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Opioids, antiepileptic and anticholinergic drugs and the risk of fractures in patients 65 years of age and older: a prospective population-based study

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Abstract

Background: in men, the concomitant use of two or more benzodiazepines or two or more antipsychotics is associated with an increased risk of fracture(s). Potential associations between the concomitant use of drugs with central nervous system effects and fracture risk have not been studied.

Opioids, antiepileptic and anticholinergic drugs and the risk of fractures in patients

Objective: the purpose was to describe the gender-specific risk of fractures in a population aged 65 years or over associated with the use of an opioid, antiepileptic or anticholinergic drug individually; or, their concomitant use with each other; or the concomitant use of one of these with a psychotropic drug.

Methods: this study was part of a prospective, population-based study performed in Lieto, Finland. Information about fractures in 1,177 subjects (482 men and 695 women) was confirmed with radiology reports.

Results: at 3 years of follow-up, the concomitant use of an opioid with an antipsychotic was associated with an increased risk of fractures in men. During the 6-year follow-up, the concomitant use of an opioid with a benzodiazepine was also related to the risk of fractures for males. No significant associations were found for females.

Conclusion: the concomitant use of an opioid with an antipsychotic, or with a benzodiazepine may increase the risk of fractures in men aged 65 years and older.

Introduction

A growing literature identifies medication-specific increased fracture risks for older patients, but there is a gap in this literature concerning risks associated with drugs used in combination. Although geriatric pharmacotherapy typically focuses on reducing polypharmacy, empiric evidence is needed to indentify priority pharmacotherapy candidates for replacement in patients 65 years of age and older.

The evidence on individual drug risks varies by therapeutic class. Large cohort studies have shown that benzodiazepine use increases the risk of fractures in the aged [1–3], but there are conflicting results [4]. According to case–control and cohort studies, the use of an antidepressant increases fracture risk in old age [5–8]. A positive association between the use of an antipsychotic drug and an increased risk of fractures is reported in case–control studies [9–11], but not in a cohort study [7].

An increased fracture risk has been reported in opioid users in a nursing home [8]. A meta-analysis of the associations between opioid use and the risk of fractures stated that no firm conclusions could be made due to (i) potential publication bias, and (ii) heterogeneity of the studies [12]. The same meta-analysis of 13 studies evaluated the risk between non-barbiturate antiepileptic drug usage and fractures, estimating a risk ratio of 1.54 [12]. Risk increases with the duration of drug exposure [13]. Epilepsy creates an approximately twofold risk of fractures compared with the risk in the general population [14], with the elevated risk appearing to be independent from that due to seizures [15]. No studies were found that examined the potential association between anticholinergic drug uses and fracture risk, but their use has been shown to be a risk factor for falls in older community-dwelling patients [16].

The concomitant use of two or more benzodiazepine and the concomitant use of two or more antipsychotic medications are associated with an increased risk of fractures in men [17]. However, the risk of fractures associated with the concomitant use of antidepressant, opioid, antiepileptic or anticholinergic drug with each other or with a psychotropic drug has not been studied.

The present study examines the gender-specific individual and combined fracture risks associated with opioid, antiepileptic and anticholinergic medication use.

Methods

This study is a part of a longitudinal, population-based study performed in Lieto in South-Western Finland [18]. Baseline data were collected between 1 October 1990 and 31 December 1991. The population consisted of Lieto residents born in 1926 or earlier ($n = 1,283$), of whom 1,196 (93%), 488 men and 708 women, volunteered to participate in the study and the remaining 87 (7%) refused to take part in the study.

Radiological confirmation of fractures occurring during 1990–96 was obtained from the medical records. Data were obtained for 1,177 participants (482 men and 695 women, 98% of the study population), who formed the subjects of this study [19]. The missing 19 participants had moved away from the area during the follow-up and their paper-based medical data (until the year 1994) could not be obtained. Fracture data were collected after baseline examinations in all of the participants. The follow-up period started after the individual's baseline examination date (between 1 October 1990 and 31 December 1991). Participants were followed from that date until the first fracture's occurrence. Subjects with no fractures were followed until the end of the two follow-up periods (31 December 1993 or 31 December 1996) or to their death. During the first three study years, 113 participants (9.6%, 29 men and 84 women) experienced 121 fractures. During the 6 years studied, 178 participants (15.1%, 45 men and 133 women) experienced a total of 221 fractures. Altogether 160 participants (13.6%) died during the first 3 years, and 312 participants (26.5%) died during the 6 years of follow-up.

