

Potentially inappropriate drug use and hip fractures among older people

Pharmacoepidemiological studies

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Scientific environment

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Professor Lars B. Engesaeter, Department of Clinical Medicine, University of Bergen, and the Norwegian Arthroplasty Register.

I have attended PhD courses at the University of Bergen, participated at the Nordic Geriatric Research School and completed the 2-year training program at the European Academy for Medicine of Ageing (EAMA).

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Abbreviations

ADE	Adverse drug event
ADR	Adverse drug reaction
ATC	Anatomical therapeutic chemical
CI	Confidence interval
DDD	Defined daily dose
DDI	Drug-drug interaction
DRP	Drug-related problem
FRID	Fall-risk increasing drug
HW	Hospital ward
INHU	Intermediate-care nursing home unit
LAB	Long-acting benzodiazepine
NHFR	Norwegian Hip Fracture Register ¹
NORGE	Norwegian general practice criteria
NORPD	Norwegian prescription database
NSAID	Non-steroidal anti-inflammatory drug
PDD	Prescribed daily dose
PIM	Potentially inappropriate medicine
PPO	Potential prescribing omission
SAB	Short-acting benzodiazepine
SIR	Standardized incidence ratio
SSRI	Selective serotonergic reuptake inhibitor
START	Screening tool to alert to right treatment
STOPP	Screening tool of older people's prescriptions
TCA	Tricyclic antidepressants

¹Official translation. "Registry" was chosen in paper II and has been used consistently in paper III + body text of the thesis.

List of publications

- I. Bakken MS, Ranhoff AH, Engeland A, Ruths S. Inappropriate prescribing for older people admitted to an intermediate-care nursing home unit and hospital wards. *Scand J Prim Health Care*. 2012;30(3):169-175.
- II. Bakken MS, Engeland A, Engesaeter LB, Ranhoff AH, Hunskaar S, Ruths S. Increased risk of hip fracture among older people using antidepressant drugs: data from the Norwegian Prescription Database and the Norwegian Hip Fracture Registry. *Age Ageing*. 2013;42(4):514-20.
- III. Bakken MS, Engeland A, Engesaeter LB, Ranhoff AH, Hunskaar S, Ruths S. Risk of hip fracture among older people using anxiolytic and hypnotic drugs: a nationwide prospective cohort study. *Eur J Clin Pharmacol*. 2014;70(7):873-80.

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Abstract

Over the last decades there has been a major increase in the use of prescribed drugs, especially among older people. Although beneficial in many situations, the use of medications is also associated with potential harms. Older people are particularly vulnerable to adverse effects of drugs use, due to age- and disease-related changes, multimorbidity and (often) complex drug regimens. Psychotropic drugs are known to increase the risk of falling; hip fractures are feared consequences of falls, due to resulting loss of function, and high morbidity and mortality.

This thesis is based on two empirical studies. Study I (paper I) investigates drug use and prescribing quality among acutely hospitalized older people. Study II (papers II and III) investigates associations between psychotropic drug use and hip fractures.

Drug use and prescribing quality (study I)

Aims: To identify inappropriate prescribing among older people (≥ 70) on acute hospital admission and on discharge from an intermediate-care nursing home unit (INHU) and hospital wards (HWs). Furthermore, to compare changes in inappropriate prescribing within and between these groups during stay.

Methods: This was an observational study conducted among community-dwelling older people acutely admitted to hospitals in Bergen. The study population comprised 290 (157 transferred to the INHU, 133 treated in HWs) individuals. Drug use was obtained from medication charts.

Results: Potentially inappropriate medicines (PIMs) and drug-drug interactions (DDIs) were prevalent among community-dwelling older people acutely admitted to hospital, and increased during stay in hospital or intermediate care nursing home. Concomitant use of several psychotropic drugs and inappropriate drug combinations including non-steroidal anti-inflammatory drugs (NSAIDs) were the PIMs most frequently identified. Serious DDIs were scarce. No reductions in number of drugs, PIMs or DDIs were identified in either setting.

Psychotropic drugs and hip fractures (study II)

Aims: To examine associations between exposure to antidepressant, anxiolytic or hypnotic drugs and the risk of hip fracture among older people; to examine associations between exposure to hypnotic drugs and the time of hip fracture; and to estimate the share of hip fractures attributable to exposure to antidepressant, anxiolytic and hypnotic drugs (attributable risk).

Methods: A nationwide prospective cohort study based on merged data from three registries (the Norwegian Prescription Database, the Norwegian Hip Fracture Registry and the Central Population Registry) was conducted. The study population included all 906,422 individuals born prior to 1945 and living in Norway on study start, January 1, 2005. The study period ended on December 31, 2010.

Results: Being exposed to any antidepressant, anxiolytic or hypnotic drug was associated with an excess risk of hip fracture as compared to non-exposure. Being exposed to selective serotonin reuptake inhibitors (SSRIs) and other drugs with high/intermediate serotonergic properties was associated with the greatest excess risk – which was almost 2-fold. We found no evidence that short-acting benzodiazepines (SABs) were safer than long-acting benzodiazepines with regards to hip fracture. People exposed to z-hypnotics were at greatest excess risk at night. The attributable risk of antidepressants was estimated at about 5% and anxiolytics and hypnotics at about 3%. At the population level this corresponds to more than 3000 fractures during the 6 year study period.

Conclusion and implications

Study I revealed that inappropriate prescribing was common, increased regardless of setting, and frequently involved psychotropic drugs. In study II clinically relevant associations between widely used psychotropic drugs and the risk of hip fracture were identified. These findings imply that there is need for improving the drug treatment for older people, and that the recommended psychotropic drugs (SSRIs, SABs and z-hypnotics) offer no advantages with regard to hip fractures as compared to the traditional alternatives.

Sammendrag på norsk

De siste tiårene har det vært en betydelig økning i legemiddelbruk, spesielt blant eldre. Bruk av legemidler er nyttig i mange sammenhenger, men også forbundet med potensielt skadelige effekter. Eldre er spesielt utsatt, på grunn av alders- og sykdomsrelaterte forandringer, flersykelighet og (ofte) komplekse legemiddelregimer. Bruk av psykotrope legemidler øker fallrisiko. En fryktet konsekvens er hoftebrudd, grunnet påfølgende funksjonstap, samt høy morbiditet og mortalitet.

Denne avhandlingen er basert på to studier. Studie I (artikkel I) undersøkte legemiddelbruk og forskrivningskvalitet blant eldre akuttinnlagt i sykehus. Studie II (artikkel II og III) undersøkte sammenhenger mellom bruk av psykotrope legemidler forekomst av hoftebrudd.

Legemiddelbruk og forskrivningskvalitet (studie I)

Mål: Å identifisere uhensiktsmessig forskrivning til eldre (≥ 70 år) ved innleggelse i sykehus og utskrivelse fra en intermediaærvdeling i sykehjem og sykehusavdelinger, samt å sammenligne endringer i uhensiktsmessig forskrivning under oppholdet både innad i og mellom disse gruppene.

Metode: Dette var en observasjonsstudie gjennomført blant hjemmeboende eldre akuttinnlagt i sykehus i Bergen. Studiepopulasjonen bestod av 290 individer (157 overflyttet til intermediaærvdeling i sykehjem, 133 behandlet i sykehus). Informasjon om legemiddelbruk ble hentet fra medikamentkurver.

Resultater: Legemiddelrelaterte problemer forekom hyppig. Forskrivning av potensielt uhensiktsmessige legemidler og legemiddelinteraksjoner var vanlig, og økte under oppholdet. Samtidig bruk av flere psykotrope legemidler samt uhensiktsmessige legemiddelkombinasjoner som inkluderte NSAIDs var de hyppigst identifiserte potensielt uhensiktsmessige kombinasjonene. Alvorlige legemiddelinteraksjoner var sjeldne. Vi fant ingen reduksjon i antall legemidler, potensielt uhensiktsmessige legemidler eller legemiddelinteraksjoner i noen av settingene.

Psykotrope legemidler og hoftebrudd (studie II)

Mål: Å undersøke sammenhenger mellom bruk av antidepressiva, beroligende legemidler og sovemedisin og risiko for hoftebrudd blant eldre, å undersøke sammenhenger mellom bruk av sovemedisin og tidspunkt for brudd, samt å beregne tilskrivbar risiko; andel hoftebrudd som kan tilskrives bruk av antidepressiva, beroligende legemidler og sovemedisin.

Metode: En landsdekkende prospektiv kohortstudie basert på koblede data fra tre registre (Reseptregisteret, Nasjonalt hoftebruddregister, Folkeregisteret) ble gjennomført. Studiepopulasjonen inkluderte alle 906,422 individer født < 1945 og bosatt i Norge ved studiestart 01.01.05. Studieperioden varte til 31.12.10.

Resultater: Bruk av antidepressiva, beroligende legemidler eller sovemedisin var assosiert med økt risiko for hoftebrudd sammenliknet med ikke-bruk. Størst, nesten doblet, risiko fant vi ved bruk av serotonerge reopptakshemmere (SSRI) og andre antidepressiva med høy/intermediær serotonerg aktivitet. Vi fant ingen støtte for at korttidsvirkende benzodiazepiner var sikrere enn langtidsvirkende benzodiazepiner med tanke på faren for hoftebrudd. For de som brukte z-hypnotika var overhyppigheten mest uttalt for nattlige brudd. Tilskrivbar risiko ble beregnet til om lag 5% for antidepressiva og 3% for beroligende midler og sovemedisiner. På befolkningsnivå tilsvarer dette mer enn 3000 hoftebrudd i løpet av den 6 år lange studieperioden.

Konklusjon og betydning for praksis

Studie I viste at u hensiktsmessig forskrivning var vanlig, økte uavhengig av setting, og ofte involverte psykotrope legemidler. I studie II ble det påvist klinisk relevante assosiasjoner mellom hyppig brukte psykotrope legemidler og risiko for hoftebrudd. Studiene viser at det er behov for å øke bevissthet rundt forskrivningspraksis i behandlingen av eldre, og at de anbefalte psykotrope legemidlene (SSRI, korttidsvirkende benzodiazepiner og z-hypnotika) ikke er sikrere enn de tradisjonelle alternativene med tanke på hoftebrudd.

“

First do no harm

Unknown (although generally attributed to Hippocrates (Sokol 2013))

“

First do no net harm (Sokol 2013)

1 Introduction

Over the last decades there has been a major increase in the use of prescribed drugs, especially among older people. Although beneficial in many situations, the use of medications is also associated with potential harms. Older people are particularly vulnerable to adverse effects of drug use, due to age- and disease-related changes, multimorbidity and (often) complex drug regimens. Consequently, at least 20% of acute hospitalizations of the oldest old are fully or partially related to drug use (Beijer 2002, Dalleur 2012). Furthermore, during a 2-year period, 18% of the deaths in the department of internal medicine in a large Norwegian hospital were drug-related; older people with multimorbidity were at particular risk (Ebbesen 2001). The majority of drug-related problems leading to hospitalizations of older people are predictable, thus potentially preventable (Beijer 2002, Petrovic 2012, Socialstyrelsen 2014). Still, an active and structured approach aiming at appropriate drug use has generally been lacking among decision makers and health personnel, as well as among the population in general - in Norway and most other countries. However, there now seems to be a growing interest in appropriate drug use among all these groups (Nyborg 2012, Onder 2014, Patterson 2014, In Safe Hands 2014, Levinson 2015).

Working with this thesis, I have aimed at elucidating different aspects of prescribing quality, with a particular emphasis on, although not limited to, psychotropic drug use. Unless otherwise specified, the term “psychotropic drugs” refers to antidepressants, anxiolytics and hypnotics, thus excluding antipsychotics. This chapter begins with a brief description of the health care services in Norway followed by an introduction to the field of pharmacoepidemiology. Background information on drug use and inappropriate prescribing among older people is provided, leading up to a section on hip fractures in which the links between psychotropic drugs, falls and hip fractures is emphasized.

The thesis is based on literature published up to May 31, 2015.

1.1 Older people and health care services in Norway

1.1.1 Older people in Norway

The adjective “old” is compared (positive – comparative – superlative) like this:

English: old – older – oldest

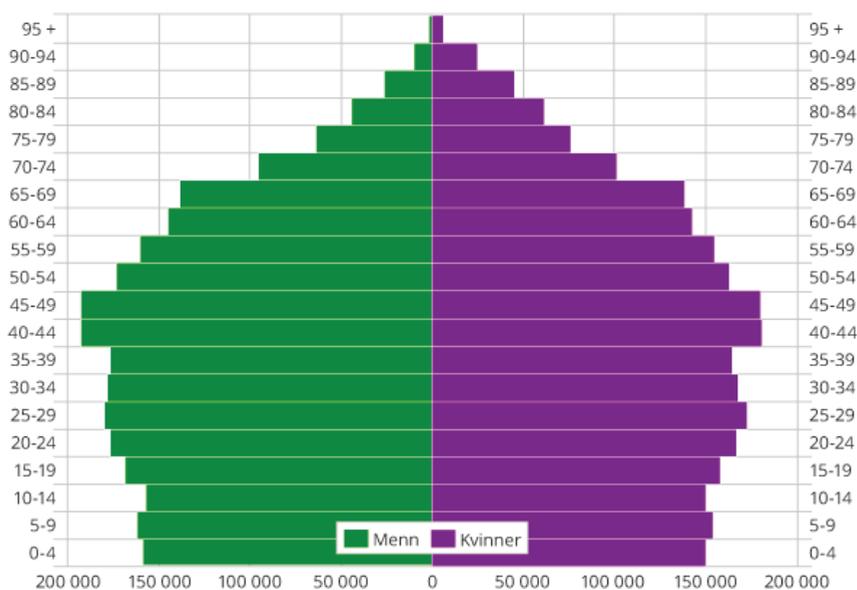
Norwegian: gammel - eldre - eldst

The terminology used when referring to people who have reached advanced chronological age, in everyday speech and official language, is confusing. As a rule of thumb, an “old” person is actually chronologically older than an “older” person, possibly because the first represents an absolute category (as opposed to young or middle-aged) - whereas the latter is the comparative of “old” (thus older than someone else, but not necessarily categorized as old). Furthermore, people who have reached very advanced age tend to be referred to as “the oldest old”, “the very old”, or simply as “nonagenarians” or “centenarians”. Thus, the terminology used is inconsistent and not coherent with the grammatically correct one. Due to negative connotations, the term “elderly” is best avoided (Quinlan 2008).

Most high-income countries have accepted the arbitrarily chosen chronological age of 65 years as a definition of an older person (World Health Organization). However, a variety of cut-offs exists, and when referring to the literature, one has to use what is actually available. For the purpose of this thesis a chronological age of 65 years has been chosen where possible.

In 2010 there were 4.9 million inhabitants in Norway, of whom 15% were 65 years and older. This share is estimated to increase to 21% (67 and older) by 2050 (Statistics Norway).

Figure 1: The population pyramid of Norway by January 1, 2015 (males to the left). Reprinted with permission from Statistics Norway (SSB).



1.1.2 Health care services for older people in Norway

Organization

Everyone living in Norway is covered by the two-level public health care system.

The municipalities are responsible for providing primary health care services, like home care services, general practitioners (GPs) and nursing homes. Nearly everyone in Norway is assigned a GP, and the GPs represent the continuity of medical care for the general population and exert important coordinating and gate keeping functions.

Secondary health care services, e.g. ambulance and hospital services including consultations in outpatient clinics and overnight hospital stays are mainly provided by the four Regional Health Authorities, under the Government's Ministry of Health and Care Services (Helse- og omsorgsdepartementet (HOD)). All institutions with local hospital functions provide acute surgical and medical care; most hospitals have established geriatric departments and may thus provide acute geriatric care for older people with complex health problems.

