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THE USE OF NERVOUS SYSTEM DRUGS AND THE RISK OF FRACTURES IN OLD ADULTS

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To Svartzonker and Kopeli lures

ABSTRACT

Janne Nurminen

THE USE OF NERVOUS SYSTEM DRUGS AND THE RISK OF FRACTURES IN OLD ADULTS

The department of General Practice, Institute of Clinical Medicine, Faculty of Medicine, University of Turku, Turku, Finland. Annales Universitatis Turkuensis, Medica – Odontologica Series D 1114, 2014, Turku, Finland.

The use of nervous system drugs is common among adults aged 65 years and older. The use of these drugs is most frequent among adults living in long-term care institutions. Literature on adverse effects of nervous system drugs is rich, and indicates that these medications are associated with the risk of fractures. However, studies concerning concomitant use of nervous system drugs and fractures are rare.

This study concluded that the concomitant use of nervous system drugs was very common among patients living in five long-term care wards of Pori City Hospital (n=154). Every third patient used at least three nervous system drugs concomitantly, and the corresponding percentage was 53 when medications taken when needed were also taken into account. Indications of inappropriate drug use were found when patients' medications, cognitive and physical abilities, and diagnoses were compared to evaluate the appropriateness of prescribing practices.

The material for fracture studies was obtained from the longitudinal and population-based Lieto Study comprising 1,177 participants 65 years of age and older. The data on medication use and fractures was used to analyze the associations between nervous system drugs and fractures. The concomitant use of two or more benzodiazepines or two or more antipsychotics was associated with an increased risk of fractures in men. Furthermore, the use of an opioid with a benzodiazepine or an antipsychotic increased the risk of fractures in men. These associations were not detected in women.

The sample for the benzodiazepine withdrawal study consisted of 89 participants 55 years of age and older participating in the Satauni Study. The study lasted six months. The participants received psychological support while the benzodiazepine dose was gradually lowered over a one month time period. The participants were frequently tested for handgrip strength and balance. The study resulted in the finding that the handgrip strength of women who had withdrawn improved significantly in comparison to non-withdrawers. The associations were weaker for men. During the six–month follow-up period, no significant change in balance test results associated with benzodiazepine withdrawal was detected.

Fractures often lead to serious consequences in late life; therefore, fracture prevention should be a top priority in senior health care policies. The role of concomitant use of nervous system drugs should be addressed in fracture prevention programs.

Keywords: Old adults, nervous system drugs, concomitant use of medications, fractures, balance, muscle strength, medication withdrawal, population-based research, follow-up, risk factors.

TIIVISTELMÄ

Janne Nurminen

HERMOSTOON VAIKUTTAVIEN LÄÄKKEIDEN KÄYTTÖ JA NIIDEN YHTEYDET MURTUMAN RISKIIN IÄKKÄÄSSÄ VÄESTÖSSÄ

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Hermostoon vaikuttavien lääkkeiden käyttö on yleistä iäkkäässä väestössä. Erityisen yleistä käyttö on pitkäaikaisessa laitoshoidossa asuvilla iäkkäillä. Hermostoon vaikuttavien lääkkeiden haittavaikutuksia on tutkittu paljon, ja useat hermostoon vaikuttavat lääkeaineryhmät on tunnistettu murtumien riskitekijöiksi. Aikaisemmin ei ole kuitenkaan tutkittu usean hermostoon vaikuttavan lääkkeen yhteiskäytön yhteyksiä murtuman riskiin 65 vuotta täyttäneillä.

Väitöskirjatutkimuksessa havaittiin, että usean hermostoon vaikuttavan lääkeaineen yhtäaikainen käyttö oli hyvin yleistä Porin kaupunginsairaalan viidellä pitkäaikaisen laitoshoidon osastolla (n = 154) vuosien 2004 ja 2005 vaihteessa. Kolmasosa tutkituista käytti säännöllisesti kolmea tai useampaa hermostoon vaikuttavaa lääkettä samanaikaisesti. Kun huomioitiin myös tarvittaessa otettavat lääkkeet, vastaava luku oli 53 %. Tutkimuksessa havaittiin myös viitteitä lääkkeiden epäasianmukaisesta käytöstä, kun potilaiden käyttämiä lääkkeitä verrattiin heidän kognitiiviseen ja fyysiseen suorituskyynsä sekä asetettuihin diagnooseihin.

Liedon kunnassa 1990-luvulla toteutettuun väestöpohjaiseen Liedon Iäkkäät -seurantatutkimukseen osallistui 1177 lietolaista 65 vuotta täyttänyttä. Lääkitystietoja sekä seuranta-aikana tapahtuneita murtumia analysoimalla havaittiin, että kahden tai useamman bentsodiatsepiinin sekä kahden tai useamman psykoosilääkkeen käyttö oli yhteydessä murtuman riskiin 65 vuotta täyttäneillä miehillä. Opioidin ja psykoosilääkkeen yhteiskäyttö sekä opioidin ja bentsodiatsepiinin yhteiskäyttö oli yhteydessä iäkkäiden miesten murtuman riskiin. Naisilla vastaavia tilastollisesti merkitseviä yhteyksiä ei havaittu.

Väitöskirjatutkimuksen uusin osa-aineisto perustui Porissa vuosina 2009–2010 toteutetun Satauni-tutkimuksen aineistoon. Tutkimuksessa osoitettiin 89 potilaan aineistossa, että hallittu, yhden kuukauden aikana lääkärin ja hoitajan tuella toteutettu bentsodiatsepiinivieroitus paransi merkitsevästi 55 vuotta täyttäneiden naisten käden puristusvoimaa kuuden kuukauden seuranta-aikana. Vastaavaa yhteyttä ei havaittu miehillä. Bentsodiatsepiinivieroituksella ei ollut yhteyttä osallistujien tasapainotestin tulosten paranemiseen kuuden kuukauden seuranta-aikana.

Murtumilla on vakavia seurauksia sekä yksilötasolla että yhteiskunnallisesti iäkkäässä väestössä. Murtumien ehkäisy on hyvin tärkeää. Siinä tulee kiinnittää huomiota potilaan käyttämään lääkitykseen ja arvioida erityisesti usean hermostoon vaikuttavan lääkkeen yhteiskäytön tarpeellisuutta.

Avainsanat: Ikääntyvät ja iäkkäät henkilöt, hermostoon vaikuttavat lääkkeet, usean lääkkeen yhtäaikainen käyttö, murtumat, tasapaino, lihasvoima, lääkevieroitus, väestötutkimus, seurantatutkimus, riskitekijät.

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ABBREVIATIONS

AD	Alzheimer's disease
ADE	Adverse drug effect
ADL	Activities of Daily Living
ADS	Anticholinergic Drug Scale
ARS	Anticholinergic Risk Scale
ATC	Anatomical Therapeutic Chemical (classification system)
BBS-9	Short Berg's Balance Scale
BZD	Benzodiazepine and related drug
CNS	Central nervous system
DBI	Drug Burden Index
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
GABA	Gamma-aminobutyric acid
HR	Hazard ratio
ICD	International Classification of Diseases
MAI	Medication Appropriateness Index
MMSE	Mini-Mental State Examination
PIM	Potentially inappropriate medication
PIP	Potentially inappropriate prescription
OR	Odds ratio
RR	Relative risk
SAA	Serum Anticholinergic Activity
SD	Standard deviation
SNRI	Selective norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
START	Screening Tool to Alert Doctors to the Right Treatment
STOPP	Screening Tool to Older Person's Prescriptions
TCA	Tricyclic antidepressant
US	United States
UK	United Kingdom
WHO	The World Health Organization
95%CI	95% confidence interval

LIST OF ORIGINAL PUBLICATIONS

I Nurminen J, Puustinen J, Kukola M, Kivelä SL. The use of chemical restraints for older long-term hospital patients: a case report from Finland. Journal of Elder Abuse and Neglect 2009;21:89–104.

II Nurminen J, Puustinen J, Piirtola M, Vahlberg T, Kivelä SL. Psychotropic drugs and the risk of fractures in old age: a prospective population-based study. BMC Public Health 2010;10:396.

III Nurminen J, Puustinen J, Piirtola M, Vahlberg T, Lyles A, Kivelä SL. Opioids, antiepileptic and anticholinergic drugs and the risk of fractures in patients 65 years of age and older: a prospective population-based study. Age & Ageing 2013;42:318–24.

IV Nurminen J, Puustinen J, Lähteenmäki R, Vahlberg T, Lyles A, Neuvonen PJ, Partinen M, Räihä I, Kivelä SL. Handgrip strength and balance in older adults following withdrawal from long-term use of temazepam, zopiclone or zolpidem as hypnotics. Manuscript.

These articles are referred to in the text by Roman numerals I–IV.

1. INTRODUCTION

The population of adults aged 65 years and older is growing both in western and in developing countries. At the same time, the number of medications used by seniors has also increased (Lernfelt et al. 2003). Greater medication use predisposes old adults to adverse effects due to drug interactions and accumulating harmful effects (Chrischilles et al. 1992). The aging human body undergoes physiological changes which further predispose an aged person to adverse medication effects (Zhan et al. 2001). The process of normal aging and simultaneous interacting morbidities reduce an individuals' capacity to tolerate the adverse drug effects (ADEs). These population changes and substantial variation between individuals result in a complex network of overlapping and interacting factors affecting an individual's health.

The adverse effects of nervous system drugs have received intensive attention. One characteristic of these ADEs is their potential to be serious, which include excess sedation, dizziness, confusion and cognitive disturbances, for example (Young-McCoughan & Miaskowski 2001; Bourin & Briley 2004; Glass et al. 2005; Landi et al. 2007). As a consequence of these ADEs, an older adult may experience a fall which in turn leads to a fracture that may then require in-hospital treatment, and/or precipitate decline in cognitive or physical capacity. Therefore, investigation into and detection of potential ADEs, particularly central nervous system (CNS) actions, and promoting safer prescribing practices and to prevent these avoidable adverse effects are critically important.

The risk of falls leading to injury increases with age (Rubenstein & Josephson 2002), even in the absence of medications. Fractures are a major and growing health problem in old adults (Cumming et al. 1997; Gullberg et al. 1997). They lower the health-related quality of life, cause the loss of independent living and can lead to permanent immobility (Wolinsky et al. 1997; Borgström et al. 2006). Finally, fractures increase the risk of mortality (Bliuc et al. 2009). From the viewpoint of society, fractures create substantial costs and decrements in patients' quality-of-life (Chrischilles et al. 1994; Borgström et al. 2006).

There are findings that practically all groups of nervous system drugs increase the risk of fractures (Takkouche et al. 2007). This evidence, however, is inconsistent (Takkouche et al. 2007). The relatively extensive evidence connects the use of benzodiazepines, antidepressants and antiepileptic drugs to increased fracture risk (Takkouche et al. 2007). Correspondingly, antipsychotics and opioid analgesics have been associated with fractures, but the data is not as comprehensive. To date, no wide-ranging data exist on anticholinergic drugs as a risk factor for fractures, and the findings on this association are sparse (Golden et al. 2010). By and large there is a lack of high quality studies that include potential confounding factors (Takkouche et al. 2007). Furthermore, the literature is mostly silent regarding data on associations between concomitant use of nervous system drugs and health outcomes, such as fracture risk.

Consequently, it is important to understand the mechanism behind the increased facture risk related to the use of nervous system drugs. There is growing evidence that antidepressants and antiepileptic drugs affect bone structure directly (Ensrud et al. 2004; Diem et al. 2007). The other widely accepted explanatory model is that nervous system drugs cause sedation, balance disturbances and muscle weakness leading to falls and, further, fractures. Gaining detailed information on this pathway is essential in order to identify effective actions to prevent fractures.

2. DEFINITIONS

2.1 Definitions of drugs

Benzodiazepines and related drugs: In this academic thesis the term "benzodiazepines and related drugs" refers to the Anatomical Therapeutic Chemical (ATC) classification index classes N05BA (anxiolytics; benzodiazepine derivatives), N05CD (hypnotics and sedatives; benzodiazepine derivatives), N05CF (benzodiazepine related drugs) and, when applicable, N05CX/N06C (benzodiazepines in combinations) (WHO 2012). In this thesis the term "benzodiazepines" is used to replace the term "benzodiazepines and related drugs" unless otherwise stated.

Antidepressants: Antidepressants are included in drug classes N06A (antidepressants) and N06CA (antidepressants in combinations) according to their ATC-classification (WHO 2012).

Antipsychotics: Antipsychotics are included in ATC-drug classes N05A (antipsychotics) and, when applicable, N06C (antipsychotics in combinations) (WHO 2012).

Opioid analgesics: Opioid analgesics are included in drug classes N02A (opioids) and R05DA (codeine; cough and cold preparations) (WHO 2012).

Antiepileptic drugs: Antiepileptic drugs are included in ATC-drug class N03A (WHO 2102).

Anticholinergic drugs: Anticholinergic drugs cannot be categorized under one ATC-class, since medicinal substances having anticholinergic properties are used widely to treat diseases and conditions of several separate organ systems. In addition, many drugs possess anticholinergic properties as their adverse effects, and, thus, are classified according to their favorable effect. Anticholinergic drugs are discussed more comprehensively in the third chapter of this academic thesis. Drugs defined as anticholinergic drugs (and used in the analyses) are presented in detail in chapter five.

Psychotropic drugs: In this thesis, the marketed psychotropic drugs being considered include benzodiazepines, antidepressants and antipsychotics. Individual medical substances used in the analyses of the original studies are defined in chapter five.

2.2 Polypharmacy

Polypharmacy is defined as the concomitant use of five or more medications (Gnjigic et al. 2012a). It is common among old adults (Thomas et al. 1999; Chen et al. 2001). Polypharmacy is an important concept, since it is associated with advancing age, increased drug-drug interactions, frequent use of non-prescribed medications, living in an institution, poor self-managed health, and medication-related adverse effects for frailty, disability, mortality and falls (Thomas et al. 1999; Chen et al. 2001; Gnjidic et al. 2012a; Doan et al. 2013). Importantly, considering the field of this thesis, the use of psychotropic drugs is more extensive in old adults on a polypharmacy regimen

(Jyrkkä et al. 2009a). Further, the concomitant use of psychotropic drugs is common among old adults (Pitkälä et al. 2004), and the prevalence of psychotropic drug use has increased (Ruths et al. 2012).

2.3 Adverse drug effect

An adverse drug effect (ADE) can be defined as "a harmful or significantly unpleasant effect caused by a drug at doses intended for therapeutic effect (or prophylaxis or diagnosis) which warrants reduction of dose or withdrawal of the drug and/or foretells hazard from future administration" (Laurence & Carpenter 1998). Here terms "adverse effect" and "adverse reaction" can be considered as synonyms, except that an adverse effect is seen from the point of view of the drug whereas an adverse reaction is seen from the point of view of the patient (Edwards & Aronson 2000). Both of these must be distinguished from "adverse event", which is an adverse happening that occurs during exposure to a drug without any assumption being made about its cause.

2.4 Potentially inappropriate medications

Potentially inappropriate medications or potentially inappropriate prescriptions are medications with no clear evidence-based indication, ones that pose a high risk of adverse drug effects or ones that are not cost-effective (O'Mahony et al. 2008).

2.5 Falls and fractures

A fall is defined as "an unexpected event in which the person comes to rest on the ground, floor, or lower level" (Lamb et al. 2005). A fracture is a complete or incomplete break in a bone resulting from the application of excessive force (Moehring & Greenspan 2000). A normal bone does not fracture without external force. However, underlying bone disease, e.g. osteoporosis or tumor, can weaken the bone leading to a fracture after lesser trauma (Moehring & Greenspan 2000).

2.6 Old adults

In this academic thesis the term "old adults" refers to individuals over 65 years of age unless otherwise stated. In medical contexts, 65 years of age and over is usually used to identify a person as aged. Within that range, the subgroup from age 65 years to 74 years is referred as young-olds (Evans 1992), while the term old-old is used when a person is between 75 to 84 years of age, and oldest-old when the age is over 85 years (Evans 1992).

2.7 Place of residence

In this thesis, the concept "place of residence" is divided into three categories: community-dwelling older adults, nursing home residents and hospital care patients. Community-dwelling old adults are those who do not require continuous assistance in activities of daily living. Nursing home residents include individuals who require continuous assistance in activities of daily living, but who do not require in-hospital treatment. Hospital care patients need specialized around-the-clock treatment, monitoring and/or assistance. In this thesis, these three terms are used as general concepts to cover the terminology of old adults' place of residence.

3. REVIEW OF THE LITERATURE

3.1 Aging individuals and age-related changes in pharmacokinetics and pharmacodynamics

Aging is a complex process consisting of several interacting and overlapping events. The genome forms the unchangeable background of the aging process, and science has just begun to understand its influence on aging. Past diseases and injuries are cumulative, leaving lifetime influences. Existing diseases disturb normal body functions and homeostasis, and the treatment of these diseases may itself produce complicating adverse effects (O´Neill 1997). These morbidities include both physical and mental diseases and disorders. Furthermore, personal lifestyle, including for example habits of alcohol use and smoking as well as the degree of physical activity shapes the aging process. An individual's nutrition both at present and in the past is an additional important factor. This complicated network of concurrent factors results in considerable variation in health condition(s) between individuals in advancing age (Cho et al. 2011).