At baseline, the average age of the study population was 73.2 years, with most (63.6%) living with other person(s) in their own home, fewer (30.9%) living alone at home and one person out of 20 lived in an institution. Regarding ambulation, 81.5% walked independently, 14.2% walked using a device and only 4.3% needed the help of other person(s)

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when walking. Participants used, on average, 2.6 drugs on a regular basis and 0.6 drugs as needed. Most participants had worked in industry (35.8%) or agriculture (38.5%) before retirement. Study methods and baseline data are described more extensively in previous reports [17–19].

Data on the drugs that participants used were collected by a trained nurse through interviews and by checking prescription forms, medication lists, pill boxes and the participants' medical records [18].

Drugs were categorised according to the Anatomical Therapeutic Chemical Classification of Medicines 2000 [20]. Drug groups defined as those having central nervous system (CNS) effects that were used in the analyses included *opioids, antiepileptic drugs, anticholinergic drugs, benzodiazepines and related drugs, antidepressants* and *antipsychotics*. The detailed list of these medications is presented in Table 1. Certain medications were classified into two groups because of their pharmacological properties (for example, amitriptyline as an antidepressant and as an anticholinergic drug). However, for analyses concerning, for example, the concomitant use of an antidepressant with an anticholinergic drug, amitriptyline was classified as being in only one group. Benzodiazepines, antipsychotics and antidepressants were classified as psychotropic drugs.

A large pool of potential risk factors was analysed but only the variables below were determined to be risk factors for fractures [19]. Confounding variables were identified from previous study results that describe predictors of fractures within the same study population [19]. For women, old age, poor handgrip strength (<76 kPa), body mass index (BMI) under 30 kg/m^2 and compression fracture in one or more upper lumbar or thoracic vertebras are independent risk factors of fractures, whereas for men risks are elevated for old age, multiple depressive symptoms and compression fracture in one or more upper lumbar or thoracic vertebras [19]. For example, smoking, rheumatoid arthritis, cardiovascular disease, polypharmacy (six or more prescription drugs) or low cognitive abilities did not prove to be risk factors for fractures [19]. As the confounder data result from the earlier study differed by gender, we preferred performing the analyses separately for men and women in this study.

The control group consisted of participants who did not use any of the target pharmaceuticals (opioid, anticholinergic, antiepileptic or psychotropic drugs) at baseline. Chi-square and Fisher's exact tests were used in comparing baseline variables measured with nominal or ordinal scales. Data on associations between drugs or drug combinations

Table 1. Generic names of medications used in the analyses

Opioids	Antiepileptics	Anticholinergics	Benzodiazepines	Antidepressants	Antipsychotics
Fentanyl, morphine, oxycodone, codeine, ethylmorphine, opium alkaloide with morphine, dextrometorphan, opium derivatives (mucolytics and expectorants)	Phenobarbital, primidone, phenytoin, ethosuximide, clonazepam, carbamazepine, valproic acid	Trihexyphenidyl, biperiden, metixene, procyclidine, orphenadrine, benzatropine, chlorpromazine, levomepromazine, promazine, dixyrazine, fluphenazine, perphenazine, prochlorperazine, periciazine, thioridazine, flupentixol, chlorprotixene, zuclopenthixol, hydroxyzine, clomipramine, trimipramine, amitriptyline, nortriptyline, doxepin, benzilone, glycopyrronium bromide, chlorbenzoamine, belladonna alkaloids, clinidium, oxyphencyclimide, pitofenone, metoclopramide, cisapride, scopolamine, quinidine, disopyramide, ipratropium bromide, methocarbamol, carisoprodol, chlormezanone, chlorzoxazone, baclofen, tizanidine, emepronium, oxybutynin, terodiline, atropine, methylscopolamine, homatropine, tropicamide, phenylpropanolamine, brompheniramine, cyclizine	Diazepam, chlordiazepoxide, medazepam, oxazepam, potassium chlorazepate, clobazam, lorazepam, flurazepam, nitrazepam, flunitrazepam, triazolam, temazepam, midazolam, clonazepam, zopiclone	Imipramine, imipramine oxide, clomipramine, opipramol, trimipramine, dibenzepin, amitriptyline, nortriptyline, doxepine, fluoxetine, citalopram, fluvoxamine, mianserin, trazodone, nialamide	Chlorpromazine, levomepromazine, promazine, dixyrazine, fluphenazine, perphenazine, prochlorperazine, periciazine, thioridazine, haloperidol, melperone, flupentixol, chlorprotixene, zuclopenthixol, pimozide, penfluridol, clozapine, sulpiride, lithium

and fractures were first described by univariate and age-adjusted Poisson regression analyses. In the second phase, drugs or drug combinations showing significant associations with fractures in age-adjusted analyses were analysed with adjustment for the confounding variables. Results were quantified using relative risks (RR) and their 95% confidence intervals (CI). Statistical analyses were performed using the SAS System for Windows version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Ethics review approval and patient consent procedures are described previously [17–19].

