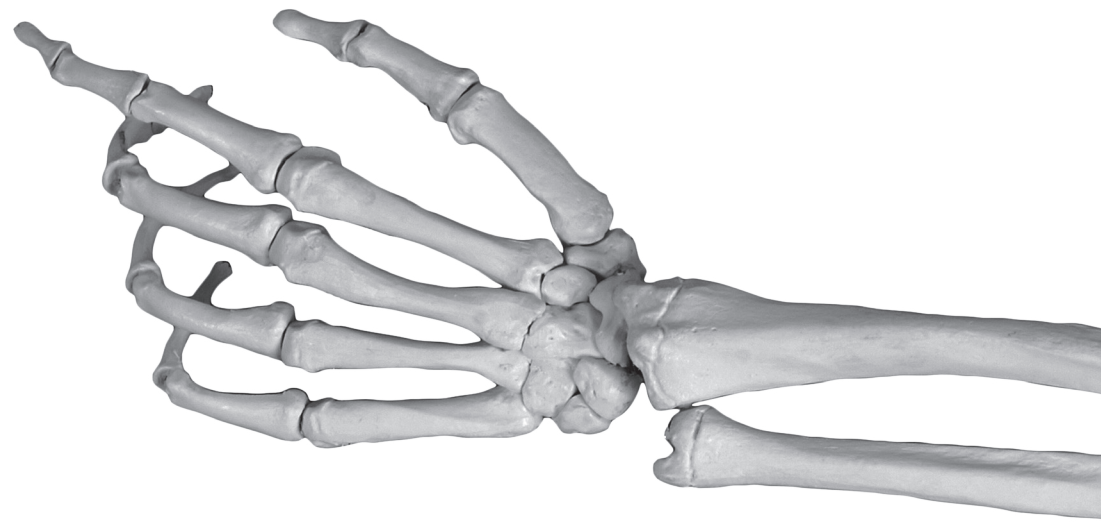


Abstract

Background: Parkinson's disease (PD) is a movement disorder associated with falling and direct detrimental effects on bone. Both are recognized risk factors for fracture. Therefore, the aim was to determine fracture risk in incident PD patients stratified by treatment, severity, duration of disease and related comorbidities.

Methods: We conducted a retrospective cohort study using the UK General Practice Research Database (1987-2011). Each PD patient was matched by age, sex, calendar time, and practice to a control patient without history of PD.

Results: We identified 4,687 incident PD patients. Compared to controls, a statistically significant increased risk was observed for any fracture (adjusted hazard ratio [AHR] 1.89; 95% confidence interval [CI], 1.67 - 2.14), osteoporotic fracture (AHR 1.99 [95% CI, 1.72 - 2.30]) and hip fracture (AHR 3.08 [95% CI, 2.43 - 3.89]). Fracture risk further increased with history of fracture, falling, low BMI, renal disease, antidepressant use and use of high-dose antipsychotics.

Conclusion: This study showed that incident PD patients have a statistically significant increased risk of fracture. Therefore, fracture risk assessment may be indicated among PD patients, who besides the general risk factors for fracture, like increasing age and female gender, have recently used selective serotonin re-uptake inhibitors or high-dose antipsychotics or have a history of fracture, falling, low BMI or renal disease.

Background

Parkinson's disease (PD) is a movement disorder with a prevalence of about 1% in people over 60 years of age [1]. PD is characterized by loss of dopaminergic neurons in the nigrostriatal pathway, which causes symptoms like bradykinesia, resting tremor, stiffness, and postural instability [2].

Subsequently, these symptoms explain the observed association between PD and an increased risk of falling [3,4]. PD has also been associated with other indirect detrimental effects on bone [5,6]. A possible explanation may be that in PD patients, reduced 25-hydroxyvitamin D levels and compensatory higher parathyroid hormone levels were observed, which may have reduced bone mineral density (BMD) [5]. This may be due to sunlight deprivation or decreased dietary intake of vitamin D [5,7]. Both falling and reduced BMD are recognized determinants for an increased fracture risk. Common drugs used in the treatment of PD are also associated with falling (e.g. levodopa and dopamine agonists). This is caused by side effects like postural hypotension and slow mentation or confusion, which results in loss of protective reflexes during falling [8,9]. Associations between PD and depression, anxiety, dementia, hallucinations and psychosis have been reported [10-13]. These comorbidities and concomitant treatment (e.g. antidepressants and antipsychotics) are risk factors of fracture [14-16].

The association between PD and fracture risk has been described in previous studies [17-21]. Vestergaard et al. and Arbouw et al. observed an increased fracture risk in respectively a Danish and a Dutch case control study among patients who used anti-Parkinson drugs. Fracture risk further increased with concomitant use of antidepressants and with high-dose antipsychotics [22,23]. However, both studies were unable to focus specifically on PD patients and did not test the role of PD severity. Therefore, the aim of this study was to determine fracture risk in a cohort of incident PD patients, stratified by severity and duration of disease,

PD medication and CNS comorbidity.

Methods

Data Source

Information for this study was obtained from the General Practice Research Database (GPRD), which comprises computerized medical records of patients derived from primary care practices throughout the UK which were linked to the national Hospital Episode Statistics (HES). These records include the patient's demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions, and major outcomes [24]. HES includes information on the date, main discharge diagnosis and duration of hospitalisation, as provided by the hospitals. Previous studies of GPRD data have shown a high level of data validity with respect to the reporting of fractures (>90% of fractures were confirmed) [25,26].

Study population

The study population consisted of all incident PD patients aged 40 years or older, with their first recorded diagnosis of PD between 1987 and 2011 at least 1 year after the start of valid data collection. They had at least two records of a prescription for anti-Parkinson medication after diagnosis (levodopa, dopamine agonists, MAO-B inhibitors, amantadine, apomorphine, anticholinergic drugs [procyclidine, trihexyphenidyl, orphenadrine, methixine, biperiden or benzatropin] or COMT inhibitors [entacapone or tolcapone]). 2,694 patients were excluded who had only one record of a prescription for anti-Parkinson medication after diagnosis. These excluded patients may have received a wrong diagnosis. Patients who had more than one record for a prescription of PD treatment before PD diagnosis were also excluded (n=1827). Each PD patient was matched by year of birth, sex and practice, to a patient without a history of PD in GPRD. If no control was found, this age-matching criterion was expanded stepwise,

in age increments of 1 year, to a maximum of 5 years. The index date of PD diagnosis was the date of the first record of PD after start of GPRD data collection. Control patients had to be enrolled in the GPRD at the time of the index date of their matched PD patient. Patients were followed up for the occurrence of fracture from their index date to either the end of GPRD data collection, the date of transfer of the patient out of the practice area, or the patient's death, whichever came first. Fracture types were classified according to the International Classification of Diseases, Tenth Revision (ICD-10) categories. A clinical osteoporotic fracture was defined as a fracture of the radius/ulna, humerus, rib, femur/hip, pelvis, or vertebrae. All other fractures were classified as non-osteoporotic [27].

Exposure

In GPRD longitudinal prescription data are available, while clinical symptoms, as described in the Hoehn and Yahr [28] classification of PD severity, are often missing. Therefore, a proxy for the severity of PD over time (stratified into mild, moderate and severe PD) was based on the treatment prescribed during the different stages of PD, according to the NICE Guideline on PD [29]. During follow-up, PD was classified as "mild" among patients who had not used COMT-inhibitors or apomorphine injections, and who were using only one of the following substances at the same time (within 3 months of a new time interval): low dose levodopa (<600 mg per day), dopamine agonists, amantadine, anticholinergics, or MAO-B inhibitors. PD was classified as "moderate" for patients without a history of COMT-inhibitors or apomorphine injections and who were using either high dose levodopa alone (≥ 600 mg per day), or more than one of the following substances at the same time: low dose levodopa (<600 mg per day), dopamine agonists, amantadine, anticholinergics, or MAO-B inhibitors. The use of a COMT inhibitor or apomorphine injections or continuous infusions ever before defined "severe" PD.

The total period of follow-up was divided into periods of 30 days, starting at the index

date. At the start of each period, the presence of risk factors and indicators of PD severity were assessed by reviewing the computerized medical records for any record of risk factors prior to each period. Furthermore, PD disease duration was noted, as measured from the index date (first record of PD). The use of dopaminergic and CNS medication was stratified to average daily dose during the 6 months before. WHO defined daily dosages were used to add up dose equivalences between the various medication [30]. Within the 6 months before each interval, the average daily dose was calculated by dividing the cumulative dose by the time between the the oldest prescription and the start date of the period.

General risk factors included age, gender, body mass index (BMI), smoking status and the use of >2 units alcohol/day, a history of fracture ever before PD diagnosis or history of falls within 3-12 months before PD diagnosis, history of chronic diseases ever before (asthma/chronic obstructive pulmonary disease [COPD], rheumatoid arthritis, thyroid disorders, renal disease [acute renal failure and chronic impaired renal function], cancer, congestive heart failure, cerebrovascular disease, diabetes mellitus, inflammatory bowel disease, dementia), and a prescription in the previous 6 months for CNS medications (antidepressants, antipsychotics, anxiolytics/hypnotics, anticonvulsants), opioids, oral glucocorticoids, and other immunosuppressants (azathioprine, ciclosporin, tacrolimus, mycophenolate mofetil, methotrexate).

Statistical analysis

Time-dependent Cox proportional hazards regression was used in order to estimate hazard ratios (HRs) of fracture risk. Fracture risk in PD patients was compared with control patients to yield an estimate of the relative risk, which was expressed as hazard ratios. All characteristics, except age, were included as categorical variables in the regression models. Adjustments were made if any potential confounder showed a change in HR exceeding 1%. For each analysis, the

regression model was fitted with the general risk factors. These characteristics were treated as time-dependent variables in the analysis, in which the total period of follow-up was divided into periods of 30 days, starting at the index date. Within the group of PD patients, analyses were stratified to severity, history of dementia, history of drug use (including PD and CNS medication) 6 months before, history of fracture before the PD diagnosis and history of falls within 3-12 months before PD diagnosis. Stratification to each group of PD medication was adjusted for other PD medication.

Sensitivity Analysis

Beside the main analysis, a sensitivity analysis was performed according to the algorithm of Hernan et al. to identify incident PD patients. Hernan et al. confirmed the PD diagnosis in 90% of PD patients included in their cohort (n=1,019) [31]. Beside the current inclusion criteria, PD patients needed to have at least 3 years of follow-up in the GPRD prior to their first PD diagnosis and were not allowed to have a history of a drug for the treatment of PD or any treatment which induces parkinsonism (antiparkinson treatment, anticholinergics, "typical" antipsychotics, prochlorperazine, metoclopramide, amiodarone, reserpine, methyldopa and cinnarizine) ever before their PD diagnosis.

Results

We identified 4,687 incident PD patients and 4,687 controls between 1987 and 2011 with a mean age of 74 years and 42% were female. Approximately 90% of PD patients were diagnosed after the age of 60 years and average follow-up was 4 years. Table 1 shows age and gender distribution among PD patients and controls and provides information on BMI, smoking and alcohol status and history of comorbidities and drug use.

Table 2 shows the risk of fracture at different sites among PD patients as compared to controls. Risk of fracture was stratified to age and gender. The risks of fracture were almost

Table 1: Baseline characteristics of patients with PD and control patients

Characteristics	PD Patients (n=4,687)	Controls (n=4,687)
Female (%)	42.3	42.3
Mean age (years)	73.9	73.9
BMI (%)		
< 20	4.2	4.1
> 30	11.6	14.3
Unknown	21.1	20.2
Smoking status (%)		
Never	55.8	46.4
Current	16.4	21.5
Ex	23.0	27.2
Unknown	4.8	4.8
Alcohol status (%)		
Never	18.4	16.6
Current	64.5	67.8
Ex	3.3	2.7
Unknown	13.8	12.8
Fracture history (%)		
Any fracture	19.2	18.7
Fracture at osteoporotic sites	11.3	10.7
Hip fracture	2.0	1.6
Vertebral fracture	1.1	1.0
Radius/ulna fracture	5.6	5.2
Comorbidity ever before index date (%)		
Asthma	11.2	12.6
COPD	4.6	6.9
Congestive heart failure	5.2	6.2
Diabetes Mellitus	9.0	10.0
Rheumatoid arthritis	1.4	1.9
Renal disease	1.4	1.9
Cerebrovascular disease	13.3	9.8
Inflammatory bowel disease	0.8	1.0
Cancer (excluding skin cancer)	21.2	22.0
Dementia	5.1	1.9
Ischaemic heart disease	19.2	19.1
Drug use in 6 months before index date (%)		
Oral glucocorticoids	3.5	4.0
Antidepressants	21.0	9.9
Antipsychotics	5.1	2.0
Anxiolytics	12.1	8.4
Anticonvulsants	4.3	2.2
Bisphosphonates	4.3	3.8
Hormone Replacement Therapy	1.9	1.6

Table 2: Risk of fracture in PD patients by type of fracture, gender and age compared to patients without PD

	Fractures (n)	(%)	Age-sex adjusted HR (95% CI)	Fully Adjusted HR (95% CI)
No PD	411	8.8	1.00	1.00
PD (Any fracture)	717	15.3	2.18 (1.93 - 2.46)	1.89 (1.67 - 2.14)
Fracture at osteoporotic sites[a]	544	11.6	2.32 (2.01 - 2.67)	1.99 (1.72 - 2.30)
Hip fracture	275	5.9	3.57 (2.84 - 4.48)	3.08 (2.43 - 3.89)
Vertebral fracture	46	1.0	1.68 (1.08 - 2.63)	1.54 (0.97 - 2.45)
Radius/ulna fracture	77	1.6	1.28 (0.93 - 1.76)	1.10 (0.79 - 1.53)
Other fracture	157	3.3	2.00 (1.55 - 2.58)	1.77 (1.35 - 2.30)
Fracture at non-osteoporotic sites	173	3.7	1.82 (1.44 - 2.31)	1.62 (1.27 - 2.07)
By Gender[a]				
Male	282	10.4	2.11 (1.74 - 2.57)	1.87 (1.53 - 2.29)
≤ 75 years	121	4.5	1.96 (1.45 - 2.64)	1.56 (1.14 - 2.13)
76 - 85 years	121	4.5	2.31 (1.71 - 3.13)	2.15 (1.57 - 2.93)
> 85 years	40	1.5	1.57 (0.97 - 2.53)	1.39 (0.85 - 2.27)
Female	435	21.9	2.21 (1.89 - 2.58)	1.92 (1.64 - 2.25)
≤ 75 years	178	9.0	2.20 (1.71 - 2.84)	1.93 (1.48 - 2.50)
76 - 85 years	198	10.0	2.43 (1.92 - 3.08)	2.10 (1.65 - 2.67)
> 85 years	59	3.0	1.46 (1.01 - 2.13)	1.27 (0.86 - 1.86)

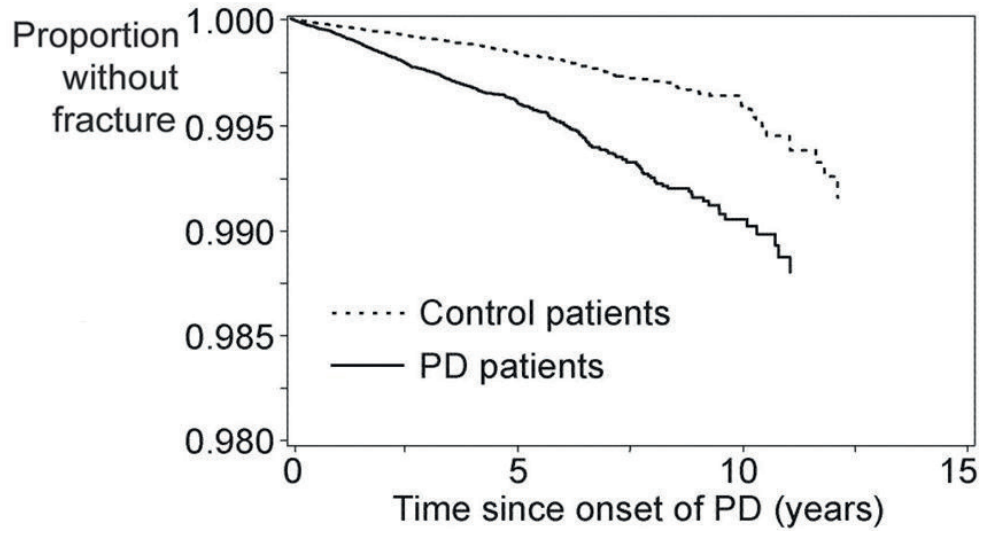
a) Patients may have received multiple osteoporotic fractures
b) Male PD patients are compared with male controls of the same age group and female PD patients with female controls of the same age group

doubled for any (adjusted HR [AHR] 1.89 [95% confidence interval (CI), 1.67 - 2.14]) and osteoporotic fracture (AHR 1.99 [95% CI, 1.72 - 2.30]) compared to control patients. Risk for hip fracture was threefold increased when compared to controls, AHR 3.08 (95% CI, 2.43 - 3.89). There was no effect modification by gender for any or osteoporotic fracture. PD patients with an age between 75 and 85 years were at highest risk of any fracture yielding AHRs of 2.15 (95% CI, 1.57 - 2.93) for male and 2.10 (95% CI, 1.65 - 2.67) for female patients compared to controls. Similar findings were observed for osteoporotic fracture. Hip fracture risk was highest among male PD patients between 75 and 85 years, AHR 3.67 (95% CI, 2.14 - 6.31) compared to AHR 2.67 (95% CI, 1.75 - 4.06) for female patients.

Figure 1 displays the corresponding Kaplan Meier survival curve for risk of osteoporotic fracture. Osteoporotic fracture risk increased non-significantly from AHR 1.51

(95% CI, 1.14 - 2.00) in the first year, towards AHR 2.10 (95% CI, 1.71 - 2.57) between 1 and 5 years, up to AHR 2.17 (95% CI, 1.57 - 3.00) more than 5 years after PD diagnosis as compared with control patients.

Figure 1: Kaplan Meier curves showing the survival of osteoporotic fracture among PD patients and control patients after their index date



In Table 3, the reference group changed from control patients towards PD patients who were unexposed to the treatment of interest. It shows that osteoporotic fracture risk further increased when PD patients were treated with MAO-B inhibitors, antidepressants or high dose antipsychotics. PD patients exposed to selective serotonin re-uptake inhibitors (SSRI) had an increased risk of osteoporotic fracture, AHR 1.72 (95% CI, 1.38 - 2.15), whereas PD patients exposed to tricyclic antidepressants (TCA) had no further increased risk of osteoporotic fracture, AHR 1.09 (95% CI, 0.83 - 1.35). No relation with dose was observed with use of SSRIs or TCAs. Patients who were prescribed < 10 mg fluoxetine equivalents per day for SSRIs, showed an equivalent risk of osteoporotic fracture, AHR 2.04 (95% CI, 1.33 - 3.13) as compared with patients who were prescribed ≥20 mg fluoxetine equivalents per day), AHR 1.68 (95% CI, 1.24 - 2.26). Patients in the lowest dose group of TCA use had an equivalent

risk AHR 1.15 (95% CI, 0.82 - 1.63) as compared with patients in the highest dose group, AHR 1.05 (95% CI, 0.70 - 1.55). PD patients exposed to other types of antidepressants were at 1.5-fold non-significantly increased risk, AHR 1.51 (95% CI, 0.92 - 2.46). Hip fracture risk further increased when patients received high dose antidepressants or high dose antipsychotics.

Table 3: Risk of osteoporotic and hip fracture among PD patients stratified to drug use in 6 months before

	Risk of osteoporotic fracture		Risk of hip fracture	
	Fractures (n)	Fully Adjusted HR (95% CI)[a]	Fractures (n)	Fully Adjusted HR (95% CI)[a]
Levodopa[b]	418	1.00 (0.82 - 1.23)	219	1.12 (0.83 - 1.52)
By average daily dose				
< 300 mg levodopa eq.[c]	154	0.97 (0.76 - 1.24)	76	1.00 (0.70 - 1.42)
300 - 600 mg levodopa eq.	179	1.03 (0.82 - 1.30)	98	1.24 (0.88 - 1.73)
≥ 600 mg levodopa eq.	85	1.00 (0.74 - 1.33)	45	1.15 (0.76 - 1.74)
Dopamine agonists[b]	72	0.83 (0.64 - 1.09)	33	0.93 (0.63 - 1.38)
By average daily dose				
< 3 mg ropinirole eq.	20	0.91 (0.58 - 1.43)	13	1.26 (0.72 - 2.23)
3 - 6 mg ropinirole eq.	19	0.87 (0.55 - 1.39)	6	0.67 (0.30 - 1.53)
≥ 6 mg ropinirole eq.	33	0.77 (0.53 - 1.12)	14	0.85 (0.48 - 1.51)
MAO-B inhibitors[b]	39	1.47 (1.05 - 2.05)	15	1.19 (0.70 - 2.02)
COMT-inhibitors[b]	34	1.17 (0.82 - 1.67)	19	1.52 (0.94 - 2.47)
Amantadine[b]	14	1.13 (0.66 - 1.94)	7	1.38 (0.64 - 2.97)
Antidepressants	194	1.52 (1.26 - 1.82)	90	1.42 (1.10 - 1.83)
By average daily dose				
< 10 mg fluoxetine eq.	60	1.52 (1.15 - 2.00)	25	1.30 (0.85 - 1.97)
10 - 20 mg fluoxetine eq.	47	1.34 (0.99 - 1.83)	23	1.32 (0.85 - 2.05)
≥ 20 mg fluoxetine eq.	87	1.64 (1.29 - 2.10)	42	1.57 (1.12 - 2.20)
Antipsychotics	44	1.28 (0.93 -1.77)	22	1.24 (0.79 - 1.96)
By average daily dose				
< 37.5 mg thioridazine eq.	15	1.00 (0.60 - 1.69)[d]	7	0.89 (0.42 - 1.91)[d]
37.5 - 150 mg thioridazine eq.	18	1.15 (0.71 - 1.85)[e]	8	1.00 (0.49 - 2.05)[e]
≥ 150 mg thioridazine eq.	11	2.98 (1.63 - 5.47)[de]	7	3.84 (1.79 - 8.25)[de]
Anxiolytics/hypnotics	111	1.23 (0.99 - 1.52)	46	0.97 (0.70 - 1.34)
By average daily dose				
< 5 mg diazepam eq.	57	1.49 (1.13 - 1.98)	21	1.06 (0.67 - 1.67)
5 - 10 mg diazepam eq.	27	0.98 (0.66 - 1.46)	12	0.81 (0.45 - 1.47)
≥ 10 mg diazepam eq.	27	1.04 (0.70 - 1.56)	13	1.00 (0.56 - 1.77)

a) The reference group are PD patients unexposed to the investigated drug
b) Additionally adjusted for PD medication, except for PD medication investigated
c) eq: equivalents
d) Statistically significant difference Wald-test ($p < 0.05$)
e) Statistically significant difference Wald -test ($p < 0.05$)

Furthermore, PD patients with a BMI <20 had a significant increased risk for osteoporotic

fracture, AHR 1.76 (95% CI, 1.24 - 2.50) and hip fracture, AHR 2.80 (95% CI, 1.82 - 4.30) as compared to PD patients with a BMI ≥20. Osteoporotic fracture risk was significantly increased in patients with a history of renal disease, AHR 1.85 (95% CI, 1.19 - 2.87), a recent history of falling, AHR 1.87 (95% CI, 1.48 - 2.37) and a history of fracture before PD diagnosis, AHR 1.29 (95% CI, 1.05 - 1.58). Hip fracture risk was significantly increased among PD patients with a history of renal disease, AHR 2.05 (95% CI, 1.17 - 3.61) and a recent history of falling, AHR 2.04 (95% CI, 1.49 - 2.78). None of the other general risk factors showed statistically significant associations with fracture.

Table 4: Risk of fracture at osteoporotic sites and hip fracture among PD patients, by severity of PD

	Risk of any osteoporotic fracture		Risk of hip fracture	
	Fractures (n)	Fully Adjusted HR (95% CI)	Fractures (n)	Fully Adjusted HR (95% CI)
By severity of PD				
Mild PD	338	1.00	174	1.00
Moderate PD	162	0.98 (0.81 - 1.20)	75	1.01 (0.76 - 1.33)
Severe PD	44	1.13 (0.81 - 1.56)	26	1.51 (0.98 - 2.33)

Severe PD patients tended to have a 1.5-fold increased risk of hip fracture as compared to mild PD patients (Table 4), although the AHR did not reach statistical significance. A sensitivity analysis was performed according to the validated algorithm of Hernan et al. [30] to include only incident PD patients (follow-up in GPRD ≥3 years before first PD diagnosis and unexposed to parkinsonism inducing drugs ever before first PD diagnosis). With this definition, 2083 PD patients were identified. The observed risks for the various types of fracture were similar to those presented in Table 2 (any, AHR 1.94 [95% CI, 1.57 - 2.40], osteoporotic, AHR 2.05 [95% CI, 1.60 - 2.63] and hip fracture, AHR 3.24 [95% CI, 2.15 - 4.90]).

Discussion

This study found an almost doubled risk of any fracture and osteoporotic fracture, and a tripled

risk of hip fracture in patients with PD as compared to the control population. Among patients with PD, the risk of osteoporotic fracture further increased with the use of MAO-B inhibitors, SSRIs, high dose antipsychotics, history of fracture, falling, low BMI and renal disease. We could not detect an association between the duration of PD, its severity and risk of fracture.

Our study adds up to the observed increased fracture risk in other studies [18-21]. The observed increased fracture risk is in line with recent findings from a Danish (Vestergaard et al. [22]) and a Dutch (Arbouw et al. [23]) case-control study that evaluated fracture risk among cases exposed to anti-Parkinson medication. The Danish study showed an adjusted odds ratio of 1.18 (95% CI, 1.01 - 1.37) for any fracture, but adjusted in their main analyses for the use of anticholinergics, dopamine agonists, levodopa containing drugs, MAO-B inhibitors and antipsychotics. When we adjusted our main analysis for any fracture for the same covariates, our AHR for any fracture decreased slightly from 1.89 (95% CI, 1.67 - 2.14) to 1.85 (95% CI, 1.54 - 2.23). It is hypothesized that the absence of non-PD patients receiving anti-Parkinson drugs in our cohort could further explain the different outcome. For example, in the Danish study also patients treated with anti-Parkinson medication for restless legs syndrome may have been included. The Dutch case-control study showed an adjusted odds ratio of 1.76 (95% CI; 1.39 - 2.22) for risk of hip fracture with current dopaminergic drug use. The use of MAO-B inhibitors, COMT inhibitors and amantadine was treated as a potential confounder. When we adjusted our main analysis of hip fracture for these covariates, our AHR for hip fracture decreased from 3.08 (95% CI, 2.43 - 3.89) to 2.80 (95% CI, 2.20 - 3.56). Again, the absence of non-PD patients receiving anti-Parkinson drugs in our cohort could further explain the difference in results.

Duration of PD did not show a clear association with fracture risk over time. However, patients seemed to have a higher risk in the first half year after onset of PD. This suggests that falls may be responsible for the increased fracture risk observed among PD patients instead of

decreased BMD. This is in line with our finding that the highest proportion of falls was reported during the first 6 months after PD diagnosis, although differences are small as compared with the amount reported between 6-12 months after PD diagnosis (6.0% versus 5.3% respectively). The difference may be caused by side effects of PD after onset. For example, tremor may take some time before properly treated [8]. Arbouw et al. also observed highest risk of hip fracture, immediately after start of antidopaminergic treatment [23].

In the general population, anxiolytics/hypnotics increase fracture risk by reducing balance [32]. However, in a PD population, which may already have poor balance, the excess increased risk of fracture caused by anxiolytic/hypnotic use, may have been masked by the stronger effect of falling in the PD population. This may also explain the absence of a dose effect. In line with previous studies, fracture risk further increased with the use of SSRIs. [15,33,34]. This may be caused by a further increased risk of falling. It may also be caused by decreased osteoblast proliferation, through 5-hydroxytryptamine receptor inhibition in bone [15]. No dose effect and no association between fracture risk and TCA use was observed, although their effect may also have been masked by the high general increased risk of falling of PD patients. Fracture risk increased with concomitant use of high dose antipyschotics (exceeding an average daily dose of 150 mg thioridazine equivalents). Vestergaard et al. stratified its Danish cohort to average daily dose of antipsychotics as well and observed the highest risks for osteoporotic and hip fracture among patients receiving high average daily doses exceeding 100 mg thioridazine equivalents [22]. Conversely, a Dutch case-control study did not observe a trend in average daily dose of antipsychotics, but their highest average daily dose group did not exceed 75 mg thioridazine equivalents. [16] This may be explained by the use of different antipsychotics in the UK as compared to the Netherlands.

Our study has several strengths. It investigated the risk of fracture in a substantial number of 4,687 incident PD patients compared to control patients. Our inclusion criteria are

based on the validated inclusion criteria used by Hernan et al. to identify incident PD patients [31]. A sensitivity analysis on incident PD patients (follow-up in GPRD ≥3 years before first PD diagnosis and unexposed to parkinsonism inducing drugs ever before first PD diagnosis) showed similar results for fracture risk in the main analyses. Furthermore, 95% of PD patients had at least three records of a prescription for anti-Parkinson medication after diagnosis, which indicates that most diagnoses were correct and that early death was uncommon. Selection bias is unlikely, because each PD patient was compared with an age-gender matched control. In contrast to other studies (Vestergaard et al. and Arbouw et.al) adjustment for well-known risk factors like smoking status and history of fracture was possible.

Our study had various limitations. We were unable to classify the severity of PD based on the Hoehn and Yahr classification [28]. Instead, an alternative approach, based on PD treatment prescribed in the different severity stages of PD, was used based on the NICE guideline [29]. A recent GPRD study by de Vries et al. [35] and a Dutch PHARMO study by Bazelier et al. [36] used a similar approach. Some PD patients may have been misclassified for mild, moderate or severe PD in our severity analysis. Moreover, it is likely that the most severe PD patients were not included in our cohort since mean follow-up did not exceed 4 years. No association between the dose of dopaminergic drugs and the risk of fracture was observed. However, we were unable to distinguish if these drugs were actually harmless or that an increasing dose ameliorated the symptoms of the disease and consequently prevented the risk of fracture. No data were present on femoral bone mineral density and history of hip fracture among the parents of patients.

In conclusion, PD patients are at an almost doubled risk of any fracture and osteoporotic fracture, and a tripled risk of hip fracture as compared to the control population. Bisphosphonates may be recommended in order to prevent hip fractures in PD patients [37]. Therefore, fracture risk assessment may be indicated among PD patients. Beside the general

risk factors for fracture, like increasing age and female gender, in particular when they have recently used MAO-B inhibitors, SSRIs or high-dose antipsychotics or have a history of fracture, falling, low BMI or renal disease.

