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Heidi Taipale

Sedative Load and Adverse Events Among Community-Dwelling Older People

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ABSTRACT

Older people are frequent users of drugs with sedative properties. However, older people are susceptible to adverse drug events. Sedative drug use has been associated with impaired physical and cognitive function, an increased risk of falls and increased mortality. Sedative load refers to cumulative exposure to multiple drugs with sedative properties.

This thesis aimed to investigate sedative load and adverse drug events among community-dwelling people aged ≥75 years. The thesis had focus on (I) the prevalence and factors associated with sedative load, (II) the association between the sedative load and balance and mobility, (III) the association between sedative load and muscle strength; and (IV) evolution of sedative load over time and the corresponding risk of death.

The study analyzed data from Geriatric Multidisciplinary Strategy for the Good Care of the Elderly (GeMS) study which was a prospective population-based, randomized comparative study conducted from 2004–2007 in Kuopio, Finland. Participants were randomized to the intervention (n=500) and comparison groups (n=500). All participants were interviewed annually by trained nurses regarding drug use, medical conditions, and other health-related factors. Physical function tests were conducted by trained physiotherapists. Data on mortality were extracted from national registers. Community-dwelling persons (n=700 at baseline) were included in the analyses. Sedative load was calculated for each participant according to a previously published model. Unadjusted and adjusted analyses were conducted using logistic regression, analysis of covariance (ANCOVA) and Cox proportional hazards models.

At the baseline of the GeMS Study, 29% of participants used one or more sedative drugs on regular basis. Factors associated with higher sedative load were female sex, poor self-rated health, impaired Instrumental Activities of Daily Living, and subjective feelings of loneliness. Sedative load was associated with poorer performance in balance and mobility tests which included 10 meter walking speed, the Timed Up and Go test and Berg Balance Scale. Sedative load was not associated with self-reported ability to walk 400 meters. Sedative load was associated with poorer performance in muscle strength tests, including hand grip strength, knee extension strength and chair stands test. Increasing sedative load was associated with poorer grip strength. Sedative load increased during the 3-year follow-up, and at the end of study, 36% of participants used sedative drugs. However, increasing sedative load was not associated with an increased risk of death.

In conclusion, cumulative exposure to drugs with sedative properties was associated with decreased physical function. This represents a threat to independent living among older people. This thesis highlights the importance of implementing strategies to optimize sedative drug use among older people.

National Library of Medical Classification: QV 85, WE 103, WE 500, WT 166
Medical Subject Headings: Hypnotics and sedatives/adverse effects; Prevalence; Drug Utilization; Postural Balance; Movement; Muscle strength; Mortality; Aged

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TIIVISTELMÄ

Sedatiivien eli väsyttävien lääkkeiden tai väsyttävän sivuvaikutuksen omaavien lääkkeiden käyttö on yleistä iäkkäillä, vaikka niiden käyttöön liittyy heillä haittatapahtumia useammin kuin nuoremmilla ihmisillä. Tässä tutkimuksessa käytettiin aiemmin kehitettyä mallia, jonka avulla voidaan arvioida kokonaislääkityksen sedatiivisuus, eli sedatiivikuorma.

Väitöskirjan tavoitteena oli tutkia lääkityksen sedatiivikuormaa ja siihen liittyviä haittatapahtumia kotona asuvilla yli 75-vuotialla henkilöillä. Tavoitteena oli tutkia (I) sedatiivikuorman esiintyvyyttä ja siihen liittyviä tekijöitä, (II) sedatiivikuorman yhteyttä tasapainoon ja liikkumiskykyyn, (III) sedatiivikuorman yhteyttä lihasvoimaan, ja (IV) sedatiivikuorman muuttumista kolmen vuoden seurantajakson aikana, sekä siihen liittyvää kuolleisuutta.

Tutkimuksessa käytettiin väestöpohjaisessa Hyvän Hoidon Strategia (HHS) tutkimuksessa kerättyä aineistoa. HHS-tutkimukseen valittiin tuhat 75-vuotiasta ja sitä vanhempaa kuopiolaista, jotka satunnaistettiin interventio- (n=500) ja verrokkiryhmään (n=500). Tähän tutkimukseen poimittiin aineistosta kotona asuvat iäkkäät, joita oli tutkimuksen alkaessa 700 henkilöä. Tutkimushoitajat haastattelivat tutkittavat vuosittain (2004-2007) terveydentilan ja lääkkeiden käytön suhteen. Fysioterapeutit testasivat tutkittavien liikkumiskykyä, lihasvoimaa ja tasapainoa. Sedatiivikuorma laskettiin aiemmin julkaistun mallin mukaan jokaiselle tutkittavalle. Haittatapahtumien yhteyttä sedatiivikuormaan tutkitiin logistisen regression, kovarianssianalyysin ja Coxin mallin avulla.

Tutkimuksen alussa 29 prosenttia tutkittavista käytti yhtä tai useampaa väsyttävää lääkettä säännöllisesti. Sedatiivien käyttäjät olivat useammin naisia ja he kokivat terveydentilansa huonoksi verrattuna henkilöihin, jotka eivät käyttäneet sedatiiveja. Lisäksi sedatiivien käyttöön liittyi heikentynyt välineellisistä päivittäisistä toiminnoista selviytyminen, sekä subjektiivinen yksinäisyyden tunne. Sedatiivikuorman todettiin olevan yhteydessä heikentyneeseen liikkumiskykyyn ja tasapainoon testeissä, joihin kuuluivat 10 metrin kävelynopeus, Timed Up and Go –testi sekä Bergin tasapainotesti. Sedatiivikuorma oli yhteydessä heikentyneeseen lihasvoimaan, jota mitattiin käden puristusvoimalla, polven ojennusvoimana sekä viiteen tuolilta ylösnousuun käytetyllä ajalla. Mitä suurempi oli sedatiivikuorma, sitä huonompi oli käden puristusvoima. Sedatiivikuorma kasvoi kolmevuotisen seuranta-ajan kuluessa, ja tutkimuksen lopussa 36 prosenttia tutkittavista käytti väsyttäviä lääkkeitä. Sedatiivikuorma ei kuitenkaan ollut yhteydessä suurentuneeseen kuoleman riskiin.

Johtopäätöksenä todetaan että altistuminen väsyttäville lääkkeille on yhteydessä heikentyneeseen fyysiseen suorituskykyyn. Tämä voi muodustua uhaksi itsenäiselle elämiselle, jossa vaaditaan suoriutumista jokapäiväisistä toiminnoista. Tutkimuksen tulokset korostavat säännöllisen lääkkeiden käytön arvioinnin merkitystä, sekä uusien menetelmien tarvetta lääkehoidon hyötyjen ja haittojen arviointiin.

Luokitus: QV 85, WE 103, WE 500, WT 166
Yleinen Suomalainen asiasanasto: lääkkeet; sedatiivit; esiintyvyys; käyttö; haitat; tasapaino; liikuntakyky; lihasvoima; kuolleisuus; ikääntyneet

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Espoo, May 2012

Heidi Taipale

List of the original publications

This dissertation is based on the following original publications which are referred to in the text by their Roman numbers:

I Taipale HT, Bell JS, Uusi-Kokko M, Lönnroos E, Sulkava R and Hartikainen S. Sedative load among community-dwelling people aged 75 years and older. A population-based study. Drugs Aging 28: 913–925, 2011.