Hospitalizations are free of charge, most other (adults') encounters with the health care system, like dispensing of prescription drugs, consultations at the GP's office and in

outpatient clinics, involve minor patient's payments. There is a maximum yearly expenditure; in 2015 a healthcare exemption card (Frikort) (Norwegian Directorate of Health) is issued when these expenditures reach NOK 2,185 (NOK100 \approx EUR 11.10 on May 31, 2015). Individuals residing in nursing homes pay up to 75% of The National Insurance Scheme's basic amount (Folketrygdens Grunnbeløp (G); 1G = NOK 90,068 from May 1, 2015), minus NOK 7,000. From any income exceeding 1G, they pay up to 85%. Still, the vast majority of the costs are covered by the community.

Utilization

The majority of older people in Norway are home-dwelling. The average number of visits to the GP increases with advancing age, as does the share of the population receiving home care services. Individuals aged 70 and above experience a greater number of hospitalizations, of longer duration, than younger individuals.

Cardiovascular diseases (about 24%), injuries and cancers (both about 12%) are the most common causes of hospitalizations in Norway (Statistics Norway). Although at least equally numerous (Beijer 2002, Dalleur 2012) and increasing the average length of stay (Vetrano 2014), hospitalizations related to drug use are not identifiable in official Norwegian statistics. Among individuals aged 90 and above, hip fracture is *the* most common reason for hospitalization (Statistics Norway).

At any time, there are some 40,000 individuals staying in nursing homes in Norway; including both short-term and long-term stays. Among individuals aged 80 and above, 18% reside in nursing homes, whereas about one third of individuals aged 90 and above reside in nursing homes (Statistics Norway).

In short, older people in Norway constitute a heterogeneous group frequently using health care services. In accordance with findings from other high income countries, the need for medical care seems to increase with age, whereas the need for multiple hospital admissions and (long-term) nursing home stay becomes common at very advanced age only (Ronksley 2015, Santoni 2015).

1.2 Pharmacoepidemiology

Pharmacoepidemiology is a relatively young discipline, combining topics from clinical pharmacology with methods from epidemiology (Strom 2006a).

Pharmacology is the study of the effects of drugs, whereas *clinical pharmacology* is the study of the effects of drugs in humans. The latter is traditionally divided in the two key fields of *pharmacokinetics* and *pharmacodynamics* (Strom 2006a).

Epidemiology is the study of the distribution and the determinants of health-related states or events, including disease, in defined populations. Various methods can be used to carry out epidemiological investigations. Descriptive study designs (e.g. case reports, case series, cohort or registry based analysis without a control group) may be utilized in order to study distributions, and are typically hypothesis-generating. Applying analytical (e.g. (nested) case-control studies and cohort-studies) or experimental (randomized controlled trials) study designs allows for investigating determinants and testing specific hypotheses (Strom 2006a).

Within the field of *pharmacoepidemiology*, the use and the effects (e.g. the efficacy and safety) of drugs in large numbers of people is studied by applying epidemiological methods (Strom 2006a).

Studies providing descriptions of current drug use and explorations of associations between drug use, predictors and clinical outcomes constitute an important knowledge base for promoting appropriate drug therapy for older people. Quality prescription registries, like the ones in the Nordic countries, provide unique possibilities for pharmacoepidemiological research (Wettermark 2013).

Non-pharmacoepidemiological methods are also highly relevant for shedding light on this topic, like qualitative designs - making it possible to “look behind the numbers” and explore patients’ preferences as well as attitudes among health personnel and decision makers.

1.3 Drug use among older people

A desire to take medicine is, perhaps, the great feature which distinguishes man from other animals.

Sir William Osler, 1891.

1.3.1 Drug use

Throughout this thesis, the words drug, medicine and medication are used synonymously.

Around 90% of community-dwelling individuals in Norway aged 70 and older receive at least one prescription drug yearly (Norwegian Prescription Database 2014). When nursing home patients are included, this share raises to 96% (Norwegian Prescription Database 2014). During 2008, a median of 7 different drugs were prescribed to the community-dwelling population aged 70 and older in Norway, and 20% received more than 10 different Anatomical Therapeutic Chemical (ATC)-coded drugs (Nyborg 2012). Medications prescribed to treat conditions in the nervous system (ATC N), blood and blood forming organs (ATC B) and the cardiovascular system (ATC C) are most frequently prescribed; all of these main groups of drugs are prescribed to more than half the community-dwelling Norwegian population aged 70 and older (Norwegian Prescription Database 2014).

Most data on drug use is derived from prescription databases, drug charts or other lists of drugs. Information on whether or not the drugs were actually consumed is usually lacking, thus “prescribed drugs” is often used as a proxy for “drug use” or the more technical term “drug exposure” (3.2.5 Exposure and 5.1.2 Defining exposure), a simplification practiced also in parts of this thesis.

Unfortunately, direct comparisons of studies investigating drug use among older people are hampered by different definitions (e.g. all prescription drugs vs reimbursed drugs only, regular drugs with/without drugs used on demand), data sources used (e.g. computerized vs self-reported data) used, populations and settings studied (e.g. all older people vs subgroups of older people: age groups, or community-dwelling vs nursing home residents).

Nevertheless, there has been a major increase in drug use in general, and among older people in particular, during the last decades (Hovstadius 2010, Petrovic 2012). In Sweden there was an almost 70% increase in drug prescribing for individuals aged 75 and above from 1990 to 2010 (Fastbom 2010). In the UK, 62% of individuals 85 years and older received three or more regularly prescribed drugs in 2011-2012; a 48% increase from 2003-2004 (Melzer 2015). There are probably several reasons for this marked augmentation. The number of drugs generally increases with age and multimorbidity (Petrovic 2012). More drugs have become available, and multiple and more complex treatment guidelines have been developed during this time period (Boyd 2005) in which demographics have been changing. Consequently, more people live longer – with, and partly possibly due to, their complex drug regimens.

Table 1 gives examples of numbers of drug used among various populations of older people, and reflects the heterogeneity existing among individuals aged 65 and above.

Table 1: Overview of studies of drug use among various groups of older people.

Author	Setting/population	Country	Data source	Number of drugs
Olsson 2010	All 3705 nursing home patients in Jönköping receiving multidose dispensing, mean age 85.0	Sweden	Prescription Registry 2002	10.3 (mean) Regular + on demand
Soraas 2014	All 1241 nursing home patients in Trondheim, mean age 84.5	Norway	Medication charts from nursing homes 2010	9.8 (mean) Regular + on demand
Dalleur 2014	92 patients acutely admitted to hospital, median age 85	Ireland	Medications charts from hospital 2011	7 (median) Regular
Hovstadius 2010	The entire population (nursing home patients with multidose dispensing included); 70 + referred here	Sweden	Prescription Registry 2005-2008	Age groups: 90+: 6.1- 6.6 80-89: 5.7 - 6.1 70-79: 4.8 - 5.0 (mean 2005-2008) All dispensed drugs
Nyborg 2012	All community-dwelling individuals aged 70 or older (nursing home patients not included)	Norway	Prescription Registry 2008	7 (median) Regular + on demand
Moriarty 2015	2051 community-dwelling individuals, 65+ (mean age 74.8) at baseline	Ireland	Self-reported 2008 -2012	4.1- 4.9 (mean baseline and 2-year follow-up) Regular

The increase has been particularly prominent within some groups of drugs. As an example, following the marketing of z-hypnotics in the mid-nineties, there has been an 80% growth of overall use of these drugs in Norway (Norwegian Prescription Database 2011, Bjorner 2013). The increased use among older people in Norway mainly results from greater use of zopiclone (Norwegian Prescription Database 2012). This pattern is even clearer in the US, where the number of prescriptions for any sleep medications showed an almost 300% raise from 1999 to 2010, and 450% for z-hypnotics (Ford 2014). The growth now possibly levels off. From 2004 onwards, there has been a minor decrease in the proportion of the older population in Norway using anxiolytics and hypnotics; for z-hypnotics this decrease was not observed until 2007 (men) and 2009 (women) (Norwegian Prescription Database 2012).

Antidepressant drug user rates have also shown marked growth in high-income countries within the same time period (Sonnenberg 2008, Ruths 2012, Abbing-Karahagopian 2014, Zhong 2014, Noordam 2015), mainly due to more prescriptions for selective serotonin reuptake inhibitors (SSRIs) (Sonnenberg 2008, Zhong 2014). The growth has now started to level off, but the absolute number of older individuals in Norway using antidepressants keeps increasing (Norwegian Prescription Database 2015). Data from the Netherlands shows a decrease in new users of antidepressants from 2000 onwards. The new user rates were highest among the oldest old (80+), and similar to the situation in Norway, the absolute number of users keeps increasing - particularly due to prescriptions for SSRIs (Noordam 2015). Depression is the main indication for antidepressant drug use. Antidepressants are also prescribed for other psychiatric disorders, mainly anxiety/panic disorders (Gardarsdottir 2007), and, particularly in nursing homes, behavioral and psychological symptoms of dementia (BPSD) (Henry 2011).

1.3.2 Polypharmacy

Definitions

The term polypharmacy usually refers to the use of a certain number of drugs concomitantly, with the cut-off value typically set at 4 or 5 (Leipzig 1999, Ziere 2006). Other definitions include duplicate prescribing, or lack of indication (“unnecessary drug”) (Patterson 2014); there is no consensus. So-called excessive polypharmacy is usually defined as using 10 drugs or more (Hovstadius 2014).

Prevalence

During the last decades, drug use has increased considerably among older people. The prevalence of polypharmacy (here: 5 drugs or more) has also escalated, exemplified by a threefold increase among older people in Sweden between 1992 and 2002 (Fastbom 2015). Since the beginning of the millennium, the Swedes have had a very structured approach towards rational drug therapy among their oldest inhabitants, e.g. by developing indicators for quality of drug therapy – to be followed up at the population level. One of these indicators is the share of people above the age of 75 using 10 or more drugs regularly or as needed, which has been stable at 10% from 2006 to 2012 (Hovstadius 2014). Excessive polypharmacy is most common among vulnerable

groups, such as home-dwelling older people with multimorbidity and individuals residing in nursing homes (Fastbom 2015). This is in line with findings from nursing homes in Trondheim, Norway, where 46% received 10 or more drugs in 2010 (Soraas 2014). Internationally, an increasing share of older people is exposed to excessive polypharmacy (Hovstadius 2014).

Consequences

There are pros and cons of increasing drug use and polypharmacy. It is encouraging that older people are not necessarily deprived of potentially beneficial drug treatment. On the other hand, many drugs prescribed does not necessarily equal good prescribing quality. With an extensive growth in the number of drugs available, numerous clinical practice guidelines designed for single chronic conditions (Goodman 2014), not well suited for older people with complex health problems, and an intense focus on “efficiency” (as reflected by the decreasing lengths of stay in Norwegian hospitals; from 7.4 days in 1990 to 4.1 days in 2013 (Statistics Norway 2), the important job of evaluating complex drug regimens in patients particularly vulnerable to drug effects, becomes very challenging (Petrovic 2012).

According to a recent systematic review, the number of drugs is the variable most frequently found to be an independent risk factor for serious adverse drug reactions (ADRs) in adults, including older people (Saedder 2015). Furthermore, both concomitant use of several drugs per se and inappropriate drug use (see section 1.4.1) are associated with hospitalizations (e.g. injurious falls), prolonged lengths of stay and increased mortality (De Buyser 2014). There might be multiple reasons for this; in addition to the ADRs per se, the associations might be due to e.g. an increased risk of drug- drug- or drug-disease-interactions, or other drug-related problems – or one could suspect that the use of several drugs serves merely as a proxy for multimorbidity and/or frailty (Rockwood 2011). Still, in a multicenter study of more than 1100 older adults, Vetrano et al found excessive polypharmacy to be a strong, independent predictor of both acute and elective hospital admissions and of increased length of stay, even when adjusting for age, sex, multimorbidity and life style factors (Vetrano 2014). At present, how to ensure appropriate drug therapy for older people is an essential question.

1.4 Prescribing quality

1.4.1 Inappropriate drug use

The term “inappropriate drug use” usually refers to a situation where the risks of using the drug(s) in question outweigh the benefits (Petrovic 2012, Fastbom 2015). Although increasingly focused on, there is no universal definition used (Fastbom 2015). Direct comparisons of studies investigating inappropriate drug use among older people are hampered by different aspects of inappropriate drug use, populations and settings studied - and the “true” prevalence of inappropriate drug use among older people thus remains unknown. Internationally, long term trends in inappropriate drug use have also been poorly investigated (Hovstadius 2014). Still, inappropriate drug use clearly exerts a major impact on public health (Pirmohamed 2004, Wu 2010, Bradley 2012).

1.4.2 Addressing potentially inappropriate drug use

Terminology

Within this field there are several partially overlapping and inconsistently used terms, actually more than 50, according to a recently published review article discussing and conceptualizing this subject (Santos 2015). In the following, the ones referred to in the remaining chapters will be briefly clarified.

Drug-related problems

There is a wide range of drug-related problems (DRPs), defined as events or circumstances involving drug therapy that actually or potentially interferes with desired health outcomes. A universal classification of DRPs, intended for use in research and clinical practice, was constructed during the working conference of the Pharmaceutical Care Network Europe (PCNE) in 1999 and has been validated and adapted regularly since, with the latest update in 2010, V6.2. The primary problem domains defined are treatment effectiveness, adverse reactions, treatment costs and “others”. DRPs within these domains can be caused by factors related to drug selection, drug form, dose selection, treatment duration, drug use/administration process, logistics, the (personality or behavior of the) patient and “other”. In research, as in real life clinical settings, a varying selection of these problem areas and causes of DRPs are included when potentially inappropriate drug use is evaluated.

Potentially inappropriate prescribing and adverse drug events

Terms frequently used to categorize and/or identify selected DRPs related to inappropriate prescribing include:

1. Potentially inappropriate medicines (PIMs), of which fall risk increasing drugs (FRIDs) constitute a clinically highly relevant subgroup.
2. Potential prescribing omissions (PPOs).

Using PIMs may lead to adverse drug reactions (ADRs), some of which may result from drug-drug-interactions (DDIs). Actual clinical manifestations resulting from the use of PIMs or PPOs will be referred to as adverse drug events (ADEs).

Implicit and explicit methods

When addressing potentially inappropriate drug use one may apply implicit or explicit methods, or a combination of the two. In general, implicit methods, like the Medication Appropriate Index (MAI), include individual clinical judgment and are time consuming; the MAI comprises 10 questions regarding each drug. The explicit methods generally consider a more limited selection of inappropriate drug use than the implicit ones, and are often organized as “checklists”. They may consist solely of DDIs (e.g. www.interaksjoner.no), lists of drugs or drug combinations that should generally be avoided among older people (e.g. NORGEP (Rognstad 2009), or a broader selection of variables. Some primarily explicit methods may require clinical information for full application (e.g. STOPP/START (Gallagher 2008a), including PPOs and PIMs, respectively). Several screening tools have been developed in different areas of the world, intending to detect inappropriate drug use (Naugler 2000, Fick 2003, Holt 2010, American Geriatrics Society Panel 2012, San-Jose 2014). With the release of STOPP/START a screening tool was finally applicable, and taken into use, across Europe as well as on other continents. The validity of this instrument is very good; median kappa coefficient between raters across Europe has been estimated at 0.93 (STOPP) and 0.85 (START) (Gallagher 2009). Following an extensive revision, including consensus within a European expert panel, STOPP/START version 2 was recently published (O'Mahony 2015).