Many of the factors mentioned above can be altered and influenced by an individual. However, normal age-related changes in the body continue to occur over time, which cannot be completely prevented (Bennett et al. 2012). These changes are mainly due to retardation of the cell renewal cycle in body tissues (Ju et al. 2011; Bennett et al. 2012; Paillard 2013).

Normal aging alters drug metabolism, both pharmacokinetic and pharmacodynamic. Pharmacokinetic changes include alterations in absorption, division, metabolism and elimination of the drugs (Bennett et al. 2012). Absorption of orally administered drugs from the gastrointestinal tract generally remains unchanged, regardless of the small decrease in gastrointestinal blood flow and motility (Bennett et al 2012). In addition, reduced secretion of saliva complicates swallowing drugs (van Eijk et al. 2013).

Once ingested and absorbed, drug distribution is altered because of change in body composition. Lean body mass is lesser in old adults compared to younger persons. This results in greater concentration of drugs per kilogram when using standard adult doses (Bennett et al. 2012). The proportion of body fat increases and total body water decreases. This results in a higher volume of distribution for lipid-soluble drugs and a lower volume of distribution for water-soluble drugs, increasing the risk of accumulation of lipid-soluble drugs and rising the concentration for water-soluble drugs, respectively (Mangoni & Jackson 2004).

Concentration of serum albumin, an important binding protein of many drugs, may be diminished due to malnutrition or acute illness. This can result in higher proportion of pharmacologically active drug in serum (Bennett et al. 2012). Hepatic metabolism, including cytochrome P450 oxidation, decreases, and this may increase the

concentration of drugs which undergo high first-pass metabolism (Mangoni & Jackson 2004).

One of the most clinically significant pharmacokinetic age-related changes is the reduction in renal elimination of drugs due to a decline in glomerular filtration and tubular secretion (Turnheim 2004). As a result, the clearance of great number of drugs is diminished (Mangoni & Jackson 2004). This phenomenon requires assessment of kidney function before prescribing drugs to old adults (Laroche et al. 2006), and periodic reassessments once started.

Pharmacodynamic changes include, for example, variation in drug sensitivity, affinity and receptor binding (Bennett et al. 2012). These changes may dampen the favorable effects of the drugs; alter the adverse effects, or both.

Pharmacokinetic, pharmacodynamic and individual conditions predispose old adults to ADEs (Aronson 2007). All of the age-related changes, difficulties in maintaining physiological homeostasis and substantial variation between individual old adults generally eliminate old adults from primary drug research studies in order to control for confounding factors and avoid bias (McLachlan et al. 2009). The fact that an aging population is consuming the majority of prescribed drugs requires the opposite, that research specifically assesses drug effects in the aged. This is crucial in order to determine a drug's effectiveness and to recognize potential adverse effects appearing in vulnerable, high using seniors.

3.2 Characteristics of nervous system drugs

3.2.1 Benzodiazepines and related drugs

Benzodiazepines and related drugs act by powering the activity of the depressive neurotransmitter gamma-aminobutyric acid (GABA) (Roy-Byrne 2005), which is one of the most important mediators in the CNS synapses. Together with the excitatory neurotransmitter glutamate, GABA regulates the neuronal excitatory state of the CNS (Wecker et al. 2010).

Rise in GABA activity results in anxiolytic, sedative, hypnotic, amnestic and anticonvulsant actions (Roy-Byrne 2005). Further, the ADEs related to benzodiazepine use are also thought to mediate through GABA-receptors located in the cerebral cortex and cerebellum, for example (Gudex 1991). The adverse effects of benzodiazepine use are similar to its favorable effects, but excessive benzodiazepine impact may produce inappropriate sedation leading to unfavorable outcomes (Bennett et al. 2012). Thus, benzodiazepine use is related to increased risk of falls, fractures and car accidents (Woolcott et al. 2009; Finkle et al. 2011; Meuleners et al. 2011). Further, benzodiazepine use is associated with decreases in cognitive performance (Glass et al. 2005).

Benzodiazepine related drugs (zopiclone, zolpidem and zaleplon) differ from the original benzodiazepines in chemical structure (Wecker et al. 2010). They bear, however, relatively similar mechanisms of action compared to the original benzodiazepines, apart from possessing clearly shorter elimination half-live than the

originals (Wecker et al. 2010). The original benzodiazepines can be further classified into long-acting, intermediate-acting and short-acting substances. This classification is based on the half-lives ($t_{½}$) of these drugs, and, thus, long-acting benzodiazepines possess a longer half-life than intermediate- and short-acting agents. Long-acting benzodiazepines ($t_{½}$ >48 hours) include chlordiazepoxide, chlorazepate, diazepam, flurazepam, nitrazepam, flunitrazepam, medazepam, clobazam, clonazepam (Wecker et al. 2010). Intermediate-acting benzodiazepines ($t_{½}$ 10–36 hours) include alprazolam, lorazepam, temazepam, whereas short-acting ($t_{½}$ <10 hours) comprise oxazepam, triazolam, midazolam (Wecker et al. 2010). The definition and measurements of benzodiazepine half-lives are not absolute epithets, and also normal aging, diseases and other drugs can affect benzodiazepine half-lives of an individiual old adult (Wecker et al. 2010; Bennett et al. 2012).

3.2.2 Antidepressants

Antidepressants produce their effect via inhibiting serotonin and norepinephrine reuptake in neuronal synapses (Bennett et al. 2012). The effects are highlighted by whether the individual drug is selective to serotonin and/or norepinephrine or not. TCAs also inhibit peripheral muscarinic, central nervous system histamine and α-adrenergic, receptors giving rise to ADEs (Bennett et al. 2012). These include dry mouth, blurred vision, nausea, sedation, constipation, urine retention and possible cardiac arrhythmia, for example (Bennett et al. 2012). More selective inhibitors, like SSRIs, possess fewer or no antimuscarinic (anticholinergic) properties, which is reflected in fewer anticholinergic side-effects (Wecker et al. 2010). SSRIs, however, produce more adverse effects affecting the gastrointestinal tract, and this is mediated by serotonin (Wecker et al. 2010). In addition, recent studies have shown that SSRIs may lower bone mineral density by affecting serotonin receptors located in the bone (Cauley et al. 2005; Warden et al. 2005; Diem et al. 2007). This effect seems to be more pronounced with SSRIs than TCAs (Diem et al. 2007).

Newer antidepressants, like selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI), were introduced and widely promoted in the 1990s, and as the number of medications taken by old adults has increased, antidepressants in particular are used more frequently (Linjakumpu et al. 2002a and 2002b). The increase has a number of causes. Diagnosing depression in late life may have improved during recent decades. On the other hand, the new antidepressants' march in to the market has changed prescribing practices (Mamdani et al. 2000). However, to date they have not totally replaced traditional tricyclic antidepressants (TCA). On the contrary, the indications for TCA use have widened as they have been noticed to relieve neuropathic pain, insomnia and symptoms of menopause and irritable bowel syndrome, for example (Wecker et al. 2010; Bennett et al. 2012).

Excessive dosing of antidepressants and/or other serotonergic drugs can result in serotonin syndrome which is associated with considerable mortality when untreated (Bennett et al. 2012).

Further, distinctions between different antidepressant classes have been proposed considering the differential risk of adverse outcomes. In a cohort study of depressed geriatric patients from the United Kingdom TCAs were established as safer than SSRIs or other antidepressants (Coupland et al. 2011). However, a contradictory previous systematic review had concluded that the efficacy of SSRIs and TCAs were equivalent but TCAs users discontinued their medications more often than the users of SSRIs due to ADEs (Mottram et al. 2006).

3.2.3 Antipsychotics

Antipsychotics are usually divided into typical and atypical subclasses (Wecker et al. 2010; Bennett et al. 2012). Typical antipsychotics include chlorpromazine, levomepromazine, promazine, dixyrazine, fluphenazine, perphenazine, prochlorperazine, periciazine, thioridazine, haloperidol, melperone, flupentixol, chlorprotixene, zuclopenthixol, pimozide, penfluridol and sulpiride (Bennett et al. 2012). Atypical antipsychotics comprise olanzapine, clozapine, quetiapine, risperidone, ziprasidone, amisulpiride, zotepine, sertindole and aripiprazole (Bennett et al. 2012).

The first typical antipsychotics were introduced in 1950. They can be subdivided according to their chemical structure (WHO 2012). Typical antipsychotics are thought to mediate their effect mostly via dopamine antagonism (Bennett et al. 2012). However, they also bear anticholinergic, prolactin-releasing, histaminergic and α-adrenergic properties. Based on these affinities, common adverse effects of typical antipsychotics include extrapyramidal symptoms, sedation, weight gain, orthostatic hypotension and anticholinergic symptoms (Bennett et al. 2012).

Atypical antipsychotics are a more heterogeneous group of medications compared to typical antipsychotics and no standard classifications system exists (Bennett et al. 2012). They were introduced in 1970 and vary from typical antipsychotics by their mechanism of action and other pharmacologic properties (Wecker et al. 2010). Their actions are, thus far, not completely understood. They have evident advantages compared to typical antipsychotics' adverse effect profile as they generate less extrapyramidal symptoms, for example (Wecker et al. 2010). However, new concerns connect atypical antipsychotics to glucose dysregulation and dyslipidemia (Coccurello & Moles 2010; Teff et al. 2013).

3.2.4 Opioid analgesics

Opioid analgesics are a relatively homogenous group of analgesics that achieve their therapeutic effect by acting on the central nervous system (Wecker et al. 2010). This mechanism differs from other analgesics, which act peripherally. Although the majority of opioid receptors (denoted as μ, δ and κ) are located in the CNS, they can, however, also be found in peripheral tissues (Wecker et al. 2010). In most nerve cells, opioid analgesics produce hyperpolarization, prevent cell excitation and block the release of substance P in presynaptic cells (Wecker et al. 2010).

Opioid analgesics are used to treat moderate to severe pain. The favorable effect of opioid analgesics is based on relief from pain but also on emotional relaxation or anxiolytic actions (Bennett et al. 2012). The adverse effects of opioid analgesics; suppression of respiration, neuroendocrine changes, nausea, sedation, miosis, constipation and pressure rise of the gall ducts, are mediated through the same receptors as the positive effects (Wecker et al. 2010). However, the appearances of opioid tolerance and dependency have become major problems for society.

Opioid agonists can be divided into four groups according to their chemical structure, but in clinical practice the division by weak, intermediate and strong opioid analgesics is more useful (Bennett et al. 2012). Codeine and tramadol are classified as weak opioids and buprenorphine as an intermediate opioid (Bennett et al. 2012). At the high end, morphine, oxycodone and fentanyl are classified as strong opioids (Bennett et al. 2012).

The use of opioids holds of particular interest because both insufficient treatment of pain and the opioid treatment itself can expose old adults to adverse outcomes. Regardless of strong evidence concerning opioids in the treatment of various pain conditions, evidence for its long-term effectiveness for persistent noncancerous pain is lacking (American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons 2009).

3.2.5 Antiepileptic drugs

The therapeutic group of antiepileptic drugs includes medications with different pharmacokinetic and pharmacodynamic properties (Bennett et al. 2012). Due to the heterogeneity of antiepileptic drugs, they possess adverse effects of varying origins (Bennett et al. 2012). Apart from the original indication for treating epilepsy, antiepileptic drugs are also increasingly used in other therapeutic purposes, for example psychiatric disorders and neuropathic pain.

Antiepileptic drugs create their effect mainly via four separate systems. First, many antiepileptic drugs, like valproate, vigabatrin and benzodiazepines, enhance GABA transmission (Bennett et al. 2012). Second, some antiepileptic drugs (topiramate, for example) mediate through excitatory glutamate and/or aspartate system, and third, drugs like phenytoin and carbamazepine hyperpolarize cells by binding Na^+ ion channels (Bennett et al. 2012). Finally, substances like pregabalin and levetiracetam block calcium channels decreasing synaptic transmission (Bennett et al. 2012).

Antiepileptic drugs pose risks for various potential adverse effects. These include hyponatremia, induction or inhibition of liver cytochrome P450 (CYP) enzymes, liver failure, exanthema, balance disturbances, sedation and cognitive decline, for example (Bennett et al. 2012). In addition, antiepileptic drugs have been identified as risk factors for reduced bone mineral density (Ensrud et al. 2004 and 2008). This association with demineralization is thought to be mediated by antiepileptic drug actions on vitamin D metabolism and secondary hyperparathyroidism (Pack et al. 2008), but the evidence is not consistent.

3.2.6 Anticholinergic drugs

Anticholinergic drugs are named after their ability to antagonize muscarinic receptors (Gerretsen & Polloc 2011). Muscarinic receptors are located in several human tissues, and they mediate physiological functions depending upon receptor location and subtype (M_1, M_2, M_3, M_4 or M_5) (Abrams et al. 2006). This action has favorable effects when treating, for example, urinary urge incontinence or obstructive pulmonary disease. However, many drugs possess anticholinergic properties as their side-effects, which are, thus, considered to have a negative benefit-risk ratio. The adverse effects related to anticholinergic drug use comprise mild to severe effects, and they are, as well as their favorable effects, mediated through anticholinergic receptor antagonism. The anticholinergic adverse effects can also be categorized as peripheral (blurred vision, constipation, mouth dryness, urinary retention, for example) or central (e.g. cognitive impairment and delirium) types (Wawruch et al. 2012). These adverse effects can occur at toxic, but also in therapeutic doses, when administrated to old individuals (Campbell et al. 2009), a matter of particular concern.

When anticholinergic drugs are considered, demented patients are of particular concern. Firstly, it has been noticed that anticholinergic drugs antagonize the cholinesterase inhibitors used to treat Alzheimer's disease, and, thus, the concomitant use of these should be avoided (Defilippi & Crismon 2003). Secondly, anticholinergic drug use has been identified as a separate, independent risk factor for mild cognitive impairment (Ancelin et al. 2006).

Many drugs have been listed as potentially inappropriate medications when treating old adults because of their anticholinergic properties. The most common classification of potentially inappropriate medications, the Beers criteria, includes first-generation antihistamines, antispasmodics, tertiary tricyclic antidepressants and skeletal muscle relaxants, which are defined as potentially inappropriate because of their anticholinergic properties (The American Geriatrics Society 2012 Beers Criteria Update Expert Panel 2012). Nevertheless, the Beers Criteria was not developed from the anticholinergic point of view and, as such, it is not a comprehensive approach.

It has been estimated that every third to every second of the most widespread drugs used by old adults have anticholinergic properties (Tune et al. 1992; Chew et al. 2008). To classify a particular drug as an anticholinergic is not, however, unambiguous, and therefore different groupings of anticholinergic drugs have been used for research purposes. The literature contains several attempts to scale anticholinergic drugs (Carnahan et al. 2006; Chew et al. 2008; Rudolph et al. 2008). These scales have been developed to quantify the risk associated with anticholinergic agents and ultimately to reduce adverse outcomes.

The Serum Anticholinergic Activity (SAA) system, developed by Tune and Coyle, has possibly been the most widely used *in vitro* method for quantifying anticholinergic activity (Tune & Coyle 1980). The SAA system relies on quantifying the serum anticholinergic assay, and it is reported in atropine equivalents. In this way, the SAA system differs from other scales, which are based on dichotomous leveling of the

potency of specific anticholinergic drugs. There is, however, great variation in reporting the results acquired with the SAA system (Carnahan et al. 2002). The SAA system has not been validated sufficiently concerning adverse effects or toxicity (Gerretsen & Pollock 2011). In addition, the SAA results do not accurately correlate with a patient's actual drug intake (Mulsant et al. 2003). Despite the disadvantages, the SAA has been a more widely studied measurement than either the Anticholinergic Drug Scale (ADS) or Anticholinergic Risk Scale (ARS) (Chew et al. 2008).

The ADS, introduced by Carnahan and his colleagues, relies on scoring drugs with anticholinergic properties in a four-step scale (from 0 to 3) (Carnahan et al. 2006). The scoring of an individual drug was determined by an expert panel including psychiatrists and geriatricians. In total, the ADS system comprises 536 drugs, of which 117 are assessed to have anticholinergic properties (Carnahan et al. 2006). To date, the ADS system has not been sufficiently validated to be accepted for routine use in clinical decision-making (Gerretsen & Pollock 2011).

The ARS is another anticholinergic drug determining system using expert panel ratings and literature search. This system was developed by Rudolph with his colleagues in 2008 (Rudolph et al. 2008). It comprises 49 anticholinergic drugs (excluding inhaled and topically used drugs). The ARS has been related to the risk of anticholinergic adverse effects and mortality (Rudoph et al. 2008; Mangoni et al. 2012), but the results are not consistent. Thus, the validation process is incomplete also for ARS scoring.