II Taipale HT, Bell JS, Gnjidic D, Sulkava R and Hartikainen S. Sedative load among community-dwelling people aged 75 years and older: association with balance and mobility. J Clin Psychopharmacol 32: 218–224, 2012.

III Taipale HT, Bell JS, Gnjidic D, Sulkava R and Hartikainen S. Muscle strength and sedative load in community-dwelling people aged 75 years and older: a population-based study. J Gerontol A Biol Sci Med Sci 66: 1384–1392, 2011.

IV Taipale HT, Bell JS, Sulkava R and Hartikainen S. Sedative load among community-dwelling older people: evolution and impact on mortality. Submitted for publication.

 In addition, some unpublished data are presented.

Contents

Abbreviations

AD	Antidepressant
ADE	Adverse drug event
ADL	Activities of Daily Living
ADR	Adverse drug reaction
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AP	Antipsychotic
ASA	Acetyl salicylic acid
ATC	Anatomical Therapeutic Chemical
BBS	Berg Balance Scale
BI	Barthel Index
BZD	Benzodiazepine
CGA	Comprehensive Geriatric Assessment
BMI	Body mass index
CI	Confidence interval
CNS	Central nervous system
DBI	Drug Burden Index
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4th edition)
DSST	Digit Symbol Substitution Test
EPESE	Physical performance test developed for the Established Populations for Epidemiologic Studies of the Elderly
FCI	Functional Comorbidity Index
GDS	Geriatric Depression Scale
GeMS	Geriatric Multidisciplinary Strategy for the Good Care of the Elderly
HR	Hazard ratio
IADL	Instrumental Activities of Daily Living
MMSE	Mini-Mental State Examination
NSAID	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
RCT	Randomized controlled trial
SD	Standard deviation
SII	Social Insurance Institution
SL	Sedative load
SPC	Summary of product characteristics
SPPB	Short Physical Performance Battery
SPSS	Statistical Package for the Social Sciences
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TUG	Timed Up & Go
UK	United Kingdom
US	United States
WHO	World Health Organization

Definitions of key terms

Adverse drug event (ADE)
Adverse drug event is an unintended incident due to a medication which causes harm to a patient.

Adverse drug reaction (ADR)
Adverse drug reaction is a noxious and unintended response to a drug at doses normally used. Adverse drug reactions are a type of adverse drug event resulting from the side effect of a drug.

Community-dwelling
This term is used when considering older persons who are not in assisted living facilities (including self-care retirement villages, residential aged care facilities, nursing homes, long-term care facilities, hospitals, or other types of institutional accommodations).

Older person
In the literature review, the main rule is that older persons are those aged ≥65 years. However, some of the included studies defined older persons as aged ≥60 years. In methods and results, older people are persons aged ≥75 years.

Sedation
Sedation refers to the objectively measured decreased psychomotor functioning and subjective feelings of drowsiness and sleepiness.

Sedative drugs
This term is used when referring to all drugs contributing to sedative load and thus, possessing sedative properties.

1 Introduction

Sedation is defined as subjective feelings of drowsiness and sleepiness, and also as objectively measured slowing of psychomotor functioning (Bourin et al. 2004). An example of declined psychomotor functioning is increased reaction time. Aging is associated with various changes in pharmacodynamics and pharmacokinetics of drugs (Turnheim 2003, McLachlan et al. 2009). One important age-related change is an increased susceptibility to sedative effects of drugs which results in more pronounced effects of drugs among older people (Bowie et al. 2007). Because drugs exert sedative effects through multiple pharmacological mechanisms, methods to quantify the effect of taking multiple drugs with sedative properties have been developed (Taipale et al. 2010).

Sedative load refers to cumulative exposure to drugs with sedative properties (Linjakumpu et al. 2003). It takes account on both drugs prescribed for intentional sedation and drugs used for somatic disorders which possess sedation as a prominent side effect. Models that take into account use of multiple drugs are important because older people often use multiple sedative drugs (Linjakumpu et al. 2004). Among community-dwelling older people in Finland in 1998–1999, 35% used one or more drugs with sedative properties.

Sedative drugs have been associated with various adverse drug events (ADEs) among older users. These include cognitive decline (Wright et al. 2009), impaired balance (Cutson et al. 1997), decreased mobility and muscle strength (Lord et al. 1995, Gray et al. 2006), and an increased risk of death (Mittal et al. 2011). One important ADE is an increased risk of falls and fractures (Cumming and Le Couteur 2003, Hartikainen et al. 2007). Falls and fractures are a threat to independent living among older people because of their potentially hazardous consequences on physical function. Decreased mobility, balance and muscle strength may increase the risk of falls (Lajoie et al. 2002, Moreland et al. 2004, Cooper et al. 2011). Furthermore, mobility is essential for performing daily activities.

Adverse drug events related to sedative and psychotropic drug use have primarily been investigated in pharmacoepidemiological studies. Randomized controlled trials (RCTs) are considered as 'gold standard' when assessing the efficacy of drugs. However, older people are often excluded from participation in RCTs (Hilmer et al. 2012). Although recommended, ADEs are often not monitored and not tested specifically among older people. Reasons for not including older persons in these trials are that they often have multiple comorbidities and polypharmacy. In addition, RCTs are often of short duration, include small number of participants and participants in both intervention and control arms may receive more intensive care than real-life patients (Hilmer et al. 2012). Thus, pharmacoepidemiological studies are needed to study ADEs in large populations that include a broader range of patients, treated according to real-life conditions.

The frequent use of sedative drugs and corresponding ADEs are a major public health concern. The proportion of Finns aged ≥75 years is increasing rapidly (Statistics Finland 2011). The number of Finns aged 75 years or older will double from 437,000 in 2010 to 847,000 in 2030. Thus, the appropriate care of older people and maintenance of active and independent living is increasingly important. One of the main goals of the Finnish health policy is that older people should be able to live independently in their own homes as long as possible (Ministry of Social Affairs 2008). This goal implies that the maintenance of

physical function is crucial because impaired physical function is often associated with loss of independence.

The purpose of this thesis was to investigate sedative load and ADEs among community-dwelling older people. These ADEs included decreased balance, mobility and muscle strength, and risk of death.

2 Review of the literature

The scope of this literature review was the sedative effects of drugs and methods used to measure these effects among older persons. Furthermore, the epidemiology of sedative drug use and corresponding adverse events were also reviewed. Adverse events included in the review were mobility, muscle strength, balance and mortality.

2.1 SEDATION

2.1.1 Definition and measurement

Sedation refers to the objectively measured decreased psychomotor functioning and subjective feelings of drowsiness and sleepiness (Buffett-Jerrott et al. 2002, Bourin et al. 2004). In the broadest sense, sedation may refer to impairments in cognitive processing including memory and attention deficits (Buffett-Jerrott et al. 2002). Both subjective and objective measures of sedation are important although they do not necessarily correlate with each other. A person may not report or feel sedated but may show psychomotor slowing in an objective test (Echizenya et al. 2007).