A potential downside of making use of explicit methods is that some might believe “the job is done” as soon as the medication list has been run through an interaction

database or a checklist has been applied - thus devaluating the importance of a thorough (and repeated) clinical assessment. Although DDIs are common, the potentially most harmful DDIs are scarce (Marengoni 2014, Soraas 2014). Furthermore, it has been shown that when STOPP/START is applied without clinical information, the prevalence of PIMs is overestimated, whereas PPOs are underestimated (Ryan 2013), supporting the idea that screening instruments can never replace a good clinician. On the other hand, using checklists may increase the awareness and reduce the prevalence of inappropriate drug use, and eventually influence clinical outcomes.

Clinical relevance of implicit and explicit methods

We know screening tools may help us identify selected PIMs and PPOs (Moriarty 2015), and reduce potentially inappropriate prescribing (Gallagher 2011). The most important question is whether or not “hits” identified when applying these implicit and explicit methods are clinically relevant; if reduction of *potentially* inappropriate prescribing *actually* affects clinical outcomes. As of today, evidence is scarce (Patterson 2014), but some research groups have been able to document effects on patient related outcomes (Gallagher 2008b, Frankenthal 2014). In addition, there are ongoing randomized controlled trials evaluating the effects of various interventions to improve drug use for older people (Patterson 2014). Several of these interventions seem inspired by the comprehensive geriatric assessment (CGA). This is a multifaceted and interdisciplinary diagnostic and therapeutic process aiming at finding, quantifying and managing appropriately the challenges encountered by frail older people. A thorough medication review (which may include checklists) is an integral part of the CGA (Ellis 2011).

Promoting appropriate drug therapy through high quality of treatment?

From a clinical point of view, aiming at *appropriate drug therapy* (e.g. valid indications, sensible drugs and dosages prescribed, aiming at a high degree of adherence and choosing non-pharmacological treatment options were applicable) for each and every older patient should be the main goal, rather than minimizing *inappropriateness* of (the narrower term) *drug use*. As mentioned earlier, this is very challenging within the framework of today’s health care system. Add the atypical and

non-specific presentation of adverse drug effects, and it is easy to understand why most DRPs remain unrevealed – unless one is particularly aware of their presence. In addition to the mentioned changes in attitudes and awareness, *how* we approach this area is important. For all clinicians, always considering DRP(s) a potential differential diagnosis could prove a rational solution when encountering older patients. For general practitioners in Norway, performing yearly medication reviews for patients using 4 or more drugs regularly has been mandatory since 2013 (Forskrift om fastlegeordning i kommunene 2012, Norwegian Directorate of Health). Multiple factors contribute to developing and maintaining DRPs. Consequently, the above mentioned growing interest in promoting multifaceted and interdisciplinary interventions may prove to be a suitable approach when aiming at improving appropriateness of drug therapy.

Outcomes

Despite the previously mentioned challenges when comparing studies investigating drug use, polypharmacy and inappropriateness, the conclusions are remarkably similar: some drugs, and groups of drugs, are more frequently associated with DRPs than others. In particular, the most frequently prescribed drugs, medications prescribed to treat conditions in the nervous system (ATC N), blood and blood forming organs (ATC B) and the cardiovascular system (ATC C), as well as non-steroidal anti-inflammatory drugs, NSAIDs, (ATC M), are associated with ADEs, including serious ADEs (Fastbom 2010).

Falling is one of the most common and feared consequences of drug use (Woolcott 2009, Fastbom 2010), particularly due to potentially very severe outcomes, like fractures and intracranial bleedings. In fact, ATC N drugs, such as antidepressants, anxiolytics and hypnotics, have been associated with falls – with similar odds ratios, for more than two decades (Leipzig 1999, Woolcott 2009, Bloch 2011, Sterke 2012ab), and all of these drugs are defined as FRIDs (Fastbom 2010, Milos 2014). A reduction in falls has been shown when ATC N FRIDs have been withdrawn (van der Velde 2007). ATC N drugs have multiple side effects including sedation, impaired cognition, impaired balance and arrhythmias. In the light of this knowledge, it is intriguing that 2/3 of older Norwegians starting treatment with anxiolytics and hypnotic drugs receive prescriptions corresponding to dosages and treatment durations

far above existing recommendations (Kjosavik 2012), and that approximately 40% of nursing home patients in Norway receive antidepressants (Ruths 2012).

1.5 Hip fractures

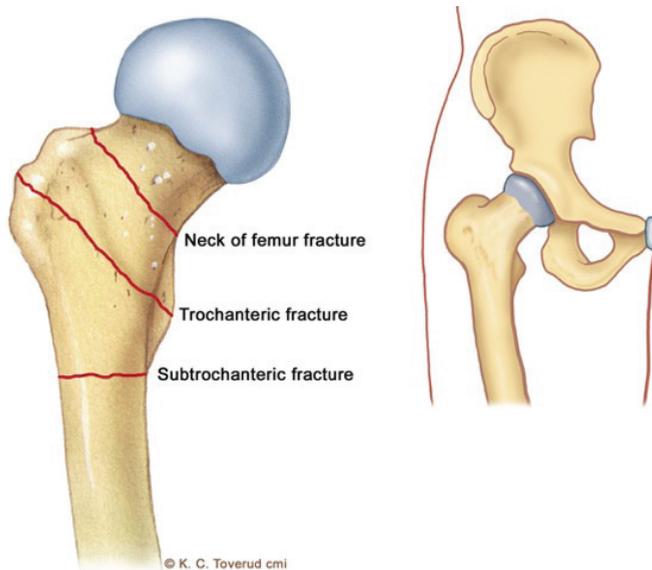


Figure 2: Hip (to the right) and subtypes of hip fractures (to the left).

Epidemiology and consequences

Hip fractures (see figure 2) are common, and due to major individual, economic and social consequences, the most feared of the osteoporotic fractures (Cooper 2011). Although the incidence has decreased from the late 1990s, the absolute number of hip fractures has shown a marginal decrease from 2011 onwards only (Norwegian Arthroplasty Registry 2015), and Norway is still among the countries with the highest risk of hip fracture (Solbakken 2014). The annual age-standardized total incidence rate was about 80 hip fractures per 10,000 person years for women and 40 for men in 2008 (Omsland 2012), implying that more than every fourth woman in Norway above the age of 50 will experience a hip fracture.

Trends in incidence of hip fracture leveled off or even started to decline from the late 1990s in other high income countries also, like Denmark, Finland, Scotland, Canada, the United States and Australia (Korhonen 2013, Requena 2014). However, because of demographic changes, absolute numbers will remain high both in these countries and worldwide. In 2000, there were an estimated 1.6 million hip fractures

worldwide (Cooper 2011). Assuming a constant age-specific rate of hip fracture in both sexes, there will be an estimated 6.3 million hip fractures in 2050 (Cooper 2011). The clinical consequences of hip fractures are extensive. Delirium is common, and increases the risk of incident dementia or worsening of pre fracture existing dementia (Krogseth 2011). At the individual level, most patients do not regain pre fracture physical function; many need (more) home care services, or even nursing home admittance (Bertram 2011, Prestmo 2015). Overall one year mortality is about 25% (Hektoen 2014); higher for men than for women (Hu 2012, Ireland 2015). Implications for the specialist health care system include occupation of hospital beds and surgical capacity, whereas the most important needs in primary health care are home care services, short-term (rehabilitation) and long-term stays in nursing homes. Total costs per hip fracture were recently conservatively estimated at NOK 800,000 – 1,000,000 during the first 2 years post fracture – in a group of relatively fit community-dwelling Norwegians aged 70 and above who were able to walk 10 meters prior to the fracture (Hektoen 2014).

Thus, hip fractures represent a major public health problem, and any preventing measures will be of importance.

Risk factors

Most hip fractures result from a fall in older individuals with low bone mineral density (BMD). Several factors are associated with increased risk of falling and/or decreased BMD. Whereas some of these risk factors are definitely non-modifiable, others are potentially modifiable, and may thus provide us with an opportunity of preventing hip fractures.

Falls

Every third person above the age of 65 experience a fall at least once yearly (Tinetti 2010); some 20% of whom suffer moderate to severe injuries, including fractures (Sterling 2001).

Many falls are multifactorial in origin. Established “intrinsic” risk factors for falling include advanced age, female gender, previous fall(s), fear of falling, physical impairment (e.g. due sarcopenia or other reasons for reduced balance and/or mobility), sensory impairments (e.g. regarding vision, hearing and/or peripheral neuropathy),

cognitive impairments (e.g. delirium, dementia and/or depression), orthostatic hypotension and use of alcohol (Ziere 2006). Home environment (e.g. heavily furnished residence, loose carpets and/or sparse illumination) (Gillespie 2012) is an essential extrinsic risk factor. Age and gender are non-modifiable risk factors, whereas the other factors mentioned are potentially modifiable.

In addition, drug use represents an important modifiable risk factor for falls. Both polypharmacy (here: 4 or more drugs) (Tinetti 2003, Kojima 2012), and the use of FRIDs, like psychotropic drugs (Leipzig 1999, Woolcott 2009, Bloch 2011, van Strien 2013) and use of cardiovascular drugs (Callisaya 2014), particularly new use of cardiovascular drugs (Butt 2013), are factors associated with falls. Most of the evidence is derived from observational studies, thus there is always a possibility the associations may be, at least partly, explained by confounders and not only by the effects of the drugs. The strongest evidence exists between the use of psychotropic drugs and falls, with biological plausibility, consistency of findings through decades (Leipzig 1999, Woolcott 2009, Bloch 2011, van Strien 2013), and an association which remains when adjusting for relevant confounders (like multimorbidity, lifestyle factors and level of disability)(Ziere 2006, van Strien 2013).

Furthermore, the use of FRIDs is associated with hip fractures (Thorell 2014). The association between psychotropic drugs and hip fracture remains after adjustments for level of multimorbidity (Thorell 2014). The association between overall use of cardiovascular FRIDs and hip fracture diminishes after adjustments for level of multimorbidity (Thorell 2014), but is relevant for new users (Butt 2012).

Bone mineral density (BMD)

Osteoporosis is a bone disease in which bone mineral density is reduced and bone microarchitecture and multiple bone modelling components are altered, thus resulting in deteriorated bone tissue (International Osteoporosis Foundation 2015). Low BMD increases the risk of fracture (Bagger 2006). The level of BMD reduction is crucial in diagnosing osteoporosis (preferably multiple site BMD ≤ 2.5 standard deviations (SDs) less than BMD measured with dual energy X-ray (DXA) in a healthy young reference population) and defining low bone mass (osteopenia) (BMD 1.0 - 2.5 SDs less than in the reference population) (Kanis 2013).

In general, peak BMD values are reached in the 30-ies, with great ethnic and sex differences; e.g. Afro-Americans on average reach higher levels than Caucasians, and men on average reach higher levels than women (Kanis 2008, Kanis 2013). Thereafter, the level of BMD decreases with age in both sexes, with an accelerated loss in women after menopause (Kanis 2008). Age, female sex, ethnicity and heredity are strong non-modifiable risk factors for low BMD (Kanis 2008).

On the other hand, lifestyle factors (e.g. level of physical activity, sun exposure (vitamin D), nutritional factors (including ground or surface water) and alcohol and smoking habits), the prevalence of preventable diseases (e.g. cardiovascular diseases) and the use of drugs that affect the BMD may be modified (Brown 2012, Orchard 2014, Solbakken 2014). Certain groups of drugs, like corticosteroids, female sex hormones and chemotherapies, have been known for decades to decrease BMD and increase the risk of osteoporosis (Panday 2014). More recently, using proton pump inhibitors (PPIs) has been recognized as a risk factor (Maggio 2013).

Selective serotonergic reuptake inhibitors and bone quality

As already mentioned, the SSRIs are very widely used, particularly among older people. They have been recommended as first choice due to having a milder adverse drug reaction profiles (e.g. regarding sedation and cognition) than the tricyclic antidepressants (TCAs). Growing evidence implies that the SSRIs are not necessarily as harmless as previously assumed; already in 1998 it was reported that SSRIs did not offer an advantage over other classes of antidepressants in terms of risk of traumatic falls (Liu 1998). More recently, the effects of SSRIs on bone tissue have been elucidated (Haney 2008, Eom 2012). The use of SSRIs is associated with reduced BMD in older (Diem 2007, Haney 2007) and middle aged (men under 90 kg) individuals (Rauma 2015), and affects several bone tissue components (Haney 2008, Warden 2010). Recent studies suggest that genetic differences in the HT-transporter might be of interest (Calarge 2011, Garfield 2014a). Thus, the effects on bone quality are very complex, and not fully understood. Still, in addition to being a potentially modifiable risk factor for falls, including injurious falls resulting in hip fractures, growing evidence implies SSRIs also affect BMD and other aspects of bone quality, further increasing the risk of hip fracture.

In 2010, a group of researchers claimed evidence to be sufficient to consider adding SSRIs to the list of medications that contribute to osteoporosis (Haney 2010). This view was supported in the medical journal *Endocrine* in 2014 (Bruyere 2014), whereas the *Journal of the American Geriatrics Society* landed on the opposite conclusion the same year, stating that the body of evidence was too weak to conclude yet (Gebara 2014).

The ongoing discussions regarding (most) safety issues associated with the use of SSRIs have reached surprisingly little attention among health authorities, clinicians and the public in general, which could have been understandable if the SSRIs were extremely efficient. Although older patients with moderate to severe depression of long duration appear to benefit from antidepressant drug treatment, these drugs do not appear to be effective in short duration depression episodes of any severity, or in mild episodes (Nelson 2013). The proportion of users is strikingly high in this age group, as is the prevalence of hip fracture among the oldest old.

2 Research aims

The overall aims of this thesis was to examine aspects of prescribing quality among older people acutely admitted to hospital (paper I) and to explore associations between exposure to psychotropic drugs and the risk of hip fracture (papers II and III). The specific aims of the three included papers were:

Paper I

- To identify inappropriate prescribing among older people (≥ 70) on acute hospital admission and on discharge from an intermediate-care nursing home unit (INHU) and hospital wards (HWs)
- To compare changes in inappropriate prescribing within and between these groups during stay

Paper II

- To examine associations between exposure to antidepressant drugs and the risk of hip fracture among older people (the whole population of Norway born prior to 1945) in 2005-2010
- To estimate the share of hip fractures attributable to exposure to antidepressant drugs (attributable risk)

Paper III

- To examine associations between exposure to anxiolytic and hypnotic drugs and the risk of hip fracture among older people (the whole population of Norway born prior to 1945) in 2005-2010
- To examine associations between exposure to hypnotic drugs and the time of hip fracture
- To estimate the attributable risk of hip fracture

3 Methods

This thesis is based on two empirical studies. Study I was an observational study conducted among older community-dwelling people acutely admitted to hospitals in Bergen (paper I), whereas study II was a nationwide prospective cohort study (papers II and III).

3.1 Study I

3.1.1 Design

We wanted to investigate aspects of drug prescribing quality among community-dwelling older people acutely admitted to hospital. In 2006, the municipality of Bergen engaged a private research agency (Agenda) to perform a broad evaluation of the, at that time, recently established intermediate-care nursing home unit (INHU). They were planning to collect drug charts (for economic calculations) allowing us to organize and conduct a parallel study with outcome measures related to prescribing quality (study I). No intervention aimed at prescribing quality, thus in the present study data was analyzed as in an observational study.