Results

Drug use

The concomitant use of the drugs targeted in this study was uncommon (Table 2), and concentrated in a small number of pharmaceuticals and combinations.

The opioids used by participants consisted mainly of dextropropoxyphene and morphine, while the most common antiepileptic drugs were phenytoin and carbamazepine. The most common benzodiazepines for both genders were triazolam, oxazepam and lorazepam. Levomepromazine and perphenazine were the most common antipsychotics, while amitriptyline and doxepine were the most common antidepressants for both genders. The three most common anticholinergic drugs were amitriptyline, levomepromazine and oxybutynin.

Table 2. Medication use at baseline among 1,177 participants by gender. opioids (OP), antiepileptics (AE) and anticholinergic drugs (ACh) and concomitant use of these drugs with each other or with benzodiazepine or a related drug (BZD), antipsychotic (AP) or antidepressant (AD)

Drug or drug combination	Men ($n = 482$) n (%)	Women ($n = 695$) n (%)	P-value*
One OP	11 (2.3)	25 (3.6)	0.23
Two or more OPs	0 (0.0)	1 (0.1)	1.00
OP and ACh[a]	5 (1.0)	9 (1.3)	0.79
OP and AP[a]	3 (0.6)	5 (0.7)	1.00
OP and BZD[a]	5 (1.04)	8 (1.2)	1.00
OP and AD[a]	1 (0.2)	5 (0.7)	0.41
OP and AE[a]	0 (0.0)	1 (0.1)	1.00
One ACh	63 (13.1)	139 (20.0)	0.002
Two or more AChs	6 (1.2)	20 (2.9)	0.07
ACh and AP[a]	24 (5.0)	51 (7.3)	0.12
ACh and BZD[a]	26 (5.4)	62 (8.9)	0.024
ACh and AD[a]	9 (1.9)	23 (3.3)	0.15
ACh and AE[a]	2 (0.4)	4 (0.6)	1.00
One AE	11 (2.3)	10 (1.4)	0.37
Two or more AEs	3 (0.6)	0 (0.0)	0.065
AE and AP[a]	3 (0.6)	1 (0.1)	0.31
AE and BZD[a]	6 (1.2)	3 (0.4)	0.17
AE and AD[a]	3 (0.6)	1 (0.1)	0.31

*Statistical difference between genders.

[a]Persons using concomitantly one drug or more drugs from each subgroup.

Drugs related to fracture risks

Table 3 reports the unadjusted and adjusted RRs of fractures when using drug combinations.

During the men's 3-year follow-up, age-adjusted analyses showed that opioid use together with an antipsychotic or a benzodiazepine was associated with an increased risk of fractures. After adjusting for other confounding factors, the concomitant use of an opioid with an antipsychotic remained a significant risk for fracture(s).

During the men's 6-year follow-up, age-adjusted analyses showed that opioid use and concomitant use of an opioid with an antipsychotic or a benzodiazepine were related to an increased risk of fracture(s). Following adjustment for confounding factors, the concomitant use of an opioid and a benzodiazepine remained significantly associated with the risk of fractures.

During the women's 3-year follow-up, the concomitant use of an antiepileptic drug with a benzodiazepine was related to an increased risk of fractures in the age-adjusted analysis. During the 6-year follow-up, age-adjusted use of an individual antiepileptic and concomitant use of an antiepileptic with a benzodiazepine were both associated with elevated fracture risks. However, no associations were detected after adjustment for the other confounding factors.

Discussion

In men 65 years and older, the concomitant use of an opioid and an antipsychotic drug was related to an increased risk of fractures at 3 years of follow-up. At the 6-year follow-up, the concomitant use of an opioid with a benzodiazepine posed elevated fracture risks.

The strengths of this study are its prospective, population-based design and accurate data about drug use, confounding variables and fractures. Although epidemiological follow-up studies do not confirm causalities, risk relations can be detected and are reported here.