Subjective assessment of sedation is often undertaken using visual analogue scales (Bourin et al. 2002). In the test, a participant indicates feelings by placing a mark on an ungraded line with opposite descriptive statements at each end (for example, calmness versus agitation). Scores are measured as a distance from a line indicating the "normal" situation. Objective measurement of sedation is conducted using psychometric tests which measure different aspects of sensory-motor processing, cognitive skills, concentration, and psychomotor and motor abilities (Hindmarch 2009). Measurement of reaction time is an example of a typical psychometric test (Bourin et al. 2004). Reaction time may be tested as the time taken to start a previously decided action (like pressing a button), or as choice reaction time in which participants have to choose the right action based on the stimulus (for example, press one of six buttons based on which is illuminated). Another widely used psychomotor test is the Digit Symbol Substitution Task (DSST) (Weingartner et al. 1995, Hege et al. 1997, Buffett-Jerrott et al. 2002, Wezenberg et al. 2007) which has been used among older people (Hilmer et al. 2007). In the test, participants learn a code in which symbols are paired with the digits 1 through 9 (Buffett-Jerrott et al. 2002). Participants are asked to copy the symbols associated with each digit, in the order presented, as quickly and accurately as possible. The DSST has been shown to measure drug effects, for example slowing after a dose of benzodiazepine (Wittenborn 1979) but it also requires memory and learning abilities which may limit the use among older people with cognitive decline.

For many years, sedation was considered as an essential component of the therapeutic effect of antipsychotics and antidepressants (Bourin et al. 2004). Introduction of atypical antipsychotics and selective serotonin reuptake inhibitors (SSRIs) challenged this belief because of having equal therapeutic effect while demonstrating considerably less sedation. Since then, sedation associated with drug use has been studied further, and is now considered an undesirable adverse effect. Sedation is no longer considered useful in the treatment of agitated patients with depression (Majeroni 1998). Nowadays, the maintenance of an active lifestyle is favored and considered important for the recovery

process from depression (Bourin et al. 2004). Sedation is a particularly unwanted effect in diseases or syndromes that impair cognition and psychomotor functioning, for example severe depression and dementia (Hindmarch 2009). Cognitive decline is another example in which efforts are made to maintain the current cognitive capacity and thus, use of drugs counteracting this objective should be avoided.

2.1.2 Pharmacology of sedative effects of drugs

Sedation is mediated by multiple pharmacological mechanisms in the central nervous system (CNS). Sedative effects of drugs mediated by agonism of the benzodiazepine receptor in GABA-A complex are well-known (Buffett-Jerrott et al. 2002, Bourin et al. 2004, Möhler et al. 2002). Benzodiazepines and barbiturates induce sedation through this mechanism. Subtypes of GABA-A receptor also mediate other effects of benzodiazepines, including anterograde amnesia, attentional impairments, anticonvulsant effects, muscle relaxation and anxiolytic effects (Möhler et al. 2002). Benzodiazepine use has been associated with various ADEs including impaired cognition, psychomotor skills, memory and driving performance among older people (Verster et al. 2007).

Sedative effects of the first generation antihistamines are mediated by antagonism of histamine H_1 receptors in the CNS (Timmerman 1999, Brown et al. 2001, Bourin et al. 2004, Turner et al. 2006). Sedative effects of histamine antagonism may be explained with the fact that histamine regulates the sleep-wake cycle (Tiligada et al. 2011). First generation antihistamines may also cause marked adverse events other than sedation, including memory impairment which may be related to their effects on cholinergic and monoaminergic systems (Turner et al. 2006). Many psychotropic drugs including antipsychotics, tricyclic antidepressants and second generation antidepressants, also bind to H_1 receptors which contributes to their sedative potential (Bourin et al. 2004, Tiligada et al. 2011).

Opioids bind to μ-opioid receptors which also mediate sedation (Young-McCauhgan et al. 2001). Opioid-induced sedation has been proposed to be a unique, disordered level of consciousness in which arousal and content processing abilities are affected. This manifests in decreased wakefulness and slowed interpretation of the environment.

A potential source of sedative effects of drugs is antagonism or agonism of α1- and α2-adrenergic receptors in the CNS (Bourin et al. 2002, Reynolds 2004). Antagonism of α1-adrenergic receptors has been used to explain sedative actions of conventional and atypical antipsychotic drugs (Reynolds 2004). Antagonism of α1-receptors is also related to cardiac events including prolongation of QT interval and arrhythmias. Alpha2-receptor antagonism is proposed to be cause of sedative potential of mianserin together with H1-antagonism (Bourin et al. 2002). However, antagonism of presynaptic α2-adrenergic autoreceptors on noradrenergic neurons enhances the synthesis and release of noradrenalin which is often referred as an activating mechanism of antidepressants (Ramaekers et al. 1998). Blockage of muscarinic receptors is also associated with sedative effects although this anticholinergic action results in many other adverse effects too (Bourin et al. 2002). There may also be other mechanisms or receptors which are involved in sedative and cognitive effects of drugs.

2.1.3 Pharmacology of sedative effects on physical function

The sedative effects of drugs may result in impaired physical function. Mechanisms behind this are not fully understood. It is likely that mechanisms leading to mobility limitation are multidimensional, and may be due to drug-related cognitive impairment, slowing of neuromuscular processing in the CNS, overall sedation, muscle-relaxant effects

and reduced muscle function (Hindmarch 1980, Davidoff 1989, Cutson et al. 1997, See et al. 2008, Hindmarch 2009).

In his review of psychotropic drugs and associated psychomotor effects, Hindmarch concluded that slowing of motor activity and co-ordination has been associated with many drugs with sedative properties (Hindmarch 1980). In the review, motor performance was measured with various tests including simple tests like finger tapping test, as well as with assessment of co-ordination of sensory and motor systems in simulated car driving tasks and reaction time tests. The conclusion was that benzodiazepines were the most often studied drugs, and have been shown to impair performance in these tasks. Besides benzodiazepines, impairment in reaction time was also reported with diphenhydramine, amitriptyline and mianserin. The reviewed studies were conducted among healthy volunteers.

All psychotropic drugs (antipsychotics, antidepressants and benzodiazepines) have been associated with impairments of cognitive function (Hindmarch 2009). Although mobility tasks like walking have been considered automatic they also require cognitive processing (Snijders et al. 2007). Thus, impaired cognitive function may lead to difficulties in walking, especially in an outdoor environment when there are many factors requiring attention.

Muscle-relaxant properties of benzodiazepines and muscle relaxant drugs are one potential mechanism behind the impaired physical function (Davidoff 1989, See et al. 2008). GABA-A receptors in motor neurons in spinal cord mediate muscle relaxant properties of benzodiazepines (Möhler et al. 2002). However, it has been stated that muscle relaxant effects requires higher doses of benzodiazepines than anxiolytic effects. The mechanism behind the impairment of physical function may also be related to neuromuscular processing and activation of muscles. Cutson and coworkers showed that diazepam delayed muscle activation during balance tests conducted among older people (Cutson et al. 1997). Rapid activation of muscles required to regain balance after a disturbation is essential for walking ability.

2.1.4 Sedation and aging

The sedative effects of drugs may be pronounced among older people due to age-related changes in organ function and body composition, leading to altered pharmacokinetics and pharmacodynamics (Turnheim 2003, McLachlan et al. 2009). Aging may be associated with reduced hepatic blood flow and a decline in liver mass that reduces drug metabolism. Declining renal function may cause an accumulation of drugs that are excreted via the kidneys. This may include drugs that undergo hepatic metabolism and then re-enter systematic circulation before being excreted as hydrophilic metabolites or conjugates. A reduction in lean body mass and an increase in the percentage of adipose tissue may result in an increased volume of distribution of lipophilic drugs, such as diazepam. These factors contribute to prolonged elimination half-lives of sedative drugs in older people compared to middle aged and younger people.