3.3 The prevalence of nervous system drug use in old adults

3.3.1 Psychotropic drugs

As the per-capita use of medications has been increasing among old Finnish adults, the prevalence of psychotropic drug use has also increased in recent decades (Linjakumpu et al. 2002a and 2002b). This increasing polypharmacy trend between 1998 and 2003 has occurred both with outpatients and in institutions, and it is particularly associated with advancing age (Jyrkkä et al. 2006). Within a Finnish population of community-dwelling old adults, an increase in psychotropic drug use prevalence has been reported between 1998 and 2004 (Desplenter et al. 2011). Further, 37% of the old adults used at least one psychotropic drug, and 12% at least two in the Kuopio 75 + study (Hartikainen et al. 2003a). In south-western Finland, every fourth old adult used at least one psychotropic drug, and the prevalence of using two or more psychotropics grew from 7 to 10% in the 1990s (Linjakumpu et al. 2002a).

Psychotropic drug use seems to be more prevalent among nursing home residents compared with community-dwelling old adults, and more common among the demented than the non-demented (Giron et al. 2001; McCowan et al. 2013). In Finnish nursing homes located in Helsinki, 79.7% of the residents used psychotropic drugs in 2003 (Hosia-Randel and Pitkälä 2005). Another Finnish study combining data from

demented patients in acute geriatric hospital care and nursing homes in years 1999 and 2000 found that 87% of the patients received at least one psychotropic drug, 66% received at least two, 36% received at least three, and 11% at least four (Pitkälä et al. 2004).

3.3.1.1 Benzodiazepines and related drugs

A population-based Finnish study concluded that hypnotics and sedatives were the most common psychotropic drugs of the 1990s (Linjakumpu et al. 2002a). During the 1990s the use of anxiolytics, hypnotics and sedatives remained constant in total, the prevalence being around 20% both in the early and late 1990s (Linjakumpu et al. 2002a). Of the drugs studied, benzodiazepines were clearly the most common group used. However, over time there were changes in the prevalence of use of specific agents within the benzodiazepine group. The prevalence of long-acting benzodiazepines (for example diazepam and chlordiazepoxide) decreased during the 1990s, while intermediate-acting (for example temazepam and lorazepam) remained at an unchanged level. The use of short-acting benzodiazepines, like oxazepam and midazolam, decreased during the 1990s mostly because they were replaced by newer benzodiazepine related drugs, zopiclone and zolpidem (Linjakumpu et al. 2002a).

The same stable prevalence of benzodiazepine use has been found in the Kuopio 75+ -study, which reported that among community-dwelling over 75 year olds the prevalence was around 30% both in 1998 and 2003 (Desplenter et al. 2011). On the contrary, an increase in benzodiazepine prevalence among old adults has been found in Sweden spanning the 1980s to 2004 (Lövheim et al. 2009).

In nursing homes in Finland, the prevalence of benzodiazepines used as hypnotics was 27.5% (Hosia-Randell & Pitkälä 2005). In the same geographic area, a mixed sample of patients both from geriatric hospital care and nursing homes, resulted in an estimate 34% prevalence of anxiolytic drug use (Pitkälä et al. 2004).

In Finland zopiclone, temazepam, diapam, zolpidem and oxazepam (in this order) were the most common benzodiazepines and related drugs in year 2012 (Fimea 2013).

3.3.1.2 Antidepressants

Among Finland's old population, the prevalence of antidepressants doubled from 4% to 7% in the 1990s (Linjakumpu et al. 2002a). This finding of increased antidepressant prevalence among the community-dwelling aged in Finland is supported by another study (Desplenter et al. 2011). In Canada, an increase in antidepressant prevalence was observed in the 1990s, despite decline in TCA use (Mamdani et al. 2000). This increase is therefore entirely due to the growth in SSRI prescribing (Mamdani et al. 2000).

In Finnish nursing homes, 44.6% of the residents were taking at least one antidepressant (Hosia-Randell & Pitkälä 2005). Of these, the SSRIs were the largest group, TCAs clearly being in the minority. This is supported by another Finnish study

conducted among demented patients in nursing homes and acute geriatric hospital care patients, where 31% of the patients used SSRIs (Pitkälä et al. 2004).

An increase in prevalence has been evident also in Sweden among demented residents in nursing homes, where a dramatic increase in antidepressant prevalence (6.8% to 43.2%) has been detected from the early 1980s to 2000 (Lövheim et al. 2009).

When individual antidepressants are concerned, citalopram and escitalopram were the most commonly used newer antidepressants, and amitriptyline the most common TCA in Finland year 2012 (Fimea 2013).

3.3.1.3 Antipsychotics

The prevalence of antipsychotic use, unlike that of antidepressants, seems not to have undergone similar substantial increase among the aged in Finland in the recent decades. In a population-based study among old Finns, researchers reported that the use of antipsychotics had decreased during the 1990s, from 6% to 3% (Linjakumpu et al. 2002a). This pattern of decrease is supported by another Finnish study among the community-dwelling aged, which reported a reduction from 9.2% to 5.7% between 1998 and 2003 (Desplenter et al. 2011). However, a third Finnish cross-sectional study analyzing the prevalence of antipsychotics in 2004, estimated prevalence to be 11%, which is a little higher than in previous studies from Finland or Sweden (Alanen et al. 2008a). In this study, the prevalence of typical and atypical antipsychotics was equal (54.9% and 52.7%), and 0.8% used concomitantly both types, respectively. Furthermore, a multicenter cross-sectional study regarding the use antipsychotics conducted in community-dwelling old adults receiving home-care in nine European countries revealed considerable variation between the attendant countries (Alanen et al. 2008b). The prevalence was found to be lowest in Denmark (3.0%) and highest in Finland (12.4%).

Old adults with dementia are more likely to be prescribed antipsychotics than the non-demented (Giron et al. 2001; Hartikainen et al. 2003b). This finding is supported by a study among Finnish community-dwelling patients with Alzheimer's disease (AD), where the prevalence of antipsychotics was 22.1% compared to 4.4% with patients without AD (Laitinen et al. 2011).

In a Finnish nursing home setting the prevalence of any antipsychotic was 42.6%, with atypical antipsychotics being more common than typical (Hosia-Randell & Pitkälä 2005). Opposing result is seen in another Finnish study among demented nursing home residents, which concluded that only 13% used atypical antipsychotics compared to 42% prevalence of typical types (Pitkälä et al. 2004).

In Sweden, patients in geriatric care were less likely to be treated with antipsychotics in 2000 than in 1982 (Lövheim et al. 2009). In this study at the end of the millennium, 38.0% of the patients took antipsychotics.

Of typical antipsychotics, perphenazine has been the most commonly prescribed drug in Finland year 2012 (Fimea 2013). When atypical antipsychotics are concerned, the most common have been olanzapine and quetiapine.

3.3.2 Opioid analgesics

Among old Finns, 45.4% of the population used at least one analgesic drug. Of these, 21.1% were users of weak opioids and only 0.3% used strong opioids (Pokela et al. 2010). In this study, codeine and tramadol were the most commonly used opioids. In addition, the concomitant use of opioids and psychotropic drugs becomes more frequent with increasing age, and the prevalence of this kind of concomitant use was highest, 9.6%, among over 85 year olds (Hartikainen et al. 2005). The prevalence of total opioid use was lower with patients suffering from AD in another Finnish study among community-dwelling old adults (Bell et al. 2011a). However, when strong opioids and fentanyl were analyzed separately from weaker opioids, persons with AD had more prescriptions of strong opioids (Bell et al. 2011a). Transdermal fentanyl was the most frequently mentioned strong opioid among community-dwelling old adults aged 80 years or over, and it was used more commonly to treat nonmalignant pain than cancer pain (Bell et al. 2009).

In Sweden, a population-based study among old adults concluded that the use of opioids was not statistically different among demented and non-demented old adults (Haasum et al. 2011). This study correspondingly revealed that both the non-demented and the demented living in institutional settings used opioids more frequently than did non-institutionalized (community-dwelling) old adults.

In Finland, codeine has been the clearly most commonly prescribed opioid analgesic, followed by tramadol (Fimea 2013).

3.3.3 Antiepileptic drugs

Among community-dwelling old adults, the prevalence of antiepileptic drug use was found to be 9.4% in Italy between 2004 and 2007, and 2% in Sweden in 2008 (Oteri et al. 2010; Johnell & Fastbom 2011). When community-dwelling old adults are concerned, the use of antiepileptic drugs in Finland is more common among demented persons than non-demented, with the prevalence being 5.0% and 3.4%, respectively (Bell et al. 2011b). Of the older patients with epilepsy, 90.5% used one antiepileptic drug, and 8.9% used two concomitantly (Harms et al. 2005).

The prescribing trend in epilepsy is moving towards newer antiepileptic drugs which have better side-effect profiles (Pugh et al. 2008), but this movement is relatively slow despite the new guidelines published in 2009 in Lancet Neurology (Brodie et al. 2009).

In addition, antiepileptic drugs are increasingly being used for non-epileptic purposes. These include neuropathic pain and anxiety disorders (Johannessen Landmark et al 2012).

In Finland, the use of pregabalin has increased in recent years (Fimea 2013). This is mostly due to its use in treatment of neuropathic pain. Other commonly used antiepileptic drugs in Finland were valproic acid and oxcarbazepine (Fimea 2013).

3.3.4 Anticholinergic drugs

A population-based sample of old adults aged 65 years or over demonstrated that utilizing the Anticholinergic Cognitive Burden Scale and defining cognitive impairment with the Mini-Mental State Examination (MMSE), 47% of respondents used drugs with potential anticholinergic properties and 4% used definite anticholinergic drugs (Fox et al. 2011). According to literature, 9 to 37% of community-dwelling old adults used anticholinergic drugs (Ancelin et al. 2006; Hilmer et al. 2007). In addition, community-dwelling demented old adults are more likely to receive anticholinergic drugs compared to matched controls (Roe et al. 2002).

In Finnish geriatric hospital care and nursing homes, 80.2% of patients were treated with two or more drugs with anticholinergic properties (Luukkanen et al. 2011). A little lower prevalence was observed in another Finnish study among long-term care patients in a metropolitan area, which calculated the prevalence of any anticholinergic drug use to be 55% (Kumpula et al. 2011).

3.4 Potentially inappropriate medications in old adults

3.4.1 Criteria for determining potentially inappropriate medications

Potentially inappropriate medications (PIMs) or potentially inappropriate prescriptions (PIPs) can be defined as medications with no clear evidence-based indication, ones that pose high risk ADEs or ones that are not cost-effective (O'Mahony et al. 2008). Several criteria defining potentially inappropriate medications in old adults have been described in literature (Dimitrow et al. 2011). These criteria have been proposed since the early 1990s, but none is definitive. The measures are either implicit (judgment-based) or explicit (criteria-based).

Implicit criteria are based on individual assessment of certain medications' indications and other properties to determine appropriateness (Spinewine et al. 2007). Implicit criteria are dependent on physician's expertise and attitudes (Spinewine et al. 2007). The Medication Appropriateness Index (MAI) is the most commonly used implicit criteria, and patient's individual drugs are each evaluated with ten questions to determine its appropriateness (Hanlon et al. 1992). These questions include estimation of drug's indication, effectiveness, dosing, instructions, drug-drug interactions, drug-disease interactions, functionality, duplication, duration and expense.

Explicit criteria are validated by expert consensus to form a list of medications to be avoided when treating old adults. Most of them are based on the Beers Criteria and its updates (Beers et al. 1991; Beers et al. 1997; Fick et al. 2003; The American Geriatrics Society 2012 Beers Criteria Update Expert Panel 2012). Explicit criteria, such as that by Beers, have been in more extensive scientific use compared to implicit criteria mostly because they are easier to implement in research programs. The Beers Criteria, however, have also been criticized because up to half of the listed medications may not

be available in certain countries (Fialova et al. 2005), and some medications have, according to some experts, debatable appropriateness (Spinewine et al. 2007).

The first Beers Criteria, developed in the US, was published in 1991 and focused on nursing home residents (Beers et al. 1991). The newer updates extended the criteria to all persons aged 65 years and older regardless of place of living or type of care (Beers et al.1997; Fick et al. 2003; The American Geriatrics Society 2012 Beers Criteria Update Expert Panel 2012).

The newest Beers Criteria comprises several potentially inappropriate therapeutic medication categories, of which the most important concerning the focus of this doctoral thesis are anticholinergic drugs and certain groups of central nervous system drugs (The American Geriatrics Society 2012 Beers Criteria Update Expert Panel 2012). The anticholinergic category in the Beers Criteria includes first generation antihistamines, older antidepressants and antispasmodics, for example. Nervous system drugs include tertiary tricyclic antidepressants (TCAs), typical and atypical antipsychotics, barbiturates, non-benzodiazepine hypnotics, and short-, intermediate- and long-acting benzodiazepines (The American Geriatrics Society 2012 Beers Criteria Update Expert Panel 2012).

Other explicit criteria have also been validated that are not based on the Beers Criteria. These include, for example, STOPP (Screening Tool to Older Person's Prescriptions) and START (Screening Tool to Alert Doctors to the Right Treatment) criteria developed in Ireland (Barry et al. 2007; Gallagher et al. 2008; Hamilton et al. 2011). These differ from the Beers Criteria in that they are arranged according to physiological systems (STOPP) and indicators for common diseases (START) (Barry et al. 2007; Gallagher et al. 2008).

Besides the Beers Criteria and START/STOPP criteria, also other criteria, designed primarily for national use, have been developed. In chronological order, they include Swedish, French, Norwegian, Finnish, German and Italian recommendations (Socialstyrelsen 2003; Loroche et al. 2007; Rognstad et al. 2009; Fimea 2010; Holt et al. 2010; Maio et al. 2010). The Swedish criteria (updated in 2010) as well as the French criteria are designed for old adults 75 years of age or over (Laroche et al. 2007; Socialstyrelsen 2010). The Finnish database of medications for the elderly classifies several hundreds of common drugs used by old adults (Fimea 2010). It contains determination of inappropriate drugs, but it also describes drugs suitable for old adults using a four-step rating scale (Bell et al. 2013). The Norwegian General Practice criteria is partly based on the Beers Criteria (Rognstad et al. 2009).

As a large review noted, the evidence regarding PIMs and adverse health outcomes is inconsistent, and further studies are required to test the predictive value of existing criteria or new criteria need to be created (Spinewine et al. 2007).

3.4.2 Prevalence of potentially inappropriate medication use

In a multicenter study among European home care patients, the prevalence of PIM use varies significantly using the Beers Criteria from years 1997 and 2003 (Fialova et al.

2005). In general, use was more extensive in Eastern-Europe (41.1% in Czech Republic) than in Western-Europe (mean 15.8%). Regardless, differences in PIM were also found between Western-European countries (Fialova et al. 2005). The prevalence of PIMs among Finnish non-institutionalized old adults has been found to be 14.7% in a nation-wide study (Leikola et al. 2011), and lower, 12.5%, in another Finnish study among the home-dwelling elderly (Pitkälä et al. 2002). Fialova and colleagues found the prevalence of PIMs in Finland to be a little higher, 20.3%, when using the same Beers Criteria 2003 (Table 1; Fialova et al. 2005). This prevalence observed by Pitkälä's study group is considered to be relatively low compared to studies conducted in other countries, where the prevalence of PIMs has been found to vary from 5.8% in Denmark (Fialova et al. 2005) to as high as 41.9% in US (Zuckerman et al. 2006) with primary health care patients.

Patients living in institutions seem to have a higher risk of receiving PIMs compared to outpatients, with prevalences as high as 50% and 54.7% having been reported in US and Canadian nursing homes (Lau et al. 2004; Rancourt et al. 2004). A Finnish study including nursing home residents found the prevalence to be 34.9%, which is lower than in the study by Lau, but still represent a high rate (Hosia-Randell et al. 2008).

When individual PIMs are identified according to the Beers Criteria, diazepam, amiodarone and amitriptyline were the most commonly used medications in the multicenter European study (Fialova et al. 2005). In conclusion, long-acting benzodiazepines, anticholinergic drugs and certain individual medications like amiodarone and amitriptyline are the most numerous PIMs used among non-institutionalized, institutionalized and hospitalized old adults when the Beers Criteria is the standard.

Studies using the STOPP criteria to identify PIMs use are not as common as ones using the Beers Criteria. However, according to literature search, the number of studies utilizing the STOPP criteria has increased in recent years. In Ireland, where the STOPP criteria were validated, the most common PIMs were proton pump inhibitors, aspirin, benzodiazepines and duplicate drug prescriptions (Hamilton et al. 2011). In summary, in most studies the prevalence of PIMs identified using the STOPP criteria has been significantly higher than when STOPP criteria are compared to Beers in same setting (Wahab et al. 2012; Vishwas et al. 2012). In previous studies, the prevalence of PIMs in nursing homes according to the STOPP criteria has varied from 23.7% to 70% (Chen et al. 2012; O'Sullivan et al. 2013).

Table 1. Scandinavian studies using Beers Criteria to assess the prevalence of potentially inappropriate medication use.