For the purpose of the evaluation of the INHU, an open randomized study was conducted; the research agency performed the inclusion and randomization of the study population and collected and plotted data. Four hundred people were consecutively recruited on emergency admissions to internal medicine or orthopaedic departments in two hospitals in Bergen, and screened by one designated person at each hospital to see if they were eligible for INHU admission. Randomization was performed at each hospital; 200 patients were assigned to the INHU and 200 to HWs, respectively.

Inclusion criteria: The patients had to be medically stable enough to be transferred to the INHU within 72 hours after emergency hospital admission, and discharge from the INHU to the person's residence within three weeks had to be realistic.

Exclusion criteria: Patients diagnosed with delirium or severe dementia, and patients in need of surgery or intensive care, were not considered eligible for transfer to the INHU, and were thus excluded.

3.1.2 Setting

Bergen is the second largest city in Norway, with around 250,000 inhabitants at study start. Two hospitals, Haukeland University Hospital (HUS) and Haraldsplass Deaconess Hospital (HDS), provide emergency treatment in Bergen. The INHU was established in September 2005, in order to provide continued health care after discharge from short hospital stays to people aged 70 years and older living in the municipality of Bergen.

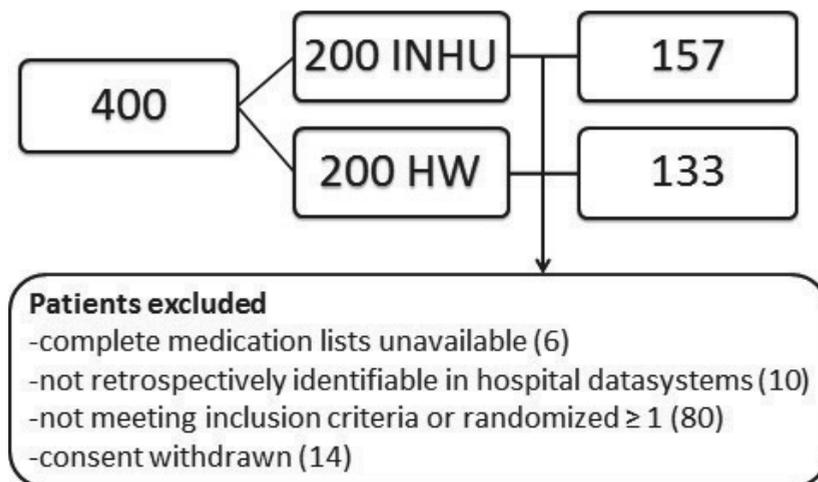
The INHU had relatively more health professionals (physicians, nurses and physiotherapists) employed than in regular nursing home units, and provided health care based on a multidisciplinary geriatric approach. Aiming at discharge to peoples' homes, there was special focus on nutrition, medication review and rehabilitation, although the procedures were not standardized.

3.1.3 Study period and study population

The study period lasted from August 2007 through June 2008. Of the 400 randomized patients, 296 patients were included in the open randomized study. Patients were excluded mainly due to practical and administrative errors during the first weeks of the study period. For the purpose of the present study (study I), an additional 6 patients were excluded because complete medication lists were unavailable, thus our study population comprised 290 individuals, see figure 3.

The 290 included patients had a mean age of 84.7 years (standard deviation (SD) 6.2 years) and 71% were women.

Figure 3: Flow chart study I.



3.1.4 Data collection

The following information was obtained from the research agency: patients' age and sex, setting (INHU or HW), length of stay and medication charts on acute hospital admission and discharge from the INHU or the HWs. Thereafter, all medications (regular and on demand) were plotted manually, and coded according to the ATC classification system (WHO Collaborating Centre for Drug Statistics Methodology).

3.1.5 Aspects of prescribing quality assessed

All medication charts were screened for potentially inappropriate medicines (PIMs) and drug-drug-interactions (DDIs) on admission and discharge according to the following explicit methods:

- The NORGEP criteria (Rognstad 2009). This screening tool includes 21 drugs (e.g. benzodiazepines with long half-life) and 15 drug–drug combinations (e.g. warfarin and non-steroidal anti-inflammatory drugs (NSAIDs)) regarded inappropriate for community-dwelling people aged ≥ 70 years, independent of their clinical condition (Appendix).

- The Norwegian interactive drug interaction database (www.interaksjoner.no). Here, potential DDIs were classified on a four-point severity scale: A: of academic interest; B: take precautions; C: should be administered 2–3 hours apart and D: should not be combined (Appendix).

3.1.6 Statistical analysis

We compared prevalence of drug use, PIMs and DDIs on admission and discharge, within and between study groups by using a chi-square test (categorical data) and Student's *t*-test (continuous data). In order to compare changes regarding drug use, PIMs and DDIs from admission to discharge between HW and INHUs (adjusted for patients' age, sex and drug use, PIMs and DDIs on admission), logistic regression was performed. P-values < 0.05 were considered statistically significant. PASW (formerly SPSS) version 17 software was used.

3.2 Study II

3.2.1 Design

This was a nationwide prospective cohort study based on merged data from three national registries; The Norwegian Prescription Database (NorPD) (Norwegian Prescription Database 2015), the Norwegian Hip Fracture Registry (NHFR) (Gjertsen 2008) and the Central Population Registry (Norwegian Central Population Registry 2015).

3.2.2 Setting, study period and study population

The study was conducted in Norway, with about 4.6 million inhabitants at study start. The study period lasted from January 1, 2005 to December 31, 2010. The study population included everyone aged 60 and above living in Norway on study start, and comprised 906,422 people with a mean age of 72.8 years (SD 8.9 years) on January 1, 2005. Fifty-six percent were women. All individuals were followed up until the day of any first hip fracture, emigration or death or until the end of the study period. Mean follow-up was 5.2 (SD 1.6) years.

3.2.3 Data collection

The Norwegian Prescription Database

The Norwegian Prescription Database (NorPD) was established in January 2004. The main task of the NorPD is to collect and prepare data on drug use among all individuals in Norway (Furu 2008), thus providing information essential for drug use surveillance, and supporting pharmacoepidemiological research and quality improving initiatives. This database contains detailed information on all prescription drugs purchased at all pharmacies in Norway.

For the purpose of this study, data were extracted on all prescriptions of antidepressants, ATC N06A (paper II) and anxiolytics and hypnotics, ATC N05B and N05C, respectively (paper III), dispensed from January 2004 through December 2010. Information included the items' generic name, ATC code and defined daily dose (DDD) (WHO Collaborating Centre for Drug Statistics Methodology), and date of dispensing. Prescriptions dispensed during 2004 were included for us to be able to differentiate between individuals who were (assumed) users and non-users at study start (exposure defined in 3.2.5 below). The NorPD does not contain individual information on institutionalized individuals, thus drugs dispensed during hospitalization and for people living in nursing homes are not included in this study. Furthermore, the NorPD does not include clinical data. Reimbursement codes, which are linked to medical diagnoses, became available from 2009. However, not all prescriptions for antidepressants are reimbursed, and no anxiolytics or hypnotics are preapproved for reimbursement in Norway. Furthermore, these reimbursement codes have not been validated against clinical data. Consequently, we chose not to include this information.

The following medications were included:

Paper II - Antidepressants

ATC code N06A Antidepressants, main indication depression:

- N06AA Non-selective monoamine reuptake inhibitors (tricyclic antidepressants (TCAs)) (clomipramine, trimipramine, amitriptyline, nortriptyline, doxepin)
- N06AB Selective serotonin reuptake inhibitors, SSRIs (fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram)

- N06AG Monoamine oxidase A inhibitors (moclobemide)
- N06AX Other antidepressants (mianserin, mirtazapine, bupropion, venlafaxine, reboxetine, duloxetine)

For the purpose of analysis, the antidepressants were divided in two different ways, according to 1) therapeutic subgroups (ATC group): TCAs (N06AA), SSRIs (N06AB) and other antidepressants (N06AG, N06AX) and 2) the drugs' serotonergic effects (Lingjærde 2006, van den Brand 2009): high or intermediate serotonergic properties, or low or no serotonergic properties. The classification is shown in paper II, table 1 (footnote).

Paper III – Anxiolytics and hypnotics

ATC code N05B Anxiolytics, main indication anxiety:

- N05BA Benzodiazepine derivatives (diazepam, oxazepam, alprazolam)
- N05BB Other anxiolytics (hydroxyzine)

ATC code N05C Hypnotics, main indication: sleep disturbances:

- N05CD Benzodiazepine derivatives (nitrazepam, flunitrazepam, midazolam)
- N05CF Benzodiazepine-related drugs (z-hypnotics: zopiclone, zolpidem)
- N05CH Melatonin receptor agonists (melatonin)

The following drugs were excluded (due to main indications other than anxiety and sleep disturbances, or very rare use): clomethiazole, chlordiazepoxide, lorazepam, bromazepam, clobazam, meprobamate, busperione, barbital, flurazepam, triazolam, zaleplon and scopolamine.

For the purpose of analyses, the benzodiazepine anxiolytics and hypnotics were also classified according to their half-lives. The classification is shown in paper III, table 2 (footnote). Furthermore, in order to perform subanalyses investigating associations between hypnotic drug exposure and time of fracture, time of fracture was dichotomized into night (20:00-07:59) or daytime (08:00-19:59) fractures.

The Norwegian Hip Fracture Registry

The Norwegian Hip Fracture Registry was established in January 2005, and contains national data (injury, fracture and surgery) on people operated on for hip fracture at all hospitals in Norway performing such surgery.

For the purpose of this study, we extracted the date of first hip fracture (hereafter referred to as primary hip fracture) registered during the study period.

The Central Population Registry

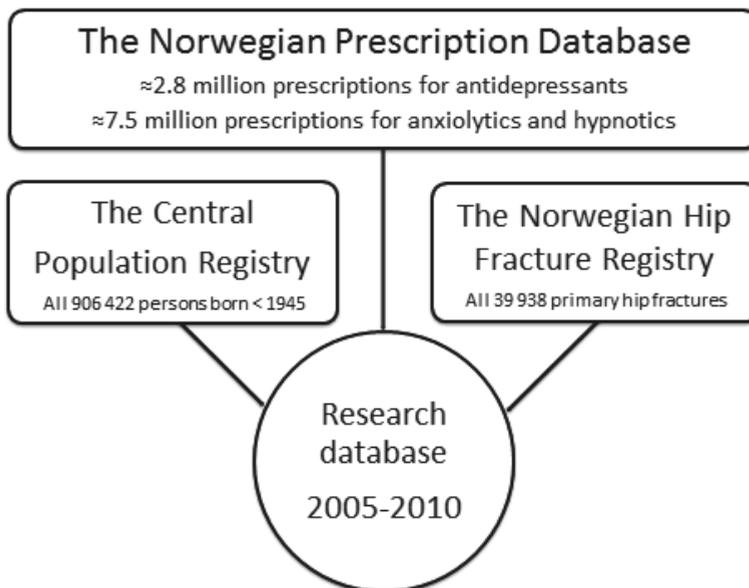
The Central Population Registry contains demographic information on the entire population of Norway.

Information on birth year, sex and date of death or emigration (if applicable) was extracted.

3.2.4 Data linkage

From 1960, all citizens in Norway have been assigned a unique 11-digit personal identity number. This number was used to link the variables selected from the three registries. Data linkage was performed by a trusted third party (Statistisk Sentralbyrå).

Figure 4: Research database study II.



3.2.5 Exposure

The NorPD does not include information on whether or when the purchasers consumed the dispensed drugs, thus we had to make assumptions on drug exposure. First of all, we assumed that all the dispensed drugs were consumed. Next, that they were consumed from the day they were purchased. For the purpose of investigating associations between hypnotic drug exposure and time of fracture, hypnotics were assumed to be taken at bedtime.

The defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication among adults (WHO 2013). As prescribed daily dose (PDD) and actual drug consumption vary within a population, we calculated the risk of hip fracture for various assumed total exposure times. For antidepressants (paper II), the risk of hip fracture was calculated for 3 days, 14 days and the number of days corresponding to the number of (1.0) DDDs prescribed. For anxiolytics and hypnotics (paper III), the risk of hip fracture was calculated for 3 days, 7 days and 14 days and the number of days corresponding to the number of DDDs prescribed; calculations were performed for both 0.5 and 1.0 DDD.

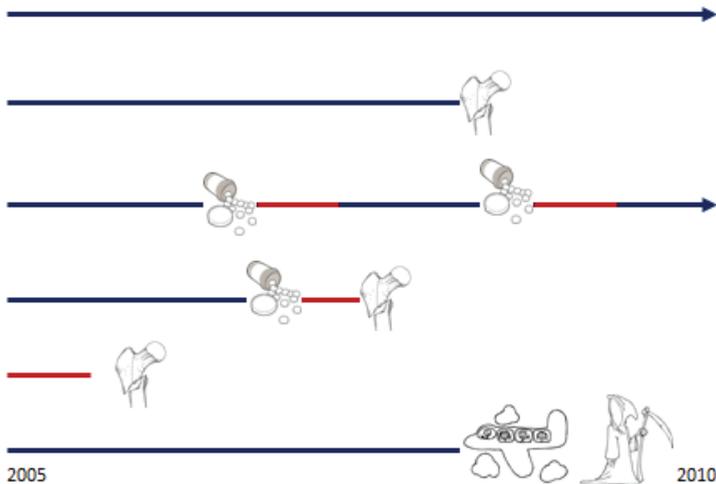
Overall use was defined as any exposure to the drug group(s) in question within the study period, all exposure periods included. This is illustrated in figure 5 below. For all drug groups, we considered 1.0 DDD the best proxy for the number of person-days exposed (discussed in 5.1.2 Defining exposure). *Recently started drug use* was defined as the first 14 days of first-time exposure to the drug group(s) in question after a 360-day wash-out period.

3.2.6 Statistical analysis

We compared the incidence of primary hip fracture during the person-time exposed and unexposed (red and blue, respectively, in figure 5 below) to the drug(s) in question throughout the study period by calculating standardized incidence ratios, SIRs (Engeland 2007). If a person received the drug (group) in question more than once during the study period, all exposed person-time periods were included in the main analyses, until the end of follow-up (the day of any first hip fracture, emigration or death, or until the end of the study period).

Figure 5: Examples of individual patterns of exposure and duration of follow-up.

Exposed and unexposed person-time



Each line represents 1 individual. Individuals were followed up until the day of any first hip fracture, emigration (airplane) or death, or until the end of the study period.

Subanalyses were performed on recently started drug use (papers II and III) and associations between hypnotic drug use and time of fracture (paper III).

An SIR greater than 1 indicates an increased risk of hip fracture associated with exposure to the drug(s) in question. We adjusted the SIR for sex, birth year and time period (divided into 2-month intervals).

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

In order to calculate the attributable risk of exposure to the drug(s) in question on hip fracture, we divided the observed minus the expected number of fractures during the

number of person-days exposed to the selected drug(s) by the observed number of fractures in the study population.

4 Summary of results

4.1 Paper I

Bakken MS, Ranhoff AH, Engeland A, Ruths S. Inappropriate prescribing for older people admitted to an intermediate-care nursing home unit and hospital wards. *Scand J Prim Health Care*. 2012;30(3):169-175.

This observational study examined established drug use among 290 community-dwelling older (70 and above) people who were acutely hospitalized, and changes during stay in the HWs (133 remained) and the INHU (157 transferred), respectively.