Older people are more susceptible to sedative effects of drugs than younger people (Bowie et al. 2007). Mechanisms contributing to pharmacodynamic changes include altered neurotransmitters or their receptors, particularly reduction in dopamine and acetylcholine content in the brain (Turnheim 2003). Reduction in dopamine content predisposes aging brain to an increased frequency and severity of extrapyramidal symptoms related to antipsychotic drugs. One important factor is that with aging the blood-brain barrier becomes more permeable and drugs penetrate the CNS more readily (Bowie et al. 2007). It has been shown that activity of efflux pump protein p-glycoprotein

decreases and brain may be exposed to higher drug levels in older people (Toornvliet et al. 2006). This is problematic because a serum concentration is not correlated with elevated drug level in the brain. In addition, decreased efflux properties also lead to prolonged residence time in the brain. Age-related changes have been observed in $GABA_A$-benzodiazepine receptor complex in relation to number of receptors and their subunit composition which possibly is associated with attenuated sedative effects of benzodiazepines (Turnheim 2003).

Data on aging-related changes in pharmacokinetics and pharmacodynamics of drugs has been increasing during recent years (Turnheim 2003, Bowie et al. 2007, McLachlan et al. 2009). However, there are still limited data on sedative effects of drugs among older people. One reason is that older people are often excluded from clinical trials because of their multiple comorbidities and medications (Hilmer et al. 2011). Furthermore, clinical trials are often not powered to detect adverse functional outcomes, and functional outcomes are not often considered as adverse drug reactions (ADRs) in the clinical trials.

2.2 METHODS TO QUANTIFY THE CUMULATIVE EFFECT OF TAKING MULTIPLE DRUGS WITH SEDATIVE PROPERTIES

The premarketing clinical trials of drugs may not provide adequate information on drug response and ADEs among older people (Hilmer et al. 2011). In these RCTs, participants may receive more intensive care than in real-life settings, the number of participants is usually small and studies are often of limited duration. Thus, knowledge of ADEs specific to older people is often obtained in postmarketing studies utilizing pharmacoepidemiologic methods (Hilmer et al. 2011).

Quantifying the cumulative effect of taking multiple drugs with sedative properties is complicated because drugs with sedative properties do not have a common pharmacology. Four methods to assess cumulative effect of taking multiple drugs with sedative properties have been developed and utilized in the research literature (Taipale et al. 2010). Each method has been developed for different purposes and thus, drugs included in the methods differ (Table 1).

Table 1. Comparison of the different methods to calculate cumulative effect of taking multiple drugs with sedative properties and ratings proposed to drug classes

Drug class	Sedative Load Model	Sloane Model	Drug Burden Index[a, b]	CNS Drug Model[b]
Conventional antipsychotics	rating: 2	rating: 3 (except molindone rating 6)	included	included
Atypical antipsychotics	rating: 1	rating: 3	included	included
Tricyclic antidepressants and non-selective MAO inhibitors	rating: 2	rating: 3 (except phenelzine rating 6)	included	included
SSRIs	rating: 1	rating: 3	included	included
Second generation antidepressants	rating: 1 (except mianserin rating 2)	rating: 3	included	included
Benzodiazepines	rating: 2	rating: 6	included	included
Other anxiolytics and hypnotics (clometiazole, valerian, barbiturates, first generation antihistamines, buspiron, chloral hydrate)	rating: 2	rating: 3 (except diphenhydramine and chloral hydrate rating 6)	included	not included
Opioids	rating: 1	rating: 3	included	included
Antiepileptics	rating: 1	rating: 3	included	not included
Antiemetics (metoclopramide, scopolamine)	rating: 1	rating: 3	included	not included
Antispasmodics with psychotropics	rating: 1	no	included	not included
Centrally acting muscle relaxants	rating: 1	no	included	not included
Anticholinergic anti-parkinson drugs	rating: 1	rating: 3	included	not included
Indomethacin (with ethylmorphine)	rating: 1	rating: 3	not included	not included
Other drugs scored in a model	Xanthines, antitussives with sedating components and antiemetics and drugs for dizziness incl. psychotropics, anticholinergic drops for eyes: rating 1	donepezil, atenolol, clonidine, levodopa, doxazosin, terazosin, prazosin: rating 1	wide range of other anticholinergic drugs[a]	

DBI = Drug Burden Index, CNS = central nervous system, MAO = monoamine oxidase, SSRIs = selective serotonin reuptake inhibitors.
[a] Drugs with both anticholinergic and sedative properties are classified as anticholinergics.
[b] The DBI and the CNS Drug Model do not include ratings of sedative drugs but consider only doses.
Adapted according to Taipale et al. 2010

2.2.1 Sedative Load Model

The Sedative Load Model was developed by reviewing the summary of product characteristics for all drugs available in Finland from 1998 to 2001 (Linjakumpu et al. 2003). The model was developed to represent a comprehensive classification of all drugs

on market and to include also drugs for somatic disorders. All drugs were classified into 1 of 4 groups based on their sedative potential. The 4 groups were: (1) primary sedatives; (2) drugs with sedation as a prominent side effect or preparations with a sedating component; (3) drugs with sedation as a potential adverse effect; and (4) drugs with no known sedation. The classification was based on consensus between a psychogeriatrician, a geriatrician, and a physician specialized in pharmacoepidemiology. Each drug in group 1 was assigned a sedative rating of 2, and each drug in group 2 was assigned a sedative rating of 1 (Linjakumpu et al. 2004). Drugs in groups 3 and 4 were not assigned a sedative rating. According to the model, sedative load was calculated by summing the sedative rating for each drug in a person's medication regimen according to the following formula:

$$\text{Sedative load} = \sum_{k=1}^{n} SR_k$$

where n stands for the number of drugs and SR_k indicates the sedative rating for drug k.

2.2.2 Sloane Model

Sloane et al. published an adaption of the Sedative Load Model (Sloane et al. 2008). Their objective was to develop a method to control for possible confounding caused by sedative and analgesic drug use in therapeutic trials. In the Sloane Model, group 3 from the Sedative Load Model ("drugs with sedation as a potential adverse effect") was modified to become "drugs with sedation as a potential adverse effect that can persist beyond initiation of the drug." Group 1 ("primary sedatives" in the sedative load model) was redefined to only include benzodiazepines, diphenhydramine, phenelzine, molindone, and chloral hydrate, and all other drugs were transferred to group 2 (ie, other conventional antipsychotics, tricyclic antidepressants, anxiolytics [such as hydroxyzine]). Sedative ratings of 6, 3, and 1 were assigned to groups 1, 2, and 3, respectively (instead of 2, 1, and 0 in the Sedative Load Model). The adaption by Sloane et al. also considers the dose of each drug. According to the Sloane model, the cumulative effect of taking multiple drugs with sedative properties is calculated according to the formula:

$$SL_{ij} = \sum_{k=1}^{m} \frac{D_{ijk} \times SR_k}{ADMD_k}$$

where *SL* is sedative load (for resident *i* on day *j*), *D* is daily dose for medication *k* (by resident i on day j), *SR* is sedative rating of medication k, and *ADMD* is average daily maintenance dose for drug k.