Setting	Author	Country	Number of participants, age of participants (years)	Prevalence of PIM use	Most common PIMs
home-dwelling	Pitkälä et al. 2002	Finland	3219, ≥75	12.5%	dipyridamole, long-acting benzodiazepines, amitriptyline
	Klarin et al. 2005*	Sweden	785, ≥75	18.6%	not specified
	Fialova et al. 2005†	Denmark	400, ≥65	5.8%	diazepam, dipyridamole
		Finland	187, ≥65	20.3%	diazepam, amitriptyline
		Iceland	405, ≥65	15.1%	unopposed oestrogens (in women ≥75 years of age), amiodarone, amitriptyline
		Norway	388, ≥65	14.7%	diazepam, amitriptyline
	Leikola et al. 2011	Finland	841 509, ≥65	14.7%	temazepam, amitriptyline, diazepam
nursing home	Raivio et al. 2006‡	Finland	425, ≥65	36.2%	temazepam, oxybutynin, dipyridamole
	Hosia-Randell et al. 2008	Finland	1 987, ≥65	34.9%	temazepam, hydroxyzine, nitrofurantoin
hospital care	Saltvedt et al. 2005	Norway	254, ≥75	9.8%	not specified
	Raivio et al. 2006‡	Finland	425, ≥65	36.2%	temazepam, oxybutynin, dipyridamole

* Population-based study using modified Beers Criteria

† Participants receiving home-care

‡ Both nursing home and hospital patients included

3.5 Nervous system drugs and fractures in old adults

3.5.1 Falls and fractures in old adults

It has been estimated that every third person over 65 years of age experiences at least one fall yearly (Lord et al. 1993). Of these falls about 10% lead to serious injuries (O'Laughlin et al. 1993). The risk of injurious fall increases with advancing age (Campbell et al. 1990; Rubenstein & Josephson 2002). Further, falls and fractures are common causes of hospitalization, decline in locomotion and increase in mortality in old adults (Wolinsky et al. 1997; Bliuc et al. 2009). They also reduce the patient's quality of life (Borgström et al. 2006).

Fracture is normally caused by a fall and a concurrent bone disease, usually osteoporosis (Järvinen et al. 2008). Most common fall-related injuries leading to hospitalization include fractures of the forearm, femur, lower leg or ankle, upper arm or shoulder and lumbar spine or pelvis (Kreisfeld et al. 2010).

Most widely recognized individual risk factors for falls comprise muscle weakness, a history of falls, gait and balance deficit, use of assistive device(s), visual deficit, arthritis, impaired Activities of Daily Living (ADL), depression, cognitive impairment and age over 80 years (Rubenstein & Josephson 2002). Medications may predispose or otherwise contribute to old adults' experiencing many of these risk factors. Many of these risk factors are preventable and therefore reducing fall, and fracture risk in old adults is an important objective (Sattin 1992). From the viewpoint of society, treatment of falls and fractures generates high avoidable costs (Englander et al. 1996; Moller 2003; Nurmi et al. 2003).

3.5.2 Psychotropic drugs and fractures

Psychotropic agents including benzodiazepines, antidepressants and antipsychotics have been independently found to increase the risk of falls in old adults (Bloch et al. 2011). Many studies have investigated the associations between psychotropic drugs and falls or fractures separately for different psychotropic drug classes and did not calculate the cumulative effect for psychotropic drugs as one group. Most of the case-control studies that have reported the relative risk for fractures in any psychotropic drug use have resulted in an increased risk (Shorr et al. 1992; Grisso et al. 1997). However, case-control studies with negative associations also exist (Jensen et al. 1991). The majority of these case-control studies had hip fracture as the primary outcome measure.

Relatively few cohort studies have investigated the total effect of all psychotropic use on fracture risk. A study from South Korea with a cohort of 6,043 city dwelling women 65 years or over resulted in the estimate that use of psychotropic drugs creates 4-fold increase in risk for hip fractures (Bae et al. 2002). This study had a follow-up of two years, and the primary result was adjusted for age, body mass index and history of alcohol use. This hypothesis that women are at high risk of fractures is supported by

results from a retrospective cohort study conducted in southern Australia, where the use of a psychotropic drug was associated with falls and fractures in women, but not in men (Vitry et al. 2010).

3.5.2.1 Benzodiazepines and related drugs

Clear evidence connects the use of benzodiazepines to an increased risk of falls in the aged (Woolcott et al. 2009). Further, an extensive meta-analysis comprising 23 studies resulted in an estimated relative risk (RR) of 1.34 (95% CI 1.24–1.45) for fractures when using benzodiazepines, compared to non-users (Takkouche et al. 2007). It is worth noting that this particular meta-analysis also included participants under 65 years of age. This same meta-analysis did not find significant differences in relative risks according to study design, duration of use or type of control participants. However, regarding the number of benzodiazepines used, there is evidence that the concomitant use of more than one benzodiazepine increases the risk of fractures greater than one alone (Herings et al. 1995; Pierfitte et al. 2001).

As expected, case-control studies show a trend similar to that in the meta-analysis by Takkouche and his colleagues. However, there seem to be differences in fracture risk when benzodiazepine users are divided into two groups according to their medication's elimination half-life. In some case-control studies, benzodiazepines with a short elimination half-life have been found to bear a lower or no risk of fractures compared to long-acting drugs (Ray et al. 1989; Vestergaard et al. 2008), while another case-control study has concluded the opposite (Herings et al. 1995).

The cohort studies presented in Table 2 present somewhat inconsistent results, showing both positive and negative associations. Nevertheless, the total relative risk of fractures in benzodiazepine users seems to be higher than with non-users, as pointed by Takkouche's meta-analysis.

The role of benzodiazepine related drugs has also been studied, but the results are conflicting. Two case control studies resulted in opposite findings (Pierfitte et al. 2001; Wang et al. 2001). On the other hand, a cohort study by Finkle, et al. reported that zolpidem use had a strong association with fractures (Finkle et al. 2011).

3.5.2.2 Antidepressants

Both tricyclic antidepressants (TCAs) and newer antidepressant classes, especially selective serotonin reuptake inhibitors (SSRIs), have been identified as risk factors for falls, but evidence concerning the differences in the risk of falls between these two classes is still controversial (Draper & Berman 2008). However, a meta-analysis concerning antidepressants use and fractures showed SSRIs to pose a higher risk for fractures than non-SSRIs or TCAs (Takkouche et al. 2007). This meta-analysis by Takkouche and colleagues calculated that the fracture risk was 33% higher for SSRIs compared to non-SSRIs, and that the risk posed by TCAs is similar to that of all antidepressants once their data are pooled. Another meta-analysis concluded that the

summary odds ratio for TCAs was 1.71 (95% CI 1.43–2.04) and 1.94 (1.37–2.76) for newer, second-generation, antidepressants for example SSRIs compared to non-use (Oberda et al. 2012).

A third meta-analysis reporting fracture risk associated with SSRI use estimated the overall relative risk at 1.72 (1.52–1.95), and that risk may be independent from other factors such as depression and bone mineral density (Wu et al. 2012). Using the same methods, Wu and colleagues concluded that the safety profile of TCAs is relatively similar to that of SSRIs, and TCAs' overall relative risk was 1.45 (CI 1.31 to 1.60) (Wu et al. 2013). In this study, the duration of TCA use was remarkable in that the fracture risk was substantially higher when the exposure had lasted for less than 6 weeks.

Table 3 summarizes findings from cohort studies concerning the use of antidepressants and fractures.

3.5.2.3 Antipsychotics

A meta-analysis on drugs and falls established increased fall risk between both typical and atypical antipsychotics (Woolcott et al. 2009). Furthermore, the evidence shows that antipsychotics specifically increase fall risk in various geriatric care settings, and among the most vulnerable patients (Kallin et al. 2004).

When the observation is shifted to associations between antipsychotics and fractures, there is a shortage of cohort studies. The meta-analysis by Takkouche and colleagues concluded that when only case-control studies are examined, the increase in fracture risk is around 60% (RR 1.59 with 95% CI from 1.27 to 1.98) (Takkouche et al. 2007). On the contrary, no positive relationship was found in two cohort studies included in Takkouche's meta-analysis. The first of these cohort studies was conducted in Sweden and consisted of 1,608 patients aged 75 years or over (Guo et al. 1998). This study concluded that the relative risk of fracture using antipsychotics was not statistically significant. The second cohort study by Jacqmin-Gadda and her team had a cohort of 3,216 men and women aged 65 years and over living in southwestern France (Jacqmin-Gadda et al. 1998). The fracture risk in this study did not prove significant for non-hip fractures or hip fractures. However, a more recent cohort study with over a million Canadian old adults examined the risk of hip fracture associated with atypical antipsychotic use, concluding that the odds ratio was 2.2 (95% CI 2.1–2.4) (Normand et al. 2005).

Another newer meta-analysis concerning hip fracture risk and antipsychotic drugs, comprising cohort and case-control studies, found that both typical and atypical antipsychotic drugs possess an increased risk for fractures, with the odds ratios (95% CI) being 1.68 (1.43–1.99) and 1.30 (1.14–1.49), respectively (Oberda et al. 2012).

Question concerning safety differences between typical and atypical antipsychotics remains unsolved, in general. Two cohort studies exploring these possible differences in fracture risk concluded that no significant difference exists (Normand et al. 2005; Mehta et al. 2010).

Table 2. Cohort studies concerning the use of benzodiazepines and related drugs and the risk of fractures in old age.

Authors Year Country	Population / Age in years	Study design / Outcome	Medications studied	Follow-up	Results OR / RR (95 % CI)
Cummings et al. 1995 United States	9 516 women / ≥65	prospective cohort / risk of hip fracture	benzodiazepines, anticonvulsants	4.1 years on average	long-acting BZD: RR 1.6 (1.1–2.4), short-acting BZD: RR 1.2 (0.8–2.1)
Wysowski et al. 1996 United States	76 461 exposures to triazolam and 94 134 to temazepam / ≥65	retrospective cohort / risk of hip fracture	triazolam (used as a referent cohort), temazepam	17 318 030 person months (triazolam), 20 930 829 person months (temazepam)	temazepam: RR 0.84 (0.66–1.08), triazolam cohort used as a referent group
Jacqmin-Gadda et al. 1998 France	3 216 community dwellers / ≥65	prospective cohort / risk of hip fracture or non-hip fracture	psychotropics	5 years	anxiolytics: OR 2.25 (1.31–3.88), hypnotics: OR 1.18 (0.60–2.31)
Forsen et al. 1999 Norway	18 612 women / ≥50	prospective population-based cohort / risk of hip fracture	tranquillisers / sedatives, hypnotics	3 years	tranquillisers / sedatives or hypnotics (daily use): RR 1.48 (0.99–2.21)
Ensrud et al. 2003 United States	8 127 community dwelling women / ≥65	prospective population based cohort / risk of non-vertebral fracture	benzodiazepines, antidepressants, anticonvulsants, narcotics	4.8 years on average	BZD: RR 1.12 (0.88–1.42)
Hasselman et al. 2003 United States	9 704 women / ≥65	prospective cohort / risk of foot fracture	long- and short-acting benzodiazepines	10.2 years on average	short-acting BZD: RR 1.62 (1.09–2.40), long-acting BZD: 1.72 (1.24–2.40)

Wagner et al. 2004 United States	125 203 Medicaid enrollees / ≥65	prospective cohort / risk of hip fracture	benzodiazepines	42 months	BZD: incidence rate ratio (IRR) 1.24 (1.06–1.44), short half-life: IRR 1.27 (1.01–1.59), during the first 2 weeks after stating a BZD: IRR 2.05 (1.28–3.28)
Spector et al. 2007 United States	2 711 nursing home residents / ≥65	prospective cohort / risk of any fracture	benzodiazepines, opioids, antidepressants, anticonvulsants	1 year	benzodiazepines: OR not significant
Avidan et al. 2005 United States	34 163 nursing home residents / ≥65	prospective cohort / risk of hip fracture	hypnotics	6 months	hypnotics: OR 0.85 (0.58–1.22)
Finkle et al. 2011 United States	43 343 users of zolpidem, 103 790 of alprazolam, 150 858 of lorazepam, 93 618 of diazepam who were Health maintenance members / ≥65	retrospective community-based cohort / risk of non-vertebral fracture and hip fracture	zolpidem, alprazolam, lorazepam, diazepam	3 months	zolpidem RR: 2.55(1.78–3.65), alprazolam: 1.14(0.8–1.64), lorazepam: 1.53(1.23–1.91), diazepam: 1.97 (1.22–3.18)

BZD=benzodiazepines
AP= antipsychotics
TCA= tricyclic antidepressants
OR= odds ratio
RR= relative risk

Table 3. Cohort studies concerning the use of antidepressants and the risk of fractures in old age.

Authors Year Country	Population / Age in years	Study design / Outcome	Medications studied	Follow-up	Results OR / HR / RR (95 % CI)
Jacqmin-Gadda et al. 1998 France	3 216 community dwellers / ≥65	prospective cohort / risk of hip fracture or non-hip fracture	psychotropics	5.0 years	AD: OR 2.53 (1.05–6.12)
Ensrud et al. 2003 United States	8 127 community dwelling women / ≥65	prospective population based cohort / risk of non-vertebral fracture	benzodiazepines, antidepressants, anticonvulsants, narcotics	4.8 years on average	AD: HR 1.25 (0.99–1.58)
Schneeweiss & Wang 2004 United States	7 126 men and women / ≥65	prospective cohort / risk of hip fracture	SSRI	4.0 years	SSRI: RR 1.8 (1.5–2.1)
Lewis et al. 2007 United States	5 995 men / ≥65	prospective cohort / risk of non-vertebral fracture	antidepressants	4.1 years	TCA: HR 2.36 (1.25–4.46)
Richards et al. 2007 Canada	5 008 participants / ≥ 50	prospective population-based cohort / risk of any fracture	SSRI	5.0 years	SSRI: HR 2.1 (1.3–3.4)
Spector et al. 2007 United States	2 711 nursing home residents / ≥65	prospective cohort / risk of any fracture	opioids, antidepressants, anticonvulsants	1.0 year	AD: OR 1.5 (1.05–2.13)
Spangler et al. 2008 United States	93 676 women / ≥50–79	prospective cohort / risk of fracture	antidepressants	7.4 years	AD: HR 1.22 (1.15–1.30)

Ziere et al. 2008 The Netherlands	7 983 participants / ≥55	prospective population-based cohort / risk of non-vertebral fracture	antidepressants	8.4 years on average	SSRI: RR 2.35 (1.32–4.18), TCA 1.69 (0.97–2.93)
Coupland et al. 2011 United Kingdom	60 746 participants / ≥65	population-based cohort / risk of fracture	antidepressants	5.0 years	SSRI: 1.58 (1.48–1.68), TCA: 1.26 (1.16–1.37), other AD: 1.64 (1.46–1.84)
Diem et al. 2011 United States	8 217 community-dwelling women / ≥69	prospective population-based cohort / risk of non-vertebral fracture	antidepressants	10.0 years	SSRI: HR 1.30 (1.04–1.62) for non-vertebral fracture, TCA: HR 1.16 (0.95–1.41) for non-vertebral fractures

AD= antidepressants
SSRI= selective serotonin reuptake inhibitors
TCA= tricyclic antidepressants
OR= odds ratio
HR= hazard ratio
RR= relative risk

Table 4. Cohort studies concerning the use of opioid analgesics and the risk of fractures in old age.

Authors Year Country	Population / Age in years	Study design / Outcome	Medications studied	Follow-up	Results OR / HR (95 % CI)
Guo et al. 1998 Sweden	1 608 community dwellers / ≥75	prospective community based cohort / risk of hip fracture	benzodiazepines, hypnotics, sedatives, antidepressants, neuroleptics, opioid analgesics	71 123 person years in total	opioid analgesics (mainly propoxyphene): OR 1.79 (1.05–3.05)
Ensrud et al. 2003 United States	8 127 community dwelling women / ≥65	prospective population based cohort / risk of non-vertebral or hip fracture	benzodiazepines, antidepressants, anticonvulsants, narcotics	4.8 years on average	narcotics: HR 1.40 (1.06–1.83) for non-vertebral fractures, HR 1.22 (0.69–2.15) for hip fractures
Kamal-Bahl et al. 2006 United States	362 503 outpatients / ≥65	prospective cohort study / risk of hip fracture	propoxyphene	464 days on average	propoxyphene: HR 2.05 (1.87–2.25), other opioids: 2.28 (2.13–2.45)
Spector et al. 2007 United States	2 711 nursing home residents / ≥65	prospective cohort / risk of any fracture	opioids, antidepressants, anticonvulsants	1 year	opioid analgesics: OR 1.52 (1.03–2.24)
Miller et al. 2011 United States	12 436 initiators of opioids suffering from osteoarthritis or rheumatoid arthritis / ≥65	retrospective cohort / risk of fractures	NSAIDs, opioids	4 877 person years in total	all opioids: HR 4.9 (3.5–6.9), short-acting opioids: HR 5.1 (3.7–7.1), long-acting: HR 2.6 (1.5–4.4)

BZD= benzodiazepines
HR= hazard ratio
NSAID= non-steroidal anti-inflammatory drugs
OR= odds ratio

3.5.3 Opioid analgesics and fractures

According to a meta-analysis on opioid use and the risk of falls concluded that the risk is nonexistent (Leipzig et al. 1999). However, a more recent Canadian case-control study found a positive association between opioid use and injurious falls (Kelly et al. 2003). When fractures are concerned, the meta-analysis by Takkouche reported a small but statistically significant increase in fracture risk among opioid users (Takkouche et al. 2007). The meta-analysis included both cohort and case-control studies, and heterogeneity was identified among case-control studies but not among the cohort studies.