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Chapter 3.3

Five-year fracture risk estimation in patients with Parkinson's disease

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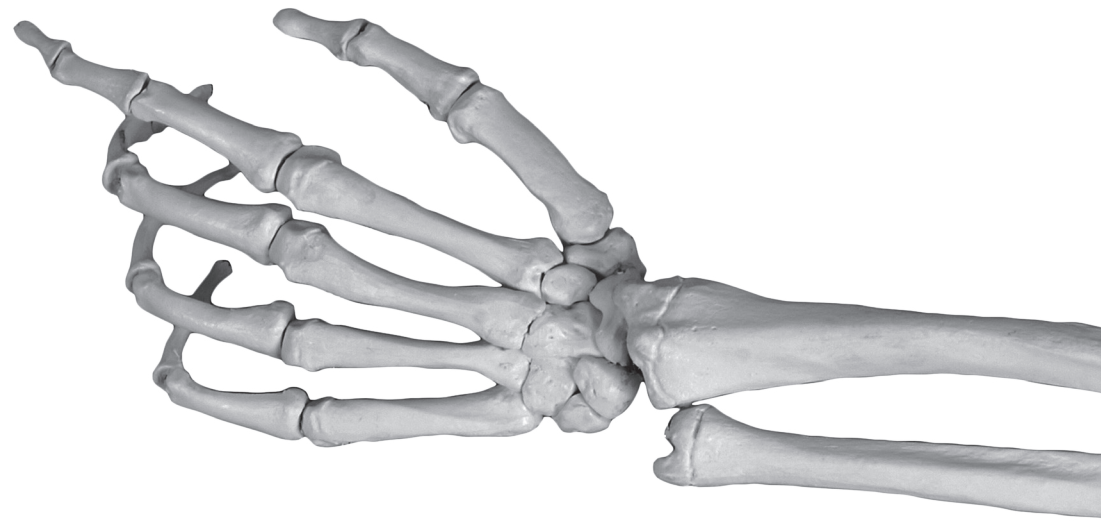

Abstract

Background: Previous studies have shown that patients with Parkinson's Disease (PD) are at increased risk of fractures. However, no specific prediction model for fracture estimation among PD patients is currently available. Therefore, the aim of this study was to develop a simple score for estimating the 5-year osteoporotic and hip fracture risk among patients with PD.

Methods: The UK Clinical Practice Research Datalink (1987-2011) was used to identify incident PD patients. Cox proportional-hazards models were used to calculate the 5-year risk of osteoporotic and hip fracture among PD patients. The regression model was fitted with various risk factors for fracture and the final Cox model was converted into integer risk scores.

Results: We identified 4,411 incident PD patients without a history of osteoporotic treatment. The 5-year risks of osteoporotic and hip fracture were plotted in relation to the risk score. Risk scores increased with age, female gender, history of renal disease and history of dementia. The C-statistic, which is a parameter to test the internal validity of the model, was reasonable for the prediction of osteoporotic fracture (0.69) and hip fracture (0.73).

Conclusion: In this study, we developed a simple model to estimate 5-year fracture risk among incident PD patients. It may be useful in daily practice after external validation.

Background

Parkinson's disease (PD) is a movement disorder, which has a prevalence of about 1% in people over 60 years of age [1]. Symptoms of PD include bradykinesia, resting tremor, stiffness, and postural instability, caused by loss in dopaminergic neurons of the nigrostriatal pathway [2]. PD has been associated with an increased risk of falling [3-5] and with detrimental effects on bone [6,7]. Both falling and low bone mineral density (BMD) are known risk factors for fracture. Consequently, several studies observed an association between PD and fracture risk [8-11]. Recently we have shown that osteoporotic fracture risk was doubled and hip fracture risk was tripled compared with a large group of control patients derived from the United Kingdom Clinical Practice Research Datalink (CPRD), formerly known as the General Practice Research Database [12].

In our previous study we did not focus on fracture risks for individual PD patients. Some universal prediction programs are currently available, of whom the fracture risk assessment tool named FRAX is most common [13]. FRAX is a computer-based algorithm developed by the World Health Organization to perform a clinical assessment for 10-year fracture probability [14]. Currently, it takes several known risk factors for fracture into account, including age, gender, body mass index (BMI), history of fracture, parenteral history of hip fracture, rheumatoid arthritis, smoking, use of oral glucocorticoids, other causes of secondary osteoporosis and high alcohol consumption [14]. PD has recently been described as a predictor for fracture in FRAX, but has not been included in the algorithm yet [15]. The tool can be accessed on the web via http://www.shef.ac.uk/FRAX and includes 45 FRAX models available for 40 countries [16,17]. Validity has been assessed by calculating the C-statistics in several validation cohorts, comprising populations in different countries. The C-statistics for hip fracture and osteoporotic fracture prediction were respectively 0.66 and 0.60 without using BMD as a risk factor in the validation analysis [18].

A limitation of FRAX is that it is not specific for a wide variety of patient groups who are at risk of fracture, such as PD patients. As far as we know, no specific risk score estimation for PD patients has been described. A clinical risk score would be useful to identify those PD patients who may need a further fracture risk assessment. Therefore, the aim of this study was to develop a score for estimating the 5-year osteoporotic and hip fracture risk among patients with PD.

Methods

Data Source

This study used computerized medical records of more than 10 million patients under the care of general practitioners in the UK, obtained from the CPRD. Data include the patient's demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions, and major outcomes [19]. Moreover, previous studies of CPRD data have shown a high level of data validity with respect to the reporting of fractures (>90% of fractures were confirmed) [20,21].

Study population

The study population consisted of all incident PD patients aged 40 years or older during the period of CPRD data collection between 1987 and 2011. They had at least two records of a prescription for anti-Parkinson medication after diagnosis (levodopa, dopamine agonists, MAO-B inhibitors, amantadine, apomorphine, anticholinergic drugs [procyclidine, trihexyphenidyl, orphenadrine, methixine, biperiden or benzatropin] or COMT inhibitors [entacapone or tolcapone]). Patients who had more than one record for a prescription of PD treatment before PD diagnosis were excluded. This classification is based on a PD classification used by Hernan et al. who confirmed the PD diagnosis in 90% of PD patients

included in their CPRD cohort (n=1,019) [22].

The study patients were followed up from their PD diagnosis date to either the end of CPRD data collection, the date of transfer of the patient out of the practice area, the patient's death, or the occurrence of fracture whichever came first. In line with FRAX, we excluded all patients (n=276) who had ever been treated for osteoporosis (including a prescription of a bisphosphonate, selective estrogen receptor modulator, strontium ranelate or parathyroid hormone) before the PD diagnosis [23].

Study outcome

Patients were followed up for the occurrence of osteoporotic fracture or hip fracture. The fracture types were classified according to the International Classification of Diseases, Tenth Revision (ICD-10) categories. A clinical osteoporotic fracture was defined as a clinically symptomatic fracture of the radius/ulna, humerus, rib, femur/hip, pelvis, or vertebrae.

At baseline, the presence of risk factors was determined based on the computerized medical records. Potential risk factors in this study included, age, female gender, body mass index (BMI), smoking status, a previous record in CPRD for fracture, a previous record in CPRD for chronic diseases (asthma/chronic obstructive pulmonary disease [COPD], rheumatoid arthritis, hyperthyroidism, hypothyroidism, renal disease [including acute renal failure and chronic mild to severe impaired renal function], cancer [including current and previous cancer], congestive heart failure, cerebrovascular disease, diabetes mellitus, inflammatory bowel disease, dementia). The chronic diseases were identified with CPRD records which described the presence of the disease. A record for medication to treat the disease was insufficient to identify a chronic disease. Further potential risk factors in the study are a prescription in the previous 6 months for central nervous system (CNS) medication (antidepressants, antipsychotics, anxiolytics/hypnotics), anticonvulsants, opioids, oral glucocorticoids, and other

immunosuppressants (azathioprine, ciclosporin, tacrolimus, mycophenolate mofetil, methotrexate). In our study, a history of falls (non-injurious and injurious falls) was determined in the 3-12 months before baseline, because falls reported within 3 months before start of follow-up may have been associated with a later reported fracture.

Statistical analysis

Statistical analyses and data management were performed using SAS 9.1 software. Five-year risks of osteoporotic fracture and hip fracture were calculated using Cox proportional hazard models. With the Cox model, the probability of fracture (i.e. survivor function) can be calculated for individual patients. For the five-year fracture risk estimation, the regression models were fitted with the identified risk factors for fracture derived from FRAX, when available in CPRD [14]. These included age, gender, current smoking, a BMI below 20, a BMI of 30 or more, a history of fracture, the use of oral glucocorticoids in the previous 6 months and a history of RA. These risk factors were placed in the model as fixed variables. Additionally, we decided to add history of antidepressant use in the previous 6 months as a fixed variable to the model, because this variable has been identified as a risk factor for fracture in PD patients [12]. Subsequently, the regression models were fitted with all other possible risk factors for fracture determined at baseline, using forward selection with a significance level of 0.05. Except for age, all characteristics were included as categorical variables in the models, thus discriminating between ‘yes’ and ‘no’ for each specific risk factor. For some patients the BMI or smoking status was unknown. For these patients a dummy variable was added to the regression model. On top of the fixed risk factors for fracture, a history of renal disease and dementia and a history of falling 3-12 months before start of follow-up were identified for osteoporotic fracture prediction using forward selection. For the prediction of hip fracture risk, a history of renal disease and dementia were identified.

In the final Cox model, the beta coefficients were converted into integer risk scores. The value of each integer was calculated as the rounded sum of the Cox model predictor scores, multiplied by 10. The 5-year risk of fracture was then estimated using these scores, conditional on patient survival. We compared the observed 5-year probability of fracture (based on the Kaplan-Meier estimate) with the probability predicted by the Cox model. The internal validity of the model was further assessed by calculation of the C-statistic and a 10-fold cross-validation was performed. The observed shrinkage factor was applied to the beta coefficients of the model, and the C-statistic was adjusted for over-estimation.

Results

During CPRD data collection, 4,411 incident PD patients were identified meeting the inclusion criteria. They had a mean age of 74 years and 40% was female. Average follow-up of PD patients was 4 years. Table 1 provides more information regarding BMI, smoking and history of comorbidities and drug use in PD patients.

The risk score for osteoporotic and hip fracture in relation to different patient characteristics is presented in Table 2. Highest risk scores were obtained with high age, female gender, history of renal disease and history of dementia. The individual patient's risk score is the sum of the score for each of the different risk factors. For example, a female patient aged 70 years, with history of renal disease, had a risk score for hip fracture of 73 (+4 points for being female, +56 points for age, and +13 points for history of renal disease).

Table 3 shows the five-year fracture risks among incident PD patients at the 50th percentile of risk score, but also at the 5th and 95th percentiles. Female patients were at a higher risk compared to male patients and risk further increased with age. Hip fracture risk was slightly lower compared to osteoporotic fracture risk. Figures 1 and 2 show the 5-year risk of osteoporotic and hip fracture as a function of the risk scores. For example, Figure 2 shows that

the 5-year risk of hip fracture was 10% among women with a calculated score of 73. The adjusted C-statistics were moderate for both osteoporotic (0.69) and hip fracture (0.73) prediction.

Table 1: Baseline characteristics of patients with incident PD

Characteristics	PD Patients (n=4,411)
Female (%)	39.9
Mean age (years)	73.9
BMI (%)	
< 20	3.7
20 - 24	30.5
25 - 29	32.6
≥ 30	11.7
Unknown	21.5
Smoking status (%)	
Never	55.4
Current	16.8
Ex	22.9
Unknown	4.9
Fracture history (%)	
Any fracture	17.5
Fracture at osteoporotic sites	9.8
Hip fracture	1.6
Vertebral fracture	0.6
Radius/ulna fracture	5.0
Comorbidity ever before index date (%)	
Asthma	10.7
COPD	4.5
Congestive heart failure	5.1
Diabetes Mellitus	9.1
Rheumatoid arthritis	1.2
Renal disease	1.4
Cerebrovascular disease	13.0
Inflammatory bowel disease	0.8
Cancer (excluding skin cancer)	21.0
Dementia	5.1
Ischaemic heart disease	19.2
Drug use in 6 months before index date (%)	
Oral glucocorticoids	2.5
Antidepressants	20.3
Antipsychotics	5.2
Anxiolytics	11.7
Anticonvulsants	4.3

Table 2: Risk score of fracture (among PD patients)

Characteristic	Score osteoporotic fracture	Score hip fracture
Sex female	6	4
Age (for every 10 years)	6	8
Use of oral glucocorticoids in the prior 6 months	4	-
Use of antidepressants in the prior 6 months	2	0
History of rheumatoid arthritis ever before	2	1
History of renal disease ever before	10	13
History of dementia ever before	4	5
History of fracture ever before	3	1
History of falling in 3-12 months before	3	-
Current smoker	1	1
BMI < 20	3	6
BMI ≥ 30	0	-2

Adjusted C-statistic is 0.69 for osteoporotic and 0.73 for hip fracture with the current model.

Table 3: Five-year risk of fracture among PD patients at the 5th, 50th, and 95th percentiles of fracture risk score

	Osteoporotic fracture						Hip fracture					
	5th		50th		95th		5th		50th		95th	
	risk	score	risk	score	risk	score	risk	score	risk	score	risk	score
Women												
40-49	1.9	31	2.9	35	3.5	37	0.4	40	0.5	44	1.0	51
50-59	3.4	41	5.1	41	8.5	46	0.8	53	1.3	53	2.2	58
60-69	5.1	43	9.0	47	13.7	51	1.3	56	2.9	61	4.6	66
70-79	10.1	48	15.4	52	26.3	58	4.2	65	6.8	70	14.1	78
80+	18.5	54	27.3	59	47.9	66	9.8	74	15.9	79	34.7	88
Men												
40-49	1.0	24	1.5	28	2.2	32	0.2	35	0.4	40	0.5	44
50-59	1.8	34	2.7	34	4.0	38	0.5	48	0.8	48	1.2	52
60-69	2.5	36	4.8	40	7.9	45	0.7	52	1.9	57	3.0	62
70-79	5.8	42	8.2	46	14.0	51	2.7	61	4.2	65	7.6	71
80+	9.8	47	14.0	51	26.0	58	6.4	69	8.9	73	19.8	81

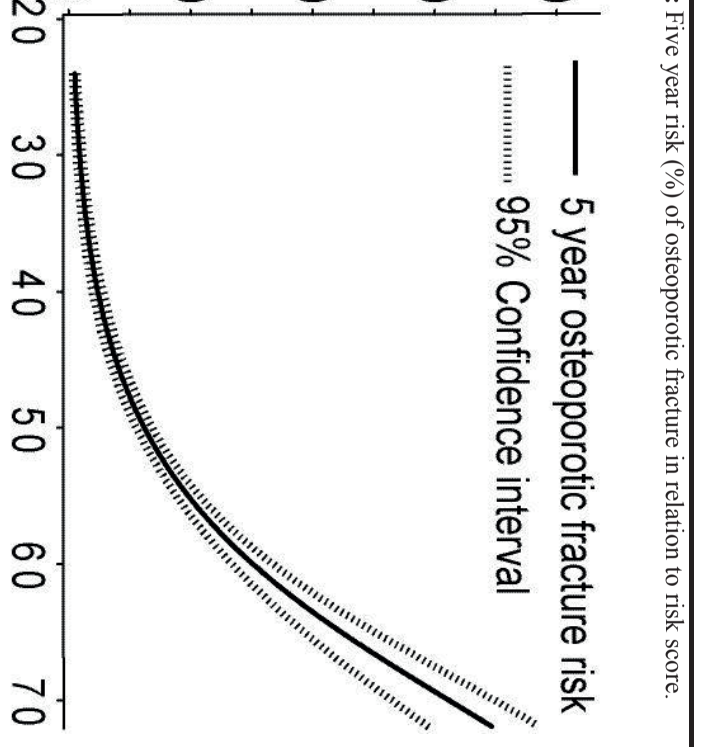

Figure 1: Five year risk (%) of osteoporotic fracture in relation to risk score.

Figure 2: Five year risk (%) of hip fracture in relation to risk score.

Discussion

This study describes a simple model for the assessment of osteoporotic fracture risk estimation and hip fracture risk estimation for incident PD patients. Identified risk factors for osteoporotic fracture in the model are female gender, increasing age, current smoking, low BMI, history of rheumatoid arthritis, dementia, renal disease, fracture, falling and use of antidepressants or oral glucocorticoids in the previous 6 months. For hip fracture, the same risk factors were observed, with the addition of a lowered risk for high BMI. Histories of falling and recent use of antidepressants or oral glucocorticoids were not identified as risk factors.

The association between fracture risk and PD may be fall-related, caused by common side effects of PD treatment, including postural hypotension and confusion or caused by uncontrolled symptoms of PD itself, including tremor, stiffness, and postural instability [2,24]. It may also be bone-related through reduced BMD, caused by direct detrimental effects on bone. An explanation may be that in PD patients, reduced 25-hydroxyvitamin D levels and compensatory higher parathyroid hormone levels were observed [6]. This may be due to sunlight deprivation or decreased dietary intake of vitamin D [6,25]. Moreover, fracture risk may be increased by levodopa-induced hyperhomocysteinemia [26]. Other explanations include menopausal status, a low BMI, low serum calcium concentrations and the duration of PD [27].

In line with the risk factors for fracture in FRAX [23], our model predicts an increased osteoporotic and hip fracture risk for female gender, increasing age, current smoking, low BMI, history of rheumatoid arthritis and history of fracture. Conversely, our model predicts a decreased risk of hip fracture with a BMI of 30 or more. The use of oral glucocorticoids was a predictor for osteoporotic fracture, which is in line with previous studies [22]. However it did not predict hip fracture. This may have been caused by the exclusion of patients who had ever been treated for osteoporosis. Consequently, only 112 of 165 incident PD patients who used

oral glucocorticoids at baseline were included in the model, whereof only 4 incident PD patients who experienced a hip fracture during follow-up.

On top of the predictors for fracture described in FRAX, dementia and renal disease were observed as predictors for osteoporotic and hip fracture risk among incident PD patients. Additionally, a history of falling and use of antidepressants in previous 6 months were identified for osteoporotic fracture. Dementia has been associated with PD [28] and with an increased risk of falling [29]. Both are risk factors for fracture [12,30]. For renal disease, the causal pathway for an increased risk of fracture among PD patients is less obvious. It is hypothesized that PD patients may develop a neuroleptic malignant syndrome, caused by abrupt cessation of levodopa treatment among PD patients [31]. Furthermore, concomitant antidepressant use among PD patients may result in a serotonin-syndrome [32]. Both syndromes may cause rhabdomyolysis followed by renal failure. Consequently, renal disease may cause severe bone loss through treatment received after kidney transplantation and by post-operative immobility followed by increased activities [33]. On the other hand, renal disease may also increase risk of fracture irrespective of PD, which is an alternative explanation for its predictive effects for osteoporotic and hip fracture [33]. Finally, antidepressant use has been associated with increased fracture risk in PD patients [12]. This may be caused by an increased risk of falling. It may also be caused by decreased osteoblast proliferation, through 5-hydroxytryptamine receptor inhibition in bone [34].

This study has several strengths. As far as we know, this is the first specific study, which provides a clinical risk score for fracture risk estimation among incident PD patients. It had a substantial number of 4,411 incident PD patients who met the inclusion criteria. The predictive accuracy of the models in this study is moderate. They showed reasonable results with C-statistics of 0.69 for osteoporotic and 0.73 for hip fracture respectively. Additionally, the concordance between predicted and actual probabilities (i.e. the calibration of the model),

which was determined by a 10-fold cross-validation, showed shrinkage factors close to 1, which confirms validity of the model.

Limitations of our study were the inability to include BMD measurements, a history of secondary osteoporosis, a history of alcohol use and a history of hip fracture among parents to the model. These are established risk factors for fracture risk [14]. The predicted risks are based on a single measurement of the risk factors at baseline, with the unlikely assumption that these risk factors do not change over time. The prediction models are only applicable for incident PD patients, which limits their use to PD patients in the early phase of the disorder. The occurrence of falls has not been validated in CPRD. Subsequently, there may be an underestimation of falls in CPRD, because of underreporting. Only those falls reported in CPRD by the general practitioner or specialist were included in our model. Presumably, several non-injurious falls were not reported to the general practitioner or specialist. Therefore it is suggested that most records in CPRD for falls were injurious falls. With a mean follow-up of 4 years we were unable to determine 10-year fracture risk like FRAX. Finally, the developed models for fracture risk estimation should also be validated in an external population [35]. The authors can be contacted to provide details of the exact methods for external validation studies.

In conclusion, this study described the development of a specific model to estimate 5-year osteoporotic and hip fracture risk among incident PD patients. It may be useful in daily practice after external validation.

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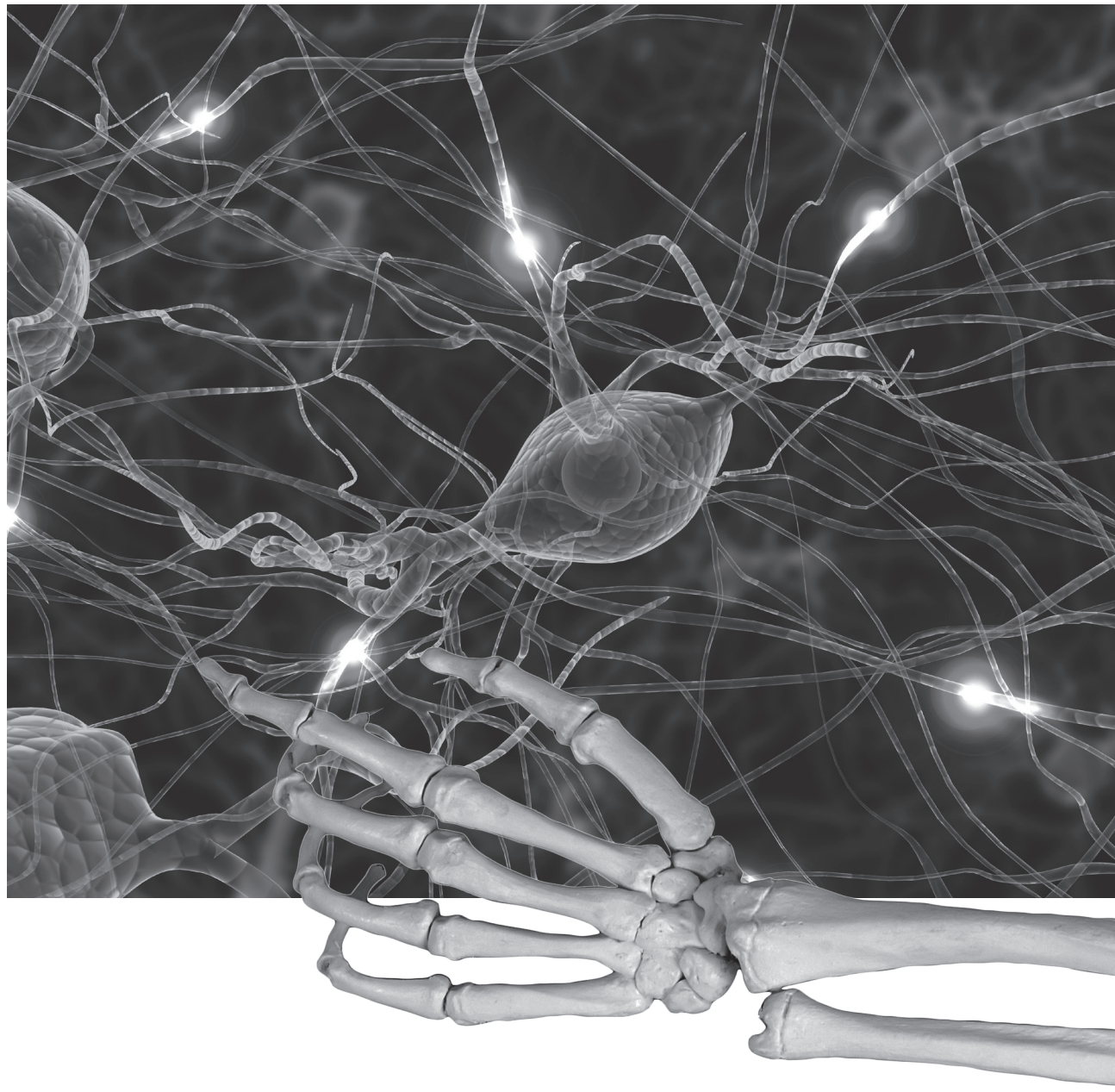
Chapter 4

Other neurological disorders and risk of fracture



Chapter 4.1

Fracture rate in patients with Myasthenia Gravis: the General Practice Research Database

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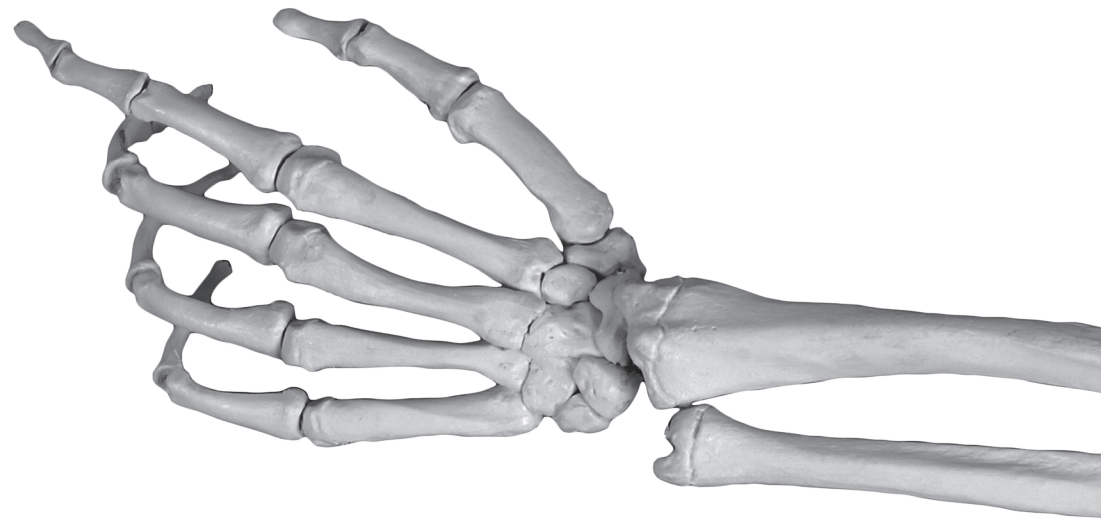


Abstract

Background: Myasthenia Gravis (MG) is a neuromuscular disease, which has been associated with an increased falls risk and glucocorticoid induced osteoporosis, recognized determinants of increased fracture risk. The aim of this study was to evaluate the risk of fracture after onset of MG.

Methods: We conducted a retrospective cohort study using the UK General Practice Research Database (1987-2009). Each MG patient was matched by age, sex, calendar time, and practice to up to 6 patients without a history of MG and we identified all fractures and those associated with osteoporosis.

Results: Compared to the control cohort, there was no statistically significant increased risk observed in patients with MG for any fracture (adjusted hazard ratio [AHR] 1.11 [95% confidence interval (CI), 0.84 - 1.47]) or osteoporotic fractures (AHR 0.98 [95% CI, 0.67 - 1.41]). Further, use of oral glucocorticoids up to a cumulative dose exceeding 5 grams prednisolone equivalents did not increase risk of osteoporotic fracture (AHR 0.99 [95% CI, 0.31 – 3.14]) compared with MG patients without glucocorticoid exposure. However, fracture risk was higher in patients with MG prescribed antidepressants (AHR 3.27 [95% CI, 1.63 – 6.55]), anxiolytics (AHR 2.18 [95% CI, 1.04– 4.57]) and anticonvulsants (AHR 6.88 [95% CI, 2.91 – 16.27]).

Conclusion: Overall risk of fracture in patients with MG is not statistically increased compared with age and gender matched controls irrespective of glucocorticoid use but was increased in those using antidepressants, anxiolytics or anticonvulsants. These findings have implications in strategies preserving bone health in patients with MG.

Introduction

Myasthenia Gravis (MG) is an automimmune disorder with symptoms of muscle weakness and fatiguability, in which antibodies reduce the number of acetylcholine receptors at the post-synaptic region of the neuromuscular junction [1]. MG is relatively rare with an estimated pooled incidence rate of 5.3 per million person-years and an estimated pooled prevalence rate of 77.7 per million persons [2]. Treatment options for MG include use of cholinesterase inhibitors and immunosuppressants, including oral glucocorticoids and in selected patients plasmapheresis and thymectomy [3]. Patients with a diagnosis of MG have a normal life expectancy based on the currently available therapies [4].

MG is associated with an increased falls risk [5-7] and glucocorticoid induced osteoporosis [8,9]. The increased risk of falls from MG is likely to be multifactorial including severe muscle weakness [1], impaired vision as a result of ocular MG and steroid induced myopathy [10,11]. Recent studies in a representative sample of the total UK population have shown that treatment with glucocorticoids is associated with a substantial risk of fracture, in a wide range of chronic diseases [12-13]. Oral glucocorticoid treatment in MG patients is regularly started with 10 mg prednisolone per day and is quickly increased towards about 60 mg per day [14-15]. Once an effective clinical response is obtained (within about 10-12 weeks), this dose is slowly tapered down, towards 2.5 – 10 mg prednisolone equivalents each day or an equivalent dose on alternate days for maintenance [15]. Hence these patients are routinely exposed to significant cumulative doses of prednisolone far exceeding 1 gram.

In addition to falls risk and glucocorticoid therapy, the increased risk of fracture in patients with MG may also relate to psychiatric comorbidity and its treatment. As compared with healthy patients, MG patients are more likely to have a history of central nervous system (CNS) disorders [16]. This could be the result of a central cholinergic transmission deficit, caused by blocking of acetylcholine receptors within the central nervous system [17]. Both

CNS drugs such as antidepressants and antipsychotics, and the CNS diseases like epilepsy and depression have been associated with an increased risk of fracture [18-21], or osteoporosis [22,23].

Objectives of this study are to determine the risk of fracture in patients with MG, as compared with population-based controls, and to evaluate the effects of oral glucocorticoids and CNS medication on fracture risk in patients with MG.

Methods

Data Sources

Information for this study was obtained from the General Practice Research Database (GPRD), which comprises the computerized medical records of all patients under the care of general practitioners in the UK. Medical information on patients who are registered for medical care with a practice is supplied to the GPRD [23]. The data in GPRD have been linked to the national Hospital Episode Statistics (HES) in England, for approximately 45% of all practices. HES includes information on the date, main discharge diagnosis and duration of hospitalisation, as provided by the NHS hospitals. Data were linked from April 2001 up to March 2007. Previous studies of GPRD data have shown a high level of data validity with respect to the reporting of fractures (>90% of fractures were confirmed) [25,26].

Study population.