2.2.3 Drug Burden Index

The Drug Burden Index (DBI) was developed by Hilmer et al. to assess the possible impact of drug burden on physical and cognitive function among older people (Hilmer et al. 2007). It was designed to be an evidence-based guide for prescribing in older people. The DBI considers both anticholinergic and sedative drug burden. Drugs that possess both anticholinergic and sedative properties are classified as anticholinergic drugs when calculating the DBI. The DBI was developed according to the principles of pharmacologic dose–response effect, and the model includes the doses of drugs. The DBI is covered by an international patent. Hilmer et al. defined *total drug burden* as the sum of anticholinergic and sedative burden according to the formula:

$$\frac{E}{\alpha} = \sum \frac{D}{\delta + D}$$

where E is the pharmacologic effect, α is the proportionality constant, D is the daily dose, and δ is the recommended minimum daily dose as approved by the US Food and Drug Administration. When the DBI has been used outside of the US other reference doses have been used.

2.2.4 CNS drug model

Hanlon et al. developed a model to investigate the relationship between use of CNS-active drugs and various adverse outcomes (Hanlon et al. 2009, Wright et al. 2009). According to this method, CNS drugs include opioid receptor agonists, benzodiazepine receptor agonists, antidepressants, and antipsychotics. The authors computed the overall CNS standardized daily dose by considering use of drugs from these drug groups. The following formula was used:

$$SDD = \frac{D}{MED}$$

where the mean daily dose (D) of a CNS drug is converted to a summated standard daily dose (SDD) by dividing it with the minimum effective dose (MED) per day recommended for older people in the *Geriatric Dosage Handbook: Including Clinical Recommendations and Monitoring Guidelines (*Semla et al. 2007). The CNS standardized daily dose is the sum of the SDDs.

2.3 USE OF PRIMARY SEDATIVES AND OTHER DRUGS WITH SEDATIVE PROPERTIES

Few studies have been conducted specifically concerning the epidemiology of sedative load among older people. On the contrary, there are numerous epidemiological studies about the use of specific classes of sedative drugs and psychotropic drugs. The focus of this review was on the prevalence of sedative load and sedative drug use studied using one of the four methods to quantify cumulative exposure to sedative drugs.

2.3.1 Epidemiology of sedative load

The epidemiology of sedative load has been studied only in four studies (Table 2). Among community-dwelling Finns aged 64 years and older in 1998–99, 35% had sedative load ≥1, and 12% had a sedative load of ≥3 (Linjakumpu et al. 2004). Among residents with dementia living in residential aged care facilities in Northern Ireland in 2008–2010, 67% had a sedative load ≥1 and 12% had a sedative load of ≥3 (Parsons et al. 2011). Among residents of long-term care facilities in Helsinki, 85% had a sedative load ≥1 and 53% had a sedative load ≥3 in 2003 (Taipale et al. 2009). A study comparing sedative load between those with and without dementia in the same study population found that residents with and without dementia had a similar sedative load (mean 3.0 versus 2.7) (Bell et al. 2010).

Factors associated with sedative load have been investigated in one study (Linjakumpu et al. 2004). Among community-dwelling Finns, older age (≥80 years) and female gender were associated with sedative load ≥3. Sociodemographic factors associated with sedative load included also education (less than primary school) and current smoking. Other

factors associated with sedative load were poor self-rated health, depression, dementia and mobility difficulties.

Table 2. Prevalence of sedative drug use according to Sedative Load Model, Drug Burden Index, Sloane Model and CNS Drug Model

Study, country	Year	N	Age	Setting	Description of sedative drug use in the population
Sedative load					
Linjakumpu et al. 2004 Finland	1998–1999	1197	≥64 years, 57% women	C	35% were users sedative drugs, 12% had sedative load of ≥3
Taipale et al. 2009 Finland	2003	1004	Mean age 81 years, 75% women	I	85% were users of sedative drugs, 53% had sedative load of ≥3
Bell et al. 2010 Finland	2003	1052, 781 with dementia		I	Mean sedative load 3.0 among those with dementia, mean sedative load 2.7 among those without dementia
Parsons et al. 2011 UK	2008–2010	115	Mean age 86 years, 79% women	I	67% were users of sedative drugs, 12% had sedative load of ≥3
Drug Burden Index					
Hilmer et al. 2007 US, Health ABC study	1997–1998	3075	Age range 70−79 years, mean age 74 years, 52% women	C	14% were users of sedative drugs
Cao et al. 2008 US, Women's Health and Ageing Study	1992	932	≥65 years, median age 78 years, 100% women	C	16% were users of sedative drugs, mean DBI_{SED} 0.37 among users
Gnjidic et al. 2009 Australia, Concord Health and Ageing in Men Project	2005–2007	1705	≥70 years, mean age 77, 100% men	C	Of users of medicines, 13% were users of sedative drugs, mean DBI_{SED} 0.07, most common sedative drugs anxiolytics (5% using)
Hilmer et al. 2009b US, Health ABC Study	1997–1998 and 6 years of follow-up	2172	70−79, 52% women	C	34% were users of DBI drugs at baseline, 26% were users of DBI drugs at year 3, 29% were users of DBI drugs at year 5
Wilson et al. 2010 Australia		526	Mean age 86 years, 72% women	I	42% were users of sedative drugs; mean DBI_{SED} 0.33, most common sedative drugs were anxiolytics (18% using)
Gnjidic et al. 2010 Australia	2008–2009	115		I	23% exposed to sedative DBI drugs in intervention group and 29% exposed to sedative DBI drugs in control group
Castelino et al. 2010 Australia		372	Mean age 76 years, 55% women	C	61% were exposed to DBI drugs

Table 2. Continued

Study, country	Year	N	Age	Setting	Description of sedative drug use in the population
Gnjidic et al. 2011a Finland, the GeMS Study	2004	700	Mean age 82 years (all ≥75 years), 69% women	C	37% exposed to DBI drugs
Gnjidic et al. 2011b Australia	2008–2009	115	Mean age 82 years, 73% women	I	26% were users of regular sedative drugs, mean DBISED 0.12
Lowry et al. 2011 UK		362	Mean age 84 years, 59% women	I	41% were users of sedative drugs
Gnjidic et al. 2012 Australia, Concord Health and Ageing in Men Project	2005–2007, follow-up of 2 years	1662, 156 frail	≥70 years, mean age 77, 100% men	C	46% of frail participants were exposed to DBI drugs compared to 20% of robust participants
CNS Drug Model					
Wright et al. 2009 US, Health ABC Study	1997–1998	2737	≥65, 53% women	CNS Drug Model	14% were users of CNS drugs at baseline
Boudreau et al. 2009 and Hanlon et al. 2009, US, Health ABC Study	1997–1998	3055	70–79, 52% women	CNS Drug Model	14% were users of CNS drugs

C=community-dwelling, I=institutional living (in long-term care facilities, residential aged care facilities, self-care retirement villages), DBI = Drug Burden Index, DBI_{SED} = sedative component of Drug Burden Index, CNS = central nervous system, HR= hazards ratio, Health ABC = Healthy, Aging and Body Composition

2.3.2 Epidemiology of sedative use according to other models

The only study utilizing the Sloane model included data on 90 institutionalized patients of a clinical trial and all of them were users of drugs with sedative properties (Sloane et al. 2008). Among those participants, men used drugs with sedative properties more frequently than women. The most frequently used Group 1 drugs was lorazepam, Group 2 drugs were olanzapine and risperidone, and Group 3 drugs were donepezil and atenolol. Participants without dementia had a higher sedative load than participants with dementia. The generalizability of these findings is unknown.