A large case-control study of fracture risk associated with morphine and opiates connects a wide range of frequently used opioids to increased fracture risk (Vestergaard et al. 2006). Although this study also included younger participants, it showed that morphine, fentanyl, oxycodone, tramadol and codeine were associated with increased fracture risk. However, buprenorphine and propoxyphene were not associated with fractures. A sub-analysis within the same Danish study showed that among women aged 60 years or over the results were similar to the main outcome findings.

Table 4 lists cohort studies on the association between opioid use and fractures. All studies presented in the table show significant associations. However, Ensrud and her colleagues did not find that opioids increased hip fracture risk, but a significant association with any non-spine fracture was present (Ensrud et al. 2003). Opioids increase fracture risk also in the nursing-home setting (Spector et al. 2007).

3.5.4 Antiepileptic drugs and fractures

Antiepileptic drug use is associated with falls in two cohort studies (Tromp et al. 2001; Ensrud et al. 2002), but conflicting results have been published (Kallin et al. 2004). However, the role of antiepileptic drugs in fracture risk has been investigated more intensively. This is due to the potency of antiepileptic drugs in altering bone physiology and metabolism (Petty et al. 2005). Additionally, due to the often chronic, incurable nature of epilepsy as a disease, the use of these drugs is in many cases long-term, and thus, the potential adverse effects may accumulate during this long period of time.

The meta-analysis by Takkouche also examined the effects of antiepileptic drug use on fracture risk (Takkouche et al. 2007). This study concluded that the relative risk for fractures using non-barbiturate antiepileptic drugs was 1.54 (95% CI 1.24–1.93). There was, however, evidence of publication bias concerning negative or null studies on non-barbiturate antiepileptic drugs. The writers also reported that the four cohort studies on non-barbiturates included in their meta-analysis did not support a positive association.

Most case-control studies have included younger adults. Two large case-control studies have resulted in positive associations between antiepileptic drug use and fractures (van Staa et al. 2002; Vestergaard et al. 2004). Van Staa with colleagues

analyzed 231,778 cases and an equal number of controls, resulting in an odds ratio of 2.1 (95% CI 2.0–2.2) for any anticonvulsant use. Vestergaard et al. utilized 124,655 cases and 373,962 controls in order to investigate the odds ratios for use of individual drugs. Vestergaard reported that risk for any fracture was elevated for carbamazepine (1.18 (OR), 1.10–1.26 (95% CI)), oxcarbazepine (1.14, 1.03–1.26), clonazepam (1.27, 1.15–1.41), phenobarbital (1.79, 1.64–1.95) and valproate (1.15, 1.05–1.26). However, a negative association was found for ethosuximide, lamotrigine, phenytoin, primidone, tiagabine, topiramate and vigabatrin. The grouped analysis of all anticonvulsants showed positive association for any type of fracture.

One out of three cohort studies that focused on old adults' antiepileptic drug use and the risk fractures resulted in a positive association (Spector et al. 2007), while two reported negative associations (Cummings et al. 1995; Ensrud et al. 2003).

Both men and women are at risk for fractures when using antiepileptic drugs, but women seem to be more frequently studied and, thus, the evidence is stronger (Ensrud et al. 2003; Souverein et al. 2006).

3.5.5 Anticholinergic drugs and fractures

It has been estimated that every third to every second of the most widespread drugs used by old adults have anticholinergic properties (Tune et al. 1992; Chew et al. 2008). From the foregoing, it is not surprising that the role of anticholinergic drugs as predictors of falls or fractures has not been studied in detail or that the results are frequently non-commensurable. There is little evidence associating anticholinergic drug to an increased fall risk (Aizenberg et al. 2002). Centrally acting muscle relaxants have strong anticholinergic properties, and they have been associated with fractures in old adults (Golden et al. 2010). In this case-control study, the writers concluded that the odds ratio for fractures when using muscle relaxants was 1.40 (95% CI 1.15–1.72). Further evidence is needed to establish the effects of anticholinergic drugs and its subgroups on fall and fracture risk.

3.6 The effect of nervous system drugs on balance and muscle strength

3.6.1 Balance

Poor balance and increased body sway are associated with higher risk of falls and fractures (Fernie et al. 1982; McClelland 1989; Cummings et al. 1995; Muir et al. 2010).

The use of nervous system drugs has been associated with decreased balance control (Lord et al. 1995). Furthermore, having a higher Drug Burden Index (Hilmer et al. 2007) and/or greater sedative load (Sedative Load Model, Taipale et al. 2010) have been associated with poor balance (Wilson et al. 2010; Taipale et al. 2012).

Regarding pharmacotherapy and balance, benzodiazepines and related drugs are the most widely studied group of nervous system drugs. Research has focused largely on their single dose effects on balance or balance-related measurements in the laboratory setting. While the laboratory technique in these studies is well established (Patat 2000), the experimental conditions under which the studies were performed require additional consideration (Allain et al. 2005). Even with their limitations, these studies support the findings from clinical practice (Robin et al. 1996). The laboratory studies usually utilize body sway to assess of balance effects. The evidence shows that benzodiazepine and related drug use increases body sway (Patat & Foulhoux 1985; Patat et al. 1995). Balance decrements appear to be dose-dependent (Ancoli-Israel 2000). For benzodiazepines, the medication effects result in larger postural sway in old adults than in younger participants (Robin et al. 1996). Evidence, however, is largely missing on long-term use of these medications' effects on body sway or other balance-related measurements. In addition, little evidence exists concerning withdrawal from benzodiazepines (or any other nervous system drugs) and subsequent balance or body sway (Tsunoda et al. 2010).

Evidence on antidepressants and balance also connects this drug class to impaired body sway and postural control (Mattila et al. 1989; Potter 1990). Further, a study shows that tricyclic antidepressants impair balance functions more than selective serotonin uptake inhibitors do (Li et al. 1996). The evidence also supports the theory that antiepileptic drugs worsen balance measurements (Sirven et al. 2007). The proof, however, is meager regarding opioid analgesics and balance (Menefee et al. 2004).

An Italian study on anticholinergic drugs and physical function (including balance measurement) found a significant association (Landi et al. 2007), a finding that is supported by other studies (Mintzer et al. 2000; Aizenberg et al. 2002).

3.6.2 Muscle strength

Muscle weakness has long been associated with an increase in fall risk (de Rekeneire et al. 2003). A review and meta-analysis concluded that considering lower extremity weakness the combined odds ratio for any fall was 1.76 (95% CI 1.31–2.37), and for recurrent falls 3.06 (1.86–5.04) (Moreland et al. 2004). Additionally, upper extremity weakness was established as having a lower, but still significant, risk for falls and recurrent falls as compared with lower extremity weakness (Moreland et al. 2004). A study conducted among women aged 65 years or more concluded that older age, poorer baseline handgrip strength, weight and height loss, difficulties in functional tasks, and decreased physical activity are independently associated with greater loss in handgrip strength (Forrest et al. 2007).

Surprisingly little evidence is available on the role of medications and the risk of muscle strength loss. In order to more deeply understand the nuances of fall and fracture risk, the possible effects of medications on muscle strength should be studied.

The use of nervous system drugs has been associated with poorer lower limb muscle strength (Lord et al. 1995). Separate nervous system drug classes or individual drugs have not been extensively studied regarding muscle strength. Two older studies

examined the relationship between triazolam, flunitrazepam and nitrazepam use, and handgrip strength or muscle performance (Lahtinen et al. 1978; Zinzen et al. 1994). These studies concluded that nitrazepam did not affect handgrip strength negatively (Lahtinen et al. 1978), but flunitrazepam associated with lower values for isometric force (Zinzen et al. 1994). Triazolam did not associate with significant changes in isokinetic or isometric force values (Zinzen et al. 1994). These studies, however, included younger participants and so the consequences for old patients cannot be disaggregated.

The Italian study by Landi and colleagues stated that the use of anticholinergic agents is associated with lower handgrip strength in persons aged 80 years or over (Landi et al. 2007). This result remained significant, although decreased, after adjustment for several confounding factors. Another study on anticholinergic burden was associated with weak handgrip strength, with an odds ratio of 2.4 (95% CI from 1.1 to 5.3) (Cao et al. 2008). Similarly, in the same study, sedative burden was associated with impaired handgrip strength with an odds ratio of 3.3 (95% CI from 1.5 to 7.3).

Research activity in this field seems to be centered on the Drug Burden Index (DBI) (Hilmer et al. 2007). A study by Hilmer reported poorer handgrip strength in persons with higher index values at six years follow-up (Hilmer et al. 2009). DBI has also been associated with lower handgrip strength in community-dwelling older Australian men (Gnjigic et al. 2009), but not with the community-dwelling old men or women in Finland (Gnjigic et al. 2012b). Another measurement of drug burden, the Sedative Load Model, has also been linked to poorer handgrip strength among a Finnish population of persons over 75 years of age (Taipale et al. 2010 and 2011).

4. AIMS OF THE STUDY

The aim of this study was to describe the use of medications affecting the central nervous system, and analyze the relationships between use of these medications and the risk of fractures in old adults.

In detail, the aims were:

1. To describe the prevalence of the use of medications affecting the central nervous system in adults 65 years of age and older, and to evaluate the prescribing practices (studies I, II and III).
2. To analyze associations between medications affecting the central nervous system and fractures in adults 65 years of age and older (studies II and III).
3. To assess whether withdrawal from long-term use of temazepam, zopiclone or zolpidem enhances balance and handgrip strength in adults 55 years of age and older (study IV).

5. MATERIALS AND METHODS

5.1 Study settings, samples and populations

The four studies in this academic thesis included three separate samples and populations.

Study I was a cross-sectional study. In study I the sample consisted of 154 patients (112 women and 42 men) residing in long-term care wards in Pori City Hospital, Finland. Only patients, who were born in 1939 or earlier were included. The data collection for study I occurred between December 20, 2004, and January 9, 2005. In Pori City Hospital there were six long-term care wards at the time of the study data collection. The sample consisted of patients residing in five of these wards. Because of limited time resource, data of patients of the sixth ward was not reached. The mean age of the patients was 84.2 years (SD ± 8.0 years).

Studies II and III were part of a larger, longitudinal, population-based Lieto Study conducted in the municipality of Lieto, Finland in the 1990s (Isoaho et al. 1994). The baseline data for the original Lieto Study was collected between October 1, 1990, and December 31, 1991 (Isoaho et al 1994). The population consisted of all residents in Lieto born in 1926 or earlier (n=1,283), of whom 93% (n=1,196) were willing to participate to the Lieto Study (Isoaho et al. 1994). Data on fractures were obtained for 1,177 (482 men and 695 women) out of original 1,196 participants. They formed the subjects of studies II and III of this academic thesis (Piirtola et al. 2007). The mean age of men was 72.4 years, and it was 73.8 years for women at baseline (Piirtola et al. 2007).

Study IV was part of the Satauni Study, which was a single-centered, randomized and placebo-controlled double-blind study (Lähteenmäki et al. 2013). The Satauni Study was primarily targeted to assess the effect of melatonin use in relation to withdrawal from long-term use of benzodiazepines and related drugs (Lähteenmäki et al. 2013). In the Satauni Study, participants received either 2mg of oral melatonin or placebo, counseling in sleep hygiene, information about possible withdrawal symptoms and psychosocial support, while the dose of the benzodiazepine or related drug was gradually lowered during a one month period (Lähteenmäki et al. 2013). The participants were followed up to six months.

In the Satauni Study volunteer participants were recruited via local health centres and two advertisements in a local newspaper. The recruitment took place between 16 February 2009 and 14 January 2010, and follow-up lasted until 23 July 2010. Persons aged 55 years or over using temazepam, zopiclone or zolpidem on a regular long-term basis (prior 30 days of daily use or longer) due to primary insomnia according to DSM-IV criteria (APA 1994) were included in the study (Lähteenmäki et al. 2013). Of the 92 initial participants, 89 (59 women and 30 men) completed the entire study, and their handgrip strength and balance test data are reported in the study IV of this academic thesis. Their mean age (range) was 67 (55–91) years.

5.2 Informed consent and ethical approvals

Study I's protocol was approved by the Ethics Committee of Satakunta Central Hospital and the Board of Pori City Hospital.

Informed consent was obtained from all participants or their caregivers in studies II and III. The baseline plan for these was approved by the Joint Ethics Committee of the University of Turku and the Turku University Central Hospital. Data collection for follow-up was approved by the Finnish Ministry of Social Affairs and Health, the Finnish National Research and Development Centre for Welfare and Health, and the Lieto District Health Authority.

Study IV, as part of the Satauni Study, was approved by the Ethics Committee of Satakunta Hospital District and the National Agency for Medicines of Finland (EudraCT 2008-0006795-30). Written informed consent was received form each participant before entering the trial.

5.3 Data collection

5.3.1 Background data

The author of this thesis collected the data for study I. As part of study I, data about age, drugs, and diagnoses were collected from the medical records. The names, dosages, and frequencies of dosing of all regularly prescribed drugs and of those given irregularly (when needed) were recorded. Ability to walk was assessed and recorded by the nurses responsible for the patient's care. The Mini Mental State Examination (MMSE) test was performed and recorded for all study patients in assessing cognitive abilities (Folstein & Folstein 1975). Notes in medical and nursing records were used in assessing the documentation on the effects and side effects of the drugs. During the data collection period, the author of this thesis worked as a medical student in these five long-term care wards. His observations about the documentation of effects and side effects of drugs in medical or nursing records, about the prescribing pattern of psychotropic drugs and other potentially harmful drugs, and about non-pharmacological care were used in describing the overall care.

Regarding studies II and III, extensive data concerning for example participants' education, socio-demographic, health behavior, cognitive and functional abilities, diseases was collected in the Lieto Study by interviews, measurements, tests and clinical examinations (Isoaho et al. 1994). Additional data was also collected from the Finnish Hospital Discharge Register and Cause of Death Statistics. All of this data formed the background for studies II and III. The participants of the Lieto Study made two visits to the Lieto Health Centre (Isoaho et al. 1994). The interviews, measurements and tests were executed by two trained nurses. The clinical examinations were performed by one experienced general practitioner. If a person was not able to visit the health centre, a home visit or a visit to the nursing home was made. These kinds of visits were made for 75 participants.

In Lieto Study, participants were asked to bring their prescription forms, medication lists and pill boxes to the examinations. Data on the use of drugs were collected by a trained nurse by interview and by checking the prescription forms, medication lists, pill boxes and medical records of the participants (Isoaho et al. 1994).

Concerning study IV, background data (gender, age, marital status, education and occupation) and data concerning health behavior, diseases, sleep behavior and especially medication use were collected at baseline (Lähteenmäki et al. 2013). Clinical examinations were performed on each patient. Information on cognitive performance, mood and quality of life was measured and recorded. The patient's balance was assessed with the Short Berg's Balance Scale (BBS-9) (Hohtari-Kivimäki et al. 2012), which is a 9-item version of the original BBS (Berg et al. 1989). The BBS-9 consists of seven dynamic aspects of balance (sitting to standing, transfers, reaching forward with outstretched arm, retrieving object from floor, turning to look behind, turning 360^{o} and placing alternate foot on stool), and two static aspects of balance (standing with one foot in front and standing on one foot) (Hohtari-Kivimäki et al. 2012). Handgrip strength (both hands, three times consecutively) was measured with Jamar® dynamometer in kilograms (kg) (Abidanza et al. 2012). The average value of the stronger hand was recorded. BBS-9 and handgrip strength were measured seven times during the study (at baseline and at 1, 2, 3 and 4 weeks and 2 and 6 months from baseline).

In study IV, venous blood samples were taken in order to determine the residual plasma concentration of temazepam, zopiclone, zolpidem and other benzodiazepines or their metabolites (diazepam, desmetyldiazepam and oxazepam). The samples were taken at baseline and one month after the start of withdrawal. A liquid chromatographic-tandem mass spectrometric method was used in the analyses (Quintela et al. 2006). Participants with no measurable plasma concentration of the study drugs at one month after the start of the withdrawal were classified as short-term withdrawers (n=69, 78%) and those with a measurable concentration as short-term non-withdrawers (n=20, 22%). The division of participants into long-term withdrawers (n=34, 38%) and non-withdrawers (irregular users, n=44, 49%; regular users, n=11, 12%) was determined by interviewing the participants and checking their medical records and prescriptions in detail six months after the start of the withdrawal (Lähteenmäki et al. 2013).

At study IV's baseline, the short-term withdrawers and non-withdrawers did not vary in age, gender, marital status, education, body measures, self-related quality of life, number of medications, duration of BZD use or alcohol consumption (Lähteenmäki et al. 2013; Puustinen et al. 2013). The original study showed that sixty-nine participants (78%) had withdrawn from temazepam, zopiclone or zolpidem at the one–month time point. At the 6 month time point, 34 (38%) participants had remained withdrawers, and 35 (39%) participants had returned to irregular or daily use (Lähteenmäki et al. 2013). The background data related to study IV is presented in detail in previous reports (Lähteenmäki et al. 2013; Puustinen et al. 2013).

5.3.2 Fracture data

Fracture data was used in studies II and III. Information about fractures confirmed with radiology reports was collected individually from the medical records from the study's baseline until the end of 1996. Data on fractures were obtained for 1,177 participants (98% of the baseline population) (Piirtola et al. 2007). The missing 19 participants from the baseline population (n=1,196) had moved away from the area during the follow-up and their medical data could not be reached.