A proxy for identifying MG patients was agreed upon by two neurologists, an expert in bone diseases and a pharmacoepidemiologist (JV, DHJ, KJ and FV). The study population consisted of all patients aged 18 years or older with at least one recorded diagnosis of MG during the period of HES or GPRD data collection (for this study, GPRD data collection started in January 1987 and ended in July 2009). Incident cases of MG were defined as individuals

whose first recorded GP or hospital visit for MG was at least 1 year after their inclusion into the database. Each MG patient was matched by year of birth, sex and practice to up to 6 patients without a history of MG to generate a matched cohort. The index date of MG diagnosis was the date of the first record of MG after GPRD data collection had started. Each control patient was assigned the same index date as his matched MG patient. The study patients were followed up from this index date to either the end of GPRD data collection, the date of transfer of the patient out of the practice area, the patient's death, or the occurrence of fracture, whichever came first. All types of fracture were included in the analyses and classified according to the International Classification of Diseases, Tenth Revision (ICD-10) categories (HES) and corresponding read codes (GPRD). A typical osteoporotic fracture was defined as a fracture of the radius/ulna, humerus, rib, femur/hip, pelvis, or vertebrae (clinically symptomatic).

Subsequently, this population was then divided into a group of probable MG cases (n=834) with their matched controls and a group of possible MG cases (n=232) with their matched controls. The following criteria were used to determine a probable case MG: a recording of MG in two different registries (GPRD and HES) (n=205), or it has a recording of MG in at least one registry with either a letter from a neurologist confirming the patient has seen a neurologist ever before or 1 year after the diagnostic code (n=291), or a record of thymectomy (n=48) any time during follow-up (recorded either in GPRD or HES) or at least two prescriptions on different days of pyridostigmine, oral glucocorticoids, azathioprine, methotrexate, ciclosporin or mycophenolate mofetil any time during enrollment (n=754). Possible cases were identified if they had a recording of MG recording in either GPRD or HES without the abovementioned prescription data, recording of thymectomy or a letter from a neurologist. Patients were excluded if they had a record of Lambert-Eaton type myasthenic syndrome, which mimics MG.

Exposure

The indicators of MG severity selected for the study were selected from the Myasthenia Gravis Foundation of America postintervention status that were also recorded in the GPRD [26]. Grade 1 included patients who did not use cholinesterase inhibitors or immunosuppressants during the past 6 months. Grade 2 included patients who used immunosuppressants, but not cholinesterase inhibitors during the past 6 months. Grade 3 included patients who used pyridostigmine only during the past 6 months (and no immunosupressants), and grade 4 included patients who had been on both immunosuppressants and cholinesterase inhibitors. MG severity grade may fluctuate over time.

Potential confounders that were determined at baseline included body mass index (BMI), smoking status, alcohol status and occurrence of prior fractures. Missing data for BMI, smoking or alcohol status was treated as a separate group in the statistical models. Potential confounders that were determined for a time-dependent analysis during follow-up included age, a history of chronic diseases (including asthma/chronic obstructive pulmonary disease [COPD], rheumatoid arthritis, thyroid disorders, renal failure, cancer, congestive heart failure, cerebrovascular disease, diabetes mellitus, inflammatory bowel disease, secondary osteoporosis (based on the definition of FRAX [28])), a prescription in the 6 months before an interval for CNS medication, anti-Parkinson medication, non-steroidal anti-inflammatory drugs (NSAIDs), oral glucocorticoids, and other immunosuppressants (azathioprine, cyclosporine, tacrolimus, mycophenolate mofetil, methotrexate). In this approach it was assumed that no residual effect was left for medication used more than 6 months before an interval. The use of oral glucocorticoids and CNS medication were stratified to average daily dose in 6 months before an interval, and use of oral glucorticoids was also stratified to cumulative dose in the year before an interval. WHO defined daily dosages were used to add up dose equivalences of

various CNS medication and oral glucocorticoid substances. Within the 6 months before each interval, the average daily dose was calculated by dividing the cumulative dose by the time between the oldest prescription and the start date of the period. In addition, MG disease duration was noted, as measured from the start of follow-up.

Statistical analysis

Time-dependent Cox proportional hazards regression was used in order to estimate hazard ratios (HRs) of fracture risk. The first analysis compared the fracture rate in MG patients with that in control patients, to yield an estimate of the HRs of fracture in MG. The second analysis examined the effect of disease severity and use of oral glucocorticoids, antidepressants, anxiolytics or anticonvulsants on fracture risk in the MG cohort.

For each analysis, the regression model was fitted with the indicators for MG severity and general risk factors. These characteristics were treated as time-dependent variables in the analysis, in which the total period of follow-up was divided into periods of 30 days, starting at the index date. At the start of each period, the presence of risk factors and indicators of MG severity were assessed by reviewing the computerized prescription and diagnosis records prior to the right censoring date. BMI, alcohol status, smoking status and occurrence of prior fracture were determined at baseline. During follow-up, the presence of a previous record for a chronic disease ever before each period of 30 days was assessed, while the presence of a medical prescription was assessed in the 6 months before each period. All characteristics, except age, were included as categorical variables in the regression models. A priori we tested for interactions between age and gender with fracture risk. Adjustments were made if any potential confounder showed a change in HR exceeding 1%.

Sensitivity analyses

A separate analysis was performed for probable and for possible MG patients. In a second sensitivity analysis, we excluded all patients and their matched subjects who had ever been prescribed a bisphosphonate, selective estrogen receptor modulator (SERM), strontium ranelate or parathyroid hormone during follow-up. This in order to evaluate whether the use of bone protecting treatment had masked a true association between MG or glucocorticoid use and fracture.

Results

Table 1 shows that there were 1,066 incident patients with probable or possible MG were matched to 6,392 controls identified between 1987 - 2009. The mean age of patients with MG was 62 years and 50% were female. Most patients with incident MG (78%) were able to be classified with probable MG. Patients were followed for a median of 4 years.

When compared with their matched controls, patients with a diagnosis of MG had no increased risk of either all fractures in both unadjusted and adjusted models (adjusted hazard ratio [AHR] for any fracture 1.11 [95% Confidence Interval (CI), 0.84 - 1.47] or typical osteoporotic fractures AHR 0.98 [95% CI, 0.67 - 1.41]) (Table 2). The fracture risk did not differ significantly among patients with probable MG (AHR for any fracture 0.89 [95% CI, 0.67 - 1.25], AHR for classical osteoporotic fracture 0.79 [95% CI, 0.50 - 1.25]). In addition, no associations were observed between incident MG patients stratified by gender and by age categories.

We then examined the effect of exposure to medications well known to be associated with an increased risk of fracture (Table 3). Surprisingly recent exposure to oral glucocorticoids did not significantly alter fracture risk within MG patients. At osteoporotic sites of incident MG patients, fracture risk yielded an AHR of 0.81 (95% CI, 0.40 – 1.61) compared to MG patients who did not use oral corticosteroids in the past 6 months.

Table 1: Baseline characteristics of patients with incident myasthenia gravis and control patients

Characteristics	MG Patients (n=1,066)	Controls (n=6,392)	Probable MG Patients (n = 834)	Possible MG Patients (n=232)
Female	49.7	49.8	45.6	64.7
Mean age (years)	61.6	61.4	62.4	58.4
BMI (%)				
< 20	5.2	5.5	4.3	8.2
> 30	21.5	16.6	22.9	16.4
Unknown	13.0	15.5	12.6	14.7
Smoking status (%)				
Never	47.7	43.2	46.6	51.7
Current	13.8	17.6	13.5	14.7
Ex	23.2	22.0	25.5	14.7
Unknown	15.3	17.1	14.3	19.0
Alcohol status (%)				
Never	14.7	10.4	15.2	12.9
Current	57.5	59.6	57.6	57.3
Ex	5.5	3.9	6.0	3.9
Unknown	22.2	26.1	21.2	25.9
Fracture history (%)				
Any fracture	15.1	15.7	15.0	15.5
Fracture at osteoporotic sites	6.8	7.5	6.7	6.9
Hip fracture	0.8	0.6	0.8	0.4
Vertebral fracture	0.8	0.6	0.5	0.9
Radius/ulna fracture	2.8	3.9	2.6	3.4
Comorbidity ever before index date (%)				
Asthma	13.1	10.5	12.8	14.2
COPD	3.0	4.2	3.1	2.6
Congestive heart failure	2.3	2.9	2.0	3.4
Diabetes Mellitus	7.9	6.9	8.8	4.7
Rheumatoid arthritis	2.6	1.3	2.8	2.2
Renal failure	1.1	0.9	1.2	0.9
Cerebrovascular disease	8.0	6.1	8.8	5.2
Inflammatory bowel disease	0.8	0.8	0.7	1.3
Cancer	18.3	18.1	18.6	17.2
Thyroid disorders	18.7	11.0	18.0	21.1
Secondary osteoporosis	6.6	4.5	6.5	6.9
Drug use in 6 months before index date (%)				
Pyridostigmine	13.0	0.0	16.5	0.4
Oral glucocorticoids	8.7	2.8	9.2	6.9
Immunosuppressantsa	2.2	0.4	2.8	0.0
Antidepressants	10.4	8.4	10.9	8.6
Antipsychotics	1.2	1.3	1.2	1.3
Anxiolytics	8.4	5.9	7.4	12.1
Anticonvulsants	3.3	1.8	3.2	3.4
Bisphosphonates	4.1	1.8	4.2	3.9
Hormone Replacement Therapy	1.9	1.7	1.6	3.0

a: Ciclosporine, azathioprine, tacrolimus, mycophenolate mofetil and methotrexate are included

Table 2: Risk of fracture in incident MG patients by type of fracture, gender and age compared to patients without MG

	Number of fractures	Rate / 1000 person-years	Age-sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)[a]
No MG	426	12.6	1.00	1.00
MG (Any fracture)	75	14.2	1.19 (0.93 - 1.52)	1.11 (0.84 - 1.47)
Fracture at osteoporotic sites	43	8.2	1.13 (0.82 - 1.56)	0.98 (0.67 - 1.41)
Hip fracture	8	1.5	0.85 (0.41 - 1.77)	0.61 (0.26 - 1.45)[b]
Vertebral fracture	9	1.7	2.85 (1.31 - 6.18)	2.13 (0.82 - 5.51)[c]
Radius/ulna fracture	11	2.1	0.92 (0.49 - 1.73)	1.02 (0.51 - 2.04)[d]
Other fracture	15	2.8	1.00 (0.58 - 1.71)	0.86 (0.47 - 1.59)[e]
Fracture at non-osteoporotic sites	32	6.1	1.29 (0.89 - 1.89)	1.42 (0.93 - 2.17)[f]
By Gender[g]				
Male	27	10.5	1.11 (0.74 - 1.67)	0.86 (0.52 - 1.42)
Female	48	18.6	1.24 (0.91 - 1.68)	1.20 (0.86 - 1.69)
By age at MG diagnosis[h]				
18 – 39	10	12.4	1.83 (0.90 - 3.69)	1.76 (0.80 - 3.86)
40 – 59	10	6.5	0.68 (0.36 - 1.31)	0.62 (0.29 - 1.29)
60 – 69	18	14.5	1.36 (0.82 - 2.25)	1.42 (0.80 - 2.52)
70 – 79	25	19.5	1.29 (0.84 - 4.34)	1.18 (0.72 - 1.92)
≥ 80	12	30.4	1.11 (0.60 - 2.05)	0.97 (0.47 - 2.00)

a) Adjusted for age, gender, use of immunosuppressants, oral glucocorticoids and antidepressants in the previous six months, history of smoking and alcohol use
b) Addionally adjusted for anxiolytics and antipsychotics in the previous six months, history of asthma and cerebrovascular disease
c) Additionaly adjusted for use of anxiolytics, NSAIDs, anti-Parkinson medication in the previous six months, history of COPD, rheumatoid arhtritis, asthma, secondary osteoporosis and BMI status but not for history of smoking.
d) Not adjusted for history of smoking
e) Not adjusted for use of antidepressants in the previous 6 months and not for history of smoking
f) Additionally adjusted for history of stroke in the previous year, history of hypothyroidism, secundary osteoporosis. Not adjusted for antidepressant use and not for history of alcohol use
g) Male MG patients are compared with male controls and female MG patients with female controls
h) MG patients in each age group are only compared with control patients in the same age group

Furthermore, an average daily dose exceeding 15 mg prednisolone equivalents in the past 6 months (AHR 1.17 [95% CI, 0.47 – 2.89]) or a cumulative dose in the year prior to each interval, exceeding 5 grams prednisolone equivalents (AHR 0.99 (95% CI, 0.31 – 3.14) did not significantly alter osteoporotic fracture risk. In these analyses, osteoporotic fractures were reported in respectively 7 and 4 MG patients. The interaction term between MG and oral glucocorticoids did not reach statistical significance (p-value > 0.05) for any and for typical osteoporotic fractures (Table 4). Finally, a sensitivity analysis in which 645 MG patients without exposure to osteoporosis therapies and their 3647 controls were left, a diagnosis of

Table 3: Risk of any and osteoporotic fracture among incident MG patients by drug exposure

	Risk of any Fracture		Risk of fracture at osteoporotic sites	
	Fractures (n)	Fully adjusted HR (95% CI)[a]	Fractures (n)	Fully adjusted HR (95% CI)[a]
MG by use of oral glucocorticoids by cumulative dose in grams prednisolone eq. in the previous year				
No oral glucocorticoid use	47	1.00	27	1.00
Any oral glucorticoid use	28	0.88 (0.52 – 1.47)	16	0.75 (0.38 – 1.50)
< 2.5 gram prednisolone eq[b]	13	0.80 (0.42 – 1.53)	7	0.63 (0.26 – 1.53)
2.5 – 5.0 gram prednisolone eq	10	1.11 (0.54 – 2.26)	5	0.83 (0.31 – 2.25)
≥ 5.0 gram prednisolone eq	5	0.73 (0.27 – 1.94)	4	0.99 (0.31 – 3.14)
MG by history of drug use in previous 6 months				
No oral glucocorticoid use	48	1.00	28	1.00
Oral glucocorticoid use	27	0.97 (0.58 – 1.63)	15	0.81 (0.40 – 1.61)
< 7.5 mg prednisolone eq/day	10	0.99 (0.49 – 2.03)	5	0.70 (0.26 – 1.92)
7.5 – 15 mg prednisolone eq/day	8	1.00 (0.46 – 2.16)	3	0.57 (0.17 – 1.93)
≥ 15 mg prednisolone eq/day	9	0.93 (0.44 – 1.99)	7	1.17 (0.47 – 2.89)
No antidepressant use	59	1.00	31	1.00
Antidepressant use	16	2.15 (1.22 – 3.79)	12	3.27 (1.63 – 6.55)
< 20 mg fluoxetine eq/day	9	1.88 (0.92 – 3.86)	7	2.77 (1.18 – 6.50)
≥ 20 mg fluoxetine eq/day	7	2.61 (1.18 – 5.80)	5	4.32 (1.64 – 11.38)
No anxiolytic use	61	1.00	32	1.00
Anxiolytic use	14	1.80 (0.97 – 3.34)	11	2.18 (1.04 – 4.57)
< 10 mg diazepam eq/day	10	1.72 (0.85 – 3.47)	8	2.10 (0.90 – 4.86)
≥ 10 mg diazepam eq/day	4	2.07 (0.73 – 5.82)	3	2.41 (0.71 – 8.12)
No anticonvulsant use	64	1.00	36	1.00
Anticonvulsant use	11	5.36 (2.76 – 10.39)	7	6.88 (2.91 – 16.27)
< 1.0 g carbamazepine eq/day	8	4.88 (2.27 – 10.50)	5	5.45 (2.03 – 14.62)
≥ 1.0 g carbamazepine eq/day	3	7.10 (2.13 – 23.62)	2	18.18 (3.88 – 85.15)
No antipsychotic use	74	1.00	42	1.00
Antipsychotic use	1	1.30 (0.17 – 9.76)	1	1.41 (0.17 – 11.65)

a) Adjusted for the same confounders as described below table 2 for any and osteoporotic fracture, but the confounder is not added to the model if it is similar to the drug being investigated.
b) eq: equivalents

Table 4: Risk of any and osteoporotic fracture among incident MG patients and controls by drug exposure

	Risk of any fracture, fully adjusted HR (95% CI)[a]		p-value of interaction term[b]	Risk of fracture at osteoporotic site, fully adjusted HR (95% CI)[a]		p-value of interaction term[b]
	MG Patients	Controls		MG Patients	Controls	
Drug use in previous 6 months						
No oral glucocorticoid use	1.00	1.00		1.00	1.00	
Any oral glucorticoid use	0.88 (0.52 – 1.47)	1.50 (1.02 - 2.20)	0.217	0.75 (0.38 – 1.50)	1.86 (1.23 - 2.83)	0.065
No antidepressant use	1.00	1.00		1.00	1.00	
Antidepressant use	2.15 (1.22 – 3.79)	1.50 (1.15 - 1.96)	0.608	3.27 (1.63 – 6.55)	1.63 (1.18 - 2.27)	0.260
No anxiolytic use	1.00	1.00		1.00	1.00	
Any anxiolytic use	1.80 (0.97 – 3.34)	1.14 (0.82 - 1.59)	0.101	2.18 (1.04 – 4.57)	1.17 (0.79 - 1.73)	0.044
No anticonvulsant use	1.00	1.00		1.00	1.00	
Anticonvulsant use	5.36 (2.76 – 10.39)	0.96 (0.53 - 1.76)	0.000	6.88 (2.91 – 16.27)	1.19 (0.61 - 2.33)	0.002

a) Adjusted for the same confounders as described below table 2 for any and osteoporotic fracture, but the confounder is not added to the model if it is similar to the drug being investigated.

b) The interaction term (MG * drug use in the previous 6 months) was investigated within the cohort of MG patients and controls

Table 5: Risk of any fracture and fracture at osteoporotic sites in incident MG patients, by duration of MG and severity compared to patients without MG

	Risk of any Fracture		Risk of fracture at osteoporotic site	
	Fractures (n)	Fully Adjusted HR (95% CI)[a]	Fractures (n)	Fully Adjusted HR (95% CI)[a]
MG by severity steps based on pyridostigmine and immunosuppressants use in the 6 months prior[b]				
Grade 1: No use	28	1.00	15	1.00
Grade 2: Immuno-suppressants only	13	0.67 (0.16 - 2.80)	6	0.81 (0.13 - 5.04)
Grade 3: Pyridostigmine only	17	0.99 (0.54 - 1.83)	11	1.14 (0.51 - 2.54)
Grade 4: Both immunosuppressant and pyridostigmine use	17	0.34 (0.07 - 1.60)	11	0.48 (0.07 - 3.42)

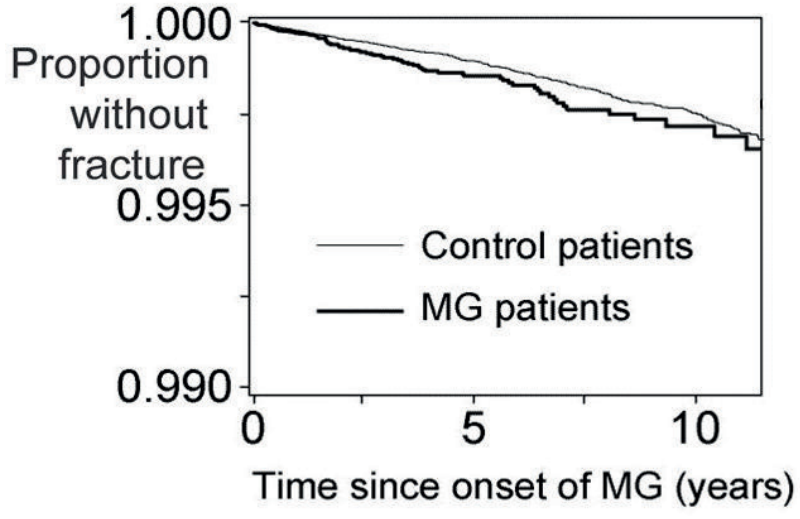
a) Adjusted for the same confounders as described below table 2 for any and osteoporotic fracture, but the confounder is not added to the model if it is similar to the drug being investigated.

b) Immunosuppressants involved are oral glucocorticoids, azathioprine, tacrolimus, ciclosporine, mycophenolate mofetil and methotrexate

MG did not alter risk of any (AHR 1.21 [95% CI, 0.84 - 1.74]) or typical osteoporotic fracture (AHR 1.44 [95% CI, 0.89 - 2.34]). Conversely, within the group of incident MG patients risk of fracture was two-fold higher in those with a recent use of antidepressants (AHR 2.15 [95% CI, 1.22 – 3.79]), two-fold higher for anxiolytics (AHR 1.80 [95% CI, 0.97 – 3.34]) and five-fold increased with recent use of anticonvulsants AHR 5.36 [95% CI, 2.76 – 10.39]). Typical osteoporotic fracture risk was three fold higher within incident MG patients with recent use of antidepressants (AHR 3.27 [95% CI, 1.63 – 6.55]), two-fold higher with recent use of anxiolytics (AHR 2.18 [95% CI, 1.04 - 4.57]) and seven-fold higher with recent use of anticonvulsants (AHR 6.88 [95% CI, 2.91 – 16.27]). None of the remaining risk factors for fracture, which are described in the method section, showed a significant increased or decreased risk for any fracture or for fractures at osteoporotic sites. Finally, within the complete cohort with both incident MG patients and control patients, the interaction term between MG and anxiolytics showed statistical significance for osteoporotic fracture (p-value < 0.05). The interaction term between MG and anticonvulsants showed statistical significance for both osteoporotic and any fracture (p-value < 0.05).

To further investigate whether a true association between MG and fracture risk had been averaged out by a fluctuating hazard function, we showed that MG duration was not related to fracture risk: one-year risk of any fracture yielded an AHR of 1.15 (95% CI, 0.88 - 1.52) in patients with MG versus population based controls, while 5-year risk (AHR of 0.97 [95% CI, 0.74 - 1.28]) and 10 year risk (AHR 0.94 [95% CI, 0.71 - 1.23]) were not different. The Kaplan Meier curve as presented in Figure 1 showed similar results with a non-significant log-rank test (p-value > 0.05) when MG-patients were compared with control patients. In addition the severity of MG was not related to increased risk of fracture (Table 5). Finally, using MG patients only from the GPRD (without HES data) did not alter the findings.

Figure 1: Kaplan-Meier survival curve for any fracture among MG patients versus patients without MG



Discussion

Our results show that an incident diagnosis of MG was not associated with a statistically increased risk of fracture or fracture at osteoporotic sites. Further the use of oral glucocorticoids did not alter overall fracture risk, not even when cumulative exposure had exceed >5 gram prednisolone equivalents. No association was present between fracture risk and duration or severity of MG. However, MG patients who used CNS medication are at significantly increased risk compared to MG patients without CNS medication.

The most striking finding of this study was that in patients with MG, the use of oral glucocortiods and in particular in high dosages was not associated with an increased risk of fracture. Alternatively, this subgroup of MG patients may have been underpowered, especially the stratification to cumulative high dose glucocorticoids, with only 4 reported osteoporotic fractures in the MG population. A different explanation for the lower HRs in MG patients on glucocorticoids, is that pyridostigmine may have anabolic effects, and therefore level out any

detrimental effects of glucocorticoids [12,13]. Cholinesterase inhibitors elevate acetylcholine levels in MG patients [3]. In vitro studies have shown that osteoblasts express acetylcholine receptors, while elevated acetylcholine levels induced osteoblast proliferation [29,30], which may ultimately result in anabolic effects of bone. In theory the positive effects of acetylcholine on bone turnover could level out the negative effects of oral glucocorticosteroids on bone, which would explain our findings. Moreover, a recent study performed by Wakata et al. [31] showed that Japanese MG-patients who received long-term (8.2 years) high dose prednisolone therapy (maximum 80-100 mg for 4-6 weeks), had a 50% reduced osteoporosis rate, as compared to the general population. A second explanation for lower HRs in MG patients on glucocorticoids is that generally, patients treated with glucocorticoids are exposed to an inflammatory disease. Subsequently, the disease may increase the risk for fracture itself, like rheumatoid arthritis [32]. This inflammatory compound is generally not present in MG-patients, except for some inflammatory cells that may be present in muscle [33]. An alternative explanation is that glucocorticoids may decrease fracture risk associated with the disease, thus cancelling out its adverse effects. A last explanation is that MG patients are often treated on alternate days with glucocorticoids [15]. In theory, this might reduce side effects.

Despite associations of MG with falling [5-7] and with glucocorticoid-induced osteoporosis [8,9], our findings showed no significantly increased risk of fracture. In contrast, our finding of an increased risk of fracture in users of various classes of CNS drugs is in keeping with previous findings. [18-21,34]. The increased fracture risk may be caused by side effects of CNS medication, such as sedation and dizziness, through an increased risk of falling [35-37]. Use of antidepressants has been associated with orthostatic hypotension [35] and the use of anticonvulsants can be considered a marker for seizures [38]. Both orthostatic hypotension and seizures are risk factors for falling and subsequently for fracture. In addition, the use of SSRIs has been shown to reduce bone mineral density in humans and negatively affected bone strength

in rodents [39,40] probably due to serotonin transporter inhibition in osteoblasts. This can ultimately lead to an increased risk of fracture. Finally, reduced bone mineral density has also been observed among users of anticonvulsants through an increase of vitamin D catabolism, resulting in an increased bone resorption [41]. MG patients using anticonvulsants had a significantly higher fracture risk as compared with control patients using anticonvulsants, for which the cause is unknown. MG patients and controls using anticonvulsants were equally distributed when stratified to a confirmed diagnosis of epilepsy in the GPRD database. The same applies for a diagnosis of neurological pain, which makes effect modification unlikely. This finding warrants further research.

Our study has several strengths. It is the first study that investigated the risk of fracture in a substantial number of MG patients, and for whom longitudinal drug exposure data were available. It had a reasonable sample size, comprising 1,066 incident MG patients who met the inclusion criteria. The study was population-based and compared MG patients directly with age-gender matched control patients from the same general practice in a sample that is representative for the total UK population. This makes selection bias unlikely. We had the ability to statistically adjust our analyses for well-known risk factors of fracture such as gender, age, BMI, smoking status and occurrence of prior fractures.

Our study had various limitations. We did not have access to neurology records, including lab-test results for presence of acetylcholine receptor antibodies, which are a diagnostic tool for MG [1]. Information on the diagnosis of MG patients was therefore limited. For this reason, we determined fracture risk not only among all patients with a MG recording in either GPRD or HES, but also among more probable MG patients with more than one recording of MG only. We could only use variables recorded in the GPRD to assign disease severity and classification of severity of disease could have been improved, if we would have had access to tertiary care data such as plasmapheresis. We did not have data on femoral bone mineral density

and no data on history of hip fracture among the parents of patients. Only small numbers of incident MG-patients were present in the subgroup analyses. For this reason, these data should be interpreted with care. Moreover, no data were present about Vitamin D plasma levels, degree of exercise or longitudinal data on body weight. This could have confounded the observed increased fracture risks in patients using CNS medication.

We showed an absence of fracture risk among MG patients using oral glucocorticoids compared to unexposed MG patients and a lower risk compared to control patients using oral glucocorticosteroids, but we were unable to determine any significant difference. This issue warrants further research. In theory, high dose prednisolone might exacerbate MG, which could have interfered with the analyses. However, glucocorticoid treatment is regularly started with a low dose, which is gradually increased [14,15]. This minimizes the risk of an exacerbation.

In conclusion, this study showed that MG was not associated with a statistically significant increased fracture risk, not even among MG patients who received high dose oral glucocorticoids. This suggests that there is no need to alter current management of MG. In contrast, fracture risk was increased among patients using CNS medication. Therefore, fracture risk assessment may be indicated among patients with MG who have recently used CNS medication. Further investigation should be performed to address the underlying mechanism for the observed absence of an increased fracture risk among MG patients exposed to high dose oral glucocorticoids.

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Chapter 4.2

Risk of fracture in patients with Muscular Dystrophies

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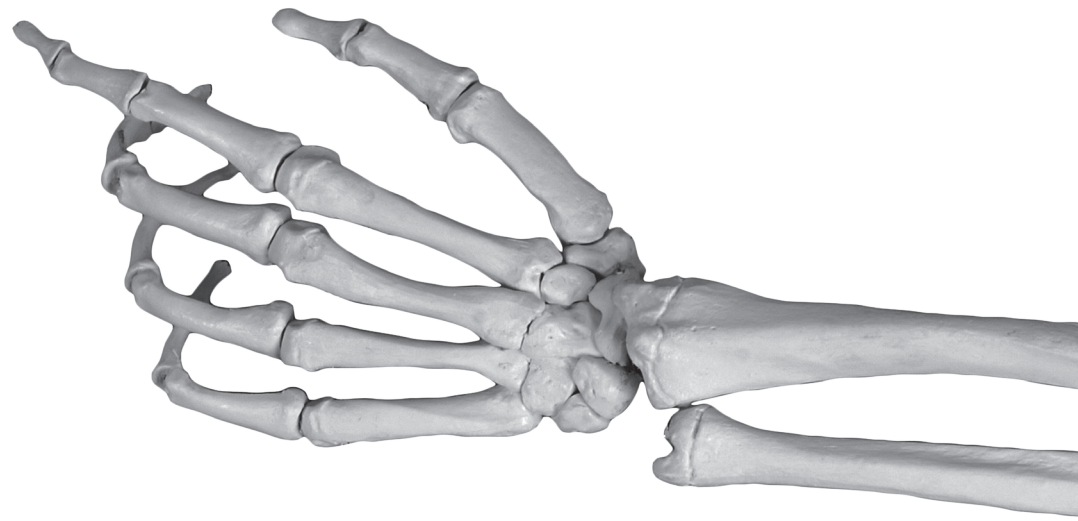


Abstract

Background: Muscular dystrophies (MDs) are inherited diseases causing muscles weakness and thereby increase the risk of falling and detrimental effects on bone. Both are recognized risk factors for fracture. Therefore, the aim of this study was to determine the hazard ratio of fracture in patients with MD.

Methods: We conducted a retrospective cohort study using the UK General Practice Research Database (1987-2012). Each patient with MD was matched by year of birth, sex and practice to up to six patients without a history of MD. Outcome measure was all fractures.

Results: As compared with control patients, risk of any fracture was statistically significantly increased in MD patients (adjusted hazard ratio [AHR] 1.40, 95% Confidence Interval [CI], 1.14 - 1.71). An increased risk of fracture was observed among MD patients with female gender, AHR 1.78 (95% CI; 1.33 - 2.40) and an increasing age as compared with control patients. Stratification to Duchenne MD showed no association with fracture, whereas risk of fracture was two-fold increased among patients with myotonic dystrophy AHR 2.34 (95% CI, 1.56 - 3.51). MD patients had an almost tripled risk of fracture when they used oral glucocorticoids in the previous six months, as compared to non-users with a MD.

Conclusion: Patients with MD are at a 1.4-fold increased risk of fracture as compared with population-based control patients. Especially in older age groups and female gender the fracture risk of MD versus non-MD patients is increased, whereas exposure to glucocorticoids further increased fracture risk among MD patients.