The mean number of prescription drugs per person increased from 6.0 (SD 3.3) on admission to 9.3 (3.8) on discharge. PIMs, as judged by the NORGEF checklist, were frequent on admission (24% of the patients had ≥ 1 PIM) – and increased to 35% during stay ($p < 0.01$), due to more PIMs in the HWs ($p = 0.02$). Hits in 23 out of 34 NORGEF items were identified; concomitant use of ≥ 3 psychotropic or opioid drugs was the one most frequently met. The number of individuals receiving combinations NSAIDs/steroids, as well as NSAIDs/SSRIs, both increased, with p-values ≤ 0.05 and ≤ 0.001 , respectively. We could not identify significant reductions within any item, in either groups. Patients in the INHU were less likely to have initiated diazepam treatment during stay (OR=0.17, 95% CI 0.04-0.79). More than half the patients (54%) had ≥ 1 DDI of any severity on admission; at discharge this share had increased to 68% ($p \leq 0.01$). The serious DDIs were scarce on both occasions (both 0.7%). There were no differences between the two study groups.

In conclusion, this study confirmed that community-dwelling older people used a high number of drugs, and revealed that inappropriate prescribing (PIMs and DDIs) was frequent, on acute hospital admission. Drug use and inappropriate prescribing increased during stay, regardless of setting.

4.2 Paper II

Bakken MS, Engeland A, Engesaeter LB, Ranhoff AH, Hunskaar S, Ruths S. Increased risk of hip fracture among older people using antidepressant drugs: data from the Norwegian Prescription Database and the Norwegian Hip Fracture Registry. *Age Ageing*. 2013;42(4):514-20.

In this nationwide registry-based prospective cohort study associations between antidepressant drug exposure and the risk of hip fracture was investigated. All 906,422 individuals aged 60 or above and living in Norway in 2005 were included. We compared hip fracture incidences during drug exposure and non-exposure by calculating standardized incidence ratios (SIRs).

Altogether, 39,938 people fractured their hips during the 6 year study period. Being exposed to any antidepressant drug was associated with a 70% increased risk of hip fracture as compared to non-exposure (SIR 1.7, 95% CI 1.7-1.8). The association was most prominent among people using SSRIs (SIR 1.8, 95% CI 1.7-1.8) and other drugs with high/intermediate serotonergic properties (SIR 1.7, 95% CI 1.7-1.8) and least prominent in the TCA group (SIR 1.4, 95% CI 1.3-1.5) and antidepressants with low/no serotonergic properties (SIR 1.2, 95% CI 1.1-1.5). Generally, the excess risk of hip fracture during antidepressant drug exposure as compared to the risk during non-exposure decreased with increasing age. Furthermore, the excess risk was more pronounced among exposed men, (SIR 1.9, 95% CI 1.8-2.0), than among exposed women (1.7, 95% CI 1.6-1.7). This difference was most prominent among the youngest individuals, born 1935-44, with SIRs 2.9 (95% CI 2.6-3.4) for men and 2.5 (95% CI 2.3-2.7) for women, respectively. The attributable risk was estimated at nearly 5%, corresponding to almost 2000 hip fractures at the population level during the 6 year study period.

In conclusion, being exposed to any antidepressant drug was associated with an excess risk of hip fracture as compared to non-exposure. SSRIs and other antidepressants with high/intermediate serotonergic properties were associated with the greatest excess risk, implying that pharmacological properties may affect fracture risk.

4.3 Paper III

Bakken MS, Engeland A, Engesaeter LB, Ranhoff AH, Hunskaar S, Ruths S. Risk of hip fracture among older people using anxiolytic and hypnotic drugs: a nationwide prospective cohort study. *Eur J Clin Pharmacol.* 2014;70(7):873-80.

In this nationwide registry-based prospective cohort study associations between anxiolytic and hypnotic drug exposure and the risk of hip fracture was investigated. All 906,422 individuals aged 60 or more and living in Norway in 2005 were included. We compared hip fracture incidences during drug exposure and non-exposure by calculating standardized incidence ratios (SIRs).

Altogether, 39,938 people fractured their hips during the 6 year study period. Being exposed to any anxiolytic or hypnotic drug was associated with an elevated risk of hip fracture, SIR 1.4 (95% CI 1.4-1.5), and SIR 1.2 (95% CI 1.1-1.2), respectively, as compared with non-exposure. The association between drug exposure and hip fracture was most prominent regarding short-acting benzodiazepines (SABs), SIR 1.5 (95% CI 1.4-1.6). We found exposure to benzodiazepine-like hypnotics (z-hypnotics) to be associated with higher excess risk of hip fracture at night (20.00-07.59), SIR 1.3 (95% CI 1.1-1.2) than during the day (08.00-19.59), SIR 1.1 (95% CI 1.1-1.2). Overall, the excess risk of hip fracture associated with drug exposure decreased with increasing age. Also, the excess risk was more pronounced among men than among women; for anxiolytics SIR was 1.6 (95% CI 1.4-1.7) for men and 1.4 (95% CI 1.4-1.5) for women. The attributable risk for any anxiolytics and z-hypnotics combined was estimated at 3.2%; the attributable risk of hip fracture associated with z-hypnotics was higher at night than during the day.

In conclusion, being exposed to any anxiolytic or hypnotic drug was associated with an excess risk of hip fractures as compared to non-exposure. We found no evidence that the recommended SABs were safer than long-acting benzodiazepines. People exposed to z-hypnotics were at greatest excess risk at night; this is not an established association, and deserves further investigation.

5 Discussion

This thesis is based on two empirical studies. By conducting a local observational study (study I, paper I), and a nationwide prospective cohort study (study II, papers II and III) various potential harms of drug use among older people were illuminated. In this chapter I will discuss selected methodological issues and results. Due to essential methodological differences, the main discussion of strengths and limitations is split in two sections - one for each study. The generalizability of the results of both studies will be discussed in 5.1.3. The results from study I and study II are discussed in chapter 5.2.

5.1 Methodological considerations

The studies included no (study I) or limited (study II; hip fractures) clinical information, and were thus vulnerable to bias and confounding.

Study I was based on “a convenience sample” where we had no influence on data collection or study sample. Study II was planned and conducted because we wanted to investigate associations between psychotropic drug use and the risk of hip fracture in the entire older population, based on the well-established link between psychotropic drug use and falls, and new insights in associations between these drugs and fractures.

5.1.1 Study I

Design

This was an observational study in which we aimed at examining aspects of drug use and prescribing quality among community-dwelling older people acutely admitted to hospital. Data was primarily collected for another study, designed for other research purposes, but offered an opportunity for us to explore aspects of drug use in a vulnerable population which, to the best of our knowledge, had not previously been investigated. A possible limitation with the study design is that there might have been differences between the participants treated in the HWs and in the INHU, of which the potential impact on the outcomes is unknown. The lack of clinical information limited the aspects of drug use and prescribing quality available for assessment. As an example, we were unable to identify underprescribing.

Data reliability and internal validity

We aimed at identifying inappropriate prescribing and to compare changes in inappropriate prescribing during stay in the two different settings. To what extent did we measure what we aimed at?

There is no reason to believe there were major errors in the medication lists obtained through “business as usual” on acute hospital admissions. Still, to what extent drug use registered as “drug use on admission” differed from *actual* drug use, or to what extent it would have differed if obtained by different health personnel, is not known.

Furthermore, as only one researcher (MSB) read the drug charts and registered the medications, registration errors cannot be ruled out. However, the impact on data reliability is likely to be very limited.

As mentioned in the introduction, the term “inappropriate drug use” usually refers to a situation where the risks of using the drug(s) in question outweigh the benefits. Due to the lack of clinical information, there was no room for individual clinical judgement in our study, and we had to apply explicit methods in order to identify inappropriate prescribing. At that time, Beers’ list, developed in the US, was the most frequently used screening tool worldwide. It was criticized because only a minor proportion of the drugs included were actually available in several countries, including Norway. Consequently, we chose to define PIMs as “hits” in the newly developed NORGEP checklist, targeted at our study population, i.e. the community-dwelling Norwegian population aged 70 and above. Limitations of this choice include the restricted number of PIMs listed, and the fact that some drugs were already withdrawn from the Norwegian market at the time of analyzes². The more comprehensive STOPP/START screening tools were recently published when study I was planned; due to lack of clinical data we chose not to use them. Later, several studies have been conducted where selected STOPP/START items have been applied to data sets lacking clinical information. As previously mentioned, PIM detection is likely to be overestimated using STOPP, and PPO detection underestimated using START, when these tools are applied without clinical information available. From this we can conclude that NORGEP was a rational choice. In order to identify DDIs, we selected the interaction

²A revised version of NORGEP, and a version specifically addressing nursing home patients, is expected any time soon.

database developed in Norway, comprising substances on the Norwegian market (www.interaksjoner.no).

We included all prescribed drugs. It could be argued this might have led to an overestimation of the chosen outcomes. On the other hand; we aimed at identifying *potentially* inappropriate *prescribing*. Thus, the combination of regularly used drugs and drugs used on demand reflected what the study participants were actually prescribed during stay; what drugs and drug combinations were approved for them, in this particular acute/subacute clinical situation, by the attending physician.

To conclude, registering all drugs prescribed and the explicit methods chosen were suitable to identify selected DRPs in the study population. Whether or not they actually measured *clinically relevant* DRPs is reflected on in the discussion of results (5.1.1).

Statistical analysis

As previously mentioned, data was primarily collected for another study, designed for other purposes. Power calculations concluding with an inclusion of 400 participants were based on the ability to identify a 10% improvement in functional outcome with a strength of 80% at a 5% significance level. An exclusion/dropout rate of up to 30% was taken into account, as described in a recent publication (Herfjord 2014). A total of 290 participants were eligible for study I. Lack of power may have resulted in type II errors, meaning that we may have failed to identify actual differences between the two settings concerning single items in the NORGEP list.

5.1.2 Study II

Design

The main purpose of pharmacoepidemiology is to study the use of and the effects of drugs in large numbers of people. Although randomized controlled trials (RCTs) are generally considered to generate the highest level of evidence, they are often neither feasible nor sensible to conduct, due to high costs (regarding time as well as money) and limited generalizability. Also, performing RCTs within this area is often ethically challenging.

Study II was a nationwide prospective registry-based cohort study. This design has several strengths. A nationwide prospective cohort design is suitable when the aim is to compare people exposed and non-exposed to a certain factor (here: psychotropic drug use) with regard to a predefined (relatively) infrequent outcome (here: hip fracture), without being prone to selection and recall bias.

The three quality national registries provided us with a unique opportunity to link data on antidepressant, anxiolytic and hypnotic drugs purchased by an unselected community-dwelling older population with all primary hip fractures registered in Norway, and the extensive follow-up period yielded a high number of cases. Another advantage of this design is that registry-derived data represent routine clinical practice, as opposed to data derived in most RCTs. On the other hand, in registry-based studies inherent weaknesses related to the completeness and quality of the data, and the lack of information on potential confounding variables (i.e. relevant clinical information) threaten internal validity, and must be addressed when planning the study (where possible), and when interpreting the results (always). These main limitations will be discussed below, as will the essential pharmacoepidemiological question of how to define exposure.

Alternative designs for investigating associations between psychotropic drug use and the risk of hip fracture include case-control studies, in which selection of suitable controls and the susceptibility to information bias and misclassification of exposure are well-known challenges, and self-controlled case series (SCCS). Advantages with the latter design include the elimination of fixed confounders through “ultimate matching” (the patient is its own control), and that time-varying exposure is taken into account. This method was developed to investigate associations between acute outcomes and transient exposures (Whitaker 2006), and is less suitable for drugs used on a regular basis with limited variations of drug use patterns between and within individuals (Strom 2006b). Thus, it might have been suitable for investigating associations between anxiolytic and hypnotic drug use and the risk of hip fracture (particularly if they were in fact used intermittently, as recommended), but not for antidepressants.

Data reliability and internal validity

Systematic errors, e.g. selection bias, information bias, misclassification and confounding, threaten the internal validity of a study. There was limited room for in-depth methodological considerations in papers II and III based on study II. In this section I will therefore elaborate on aspects essential to the internal validity of study II: how elements related to the registries may have affected the data obtained, and how the lack of clinical information and our definition of exposure may have affected the study results.

Data obtained from the registries***The Norwegian Prescription Database***

All pharmacies in Norway are legally required to send electronic data to the NorPD on all prescription drugs dispensed (Furu 2008). The reporting is computerized and reporting and quality control systematized, thus minimizing the occurrence of errors. Data from the NorPD is considered reliable and valid (Furu 2008, Furu 2010). Still, even in (theoretical) conditions of 100% reliability and validity, there would not be any information regarding if or when the drugs were actually consumed. The fact that only dispensed drugs are registered reduces, but does not exclude, the probability of misclassifying individuals as exposed (defining exposure is addressed below) when they are in fact non-adherent. Including reimbursed drugs only would have further reduced the risk of misclassifying non-users as users, but would on the other hand have led to an undesirable selection bias (e.g. probably favoring individuals tolerating ADRs) as well as misclassification of a large number of users as non-users. Detailed adherence analyses were beyond the scope of our study, and closer follow-up, like day-day registrations of drug charts among individuals receiving home care services, would have introduced selection bias and dramatically reduced the sample size, consequently undermining the internal validity of the study.

The most important limitation of the NorPD is the lack of individual information on medications dispensed during hospital stays and to people living in nursing homes, about 13,000 and 40,000 at any time, respectively (Statistics Norway). Hospital stays are generally very short, and any prescription issued to the individual on discharge or by the patient's general practitioner (GP), or by any other doctor, will be registered in

the NorPD when the drug is dispensed. Whereas relatively few patients were misclassified as drug non-users during hospitalization, we know there has been a systematic misclassification of people living in nursing homes as drug non-users. This is important, since both hip fractures and psychotropic drug use are highly prevalent among nursing home residents (Ranhoff 2010, Ruths 2012). Consequently, the excess risk of hip fracture has been underestimated among exposed people living in nursing homes, yielding more conservative estimates of the associations between drug use and hip fractures among the oldest old.

Some prescriptions lack the 11-digit personal identifier necessary to merge prescription data with data from the two other registries. This proportion is very small (<0.1 %) among individuals aged 65 and above (personal communication, Kari Furu, NorPD, Norwegian Institute of Public Health, May 27, 2015), and thus unlikely to have influenced the results of the present study. Finally, the NorPD does not contain information on drugs sold over the counter (OTC). As the drug groups investigated in the present study are not available as OTC drugs in Norway, this has not affected the strength of the associations identified between psychotropic drug use and the risk of hip fracture.

The Norwegian Hip Fracture Registry

Data in the Norwegian Hip Fracture Registry (NHFR) rely on a large group of orthopaedic surgeons' reporting, and is thus susceptible to reporting and recall bias. There is limited data on the reliability and validity of the information registered in the NHFR. The hip fracture diagnoses are considered valid (only operated hip fractures are registered), whereas the registration of other parameters is less definitive. As an example, delirium is very common among hip fracture patients, and not readily distinguished from dementia. Information on medical history in general and dementia in particular, is often scarce. Consequently, we chose not to include the dementia-variable (categorized as yes, no, or uncertain/not known in the data collection form) in our study.

Although all hospitals in Norway performing hip fracture surgery report to the NHFR, reporting is not complete. Any case of primary hip fracture not registered in the NHFR, for any reason, will be missed in our study. A recent analysis has shown that

the level of coverage was about 90% for primary hip fractures (Norwegian Arthroplasty Registry 2014); it was somewhat lower during the first years (Gjertsen 2008). The level of coverage varies between hospitals (Norwegian Arthroplasty Registry 2014), indicating that the hospitals' routines for reporting play an important role. We consider it implausible that the underreporting was systematically biased due to patient factors related to the exposure (drug group) or outcome (hip fracture) in question, which could have affected the results of our study. Erroneously ticking off "reoperation" instead of "primary operation" would have excluded a patient who should have been included, and vice versa. The extent and consequences of such reporting bias in our material, is not known, but it is assumed to be of little importance. Finally, each year, some very few patients with verified hip fracture are not operated (< 0.1%, (personal communication, Lars B. Engesæter, NHPR, May 31, 2015). All in all, the level of coverage is high, and we consider the included hip fractures to be representative of primary hip fractures occurring during the study period. Approximately 10% experience a second hip fracture within 2 years (Omsland 2013). These individuals may differ significantly from other individuals fracturing their hips. We therefore chose to only include primary (within the defined study period) hip fractures in our dataset.