The Drug Burden Index has been used to describe sedative and anticholinergic drug use among various patient populations and in a range of countries (Table 2). The prevalence of sedative drug use in studies utilizing the DBI is not fully comparable to other studies because drugs with both anticholinergic and sedative properties are classified as anticholinergic (for example, antipsychotics and tricyclic antidepressants). Among community-dwelling participants, the use of sedative drugs has varied from 13% to 16% (Hilmer et al. 2007, Cao et al. 2008, Gnjidic et al. 2009). A recent study of DBI among frail older community-dwelling participants found that 46% frail participants were exposed to DBI drugs compared to 20% of robust participants (Gnjidic et al. 2012). Among

institutional based samples, the prevalence of sedative drug use ranged from 26% to 42% (Wilson et al. 2010, Gnjidic et al. 2011, Lowry et al. 2011).

Among community-dwelling Finns participating in the GeMS Study, 37% were exposed to DBI contributing drugs. DBI exposure was higher than among community-dwelling older people in Australia (Gnjidic et al. 2009) and the United States (US) (Hilmer et al. 2007). The most frequently used drugs contributing to DBI were zopiclone, temazepam, and tamsulosin.

Studies utilizing the CNS drug model have all been conducted among the community-dwelling participants of the Health, Aging and Body Composition Study (Table 2). In this study, 14% were users of CNS active drugs. Of drugs included in the CNS drug model, the most commonly used drugs were benzodiazepines (6%) and antidepressants (6%). Interestingly, Hilmer et al. conducted a study with DBI in the same study sample, and reported that 14% were users of sedative drugs according to DBI definition (Hilmer et al. 2007). The Health ABC Study was a longitudinal study, and prevalence of CNS drug use increased from 14% to 18% during a 5-year follow-up (Hanlon et al. 2009).

2.3.3 Prevalence of use of primary sedatives and drugs with sedation as a prominent side effect

In a study by Linjakumpu et al., 88% of community-dwelling Finns aged ≥64 years used any drugs (Linjakumpu et al. 2003). Of them, 29% used Group 1 sedative drugs and 19% used Group 2 sedative drugs. Use of specific drug groups is outlined in Table 3. Hypnotics (15%) and anxiolytics (10%) were the most prevalent drugs whereas antidepressant use (6%) and antipsychotic use (3%) was less common (Linjakumpu et al. 2002).

Table 3. Prevalence of use of primary sedatives and drugs with sedation as a prominent side effect among community-dwelling older people and residents of long-term care facilities

Drug group	Linjakumpu et al. 2002 community-dwelling[a] Users %	Taipale et al. 2009 long-term care facilities Users %
Primary sedatives		
Anxiolytics	10	36
Hypnotics	15	29
Conventional antipsychotics		17
Tricyclic antidepressants		3
Drugs with sedation as a prominent side effect		
Atypical antipsychotics		30
SSRIs		28
Other 2nd gen. antidepressants		10
Antiepileptics	1	21
Opioids	4	19

[a] Prevalence reported among users of drugs (88% of the study sample)
SSRIs = selective serotonin reuptake inhibitors

Among residents with dementia in residential aged care facilities in Northern Ireland, drug use was compared between the six facilities included in the study (Parsons et al. 2011). The prevalence of regular antidepressant use ranged from 33% to 68% and SSRIs were the most frequently used antidepressants. Regular use of hypnotics and anxiolytics ranged from 5% to 21% across the facilities. Residents of one facility were not using hypnotics whereas anxiolytic use was not found in two of the six facilities compared. The prevalence of antipsychotic use ranged from 10% to 41% across facilities. Atypical

antipsychotics were the most commonly used but there was one facility in which only conventional antipsychotics were prescribed.

In a study conducted among residents of long-term care facilities in Helsinki, only 15% of all 1004 participants were nonusers of drugs with sedative properties (Taipale et al. 2009). The residents had a high level of comorbidity, with 77% diagnosed a dementia, 26% depression and 46% had suffered a stroke. Use of Group 1 and 2 sedative drugs was about two to five times more frequent among residents of long-term care facilities than among community-dwelling Finns in studies conducted by Linjakumpu et al. (Table 3). The difference may be even larger because Linjakumpu et al. reported that the prevalence among users of drugs (88% of the sample), and included also when-required drug use whereas in long-term care facilities only regular drug use was considered. However, anxiolytics and hypnotics were the most frequently used drug groups in both settings.

Bell et al. reported sedative drug use in the same long-term care facilities comparing drug use among those with and without dementia (Bell et al. 2010). Residents with dementia were more frequent users of antipsychotics but less frequent users of antidepressants and benzodiazepines than residents without dementia. The most frequently used Group 1 drugs among residents with dementia were temazepam (16%), oxazepam (13%) and lorazepam (12%).

2.4 PHYSICAL FUNCTIONING IN OLD AGE

2.4.1 Changes in physical function related to aging

Aging is typically associated with a gradual decrease in muscle mass and muscle strength. Significant decreases in muscle mass are seen between ages of 60 and 80 years (Kyle et al. 2001). This slow decline may not be noted by older persons themselves. An aging-related decline in physical activity contributes to the loss of muscle mass and the accumulation of adipose tissue (Evans et al. 1993). Among older people, overall loss of weight may be hazardous because loss of fat body mass has been associated with bone loss (Bleicher et al. 2011).

Muscle strength is required in daily motor tasks such as walking, and in control of postural balance during standing, walking and recovering from balance disturbations (Rantanen 2003b). The minimum amount of muscle strength for motor tasks such as walking varies, and one important factor mediating the variance is presence or absence of balance impairment. Muscle strength is needed to compensate balance impairment caused by other factors. However, muscle strength is a major factor in balance, walking and the occurrence of falls (Wolfson et al. 1995).

A certain amount of muscle strength is needed to perform necessary Activities of Daily Living (ADLs) (Rantanen 2003b). When strength is adequate, there is a certain amount of reserve capacity which is a safety margin that helps to prevent disability from developing. Without reserve capacity, physical inactivity related to an illness or other factors causing immobilization may decrease muscle strength so that ADLs cannot be performed anymore. Impaired muscle strength has been associated with important outcomes including impaired performance in ADLs, Instrumental Activities of Daily Living (IADLs), and with an increased risk of death (Newman et al. 2006, Cooper et al. 2010, Hairi et al. 2010). Lower extremity muscle weakness has also been associated with an increased risk of falling (Moreland et al. 2004). Thus, poor muscle strength possesses a threat to independent living and functioning among older people (Gill et al. 1995, Penninx et a. 2000).

Besides muscle strength, aging also affects other factors involved in control of postural balance. Postural balance is interplay between sensory information from somatosensory, vestibular and visual systems, processing this information in the CNS and then producing different movement strategies depending on the goals and environmental challenges (Horak 2006). With aging, declines occur in all these systems which challenge the maintenance of postural balance and independent mobility. Furthermore, mobility and postural reactions require cognitive processing and abilities to rapidly reallocate attention which may also be challenged by the aging process and comorbid diseases (Maki et al. 2001, Woollacott et al. 2002).