This study has limitations. The number of participants using a specific drug or drug combination(s) and the number of observed fractures were quite small. CIs tended to be wide, which means that the true effect of the drug use related to fracture risk is contained in a wide interval of RRs. This must be considered when making conclusions. Consistent with the conservative approach of identifying exposures as cases, data about drug use were only collected at baseline. It is possible that there were changes in some participants' prescription medication use during the follow-up periods. This would mean that if some participants had started using a medication or stopped using one during the follow-up periods, it could cause errors in the results as the participants would be placed in incorrect groups in the analyses. This potential error is thought to be of little significance, because the relatively small number of fractures is a more limiting factor in this study. The effect of potential changes in medication use on the results is difficult to predict. Collecting data about changes in medication use

Table 3. Relationships between the use of opioids (OP), antiepileptics (AE) or anticholinergic drugs (ACh) or concomitant use of these drugs with each other or with benzodiazepine or related drug (BZD), antipsychotic (AP) or antidepressant (AD) and risk of fractures in men and women

Drug or drug combination	Number of fractures in cases (%)/in controls (%)	Univariate analysis (n = 352–396)		Age-adjusted analysis (n = 352–360)		Adjusted analysis[a] (n = 331–336)	
		RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
Men							
Three-year follow-up							
One OP	2 (18.2)/20 (5.7)	5.0 (1.2–21.2)	0.03	3.1 (0.7–14.4)	0.15	—	—
Two or more AEs	1 (33.3)/20 (5.7)	8.2 (1.1–60.8)	0.04	6.6 (0.9–49.6)	0.07	—	—
OP and AP[b]	1 (33.3)/20 (5.7)	14.6 (2.0–108.7)	0.009	10.2 (1.4–77.2)	0.02	21.1 (1.7–256.9)	0.02
OP and BZD[b]	2 (40.0)/20 (5.7)	12.9 (3.0–55.1)	0.0006	7.2 (1.4–37.2)	0.02	3.8 (0.7–21.1)	0.12
Six-year follow-up							
One OP	3 (27.3)/29 (8.3)	5.8 (1.8–19.1)	0.004	4.5 (1.3–15.6)	0.02	3.2 (0.7–14.9)	0.15
OP and AP[b]	1 (33.3)/29 (8.3)	9.5 (1.3–70.1)	0.03	7.4 (1.0–55.5)	0.05	—	—
OP and BZD[b]	2 (40.0)/29 (8.3)	17.0 (4.1–71.4)	0.0001	12.0 (2.5–58.4)	0.002	5.0 (1.0–25.2)	0.05
Drug or drug combination	Number of fractures in cases (%)/in controls (%)	Univariate analysis (n = 391–398)		Age-adjusted analysis (n = 391–398)		Adjusted analysis[c] (n = 369–375)	
		RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
Women							
Three-year follow-up							
AE and BZD[b]	2 (66.7)/46 (11.9)	11.3 (2.8–46.7)	0.0008	7.5 (1.8–32.4)	0.007	6.3 (0.7–52.8)	0.09
Six-year follow-up							
One AE	4 (40.0)/76 (19.6)	3.5 (1.3–9.7)	0.01	3.0 (1.1–8.2)	0.03	2.7 (0.8–9.2)	0.1
AE and BZD[b]	2 (66.7)/76 (19.6)	13.2 (3.2–53.6)	0.0003	9.0 (2.1–38.1)	0.003	5.8 (0.7–45.9)	0.1

P-value, statistical significance; RR, relative risk; CI, confidence interval.
[a]Adjusted for age, amount of depressive symptoms and a compression fracture in one or more upper lumbar or thoracic vertebras at baseline (men).
[b]Persons using concomitantly one drug or more drugs from each subgroup.
[c]Adjusted for age, hand grip strength, body mass index (BMI) and a compression fracture in one or more upper lumbar or thoracic vertebras at baseline (women).

during the follow-up periods would have been difficult and more unreliable in comparison with baseline data.

An increased non-spine fracture risk has been reported in women who use narcotics (mainly propoxyphene, codeine, hydrocodone and oxycodone) [4], as has an association between opioid analgesic (individual drugs not specified in the paper) use and the risk of fractures for nursing home residents [8]. The authors of a 2007 meta-analysis of the associations between opioid use and the fracture risks could make no firm conclusions due to (i) potential publication bias and (ii) heterogeneity of the studies [12]. The opioids used by the men in our study consisted mainly of dextropropoxyphene or morphine. Two previous studies that examined propoxyphene use have demonstrated a twofold risk of fractures in propoxyphene users compared with non-users [21, 22]. Morphine has been associated with an increased fracture risk also [23]. Our results support and extend these findings.