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.

Only the first fracture of each participant during the follow-up period was included. Pathological fractures and those caused by the most serious accidents were excluded in order to avoid bias in the analyses (Piirtola et al. 2007 and 2008). In the case of persons who sustained more than one fracture in an accident, the main fracture contributing to the need for treatment was taken into account. Fractures were classified using ICD-10 codes (WHO 1995; Piirtola et al. 2007).

5.3.3 Medication data and classification of medications

In study I, medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification index (WHO 2004). Both psycholeptics (N05) and psychoanaleptics (N06) were included in psychotropic drugs. Antipsychotics were classified into typical and atypical categories. Typical antipsychotics included chlorpromazine, levomepromazine, promazine, dixyrazine, fluphenazine, perphenazine, prochlorperazine, periciazine, thioridazine, haloperidol, melperone, flupentixol, chlorprotixene, zuclopenthixol, pimozide, penfluridol and sulpiride. Atypical included olanzapine, clozapine, quetiapine, risperidone, ziprasidone, amisulpiride, zotepine, sertindole and aripiprazole. Benzodiazepines were classified according to their half-lives into those with long (diazepam, chlordiazepoxide, nitrazepam, clonazepam, clobazam, flurazepam), medium (alprazolam, lorazepam, temazepam), and short (oxazepam, triazolam, midazolam) half-lives. Benzodiazepine related drugs included zopiclone, zolpidem and zaleplon. Opioids included medications belonging to ATC class N02A. The list of strongly anticholinergic drugs was based on the Beers criteria (Fick et al. 2003) modified on the criteria by the Swedish expert group (Socialstyrelsen 2003). The list included the following medications: amitriptyline, aprepitant, atropine, belladonna alkaloids, biperiden,

butylscopolamine, chlorpromazine, chlorprothixene, clinidium, clomipramine, fluphenazine, difenhydramine, disopyramide, dixyrazine, doxepin, glycopyrronium, hydroxyzine, hyoscyamine, levomepromazine, orphenadrine, oxybutynin, perphenazine, periciazine, prochlorperazine, thioridazine, tolterodine, trospium, scopolamine, trimipramine, and quinidine. Atropine, glycopyrronium, mepenzolate, scopolamine, butylscopolamine, quinidine, emepronium, anticholinergic anti-parkinson drugs, levomepromazine, prochlorperazine and chlorprothixene were added to the list of anticholinergic drugs from the Swedish criteria.

In data collection for studies II and III, drugs were classified according to ATC-classification (version of the year 2000) (WHO 2000). Table 5 includes a detailed list of medications used in the analyses of studies II and III.

5.4 Statistical analyses

5.4.1 Use of nervous system drugs (study I)

Cross-tabulations were used as part of the explanatory data analysis on medication use. Analyses were performed using MS Exel version 10 (Microsoft Corporation).

5.4.2 Nervous system drugs and fractures (studies II and III)

Confounding variables were identified from previous study results that describe predictors of fractures within the same study population (Piirtola et al. 2008). For women, old age (75 years or over), 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 (75 to 84 years), multiple depressive symptoms and compression fracture in one or more upper lumbar or thoracic vertebras.

The control group consisted of participants who did not use any of the target medication substances (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 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 analyzed with adjustment for the confounding variables.

Results were quantified using relative risks 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).

Table 5. Generic names of medications used in the analyses (from study III).

Opioids	fentanyl, morphine, oxycodone, codeine, ethylmorphine, opium alkaloids with morphine, dextrometorphan, opium derivatives (mucolytics and expectorants
Antiepileptics	phenobarbital, primidone, phenytoin, ethosuximide, clonazepam, carbamazepine, valproic acid
Anticholinergic medications	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
Benzodiazepines	*Long half-life:* chlordiazepoxide, chlorazepate, diazepam, flurazepam, nitrazepam, flunitrazepam, medazepam, clobazam, clonazepam *Intermediate half-life:* alprazolam, lorazepam, temazepam *Short half-life:* oxazepam, triazolam, midazolam *Benzodiazepine related drugs:* zopiclone
Antidepressants	imipramine, imipramine oxide, clomipramine, opipramol, trimipramine, dibenzepin, amitriptyline, nortriptyline, doxepine, fluoxetine, citalopram, fluvoxamine, mianserin, trazodone, nialamide
Antipsychotics	*Typical:* chlorpromazine, levomepromazine, promazine, dixyrazine, fluphenazine, perphenazine, prochlorperazine, periciazine, thioridazine, haloperidol, melperone, flupentixol, chlorprotixene, zuclopenthixol, pimozide, penfluridol, sulpiride *Atypical:* clozapine *Other:* lithium

5.4.3 Nervous system drugs, balance and handgrip strength (study IV)

The original Satauni Study concluded that the use of 2 mg of melatonin in the evenings neither benefitted benzodiazepine withdrawal nor caused adverse effects (Lähteenmäki et al. 2013). Based on this result, data from the melatonin and placebo groups were pooled and analyzed together in the study IV.

At baseline, differences between short-term withdrawers and non-withdrawers were tested with the Mann-Whitney U-test (BBS-9), two-sample t-test (handgrip strength) or χ^2 -test (BBS-9 ≥33 vs. <33 points).

For the analysis of BBS-9, we pooled the data for men and women. BBS-9 points (≥33 vs. <33) between short- and long-term withdrawers and non-withdrawers were compared at baseline and during time points of 1, 2, 3 and 4 weeks and 2 and 6 months from baseline using binary logistic regression analysis with generalized estimating equations (GEE) with an exchangeable working correlation matrix. Group and gender were used as a fixed factors and time was used as a repeated factor in a logistic model. The interaction effect of group x time was also tested.

The data concerning handgrip strength was analyzed separately for women and men. Handgrip strength between short- and long-term withdrawers and non-withdrawers was compared at baseline and during the various planned study time points using repeated measures analysis of variance using a heterogeneous compound symmetry covariance structure. Group was used as a fixed factor and time was used as a repeated factor. The interaction effect of group x time was also tested. Dunnett's method was used in comparing different follow-up time points to baseline.

P-values less than 0.05 were considered statistically significant. SAS version 9.2 and SAS Enterprise Guide 4.1 was used in the analyses.

6. RESULTS

6.1 Background data

The mean age of patients in the long-term care wards of Pori City Hospital included in study I was 84.2 years (Table 6). Their cognitive and physical abilities were poor; the median MMSE score was zero points and 79% were immobile (Table 6). Nearly half of the patients (46%) were diagnosed as having dementia and 78% had at least one neurological diagnosis (Table 7). Further, 13% of the patients had psychiatric diagnoses.

The population in studies II and III (the Lieto Study) was clearly more independent and had higher well-being compared with the sample in study I; thus, only 5.4% of the participants lived in an institution (Table 8). The vast majority of patients could walk independently at least 400 meters.

Table 6. Study I background data (from study I).

	Mean ± SD	Median
Age	84.2 ± 8.0	85
Number of diagnoses	3.5 ± 1.7	3
Number of medications	9.7 ± 3.8	9
Regular medications	6.7 ± 2.9	6
Irregular medications	3.0 ± 2.0	3
Length of stay (months)	28.3 ± 30.0	17
MMSE sum points	3.4 ± 6.2	0

MMSE=Mini-Mental State Examination; variation in the sum score is 0–30.

Table 7. The most common diagnoses in study I population (from study I).

	% of patients
Essential hypertension	29
Chronic ischemic heart disease	27
Unspecified dementia	25
Atrial fibrillation/flutter	19
Non-insulin dependent diabetes	19
Heart failure	16
Alzheimer's disease	11
Vascular dementia	10
Depression	6

Table 8. Participant characteristics of studies II and III, n=1 177 (from study II).

	No. (%)
Sex	
Women	695 (59.0)
Men	482 (41.0)
Marital status	
Married	649 (55.1)
Unmarried or divorced	131 (11.1)
Widowed	397 (33.7)
Place of living	
Home, with other person(s)	749 (63.6)
Home, alone	364 (30.9)
Institution	64 (5.4)
Basic education	
Less than basic	118 (10.0)
Basic	979 (83.2)
More than basic	80 (6.8)
Walking ability	
Independently	956 (81.5)
Using a device	167 (14.2)
With help of other person(s)	50 (4.3)
Previous occupation	
Service	205 (17.4)
Industry	421 (35.8)
Agriculture	453 (38.5)
Family	98 (8.3)
Smoking	
Current	94 (8.0)
Former	303 (25.8)
	Mean ± SD
Age, years	73.2 ± 6.9
Body mass index, kg/m²	27.7 ± 4.9
Number of drugs	
Regular	2.6 ± 2.5
Irregular	0.6 ± 1.0

6.2 Prevalence of nervous system drug use

The use of nervous system drugs among patients in study I was extensive (Tables 9, 10 and 11). Nearly four patients out of five (79%) used at least one psychotropic drugs on a regular basis, and the prevalence was higher (87%) when all psychotropic drugs given when needed were added. When individual drug classes are analyzed separately, benzodiazepines and antipsychotics in particular were frequently

prescribed (Table 9). Furthermore, the concomitant use of psychotropic drugs was common as, 33% of the patients used at least three psychotropics on a regular basis (Table 10). The concomitant use of two or more benzodiazepines was particularly common, but also two or more antipsychotics were used frequently when drugs given when needed were taken into consideration (Table 11).

Table 9. Use of psychotropics, opioids and strongly anticholinergic medications in study I (from study I).

	Regular use		Irregular use	
	n	**%**	**n**	**%**
Antidepressants	40	26	0	0
Antipsychotics	74	48	44	29
Atypical antipsychotics	58	38	9	6
Typical antipsychotics	22	14	41	27
Benzodiazepines and related drugs	100	65	84	55
Benzodiazepines, long half-life	11	7	27	18
Benzodiazepines, medium half-life	95	62	68	44
Benzodiazepines, short half-life	0	0	1	1
Benzodiazepine related drugs	31	20	21	14
Opioids	29	19	76	49
Codeine	7	5	21	14
Tramadol	12	8	25	16
Phentanyl	11	7	1	1
Oxycodone	1	1	46	30
Dextropropoxyphene	0	0	1	1
Hydromorphone	0	0	1	1
Morphine	0	0	12	8
Buprenorphine	0	0	1	1
Strongly anticholinergic medications	26	17	10	6

Table 10. Concomitant use of psychotropics in study I (from study I).

	Regular use		Regular and irregular use	
Medication combination	**n**	**%**	**n**	**%**
BZD or related drug + antidepressant + antipsychotic	16	10	19	12
Two BZDs or related drugs + antidepressant + antipsychotic	5	3	15	10
Three or more psychotropics	51	33	82	53

BZD=benzodiazepines derivative

Table 11. Concomitant use of medications with similar pharmacodynamic properties in study I (from study I).

	Number of medications					
	1		2		3	
	n	**%**	**n**	**%**	**n**	**%**
Antipsychotics						
Regular use	66	43	7	5	1	1
Regular or irregular use	49	32	25	16	9	6
Benzodiazepines and related drugs						
Regular use	63	41	36	23	1	1
Regular or irregular use	41	27	43	28	28	18
Opioids						
Regular use	27	18	2	1	0	
Regular or irregular use	42	27	31	20	9	6
Antidepressants						
Regular use	39	25	1	1	0	
Regular or irregular use	39	25	1	1	0	

The use of medications by the population in studies II and III was minor compared to that of the study I sample. On average, the participants in studies II and III used 2.6 medications on a regular basis and 0.6 medications when needed. The prevalence of nervous system drug use is presented in detail in Tables 12 and 13.

Table 12. Use and concomitant use of psychotropics at baseline in studies II and III, n=1 177 (from study II).

Drug	Men (n=482) No. (%)	Women (n=695) No. (%)	*P*-value*
One BZD	76 (15.8)	187 (26.9)	<.001
One AP	31 (6.4)	64 (9.2)	0.10
One AD	14 (2.9)	38 (5.5)	0.04
At least two BZDs	13 (2.7)	37 (5.3)	0.03
At least two APs	5 (1.0)	9 (1.3)	0.79
At least two ADs	1 (0.2)	0 (0.0)	0.41
BZD and AP†	19 (3.9)	29 (4.2)	0.88
BZD and AD†	10 (2.1)	25 (3.6)	0.16
AP and AD†	5 (1.0)	13 (1.9)	0.34
At least one psychotropic drug	92 (19.1)	229 (32.9)	<.001

* statistical difference between the sexes
† persons using concomitantly one drug or more drugs from each subgroup
BZD=benzodiazepines and related drugs
AP=antipsychotic drug
AD=antidepressant

Table 13. Use and concomitant use of opioids (OP), antiepileptics (AE) and anticholinergic drugs (ACh) and concomitant use of these drugs with each other or with a benzodiazepine or a related drug (BZD), antipsychotic (AP) or antidepressant (AD) at baseline in studies II and III, n=1 177 (from study III).

Drug or drug combination	Men (n=482) No. (%)	Women (n=695) No. (%)	*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†	5 (1.0)	9 (1.3)	0.79
OP and AP†	3 (0.6)	5 (0.7)	1.00
OP and BZD†	5 (1.04)	8 (1.2)	1.00
OP and AD†	1 (0.2)	5 (0.7)	0.41
OP and AE†	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†	24 (5.0)	51 (7.3)	0.12
ACh and BZD†	26 (5.4)	62 (8.9)	0.024
ACh and AD†	9 (1.9)	23 (3.3)	0.15
ACh and AE†	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†	3 (0.6)	1 (0.1)	0.31
AE and BZD†	6 (1.2)	3 (0.4)	0.17
AE and AD†	3 (0.6)	1 (0.1)	0.31

* statistical difference between genders

† persons using concomitantly one drug or more drugs from each subgroup

6.3 Nervous system drugs and the risk of fractures

The distribution and incidence of fractures in studies II and III during the follow-up periods are shown in Table 14.

In univariate analyses, the use of two or more benzodiazepines was associated with an increased risk of fractures in men during both follow-up periods. These relationships remained significant after adjusting for confounding variables (Table 15). Poisson regression analysis adjusted for confounding variables also showed the use of two or more antipsychotics to be associated with an increased risk of fractures in men during both follow-up periods. 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 (Table 16). After adjusting for other confounding factors, 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, concomitant use of an opioid and a benzodiazepine remained significantly associated with the risk of fractures.

In women, the use of two or more antipsychotics was related to an increased risk of fractures in univariate analysis in the three-year follow-up, but this relationship did not remain significant after adjusting for age (Table 17). During the women's three–year follow-up, 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 (Table 18). However, no associations were discovered after adjustment for the other confounding factors.

Table 14. Distribution of fracture types in studies II and III during the follow-up periods of three and six years taking into account the first fracture, n=1 177 (from study II).

Type of fracture	Men (n=482)		Women (n=695)	
	Three years No. (%)	Six years No. (%)	Three years No. (%)	Six years No. (%)
Total	29 (100)	45 (100)	84 (100)	133 (100)
Hip	6 (20.7)	8 (17.8)	17 (20.2)	29 (21.8)
Wrist	3 (10.3)	5 (11.1)	25 (29.8)	40 (30.1)
Tibial and ankle	7 (24.1)	9 (20.0)	10 (11.9)	12 (9.0)
Prox. humerus	1 (3.4)	2 (4.4)	10 (11.9)	15 (11.3)
Rib(s)	2 (6.9)	9 (20.0)	3 (3.6)	7 (5.3)
Vertebral compression	3 (10.3)	3 (6.7)	6 (7.1)	8 (6.0)
Other	7 (24.1)	9 (20.0)	13 (15.5)	22 (16.5)

Table 15. Relationships between use of psychotropics and risk of fractures in men (from study II).