2.4.2 Muscle strength measures

The grip strength test is one of the most common muscle strength tests among older people. Hand grip strength is straightforward to measure with dynamometer, and results of it has been shown to correlate well with strength of other muscle groups and can be used as an indicator of overall strength (Rantanen et al. 1994). Impaired hand grip strength has been associated with various adverse events among older people including an increased risk of falling (Pijnappels et al. 2008), disability in IADLs (Giampaoli et al. 1999, Hairi et al. 2010), and mortality (Rantanen et al. 2003a, Newman et al. 2006). In the Hertfordshire Cohort Study conducted in the United Kingdom it was demonstrated that a 2.0 kg decline in grip strength among men and women aged 59–73 years was equivalent to five years of chronological ageing (Ashfield et al. 2010).

Knee extension strength can be measured in sitting position using a dynamometer chair. This test measures maximal strength produced by lower extremities against unmoving target. Poor results in knee extension strength test has been associated with risk of mobility decline (Visser et al. 2005, Buchman et al. 2007), falling (Pijnappels et al. 2008), and mortality (Newman et al. 2006). Muscle strength and mobility are correlated with each other because poor muscle strength in lower extremities has been associated with slower walking speed (Tiedemann et al. 2005).

The chair stands test assesses the basic ability to perform sit-to-stand transfers (Guralnik et al. 1994). It measures the strength of lower extremities but also aspects of balance that are needed in this basic activity of daily living. Poor performance in the chair stands test has been associated with clinically important outcomes. Those who need ≥17.1 seconds to complete five chair stands have been shown to be at higher risk of developing persistent severe lower extremity limitation, and at higher risk of death (Cesari et al. 2009).

A recent systematic review and meta-analysis of objective measures of physical capability concluded that weaker grip strength is associated with an increased risk of fractures and cognitive decline in most studies conducted among older people (Cooper et al. 2010). The same review reported similar findings in relation to chair stands, although the number of studies examining this parameter was relatively small. The review concluded that objective performance measures are predictors of all-cause mortality, and these measures can be useful as markers of current and future health status.

2.4.3 Mobility and balance measures

Mobility among older persons can be measured with various performance based tests. One of the most common tests is measurement of maximal walking speed (Guralnik et al. 2000, Cesari et al. 2005). The method is quick and easy to use, inexpensive and highly reliable. Walking speed measured over a short distance, such as 10 meters, assesses neuromuscular function of the lower extremities (Aniansson et al. 1980). In the walking speed test, a substantial and meaningful change is 0.10 m/s (Gill et al. 2010). This level of

change has been related to adverse outcomes. Slow walking speed among older people is associated with an increased rate of hospitalization, an increased risk of falls and fractures, need for a caregiver, and mortality (Montero-Odasso et al. 2005, Morris et al. 2007).

Walking is also a component of another test called the Timed Up & Go Test (TUG) where a participant is asked to stand up from a chair, walk 3 meters, turn around, walk back and sit down (Podsiadlo et al. 1991). The TUG is more of a functional task involving activities required in daily living. Poor performance in TUG has been associated with an increased risk of falling (Shumway-Cook et al. 2000, Morris et al. 2007). In the TUG, those who need longer than 14.0 seconds to complete the test have been shown to be at higher risk of falling (Shumway-Cook et al. 2000).

Mobility may also be assessed using participant self-reports to assess participant's perception of his or her own mobility status. Typically, participants are asked about their abilities, difficulties or need for help in specific tasks, such as ability to walk 400 meters (Sayers et al. 2004). Self-reported difficulty in walking has been found to be a reliable and valid measure of mobility limitation (Fried et al. 2001). Self-reported measures complement performance based measures because they reflect actual performance in daily living whereas performance measures assess performance in ideal and controlled conditions (Latham et al. 2008).

Berg Balance Scale (BBS) measures various abilities related to balance, including standing and reaching tasks (Berg et al. 1992). Tasks begin with easier and progress to tasks that require higher balancing functions. Berg Balance Scale has found to be reliable measure of balance among older people (Berg et al. 1992, Steffen et al. 2002). Low BBS scores have been shown to predict a risk of falling (Lajoie et al. 2002).

2.5 APPROACHES TO OPTIMIZE DRUG USE AMONG OLDER PEOPLE

Studies regarding adverse events associated with psychotropic and sedative drug use among older people have prompted initiatives to optimize drug use. These approaches include regulatory warnings of ADEs (Dorsey et al. 2010), education of health care professionals (Pimlott et al. 2003), education and counseling of patients regarding withdrawal or reduction of benzodiazepine use (Salonoja et al. 2010, Smith and Tett 2010), medication reviews by pharmacists (Zermansky et al. 2006, Holland et al. 2008), medication assessments by physicians (Pit et al. 2007), multidisciplinary team interventions including Comprehensive Geriatric Assessment (CGA) (Frankfort et al. 2006, Tulner et al. 2010), and withdrawal programs (Voshaar et al. 2003, Parr et al. 2009). In this literature review, CGA, medication reviews and withdrawal strategies from use of benzodiazepines are briefly reviewed in terms of optimizing sedative drug use.

2.5.1 Comprehensive Geriatric Assessment (CGA)

Comprehensive Geriatric Assessment is a diagnostic process to determine an older person's medical, psychosocial, and functional capacity related problems (Rubenstein 1984). The process is multidimensional and utilized with an objective of developing a plan for treatment and rehabilitation, and to promote older person's health and independence. The CGA typically involves a geriatrician, nurse, physiotherapist and depending on the problems other healthcare providers such as occupational therapist, social worker, psychologist and other consultants such as physicians specialized in orthopedics or cardiology. The process is individually tailored according to needs and problems of the participant.

Geriatric clinical examination including laboratory tests and interview in CGA is targeted to identify new diseases, to assess cognition and status of chronic diseases and other medical problems (Rubenstein 1984). Functional capacity is one important dimension which focuses on how person copes with ADLs and IADLs, and mobility tasks. Psychosocial health includes examination of mood and quality of life. Finally, socio-environmental aspect includes social networks and support, environmental safety and need of services.

The effectiveness of CGA has been studied mainly when a person is discharged from hospital to geriatric evaluation and management units (Van Craen et al. 2010). A meta-analysis by van Craen et al. concluded that CGA significantly affected functional decline and institutionalization after one year. However, mortality, hospital readmission and length of hospital stay were not affected by this intervention.

Medication assessment is a central part of the CGA because polypharmacy and ADEs are frequent among older people (Jyrkkä et al. 2006, Hilmer et al. 2009b). The CGA and medication assessment conducted at a diagnostic geriatric day clinic have resulted in relevant changes in medications in one study (Frankfort et al. 2006). These changes were often discontinuations of drugs when indication of drug was no longer relevant. Adverse events were detected and better pharmacotherapeutic options were proposed. However, the number of drugs was reduced in only a minority of patients because of prescribing new drugs for diseases diagnosed in the CGA. This is consistent with another study assessing effects of CGA on drug use (Tulner et al. 2010). The CGA increased mean number of drugs used and the prevalence of polypharmacy. The increase was caused by new indications treated with drug therapy and a decrease in the under-treatment of existing diseases. The effect of medication assessment cannot be only judged by the number of drugs but quality of drug use and optimal care of diagnosed diseases.