Exact time of fracture was registered in only half the cases, of which about two thirds occurred during daytime. Although probably influenced by recall bias (e.g. when it is difficult for the patient to remember (or know) for how many hours she or he lay on the floor after fracturing the hip) and possibly by reporting bias (e.g. if the surgeon does not want to report extensive waiting hours prior to the operation), it is difficult to imagine that these biases have systematically drawn towards either daytime or nighttime fractures. This is supported by the diurnal distribution of hip fractures in our study being similar to Swedish findings (Leavy 2013).

The Central Population Registry

All formal residents in Norway receive a unique 11-digit personal identity number. This number was used to link the variables selected from the three registries. There will always be some few people living in Norway without this identifier, thus lacking the key used to link the three registries; a) foreign people who intend to stay less than

6 months (e.g. for employment reasons - these are assigned a so-called “D-number”) and people without residence permit (usually middle aged or younger). The results of the present study, including individuals born prior to 1945 only, is unlikely to have been affected by this.

Lack of clinical information

Whereas the large sample size is an obvious strength, the sparse amount of information available per individual is the most important limitation of our nationwide registry based study, necessarily vulnerable to confounding. Confounding occurs when the estimate of an association between exposure and outcome is biased by (one or more) external variables that may also affect the outcome (Strom 2006c). In pharmacoepidemiological studies, confounding by indication is of particular interest. As there should always be a reason for prescribing, the outcome may be influenced by the disease (e.g. reduced level of physical activity in depression) and its duration and severity (e.g. lower BMD following long lasting inactivity in severe depression). Additionally, the drug treatment may influence the outcome (e.g. hypotension or arrhythmia after initiation of SSRI treatment, resulting in injurious falls).

Reasons for both falls and fractures are multifactorial, thus adjusting for relevant comorbidities would have been preferable. Diagnostic information was not available in the NorPD at study start. Reimbursement codes became available towards the end of the study period, and were, as mentioned in the methods section, unsuitable.

Alternatives would have included diagnoses set during hospital stays from the NPR (Norwegian Patient Register) or diagnoses from primary health care encounters from HELFO (Norwegian Health Economics Administration), of which neither are validated nor capture the entire study population. Yet another option could have been to use prescribed drugs as proxies for comorbid conditions. Even though some drugs could act as valid proxies for a specific disease (e.g. insulin – diabetes), prescriptions are generally not well suited, because numerous drugs have several indications, and because of the uncertainty that would have been introduced when defining proxies for daily use and exposure periods for numerous groups of drugs (see *Defining exposure below*). Most importantly, with the time-varying exposure used in our study, this was not feasible, or even possible.

Other examples of clinical factors ideally adjusted for include osteoporosis, smoking and alcohol habits, and level of physical activity. There is no information of osteoporosis diagnoses or life style variables available in the data sources used in study II.

Although residual confounding cannot be ruled out, other studies have shown the associations between psychotropic drug use and the risk of hip fracture to remain at a somewhat attenuated level even after adjusting for concomitant drug use and/or life style factors and multimorbidity (Vestergaard 2013, Thorell 2014).

Defining exposure

Defining exposure based on prescription data is one of the most important, and demanding, tasks within the field of pharmacoepidemiological research. Including dispensed drugs only, as in the NorPD, reduces the problem of misclassifying due to non-adherence to drug treatment (Furu 2008). Nonetheless, information regarding the dispensed drugs must be transformed into periods of assumed drug use, and the question is not whether or not there will be misclassification, but how to keep the consequences of the resulting bias at a minimum. Several aspects (e.g. choice of proxy for exposure and how/whether to define and handle treatment gaps) must be taken into consideration. The mutual weighting of these, and the final choice of definition, will depend upon the aims of the specific project and the drugs included. Obtaining valid information on periods of drug use is strenuous also in non-registry based studies, due to e.g. information and recall bias.

One possible way of transforming prescription data into periods of drug use is to assume fixed dosages (e.g. tablets or DDDs); the suitability of this approach differs between drug groups due to the diversity of prescription and drug use patterns. In a study based on prescription data for all individuals aged 75 and older in Sweden in 2006, mean DDDs/day were estimated at 0.76 for antidepressants, 0.64 for hypnotics and 0.42 for anxiolytics, respectively (by reviewing free text instructions on actual prescribed daily dose (PDD)) (Lesen 2009). These results regarding individuals of similar age, from a neighboring country with similar drug use, were considered generalizable to Norwegian conditions in the same period of time. Alternative methods were either unavailable (dosage instructions on PDDs (Lesen 2009)) or unsuitable for

drugs without a predominantly chronic use pattern (the waiting time distribution (Hallas 1997), further developed in 2013 (Pottegard 2013).

The main aim of the present study was to explore associations between exposure to antidepressant, anxiolytic or hypnotic drugs and the risk of hip fracture in a large population. For this reason, high specificity was more important than high sensitivity when defining exposure. In other words, a high probability that what we defined as exposure represented true exposure periods was given higher priority than capturing all days with exposure (which would have been very important in e.g. a drug adherence study). Consequently, we considered the quite strict definition of days corresponding to 1.0 DDD as the best proxy for drug use. Time-varying exposure, the fact that each individual could alternate between exposure and non-exposure throughout the study period, was chosen to reduce misclassification. This approach also reduces immortal time bias (the follow-up time during which the outcome in question cannot occur). No non-adherence was allowed, thus real life long-term regular drug use with even minor treatment gaps would have been identified as several exposure episodes. The time-varying exposure is one of the major strengths of study II, as the alternative, fixed exposure, would have led to extensive and unmeasurable misclassification yielding unreliable results. In order to minimize misclassification at study start, a run-in period of 12 months was included.

Patterns of drug use vary more for anxiolytics and hypnotics (different dosages, daily use, periodic use, drug use on demand) than for antidepressants (usually regular, daily use). Furthermore, antidepressants had an estimated mean DDD/day closer to the proxy than the other drug groups. The suitability of using 1.0 DDD also differs between therapeutic subgroups of antidepressants, though; 70% of older people diagnosed with depression who were prescribed TCAs received < 0.5 DDD, as opposed to 15% of those who were prescribed SSRIs, according to a large cohort study performed in the UK (Coupland 2011). In conclusion, the chosen proxy has generally resulted in conservative risk estimations; this is particularly true regarding the associations between TCAs, anxiolytic and hypnotic drugs and the risk of hip fracture.

Statistical analysis

There are three possible types of errors that can be produced in a study: random error (the possibility of which can be quantified by using statistics), bias (which needs to be prevented by designing the study properly) and confounding (which can be controlled either in the design of the study or in its analysis) (Strom 2006c). The nationwide prospective study design prevented selection and information bias; data were analyzed strictly prospectively, thus avoiding “crystal-balling”. Misclassification of nursing-home patients as drug non-users is accounted for under the heading “Data obtained from the registries”, and choices made in order to minimize the influence on study results of misclassification of exposure in “Defining exposure”. Confounding was partly controlled for by the important confounders age, sex, time of year for fracture (higher risk during winter; (Solbakken 2014)) being incorporated in the SIR method. Due to lack of clinical information, residual confounding, in particular confounding by indication, could not be accounted for in our study, as discussed elsewhere (“Lack of clinical information” and “Discussion of results”). Propensity score analyses are increasingly used to reduce biases and thus increase internal validity; such analyses were also impossible to perform due to the limited information available per study participant.

Subanalyses regarding new users supported the findings of the main analyses (papers II and III). Significant results were obtained regarding the most frequently used drug groups only, reflecting that loss of power is a challenge when applying this design, even with a very large sample size.

From clinical experience, sedation is known to increase the risk of falling. For the purpose of analysis, the antidepressants were actually divided in three different ways, according to 1) therapeutic subgroups and 2) the drugs’ serotonergic effects, as reported in paper II, and 3) according to their sedative effects (sedatives: TCAs, mianserin and mirtazapine; non-sedatives: SSRIs, moclobemide, bupropion, venlafaxine, reboxetine and duloxetine). The results for sedative antidepressant were similar to the TCA-results and slightly more pronounced than for antidepressants with low/no serotonergic properties (not including mianserin and mirtazapine). The results for non-sedatives were similar to those calculated for SSRIs and antidepressants with intermediate/high serotonergic properties. As the analysis regarding sedative

properties did not provide essential additional information, it was not included in the published paper.

5.1.3 Generalizability

From the above considerations, we can conclude that both studies included in this thesis have reasonably high internal validity. This is a prerequisite of the generalizability, or external validity, of the results, that is to say whether or not they are valid outside the study population. Study I (paper I) included a selected group of community-dwelling older people aged 70 and above and living in Bergen, which could lead to limited generalizability. As seen in the table below, the proportions of individuals identified with PIMs and DDIs in the present study were similar to findings in Norwegian studies applying the same tools to subgroups of older people in different settings (Brekke 2008, Halvorsen 2011) as well as the entire population aged 70 and above (Nyborg 2012), during the same time period. This indicates that the results of the present study are generalizable to the entire older population of Norway.

Table 2a: Proportion of older people in study I and various populations in Norway with ≥ 1 potentially inappropriate medicine (PIM) (according to the NORGEF checklist) or drug-drug interaction (DDI) (according to www.interaksjoner.no).

Author	Population	Data source	Inappropriate drug use
Nyborg 2008	All community-dwelling ≥ 70	All prescription data (NorPD) from 2008	≥ 1 PIM: 37%
Brekke 2008	Community-dwelling individuals ≥ 70 (mean 79) (GPs in continuous medical education)	All prescription data (NorPD) from 2005	≥ 1 PIM: 18%
Halvorsen 2011	Individuals residing in NHs (mean age 85) or receiving HCS (83)	MDD database, cross-sectional, September 9, 2009	≥ 1 PIM: 31% NHs; 25% HCS ≥ 1 DDI: 48% NHs; 57% HCS Serious DDIs: < 2%
Study I 2012	290 community-dwelling individuals ≥ 70 (mean age 85) acutely admitted to hospital	Medication charts (2007/2008)	≥ 1 PIM: 24% admission - 35% discharge ≥ 1 DDI: 54% admission - 68% discharge Serious DDIs: < 2% on both occasions

PIM – potentially inappropriate medicines

DDI – drug-drug interaction

MDD – multidose dispensed drug

NH– nursing home

HCS – home care services

Whereas the internal validity is high in RCTs, external validity is often limited due to strict inclusion criteria and far from real life clinical conditions. This is particularly true regarding older people, who are frequently excluded from such studies. Major advantages with study II (papers II and III) include capturing the entire older population of Norway and that data from the national registries reflects clinical practice. Place of residence was unknown in our study. Although “the average” hip fracture patient is a frail individual in her eighties, nursing home residents may differ from other subgroups of older hip fracture patients, and may have affected the results of our study. Still, there is no reason to believe that the associations identified between psychotropic drug exposure and the risk of hip fracture are not relevant for nursing home residents.

Due to lack of comparable data on national level, it is challenging to evaluate (potential) differences in prescribing of psychotropic drugs between countries. Hip fracture rates and organization of health care services vary. Still, the results of study II are in line with results from studies originating in countries with various hip fracture rates and health care systems. These publications have primarily emerged from high-income countries.

In conclusion, the results of study I are generalizable to the entire community-dwelling older population in Norway, whereas the results of study II are generalizable to older people, including nursing home residents, in other high-income countries; possibly also to low-income countries.

5.1.4 Ethics and approvals

This thesis comprises two pharmacoepidemiological studies with no clinical intervention. The data material necessary for conducting analyses included information gathered during stay (study I) or registered in national registries (study II), requiring no active participation by the study participants.

Study I was approved by the Regional Committee for Medical and Health Research Ethics (295-07096a 1.2007.672) and the Norwegian Data Inspectorate (07/16946). All study participants provided informed consent, and could withdraw from the study at any time. Study II was approved by the Regional Committee for Medical and Health Research Ethics (138/07) and the Norwegian Data Inspectorate (08/00133). The

Norwegian Directorate of Health granted an exemption from the duty of confidentiality (08/1843). In both projects, each patient's identity was preplaced by a serial number and the key was kept by a third party. Thus, the researchers did not have access to patient identity.

5.2 Discussion of results

5.2.1 Drug use and prescribing quality

Number of prescribed drugs, PIMs and DDIs

Study I was, to our knowledge, the first to examine potentially inappropriate prescribing in an INHU. It revealed that the number of drugs increased markedly during stay. Similarly, in an observational study of 1550 patients, the average number of drugs increased from 8.2 to 9.9 during stay in a geriatric hospital department in Denmark (Larsen 2014). There has been a general increase in the number of drugs prescribed throughout the last decades, particularly for individuals aged ≥ 70 (Hovstadius 2010). This coincides with the age from which older people encounter health care services more frequently, and should ideally be explained by increased morbidity and subsequent optimized treatment. Whether or not this is the case, is not known; there is reason to believe other factors, e.g. the number of prescribers (Nyborg 2012) and “the prescribing cascade” (in which ADRs of one drug is misinterpreted as a medical condition, and results in the prescribing of another drug) (Petroni 2005), also contribute.

Polypharmacy is associated with drug-related problems (DRPs). The number of potential DRPs increases with increasing number of drugs. For DDIs in particular, an exponential growth is seen with an increasing number of drugs (Soraas 2014). In accordance with this, we found that the increase in the average number of drugs used per individual was accompanied by an increased proportion of the overall study population receiving potentially inappropriate medicines (PIMs) and drug-drug interactions (DDIs).

The proportions of individuals identified with PIMs and DDIs on admission, according to the chosen tools, were high, 24% and 54%, respectively. As previously mentioned, the proportions of individuals receiving PIMs on admission and discharge were similar to findings in the other Norwegian studies applying the same instruments to subgroups of older people in different settings (Brekke 2008, Halvorsen 2011) and the entire older population (Nyborg 2012). Furthermore, they are comparable to a Swiss study revealing that some 21% of community-dwelling older people received PIMs according to Beers (American Geriatrics Society 2012) or PRISCUS (Holt 2010) lists,

based on reimbursed drugs only (Blozik 2013). Still, a recently published Irish prospective cohort study (Moriarty 2015) nicely showed how the proportion of community-dwelling older people registered as receiving ≥ 1 PIM differed depending on the screening tool used, from 20% when applying ACOVE (San-Jose 2014) to 53% with STOPP (O'Mahony 2014).

Fifty-four percent of the community-dwelling individuals in study I had potential DDIs on hospital admission. This overall figure lies in between the ones identified for older people receiving home care services (48%) and residing in nursing homes (57%) in the study by Halvorsen et al. using the same interaction database, see table 2b.

Clinical relevance of DRPs identified by explicit methods

Explicit methods capture selected DRPs - the most important question is whether or not they capture clinically relevant DRPs. Table 2b shows the same studies as table 2a (5.1.3); here the drug groups most frequently involved in PIMs are added.

Table 2b: Proportion of older people with ≥ 1 potentially inappropriate medicine (PIM) in study I and various Norwegian studies applying the NORGEP checklist, and the drug groups most frequently involved.