Background

Muscular dystrophies (MDs) refer to a group of inherited diseases in which muscles are affected and muscle strength is weakened. Duchenne muscular dystrophy (Duchenne MD) is the most well known form, whereas myotonic dystrophy is most common. Age of onset varies between the different MDs, whereby congential MD is diagnosed early after birth, Duchenne and Becker MD during childhood and other types of MD, like myotonic dystrophy, regularly during adulthood. The diseases are caused by defects in several genes encoding for muscle function [1,2]. Due to muscle weakness, MDs have been associated with an increased prevalence of osteoporosis, vertebral deformities and fracture [3-7]. Furthermore, MDs have been associated with falling due to instability, which may further increase the risk for fracture [8,9].

In addition to surgery, rehabilitation and exercise, patients are often treated with oral glucocorticoids [10], while the use of systemic glucocorticoids is a known risk factor for fractures [11,12]. MDs have been associated with depression and other psychiatric disorders [13,14], while psychotropic medications like antidepressants, anxiolytics/hypnotics may further elevate the risk of fracture [15-17].

The risk of fracture has previously been determined in patients with Duchenne MD and Becker MD [3-7], but this is the first study, which compares Duchenne MD and Becker MD patients with population-based control patients and has the ability to statitiscally adjust for drug use and comorbities associated with fracture. In patients with other forms of MD, the risk of fracture has not been determined yet. Therefore, the aim of this study was to determine the incidence rates for fracture and hazard ratio [HR] of fracture in patients with different types of MD as compared with population-based control patients.

Methods

Information for this study was obtained from the General Practice Research Database (GPRD),

currently known as the “Clinical Practice Research Datalink”. It comprises the computerized medical records of approximately 8% of all patients under the care of general practitioners in the United Kingdom. These records include the patient’s demographic information, clinical events, prescription details, preventive care provided, specialist referrals, hospital admissions, and major outcomes [18]. Previous studies conducted in GPRD have shown a high level of data validity with respect to reporting of fractures (>90% of fractures were confirmed) [19,20].

Study population.

The study population consisted of all patients with at least one recorded diagnosis of MD during the period of GPRD data collection (for this study, GPRD data collection started in January 1987 and ended in August 2012). Incident cases were defined as individuals whose first recorded general practitioner visit for a MD (i.e. the index date) occurred during valid data collection. We distinguished between Duchenne MD, Becker, Emery-Dreifuss, distal, facioscapulohumeral, oculopharyngeal, limb-girdle and congenital MD and myotonic dystrophy. Female carriers of the X-linked recessive disorders Duchenne MD and Becker MD were excluded, because these patients have no or only mild symptoms [21].

Each MD patient was matched by year of birth, sex and practice up to six patients without a history of MD. Control patients had to be enrolled in the GPRD before or at the time of the index date of their matched MD patient and were assigned the same index date. The study patients were followed up from the index date to either the end of GPRD data collection, the date of transfer of the patient out of the practice area, or the patient’s death, whichever came first. Patients were followed up for the occurrence of fracture, which was defined as the patient's first GPRD record for the occurrence of fracture after their index date. The fracture types were classified according to the International Classification of Diseases, Tenth Revision (ICD-10) categories [22]. The stratification to osteoporotic fractures includes fracture of the radius/ulna,

humerus, rib, femur/hip, pelvis, or vertebrae.

Exposure

The total period of follow-up was divided into periods of 30 days, starting at the index date. At the start of each period the presence of risk factors was assessed, by reviewing the computerized medical records. General risk factors included age, sex, body mass index (BMI), smoking and alcohol status, a history of fracture or falls before MD diagnosis, a history of chronic diseases before the start of each 30-day interval (asthma/chronic obstructive pulmonary disease [COPD], thyroid disorders, renal disease [acute renal failure and chronic renal disease], cancer [excluding skin cancer], congestive heart failure, ischaemic heart disease, hypertension, cerebrovascular disease, diabetes mellitus), and a prescription in the previous six months before the start of each interval for psychotropic medications (antidepressants, antipsychotics, anxiolytics/hypnotics, anticonvulsants), opioids, antiarrhythmics, oral glucocorticoids, and other immunosuppressants (azathioprine, ciclosporin, tacrolimus, mycophenolate mofetil, methotrexate).

Statistical analysis

Cox proportional hazards models with time varying covariates (the potential risk factors for fracture) were used in order to estimate HRs of fracture risk. In order to yield an estimate of the HR, fracture rates in MD patients were compared with the rates in control patients. The main analyses were stratified for age, sex, the use of oral glucocorticoids and psychotropic medications. Adjustments were made for age and sex or if any potential confounder showed a >2.0% change in the beta-coefficient of the age-gender adjusted HR.

Sensitivity analyses

To further exclude possible prevalent cases in the cohort, a separate analysis was performed in which incident cases were defined as individuals whose first recorded general practitioner visit

for a MD (i.e. the index date) occurred at least one year after start of valid data collection.

Results

We identified 1038 incident MD patients and 6218 controls. 41% of the patients were female and their mean age was 46 years. The mean age of male patients was 33 years. The average duration of follow-up was 8.8 years for both MD and control patients. Table 1 provides further information on type of MD, BMI, smoking status, alcohol status and history of comorbidities and drug use among MD patients and controls. Some patients received the status unknown for BMI, smoking or alcohol. This implies that no information about these variables was available in GPRD for these patients.

We observed a total number of 106 incident Duchenne MD patients and 636 controls with a mean age of nine years and median age of two years at baseline. The Duchenne MD patients are a subgroup of the total MD cohort. In 67% of these patients the diagnosis was recorded before the age of five. The mean duration of follow-up was 9.5 years for both Duchenne MD and control patients. Table 2 provides more information on baseline characteristics among Duchenne MD and control patients, including history of comorbidities and drug use.

Table 3 shows that the risk of fracture was increased among MD patients after full adjustment for any fracture (adjusted hazard ratio [AHR] 1.40, 95% confidence interval [CI], 1.14 - 1.71). Osteoporotic fracture risk was not statistically significantly increased, AHR 1.33 (95% CI, 0.91 - 1.82), whereas highest risk was observed for fracture of the foot or ankle, AHR 2.09 (95% CI, 1.35 - 3.23). The age-gender adjusted hazard ratio for hip fracture is shown for information only, although the number of hip fractures was actually too low to adjust for both age and gender. The number of hip and vertebral fractures was too low to calculate the AHR for MD patients. Fracture risk was increased among female MD patients, but not among male MD

Table 1: Baseline characteristics of patients with incident MD compared with control patients.

Characteristics	MD patients (n=1038)	(%)	Control patients (n=6218)	(%)	Female MD patients (n=430)	(%)	Male MD patients (n=608)	(%)
Mean age (years)	38.6		38.6		45.9		33.5	
Median age (years)	39		39		48		32	
Type of MD								
Duchenne	106	10.2	636	10.2	0	0.0	106	17.4
Becker	23	2.2	138	2.2	0	0.0	23	3.8
Emery-Dreifuss	2	0.2	12	0.2	0	0.0	2	0.3
Distal	2	0.2	12	0.2	2	0.5	0	0.0
Facioscapulohumeral	33	3.2	198	3.2	21	4.9	12	2.0
Ocupharyngeal	23	2.2	137	2.2	18	4.2	5	0.8
Limb-Girdle	12	1.2	71	1.2	4	0.9	8	1.3
Congenital	4	0.4	24	0.4	1	0.2	3	0.5
Myotonic dystrophy	217	20.9	1302	20.9	114	26.5	103	16.9
Non-specified	616	59.3	3688	59.3	270	62.8	346	56.9
BMI (%)								
< 20	74	7.1	285	4.6	40	9.3	34	5.6
20-25	222	21.4	1201	19.3	124	28.8	98	16.1
25-30	181	17.4	1114	17.9	87	20.2	94	15.5
≥ 30	100	9.6	664	10.7	55	12.8	45	7.4
Unknown	461	44.4	2954	47.5	124	28.8	337	55.4
Smoking status (%)								
Never	350	33.7	2031	32.7	185	43.0	165	27.1
Current	182	17.5	1156	18.6	90	20.9	92	15.1
Ex	110	10.6	565	9.1	52	12.1	58	9.5
Unknown	396	38.2	2466	39.7	103	24.0	293	48.2
Alcohol status (%)								
Never	117	11.3	647	10.4	69	16.0	48	7.9
Current	446	43.0	2547	41.0	226	52.6	220	36.2
Unknown	475	45.8	3024	48.6	135	31.4	340	55.9

Table 1 continued: Baseline characteristics of patients with incident MD compared with control patients

Characteristics	MD patients (n=1038)	(%)	Control patients (n=6218)	(%)	Female MD patients (n=430)	(%)	Male MD patients (n=608)	(%)
Fracture history (%)								
Any fracture	166	16.0	835	13.4	80	18.6	86	14.1
Fracture at osteoporotic sites	65	6.3	348	5.6	33	7.7	32	5.3
Hip fracture	7	0.7	28	0.5	4	0.9	3	0.5
Vertebral fracture	6	0.6	27	0.4	2	0.5	4	0.7
Radius/ulna fracture	29	2.8	174	2.8	15	3.5	14	2.3
Comorbidity ever before index date								
Asthma	126	12.1	733	11.8	73	17.0	53	8.7
COPD	22	2.1	107	1.7	15	3.5	7	1.2
Congestive heart failure	22	2.1	47	0.8	10	2.3	12	2.0
Diabetes Mellitus	62	6.0	223	3.6	26	6.0	36	5.9
Renal disease	8	0.8	24	0.4	9	2.1	2	0.3
Cerebrovascular disease	33	3.2	141	2.3	11	2.6	22	3.6
Inflammatory bowel disease	6	0.6	24	0.4	6	1.4	0	0.0
Cancer (excluding skin cancer)	45	4.3	193	3.1	30	7.0	15	2.5
Hypothyroid disorder	43	4.1	132	2.1	36	8.4	7	1.2
Hypertension	129	12.4	735	11.8	69	16.0	60	9.9
Ischaemic heart disease	66	6.4	261	4.2	28	6.5	38	6.3
Drug use in 6 months before index date								
Bisphosphonates	31	3.0	53	0.9	19	4.4	12	2.0
Opioids	33	3.2	74	1.2	20	4.7	13	2.1
NSAIDs	137	13.2	535	8.6	79	18.4	58	9.5
Oral glucocorticoids	76	7.3	109	1.8	42	9.8	34	5.6
Inhaled glucocorticoids	55	5.3	305	4.9	31	7.2	24	3.9
Statins	94	9.1	422	6.8	44	10.2	50	8.2
Antiarrhytmics	12	1.2	36	0.6	7	1.6	5	0.8
Antidepressants	90	8.7	389	6.3	50	11.6	40	6.6
Antipsychotics	11	1.1	54	0.9	7	1.6	4	0.7
Anxiolytics/hypnotics	75	7.2	233	3.7	48	11.2	27	4.4
Anticonvulsants	24	2.3	92	1.5	12	2.8	12	2.0
Falls in 6 months before index date	21	2.0	28	0.5	9	2.1	12	2.0

Table 2: Baseline characteristics of patients with incident Duchenne MD compared with control patients.

Characteristics	Duchenne MD patients (n=106)	(%)	Control patients (n=636)	(%)
Mean age (years)	8.9		8.9	
Median age (years)	2		2	
Age				
0 - 5 years	71	67.0	426	67.0
5 -10 years	14	13.2	84	13.2
10 - 20 years	6	5.7	36	5.7
≥ 20 years	15	14.2	90	14.2
BMI				
< 20	2	1.9	9	1.4
20-25	2	1.9	20	3.1
25-30	4	3.8	16	2.5
≥ 30	1	0.9	10	1.6
Unknown	97	91.5	581	91.4
Smoking status				
Never	7	6.6	33	5.2
Current	1	0.9	20	3.1
Ex	4	3.8	6	0.9
Unknown	94	88.7	577	90.7
Alcohol status				
Never	2	1.9	8	1.3
Current	5	4.7	41	6.4
Unknown	99	93.4	587	92.3
Fracture history				
Any fracture	5	4.7	21	3.3
Fracture at osteoporotic sites	1	0.9	9	1.4
Hip fracture	1	0.9	0	0.0
Vertebral fracture	0	0.0	0	0.0
Radius/ulna fracture	0	0.0	6	0.9

Table 2 continued: Baseline characteristics of patients with incident Duchenne MD compared with control patients.

Characteristics	Duchenne MD patients (n=106)	(%)	Control patients (n=636)	(%)
Comorbidity ever before index date				
Asthma	5	4.7	37	5.8
COPD	0	0.0	4	0.6
Congestive heart failure	1	0.9	3	0.5
Diabetes Mellitus	0	0.0	1	0.2
Renal disease	0	0.0	0	0.0
Cerebrovascular disease	0	0.0	1	0.2
Inflammatory bowel disease	0	0.0	0	0.0
Cancer (excluding skin cancer)	1	0.9	3	0.5
Hypothyroid disorder	0	0.0	2	0.3
Hypertension	2	1.9	10	1.6
Ischaemic heart disease	4	3.8	5	0.8
Drug use in 6 months before index date (%)				
Bisphosphonates	0	0.0	0	0.0
Opioids	2	1.9	0	0.0
NSAIDs	2	1.9	21	3.3
Oral glucocorticoids	3	2.8	4	0.6
Inhaled glucocorticoids	3	2.8	4	2.2
Statins	2	1.9	2	0.3
Antiarrhytmics	0	0.0	1	0.2
Antidepressants	1	0.9	3	0.5
Antipsychotics	0	0.0	1	0.2
Anxiolytics/hypnotics	2	1.9	4	0.6
Anticonvulsants	0	0.0	0	0.0
Falls in 6 months before index date	3	2.8	0	0.0

Table 3: Risk of fracture in incident MD patients by type of fracture, sex and age compared to patients without MD

	Fractures (n)	Rate / 1000 person-years	Age-sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)[a]
No MD	475	8.7	1.00	1.00
MD	123	13.5	1.62 (1.33 - 1.97)	1.40 (1.14 - 1.71)
Fracture at osteoporotic sites	51	5.6	1.68 (1.23 - 2.29)	1.33 (0.97 - 1.82)[b]
Hip fracture	2	0.2	0.40 (0.10 - 1.68)	Not determined[c]
Vertebral fracture	8	0.9	7.27 (2.64 - 20.05)[c]	Not determined[c]
Radius/ulna fracture	17	1.9	1.27 (0.75 - 2.13)	1.01 (0.59 - 1.71)[d]
Other osteoporotic fracture	24	2.6	2.14 (1.34 - 3.40)	1.80 (1.12 - 2.89)[e]
Fracture at non-osteoporotic sites	72	7.9	1.57 (1.22 - 2.04)	1.41 (1.08 - 1.83)[f]
Ankle or foot	28	3.1	2.22 (1.44 - 3.42)	2.09 (1.35 - 3.23)[g]
Other fracture	44	4.8	1.33 (0.96 - 1.84)	1.18 (0.85 - 1.64)
By sex[h]				
Male	62	11.4	1.29 (0.98 - 1.70)	1.15 (0.87 - 1.52)
Female	61	16.5	2.20 (1.64 - 2.93)	1.78 (1.33 - 2.40)
By age at MD diagnosis[i]				
0 - 19	31	12.2	1.03 (0.71 - 1.51)	0.91 (0.61 - 1.34)
20 - 39	26	11.0	1.91 (1.23 - 2.97)	1.77 (1.14 - 2.77)
40 - 59	30	13.1	2.10 (1.39 - 3.18)	1.90 (1.25 - 2.90)
≥ 60	36	18.5	2.03 (1.40 - 2.94)	1.54 (1.04 - 2.26)
By type of MD[j]				
Duchenne	13	13.0	1.30 (0.72 - 2.37)[k]	1.00 (0.52 - 1.91)
Becker	1	8.2	0.59 (0.07 - 4.57)[ck]	Not determined[c]
Facioscapulohumeral	2	12.0	1.08 (0.24 - 4.82)[c]	Not determined[c]
Limb-Girdle	1	9.8	1.24 (0.14 - 10.64)[c]	Not determined[c]
Myotonic dystrophy	33	16.0	2.49 (1.67 - 3.72)	2.34 (1.56 - 3.51)
Non-specified	73	13.3	1.58 (1.22 - 2.05)	1.32 (1.02 -1.72)

a) Adjusted for age, sex, use of oral glucocorticoids, antidepressants, anticonvulsants and opioids in the previous six months or history of fracture before the MD diagnosis
b) Also adjusted for history of cerebrovascular disease or hypothyroidism
c) The age-gender adjusted hazard ratio is shown for information only, although the number of fractures was too low to adjust for two confounders. The number of fractures was too low to calculate the AHR.
d) Also adjusted for use of NSAIDs in the previous six months and history of hypothyroidism
e) Not adjusted for use of opioids or anticonvulsants in the previous six months
f) Also adjusted for use of NSAIDs in the previous six months
g) Adjusted for age, sex, use of oral glucocorticoids and NSAIDs in the previous six months
h) Male MD patients are compared with male controls and female MD patients with female controls
i) MD patients in each age group are only compared with control patients in the same age group
j) Patients with Emery-Dreifuss, distal, ocupharyngeal or congenital MD did not sustain any fracture during follow-up
k) Only adjusted for age

Table 4: Risk of fracture among MD patients stratified to drug use in previous 6 months

		Risk of fracture[a]	
	Fractures (n)	Age-sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)[b]
Drug use in previous 6 months			
No oral glucocortioid use	103	1.00	1.00
Oral glucocorticoid use	20	3.73 (2.30 - 6.05)	2.89 (1.74 - 4.80)
By average daily dose equivalents (eq.)			
< 5 mg prednisolone eq.	7	4.29 (1.98 - 9.30)	3.55 (1.62 - 7.77)
≥ 5 mg prednisolone eq.	13	3.50 (1.95 - 6.26)	2.63 (1.44 - 4.82)
No antidepressant use	107	1.00	1.00
Antidepressant use	16	1.67 (0.98 - 2.84)	1.12 (0.63 - 1.98)
No antipsychotic use	121	1.00	1.00
Antipsychotic use	2	1.72 (0.43 - 7.00)	0.92 (0.22 - 3.94)
No anxiolytic/hypnotic use	112	1.00	1.00
Anxiolytic/hypnotic use	11	1.49 (0.79 - 2.82)	0.91 (0.46 - 1.81)

a) The reference group are MD patients unexposed to the investigated drug

b) Adjusted for the same confounders as described below table 3 for any fracture, but the confounder is not added to the model if it is identical to the drug being investigated.

patients. Furthermore, only patients with an age exceeding 20 years were at increased risk of fracture. After stratification to gender and age, female patients in the age category between 20 and 40 years of age were at highest risk of fracture, AHR 2.46 (95% CI, 1.23 - 4.93) (data not shown).

Among Duchenne MD patients, we observed 13 patients who sustained a fracture during follow-up. As compared with control patients no association with fracture was observed, AHR 1.00 (95% CI, 0.52 - 1.91). No fractures were observed among the small number of patients with Emery-Dreifuss, distal, ocupharyngeal or congenital MD, whereas only one or two fractures were observed for Becker, limb-girdle and facioscapulohumeral MD. No associations with fractures were observed for these types of MD. Conversely, myotonic dystrophy patients had a more than doubled increased risk of fracture, AHR 2.34 (95% CI, 1.56 - 3.51). The age-gender adjusted hazard ratio of fracture for Becker, limb-girdle and facioscapulohumeral MD is shown for information only, although the number of fractures was too low to adjust for both age and gender. Consequently, the number of fractures was also too low to calculate the AHR.

Figure 1 displays the corresponding Kaplan Meier survival curve for risk of fracture among MD patients and controls. Fracture risk was highest in the first year after diagnosis, AHR 1.89 (95% CI, 1.23 - 2.92) as compared with control patients. Subsequently, the risk was 1.3-fold increased between one and five years after diagnosis, AHR 1.31 (95% CI, 0.96 - 1.79) and then remained stable (>five years after diagnosis, AHR 1.33 [95% CI, 1.01 - 1.76]). Figure 2 displays the Kaplan Meier curve for risk of fracture among Duchenne MD patients and controls. The shape is similar to the shape of the Kaplan Meier curve for MD patients.

Table 4 shows that MD patients had an almost tripled risk of any fracture when they used oral glucocorticoids in the previous six months during follow-up, as compared to non-users with a MD, AHR 2.89 (95% CI, 1.74 - 4.80). The risk of osteoporotic fracture was even further increased, AHR 4.54 (95% CI, 2.26 - 9.11), whereas the risk for non-osteoporotic fracture was non-significantly increased, AHR 1.93 (95% CI, 0.89 - 4.15) for MD patients exposed to oral

Figure 1: Proportion of patients without fracture among MD patients and controls.

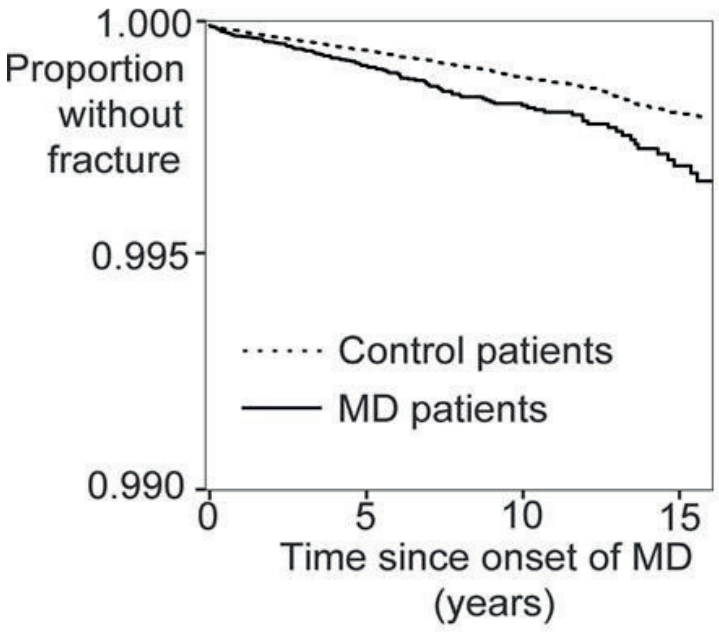
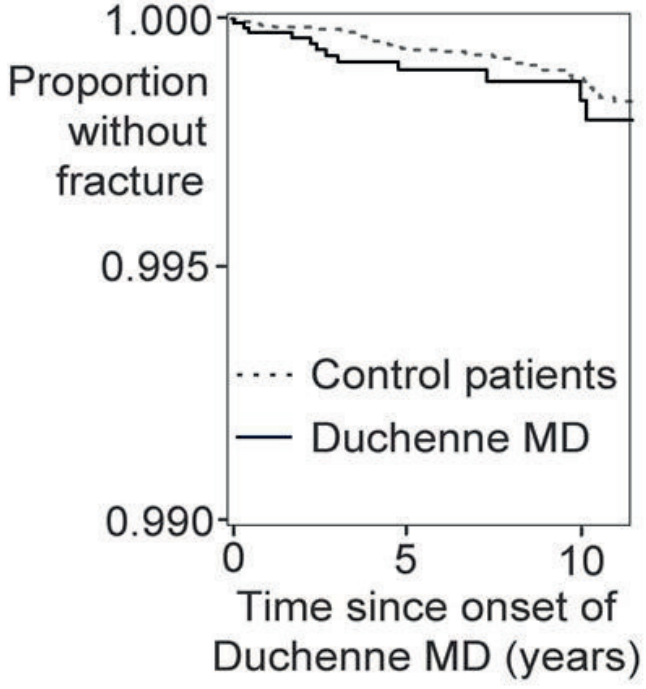


Figure 2: Proportion of patients without fracture among Duchenne MD patients and controls.



glucocorticoids in the previous six months. The interaction term between MD and use of oral glucocorticoids in the previous six months showed no statistical significance for any fracture in the cohort (p-value 0.24). The average daily dose of oral glucocorticoids did not modify the risk. The use of psychotropic medication was not associated with fracture risk. Finally, within the cohort with Duchenne MD, we identified seven patients who used oral glucocorticoids in the previous six months before their fracture. Their fracture risk was 11-fold increased in an age-adjusted analysis, HR 11.46 (95% CI, 3.46 - 37.90), as compared with Duchenne MD patients who did not use oral glucocorticoids. As compared with the control population, their fracture risk was 7.5-fold increased after full adjustment, AHR 7.56 (95% CI, 3.32 - 17.25).

Lastly, 946 incident MD patients were included in the sensitivity analysis with their first recorded general practitioner visit for MD at least one year after start of valid data collection. They had a mean age at baseline of 38.5 years and a mean follow-up of 8.3 years. Their risk of any fracture was AHR 1.40 (95% CI, 1.13 - 1.73) as compared with control patients and was equivalent to risk of any fracture in the main analysis.

Discussion

This study showed a 1.4-fold increased risk for any fracture and a twofold increased risk for fracture of foot or ankle in patients with MD as compared with population-based controls. The risk was not increased among patients with an age below 20 years and among male patients. Furthermore, patients with Duchenne MD were not at increased risk, whereas risk was doubled among patients with myotonic dystrophy. No association between fracture risk and other types of MD was observed, although patient numbers in these sub-groups were small. Fracture risk was threefold increased and osteoporotic fracure risk was 4.5-fold increased when MD patients were exposed to oral glucocorticoids in the previous six months as compared to non-exposed MD patients.

According to our knowledge, this is the first study, which determined fracture risk among

patients with various types of MD. Therefore, our results are difficult to compare with other studies. However, several studies described the presence of fractures in patients with Duchenne MD before [3-7]. In four neuromuscular clinics in the United Kingdom, cumulative incidence of fracture was 21% among 378 Duchenne MD patients, although no follow-up time was mentioned [4]. Among 25 Duchenne MD patients who attended a neuromuscular clinic in the United Kingdom, cumulative incidence of fracture was 28% during seven years of follow-up [6]. These numbers are higher as compared with our population, in which 12.3% of patients sustained a fracture during a mean follow-up of 9.5 years. It must be noticed that the mentioned studies only included patients who attended neuromuscular clinics. Therefore, they may have included more severe patients in comparison with our cohort. In contrast to our study, Vestergaard et al. [7] observed a significant twofold increased risk of fracture among Duchenne MD patients as compared with population-based control patients, regardless of glucocorticoid use. Patients were sent a questionnaire to determine their fracture rate. A limitation of this approach is possible underreporting of fractures among control patients, which could partly explain the observed twofold increased risk of fracture. Underreporting of glucocorticoid use among the Duchenne MD population may further explain the difference. Conversely, in a neuromuscular clinic in Ohio the incidence of fractures was slightly higher among 68 Duchenne MD patients unexposed to oral glucocorticoids (71%) as compared with 75 Duchenne MD patients exposed to oral glucocorticoids (81%). However, multiple fractures were more common among treated patients (28%) as compared with non-treated patients (12%) [3]. Lastly, Bothwell et al. showed that 75% of Duchenne MD patients using glucocorticoids developed a fracture within 100 months after initiation of treatment [5]. Consequently, our finding that Duchenne MD patients treated with oral glucocorticoids are at an increased risk of fracture adds up to previous studies, although the magnitude (11-fold increased risk) as compared with non-treated Duchenne MD patients cannot be fully explained.

There are various mechanisms, which may explain the increased risk of fracture among MD

patients. Genetic defects in muscle function may play an important role in its aetiology. Duchenne MD patients have a defect in the Xp21 gene, which results in absence of the protein dystrophin [23]. Emery-Dreifuss MD patients lack the protein emerin caused by a mutation in the Xq28 gene [24]. Myotonic dystrophy type 1 disease is caused by a defect in chromosome 19q13.3,6.8 whereas type 2 disease is due to a defect in chromosome 3q21.3.9,10. Both mutations lead to formation of transcript aggregates in the nucleus, so-called foci, which interfere with proteins that play a part in RNA metabolism [2]. The absence or interference of important proteins involved in muscle function results in mild to severe muscle weakness depending on type of MD [1,2]. Muscle weakness is an important risk factor for falls [8] and subsequent fractures. Moreover, muscle weakness may result in immobility [25]. Immobilization can lead to bone mineral loss and subsequent osteoporosis, which further increases the risk of fracture [26,27]. Specific weakness of foot and ankle muscles has been described in MD patients and early osteoporosis has been reported in the extremities of Duchenne MD patients [27-29]. This may explain the twofold observed increased risk of fracture at this specific site. Moreover, the genetic defects discovered in MD patients may interact with recently discovered genetic markers of osteoporosis [30]. The potential relevance of specific associations among the various MDs and fracture may point to key functional pathways that link bone and muscle metabolism, rather than just the generalised excess fracture risk that would be expected in MD.

MD patients had a 1.9-fold increased risk of fracture in the first year after diagnosis as compared to control patients. Therefore, it is suggested that falls are responsible for the increased fracture risk observed shortly after onset of MD instead of decreased bone mineral density. After one year, fracture risk decreased towards a 1.3-fold increased risk of fracture, probably due to improved symptom control, but remains increased. Both falls and decreased bone mineral density may be responsible for this increased risk of fracture more than one year after MD diagnosis.

The use of psychotropic drugs in MD patients showed no association with fracture, which

may be a consequence of the relative young population in our cohort, whereas an increased risk of fracture is particularly observed among elderly patients using psychotropic medication except for the use of anxiolytics/hypnotics [15-17].

Our study has several strengths. It is the first study that investigated the risk of fracture among MD patients as compared to population-based control patients, in which the outcome was statistically adjusted for well-known risk factors of fracture, like sex, age and the use of oral glucocorticoids. The study compared MD patients directly with age and sex matched control patients from the same general practice. Therefore, selection bias is unlikely.

A limitation of the study was the small number of patients classified for each different type of MD, which was mainly caused by the large number of non-specified MD diagnoses. Consequently, we had the ability to determine fracture risk for Duchenne MD and myotonic dystrophy patients only. Secondly, the subgroup analyses may have been underpowered with only small numbers of incident MD-patients and should be interpreted with care. Some prevalent MD patients may have been included in the cohort, because no precise date of diagnosis for MD was described in CPRD. Moreover, MDs are a group of inherited disorders. Therefore, patients are regularly diagnosed later than the date on which their first symptoms appear. Subsequently, it cannot be ruled out that some prevalent patients may have been present in our cohort. However, our results showed that exclusion of those MD patients with a MD diagnosis within their first year of follow-up since start of valid data collection did not significantly alter the risk of any fracture as compared with control patients. This suggests that our results have not been seriously biased by the presence of prevalent MD patients. Additionally, some MD patients may have been at an increased risk of fracture before MD diagnosis, whereas fractures may increase mortality. Subsequently, the incident MD patients included in this study may represent survivors which are less prone to fractures. This may partly explain the absence of an increased risk of hip fracture. Lastly, no information was available about severity of disease and degree of physical impairment.