Drug or drug combination	Number of fracture cases No. (%) / controls No. (%)	Age-adjusted analysis		Adjusted analysis*	
		RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
3-year follow-up					
One BZD	7 (9.2) / 20 (5.7)	1.4 (0.6–3.4)	0.44	-	-
One AP	2 (6.5) / 20 (5.7)	0.9 (0.2–4.1)	0.93	-	-
One AD	1 (7.1) / 20 (5.7)	1.0 (0.1–7.9)	0.97	-	-
Two or more BZDs	3 (23.1) / 20 (5.7)	4.7 (1.4–15.7)	0.01	4.7 (1.4–16.3)	0.01
Two or more APs	1 (20.0) / 20 (5.7)	9.4 (1.2–71.1)	0.03	8.3 (1.0–66.2)	0.05
Two or more ADs	0 (0.0) / 20 (5.7)	-	-	-	-
BZD and AP†	2 (10.5) / 20 (5.7)	2.5 (0.8–8.4)	0.13	-	-
BZD and AD†	1 (10.0) / 20 (5.7)	1.5 (0.2–11.3)	0.67	-	-
AP and AD†	1 (20.0) / 20 (5.7)	4.9 (0.7–36.0)	0.12	-	-
6-year follow-up					
One BZD	11 (14.5) / 29 (8.3)	1.8 (0.9–3.7)	0.09	-	-
One AP	4 (12.9) / 29 (8.3)	1.6 (0.6–4.8)	0.37	-	-
One AD	1 (7.1) / 29 (8.3)	0.9 (0.1–6.6)	0.91	-	-
Two or more BZDs	4 (30.8) / 29 (8.3)	5.7 (2.0–16.2)	0.001	5.8 (2.0–16.6)	0.001
Two or more APs	1 (20.0) / 29 (8.3)	7.6 (1.0–56.7)	0.05	7.9 (1.1–59.0)	0.04
Two or more ADs	0 (0.0) / 29 (8.3)	-	-	-	-
BZD and AP†	3 (15.8) / 29 (8.3)	2.5 (0.8–8.4)	0.13	-	-
BZD and AD†	1 (10.0) / 29 (8.3)	1.5 (0.2–11.3)	0.67	-	-
AP and AD†	1 (20.0) / 29 (8.3)	4.9 (0.7–36.0)	0.12	-	-

* adjusted for age, amount of depressive symptoms in Zung Self-rating Depression Scale and a compression fracture in one or more upper lumbar or thoracic vertebras at baseline
† persons using concomitantly one drug or more drugs from each subgroup
BZD=benzodiazepines or related drugs
AP=antipsychotic drug
AD=antidepressant
P-value=statistical significance
RR=relative risk
CI=confidence interval

Table 16. Relationships between the use of opioids (OP), antiepileptics (AE) or anticholinergic drugs (ACh) or concomitant use of these drugs with each other or with a benzodiazepine or a related drug (BZD), antipsychotic (AP) or antidepressant (AD) and risk of fractures in men (from study III).

Drug or drug combination	Number of fractures in cases (%) / in controls (%)	Age-adjusted analysis n=352–360		Adjusted analysis* n=331–336	
		RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
3-year follow-up					
One OP	2 (18.2) / 20 (5.7)	3.1 (0.7–14.4)	0.15	-	-
Two or more AEs	1 (33.3) / 20 (5.7)	6.6 (0.9–49.6)	0.07	-	-
OP and AP†	1 (33.3) / 20 (5.7)	10.2 (1.4–77.2)	0.02	21.1 (1.7–256.9)	0.02
OP and BZD†	2 (40.0) / 20 (5.7)	7.2 (1.4–37.2)	0.02	3.8 (0.7–21.1)	0.12
6-year follow-up					
One OP	3 (27.3) / 29 (8.3)	4.5 (1.3–15.6)	0.02	3.2 (0.7–14.9)	0.15
OP and AP†	1 (33.3) / 29 (8.3)	7.4 (1.0–55.5)	0.05	-	-
OP and BZD†	2 (40.0) / 29 (8.3)	12.0 (2.5–58.4)	0.002	5.0 (1.0–25.2)	0.05

* adjusted for age, amount of depressive symptoms and a compression fracture in one or more upper lumbar or thoracic vertebras at baseline

† persons using concomitantly one drug or more drugs from each subgroup

P-value=statistical significance

RR=relative risk

CI=confidence interval

Table 17. Relationships between use of psychotropics and risk of fractures in women (from study II).

Drug	Number of fracture cases No. (%) / controls No. (%)	Age-adjusted analysis		Adjusted analysis*	
		RR (95% CI)	*P*-Value	RR (95% CI)	*P*-value
3-year follow-up					
One BZD	22 (11.8) / 46 (11.9)	0.9 (0.5–1.5)	0.66	-	-
One AP	9 (14.1) / 46 (11.9)	1.1 (0.5–2.2)	0.83	-	-
One AD	3 (7.9) / 46 (11.9)	0.6 (0.2–1.9)	0.36	-	-
Two or more BZDs	6 (16.2) / 46 (11.9)	1.3 (0.5–3.0)	0.60	-	-
Two or more APs	3 (33.3) / 46 (11.9)	3.3 (1.0–10.7)	0.05	1.0 (0.1–7.0)	0.98
Two or more ADs	0 (0.0) / 46 (11.9)	-	-	-	-
BZD and AP†	5 (17.2) / 46 (11.9)	1.4 (0.6–3.6)	0.46	-	-
BZD and AD†	2 (8.0) / 46 (11.9)	0.6 (0.1–2.5)	0.47	-	-
AP and AD†	2 (15.4) / 46 (11.9)	1.1 (0.3–4.7)	0.86	-	-
6-year follow-up					
One BZD	33 (17.7) / 76 (19.6)	0.8 (0.6–1.3)	0.43	-	-
One AP	13 (20.3) / 76 (19.6)	1.0 (0.6–1.8)	0.98	-	-
One AD	5 (13.2) / 76 (19.6)	0.6 (0.2–1.5)	0.30	-	-
Two or more BZDs	7 (18.9) / 76 (19.6)	0.9 (0.4–2.0)	0.81	-	-
Two or more APs	3 (33.3) / 76 (19.6)	2.6 (0.8–8.3)	0.10	-	-
Two or more ADs	0 (0.0) / 76 (19.6)	-	-	-	-
BZD and AP†	7 (24.1) / 76 (19.6)	1.4 (0.6–3.0)	0.43	-	-
BZD and AD†	3 (12.0) / 76 (19.6)	0.6 (0.2–1.8)	0.34	-	-
AP and AD†	4 (30.8) / 76 (19.6)	1.6 (0.6–4.4)	0.38	-	-

*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
† Persons using concomitantly one drug or more drugs from each subgroup
BZD=benzodiazepines or related drugs
AP=antipsychotic
AD=antidepressant
P-value=statistical significance
RR=relative risk
CI=confidence interval

Table 18. Relationships between the use of opioids (OP), antiepileptics (AE) or anticholinergic drugs (ACh) or concomitant use of these drugs with each other or with a benzodiazepine or a related drug (BZD), antipsychotic (AP) or antidepressant (AD) and risk of fractures in women (from study III).

Drug or drug combination	Number of fractures in cases (%) / in controls (%)	Age-adjusted analysis n =391-398		Adjusted analysis* n =369-375	
		RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
3-year follow-up					
AE and BZD†	2 (66.7) / 46 (11.9)	7.5 (1.8–32.4)	0.007	6.3 (0.7–52.8)	0.09
6-year follow-up					
One AE	4 (40.0) / 76 (19.6)	3.0 (1.1–8.2)	0.03	2.7 (0.8–9.2)	0.1
AE and BZD†	2 (66.7) / 76 (19.6)	9.0 (2.1–38.1)	0.003	5.8 (0.7–45.9)	0.1

* 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
† persons using concomitantly one drug or more drugs from each subgroup
P-value=statistical significance
RR=relative risk
CI=confidence interval

6.4 Benzodiazepine withdrawal, balance and handgrip strength

6.4.1 Short Berg's Balance Scale (BBS-9)

The median result of BBS-9 was 33 points (interquartile range (IQR) 3) for men, and it was 33 points (IQR 3) for women, respectively. The results of the BBS-9 did not differ significantly between men and women (p=0.904).

Changes in BBS-9 scores did not differ between the short-term withdrawers and non-withdrawers (group x time interaction effect p=0.474, Table 19). There was no difference in BBS-9 scores between groups (group effect p=0.997); however, balance was better in the follow-up measurements compared to baseline (time effect p<0.0001).

The changes in BBS-9 scores did not differ between long-term withdrawers and non-withdrawers (group x time interaction effect, p=0.054), and there was no difference in BBS-9 scores between groups (group effect p=0.165). However, balance was better in the follow-up measurements compared to baseline (time effect p<0.0001).

Table 19. **Balance by success of short-term ("ONE MONTH") and long-term ("SIX MONTHS") withdrawal. Men and women combined (*n*=89). Number of withdrawers and non-withdrawers under 33 points (and their percentage from all participants) at different time points are given (from study IV).**

ONE MONTH	Measurement point									
	Baseline	1 week	2 weeks	3 weeks	1 month	2 months	6 months			
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	P[1]	P[2]	P[3]
Withdrawers under 33 points[a]	27 (40)	19 (28)	17 (25)	14 (21)	13 (19)	9 (13)	9 (13)	0.474	0.997	<0.001
Non-withdrawers under 33 points[a]	7 (35)	5 (26)	4 (22)	2 (11)	5 (26)	4 (24)	1 (6)			
SIX MONTHS	**Measurement point**									
	Baseline	1 week	2 weeks	3 weeks	1 month	2 months	6 months			
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	P[1]	P[2]	P[3]
Withdrawers under 33 points[a]	10 (30)	8 (25)	4 (12)	4 (12)	3 (9)	3 (9)	2 (6)	0.054	0.165	<0.001
Non-withdrawers under 33 points[a]	24 (44)	16 (30)	17 (32)	12 (23)	15 (27)	10 (20)	8 (15)			

P^1 = Statistical significance for group x time interaction effect; logistic regression analysis using GEE estimation; adjusted for sex.
P^2 = Statistical significance for group effect; logistic regression analysis using GEE estimation; adjusted for sex and time.
P^3 = Statistical significance for time effect; logistic regression analysis using GEE estimation. After adjustment for sex and group at one month's time point balance was better at 1 week (P=0.003), 2 weeks (P=0.003), at 3 weeks (P<0.001), at 1 month (P<0.001), at 2 months (P<0.001), and at 6 months (P<0.001) compared to baseline. After adjustment for sex and group at six months' time point balance was better at 1 week (P=0.003), at 2 weeks (P=0.003), at 3 weeks (P<0.001), at 1 month (P<0.001), at 2 months (P<0.001), and at 6 months (P<0.001) compared to baseline.
[a] Cut off -point (<33) suggests increased fall risk (Hohtari-Kivimäki et al. 2013).

Table 20. **Handgrip strength (kg) in men (*n*=30) by success of short-term ("ONE MONTH") and long-term ("SIX MONTHS") withdrawal (from study IV).**

ONE MONTH	Measurement point									
	Baseline	1 week	2 weeks	3 weeks	1 month	2 months	6 months			
	mean, SD	mean, SD	mean, SD	mean, SD	mean, SD	mean, SD	mean, SD	P[1]	P[2]	P[3]
Withdrawers (n=24)	42.9, 6.5	44.9*, 5.7	44.6*, 6.6	44.6*, 5.5	44.5*, 6.5	44.5*, 5.2	44.2*, 6.0	0.296	0.619	0.002
Non-withdrawers (n=6)	40.3, 5.8	44.0*, 7.0	42.8*, 6.2	41.5*, 6.0	41.9*, 6.6	43.6*, 7.7	43.9*, 8.4			
SIX MONTHS	Measurement point									
	Baseline	1 week	2 weeks	3 weeks	1 month	2 months	6 months			
	mean, SD	mean, SD	mean, SD	mean, SD	mean, SD	mean, SD	mean, SD	P[1]	P[2]	P[3]
Withdrawers (n=15)	41.5, 5.6	43.5§, 5.5	43.7§, 5.4	43.7§, 5.2	43.7§, 6.3	44.4§, 4.5	43.9§, 5.5	0.357	0.897	0.002
Non-withdrawers (n=15)	43.3, 7.1	46.0§, 6.1	45.0§, 7.5	44.6§, 6.1	44.2§, 6.9	44.2§, 6.8	44.3§, 7.4			

P^1 = Statistical significance for group x time interaction effect; repeated measures analysis of variance.
P^2 = Statistical significance for group effect; repeated measures analysis of variance; adjusted for time.
P^3 = Statistical significance for time effect; repeated measures analysis of variance. After adjustment for group at one month's time point handgrip strength was better* at 1 week (P=0.002), at 2 weeks (P=0.001), at 3 weeks (P=0.001), at 1 month (P=0.013), at 2 months (P=0.001), and at 6 months (P=0.006) compared to baseline. After adjustment for group at six months' time point handgrip strength was better§ at 1 week (P=0.002), at 2 weeks (P=0.002), at 3 weeks (P=0.001), at 1 month (P=0.013), at 2 months (P=0.001), and at 6 months (P=0.006) compared to baseline.
SD = Standard deviation

Table 21. **Handgrip strength (kg) in women (*n*=59) by success of short-term ("ONE MONTH") and long-term ("SIX MONTHS") withdrawal.**

ONE MONTH	Measurement point									
	Baseline	1 week	2 weeks	3 weeks	1 month	2 months	6 months			
	mean, SD	mean, SD	mean, SD	mean, SD	mean, SD	mean, SD	mean, SD	P[1]	P[2]	P[3]
Withdrawers (n=45)	23.5, 5.4	24.2, 5.8	24.4, 5.5	24.8*, 5.6	24.7*, 5.7	24.9*, 5.5	24.8*, 5.8	0.350	0.032	0.003
Non-withdrawers (n=14)	20.4, 4.1	21.0, 4.5	19.9, 4.1	20.3, 5.7	21.0, 5.5	21.2, 5.8	20.8, 6.2			
SIX MONTHS	**Measurement point**									
	Baseline	**1 week**	**2 weeks**	**3 weeks**	**1 month**	**2 months**	**6 months**			
	mean, SD	**mean, SD**	**mean, SD**	**mean, SD**	**mean, SD**	**mean, SD**	**mean, SD**	**P[1]**		**P[4]**
Withdrawers (n=19)	23.3, 5.4	24.1, 6.7	24.7, 5.6	25.6§, 5.9	25.2§, 5.7	25.6§, 5.6	25.3§, 5.5	0.040		0.001
Non-withdrawers (n=40)	22.5, 5.2	23.1, 5.2	22.7, 5.4	22.9, 5.8	23.1, 5.8	23.1, 5.7	23.2, 6.3			0.427

P^1 = Statistical significance for group x time interaction effect; repeated measures analysis of variance.
P^2 = Statistical significance for group effect; repeated measures analysis of variance; adjusted for time.
P^3 = Statistical significance for time effect; repeated measures analysis of variance. After adjustment for group, handgrip strength was better* at 3 weeks (P=0.002), at 1 month (P=0.004), at 2 months (P=0.005), and at 6 months (P=0.004) compared to baseline.
P^4 = Statistical significance for time effect within groups; repeated measures analysis of variance. Handgrip strength was better§ at 3 weeks (P=0.005), at 1 month (P=0.006), at 2 months (P<0.001) and at 6 months (P=0.003) among withdrawers compared to baseline.
SD = Standard deviation

6.4.2 Handgrip strength

The average value of handgrip strength in men was 42.4 kg (SD 6.2), and it was 22.9 kg (SD 5.1) for women. The handgrip strength results were statistically different between men and women ($p<0.0001$), and, thus, the data was analyzed separately by gender.

Among men, the changes in the handgrip strength did not differ between the short-term withdrawers and non-withdrawers (group x time interaction effect $p=0.296$, Table 20). There was no difference in the handgrip strength between groups (group effect $p=0.619$). However, handgrip strength was better in the follow-up measurements compared to those at baseline (time effect $p=0.002$). When the analyses were done for the long-term withdrawers and non-withdrawers, the changes did not differ between the groups (group x time interaction effect $p=0.357$), and there was no difference in the handgrip strength between groups (group effect $p=0.897$). However, handgrip strength was better in follow-up measurements compared to those at baseline (time effect $p=0.002$).

Among women, the changes in handgrip strength did not differ between the short-term withdrawers and non-withdrawers (group x time interaction effect $p=0.350$, Table 21), but handgrip strength was better in the withdrawers group compared to non-withdrawers (group effect $p=0.032$). Handgrip strength was better at 3 weeks ($p=0.002$), 1 month ($p=0.003$), 2 months ($p=0.005$) and 6 months ($p=0.004$) compared to baseline (time effect $p=0.003$). However, the changes in handgrip strength between the long-term withdrawers and non-withdrawers were statistically different (group x time interaction effect $p=0.040$). Handgrip strength was better among withdrawers compared to baseline at 3 weeks ($p=0.005$), 1 month ($p=0.006$), 2 months ($p=0.0005$) and 6 months ($p=0.003$), and the time effect was not statistically significant among non-withdrawers ($p=0.427$).

7. DISCUSSION

7.1 Study limitations and strengths

7.1.1 Study settings, samples and populations

Study I aimed to provide an example of the pattern of nervous system drug use in a Finnish long-term care hospital. The results from study I represent an extreme. In order to define the other end, a population-based sample of Finnish old adults was investigated. These two different samples represent comparatively opposite aspects of nervous system drug use in Finland. However, studies II and III showed that even relatively modest concomitant use of these drugs is associated with fractures in old adults. Further, fractures are one of the most serious disorders confronted by old adults. In order to research tools for effective fracture prevention, a benzodiazepine withdrawal study was performed. Study IV demonstrated that benzodiazepine withdrawal is effective and that it rapidly improves handgrip strength, especially in women. Lowered handgrip strength is a known risk factor for falls and fractures. The three samples presented in this academic thesis form a path that starts from recognizing concomitant nervous system drug use in old adults, continues with that use being associated with fractures and ends with a concrete demonstration of the benefits of drug withdrawal.

In study I the sample of 154 patients was medium sized, and the patient sample was relatively homogeneous. This setting and sample was selected to complement prior data from the acute care wards of the same hospital (Puustinen et al. 2007). These data also provided the background for the author's thesis as part of his medical studies.