Author	Population	Data source	Inappropriate drug use
Nyborg 2008	All community-dwelling ≥ 70	All prescription data (NorPD) from 2008	≥ 1 PIM: 37 % Psychotropic drugs, NSAIDs or ACE inhibitors in potentially harmful combinations with other drugs
Brekke 2008	Community-dwelling individuals ≥ 70 (mean 79) (GPs in continuous medical education)	All prescription data (NorPD) from 2005	≥ 1 PIM: 18 % NSAIDs in potentially harmful combinations with other drugs, sustained use of LABs
Halvorsen 2011	Individuals residing in NHs (mean age 85) or receiving HCS (83)	MDD database, cross-sectional, September 9, 2009	≥ 1 PIM: 31 % NHs; 25 % HCS Psychotropic drugs NSAIDs or ACE inhibitors in potentially harmful combinations with other drugs
Study I 2012	290 community-dwelling individuals ≥ 70 (mean age 85) acutely admitted to hospital	Medication charts (2007/2008)	≥ 1 PIM: 24% admission - 35 % discharge Psychotropic drugs, NSAIDs in potentially harmful combinations with other drugs

PIM – potentially inappropriate medicines

NorPD – the Norwegian Prescription Database

Psychotropic drugs – anxiolytics, hypnotics, antidepressants or antipsychotics

MDD – multidose dispensed drug

NH– nursing home

HCS – home care services

ACE inhibitors – angiotensin-converting-enzyme inhibitors

LABs – long-acting benzodiazepines

PIMs (according to the NORGEP list)

In all the studies in table 2b, concurrent use of more than 3 psychotropic³ drugs (or another item including potentially inappropriate use of a psychotropic drug) was the most frequent “hit”. Also when applying other tools in order to identify PIMs, psychotropic drugs are frequently involved (Dalleur 2014, Moriarty 2015).

Psychotropic drugs are known to cause sedation, impaired cognition and impaired balance, and are recognized as complex risk factors for e.g. falls and fractures. The latter is more thoroughly discussed in 5.2.2 Psychotropic drugs and fractures below. Furthermore, NSAIDs in potentially harmful combinations with other drugs were common. NSAIDs are associated with an increased risk of serious adverse events, like gastrointestinal ulcers, acute renal failure and myocardial infarctions (Fine 2013), particularly among older people in high-risk populations (Pratt 2010).

Due to the lack of clinical information in study I, we cannot conclude whether or not the risks of using these drugs/combinations of drugs outweighed the benefits on an individual level. From a recently published paper, which included the patients investigated in study I, we know that most participants received home care services at follow-up 12 months after the index hospitalization, and that 18% of the days (on study population level) were spent in institutions - reflecting a vulnerable population (Herfjord 2014). Also, collating prescription data with the prevalence of e.g. depression, anxiety or sleep problems during the same time period, as well as recommendations for drug use, strongly indicates that psychotropic drugs are frequently used without valid indication, and in dosages and durations beyond recommendations (Kjosavik 2012, Neutel 2012). Taken together, this implies that *actually* inappropriate medicines were identified in study I.

DDIs (according to interaksjoner.no)

Drug-drug interactions were very common, whereas the serious ones (class D – “should not be combined”) were scarce, in line with other studies (Halvorsen 2011, Marengoni 2014, Soraas 2014). Still, they may have been of importance, both at the patient and population level. Class D interactions often include warfarin or other anticoagulants in combination with other drugs that increase the risk of bleeding, e.g.

³In NORGEP, this includes all psychotropic drugs (antidepressants, anxiolytics, hypnotics and antipsychotics) and opioids.

NSAIDs. Study I was not powered to investigate single substances involved in interactions of different severity, nevertheless: two out of four class D interactions identified were warfarin-NSAIDs combinations. These drugs are also frequently involved in interactions classified as less severe (e.g. "take precautions"). In a similar, but larger, population, Brekke et al. found that 7% were prescribed NSAIDs in a potentially harmful combination with warfarin, an SSRI, a diuretic or an ACE-inhibitor (Brekke 2008). As NSAIDs are widely sold as OTC (over the counter) drugs in Norway, this is probably an underestimation.

Prescribing quality in different settings

In study I, no significant reductions were identified for any of the chosen variables (number of drugs, PIMS and DDIs) neither in the HW or the INHU. This is in line with the above mentioned Danish study, where the average number of drugs increased and only a minor proportion of drugs were switched or discontinued during stay in a geriatric hospital ward in which medication review was a cornerstone of the comprehensive geriatric assessment provided (Larsen 2014).

Furthermore, study I revealed no significant differences in prescribing quality during stay between the two settings. This may be a true finding, reflecting that there were no actual differences in the elements investigated. On the other hand, it might result from lack of power, as there was a trend towards more appropriate drug treatment in the INHU. The overall number of PIMs increased due to more PIMs in the HWs ($p=0.02$), but not in the INHU ($p=0.2$). Also, DDIs classified as "take precautions" increased significantly in the HW only. Although medication reviews (and other areas included in a comprehensive geriatric assessment (CGA)) were focused on, the procedures were not standardized.

Recently, drug reconciliation has been systematized in many Norwegian hospitals, due to increased awareness through e.g. "In safe hands", a national patient safety program (In safe hands 2014). Similarly, drug reconciliation and medication reviews have been systematized in many nursing homes, through the same national program, as have medication reviews at general practitioners' offices, through regulations (Forskrift om fastlegeordning i kommunene). Multiprofessional teams conducting structured medication reviews have proved effective in reducing the number of unidentified

DRPs (Bondesson 2013) and identifying STOPP items of major importance (Dalleur 2014); collaboration across health care levels is recommended (Bondesson 2013, Dalleur 2014, Larsen 2014). Studies with clinical outcomes are scarce, but suggest structured medication reviews alone (Clegg 2014) or as an integral part of standardized CGA may improve patient outcomes (Saltvedt 2002).

5.2.2 Psychotropic drugs and hip fractures

Psychotropic drugs are complex risk factors for hip fractures. Both the indications for treatment and the treatment itself (dependent on substance, dosages and duration) may influence the risk of falls and fractures. Interestingly, PIMs (defined as “hits” in the STOPP/START lists), of which psychotropic drugs constitute a crucial part have been shown to independently predict long term mortality in older hip fracture patients (Gosch 2014).

Overall, the differences in the strength of the associations between hip fracture and drug use across age groups in study II (papers II and III), with the youngest individuals at highest excess risk, must be interpreted with caution due to the previously mentioned misclassification among the oldest old, and the lack of information on relevant confounders. Due to this lack of information, precautionous interpretation of potential risk differences between men and women is warranted. Still, men have been found to be at higher excess risk also in other studies (Kannegaard 2010). In the following, results of study II and III will be discussed separately.

Antidepressants and hip fractures

Associations between antidepressants and hip fractures

Study II, paper II, showed that individuals using any antidepressants were at excess risk of experiencing a hip fracture, in line with data from five large European countries and the US published recently (Prieto-Alhambra 2014). These are observational studies with no or limited clinical information, and thus susceptible to confounding. Nevertheless, an association between antidepressant drug use and fractures in general (Vestergaard 2006, Richards 2007, Vestergaard 2009, Coupland 2011, Rizzoli 2012) and hip fractures in particular (van den Brand 2009, Vestergaard 2013), has been shown to remain when adjusting for e.g age, sex, depression, previous falls or fractures, comorbidities, concomitant drug use and lifestyle factors. Although residual

confounding cannot be ruled out, these studies strongly suggest that antidepressant drug use does in fact increase fracture risk. Hip fractures are of particular interest, due to the resulting high morbidity and mortality.

Prescribing of antidepressants

Depression too is associated with increased morbidity and mortality, and therefore important to identify, and adequately treat and follow-up. Despite the increase in antidepressant drug use, many severely depressed older patients do not receive antidepressant drug treatment (or any other treatment targeting their mood disorder) (Sonnenberg 2008); failure to recognize depressive disorders, and resulting undertreatment, is feared. On the other hand, there is evidence for limited efficiency of antidepressant drug treatment among older people with mild to moderate episodes of depression and depressed patients with dementia (Pinquart 2006, Boyce 2012, Nelson 2013). Several non-pharmaceutical treatment options (like bright light therapy, cognitive behavioral therapy (CBT), reminiscence therapy) have proved to be at least as efficient, with fewer and less severe side effects (Pinquart 2007, Chiang 2010, Leontjevas 2013). Still, as shown in the introduction, antidepressant drugs are very widely used among older people.

The majority of patients with depression experience episodes of mild-moderate severity, and there is even reason to suspect that treatment without a valid indication is prevalent: In a large population based cohort study in the US, Mojtabai et al. showed that most older people in primary care who were diagnosed with clinical depression by a physician, did not actually meet diagnostic criteria for this condition (severe depression, as defined by the diagnostic manual DSM-III) (Mojtabai 2013).

Furthermore, a qualitative study conducted in Norwegian nursing homes suggested that drug treatment was usually initiated without diagnostic work –up; the request for drug treatment came from auxiliary nursing staff, and was passed on by registered nurses to the physician, who felt some pressure to prescribe antidepressants. Both physicians and nurses reported having difficulties in differentiating sorrow from depression; a nurse reported the following: “We are not skilled in differentiating between these conditions. If they cry, we call it depression and give them antidepressants. And that’s it (Iden 2011)”.

Finally, despite proven efficacy in a limited share of the patients with (severe) depression only, and older people possibly using antidepressants without valid indication, follow-up (Iden 2011) and discontinuation of antidepressant drug treatment is scarce (Midlov 2014).

Antidepressants, serotonergic properties and hip fractures

In paper II, antidepressants were classified according to therapeutic subgroups and the antidepressants' serotonergic effects. Analyses revealed that the highest excess risk of experiencing a hip fracture was found among those using SSRIs or drugs with intermediate to high serotonergic effects, respectively. The methodological limitations discussed in chapter 5.1 must be borne in mind when interpreting this finding. Still, it is potentially highly clinically relevant, as hip fractures are common and severe, and there has been an intentional worldwide shift from TCAs to SSRIs. The latter group is now, due to a milder adverse reaction profile (e.g. regarding sedation and cognition), "first choice" in antidepressant drug treatment, and widely prescribed.

Through the last decades, the use of SSRIs has been associated with an increased risk of hip fracture based on (Medicare) claims data (Schneeweiss 2004), and in case-control (Liu 1998, Hubbard 2003, Vestergaard 2006, van den Brand 2009, Vestergaard 2009) and cohort (Ensrud 2003) studies, even when adjusting for the above mentioned confounders. The strengths of the associations were equal to, or more prominent than those found with TCA use, and similar to the almost two-fold increase found in our study (paper II); results regarding the pharmacologically heterogeneous group "others" were mixed. These studies investigated single substances and/or antidepressants classified according to the ATC-system. Taken together, they revealed a lack of homogeneity in results across ATC drug classes, e.g. users of the SSRI fluoxetine were not at higher risk than those who used the TCAs with most prominent serotonergic effects (clomipramine and amitriptyline). As a result, it was hypothesized that the increased risk of hip fracture was linked to the drugs' serotonergic properties (Haney 2008, Vestergaard 2009).

To the best of my knowledge, we were the first to group the antidepressants according to their serotonergic properties. We classified the TCAs clomipramine and amitriptyline, and the "others" mianserin, mirtazapine, venlafaxine and duloxetine in

the group intermediate to high serotonergic properties. A clear pattern emerged with SIR (95% CI) (all) 1.7 (1.7-1.8) for antidepressants with high/intermediate serotonergic properties and 1.2 (1.1-1.5) for antidepressants with low/no serotonergic properties, as opposed to the SIRs 1.4 (1.3-1.5), 1.8 (1.7-1.8) and 1.6 (1.5-1.7) for the therapeutic subgroups TCAs, SSRIs and others, respectively. This supports the theory of a link between serotonergic properties and the risk of hip fracture.

Observational studies tend to overestimate associations. The associations between the use of SSRIs and the risk of any fracture at any age ≥ 18 were less strong, but still clinically significant, when ≥ 4 (as opposed to < 4) confounders were adjusted for (Eom 2012). As pointed out above, the association between the use of SSRIs among *older people* and the risk of *hip fracture* identified in observational studies of different designs has been shown, after adjusting for relevant confounders, to persist at a level similar to the one identified in our nationwide prospective cohort study. Looking at time spans and dosages further supports the theory that drugs with high/intermediate serotonergic properties affect the risk of hip fracture: we found a higher excess risk of hip fracture among individuals on recently started treatment as compared to overall treatment. Numbers were small, but the finding is consistent with other studies (Rizzoli 2012). We did not investigate dose-dependency, but a dose-dependent relationship has been shown by others (Vestergaard 2006, Bolton 2008, van den Brand 2009, Vestergaard 2013). Also, the treatment-associated increased risk remains during SSRI exposure/use (Hubbard 2003, van den Brand 2009) and diminishes towards baseline in the year following discontinuation (Rizzoli 2012).

Anxiolytics, hypnotics and hip fractures

Associations between anxiolytics, hypnotics and hip fractures

In study II, paper III, being exposed to any anxiolytic or hypnotic drug was associated with an excess risk of hip fracture as compared to non-exposure. Due to differences in designs and data sources chosen, populations and settings studied, and the selection and classification of the drugs and outcomes included, direct comparisons with other studies are challenging. Nevertheless, our findings are in line with the pooled relative risk (RR) of 1.4 (1.2-1.6) associated with benzodiazepine use (defined as any

benzodiazepines or benzodiazepine-like drugs (z-hypnotics)) in a literature review by Khong et al (Khong 2012).

Although intermittent or short term use is recommended for anxiolytic and hypnotic drugs, only a minority of users receive treatment in line with the recommendations (Kjosavik 2012, Cadogan 2015). Considering the well-established link to falls, the very widespread use of the drugs in question and the severity of the outcome, there are surprisingly few studies primarily exploring the effects of anxiolytic and hypnotic drug use on *hip fractures*, particularly of recent date. All but one of the 11 observational studies included in Khong's review were published 10-25 years ago. Some of these were included in a meta-analysis of case-control and cohort studies assessing associations between the use of benzodiazepines (z-hypnotics not specifically mentioned, still included in e.g. the study by Zint et al. (Zint 2010)) and *any fractures* (Xing 2013). Here, subanalysis revealed an RR of 1.35 (1.22-1.50) for individuals (aged 30 or older; 65 or older in the majority of the included studies) using *any benzodiazepines* to experience a hip fracture.

The strength of the associations identified between exposure to anxiolytics or hypnotics and hip fractures (paper III) were weaker than for antidepressants and hip fractures (paper II), and very similar to the results of a large prospective cohort study conducted in Sweden in 2007 (Thorell 2014). Adjusting for age and sex (as in study II) and multimorbidity level, they calculated odds ratios (ORs) at 1.31 (95% CI 1.11-1.54), 1.31 (1.13-1.52) and 1.66 (1.42-1.95), for anxiolytics, hypnotics and antidepressants, respectively (Thorell 2014). Importantly, anxiety and sleep disorders were not adjusted for in these or, to the best of my knowledge, any other studies investigating the relationship between anxiolytics and hypnotics and hip fractures. Thus, the associations may, at least partly, be explained by confounding by indication. Adjusting for depression or depressive symptoms, and a various selection of other comorbidities, has been shown to slightly attenuate the magnitude of the associations between using anxiolytic and hypnotic drugs and the risk of falls (Diem 2014) and hip fractures (Ensrud 2003, Zint 2010, Vestergaard 2013, Thorell 2014). In studies also controlling for concomitant (psychotropic) drug use (Zint 2010, Vestergaard 2013), weak-moderate associations between using anxiolytic and hypnotic drugs and falls and

hip fractures still remain. A dose-dependent risk of falls (Sterke 2012a) and hip fractures (Zint 2010, Vestergaard 2013), starting from low dosages, and more prominent excess risk in recently started drugs use (Zint 2010, Berry 2013, Vestergaard 2013, Paper III) further strengthen the evidence that anxiolytic and hypnotic drug use influence hip fracture risk.