In conclusion, our findings demonstrate that patients with MD are at a 1.4-fold increased risk of fracture as compared with population-based control patients. Therefore, it may be beneficial to conduct fracture risk assessment among MD patients. Increasing age, female gender and exposure to glucocorticoids are important risk factors to take into account. Fall prevention programs and bone mineral density measurements may be considered in order to prevent fractures among MD patients.

Acknowledgement

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Chapter 4.3

Risk of Fracture in Patients with Charcot-Marie-Tooth disease

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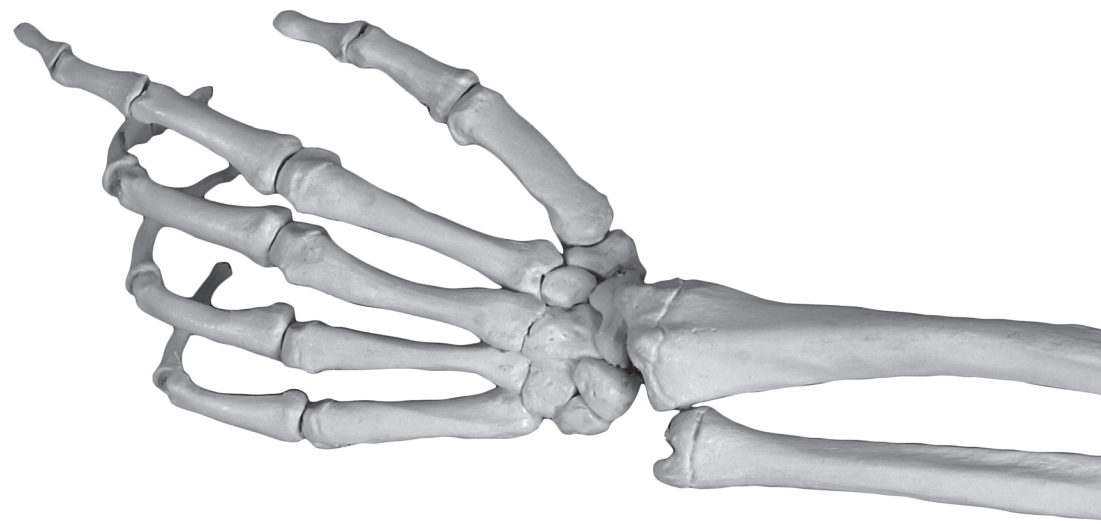

Abstract

Introduction: Aim of this study is to evaluate fracture risk in patients with Charcot-Marie-Tooth (CMT) disease.

Methods: We conducted a retrospective cohort study using the UK Clinical Practice Research Datalink (1987-2012). Each patient with CMT was matched by year of birth, sex and practice up to six patients without a history of CMT. Outcome measure was all fractures.

Results: Risk of non-osteoporotic fracture was statistically significantly increased, (adjusted hazard ratio [AHR] 1.47, 95% Confidence Interval [CI], 1.01 – 2.14), whereas risk of any and osteoporotic fracture did not reach statistical significance as compared with control patients, AHR 1.31 (95% CI, 0.98 - 1.74) and AHR 1.10 (95% CI, 0.69 - 1.74) respectively.

Discussion: CMT patients are at a 1.5-fold increased risk for non-osteoporotic fracture. Studies with larger numbers of CMT patients and with additional data on CMT subtype, bone mineral density and functional status, should be performed to confirm a true association between CMT and an increased risk of any and osteoporotic fracture.

Background

Charcot-Marie-Tooth (CMT) disease or "hereditary motor and sensory neuropathy" is a group of conditions with a prevalence of 8 to 41 per 100.000 individuals [1]. It affects up to 200.000 patients in the European Union [2]. The disease is characterized by abnormal development of the peripheral nervous system, in which both motor and sensory nerves are affected [2-3]. This is provoked by different mutations in genes encoding for proteins involved in neurotransmission [4].

CMT patients may be at an increased risk of fracture via an increased risk of falling and an increased risk of osteoporosis. Firstly, osteoporosis at ankles and feet has been reported among CMT patients and deformations of hand and feet are common [5]. Secondly, the risk of falls may be increased by symptoms like hand cramps, the absence of deep-tendon reflexes, muscle cramps, difficulty in walking and weakness [2,6].

Use of concomitant psychotropic medication like antidepressants, anxiolytics/hypnotics or antipsychotics may further elevate the risk of fracture [9-11]. Conflicting findings have been described in literature regarding psychological distress among CMT patients. Depression is common in patients with CMT. Moreover, emotional stress showed to be equivalent between CMT and stroke patients [7]. Conversely, psychological distress was equally distributed between CMT patients and unaffected patients [8].

Fracture risk has never been determined in patients with CMT. Only a few cases of CMT patients with fractures have been reported in literature [12,13]. Therefore, the aim of this study is to evaluate fracture risk in patients with CMT and stratify by the use of psychotropic medication.

Methods

Medical information was obtained from the Clinical Practice Research Datalink (CPRD),

formerly known as the General Practice Research Database. Data comprised the computerized medical records of all patients under the care of general practitioners in the United Kingdom. Medical information on patients who are registered for medical care with a practice is supplied to the CPRD [14]. Previous studies of CPRD data have shown a high level of validity with respect to the reported fractures (>90% of fractures were confirmed) [15,16].

Study population.

The study population consisted of all patients with at least one recorded diagnosis of CMT during the period of CPRD data collection. For this study, data collection started in January 1987 and ended in August 2012. Incident CMT patients were individuals whose first recorded general practitioner visit for CMT occurred during valid data collection. Each CMT patient was matched by year of birth, sex and practice, up to six patients without a history of CMT in CPRD. The date of the first CMT record after start of CPRD data collection was defined as the index date. Control patients had to be enrolled in CPRD at the index date of their matched CMT patient. From the index date, patients were followed up to either the end of CPRD data collection, the date of transfer out of the practice area, or the patient's death, whichever came first. Patients were followed up for the occurrence of fracture. Fracture types were classified according to the International Classification of Diseases, Tenth Revision (ICD-10) categories. A clinical osteoporotic fracture was defined as a fracture of the radius/ulna, humerus, rib, femur/hip, pelvis, or vertebrae [17].

Exposure

The period of follow-up was divided into periods of 30 days, starting at the index date. At the start of each period the presence of risk factors was assessed, by reviewing the computerized medical records. General risk factors included age, sex, body mass index (BMI), smoking and

alcohol status, a history of fracture or falls before CMT diagnosis, a history of chronic diseases (asthma/chronic obstructive pulmonary disease [COPD], thyroid disorders, chronic renal disease, cancer [excluding skin cancer], hypertension, congestive heart failure, ischaemic heart disease, cerebrovascular disease, diabetes mellitus), and a prescription in the previous 6 months before each period for psychotropic medications (antidepressants, antipsychotics, anxiolytics/hypnotics, anticonvulsants), opioids, antiarrhythmics, oral glucocorticoids, and other immunosuppressants (azathioprine, ciclosporin, tacrolimus, mycophenolate mofetil or methotrexate).

Statistical analysis

Time-dependent Cox proportional hazards regression was used in order to estimate hazard ratios (HRs) of fracture risk. Fracture risk in CMT patients was compared with control patients to yield an estimate of the relative risk, which was expressed as hazard ratios. The main analyses were stratified for age and gender. Within CMT patients analyses were stratified to use of antidepressants, anxiolytics/hypnotics and antipsychotics. The HRs were adjusted for age and sex or if any potential confounder showed a >2.0% change in the beta-coefficient of the age-gender adjusted hazard ratio (AHR).

Results

A total of 646 incident CMT patients and 3854 age, sex and practice matched controls were identified. They had a mean age of 47 years and 49% were female. Their average mean follow-up was 6 years. Table 1 shows the baseline characteristics, including information on BMI, smoking and alcohol status, history of comorbidities and drug use.

Table 2 shows that 58 CMT patients sustained a fracture during follow-up. As compared to control patients, the risks of any and osteoporotic fracture were not increased,

Table 1: Baseline characteristics of patients with incident CMT compared with patients without a history of CMT

Characteristics	CMT patients (n=646)	Controls (n=3854)
Female (%)	48.6	48.6
Mean age (years)	46.7	46.5
BMI (%)		
< 20	7.9	5.1
20-25	24.0	25.9
25-30	24.0	24.8
≥ 30	16.4	13.7
Unknown	27.7	30.5
Smoking status (%)		
Never	40.1	41.7
Current	22.1	20.6
Ex	18.3	14.5
Unknown	19.5	23.3
Alcohol status (%)		
Never	17.5	12.8
Current	52.8	54.0
Unknown	29.7	33.1
Fracture history (%)		
Any fracture	22.1	17.9
Fracture at osteoporotic sites	9.9	7.3
Hip fracture	0.9	0.6
Vertebral fracture	1.2	0.4
Radius/ulna fracture	5.4	4.3
Comorbidity ever before index date (%)		
Asthma	16.9	14.1
COPD	2.9	2.3
Congestive heart failure	2.3	1.3
Diabetes Mellitus	10.8	5.2
Rheumatoid arthritis	1.2	1.1
Renal disease	0.5	0.8
Cerebrovascular disease	5.1	4.0
Inflammatory bowel disease	1.1	0.9
Cancer (excluding skin cancer)	5.1	5.2
Ischaemic heart disease	8.4	7.1
Drug use in 6 months before index date (%)		
Bisphosphonates	3.7	1.8
Opioids	5.4	1.9
NSAIDs	13.0	8.4
Oral glucocorticoids	4.0	2.4
Inhaled glucocorticoids	7.7	5.7
Antidepressants	15.8	8.7
Antipsychotics	1.7	1.1
Anxiolytics/hypnotics	6.8	4.0
Anticonvulsants	7.0	1.6
Falls in 6 months before index date	2.5	0.8

Table 2: Risk of fracture in incident CMT patients as compared to patients without CMT

	Fractures (n)	Rate / 1000 person-years	Age-sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)[a]
No CMT	248	10.8	1.00	1.00
CMT				
Any fracture	58	15.1	1.43 (1.07 - 1.90)	1.31 (0.98 - 1.74)
Fracture at osteoporotic sites[b]	22	5.7	1.18 (0.75 - 1.87)	1.10 (0.69 - 1.74)[c]
Hip fracture	9	2.3	4.90 (2.03 - 11.83)	Not determined[d]
Vertebral fracture	1	0.3	0.54 (0.07 - 4.21)	Not determined[d]
Radius/ulna fracture	5	1.3	0.69 (0.27 - 1.74)	0.67 (0.26 - 1.69)[e]
Other osteoporotic fracture	8	2.1	1.05 (0.50 - 2.23)	0.94 (0.44 - 2.00)[f]
Fracture at non-osteoporotic sites	36	9.4	1.63 (1.13 - 2.35)	1.47 (1.01 - 2.14)[g]
Fracture of the foot, ankle or hand	21	5.5	1.66 (1.02 - 2.68)	1.49 (0.91 - 2.43)[h]
Other fracture	15	3.9	1.59 (0.90 - 2.80)	1.36 (0.76 - 2.44)[i]
By Gender[j]				
Male	28	14.0	1.40 (0.93 - 2.11)	1.34 (0.89 - 2.02)
Female	30	16.2	1.45 (0.97 - 2.16)	1.28 (0.85 - 1.91)
By age at CMT diagnosis[k]				
0 - 18	8	11.9	0.80 (0.38 - 1.68)	0.80 (0.38 - 1.68)
19 - 59	25	13.1	1.78 (1.14 - 2.78)	1.58 (1.01 - 2.48)
60 - 79	14	13.8	1.18 (0.66 - 2.09)	1.11 (0.62 - 1.98)
≥ 80	11	43.0	2.26 (1.13 - 4.52)	2.22 (1.10 - 4.47)
By time since CMT diagnosis (years)				
≤ 1	14	3.6	2.07 (1.21 - 3.56)	1.81 (1.05 - 3.11)
1 - 5	31	8.1	1.58 (1.09 - 2.29)	1.40 (0.96 - 2.04)
> 5	13	3.4	0.91 (0.52 - 1.60)	0.90 (0.52 - 1.58)

a) Adjusted for age, sex, the use of antidepressants in the previous six months or history of fracture before the CMT diagnosis
b) Patients may have received multiple osteoporotic fractures
c) Adjusted for age, sex, use of antidepressants in the previous six months
d) The number of fractures was too low to calculate AHR
e) Adjusted for age, sex, use of antidepressants in the previous six months and alcohol status at CMT diagnosis.
f) Adjusted for age, sex, use of antidepressants in the previous six months, alcohol status at CMT diagnosis and history of COPD
g) Adjusted for age, sex, use of antidepressants, anticonvulsants and NSAIDs in the previous six months
h) Adjusted for age, sex, use of antidepressants and anticonvulsants in the previous six months and history of asthma
i) Adjusted for age, sex, use of antidepressants, NSAIDs and opioids in the previous six months or history of fracture before the CMT diagnosis
j) Male CMT patients are compared with male controls and female CMT patients with female controls
k) CMT patients in each age group are only compared with control patients in the same age group

adjusted hazard ratio (AHR) 1.31 (95% Confidence Interval [CI], 0.98 - 1.74) and AHR 1.10 (95% CI, 0.69 - 1.74). In contrast, risk of non-osteoporotic fracture was statistically significantly increased among CMT patients, AHR 1.47 (95% CI, 1.01 - 2.14). Fracture risk did not change after stratification to fractures of the foot, the ankle or the hand, although the hazard ratio was no longer statistically significantly increased, AHR 1.49 (95% CI, 0.91 - 2.43). The number of hip and vertebral fractures was too low to calculate the AHR. The number of radius/ulna and "other osteoporotic fractures" fractures were insufficient to adjust for each confounder, which changed the beta-coefficient more than 2.0% in the age-gender adjusted analysis. Therefore, only these confounders were added to the model, which showed the highest change in beta-coefficient. Fracture risk of CMT patients compared with controls in men was equivalent to fracture risk of CMT patients compared with controls in women. Children were not at an increased risk of fracture, AHR 0.80 (95% CI, 0.38 - 1.68), whereas adults had a 1.5-fold increased risk of fracture, AHR 1.46 (95% CI, 1.06 - 1.99) as compared with control patients. Stratification to patients with an age of 80 years or older showed a 2-fold increased risk of fracture, AHR 2.22 (95% CI, 1.10 - 4.47). Further stratification to post-menopausal women with an age of 60 years or older and stratification to men with an age of 60 or older, did not show an increased risk of fracture with an AHR 1.25 (95% CI, 0.75 - 2.10) and AHR 1.71 (95% CI, 0.74 - 3.98) respectively compared with control patients. Fracture risk was highest during the first year after diagnosis, AHR 1.81 (95% CI, 1.05 - 3.11) and subsequently decreased towards, AHR 1.20 (95% CI, 0.87 - 1.66) more than 1 year after diagnosis as compared with control patients. The Kaplan Meier survival curves for risk of any fracture among CMT and control patients are shown in Figure 1.

Table 3 shows that the risk of fracture was doubled when CMT patients used psychotropic drugs in the previous six months, AHR 2.37 (95% CI, 1.47 - 3.84) when compared with control patients, whereas risk of fracture was highest among CMT

Figure 1: Proportion of patients without any fracture among CMT patients and controls.

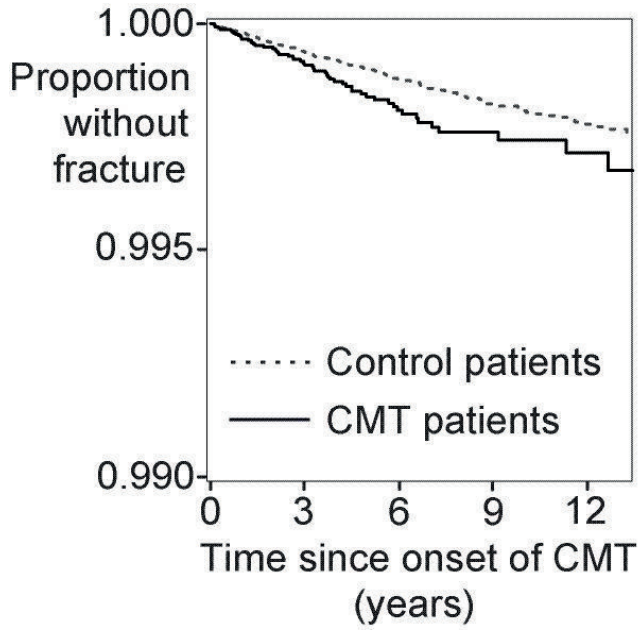

Table 3: Risk of fracture in incident CMT patients as compared to patients without CMT stratified by drug exposure in the six months before fracture

	Fractures (n)	Age-sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)[a]	p-value of interaction term[b]
No CMT	248	1.00	1.00	
CMT				
Any fracture	58	1.43 (1.07 - 1.90)	1.31 (0.98 - 1.74)	
By drug use in previous 6 months				
No psychotropic use[c]	40	1.20 (0.86 - 1.68)	1.18 (0.84 - 1.65)	
Psychotropic use	18	2.45 (1.52 - 3.97)[d]	2.37 (1.47 - 3.84)[d]	0.93
No antidepressant use	43	1.24 (0.90 - 1.72)	1.22 (0.88 - 1.68)	
Antidepressant use	15	2.50 (1.48 - 4.22)[d]	2.44 (1.45 - 4.13)[d]	0.88
No anxiolytic use	52	1.35 (1.00 - 1.82)	1.26 (0.93 - 1.70)	
Anxiolytic use	6	2.83 (1.25 - 6.38)	2.12 (0.93 - 4.82)	0.90
No antipsychotic use	55	1.37 (1.02 - 1.84)	1.27 (0.94 - 1.70)	
Antipsychotic use	3	5.50 (1.76 - 17.20)[d]	3.47 (1.10 - 10.96)	0.85

a) Adjusted for the same confounders as described below table 2 for any fracture, but the confounder is not added to the model if it is similar to the drug being investigated.
b) The interaction term (CMT * drug use in the previous 6 months) was investigated within the cohort
c) No use of antidepressants, anxiolytics/hypnotics or antipsychotics
d) Statistically significant difference compared with CMT patients unexposed to the drug being investigated ($p<0.05$)

patients who used antipsychotics, AHR 3.47 (95% CI, 1.10 - 10.96). Fracture risk was statistically significantly higher for CMT patients who used psychotropic drugs as compared with CMT patients unexposed to these drugs in the six months before fracture. However, the interaction terms between CMT and psychotropic drugs showed no statistical significance for any fracture in the cohort.

Discussion

This study showed a 1.5-fold increased risk for non-osteoporotic fractures, which mainly occurred at the ankle, the hand or the foot. However, we were unable to show a statistically significant increased risk for any and osteoporotic fracture among CMT patients. Risk of fracture was increased in adults, in the first year after diagnosis and among patients using psychotropic medication as compared with population-based control patients. No synergistic effect on the risk of fracture was observed for CMT patients who used psychotropic medication as compared with the control population, because the interaction terms between CMT and psychotropic drugs showed no statistical significance for any fracture in the cohort.

This is probably the first study, which determined fracture risk among CMT patients as compared with control patients. No increased risk of osteoporotic fracture was observed. Instead, an increased risk of non-osteoporotic fracture was shown, in which most fractures were observed at the hand, the foot or the ankle. This finding is in line with the nosology of the disease. Early symptoms include muscle weakness and wasting in the feet, including osteoporosis at this specific site [5]. Gradually, the ankles and legs become affected, whereas symptoms also appear in the hands and forearms [2]. These symptoms may have increased the risk of typical non-osteoporotic fractures, in particular of the hand, the foot or the ankle. Meanwhile, other parts of the skeleton are not affected, which may explain the absence of an increased risk for any or osteoporotic fracture as compared with control patients. In line with

this hypothesis, the relative frequency of reported fractures by site is slightly different compared to a cohort of patients at risk of osteoporosis (e.g. a cohort of patients currently exposed to oral glucocorticoids). Our cohort has a relative smaller proportion of osteoporotic fractures (2% vertebral, 9% forearm and 15% hip fracture of all types of fractures during follow-up) as compared with a cohort at high risk of osteoporosis (11% vertebral, 14% forearm and 11% hip fractures) [18].

The absence of an increased risk for any or osteoporotic fracture may also be explained by the lower severity of CMT disease as compared with other neurologic diseases. For example, patients with Parkinson's disease and muscular dystrophy were both at an increased risk of any and osteoporotic fracture [19,20]. Life expectancy of CMT patients is regularly not shortened [21], whereas patients with muscular dystrophy may not reach adulthood [22]. Similar to CMT disease, patients with Parkinson's disease often have a normal life expectancy, but it is suggested that their symptoms, like tremor and bradykinesia, are worse as compared with the symptoms of CMT patients. A further explanation may be the absence of enough statistical power to show an increased risk of fracture among CMT patients.

Risk of fracture was only increased during the first year after CMT diagnosis. This suggests that falls are responsible for the increased risk observed among CMT patients rather than osteoporosis. If CMT would be associated with the onset of reduced bone mineral density and eventually osteoporosis, this would take several months to develop, because one full cycle of bone remodeling may take up to 4 months [23]. Subsequently, risk of fracture would increase with longer durations since diagnosis of CMT, which is not the case in our study. Therefore, it is unlikely that reduced bone mineral density is responsible for the increased risk of fracture observed in the first year after diagnosis, although this cannot be ruled out.

Moreover, no association was observed between osteoporotic fracture risk and CMT. Although no true treatment is available for CMT patients, it is suggested that symptom control,

including exercise, use of ankle-foot orthoses or orthopedic foot surgery to prevent pes cavus deformity and hammer toes, may improve the severity of CMT in the year after diagnosis [2]. This could reduce the amount of falls and subsequently explain the absence of an association between CMT and fracture risk more than one year after diagnosis.

Based on the data presented in Table 1 (baseline table), CMT patients are more likely to have comorbidities and are prescribed more drugs as compared with control patients. It is suggested that CMT patients see their practitioners more often than control patients. Consequently, more comorbidities may be detected and subsequently more drugs may be prescribed for these patients. Additionally, CMT has been associated with depression [7], which may explain the high proportion of antidepressants use at baseline for CMT patients (15.8%) as compared with control patients (8.7%). More comorbidities and more use of drugs in CMT patients may have an influence on the fracture rate. Therefore, the analyses were adjusted for the relevant comorbidities and drugs, which changed the beta-coefficients of the age-gender adjusted analyses changed more than 2.0%. For this reason it is suggested that the higher amount of comorbidities and drugs used in CMT patients as compared with control patients, has negligible influence on the outcome.

The observed increased risk of fracture among CMT patients who used psychotropic drugs is in line with previous findings. In the general population, anxiolytics/hypnotics, antipsychotics and antidepressants increase fracture risk by reducing balance [9,10,24]. Moreover, antidepressants and antipsychotics may decrease bone mineral density indirectly. Antidepressants may decrease osteoblast proliferation, through 5-hydroxytryptamine receptor inhibition in bone [9], whereas antipsychotics may elevate serum prolactin, which may reduce bone mineral density [10].

Our study has several strengths. It is the first study, which investigated the risk of fracture among CMT patients and for whom longitudinal drug exposure data were available.

This study was population-based and compared CMT patients directly with age and sex matched control patients from the same general practice, which makes selection bias unlikely. Moreover, we had the ability to statistically adjust the outcome for well-known risk factors of fracture, like sex, age and the use of antidepressants.

A limitation of the study was the inability to determine fracture risk stratified to different types of CMT. CMT can be classified in several subtypes (e.g. CMT1, CMT2, CMTX, CMT4), which vary in age of onset, disease course, severity of disease and type of gene mutation. For example, onset of CMT1 usually starts in the first two decades of life. This type is slowly progressive and relatively benign, whereas CMT2 has a late onset and a more severe disease course [2,25]. It has been suggested that patients with CMT2 may have a higher fracture risk as compared with patients with CMT1. Furthermore, a true increased risk of any fracture among CMT patients may have been masked by insufficient statistical power in this study. No data on bone mineral density and functional status (eg. severity of disease, including wearing of ankle-foot orthoses or ambulatory status) are available in our cohort, hence we were unable to adjust our analyses for these parameters at baseline or stratify to these parameters during follow-up. Lastly, only small numbers of CMT patients were present in the subgroup analyses. Therefore, these data should be interpreted with care.

In conclusion, our findings demonstrate that patients with CMT are at a 1.5-fold increased risk for non-osteoporotic fracture, which mainly occurred at the ankle, the hand or the foot. Therefore, it may be beneficial to conduct fracture risk assessment for these specific sites in order to prevent fractures among CMT patients. Further studies, with larger number of CMT patients and with additional data on CMT subtype, bone mineral density and functional status, should be performed to confirm if a true association between CMT and an increased risk of any and osteoporotic fracture exists.

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Chapter 4.4

Risk of Fracture in Patients with Guillain-Barré Syndrome

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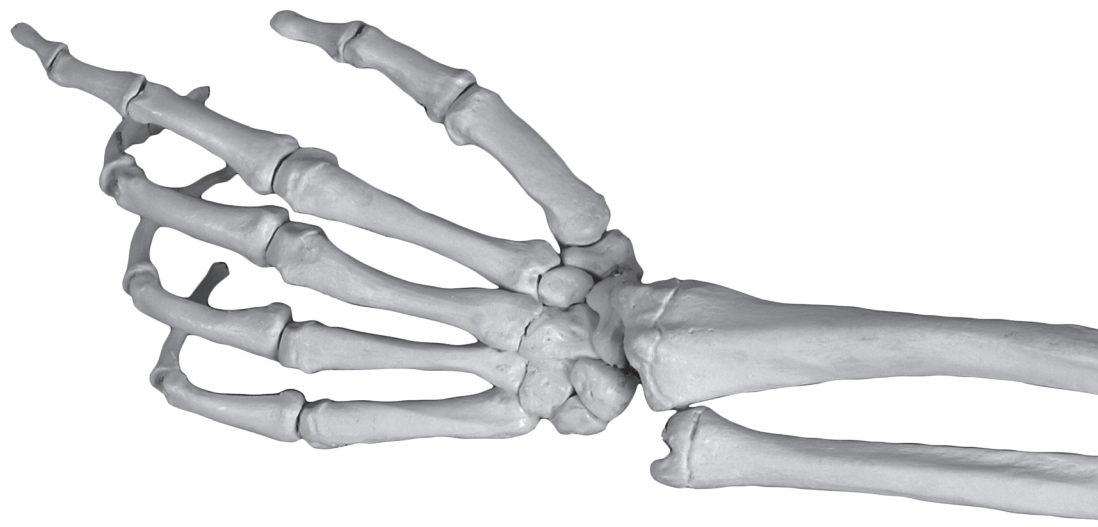


Abstract

Background: Symptoms of Guillain-Barré Syndrome (GBS) may vary from mild difficulty in walking to complete paralysis. This may increase the risk of fractures. Therefore, the aim of this study is to evaluate fracture risk in patients with GBS.

Methods: We conducted a retrospective cohort study using the United Kingdom Clinical Practice Research Datalink (1987-2012). Each patient with GBS was matched by year of birth, sex and practice up to six patients without a history of GBS. Outcome measure was any fracture.

Results: There were no associations between GBS and any fracture, adjusted hazard ratio (AHR) 1.01 (95% confidence interval [CI], 0.77- 1.33) or osteoporotic fracture, AHR 0.76 (95% CI, 0.50 - 1.17) compared with control patients. Stratification to gender, age and duration since diagnosis did not show an association either. Only for GBS patients using pain treatment risk of fracture was doubled, AHR 1.97 (95% CI, 1.21 - 3.21) compared with control patients. Although risk of fracture in GBS patients exposed to pain treatment was equivalent to risk of fracture among control patients exposed to pain treatment.

Discussion: No association with risk of fracture was observed for GBS patients compared with control patients. Only GBS patients using pain treatment had a doubled risk of fracture, but their risk was equivalent to fracture risk among control patients exposed to pain treatment.

Background

The Guillain-Barré Syndrome (GBS) has an incidence of about 1.5 per 100.000 patients in Europe [1,2]. The onset of disease is usually preceded by an infection and may vary from mild difficulty in walking to complete paralysis of all extremity, facial, respiratory and bulbar muscles. A proportion of GBS patients become bedridden [3,4].

Patients with GBS may be at an increased risk of fracture, as a consequence of falling and osteoporosis. Patients with GBS are at increased risk of falling [5], most likely caused by symptoms ranging from difficulty in walking, up to complete paralysis. Moreover, when bedridden, bone mineral density may decrease and bone structure may alter, which may result in osteoporosis [6,7].

Pain treatment, which is commonly prescribed for GBS patients, may further elevate the risk of fracture [8-11]. About 50% of GBS patients report pain (often neuropathic pain) for which they are initially treated with analgesics or non-steroidal anti-inflammatory drugs (NSAIDs). However, these drugs regularly do not provide adequate pain relief. Therefore, patients are frequently prescribed opioids, anticonvulsants or tricyclic antidepressants [12].

Furthermore, patients are often treated with intravenous immunoglobulin gamma (IV-IgG) or plasma exchange, which has shown to be better than supportive treatment alone [13,14]. It is hypothesized that use of IV-IgG has an opposite mechanism of action as compared with denosumab, which is a human monoclonal IgG antibody, which inhibits osteoclastogenesis and bone turnover [15]. The drug is authorized for the treatment of menopausal osteoporosis in women at increased risk of fracture and for the treatment of bone loss in men with hormone ablation therapy for prostate cancer, who are at increased risk of fracture [16]. Consequently, it is suggested that treatment of IV-IgG may increase bone turnover and induce osteoporosis.

As far as we know no studies have determined fracture risk among GBS patients.

Therefore, the aim of this study was to evaluate the risk of fracture among GBS patients as compared with population-based control patients.

Methods

Data source:

Information for this study was obtained from the Clinical Practice Research Datalink (CPRD), formerly known as the General Practice Research Database. The data comprised the computerized medical records of all patients under the care of general practitioners in the UK. Medical information on patients who are registered for medical care with a practice is supplied to the CPRD [17]. Previous studies of CPRD data have shown a high level of data validity with respect to the reporting of fractures (>90% of fractures were confirmed) [18,19].

Study population.

The study population consisted of all patients with at least one recorded diagnosis of GBS during the period of CPRD data collection (for this study, CPRD data collection started in January 1987 and ended in August 2012). Incident cases were defined as individuals whose first recorded general practitioner visit for GBS was present during valid data collection. Each GBS patient was matched by year of birth, sex and practice, to six patients without a history of GBS in CPRD. The index date of GBS diagnosis was the date of the first record of GBS after CPRD data collection started. Control patients also had to be enrolled in the CPRD at the time of the index date of their matched GBS patient and had no history of GBS at the index date. The study patients were followed up from this index date to either the end of CPRD data collection, the date of transfer of the patient out of the practice area, or the patient's death, whichever came first. Patients were followed up for the occurrence of fracture. The fracture types were classified according to the International Classification of Diseases, Tenth Revision

(ICD-10) categories [20]. A clinical osteoporotic fracture was defined as a fracture of the radius/ulna, humerus, rib, femur/hip, pelvis, or a clinical symptomatic vertebrae fracture [21].