Two previous studies examining the use of one or more antiepileptics in older women did not find an elevated fracture risk [1, 4]. These results are consistent with our findings for phenytoin and carbamazepine. In two case–control studies, both of these antiepileptics had an elevated risk of fractures [24, 25]. Subjects in these earlier studies were younger than those in our study, which may partially explain the difference in findings.

No study about anticholinergic drug use and the risk of fractures was found in our literature search. Thus, we are unable to compare our results with this drug category to the previous findings.

Previous studies demonstrate increased fracture risks for benzodiazepine users [1–4, 17], but our results did not support those findings. This contrast may be due to different benzodiazepine use profiles between our study and the other studies. In our study, triazolam, oxazepam and lorazepam were the most common benzodiazepines used [17], and this differs from those in the other studies [1–4]. In our earlier study from the same material, the use of two or more benzodiazepines simultaneously was associated with fractures [17]. This could suggest that using two benzodiazepines creates a more consistent risk of fractures than does use of a benzodiazepine combined with other drugs affecting the central nervous system.

Two separate mechanisms are hypothesised for the increased fracture risk related to opioid or antiepileptic drug use. A drug's adverse effects, such as causing balance disturbances or dizziness, can increase the propensity for an individual to fall [26–28] or the drug may directly cause demineralisation, weakening the bone structure [28, 29]. For example, opioids may decrease bone mineral density by impairing the production of endogenous sex steroids [28]. It has been suggested that antiepileptics can increase the catabolism of vitamin D and parathyroid hormone [29]. A duration–response relationship has been detected for drugs with CNS effects, indicating that the longer a medication is used, the lower is the patient's bone mineral density [27]. Therefore, epilepsy itself may be only one of the possible explanations for higher fracture rates in antiepileptic drug users [13].

The gender difference in our results is surprising. Differences between men and women have not been described in previous studies that have examined opioid use [23] or central nervous system active medications [4] and fracture risk.

In our study, no major differences in the use of targeted study drugs were detected between men and women, excluding anticholinergic drugs. Men and women used similar preparations of opioids (dextropropoxyphene, codeine or morphine) and antiepileptic drugs (phenytoin or carbamazepine), and the proportions of users were similar for both genders. These findings indicate that differences in drug use are unlikely to be an explanation for the gender differences.

Unfortunately, the baseline data did not contain the amount of alcohol consumed or bone mineral density. In Finland, older men tend to consume more alcohol than women, but the consumption decreases with advancing age. Finnish alcohol consumption to the point of drunkenness is more culturally accepted in men. Men are thus more prone to falls (leading to fractures) due to alcohol use than are women. Also, diagnosing and treating osteoporosis are less thoroughly performed in men [30]. Collectively, these factors may have contributed to our results, which suggest that men are at a higher fracture risk when there is concomitant use of an opioid and an antipsychotic or a benzodiazepine.

In conclusion, careful prescribing practices should be followed when central nervous system-acting medications are used in combination in older patients. Patient's medication use should be critically assessed when evaluating individual fracture risk.

Key points

- Previous studies have shown that the concomitant use of two or more benzodiazepines or two or more antipsychotics is associated with an increased risk of fractures in men.
- Associations between the concomitant use of drugs with central nervous system effects and fracture risk have not been studied previously.
- Our results suggest that men who concomitantly use an opioid and an antipsychotic or a benzodiazepine have an increased risk of fracture(s).
- In our study, women who concomitantly use drugs affecting the central nervous system did not have an elevated risk for fracture(s).

Conflicts of interest

None declared.

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Which part of the Quick mild cognitive impairment screen (Q*mci*) discriminates between normal cognition, mild cognitive impairment and dementia?

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Abstract

Introduction: the Q*mci* is a sensitive and specific test to differentiate between normal cognition (NC), mild cognitive impairment (MCI) and dementia. We compared the sensitivity and specificity of the subtests of the Q*mci* to determine which best discriminated NC, MCI and dementia.
Objective: the objective was to determine the contribution each subtest of the Q*mci* makes, to its sensitivity and specificity in differentiating MCI from NC and dementia, to refine and shorten the instrument.

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