Short-acting and long-acting benzodiazepines

In existing guidelines, short-acting benzodiazepines (SABs) have been considered safer than long-acting benzodiazepines (LABs), as reflected in e.g. the previously mentioned NORGEP and STOPP lists. We found no evidence supporting that the recommended SABs were safer than LABs with regards to hip fracture. This is in line with a retrospective cohort study published in 2004 (Wagner 2004), a nested case-control study from 2010 (Zint 2010), and recently published results from studies investigating benzodiazepines and the risk of falls (Sterke 2012a, Diem 2014). In the review by Khong et al., pooled RRs were estimated at 1.23 for SABs and 1.32 for LABs. Differences in classification of drugs (e.g. z-hypnotics defined as SABs in Khong's study) and possible changes in drug prescribing habits the last decades (e.g. shifting from LABs to the recommended SABs when prescribing for individuals particularly vulnerable to adverse drug reactions) may explain the discrepancies.

Hypnotics and time of hip fracture

People exposed to hypnotics were at greatest excess risk at night. Overall, a 40% increased risk was seen during the first 14 days following a prescription for a hypnotic drug, as compared with non-exposure. Within the youngest birth cohort (persons born 1935-1944), a two-fold risk of experiencing a night-time hip fracture was identified among individuals during the first 14 days exposed to any hypnotic drug (SIR 2.0, 95% CI 1.6-2.5); people exposed to z-hypnotics were at even higher excess risk (SIR 2.7, 95% CI 1.9-3.8) (not shown in paper III).

About 2/3 of hip fractures, take place during daytime, whereas about 1/3 occur at night (Formiga 2008). A similar diurnal pattern was observed in our study, 30% of *all* fractures occurred at night (not shown in papers), and 32% of the *hip fractures registered during exposure to hypnotic drugs* where night-time fractures (table 3,

paper III). An increased risk for night-time hip fractures has been identified among older people using psychotropic drugs, regardless of dementia diagnosis or place of residence (Leavy 2013), and among nonagenarians (Formiga 2008, Nuotio 2014). There is an intriguing paucity of knowledge regarding the use of hypnotics and time of fracture. According to unpublished data from our study, the proportion of night-time fractures increased with age, from 28 % (among individuals born 1935-1944) to 33% (born <1915), respectively) within the entire study population and from 31% to 40% among those fracturing during exposure to hypnotic drugs (comparing the same birth cohorts). These results imply that there is a less clear diurnal hip fracture pattern among nonagenarians using hypnotic drugs.

Whether this relatively higher proportion of night-time fractures is explained by the indication for using hypnotics, the drug itself and/or other factors, remains unclear. Sleep patterns are altered, and the prevalence of insomnia increases, with advancing age. More than 50% of community-dwelling Norwegian nonagenarian women receive at least one prescription for hypnotics yearly; z-hypnotics (mainly zopiclone) constitute the vast majority (Norwegian Prescription Database 2012). Due to their short half-lives and preservation of normal sleep architecture, z-hypnotics have traditionally been considered less harmful than benzodiazepines for treatment of sleep disorders (Allain 2005, Diem 2014). In recent years, clinical studies have shown z-hypnotics to produce significant balance and cognitive impairments upon awakening from sleep among younger (mean age 22) (Frey 2011) and older (mean age late 60-ies) individuals (Zammit 2008, Frey 2011). Observational data have revealed associations between the use of z-hypnotics and falls among older men (Diem 2014), between the use of z-hypnotics and any fractures among older people with insomnia (Kang 2012) and between the use of z-hypnotics and hip fractures among older people (Wang 2001, Zint 2010), including nursing home residents (Berry 2013). In a recently published retrospective cohort study, Fang-Yu et al. estimated a two-fold excess risk among older users of zolpidem as compared with non-users; the fractures occurred mainly on exposure days (Lin 2014). A dose-dependent increase of falls (Sterke 2012a) and hip fractures (Zint 2010, Berry 2013) starting from low dosages, and more prominent excess risk of hip fracture in recently started use (Berry 2013, Paper III) further strengthen the evidence z-hypnotic drug use affect hip fracture risk. There was no

information on time of fracture in the studies reported; also the majority of studies have investigated zolpidem only.

Attributable risk

The attributable risks of antidepressant (paper II) and anxiolytic and hypnotic (paper III) drug exposure on hip fracture were estimated at 4.7% and 3.3%, respectively. At the population level, this corresponds to some 1900 and 1300 hip fractures during the 6 year study period. These estimates should be interpreted with caution. Nevertheless, comparable estimates of population attributable risks (PARs) were found in two large reviews including data from five large European countries and the US (Khong 2012, Prieto-Alhambra 2014). Also, SSRIs were associated with substantially higher PARs than TCAs, and SABs (including z-hypnotics) with higher PARs than LABs. Taken together, study II (papers II and III) and these reviews imply a substantial number of hip fractures are related to antidepressant, anxiolytic and hypnotic drugs use in general, and by the recommended SSRIs, SABs and z-hypnotics in particular.

5.2.3 Established challenged “truths” - recommended drugs not safer?

Study II (papers II and III) and the discussion above strongly suggest that the recommended drugs (SSRIs, SABs and z-hypnotics) offer no advantages with regard to hip fractures as compared to the traditional alternatives (TCAs, LABs and (any) benzodiazepines, respectively). But is there a causal relationship between using these drugs and the risk of hip fractures?

Associations versus causality

When considering whether or not there is sufficient evidence for a causal nature of an association, looking at the data from the following viewpoints, proposed by Bradford Hill (Hill 1965), here as adapted by Strom and Kimmel (Strom 2006d), may prove useful:

1. Coherence with existing information or biological plausibility
2. Consistency of the association (reproducibility)
3. Time sequence (does the exposure precede the outcome in question?)
4. Specificity of the association
5. Strength of the association (quantitative strength, dose-response, study design)

With these factors in mind, I will discuss the collated results from our nationwide prospective cohort study and current knowledge from other studies.

Antidepressants, serotonergic properties and hip fractures

Our finding of an increased risk of hip fracture among individuals using SSRIs and antidepressants with similar properties coheres with existing information, and has been shown for SSRI use in different populations through several observational studies of various designs, adjusting for various confounders (though unable to exclude confounding by indication) during the last decades, at about a two-fold magnitude.

There is a well-established link between SSRIs and antidepressants with similar properties and falls, mediated through frequent ADRs (e.g. sedation, sleepiness, dizziness, hyponatremia, arrhythmias and gastrointestinal symptoms). Growing evidence suggests an additional biological explanation; their serotonergic properties exert overall negative effects on bone strength, thus increasing fracture risk.

Serotonergic receptors are identified in all bone cell lines (osteoblasts, osteoclasts and osteocytes) (Haney 2008). The mechanisms involved are complex and not yet fully elucidated, but bone tissue seems to be affected in a dose-dependent manner, linked to the antidepressants' affinity for the serotonin transporter system (Rizzoli 2012).

Mixed results have been published regarding the effect on BMD (Diem 2013, Gebara 2014). This heterogeneity is possibly explained by genetic variations in serotonergic transporter and serotonergic receptors (Garfield 2014b) and/or lack of study power, as well as true negative findings in some (younger) populations, regardless of genetic variations (Diem 2013). Importantly, bone strength relies not only on bone quantity (BMD), but also on bone quality parameters (e.g microarchitecture, micro damage accumulation, degree of remodeling) (Djonic 2013). The fact that the excess risk is most pronounced during recently started treatment, and diminishes towards baseline after discontinuation, further strengthens the evidence for a biological explanation. The criterion regarding specificity is not met, but as diseases may have more than one cause, it rarely is (Hill 1965). Hip fractures are usually multifactorial in origin, thus identifying one single causative factor is very unlikely.

There is no clear-cut limit as to when evidence is sufficient to implement knowledge on causality into clinical work. Paradoxically, whereas clinical practice reveal a

widespread acceptance of the limited efficacy of antidepressant drug use for most older patients with depression, there seems to be a demand for definite evidence until accepting the resulting harms.

One single review recently published in the *Journal of American Geriatrics (JAGS)*, concluded evidence is not sufficient to prove causality between *SSRIs and reduced BMD* (Gebara 2014). Others (Haney 2010, Tsapakis 2011, Rizzoli 2012, Bruyere 2014) have concluded there is enough evidence of a causal relationship between *SSRIs and osteoporosis* (deteriorated bone tissue; for which reduced BMD and alteration of bone microarchitecture/bone modelling components are important determinants), and that SSRIs should be included in the list of medications that increase the risk for osteoporotic fractures. The findings in paper II favor this latter conclusion.

Furthermore, paper II provides important additional knowledge with regards to antidepressants with high/intermediate serotonergic properties and the risk of hip fracture. Antidepressants with high/intermediate serotonergic properties affect bone tissue through the same mechanisms as and to a similar extent as SSRIs.

Consequently, they should, in my opinion, be considered included in the same list.

Anxiolytics, hypnotics and hip fractures

The association between anxiolytic and hypnotic drug use and the risk of hip fracture became evident more than two decades ago, and has been reproduced in recent studies (Khong 2012, Paper II, Thorell 2014). As discussed above, observational studies other than study II have revealed weak-moderate associations between anxiolytic and hypnotic drug use and hip fractures, with a dose-response relationship starting from low dosages. Obviously, these associations are weaker than for the SSRIs and antidepressants with similar properties, and based on studies in which residual confounding can never be ruled out. There are few studies looking specifically at z-hypnotics (zopiclone in particular) and the risk of hip fracture.

The vast majority of hip fractures results from a person with reduced BMD (or deterioration of other aspects of bone quality) falling. There is no evidence anxiolytic and hypnotic drugs exert biological effects on bone tissue. This would have supported the evidence of a causal relationship between these drugs and hip fractures, but is not a necessity. Still, a causal relation is definitely plausible; there is a well-established link

between the use of any group of anxiolytic and hypnotic drug use and falls, which provide a biological explanation for the association between these drugs and the risk of hip fractures. Every third person above the age of 65 experiences a fall at least once yearly, of whom some 50% suffer more than one fall (Tinetti 2010). Resulting injuries are frequent. Also, anxiolytic and hypnotic drugs have been associated with injurious falls (Bauer 2012). Furthermore, these drugs have limited efficacy, and are associated with ADRs other than falls (e.g. dependency, sedation, sleepiness, paradox insomnia, dizziness and balance impairments) and increased mortality (Glass 2005, Weich 2014). Still, only a minority of users receive treatment in line with the recommendations (Kjosavik 2012, Cadogan 2015). The importance of monitoring and auditing benzodiazepine and z-drug prescribing practices (Cadogan 2015) and the question why benzodiazepines are not yet controlled substances (Moore 2015) are elements of prescribing quality recently highlighted.

In conclusion, although plausible and probable, it still might be argued whether or not there is sufficient evidence to *prove* direct causality between the use of anxiolytic and hypnotic drugs (particularly regarding z-hypnotics) and hip fractures. However, even a weak association between these very widely used drugs and a severe outcome like hip fracture may exert major impact on the population level. From a clinical point of view, we probably know enough about the limited efficacy and the high risk of ADRs associated with anxiolytic and hypnotic drugs to aim at reducing the use of these drugs among older people. The question is how to get there.

6 Conclusions

Taken together, the papers included in the thesis illuminated various potentially harmful aspects of drug use among older people. The main findings were:

Study I: Drug-related problems (DRPs) were common among community-dwelling older people acutely admitted to hospital; potentially inappropriate medicines (PIMs) and drug-drug interactions (DDIs) were frequent and increased during stay in both hospital wards and an intermediate care nursing home.

- Concomitant use of several psychotropic drugs and unadvisable drug combinations including NSAIDs were the PIMs most frequently identified.
- Serious DDIs were scarce.
- No reductions in number of drugs, PIMs or DDIs were identified in either setting.

Study II: Being exposed to any antidepressant, anxiolytic or hypnotic drug was associated with an excess risk of hip fracture as compared to non-exposure.

- Being exposed to SSRIs and other drugs with prominent serotonergic properties was associated with the greatest excess risk – which was almost 2-fold.
- The recommended short-acting benzodiazepines were apparently not safer than long-acting benzodiazepines regarding risk of hip fracture.
- People exposed to z-hypnotics were at greatest excess risk at night.
- The attributable risks on hip fracture were estimated at about 5% for antidepressant drug exposure, and at about 3% for anxiolytics and hypnotics, respectively. At the population level, this corresponds to more than 3000 hip fractures during the 6 year study period.

7 Implications for practice and research

The main findings of the studies constituting this thesis, seen in the light of current knowledge, imply that there is need for improving the drug treatment for older people, and that the recommended psychotropic drugs (SSRIs, SABs and z-hypnotics) offer no advantages with regard to hip fractures as compared to the traditional alternatives. The following specific topics emerged:

Drug-related problems - clinical outcomes needed

Drug-related problems (DRPs) are frequent among older people, with plausible clinical relevance.

- Routinely looking for DRPs in clinical practice is advisable. Multidisciplinary teams (pharmacist, physician and nurse) conducting structured medication reviews have proved effective in reducing the number of DRPs.
- Studies including clinical outcomes like quality of life, falls, fractures, (re-) admissions to hospital and/or mortality are needed in order to establish which DRPs are clinically relevant. Also, clinical outcomes should be included in studies evaluating interventions aiming at improving the prescribing quality.

Treatment recommendations – time for action?

Evidence strongly suggests that the recommended drugs (SSRIs, SABs and z-hypnotics) offer no advantages with regard to hip fractures as compared to the traditional alternatives (TCAs, LABs and (any) benzodiazepines, respectively). In fact, there seems to be a causal relationship between antidepressants with prominent serotonergic properties and hip fractures. Furthermore, evidence suggests treatment recommendations (duration, dosages) are frequently not followed.

- Clinicians should be more aware of the connection between psychotropic drugs and fall risk (Bell 2015).
- Due to the limited efficacy and the risk of harmful adverse effects associated with anxiolytic, hypnotic and antidepressant drugs, an increased use of non-pharmacological treatment options will probably be beneficial. When choosing drug prescribing precautionous follow-up is mandatory.

- SSRIs and other antidepressants with prominent serotonergic properties should be added to the “bad to the bone”- list.
- The authorities may launch national health professional-led campaigns promoting quality use of medicines, like Choosing Wisely (Levinson 2015), focusing on communication between health personnel and patients. Also, they may intensify the surveillance of selected generic substances (including SSRIs, other antidepressants with prominent serotonergic properties and z-hypnotics, as notified by the European Medicines Agency (EMA) in May 2015).

Psychotropic drug use and hip fractures – suggestions for further research

Hip fractures represent a major public health problem, and any preventing measures will be of importance. Psychotropic drugs are widely used and increase the risk of falls and hip fractures; the potential impact on (the individual and) the population level is substantial.

- The effects of serotonergic effects on bone tissue should be further investigated (e.g. by imaging, bone biopsy, bone turnover markers) in prospective studies adjusted for relevant confounders; serum-concentrations could verify drug use.
- The association between z-hypnotics and night-time fractures deserves further investigation, possibly an RCT comparing drug treatment and non-pharmacological treatment.
- The reasons why doctors keep prescribing anxiolytics and hypnotics beyond recommendations and current knowledge could be explored in qualitative studies.

All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.

Sir Bradford Hill, 1965.

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