Exposure

The total period of follow-up was divided into periods of 30 days, starting at the index date. At the start of each period the presence of risk factors was assessed by reviewing the computerized medical records prior to the right censoring date.

General risk factors included are body mass index (BMI), smoking status on the date of GBS diagnosis, a history of fracture and a history of falls within the previous 3-12 months before diagnosis, chronic diseases (asthma/chronic obstructive pulmonary disease [COPD], rheumatoid arthritis, thyroid disorders, chronic renal disease, cancer, congestive heart failure, cerebrovascular disease, diabetes mellitus, hypertension, inflammatory bowel disease, dementia), and a prescription in the previous six months before the start of each period of 30 days during follow-up for antidepressants, antipsychotics, anxiolytics/hypnotics, anticonvulsants, opioids, non-steroidal anti-inflammatory drugs (NSAIDs), oral glucocorticoids, and other immunosuppressants (azathioprine, ciclosporin, tacrolimus, mycophenolate mofetil, methotrexate).

Statistical analysis

Time-dependent Cox proportional hazards regression was used in order to estimate hazard ratios (HRs) of fracture risk. Fracture risk in GBS patients was compared with that among control patients to yield an estimate of the relative risk, which was expressed as hazard ratios. Analyses were stratified to use of pain treatment (use of NSAIDs, opioids, anticonvulsants and tricyclic antidepressants [TCAs]) and IV-IgG in the previous three months. The main analyses were stratified to age and gender. The HRs were adjusted for age and sex or if any potential confounder showed a >3.0% change in the beta-coefficient of the age-gender adjusted HR.

Results

We identified 897 incident GBS patients and 5345 control patients between 1987 and 2012. They had a mean age of 51 years and 43% were female. Average follow-up of GBS and control patients was eight years. Table 1 shows the age and gender distribution among GBS and control patients. It also provides information on BMI, smoking and alcohol status, history of comorbidities and drug use.

In Figure 1 the Kaplan Meier survival curves for risk of fracture among GBS and control patients are shown. No difference in fracture risk is observed between GBS patients and control patients.

Table 2 shows that 63 GBS patients sustained a fracture during follow-up as compared with 342 control patients. No association between GBS and any fracture (adjusted hazard ratio [AHR] 1.01, [95% confidence interval (CI), 0.77- 1.33] or osteoporotic fracture, AHR 0.76 (95% CI, 0.50 - 1.17) was observed as compared with control patients. Stratification to fracture of the hip, vertebral or radius/ulna did not show an association with GBS either. Furthermore, in Figure 1 the Kaplan Meier survival curves for risk of fracture among GBS and control patients are shown. No difference in fracture risk is observed between GBS patients and control patients.

The number of hip fractures was insufficient to include each confounder to the model. Therefore, only these confounders were added to the model, which showed the highest change in beta-coefficient in the age-gender AHR. Fracture risk of GBS patients compared with controls in men was equivalent to fracture risk of GBS patients compared with controls in women. No differences in fracture risk were observed in GBS patients of different age groups as compared with control patients of the same age group. A non-significant trend was observed for fracture risk since diagnosis of GBS, whereby the highest AHR was observed during the

Table 1: Baseline characteristics of patients with incident GBS compared to patients without a history of GBS

Characteristics	GBS patients (n=897)	Control patients (n=5345)
Female (%)	43.0	43.0
Mean age (years)	51.2	51.0
BMI (%)		
< 20	3.9	4.7
20-25	23.7	25.3
25-30	27.3	23.9
≥ 30	17.3	13.9
Unknown	27.8	32.2
Smoking status (%)		
Never	42.7	41.3
Current	22.1	22.5
Ex	15.7	13.6
Unknown	19.5	22.6
Alcohol status (%)		
Never	12.5	12.0
Current	57.1	54.1
Unknown	30.4	33.9
Fracture history (%)		
Any fracture	18.7	17.2
Fracture at osteoporotic sites	8.5	7.6
Hip fracture	0.6	0.6
Vertebral fracture	0.8	0.4
Radius/ulna fracture	3.9	4.2
Comorbidity ever before index date (%)		
Asthma	12.8	12.5
COPD	2.1	2.5
Congestive heart failure	2.0	1.5
Diabetes Mellitus	7.0	5.6
Rheumatoid arthritis	1.4	1.0
Renal disease		
Hypertension	22.2	18.6
Cerebrovascular disease	5.1	3.8
Inflammatory bowel disease	1.1	0.6
Cancer (excluding skin cancer)	4.7	5.0
Ischaemic heart disease	8.9	8.1
Drug use in 6 months before index date (%)		
Bisphosphonates	2.3	1.4
Opioids	4.8	2.3
NSAIDs	19.5	10.1
Oral glucocorticoids	6.8	2.2
Inhaled glucocorticoids	6.6	5.4
Antidepressants	11.3	7.8
Antipsychotics	0.4	1.3
Anxiolytics/hypnotics	8.9	5.3
Anticonvulsants	5.7	1.7

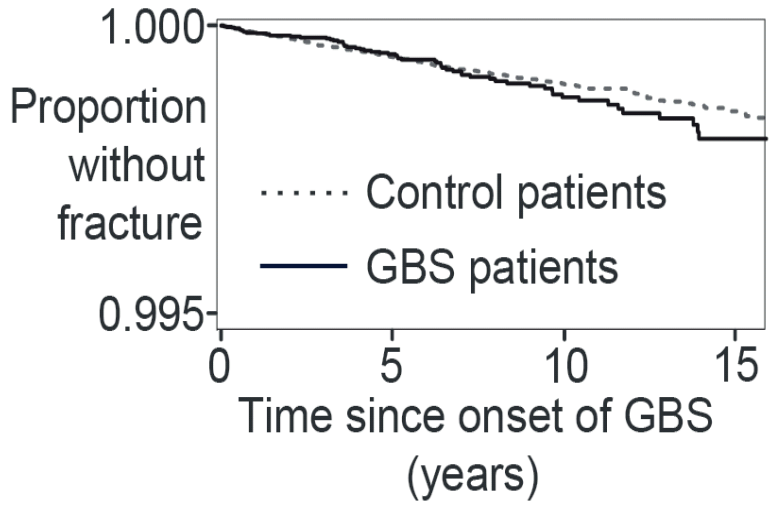
Table 2: Risk of fracture in incident GBS patients compared to patients without GBS

	Number of fractures	Rate / 1000 person-years	Age-sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)[a]
No GBS	342	7.8	1.00	1.00
GBS				
Any fracture	63	8.6	1.10 (0.84 - 1.44)	1.01 (0.77 - 1.33)
Fracture at osteoporotic sites	25	3.4	0.88 (0.58 - 1.35)	0.76 (0.50 - 1.17)[b]
Hip fracture	6	0.8	1.19 (0.50 - 2.87)	1.06 (0.43 - 2.59)[c]
Vertebral fracture	4	0.5	1.31 (0.44 - 3.86)	Not determined[d]
Radius/Ulna fracture	8	1.1	0.73 (0.35 - 1.51)	0.67 (0.32 - 1.39)[e]
Other	7	1.0	0.73 (0.33 - 1.60)	0.61 (0.27 - 1.35)[f]
Fracture at non-osteoporotic sites	38	5.2	1.31 (0.92 - 1.86)	1.26 (0.88 - 1.79)[g]
By Gender[h]				
Male	30	7.2	1.04 (0.71 - 1.54)	0.98 (0.66 - 1.45)
Female	33	10.6	1.15 (0.79 - 1.68)	1.05 (0.72 - 1.54)
By age at GBS diagnosis[i]				
0 - 19	10	17.2	1.58 (0.79 - 3.17)	1.47 (0.72 - 3.00)
20 - 39	11	6.8	1.32 (0.69 - 2.54)	1.24 (0.64 - 2.40)
40 - 59	16	6.7	1.01 (0.59 - 1.71)	0.96 (0.56 - 1.65)
≥ 60	26	9.5	0.97 (0.64 - 1.47)	0.89 (0.58 - 1.35)
By time since GBS diagnosis (years)				
≤ 0.5 year	6	0.8	1.68 (0.75 - 3.77)	1.39 (0.61 - 3.13)
0.5 - 1 year	5	0.7	1.57 (0.65 - 3.80)	1.27 (0.52 - 3.11)
1 - 2 years	4	0.5	0.66 (0.25 - 1.77)	0.56 (0.21 - 1.52)
2 - 5 years	16	2.2	1.07 (0.64 - 1.76)	0.96 (0.58 - 1.59)
≥ 5 years	32	4.4	1.09 (0.76 - 1.57)	1.06 (0.74 - 1.53)
By use of pain treatment in the previous 3 months[j]				
No pain treatment	46	6.3	0.95 (0.70 - 1.29)[k]	0.95 (0.70 - 1.29)[k]
Any pain treatment	17	2.3	1.97 (1.21 - 3.21)[k]	1.97 (1.21 - 3.21)[k]
No NSAID use	55	7.5	1.02 (0.77 - 1.36)[k]	0.96 (0.72 - 1.29)
NSAID use	8	1.1	2.26 (1.12 - 4.56)[k]	1.69 (0.82 - 3.46)
No opioid use	59	8.1	1.06 (0.81 - 1.40)	1.00 (0.76 - 1.32)
Opioid use	4	0.5	2.39 (0.89 - 6.43)	1.41 (0.51 - 3.91)
No TCA use	55	7.5	1.01 (0.76 - 1.35)[k]	0.97 (0.73 - 1.30)[k]
TCA use	8	1.1	2.79 (1.38 - 5.63)[k]	2.19 (1.05 - 4.54)[k]
No anticonvulsant use	57	7.8	1.06 (0.80 - 1.40)	1.04 (0.78 - 1.37)
Anticonvulsants	6	0.8	1.75 (0.78 - 3.93)	1.38 (0.61 - 3.12)

a) Adjusted for age, sex, use of antidepressants and anticonvulsants in the previous six months
b) Adjusted for age, sex, use of antidepressants, anticonvulsants, opioids and oral glucocorticoids in the previous six months
c) Adjusted for age, sex and use of anticonvulsants in the previous six months
d) The number of fractures was too low to calculate AHR
e) Adjusted for age, sex, use of antidepressants in the previous six months and history of hypothyroidism
f) Adjusted for age, sex, use of anticonvulsants, opioids and immunosuppressants in the previous six months
g) Adjusted for age, sex and use of antidepressants in the previous six months
h) Male GBS patients are compared with male controls and female GBS patients with female controls
i) GBS patients in each age group are only compared with control patients in the same age group
j) Adjustment for the use of antidepressant and anticonvulsant in the previous six months was not performed when these drugs were investigated in the model
k) Statistically significant difference compared with GBS patients unexposed to the drugs being investigated ($p<0.05$)

first half year since GBS diagnosis, AHR 1.39 (95% CI, 0.61 - 3.13). Subsequently, the AHR declined towards 1.06 (95% CI, 0.74 - 1.53) after more than 5 years since GBS diagnosis.

Figure 1: Proportion of patients without fracture among GBS patients and controls.



However, stratification to history of pain treatment in the previous three months before fracture yielded a twofold increased risk of fracture, AHR 1.97 (95% CI, 1.21 - 3.21) as compared with control patients. These GBS patients had a statistically significant increased risk of fracture as compared with GBS patients unexposed to pain treatment. Additionally, the stratification to GBS patients who used TCAs in the previous three months were also at a twofold increased risk of fracture compared with control patients, AHR 2.19 (95% CI, 1.05 - 4.54). The interaction terms between GBS and use of pain treatment in the previous three months showed no statistical significance for any fracture in the cohort, which implies that risk of any fracture is equivalent between GBS patients exposed to pain treatment as compared with control patients exposed to pain treatment.

We identified two GBS patients with a history of IV-IgG treatment as compared with 23 control patients during follow-up. None of these patients sustained a fracture within the next three months of follow-up. Therefore, we were unable to calculate a hazard ratio for the

stratifications to IV-IgG treatment.

Discussion

This study showed that GBS patients had no association with risk of any, osteoporotic or other types of fracture as compared with population-based control patients. Stratification to age, gender and time since GBS diagnosis did not show an association with fracture risk. Only, those patients who were exposed to pain treatment or TCA use in the previous three months before fracture were at a twofold increased risk of fracture as compared with control patients. However, risk of any fracture is equivalent between GBS patients exposed to pain treatment as compared with control patients exposed to pain treatment.

This is the first study, which determined fracture risk among GBS patients. Despite associations of GBS with falling [5] and with reduced bone mineral density [4], no association with fracture has been observed, except for patients who were exposed to pain treatment. The absence of association may be explained by the relative short duration of disease for a major part of GBS patients. A clinical trial with 147 GBS patients showed that about 50% of patients were already able to walk again within eight weeks after onset and this amount increased up to 76% after six months of onset [22]. These findings suggest that GBS is most severe early after onset, which is in line with our finding that fracture risk was highest in the first half year after onset of GBS, AHR 1.39 (95% CI, 0.61 - 3.13). During the first eight weeks after onset of GBS fracture risk seemed even higher, AHR 1.50 (95% CI, 0.37 - 6.03). These results suggest that GBS patients may have an increased risk of fracture during the first months after diagnosis. However, the current results are non-significant with only two GBS patients who sustained a fracture during this eight-week time period. Therefore, these findings should be interpreted with care and should be confirmed in a larger population of GBS patients.

In CPRD no data were available to determine severity of GBS, including data about the

amount of time a patient spent bedridden, whereas a reduction in bone mineral density can already been observed after eight weeks of bed rest [7]. Moreover, some patients need years to recover and 19% were still disabled 12 months after onset of GBS [23]. Consequently, it is hypothesized that severe GBS patients who have been bedridden for a long time-period may have an increased risk of fracture.

The observed increased risk of fracture among GBS patients who used pain treatment is in line with previous studies which determined fracture risk among patients who used pain treatment [8-10,24,25], although stratifications to NSAID, opioid and anticonvulsant use did not reach statistical significance in our study. Common side effects of opioids are dizziness and an altered postural balance, which both may result in an increased risk of falling and subsequently cause an increased risk of fracture [8,24]. Likewise, TCAs and anticonvulsants increase fracture risk by reducing balance [9,10]. Moreover, anticonvulsants may also increase bone turnover, and thereby reduce bone mineral density, which ultimately leads to an increased risk of fracture [25]. One of these mechanisms to increase bone turnover is hepatic induction of the P-450 enzyme system, which increases catabolism of Vitamine D. This may result in relative hypocalcemia, increased parathyroid hormone and subequent bone loss [9,25]. Furthermore, an increased risk of fracture with NSAID use has been observed before, although the mechanism of action remains unclear. It is suggested that NSAIDs may decrease bone strength via a different mechanism than reduction in bone mineral density [11,26].

This study has several strengths. It is the first study that investigated the risk of fracture among GBS patients as compared to population-based control patients. The study compared GBS patients directly with age and sex matched control patients from the same general practice. Therefore, selection bias is unlikely. Furthermore, we had the ability to statistically adjust our analyses for well-known risk factors of fracture such as gender, age, and use of antidepressants.

A limitation of the study was the inability to determine fracture risk stratified to severity of GBS, including the amount of time a patient has spent bedridden. Moreover, reported numbers of IV-IgG treatment were too small to determine their influence on the risk of fracture. Possibly, some prevalent GBS patients have been included in our cohort as well. For example, the baseline characteristics show that pain treatment (opioid, NSAID, antidepressant and anticonvulsant use) is more common in GBS patients as compared with control patients. It was hypothesized that risk of fracture is highest early after GBS diagnosis. Therefore, inclusion of prevalent GBS patients in the cohort may have resulted in depletion of susceptible bias, because these patients were at highest risk of fracture prior to start of follow-up. We were unable to determine if TCAs and anticonvulsants were used for pain treatment only. This medication may also have been used to treat depression and epilepsy. Lastly, only small numbers of GBS patients were present in the subgroup analyses. Therefore these data should be interpreted with care.

In conclusion, our findings demonstrated that patients with GBS had no association with fracture risk. Only GBS patients using pain treatment had a doubled risk of fracture, but their risk was equivalent to fracture risk among control patients exposed to pain treatment.

Acknowledgement

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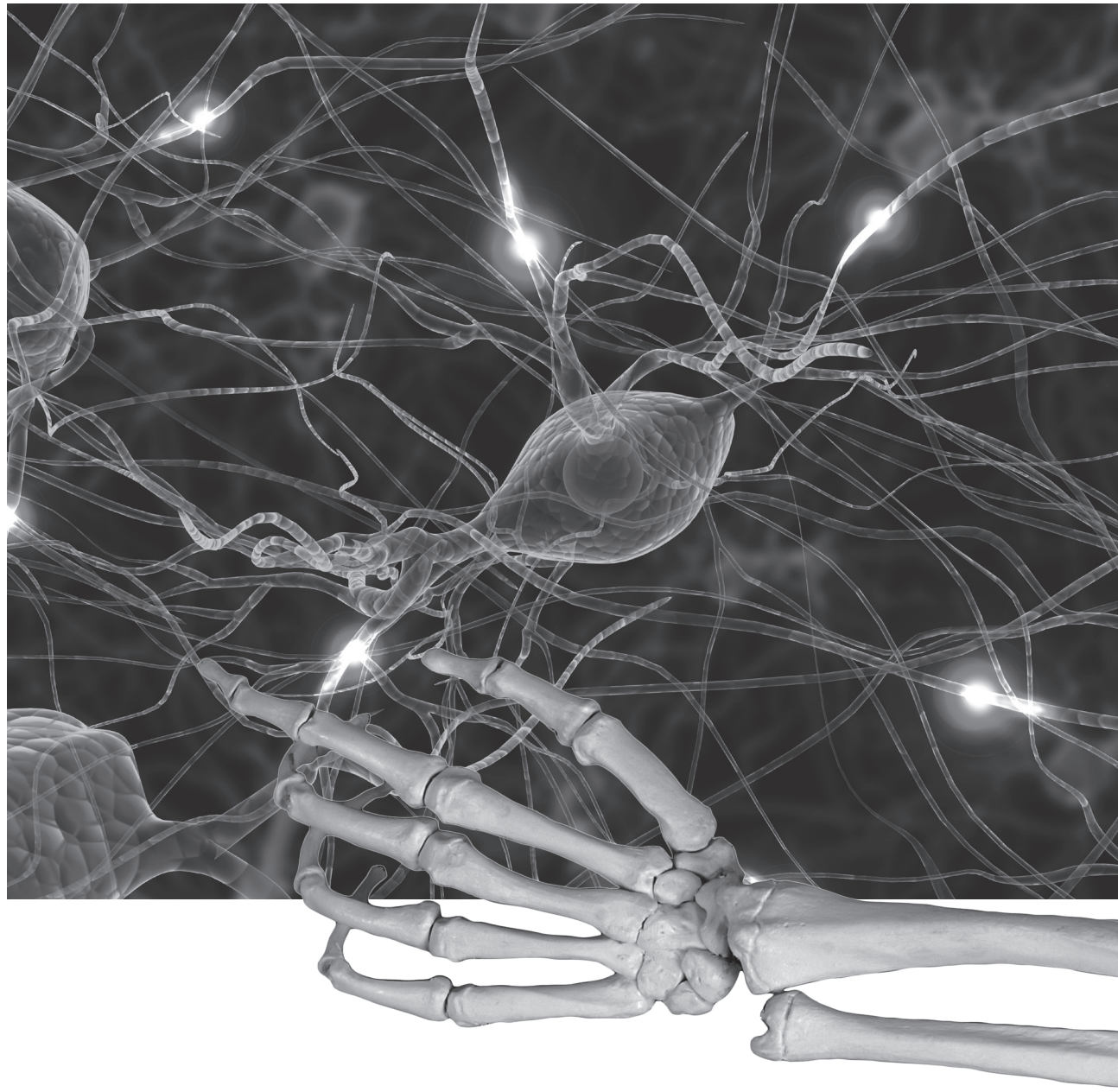
Chapter 5

Discussion



This general discussion starts with a summary of the key findings. Next, the association between proton pump inhibitor (PPI), antidepressant and antipsychotic use and fracture risk will be evaluated. This includes hypotheses about the causal pathways for fracture. It will be followed by a discussion about the associations of neurological disorders with fracture risk. Subsequently, fracture risk in patients with neurological disorders with concomitant exposure to glucocorticoids (GCs), dopaminergic drugs, antidepressants, antipsychotics, anxiolytics / hypnotics and anticonvulsants will be evaluated. Finally, this chapter will conclude with strengths, limitations, clinical messages, final considerations for the future and the overall conclusion.

Main findings

This thesis shows that current use of PPIs, antidepressants and antipsychotics were associated with 1.2-2.4-fold increased risks of hip/femur. Current use of PPIs was associated with a 1.2 fold increased risk of hip/femur fracture. Current antidepressant use was divided into selective serotonin reuptake-inhibitor (SSRI) and tricyclic antidepressant (TCA) use, which yielded a 2.4 and 1.8-fold increased risk of hip/femur fracture respectively. Current antipsychotic use was associated with a 1.7-fold increased risk of hip/femur fracture, with a 1.8-fold increased risk of hip/femur fracture after stratification to conventional antipsychotics, but no increased risk after stratification to atypical antipsychotics.

For stroke, Parkinson's disease (PD), muscular dystrophy (MD) and Charcot-Marie-Tooth disease (CMT) patients, we observed an increased risk of fracture compared with population-based control patients, whereas patients with myasthenia gravis (MG) or Guillain-Barré Syndrome (GBS) had no increased fracture risk. After stroke, patients had a 2.0-fold increased risk of hip/femur fracture. Patients who had experienced a hemorrhagic stroke tended to have higher hip/femur fracture risk compared with those who had experienced an ischemic

stroke. Incident PD patients had a 1.9, 2.0 and 3.1-fold increased risk of any, osteoporotic and hip fracture, respectively. Incident MD patients were at a 1.4-fold increased risk of any fracture. Stratification to patients with myotonic dystrophy showed a 2.3-fold increased risk of fracture, but stratification to Duchenne MD patients showed no association with fracture risk. Lastly, risk of any and osteoporotic fracture was not increased in incident patients with CMT. However, stratification to non-osteoporotic fractures, which mainly occurred at the ankle, the hand or the foot showed a 1.5-fold increased risk of fracture.

For incident PD patients we developed a simple model for the assessment of osteoporotic fracture risk estimation and hip fracture risk estimation. Identified risk factors for osteoporotic fracture in the model were age, female gender, current smoking, low BMI, history of rheumatoid arthritis, dementia, renal disease, fracture, falling and use of antidepressants or oral glucocorticoids.

Patients with neurological disorders who used GCs and antidepressants may be at an additional increased risk of fracture, while the contribution to an additional risk of fracture is not clear for use of dopaminergic drugs, antipsychotics, anxiolytics/hypnotics and anticonvulsants.

The association between drug use and risk of fracture in the general population and speculation about the causal pathway

This paragraph discusses the risk of fracture in patients who used PPIs, antidepressants or antipsychotics. It will be explored whether this risk is caused by a fall-related or bone fragility mechanism.

Use of PPIs

In line with several other studies that have confirmed an increased risk of fracture with the use of acid suppressants [1-8], our findings showed that PPI use was associated with a modest increased risk of hip/femur fractures compared with unexposed population-based control patients (chapter 2.1). The mechanism, which may explain this association between PPIs and an increased risk of fracture could be related to changes in bone fragility. If PPIs would reduce bone strength, this would take several months, because a full cycle of bone remodeling may take up to 4 months [9]. We found that the highest risk of hip/femur fracture was observed within the first months after initiation of PPI use and risk attenuated with prolonged use (Figure 2 of Chapter 2.1). Most published studies have not observed a duration of use effect between PPI use and fracture risk either [1-3,10,11], except for Yang et al. [4] and Targownik et al. [5]. However, using the same Clinical Practice Research Datalink (CPRD) database as Yang et al., de Vries et al. did not observe a duration of use effect [1]. We repeated the analysis performed by Yang et al. ourselves in PHARMO Record Linkage System (RLS), but we did not find a duration of use effect. These findings do not support a causal effect of PPIs on bone, but may point at an association with falling. According to our knowledge, no association between PPI use and falls has been described in literature. Therefore, it is likely that bias and residual confounding explains our findings. In line with this conclusion, Targownik et al. recently performed a new study in which they were [8] able to adjust for bone mineral density (BMD) at baseline. They observed a modest increased risk of fracture after exposure to PPIs. They concluded that the lack of a proven mechanism through which PPIs increase the risk of fracture suggests that this association may not be causal [12].

Use of antidepressants and antipsychotics

Our findings demonstrate an increased risk of hip/femur fracture with the use of antipsychotics or antidepressants (Chapter 2.2 and 2.3). This is in line with previous studies, which observed an increased risk of fracture among users of these drugs [13-18]. After discontinuation of these drugs, the risk of hip/femur fracture decreased, which indirectly suggests that the observed increased risk of hip/femur fracture may be causal. Our results suggest that both falling and changes in bone fragility may be involved in increasing the risk of hip/femur fracture (Figure 2, Chapter 2.2 and Figure 1, Chapter 2.3).

Shortly after start of treatment, risk of hip/femur fracture was increased about 3.5-fold and 2.5-fold for antidepressant and antipsychotic use, respectively, which may be explained by an increased risk of falls due to e.g. sedation, extrapyramidal side effects and orthostatic hypotension [19-21]. These results are in line with findings from a case-control study that observed highest risks of hip fracture within the first 14 days after start of antidepressant treatment with adjusted odds ratios of 4.76 (95% confidence interval [CI], 3.06 - 7.41) for TCAs and 6.30 (95% CI, 2.65 - 14.97) for SSRI use [16]. Another case-control study showed that risk of hip fracture was higher for new antidepressant users compared with continuous antidepressant users, although the difference was not significant for SSRI users [17]. Also with antipsychotic use, an increased risk of hip fractures has been observed within the first 8 weeks of antipsychotic use [22].

The initial side effects of treatment, like extrapyramidal and sedative side effects may be transient [23], possibly because adaptive changes occur that reduce the extent of the side effects [24]. This effect may explain the observed decrease in fracture risk after about half a year of treatment [23]. However, risk of hip/femur fracture increased again after about 1.5 year of treatment for antidepressants and antipsychotics, which may indicate the presence of a long-term fragility of bone related effect. For antidepressants this long-term effect showed to be

more associated with use of SSRIs than with TCAs or other antidepressants. SSRIs have a higher degree of 5-hydroxytryptamine (5-HT) inhibition compared with TCAs and other antidepressants, which may affect bone metabolism and result in a long-term increased risk of fracture [18]. In line with this effect, we observed that patients currently exposed to antidepressants with a high 5-HT transporter inhibition were at highest increased risk of hip/femur fracture. A meta-analysis showed that duration ≥6 weeks of TCA exposure had a substantially weaker association with an increased risk of fracture, relative risk (RR) 1.13 (95% CI, 1.00 - 1.28), compared with TCA exposure duration <6 weeks, RR 2.40 (95% CI, 1.41 - 4.08) [25].

For antipsychotics the long-term increased risk of hip/femur fracture seems to be highest for conventional antipsychotics. They have a higher degree of D_2 receptors stimulation compared with atypical antipsychotics increasing the risk of extrapyramidal side effects (although this effect may be transient). They may also increase prolactin levels, which decrease BMD over time [26]. In line with this hypothesis, our results showed that only those patients who used conventional, but not atypical antipsychotics, had an increased risk of hip/femur fracture. However, data of the atypical antipsychotic users must be interpreted with care because the amount of atypical antipsychotic users was rather low. Only 11 patients who used atypical antipsychotics sustained a hip/femur fracture. A recent meta-analysis of observational studies determined fracture risk again among patients who used either atypical or conventional antipsychotics and found that the risk of fracture was higher for conventional antipsychotics, dds ratio [OR] of 1.69 (95% CI, 1.43 - 1.99) than for atypical antipsychotics, OR 1.30 (95% CI, 1.14 - 1.49) [27].

In conclusion, our results support the hypothesis that use of antidepressants and antipsychotics is associated with a fall-related increased risk of hip/femur fracture. Furthermore, use of SSRIs and antipsychotics with a high affinity for D2-receptor stimulation

(thus prolactin raising) may also be associated with a bone fragility related increased risk of hip/femur fracture. We were unable to distinguish between the effects on the outcome of the underlying disorders (eg depression and schizophrenia) and the use of antidepressants and antipsychotics, respectively. Therefore, we are unable to conclude whether the increased risks of fracture are solely caused by antidepressants and antipsychotics or that the underlying disease may have contributed to the observed risks of fracture.

Neurological disorders associated with an increased risk of fracture in relation with timing since diagnosis

Patients with PD had an increased risk of fracture (chapter 3.2) irrespective of timing since diagnosis, whereas stroke patients (chapter 3.1), MD patients (chapter 4.2) and patients with CMT (chapter 4.3) had their highest increased risk of fracture shortly after diagnosis. Subsequently risk of fracture attenuated for stroke, MD and CMT patients, but remained increased for patients who experienced a stroke and MD patients. MG and GBS were not associated with an increased risk of fracture (chapter 4.1 and 4.4). Concomitant treatment with antidepressants, anxiolytics/hypnotics, antipsychotics and anticonvulsants in patients with neurological disorders is discussed in a separate paragraph. An overview of the associations between neurological disorders and fractures observed in this thesis is presented in Table 1.

Parkinson's disease

A two-fold increased risk of any and osteoporotic fracture and a three-fold increased risk of hip fracture was observed for PD patients (Chapter 3.2). These results are in line with other studies, which showed two-fold increased risk in any fracture, a 2.4 -fold increased risk of non-spine fractures in men and a 2.6-fold increased risk of hip fracture in women respectively [28-30].

Table 1. Neurological disorders and their associations with fractures

Neurological disorder	Underlying disease	Short-term	Long-term	Oral GC[a]	Antidepressants	Antipsychotics	Anxiolytics / hypnotics	Anticonvulsants
Stroke	+++	+++	++	ND	ND	ND	ND	ND
Parkinson's disease	+++	+++	+++	ND	++	-	+	ND
Myasthenia gravis	-	-	-	-	+++	-[b]	++	+++
Muscular dystrophy	++	++	+	+++	-	-[b]	-	ND
Charcot-Marie-Tooth disease	+	+	-	ND	++	+[b]	+[b]	ND
Guillain-Barré Syndrome	-	-	-	ND	+[bc]	ND	ND	-[b]

+ weak association, ++ medium association, +++ strong association, - no association, ND not determined
a) Glucocorticoid
b) Less than 10 patients in sub-analysis
c) Only determined for TCA users

Since PD diagnosis, PD patients are continuously at a 1.5 (within the first year after diagnosis) to 2-fold (more than one year after diagnosis) increased risk of osteoporotic fracture. Two other studies have evaluated the risk of fracture over time since PD diagnosis. A case-control study which studied the duration of parkinsonism (including a diagnosis for PD) showed a 1.7-fold increased risk of fracture in the first half year since diagnosis, a 2.2-fold increased risk in the second half year, but no increased risk after a more than 1 year [31]. It is hypothesized that an increased risk of fracture for patients with parkinsonism after 1 year since diagnosis has been masked by the presence of a large number of non-PD patients. A second case-control study studied the duration of dopaminergic drug use, which is highly associated with the presence of PD, and showed a continuously 2-fold increased risk of hip/femur fracture as compared with population-based control patients with a duration up to about 7 years of dopaminergic drug use [32].