The population-based data used in studies II and III has been the basis of a large number of earlier studies published in peer-reviewed international scientific papers (Isoaho et al. 1994; Linjakumpu et al. 2002a and 2002b; Piirtola et al. 2007 and 2008). This large Lieto Study had a high participation rate (93%) among the residents in the municipality of Lieto, Finland (Isoaho et al. 1994), which is a representative example of Finnish semi-rural municipality. Studies II and III utilized the fracture data of 1,177 participants included in the Lieto Study, whose data concerning fractures was collected based on documentation in medical records (Piirtola et al. 2007 and 2008).

The completion rate was high in study IV as 97% of 92 participants completed the Satauni Study protocol. All these 89 participants were users of benzodiazepine hypnotics and had no other psychiatric or neurologic disease than primary insomnia. The three drop-outs suffered from difficulties in achieving and maintaining sleep (a women in the placebo group); inability to lower the benzodiazepine dose (a man in the melatonin group); and transportation impediments (a woman in the melatonin group) (Lähteenmäki et al. 2013). The sample consisted of volunteer participants who contacted study personnel themselves and expressed their motivation to reduce the use of benzodiazepines. Thus, study IV sample was relatively selected. Furthermore,

study IV lacked a control group of patients who had been free of benzodiazepines. This deficit results in ambiguity regarding the inferences concerning the relationship between benzodiazepine users and a benzodiazepine free sample. As the main outcome of adjuvant melatonin use to assist benzodiazepine withdrawal in the Satauni Study was not proven to have a statistically significant effect in the withdrawal process, the only intervention was the reduction of benzodiazepines. All of the participants were also able to receive psychosocial support, but no physiotherapeutic interventions were made.

7.1.2 Data collection

All of the data for study I was gathered, structured and recorded by one person and the method is considered to be reliable. However, part of the study I data collection was based on observational findings that are potentially open to various interpretations.

Of the six long-term care wards in the Pori City Hospital, five were included in study I. Data from the sixth ward was not obtained because of the tight study schedule. The sixth ward, however, did not by any fundamental means differ from the other four wards regarding patient population or treatment practices, and its absence is therefore unlikely to bias the results.

A combination of the Beers Criteria and the Swedish experts' criteria were used in study I for anticholinergic drug definition. The Beers Criteria and the Swedish experts' criteria are designed to define PIM use in old adults, not particularly anticholinergic drugs. Their lists of anticholinergic drugs and inclusion criteria are not based on any established definition. Despite this criticism, the Beers Criteria has been the most widely used method to determine inappropriate medication use. Therefore, being widely known, it is one starting point of listing anticholinergic drugs.

In contrast to study I, the definition of anticholinergic drugs in studies II and III was not based on a set of single criteria, but rather a combination of information gained from multiple sources (Table 5; Basu et al. 2003; Fick et al. 2003; Socialstyrelsen 2003; Pharmaceutical Information Centre 2004; Ancelin et al. 2006; Bottiggi et al. 2006; Han et al. 2008; Carriere et al. 2009). Defining a certain medication as an anticholinergic drug is not unambiguous and to date no uniform definition system exists for this purpose. Tune and his colleagues published the first list of anticholinergic drugs in the 1990s (Tune et al. 1992). Since then, several other lists of anticholinergic drugs have been proposed and published (Lampela 2013). The complexity of establishing a definition for anticholinergic drug(s) is reviewed in more detail in the third chapter of this academic thesis.

The large pool of background data and measurements has permitted analyses of confounder factors in fracture studies that are part of the Lieto Study (Piirtola et al. 2008). However, a few previously described risk factors for fractures were not measured in the baseline examinations. These included vitamin D concentration, bone mineral density, family history of fractures, alcohol consumption, balance and lower limb muscle strength (Piirtola et al. 2008). Thus, the Lieto Study was not originally

targeted to evaluate fracture rates or to assess the risk of fractures among users of nervous system drugs. This shortage has to be taken into account when interpreting the results.

Furthermore, the Lieto Study data on participants' health status and background measurements was collected only at baseline. It is likely that many of these measurements (medication use for example) have undergone changes during the follow-up period and before a participant experienced a fracture. This could potentially have biased the results. For example, if a participant had started a new nervous system drug after baseline data collection and then experienced a fracture, he/she would have been classified incorrectly in the analyses, causing bias. This would potentially have weakened the associations between drug use and the risk of fractures.

The Lieto Study did not include information on drug use duration, which, according to the literature, can have an effect on fracture risk. It has been shown that the risk for fractures associated with benzodiazepine use is highest at drug initiation (Wang et al. 2001). In contrast, the fracture risk associated with antiepileptic drug use seems to be highest after more than twelve years of drug use (Souverein et al. 2006). Because of the lack of information on drug duration and initiation dates, it is not possible to link the data on fracture incidence date to the medication data and study associations between drug exposure and fracture incident on a time scale.

All fracture diagnoses were based on radiological reports. However, evidence shows that only one–third of vertebral fractures are diagnosed clinically (Old & Calvert 2004). This means that part of vertebral compression fractures may have been missed because of the lack of specific diagnoses and radiologic confirmation. Noting this, it is possible that vertebral fractures are underestimated in the Lieto Study.

Correspondingly, the data collected in study IV comprised a wide variety of background variables (Lähteenmäki et al. 2013). The evaluation of participants' benzodiazepine withdrawal success at the six month time point, however, was determined through interviews and checking filled prescription forms, not with blood samples. This inconsistency may have affected the results as patients may not have revealed all of their medication use in these interviews.

The measurements of interest in study IV, the Short Berg's Balance Scale (BBS-9) and handgrip strength, were both measured seven times during the study. Although a recent study reported that a BBS-9 score <33 points suggests increased fall risk (Hohtari-Kivimäki et al. 2013), the validation of BBS-9 and its use is not yet widespread in scientific work or clinical practice. Moreover, no comparative data on BBS-9 results in a benzodiazepine-free population exists. However, the Jamar® dynamometer is a widely used method to evaluate handgrip strength (Abidanza et al. 2012), and reference values are available in a Finnish population (Härkönen et al. 1993).

Regarding the four studies presented in this academic thesis, all interviews, recordings, measurements and interventions in these studies were performed by a small number of persons. This increases the repeatability and reliability of the study parameters.

7.1.3 Statistical analyses

Simple cross-tabulations were used in the analyses of study I to calculate the prevalence of medication use and other measures. These statistical data could not be used to determine causal relationships between medication use and the health outcomes of these patients, or the role of medications used as a method of chemical restraints, or between medication use and the quality of care.

The statistical approach in studies II and III was more demanding compared to that in study I. Baseline variables were compared using the Chi-square test and Fischer's exact test. At first, associations between fractures and medications were described by univariate and age-adjusted Poisson regression analyses. In the second phase, significant associations were analyzed with adjustment for confounding variables. The confounding variables were obtained from the results of an earlier study from the same population (Piirtola et al. 2008). This is one of the major strengths of our study. The confounders differed between men and women, and, thus, the analyses were performed separately by gender.

One notable limitation regarding studies II and III is the small number of fractures that occurred during the follow-up period. Furthermore, the use of nervous system drugs was not anywhere near the extent found in the study I sample. The small number of fractures caused statistical limitations: confidence intervals tended to be wide, which resulted in the true effect of the medication combination related to fracture risk being contained in a wide range. This observation must be considered when making conclusions.

In study IV, the most noticeable statistical problem was the small number of participants. This deficit did not allow us to analyze the study medications separately, and, thus, the data had to be combined in the analyses. As the results of handgrip strength were different between men and women, the data was analyzed separately. On the contrary, results of the BBS-9 comparisons showed no difference between the sexes, and the data was analyzed together.

7.2 Results

Study I showed that use of nervous system drugs was common among the sample, and their cognitive and physical abilities were very poor. Specifically, concomitant use of psychotropic drugs was common. In total, 79% of the patients used at least one psychotropic drug on a regular basis. Furthermore, every third patient used at least three psychotropic drugs concomitantly. These prevalences are very high for a sample with the poor overall health status described. In addition, there is strong evidence that the pharmacotherapy for behavioral and psychological symptoms of dementia (BPSD) is ineffective and raises the risk of ADEs (Ballard et al. 2001; Salzman et al. 2008). The documentation of positive or negative effects of the drugs was poor and non-pharmacological treatments, rehabilitation or activities were meager, for example. As a whole, the results highlight concerns related to the appropriateness of pharmacotherapy for these patients.

The results concerning nervous system drug use are comparable with results from another Finnish study among patients from geriatric wards and nursing homes (Pitkälä et al. 2004). That study determined that 87% of the patients received at least one psychotropic drug, 66% received at least two, 36% received at least three and 11% at least four (Pitkälä et al. 2004). In French and in German and Austrian nursing homes, approximately half of the patients used at least one psychotropic drug, and, thus, the use was not as common as in Finland (Prudent et al. 2008; Richter et al. 2012).

Contrary to the results from study I, concomitant use of psychotropic drugs in the Lieto Study (studies II and III) was minor. The use of psychotropic drugs was not as frequent in the Lieto Study as a whole. However, the samples included in study I and the Lieto Study are not comparable, because of their different settings and time periods.

The trends of increasing polypharmacy and psychotropic drug use among adults 65 years of age and older have been reported widely in Finland and in Europe (Jylhä 1994; Linjakumpu et al. 2002a and 2002b; Lernfelt et al. 2003; Jyrkkä et al. 2006; Ruths et al. 2012; Carrasco-Garrido et al. 2013). The number of simultaneously used drugs has been found to be associated with increased risk of ADEs in old adults (Chrischilles et al. 1992). This argument is, however, controversial (Veehof et al. 1999). Regardless of these conditions, polypharmacy is associated with advancing age, increased drug-drug interactions, frequent use of non-prescribed medications, living in institution(s) and poor self-rated health status (Thomas et al. 1999; Chen et al. 2001; Doan et al. 2013). Further, polypharmacy has been associated with increased mortality (Jyrkkä et al. 2009b).

Old adults are more vulnerable to the ADEs because of the age-related pharmacokinetic and pharmacodynamic changes (Shi et al. 2008). These effects include orthostatic hypotension, anticholinergic adverse effects, sedation and balance or memory disturbances. Additionally, various drugs and especially drugs affecting the central nervous system have been associated with an increased risk of falls and fractures in old adults (Hartikainen et al. 2007; Takkouche et al. 2007).

One aim of studies II and III was to describe the associations between concomitant use of psychotropic drugs and fractures. This is a topic that has not received intensive attention. Our studies determined that concomitant use of two or more benzodiazepines and two or more antipsychotics was related to an increased risk of fractures in men. Correspondingly, concomitant use of an opioid with an antipsychotic drug and an opioid with a benzodiazepine were related to the risk of fractures for men. No such associations were found in women. Little evidence exists regarding the concomitant use of benzodiazepines and elevated risk of fractures compared to non-use (Herings et al.1995; Pierfitte et al. 2001), and to date no literature on associations between other concomitantly used psychotropic drugs and fractures exists.

Our result that fracture risk is increased only in men is surprising. No obvious explanation is offered. In the Lieto Study this difference cannot be explained by different psychotropic drug types or doses between the sexes. The incidence of fractures is greater in old women than in old men (Ahmed et al. 2009). One hypothesis could, thus, be women's greater tendency to fall and sustain fractures despite the use

of psychotropic drugs, and, therefore, other risk factors may play a greater role in women. Another reason might be that the burden of chronic diseases is more substantial in men compared to women. This would suggest that the actual effect of increased fracture risk in men was partly related to diseases treated with psychotropic drugs.

Unfortunately the anamnesis of alcohol intake was not included in the Lieto Study baseline questionnaire. A point of discussion would then be whether men had greater exposure to the harmful effects of simultaneous use of alcohol and psychotropic drugs. This combination would theoretically increase the risk of fractures more than would be seen by the use of psychotropic drugs alone. A Finnish study concluded that 19% of older men with hip fractures had positive serum alcohol levels at hospital admission and 21.5% reported alcohol intake 24 hours prior to the hip fracture (Kaukonen et al. 2006). The same study resulted that 48% of men with hip fractures used four or more drugs daily, and thirty percent of all patients reported hypnotic or sedative use. However, among patients with positive alcohol levels the overall drug use was lesser compared to those with negative alcohol levels.

It has been shown that women utilize health care system services more frequently compared to men (National Institute for Health and Welfare 2013). It may be speculated, if these more numerous visits result in more frequent changes in women's medication lists compared to men's. More frequent medication changes would bias the results especially in women as the information on medication use was collected only at baseline in the Lieto Study.

The Lieto Study data did not allow investigation of the relationships between underlying diseases or conditions and increased risk of fractures. In the literature, the risk of falls (or fractures) is usually divided into three categories, which include extrinsic, intrinsic and behavioral components. Of these, the intrinsic component includes the use of medications. Medications are thought to mediate their effect on fracture risk through at least two separate mechanisms. First, a medication may produce sedation or vertigo that causes a person to fall and, further, to sustain a fracture. Second, certain medications have been identified as risk factors for bone loss. A majority of nervous system drugs bear the possible risk of causing sedation as an adverse effect. In addition, the SSRI type antidepressants and antiepileptic drugs in particular have been associated with reduced bone density (Ensrud et al. 2004; Cauley et al. 2005; Diem et al. 2007; Ensrud et al. 2008).

The most widely recognized individual risk factors for fractures comprise muscle weakness, a history of falls, gait and balance deficit, use of assistive device, visual deficit, arthritis, impaired (ADL), depression, cognitive impairment and age over 80 years (Rubenstein & Josephson 2002). The Satauni Study provided the possibility to more thoroughly study the associations between nervous system drugs and two possible risk factors for fractures: muscle weakness and balance deficit. The Satauni Study focused on benzodiazepine withdrawal and balance, together with handgrip strength, was measured during the withdrawal process and follow-up period.

Study IV determined that women who had withdrawn from benzodiazepines improved their handgrip strength statistically significantly compared to non-

withdrawers. No association was found for changes in handgrip strength in men or balance in either gender. The difference found between the sexes may be due to the lower muscle mass of women compared to men. Therefore, we suggest that the benzodiazepine-induced effect may be more significant in women. Benzodiazepine plasma concentrations did not differ between the sexes in the Satauni Study.

There is a deficiency in the research literature concerning studies on the associations between benzodiazepine withdrawal and muscle strength, making a comparison difficult. When balance is concerned, there is a little evidence that withdrawal from benzodiazepines enhances trunk motions (postural sway) or improves the level of daily functioning (Habraken et al. 1997; Tsunoda et al. 2010). However, no studies were found that utilize Berg's Balance Scale to measure changes in balance during benzodiazepine withdrawal.

In our study, a significant association was already detected during the four week withdrawal process, starting at the three weeks' time point and lasting at least to the end of the follow-up period at six months. This result is encouraging news for clinicians working with old adults. This result is good news for clinicians encouraging old adults to start benzodiazepine withdrawal.

7.3 Implications for future studies and clinical practice

The literature recognizes psychotropic drugs and, more broadly, nervous system drugs to be risk factors for fractures in old adults. There is, however, inconsistent evidence, and stronger evidence is required to confirm these associations in longitudinal studies. Specifically, more evidence is needed concerning the concomitant use of nervous system drugs and the risk of fractures. This is important since the concomitant use of several nervous system drugs is common in clinical practice.

In addition to the fracture studies, the underlying mechanisms by which this effect occurs should be identified as well. Medications studies, both on e.g. sedative properties and effects on bone structure, are needed. This requires basic research that would reveal phenomena at the cellular level through which the harmful effects of the medications are mediated.

Finally, research resources should be directed to well-designed interventional fall and fracture prevention studies, and the knowledge should then be implemented into clinical practice. This is a true team effort and should involve the authorities, general practitioners, geriatricians, orthopedists, internists, and also nurses and physiotherapists. Importantly, objective information should be addressed to physicians, nursing staff, care-givers and to the public.

An ostensibly simple solution would be to reduce and rationalize all prescribing of nervous system drugs that possess, based on evidence, high risk for adverse drug effects. The guidelines and recommendations, however, are not easily established for clinical practice and giving dichotomous instructions does not leave room for variation between patients nor promotes individualized considerations.

In general, indications for medication use should be fully satisfied before starting a new drug and the evaluation of the balance between potential adverse drug effects and efficacy of the prescribed drugs should be taken seriously. Furthermore, old adults' medication lists should be critically evaluated at least once a year and during every hospital treatment period. Non-pharmacological treatments should not be forgotten or overlooked.

8. CONCLUSIONS

1. The use of psychotropic drugs and other nervous system drugs is common among patients residing in a long-term care setting in Finland.
2. The concomitant use of benzodiazepines, antipsychotics or opioids is associated with an increased risk of fractures in men aged 65 years and older, but the concomitant use of nervous system drugs seems not to increase the risk of fractures in women at the same age group.
3. Withdrawal from long-term benzodiazepine use as a hypnotic is related to an increase in handgrip strength in older women, but not in men.

9. RECOMMENDATIONS

1. The effects and potential adverse effects of nervous system drugs should be carefully monitored, and the indications properly assessed by physicians before prescribing drugs to or renewing prescriptions for old adults.
2. Physicians should more clearly recognize nervous system drugs and especially their concomitant use in the aged as potential risk factors for fractures.
3. Benzodiazepines should be assessed as potential risk factors for muscle weakness.
4. The potential increase in risk of fractures related to concomitant use of nervous system drugs needs to be evaluated in other population-based studies.

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