Furthermore, both PD and dopaminergic drugs are associated with an increased risk of falls and reduced BMD [33-40]. Therefore, PD patients seem to be at a continuously increased risk of fracture since diagnosis, whereby both PD and dopaminergic drugs and both falls and bone fragility may play a role.

Stroke

Patients were at a two-fold increased risk of hip/femur fracture after stroke (Chapter 3.1) consistent with other studies that showed a 1.5 to 5-fold increased risk of hip fracture after stroke [41-44]. The highest risk of hip/femur fracture was observed within the first 3 months after stroke (see Figure 1, Chapter 3.1). It declined over time but remained 1.9-fold elevated more than 3 years after stroke.

An increased risk of falling soon after stroke supports our findings of highest risk of fracture in the first 3 months after stroke. Forster et al. followed 108 patients after stroke with mild to moderate disability and found that 73% had fallen in the 6 months after

discharge [45]. In an observational study, 92% of the subjects who had recurrent falls within 6 months after discharge from stroke rehabilitation had fallen at least once while being in the hospital or during stroke rehabilitation [46].

On the other hand, sudden immobility, reduced vitamin D levels, increased homocysteine levels and increased sympathetic activity may cause bone fragility in patients after stroke, which is a second explanation for the high increased risk of hip/femur fracture shortly after stroke [40,47-51]. This is in line with findings from longitudinal studies, which report substantially higher rates of BMD loss within the first 6 months after stroke (4% to 10% BMD loss of the femoral region), which attenuated to 1% to 3% BMD loss for the second half of the year. Loss of BMD was most obvious in paralyzed extremities, such as the femoral neck and the proximal humerus, as a result of decreased mobility [52-56].

Over time, most patients recover mobility which strengthens bone. Moreover, motor, sensory and visual deficits often improve, which reduces the risk for falls. Still, a 1.9-fold increased risk remained even after more than 3 years since stroke, which may be explained by a residual increased risk of falls and residual fragility of the bone.

Muscular dystrophies

A 1.4-fold increased risk of fracture has been observed in MD patients as compared with population-based control patients (Chapter 4.2). Patients with Duchenne MD were not at an increased risk, whereas risk was doubled among patients with myotonic dystrophy.

We found one other population-based study, which observed a significant twofold increased risk of fracture among Duchenne and Becker MD patients as compared with control patients, whereby patients were sent a questionnaire to determine their fracture rate [57]. A limitation of this approach is possible underreporting of fractures among control patients, which could partly explain the observed twofold increased risk of fracture.

Underreporting of glucocorticoid use among the Duchenne MD population may further explain the difference.

Risk of fracture is highest shortly after diagnosis (1.9-fold increased). This may be explained by an increased risk of falls, due to symptoms like instability [58]. It has been suggested that patients have an improved symptom control after diagnosis, which could explain the fracture risk reduction over time. Still, a small 1.3-fold increased risk of fracture remained after more than one year since diagnosis. Due to muscle weakness, MDs have been associated with bone deformities, scoliosis and immobility, which are all associated with bone fragility [57,59,60]. Subsequently, it has been suggested that long-term increased risk of fracture among MD patients may be explained by both bone fragility and fall-related mechanisms.

In our study, a 2.9-fold increased risk of fracture and 4.5-fold increased risk of osteoporotic fracture was observed among MD patients who received a GC prescription within the previous 6 month compared with MD patients unexposed to GCs, irrespective of the dose received (Chapter 4.2). This risk is higher than those observed by van Staa et al., who observed a 1.3-fold increased risk of non vertebral fractures irrespective of the dose received [61]. In contrast to the results by van Staa et al. and de Vries et al. [61,62], we did not observe a further increased risk with use of higher average daily doses of GCs. But we were only able to differentiate between an average daily dose < 5 mg prednisolone equivalents (n=7) and an average daily dose of 5 mg or more prednisolone equivalents (n=13). This showed a 3.6-fold and 2.6-fold increased risk of fracture, respectively, compared with non-users. It is possible that our study lacked statistical power to determine the influence of GC dosing in MD patients. Moreover, we were unable to adjust the average daily GC dose for the weight of the patient, which could further explain the absence of a dosing trend. Especially Duchenne MD patients may already be treated with

GCs at the age of 5. Subsequently, an average daily dosing of 5 mg prednisolone equivalents is rather high for these patients [63].

Charcot-Marie-Tooth disease

This is probably the first study which determined fracture risk in patients with CMT (Chapter 4.3). In the main analysis no increased risk of any fracture was observed. However, after stratification to risk of non-osteoporotic fracture we observed a 1.5-fold increased risk compared with control patients, whereby most fractures were observed at the hand, the foot and the ankle. This is in line with the nosology of the disease, which starts with muscle weakness and wasting in the feet. Gradually also the ankles and the hands may become affected [64]. We were unable to determine fracture risk at specific sites like the hand, the foot or the ankle, because the numbers of CMT patients were too low in these sub-analyses.

Additionally, a 1.8-fold increased risk of fracture was observed in the first year after CMT diagnosis. Symptoms like hand cramps, absence of deep-tendon reflexes, muscle cramps, difficulty in walking and weakness may have increased the risk for falls shortly after diagnosis [64]. It is suggested that symptom control after diagnosis may have reduced the amount of falls, which could explain the absence of an association between CMT and fracture risk more than 1 year after diagnosis. The absence of a long-term increased risk of fracture, suggests that falls are largely responsible for the increased risk observed among CMT patients rather than bone fragility, except for possible osteoporosis at specific sites, like hand, feet and ankles, which may be affected by CMT [65].

Myasthenia Gravis

No association with fracture risk was observed for MG (Chapter 4.1). Possibly, MG treatment has an anabolic effect on bone. Most MG patients were treated with

pyridostigmine, which is a cholinesterase inhibitor that elevates acetylcholine levels in MG patients [66]. In-vitro studies have shown that osteoblasts express acetylcholine receptors, while elevated acetylcholine levels induced osteoblast proliferation [67,68]. This may ultimately lead to an anabolic effect of bone and level out any detrimental effects on bone. Alternatively, patients with a diagnosis of MG have a normal life expectancy based on the currently available therapies [69]. This suggests that treated MG patients may have a similar risk of fracture as compared with healthy control patients.

Treatment with GCs in MG showed no association with fracture compared with MG patients unexposed to GCs, irrespective of the dose received. Alternatively, the subgroups of MG patients with highest average daily dose (≥ 15 mg prednisolone equivalents per day in the previous 6 months) and highest cumulative dose (≥ 5gram in the previous year) may have been underpowered, with only 7 and 4 MG patients reported osteoporotic fractures, respectively. An explanation for these findings is that the cholinesterase inhibitor pyridostigmine, which is often used in the treatment of MG, may have anabolic effects, and therefore level out any detrimental effects of glucocorticoids [66-68]. This is in line with a recent study performed by Wakata et al. [70] who showed that Japanese MG-patients who received long-term (8.2 years) high dose prednisolone therapy (maximum 80-100 mg for 4-6 weeks), had a 50% reduced osteoporosis rate, as compared to the general population. However, each treated MG patient was also treated with osteoporosis preventive therapy [70]. An alternative explanation for the absence of an increased risk of fracture in MG patients on GCs is that generally these drugs are used for the treatment of inflammatory disease. Subsequently, the disease itself may increase the risk for fracture itself, like rheumatoid arthritis [71]. This inflammatory compound is generally not present in MG-patients, except for some inflammatory cells that may be present in muscle [72]. A further explanation is that glucocorticoids may decrease fracture risk associated with the disease,

thus cancelling out its adverse effects.

Guillain-Barré Syndrome

No association with fracture risk was observed for GBS (chapter 4.4). The absence of an association between GBS and fracture risk may be explained by the relative short duration of disease for a major part of GBS patients. A clinical trial with 147 GBS patients showed that about 50% of patients were already able to walk again within eight weeks after onset and this amount increased up to 76% after six months of onset [73]. These findings also suggest that GBS is most severe early after onset. However, in our cohort insufficient GBS patients were present, to determine if fracture risk was increased shortly after diagnosis. This issue warrants further research.

Neurological disorders and concomitant psychotropic medication use

The neurological disorders have been associated with comorbidities like depression, anxiety, schizophrenia and epilepsy. These comorbidities are treated with antidepressants, anxiolytics/hypnotics, antipsychotics and anticonvulsants, which may decrease the symptoms of these disorders and in turn may decrease the risk of fractures, but on the other hand increase the risk of fractures through their side effects. In this paragraph the effect on fracture risk of concomitant treatment with antidepressants, anxiolytics/hypnotics, antipsychotics and anticonvulsants in neurological disorders is discussed. The main results are also presented in Table 1.

Antidepressants

In addition to our findings that antidepressants have an increased risk of fracture in the general population, antidepressants also show an additional increased risk of fracture in PD, MG and CMT patients. Osteoporotic f 1.4-fold and 3.3-fold increased for

PD and MG patients compared with unexposed PD and MG patients. Compared with control patients, CMT patients exposed to antidepressants had a statistically significant higher risk of fracture (2.2-fold increased) compared with CMT patients unexposed to antidepressants (1.2-fold non-significantly increased). Only for MD patients no additional increased risk of fracture was observed. Their effect was not tested in stroke and GBS.

The results of an additional increased risk of fracture with antidepressant use in patients with neurological disorders are in line with other studies. In a population of dopaminergic drug users overall risk of hip/femur fractures was 1.8-fold increased as compared with population-based control patients. An additional increase in risk of hip/femur fracture was observed, towards 3.5-fold increased for patients who were also currently exposed to antidepressants [32]. The additional increased risk of fracture with antidepressants has also been observed in two cohort studies with multiple sclerosis (MS) patients. Use of antidepressants showed a 1.8-fold increased risk of fracture as compared with population-based control patients without MS, whereby fracture risk was only 1.3-fold increased for MS patients unexposed to antidepressants in CPRD [74]. In the PHARMO RLS the risk of osteoporotic fracture was 1.7-fold increased for MS patients as compared with population-based control patients, which increased towards 3.3-fold increased for MS patients exposed to antidepressants. This is statistically significantly higher compared with MS patients unexposed to antidepressants [75]. A third study showed that osteoporotic fracture risk was 1.7-fold increased in MS patients exposed to antidepressants as compared with unexposed MS patients in the age-gender adjusted analysis, but this increased risk was no longer statistically increased in the fully adjusted analysis [76]. The absence of an additional increased risk of fracture for MD patients exposed to antidepressants may be a consequence of the relative young population in our cohort, whereas an increased risk of fracture is particularly observed among elderly patients using antidepressants [17].

In conclusion, antidepressant use in patients with neurological disorders may be associated with an increased risk of fracture compared with patients with neurological disorders who have not been recently exposed to antidepressants

Antipsychotics

Antipsychotics showed no additional increased risk of fracture in patients with PD, MG and MD. In CMT risk of fracture was 3.5-fold increased as compared with control patients without CMT. However, risk was not statistically different from CMT patients unexposed to antipsychotics. Risk was not determined in patients with stroke and GBS. Only high-dose (≥ 150 mg thioridazine equivalents) exposure of antipsychotics in PD patients showed an additional increased 3.0 and 3.8-fold risk of osteoporotic and hip fracture.

The absence of an additional increased risk of fracture with the use of antipsychotics may largely be explained by the fact that the analyses for antipsychotic use in neurological disorders were underpowered with one, two and three persons who used antipsychotics in the cohorts of MG, MD and CMT patients, respectively. For PD patients exposed to antipsychotics (n=44), the osteoporotic and hip fracture risk tended to be 1.3-fold increased as compared with unexposed PD patients, but these analyses did not reach statistical significance. Similarly, in MS patients exposed to antipsychotics a 1.8-fold non-significant increased risk of osteoporotic fracture was observed, whereas unexposed MS patients had a 1.4-fold increased risk of osteoporotic fracture as compared with control patients without MS [74]. This analysis was also underpowered with only 5 MS patients exposed to antipsychotics. Lastly, a case-control study showed that risk of hip/femur fracture was not different between patients treated with dopaminergic drugs as compared with patients treated with both dopaminergic drugs and antipsychotics (n=17) [32]. Based on the low numbers of patients present in each of these analyses these data should be

interpreted with care. In addition, one study had enough power to determine the risk of hip fractures in patients with a different neurological disorder and stratified to concomitant antipsychotic use. When this study started, 278 dementia patients used antipsychotics. As compared with dementia patients unexposed to antipsychotics, dementia patients currently exposed to antipsychotics had a 1.3-fold additional increased risk of hip fracture [77].

In conclusion, a possible association between antipsychotic use and a minor additional increased risk of fracture in patients with neurological disorders may be present.

Anxiolytics/hypnotics

Although use of anxiolytics/hypnotics tended to have an association with an increased risk of fracture in patients with PD and CMT patients, this association was not statistically significant. Only for MG patients a 2.2-fold increased additional risk of osteoporotic, but not for any fracture was observed as compared with MG patients unexposed to anxiolytics/hypnotics. No association was present with fracture risk for MD patients. Risk of fracture was not determined for patients after stroke and GBS who currently used anxiolytics/hypnotics.

In the general population, anxiolytics/hypnotics probably increase fracture risk by reducing balance [14]. However, on average, a population of patients with neurological may already have poor balance. Therefore, the excess increased risk of fracture caused by anxiolytic/hypnotic use, may have been masked by the stronger effect of falling in patients with neurological disorders. Similarly, in two different cohort studies of MS patients, which may also be at an increased risk of falls, risk of osteoporotic fracture tended to be higher for patients exposed to anxiolytics/hypnotics, although no statistical difference was observed either between risk of osteoporotic fracture for patients prescribed anxiolytics/hypnotics as compared with unexposed MS patients [74,76]. Also in a cohort of

dopaminergic drug users, no significant difference was observed between patients additionally exposed to benzodiazepines as compared with non-users of benzodiazepines [32]. Conversely, in a third cohort study of MS patients, the risk of osteoporotic fracture was 3.4-fold increased in patients who were dispensed anxiolytics/hypnotics, while risk of osteoporotic fracture was significantly lower for MS patients unexposed to anxiolytics/hypnotics [75]. The reason for this higher risk of fracture in the third MS study remains unclear.

In conclusion, patients with neurological disorders exposed to anxiolytics/hypnotics may have a small excess risk of fracture as compared with patients unexposed to anxiolytics/hypnotics, although it is hypothesized that this excess risk may often be masked by the falls risk of the underlying disease.

Anticonvulsants

Lastly, fracture risk with concomitant treatment of anticonvulsants was determined in MG and GBS patients, which showed a 5.3 and 6.7-fold additional increased risk of any and osteoporotic fractures in MG patients, but no additional increased risk in GBS patients. Risk of fracture was not determined for patients with PD, MD, CMT and stroke patients who used anticonvulsants.

In patients with MS a non-significantly excess risk of fracture was observed for patients exposed to anticonvulsants as compared with non-users in two cohort studies. In the first study, patients who used anticonvulsants had a 2.5-fold increased risk of hip fracture as compared with a 1.7-fold increased risk for non-users [75]. In the second cohort study, risk of osteoporotic fracture was 1.7-fold increased of osteoporotic fracture as compared with a 1.3-fold increased risk for non-users [74]. The absence of an increased risk of fracture among GBS patients exposed to anticonvulsants as compared with GBS

patients unexposed to anticonvulsants may be explained by the relative short duration of disease for a major part of GBS patients [73], whereas both MG and MS are chronic disorders. The relative young age of the GBS cohort (Chapter 4.4, mean age 43) compared with the MG cohort (Chapter 4.1, mean age 61 years), but similar to the cohorts with MS patients (mean age 44-45 years [74,75]), may further explain the absence of an additional risk of fracture.

In conclusion, anticonvulsant use may lead to an additional increased risk of fracture on top of the fracture risk observed in neurological disorders, although larger studies are needed to confirm our results.

Strengths of population-based database studies

Our studies have several strengths. They are all population-based and represent the Dutch or United Kingdom populations. The large source populations of the PHARMO RLS and CPRD made it possible to determine the association between neurological disorders and fracture risk even for rare neurological disorders like CMT and GBS. CMT has a prevalence of only 8-41 patients per 100.000 individuals and the incidence for GBS is only 1-2 patients per 100.000 person years [78,79]. A further advantage is the relative long duration of follow-up (eg. up to an average follow-up of 9 years for MD patients since diagnosis) available in the databases, which made it possible to determine fracture risk in relation with time since diagnosis. The same applies for the duration of treatment with PPIs, antidepressants and antipsychotics. Due to the relative long follow-up period, we were able to plot Kaplan-Meier plots showing fracture risk development over time since diagnosis. Moreover, with smoothing spline visualizations we were able to show increases and decreases of fracture risk over time since start or cessation of treatment with PPIs, antipsychotics and antidepressants. To avoid confounding bias in our studies, we matched

each patient of interest with one or more control patients with similar age, gender and region / practice distribution.

Limitations of population-based database studies

Our studies have several limitations. In the studies evaluating the risk of hip/femur fracture in patients who used antidepressants and antipsychotics, it was not possible to account for the effect of the underlying disease (e.g. depression and schizophrenia), which may be a major risk factor for an increased risk of fracture [50,80-82]. Subsequently, we were unable to conclude how much of the observed risks are attributable to the drugs received and to the underlying disease. The same limitation applied to our analysis of patients with PD using dopaminergic drugs.

Selection bias may have been present in our analyses. In database studies using data from CPRD and PHARMO RLS it is difficult to determine severity of disease. Consequently, the most convenient way to determine severity is by assessing prescription data. We classified PD and MG patients to mild, moderate and severe based on their treatment prescribed during the different stages of disease. This classification was based on the NICE Guideline on PD and the Guidance of the Myasthenia Gravis Foundation [83,84]. Unfortunately, this approach is sensitive to misclassification. Additionally, the diagnoses for neurological disorders have not been validated in CPRD, except for PD. For PD patients we used the same inclusion criteria for a PD diagnosis as Hernan et al. who confirmed 90% of all PD diagnoses [85]. Such a validation study has not been performed for MG, MD, CMT and GBS patients in CPRD. The diagnosis for stroke in PHARMO RLS has not been validated either.

Furthermore, some prevalent patients with neurological disorders may have been included in the different incident CPRD cohorts, because no precise date of diagnosis was

described in the database. However, several sensitivity analyses have been performed to rule out that the possible presence of prevalent patients may have altered our findings. For example, fracture risk did not change when PD patients needed to have at least 3 years of follow-up in CPRD as compared with 1 year of follow-up prior to their first PD record. No difference in fracture risk was observed for MD patients either, which needed to have at least 1 year of follow-up in CPRD prior to their first MD record as compared with patients who had their first record of MD since valid data collection. This suggests that our results have not been seriously biased by the presence of patients with prevalent neurological disorders. Lastly, some important risk factors associated with fracture risk were not available in the databases such as baseline BMD and time spent bedridden. Furthermore no data on baseline BMI and smoking was available in PHARMO RLS. Subsequently, we were unable to adjust our analyses for these baseline parameters.

In our studies we determined fracture risk among incident patients with a neurological disorder. For PD patients and some types of MD (eg. Duchenne MD) progress of disease may be rather fast, but an average of 6 years follow-up may still not have been sufficient to include the most severe patients in our cohort [33,86]. Additionally, MG, CMT and certain other types of MD (eg facioscapulohumeral MD) have a similar life expectancy as compared with healthy control patients, while these disorders may start already in childhood [69,87,88]. Subsequently, their highest severity of disease may take decades to develop. Therefore, it must be concluded that most severe patients were probably not included in our cohorts and overall risks of fracture may have been underestimated for the neurological disorders.

Only small numbers of patients were present in the subgroup analyses for the relative rare neurological disorders like CMT, MD and GBS. Therefore, these data should be interpreted with care.

We developed a specific fracture risk prediction model for PD patients. However, this model has not yet been validated in an external population. Beside a prediction model for fractures in PD patients, we did not develop a prediction model for other patients with a neurological disorder associated with an increased risk of fracture. For CMT and MD not enough patients were available to build a model. The development of a prediction model for stroke patients would have been possible. Such a model could be developed in future.

Preventive strategies

Our results showed that patients with PD, MD and those who experienced stroke were at an increased risk of fracture. Additionally, CMT patients had an increased risk of fracture in the first year after diagnosis and patients exposed to antidepressants and antipsychotics were also at an increased risk of fracture. Therefore, fracture risk assessment may be indicated among these patients.

Several clinical risk scores for fracture risk prediction are currently available such as the Garvan calculator and FRAX [89,90]. However, a limitation of these scores is that they do not take into account a wide range of neurological disorders as determinants. Consequently, we developed a specific risk score to determine a PD patient's risk of osteoporotic and hip fracture (Chapter 3.3). For patients with MS a similar risk score is currently available [91]. These scores are an aid for fracture risk prediction in PD and MS patients in daily practice after external validation. For other patients with neurological disorders at increased risk of fracture (patients with a diagnosis of MD, CMT or after a stroke), no specific risk score is available yet. Until the models for PD and MS have been validated in an external population and until specific risk scores are available for other patients with neurological disorders at risk of fracture, it is recommended to use the general clinical risk scores [89,90]. Additionally, BMD measurements are an alternative to quickly

determine whether a patient has an increased risk of fracture [92]. Community pharmacists may play a role in screening for low BMD [93]. Furthermore, they are able to identify patients which use drugs that are associated with an increased risk of falls (like anxiolytics) or with bone fragility (like GCs) [94,95].

When fracture risk prediction shows that fracture risk is increased, preventive strategies may be recommended to reduce falls and to reduce bone fragility in those patients at risk. However, the next step is to determine at which magnitude of fracture risk one should start with fracture risk prevention. The patient, the general practitioner/specialist, the insurance company, the pharmaceutical industry and many others will have different opinions about when to start with fracture risk prevention. Furthermore, will discontinuation of for example psychotroptic drugs to reduce fracture risk in PD patients, outweigh the benefits of psychotropic drug use in these patients? These questions are difficult to answer and are outside the scope of this thesis. But, when it is decided that fracture risk prevention will be beneficial, fall prevention programs may be recommended after diagnosis of stroke, PD, MD, CMT or shortly before start of antidepressant or antipsychotic use. Moreover, randomized clinical trials showed that use of bisphosphonates prevented hip fractures in Japanese PD patients or those who had experienced a stroke via a reduction in bone fragility [96]. Therefore, bisphosphonates may be recommended for these patient groups. Bisphosphonates may also be beneficial for patients with MD or those who are exposed to antidepressants or antipsychotics, although no clinical trials have been performed for these patients yet.

Final considerations, future studies

Randomized clinical trials have recently shown that use of bisphosphonates prevented hip fractures in PD patients and patients who experienced stroke. Some trials included only

patients with reduced BMD, while others did not [96]. Our data suggests that bisphosphonates may also be beneficial for MD patients and those who used antidepressants and antipsychotics. Consequently, new randomized clinical trials to confirm fracture risk prevention are awaited for these patient groups.

Some analyses should be extended in the future. Only small numbers of patients were present in the subgroup analyses for the relative rare neurological disorders like CMT, MD and GBS. For example, it was not possible to properly determine fracture risk in patients with GBS, shortly after diagnosis. In the future, when more patients with these neurological disorders have been identified, fracture risk should be determined again in a similar setting to confirm our results. Alternatively, fracture risk could also be determined prospectively in newly diagnosed patients with CMT and MD, who visit a neuromuscular clinic on a regular basis or in a hospital setting for patients admitted for GBS. These settings are less prone to information bias compared with observational studies. Also stratifications of neurological disorders to use of antipsychotics, anxiolytics/hypnotics and anticonvulsants should be performed again in the future to confirm our results. Moreover, validation of the CPRD diagnoses for MG, CMT, MD and GBS and the PHARMO RLS diagnoses for stroke would further strengthen the results. Additionally, average follow-up was currently about 6 years since diagnosis of the neurological disorders. Therefore, most severe patients were probably not included in our cohort. When longer follow-up data are available in future, fracture risk should be determined again to evaluate long-term fracture risk in patients with neurological disorders.

Recently, it is suggested that sarcopenia (reduction in muscle mass and function) and osteoporosis show many parallels in decreasing strength of the musculoskeletal organ, whereby the strongest mechanical forces that condition bone density, microarchitecture and bone strength, are muscle contractions [97,98]. This suggests that reduced muscle strength is directly associated with decreased bone strength. As sarcopenia may be associated with neurological disorders like stroke and PD [99,100], this theory and its implications for patients with neurological disorders warrants further research.

Furthermore, PD, MD, stroke, the use of antidepressants and antipsychotics may all be potential predictors for fracture. It should be investigated whether these risk factors for fracture could be added to the FRAX model to further improve this model [89]. Additionally, specific fracture risk prediction models should be developed to better determine fracture risk for patients with MD, CMT, after stroke and for those who started with antidepressants or antipsychotics. The specific PD and MS fracture risk scores should be validated in an external population. Alternatively, quality of CPRD data could possibly be improved by the addition of specific information from specialists (e.g. functional status to determine severity of disease), which would improve the currently available fracture risk prediction models for PD and MS patients.

Lastly, to further investigate whether a causal relationship exists between PPI use and an increased risk of fracture, fracture rates in previous randomized clinical trials could be compared between PPI users and control patients.

Conclusion

In conclusion, our findings demonstrate that patients with a diagnosis of the neurological disorders stroke, PD, MD, CMT and patients currently exposed to PPIs, antidepressants and antipsychotics have an increased risk of fracture. However, the association between PPI use and an increased risk of fracture may not be causal, but may be the result of unmeasured distortions. No association with an increased fracture risk was observed for patients with a diagnosis of MG or GBS. Concomitant use of GCs may further increase the risk of fracture in patients with MD, but not in patients with MG. Concomitant use of antidepressants in

patients with neurological disorders may further increase the risk of fracture, whereas the contribution to an additional risk of fracture is not completely clear yet for use of dopaminergic drugs, antipsychotics, anxiolytics/hypnotics and anticonvulsants. Falls and bone fragility are the principle determinants for an increased risk of fracture. Therefore, fall prevention programs to reduce the risk of falls and bisphosphonate use to reduce bone fragility may be recommended in those patients with the neurological disorders stroke, PD, MD and CMT and those patients exposed to antidepressants and antipsychotics. For these patients a specific fracture risk score may facilitate to identify those patients at increased risk of fracture.

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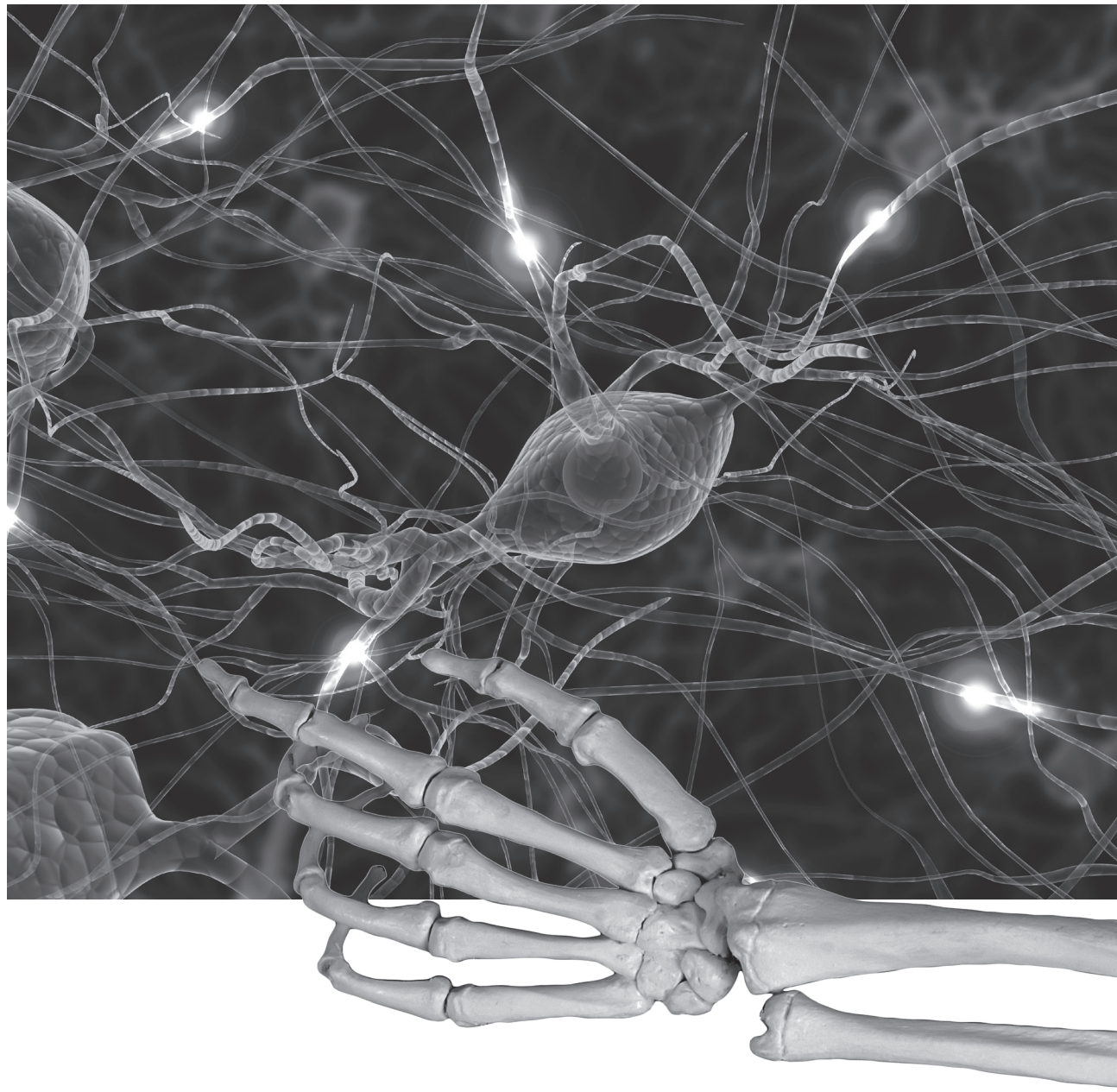
Appendices



Summary

1. Introduction

Patients with neurological disorders may be at an increased risk of fracture via multiple causal pathways, including increases in the risk of falls and changes in bone mineral density and quality of bone microarchitecture. Risk of fracture may be increased by the disease itself, by comorbidities and by their treatment.

Treatment with antidepressants, antipsychotics and proton pump inhibitos (PPIs) may cause an additional increase in fracture risk in patients with neurological disorders, but it is not clear which causal pathway (via falling or via bone fragility) contributes most. To have sufficient statistical power, this question should first be investigated in the general population before determination of an additional risk of fracture in patients with neurological disorders.

Furthermore, fracture risk has never been determined in several forms of neurological disorders including myasthenia gravis (MG), Charcot-Marie-Tooth disease (CMT), Guillain-Barré Syndrome (GBS) and other forms of muscular dystrophy (MD) than Duchenne or Becker MD. Moreover, fracture risk has never been determined in a large cohort for Parkinson's disease (PD) patients and Duchenne and Becker MD patients compared with population-based control patients with the ability to adjust for a wide range of comorbidities and drug exposure. Furthermore, fracture risk has been determined in patients after stroke as compared with population-based control patients, but information about the time course in relation with fracture risk is scarce. Information about the time course in relation with fracture risk is also scarce for other neurological disorders.

Information is also scarce about the possible additional increase of fracture risk with concomitant use of glucocorticoids (GCs), dopaminergic drugs, antidepressants, antipsychotics, anxiolytics, anticonvulsants and PPIs in patients with neurological

disorders.

Finally, several clinical risk scores for fracture risk prediction are currently available. But a limitation of these risk scores is that they do not take into account a wide range of neurological disorders as determinants. As far as we know, a specific risk score for patients with a neurological disorder is only available for patients with multiple sclerosis (MS).

Therefore, the main objectives of this thesis are:

- to determine the risk of fracture in the general population exposed to PPIs, antidepressants and antipsychotics and to indirectly determine the causal pathway of fracture risk (Chapter 2)
- to determine fracture risk in patients after stroke, in patients with PD, MG, MD, CMT and GBS compared with population-based controls (Chapters 3 and 4)
    - to determine fracture risk in relation with time since diagnosis (Chapters 3 and 4)
    - to determine fracture risk in patients with neurological disorders with concomitant exposure to GCs, dopaminergic drugs, antidepressants, antipsychotics, anxiolytics / hypnotics, anticonvulsants and PPIs (Chapters 3 and 4).
- to develop a fracture risk prediction model for patients with neurological disorders (Chapter 3.3).

Both the Dutch PHARMO Record Linkage System (RLS) database and the United Kingdom Clinical Practice Research Datalink (CPRD) database were used to determine fracture risks in patients compared with population-based control patients.

2. Drug induced fracture risk

In the first study (Chapter 2.1), PHARMO RLS was used to determine risk of hip/femur fracture among PPI users. Current users of PPIs had an increased risk of hip/femur fracture yielding an adjusted odds ratio (AOR) of 1.20 (95% confidence interval [CI], 1.04 - 1.40). Fracture risk attenuated with increasing durations of use, resulting in AORs of 1.26 (95% CI, 0.94 – 1.68) in the first 3 months, 1.31 (95% CI, 0.97 – 1.75) between 3 and 12 months, 1.18 (95% CI, 0.92 – 1.52) between 13 and 36 months and 1.09 (95% CI, 0.81 – 1.47) for use longer than 36 months.

In the next study (Chapter 2.2) we used PHARMO RLS to estimate the risk of hip/femur fracture in patients who used antidepressants. The risk of hip/femur fracture increased with current use of selective serotonin reuptake-inhibitor (SSRIs) showed AOR 2.35 (95% CI, 1.94–2.84) and tricyclic antidepressants (TCAs) AOR 1.76 (95% CI, 1.45–2.15). The risk of hip/femur fracture declined rapidly after discontinuation of use. The risk of hip/femur fracture increased as the degree of 5-hydroxytryptamine transporter (5-HTT) inhibition of all antidepressants increased from AOR 1.64 (95% CI, 1.14–2.35) for drugs with low 5-HTT inhibition to AOR 2.31 [95% CI, 1.94–2.76] for those with high 5-HTT inhibiting properties.

Chapter 2.3 showed the risk of hip/femur fracture in patients who used antipsychotics in PHARMO RLS. We found an increased risk for hip/femur fracture associated with the use of antipsychotic drugs. The risk for current users, AOR 1.68 (95% CI, 1.43 - 1.99) was significantly greater than with past use, AOR 1.33 (95% CI, 1.14 - 1.56). Current use of conventional antipsychotics, AOR 1.76 (95% CI, 1.48 - 2.08) but not atypical

antipsychotics, AOR 0.83 (95% CI, 0.42 - 1.65) was associated with an increased risk. We did not find evidence for a dose effect.

3: Central neurological disorders and risk of fracture

In PHARMO RLS an increased risk of hip/femur fracture was observed in patients who experienced a stroke at any time before the index date, AOR 1.96 (95% CI, 1.65-2.33) (Chapter 3.1). The fracture risk was highest among patients who sustained a stroke within 3 months before the index date, AOR 3.35 (95% CI, 1.87-5.97) and among female patients, AOR 2.12 (95% CI, 1.73-2.59). The risk further increased among patients younger than 71 years, AOR 5.12 (95% CI, 3.00-8.75). Patients who had experienced a haemorrhagic stroke tended to be at a higher hip/femur fracture risk compared with those who had experienced an ischaemic stroke.

In CPRD we identified 4,687 incident PD patients (Chapter 3.2). Compared to controls, a statistically significant increased risk was observed for any fracture with adjusted hazard ratio (AHR) 1.89 (95% CI, 1.67 - 2.14), osteoporotic fracture, AHR 1.99 (95% CI, 1.72 - 2.30) and hip fracture, AHR 3.08 (95% CI, 2.43 - 3.89). Fracture risk further increased with history of fracture, falling, low body mass index (BMI), renal disease, antidepressant use and use of high-dose antipsychotics.

In the next study in CPRD (Chapter 3.3), we identified 4,411 incident PD patients without a history of osteoporotic treatment. These data were used to develop a fracture risk prediction model. The 5-year risks of osteoporotic and hip fracture were plotted in relation to the risk score. Risk scores increased with age, female gender, history of renal disease and history of dementia. The C-statistic, which is a parameter to test the internal validity of the

model, was reasonable for the prediction of osteoporotic fracture (0.69) and hip fracture (0.73).

4: Other neurological disorders and risk of fracture

In the first study we used CPRD (Chapter 4.1) to determine the risk of any and osteoporotic fractures in patients with MG. Compared to the control cohort, there was no statistically significant increased risk observed in patients with MG for any fracture, AHR 1.11 (95% CI, 0.84 - 1.47) or osteoporotic fractures, AHR 0.98 (95% CI, 0.67 - 1.41). Further, use of oral glucocorticoids up to a cumulative dose exceeding 5 grams prednisolone equivalents did not increase risk of osteoporotic fracture, AHR 0.99 (95% CI, 0.31 – 3.14) compared with MG patients without glucocorticoid exposure. However, fracture risk was higher in patients with MG prescribed antidepressants, AHR 3.27 (95% CI, 1.63 – 6.55), anxiolytics, AHR 2.18 (95% CI, 1.04– 4.57) and anticonvulsants, AHR 6.88 (95% CI, 2.91 – 16.27).

A second study in CPRD (Chapter 4.2) showed that risk of any fracture was statistically significantly increased in MD patients, AHR 1.40 (95% CI, 1.14 - 1.71) compared with control patients. An increased risk of fracture was observed among MD patients with female gender, AHR 1.78 (95% CI, 1.33 - 2.40) and an increasing age as compared with control patients. Stratification to Duchenne MD showed no association with fracture, whereas risk of fracture was two-fold increased among patients with myotonic dystrophy AHR 2.34 (95% CI, 1.56 - 3.51). MD patients had an almost tripled risk of fracture when they used oral glucocorticoids in the previous six months, as compared to non-users with a MD.

In CPRD (Chapter 4.3) risk of non-osteoporotic fracture was statistically significantly

increased in CMT patients, AHR 1.47 (95% CI, 1.01 – 2.14), while risk of any and osteoporotic fracture did not reach statistical significance compared with control patients, AHR 1.31 (95% CI, 0.98 - 1.74) and AHR 1.10 (95% CI, 0.69 - 1.74) respectively.

In the last study, which used CPRD (Chapter 4.4) no associations between GBS and any fracture, AHR 1.01 (95% CI, 0.77- 1.33) or osteoporotic fracture, AHR 0.76 (95% CI, 0.50 - 1.17) were observed compared with control patients. Stratification to gender, age and duration since diagnosis did not show an association either. Only for GBS patients using pain treatment risk of fracture was doubled, AHR 1.97 (95% CI, 1.21- 3.21) compared with control patients. Although risk of fracture in GBS patients exposed to pain treatment was equivalent to risk of fracture among control patients exposed to pain treatment.

5. Discussion

The general discussion evaluated the association between fracture risk and the use of PPIs, antidepressants and antipsychotics. It was explored whether this risk was caused by a fall-related or bone fragility mechanism. We elaborated on the associations of neurological disorders with fracture risk. Subsequently, fracture risk in patients with neurological disorders with concomitant exposure to GCs, dopaminergic drugs, antidepressants, antipsychotics, anxiolytics / hypnotics and anticonvulsants was discussed. Finally, we concluded with strengths, limitations, clinical messages, final considerations for the future and the overall conclusion.

Our results showed highest risk of fracture shortly after start of PPI use, hence did not support a causal effect on bone which would take months to develop, but implied an association with falling. Because no association between PPI use and falls has been described in literature, it has been suggested that the presence of unmeasured distortion like

selection bias and/or residual confounding may explain our findings. Our results support the hypothesis that use of antidepressants and antipsychotics is associated with a fall-related increased risk of hip/femur fracture. Furthermore, use of SSRIs and antipsychotics with a high affinity for D2-receptor stimulation (thus prolactin raising) may also be associated with a bone fragility related increased risk of hip/femur fracture.

PD patients seem to be at a continuously increased risk of fracture since diagnosis, whereby both PD and dopaminergic drugs and both falls and bone fragility may play a role. An increased risk of falling soon after stroke supports our findings of highest risk of fracture in the first 3 months after stroke. A reduction in bone mineral density within the months after stroke further explains the observed increased risk. Over time, risk of fracture decreased but remained elevated, which may be explained by a residual increased risk of falls and residual fragility of the bone. In MD and CMT patients an increased risk of falls, may explain the increased risk of fracture shortly after diagnosis. Improved symptom control may have decreased fracture risk over time, but a residual risk of falls and risk of bone fragility may explain the 1.3-fold increased risk of fracture in MD patients after more than one year since diagnosis. CMT has not been associated with an increased risk of fracture after more than one year since diagnosis. MG and GBS were not associated with an increased risk of fracture.

In conclusion, our findings demonstrate that patients with a diagnosis of the neurological disorders stroke, PD, MD, CMT and patients currently exposed to PPIs, antidepressants and antipsychotics have an increased risk of fracture. However, the association between PPI use and an increased risk of fracture may not be causal, but may be the result of unmeasured distortions. No association with an increased fracture risk was observed for patients with a diagnosis of MG or GBS. Concomitant use of GCs may further increase the risk of fracture in patients with MD, but not in patients with MG. Concomitant

use of antidepressants in patients with neurological disorders may further increase the risk of fracture, whereas the contribution to an additional risk of fracture is not completely clear yet for use of dopaminergic drugs, antipsychotics, anxiolytics/hypnotics and anticonvulsants. Falls and bone fragility are the principle determinants for an increased risk of fracture. Therefore, fall prevention programs to reduce the risk of falls and bisphosphonate use to reduce bone fragility may be recommended in those patients with the neurological disorders stroke, PD, MD and CMT and those patients exposed to antidepressants and antipsychotics. For these patients a specific fracture risk score may facilitate to identify those patients at increased risk of fracture.

Samenvatting

1. Introductie

Patiënten met neurologische aandoeningen hebben mogelijk een verhoogd risico op een botbreuk. Hiervoor zijn verschillende oorzaken aan te wijzen, waaronder een verhoogd risico op vallen, veranderingen in de mineraaldichtheid van het bot en verminderde kwaliteit van de micro-architectuur van het bot. Het risico op een botbreuk kan verhoogd zijn door de aandoening zelf, door gerelateerde aandoeningen, maar ook door geneesmiddelen gebruikt tijdens de behandeling van de betreffende aandoening.

Behandelingen met antidepressiva, antipsychotica en protonpompremmers (PPIs [een bepaalde groep van maagzuurremmers]) kunnen leiden tot een verdere verhoging van het risico op een botbreuk bij patiënten met neurologische aandoeningen. Het is echter niet duidelijk welk causaal verband het meeste bijdraagt aan dit risico (een verhoogd risico op vallen of verminderde kwaliteit van het bot). Om voldoende statistische kracht te hebben, zal deze vraag eerst moeten worden onderzocht in de totale populatie. Vervolgens kan het additioneel risico van deze behandelingen op een botbreuk worden onderzocht in patiënten met neurologische aandoeningen.

Het risico op een botbreuk is nog nooit onderzocht in de neurologische aandoeningen myasthenia gravis (MG), Charcot-Marie-Tooth (CMT), Guillain-Barré Syndrome (GBS) en andere vormen van muscular dystrophy (MD) dan Duchenne of Becker MD. Tevens is het risico op een botbreuk nooit onderzocht in een groot cohort met Parkinson (PD), Duchenne en Becker MD patiënten, waarbij het model kan worden aangepast voor een grote variëteit aan gerelateerde aandoeningen en geneesmiddelgebruik en waarbij wordt vergeleken met controle patiënten uit de algehele populatie. Verder is het risico op een botbreuk reeds onderzocht na een beroerte, maar er is weinig bekend over het risico in relatie tot de tijd na de beroerte. Ook voor andere neurologische aandoeningen is

er weinig informatie beschikbaar over het verloop van het risico op een botbreuk in relatie tot de tijd sinds diagnose. Verder zijn er nauwelijks gegevens bekend over een mogelijk toegevoegd risico op een botbreuk in patiënten met neurologische aandoeningen die tevens glucocorticosteroïden (GCs), dopaminerg werkende geneesmiddelen, antidepressiva, antipsychotica, anxiolytica, anticonvulsiva of PPIs gebruiken.

Tenslotte zijn er momenteel verschillende klinische risicoscores beschikbaar om het risico op een botbreuk in te kunnen schatten. Een gebrek aan deze scores is dat ze geen rekening houden met verschillende neurologische aandoeningen. Naar ons weten is er momenteel alleen een specifieke score beschikbaar voor patiënten met de neurologische aandoening multiple sclerosis (MS).

Om deze redenen zijn de doelstellingen van deze thesis:

- het bepalen van het risico op een botbreuk in de algehele populatie in patiënten die gebruik maken van PPIs, antidepressiva of antipsychotica, alsmede het indirect achterhalen van de oorzaak van dit risico op een botbreuk (Hoofdstuk 2)
- het bepalen van het risico op een botbreuk bij patiënten na beroerte en bij mensen met PD, MG, MD, CMT en GBS in vergelijking met controle patiënten uit de algehele populatie (Hoofdstukken 3 en 4)
    - het bepalen van het risico op een botbreuk in relatie tot de tijd sinds diagnose (Hoofdstukken 3 en 4)
    - het bepalen van het risico op een botbreuk bij patiënten met een neurologische aandoening, terwijl ze tegelijkertijd GCs, dopaminerg werkende geneesmiddelen, antidepressiva, antipsychotica, anxiolytica / hypnotica, anticonvulsiva of PPIs gebruiken (Hoofdstukken 3 en 4)

- het ontwikkelen van een model om het risico in te schatten op het krijgen van een botbreuk bij patiënten met neurologische aandoeningen (Hoofdstuk 3.3).

Zowel de Nederlandse PHARMO Record Linkage System (RLS) database en de Clinical Practice Research Datalink (CPRD) database uit het Verenigd Koninkrijk zijn gebruikt om het risico op een botbreuk te bepalen in patiënten, in vergelijking met controle patiënten uit de algehele populatie.

2. Geneesmiddelgebruik en het risico op een botbreuk

In het eerste hoofdstuk (Hoofdstuk 2.1) werd PHARMO RLS gebruikt om het risico te bepalen op een botbreuk van de heup/dijbeen bij gebruikers van PPIs. Huidige gebruikers van PPIs hadden een 1.2 keer verhoogd risico op een botbreuk van heup of dijbeen, leidend tot een adjusted odds ratio (AOR) (een benadering van het relatieve risico) van 1.20 (95% betrouwbaarheidsinterval [BI], 1.04 – 1.40). Het risico op een botbreuk daalde, naarmate de PPIs langer werden gebruikt. De AOR van de eerste 3 maanden was 1.26 (95% BI, 0.94 – 1.68), tussen 3 en 12 maanden 1.31 (95% BI, 0.97 – 1.75), tussen 13 en 36 maanden 1.18 (95% BI, 0.92 – 1.52) en bij gebruik langer dan 36 maanden 1.09 (95% BI, 0.81 – 1.47).

In de daarop volgende studie (Hoofdstuk 2.2) werd PHARMO RLS gebruikt om het risico te bepalen op een botbreuk van de heup of dijbeen bij gebruikers van antidepressiva. Huidige gebruikers van selectieve serotonine heropname-remmers (SSRIs) hadden een risico op een botbreuk van heup of dijbeen van AOR 2.35 (95% BI, 1.94–2.84), gebruikers van tricyclische antidepressiva (TCAs) hadden een AOR van 1.76 (95% BI, 1.45–2.15). Het risico op een botbreuk van de heup of het dijbeen daalde snel na stoppen van de behandeling. Het risico op een botbreuk van heup of dijbeen was hoger voor gebruikers van antidepressiva die een grote remming gaven op de 5-hydroxytryptamine transporter (5-

HTT). Gebruik van antidepressiva met een lage remming van 5-HTT gaf een AOR van 1.64 (95% BI, 1.14–2.35), terwijl een hoger remming van 5-HTT leidde tot een AOR van 2.31 [95% BI, 1.94–2.76].

In hoofdstuk 2.3 werd het risico op een botbreuk van heup of dijbeen beschreven bij gebruikers van antipsychotica, gebruik makend van de PHARMO RLS database. Gebruik van antipsychotica is geassocieerd met een verhoogd risico op een botbreuk van de heup of het dijbeen. Voor huidige gebruikers, AOR 1.68 (95% CI, 1.43 - 1.99) was het risico significant groter dan gebruikers die in het verleden zijn gestopt, AOR 1.33 (95% CI, 1.14 - 1.56). Huidige gebruikers van conventionele antipsychotica hadden een verhoogd risico, AOR 1.76 (95% CI, 1.48 - 2.08), terwijl dit niet het geval was voor gebruikers van atypische antipsychotica, AOR 0.83 (95% CI, 0.42 - 1.65). We hebben geen relatie gevonden tussen het risico op een botbreuk en de dosis.

3: Centrale neurologische aandoeningen en het risico op een botbreuk

In PHARMO RLS werd een verhoogd risico op een botbreuk van de heup of het dijbeen gevonden bij patiënten die een beroerte hadden doorgemaakt voor de index datum (de datum waarop de patiënt met een botbreuk van de heup of het dijbeen binnenkwam in het ziekenhuis), AOR 1.96 (95% BI, 1.65-2.33) (Hoofdstuk 3.1). Het risico op een botbreuk was het hoogst bij patiënten die recentelijk een beroerte hadden gehad (binnen 3 maanden voor de index datum), AOR 3.35 (95% BI, 1.87-5.97) en bij vrouwelijke patiënten, AOR 2.12 (95% BI, 1.73-2.59). Het risico was nog hoger bij patiënten met een leeftijd jonger dan 71 jaar, AOR 5.12 (95% BI, 3.00-8.75). Een beroerte met interne bloedingen leek een iets hoger risico te geven dan een beroerte met blokkade van een of meerdere bloedvaten.

In de CPRD database werden 4,687 incidente PD patiënten geïdentificeerd (Hoofdstuk 3.2). In vergelijking met controle patiënten hadden PD patiënten een statistisch significant verhoogd risico op botbreuken in het algemeen, adjusted hazard ratio (AHR) (een benadering van het relatieve risico) 1.89 (95% BI, 1.67 - 2.14), op osteoporotische botbreuken, AHR 1.99 (95% BI, 1.72 - 2.30) en op heupfracturen, AHR 3.08 (95% BI, 2.43 - 3.89). Het risico op een botbreuk werd hoger indien een PD patiënt een voorgeschiedenis had van botbreuken, van vallen, van een lage body mass index (BMI), van nieraandoeningen en indien de patiënt recent antidepressiva of hoge doseringen antipsychotica gebruikte.

In de daaropvolgende studie in de CPRD database (Hoofdstuk 3.3), identificeerden we 4,411 incidente PD patiënten zonder voorgeschiedenis van behandeling van osteoporose. De data van deze patiënten werd gebruikt voor de ontwikkeling van een model om het risico op een botbreuk te voorspellen. Het 5-jaars risico op het krijgen van een osteoporotische botbreuk en het krijgen van een heupfractuur werd uitgezet tegen de risicoscore. De risicoscores werden hoger bij toenemende leeftijd, vrouwelijk geslacht, een voorgeschiedenis van nieraandoeningen en een voorgeschiedenis van dementie. De C-statistic (een parameter om de interne validiteit van het model te testen) was redelijk voor het voorspellen van osteoporotische botbreuken (0.69) en heupfracturen (0.73) (een C-statistic van 1.00 betekent dat het model alles goed voorspelt).

4: Overige neurologische aandoeningen en het risico op een botbreuk

In de eerste studie gebruikten we de CPRD database (Hoofdstuk 4.1) om bij patiënten met MG het risico te bepalen op een botbreuk in het algemeen, alsmede op het krijgen van een osteoporotische botbreuk. In vergelijking met controle patiënten was er geen statistisch

significant verhoogd risico voor MG patiënten op een botbreuk in het algemeen, AHR 1.11 (95% BI, 0.84 - 1.47) of op het krijgen van osteoporotische botbreuken, AHR 0.98 (95% BI, 0.67 - 1.41). Ook het gebruik van orale glucocorticoïden tot een cumulatieve dosering van meer dan 5 gram prednisolon equivalenten, verhoogde het risico op een osteoporotische botbreuk niet, AHR 0.99 (95% BI, 0.31 – 3.14), in vergelijking met MG patiënten die geen gebruik maakten van glucocorticoïden. Daarentegen was het risico op een botbreuk verhoogd bij MG patiënten welke een voorschrift hadden gekregen voor antidepressiva, AHR 3.27 (95% BI, 1.63 – 6.55), anxiolytica/hypnotica, AHR 2.18 (95% BI, 1.04– 4.57) of anticonvulsiva, AHR 6.88 (95% BI, 2.91 – 16.27).

Een tweede studie in de CPRD database (Hoofdstuk 4.2) liet zien dat het risico op een botbreuk statistisch significant was verhoogd voor MD patiënten, AHR 1.40 (95% BI, 1.14 - 1.71) in vergelijking met controle patiënten. MD patiënten van het vrouwelijk geslacht hadden een verhoogd risico op een botbreuk, AHR 1.78 (95% BI, 1.33 - 2.40). Tevens leidde toenemende leeftijd tot een hoger risico. Indeling op Duchenne MD patiënten gaf geen associatie met botbreuken, terwijl het risico op een botbreuk tweevoudig was verhoogd bij patiënten met myotonic dystrophy, AHR 2.34 (95% BI, 1.56 - 3.51). MD patiënten welke in de afgelopen 6 maanden een voorschrift voor orale glucocorticoïden hadden gekregen, hadden een drievoudig verhoogd risico op een botbreuk ten opzichte van MD patiënten welke geen orale glucocorticoïden waren voorgeschreven.

Bij CMT patiënten (Hoofdstuk 4.3) was het risico op niet-osteoporotische botbreuken statistisch significant verhoogd in de CPRD database, AHR 1.47 (95% BI, 1.01 – 2.14), terwijl het risico op botbreuken in het algemeen, AHR 1.31 (95% BI, 0.98 - 1.74), en osteoporotische botbreuken, AHR 1.10 (95% CI, 0.69 - 1.74), niet statistische significant

was verhoogd in vergelijking met controle patiënten.

In de laatste studie in de CPRD database (Hoofdstuk 4.4) werden geen associaties gevonden tussen patiënten met GBS en botbreuken in het algemeen, AHR 1.01 (95% CI, 0.77- 1.33) of osteoporotische botbreuken, AHR 0.76 (95% CI, 0.50 - 1.17) ten opzichte van controle patiënten. Indelingen op geslacht, leeftijd en tijd sinds de diagnose lieten ook geen associaties zien. Alleen GBS patiënten welke geneesmiddelen tegen de pijn kregen voorgeschreven hadden een tweevoudig verhoogd risico op een botbreuk, AHR 1.97 (95% CI, 1.21- 3.21) ten opzichte van controle patiënten. Daarentegen was het risico op een botbreuk gelijk tussen GBS patiënten en controle patiënten, welke medicatie tegen de pijn kregen voorgeschreven.

5. Discussie

In de algemene discussie werd de associatie tussen het risico op een botbreuk en het gebruik van PPIs, antidepressiva en antipsychotica geëvalueerd. Er werd onderzocht of dit risico werd veroorzaakt door vallen of door zwakke botten. Ook werd de associatie tussen neurologische aandoeningen en het risico op een botbreuk uitgewerkt. Vervolgens werd het risico in patiënten met neurologische aandoeningen bij gelijktijdig gebruik van GCs, dopaminerg werkende geneesmiddelen, antidepressiva, antipsychotica, anxiolytica/hypnotica of anticonvulsiva geëvalueerd. Uiteindelijk volgt een beschrijving van de kracht en de zwakte van de thesis, de klinische boodschap, slotoverwegingen voor de toekomst en de algemene conclusie.

Het hoogste risico op een botbreuk bij patiënten die PPIs gebruiken, was kort na de start van gebruik. Dit ondersteunt de hypothese dat PPIs een effect op botten hebben niet, aangezien een effect op de botten maanden kan duren. Het impliceert daarentegen wel een

val-gerelateerd effect. Echter, omdat er in de literatuur geen associatie tussen PPIs en vallen is beschreven, lijkt het erop dat het verhoogde risico mogelijk verklaard kan worden door een ongecontroleerd effect in het model, zoals selectiebias en/of resterende confounding. Onze resultaten ondersteunen de hypothese dat gebruik van antidepressiva en antipsychotica leidt tot vallen en vervolgens tot een verhoogd risico op botbreuken van de heup en het dijbeen. Verder kan het gebruik van SSRIs en het gebruik van antipsychotica met een hoge affiniteit voor de D2-receptor (leidend tot prolactine-verhoging) mogelijk ook leiden tot zwakte van de botten, hetgeen vervolgens kan leiden tot een verhoogd risico op botbreuken van de heup en het dijbeen.

PD patiënten lijken altijd een verhoogd risico te hebben op een botbreuk sinds hun diagnose, waarbij zowel de aandoening zelf als dopaminerg werkende geneesmiddelen een rol kunnen spelen en waarbij zowel vallen en zwakte van de botten een rol kunnen spelen. Een verhoogd risico op vallen kort na een beroerte, kan het hoogste risico op een botbreuk in de eerste 3 maanden na een beroerte verklaren. Een vermindering van de mineraaldichtheid van het bot in de maanden na de beroerte kan het verhoogde risico verder verklaren. Na verloop van tijd daalt het risico op een botbreuk wel, maar blijft verhoogd. Dit kan verklaard worden door een blijvend verhoogd risico op vallen en een blijvende verzwakking van de botten. Bij MD en CMT patiënten kan het verhoogde risico op een botbreuk kort na diagnose verklaart worden door een verhoogd risico op vallen. Verbeterde controle van de symptomen van deze aandoeningen na diagnose, kan verklaren waarom het risico op een botbreuk daalt na verloop van tijd. Een blijvend verhoogd risico op vallen, alsmede een verhoogd risico op zwakkere botten, kan verklaren waarom er een 1.3 keer verhoogd risico op een botbreuk blijft meer dan een jaar na diagnose van MD. Een jaar na diagnose hadden CMT patiënten geen verhoogd risico meer. MG en GBS lieten geen associatie zien met een verhoogd risico op een botbreuk.

Uit onze bevindingen kan geconcludeerd worden dat patiënten met een diagnose van de neurologische aandoeningen beroerte, PD, MD, CMT en patiënten die momenteel PPIs, antidepressiva en antipsychotica gebruiken, een verhoogd risico hebben op een botbreuk. Mogelijk is de associatie tussen PPIs en een verhoogd risico op een botbreuk echter niet causaal, maar kan deze associatie verklaard worden door een ongecontroleerd effect in het model. Er werd geen verband gezien tussen een verhoogd risico op een botbreuk en een diagnose van MG of GBS. Gebruik van GCs onder MD patiënten kan het risico op een botbreuk verder doen toenemen. Dit is niet het geval voor MG patiënten. Gebruik van antidepressiva bij patiënten met neurologische aandoeningen kan het risico op een botbreuk verder doen toenemen. Voor dopaminerg werkende geneesmiddelen, antipsychotica, anxiolytica/hypnotica en anticonvulsiva is de bijdrage op een verdere toename van het risico niet duidelijk bij patiënten met neurologische aandoeningen. Vallen en zwakke botten zijn belangrijke factoren voor het hebben van een verhoogd risico op een botbreuk. Daarom kunnen programma's ter preventie van vallen en het gebruik van bisfosfonaten om sterkere botten te krijgen, worden aangeraden aan patiënten met de neurologische aandoeningen beroerte, PD, MD en CMT en aan patiënten die antidepressiva en antipsychotica gebruiken. Voor deze patiënten zou een specifieke risicoscore kunnen bijdragen om juist die patiënten te identificeren die een verhoogd risico hebben op een botbreuk.

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* Related to work in this thesis

About the author

Sander Pouwels was born in Eindhoven, The Netherlands, on February 6, 1983. He started with the study Pharmacy at Utrecht University in August 2001. For his Master thesis he conducted the study “Antipsychotic use and the risk of hip/femur fracture: a population-based case-control study” at the Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University. He presented this thesis at a conference in Lissabon (ISPE) in August 2006 and graduated in August 2007 for his Master’s degree.

In June 2007, he started his job as Pharmacist, Pharmaceutical Development at Eurovet Animal Health, Bladel, The Netherlands. His main responsibilities were to write the pharmaceutical part of the dossier for the authorities, to answer questions from the authorities and to assist in pharmaceutical development work. Since August 2011 he obtained the status of Qualified Person for batch release. In May 2012 the company was taken over by Dechra Veterinary Products and in January 2013 he was promoted to Product Development Manager, whereby he is currently responsible for projects from early phase of product development until the regulatory authorization is obtained.

In January 2009, Sander started his part-time PhD at the Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University. In March 2009 he obtained a PhD Studentship grant from the European Calcified Tissue Society for the PhD project “Five-year Fracture risk in patients with Parkinson’s disease and neuromuscular diseases or movement disorders”. He presented his work at several international conferences and obtained two “Young Investigator Awards”.