Medication assessment outside of the CGA process has been reported to be effective in reducing regular use of benzodiazepines among older people with a recent history of falls (Salonoja et al. 2010). A Finnish randomized controlled trial included medication assessment, lecture on adverse effects of psychotropic drugs, and written instructions on how to reduce the use of psychotropic drugs. The intervention reduced the number of regular users of benzodiazepines by 35% after a 12-month follow-up. No changes were observed in irregular benzodiazepine use, or use of antipsychotics and antidepressants. However, an Australian study reported that medication assessment by a general practitioner did not decrease benzodiazepine use among community-dwelling older people (Pit et al. 2007).

2.5.2 Medication reviews related to sedative drug use and ADEs

Medication reviews are one important method to reduce and re-evaluate use of psychotropic and sedative drugs among older people (Nishtala et al. 2008). Meta-analysis by Nishtala et al. concluded that a combination of medication review and/or educational interventions for physicians and nursing staff are effective in reducing hypnotic use in long-term care facilities. Pharmacist involvement in medication review process has been successful in reducing ADEs including falls among older people (Zermansky et al. 2006). A systematic review and meta-analysis by Holland et al. concluded that pharmacist-led medication reviews aimed at optimizing drug regimens were not effective in reducing hospital admissions, or mortality (Holland et al. 2008). Medication reviews may have clearer impact on ADEs and other outcomes if they are targeted to a specific patient group (those with an increased risk of falls, or long-term users of benzodiazepines), or when pharmacists are a part of multidisciplinary team (Schmader et al. 2004).

Pharmacist-led medication reviews have reduced patient's DBI scores in both community and residential-aged care settings (Nishtala et al. 2009, Casteliano et al. 2010). In a study by Casteliano et al., DBI scores before and after Home Medicines Review by pharmacist were compared retrospectively for 372 older persons who were referred to the service (Casteliano et al. 2010). Drugs contributing to DBI were identified in 52% of the participants before the medication review which indicates high use of the DBI drugs. Medication reviews significantly reduced the total sum of DBI scores for all participants ($p<0.001$), and majority of pharmacists' recommendations were to withdraw or reduce the usage of benzodiazepines.

2.5.3 Withdrawal from benzodiazepine use

Clinical studies of drug withdrawal suggest that withdrawal is rarely associated with ADEs (Iyer et al. 2008). Withdrawal is usually associated with no deteriation in clinical status, and psychotropic drug withdrawal may improve cognition and reduce the risk of falls.

Long-term use of benzodiazepines has been found to be associated with a risk of cognitive decline among older people (Paterniti et al. 2002). Gradual decrease in dose with weekly visits to general practitioner has been successful in discontinuation of long-term benzodiazepine use (Voshaar et al. 2003). One-time counseling and medication assessment by geriatrician in combination with education of patients with history falls resulted decrease in regular benzodiazepine use (Salonoja et al. 2010). Withdrawal from addictive drugs such as benzodiazepines is shown to be effective when withdrawal is done by gradual decrease in dose (Parr et al. 2009). Withdrawal from drugs should be done in collaboration with the patient. Clinicians should emphasize the benefits of withdrawal because older users are often psychologically dependent on benzodiazepines, deny or minimize adverse effects, express resistance to discontinuation and may have tried to discontinue without results (Iliffe et al. 2004, Cook et al. 2007). However, meta-analysis conducted by Barker et al. demonstrated that long-term benzodiazepine users show recovery of cognitive function after withdrawal (Barker et al. 2004).

2.6 ADVERSE EVENTS ASSOCIATED WITH THE USE OF DRUGS WITH SEDATIVE PROPERTIES

2.6.1 Adverse events associated with cumulative exposure to sedative drugs

The Sedative Load Model, DBI and CNS drug model have been used to study the association between cumulative exposure to sedative drugs and clinically important ADEs in older people (Table 4). Associations between DBI and ADEs have been investigated in 10 studies, and seven of these have been focused on declines in physical function. Of these seven studies, five have been conducted among community-dwelling older people, one among persons in residential aged care facilities, and one among persons living in self-care retirement villages in Australia. Furthermore, one study was conducted among acutely ill hospitalized older people, and was focused on ADLs. The association between DBI and ADEs has been studied in six cross-sectional and four longitudinal studies. Three studies have reported association between CNS drug use and ADEs, and all three studies utilized longitudinal study design (Health ABC Study). One of these three studies investigated association between CNS drug use and physical function. The association between sedative load and ADEs has only been studied in one study.

DBI drugs have been shown to impair physical function in grip strength, chair stands, walking speed, self-reported physical function measures, TUG and Berg Balance Scale among community-dwelling older people in the United States, Australia and Finland (Table 4). However, studies among residents of residential aged care facilities and self-care retirement villages have demonstrated more modest associations (Wilson et al. 2010, Gnjidic et al. 2011b). A study by Boudreau et al. found an association between CNS drug use and risk of incident self-reported mobility limitation (Boudreau et al. 2009). Cognitive function has been studied in one DBI study and in one CNS Drug Model study (Hilmer et al. 2007, Wrigth et al. 2009), and both found that cumulative exposure to sedative drugs was associated with poor cognitive function.

Three studies have investigated the association between cumulative exposure to sedative drugs and risk of death (Table 4). However, there remains a lack of research on mortality associated with cumulative exposure to sedative drugs. There is also a lack of studies concerning cumulative exposure to sedative drugs and the risk of falls. One study found that CNS drug use was associated with an increased risk of falls among community-dwelling older people (Hanlon et al. 2009). A recent study found an association between DBI and an increased risk of falls among older people in residential aged care facilities (Wilson et al. 2011). The risk of falls remains an important area for further research because benzodiazepine use has been associated with falls and hip fractures (Cumming & LeCouteur 2003, Hartikainen et al. 2007). Falls may result in serious injuries, including fractures, visits to emergency department, and also admissions to nursing homes (Dunn et al. 1993, Kannus et al. 2005).

2.6.2 Impairment of physical function associated with sedative drugs

Association between sedative drug use and physical function has been studied among older people (Table 5). Benzodiazepines are the most widely studied sedative drug group in relation to physical function. Of 12 studies included in Table 5, six studied solely benzodiazepines. Antidepressant use was investigated in four studies, antipsychotic use in two studies and opioid use only in one study. Two studies investigated associations between use of ≥1 psychotropic drugs and performance in balance and muscle strength tests (Lord et al. 1992, Lord et al. 1995).

Benzodiazepines have been consistently associated with declines in ADLs/ IADLs, and self-reported declines in mobility (Table 5). Of performance-based tests, one study of muscle strength did not report an association with benzodiazepine use. SPPB/ EPESE scales and mobility (walking speed) have been investigated in two studies each, and resulted in opposite conclusions. The majority of studies (two out of three) on benzodiazepine use and poor balance have found an association. However, the lack of associations may be related to small sample sizes in studies with performance-based physical function measures (number of participants varied from 12 to 885). Furthermore, many of these studies also included users of psychotropic drugs other than benzodiazepines. However, benzodiazepines have also been shown to impair physical function among younger adults, including balance measured as body sway (McClelland 1989), and impairment of psychomotor skills and car driving ability (Verster et al. 2007). In conclusion, there is evidence of an association between benzodiazepine use and physical function decline.

Antidepressant use has been associated with a decline in ADLs/ IADLs, muscle strength and mobility (Table 5). However, there are also two studies which could not found associations, and overall number of studies regarding antidepressant use is small. In a study by Draganich et al. found an association between declines in mobility and use of

amitriptyline but not with use of desipramine or paroxetine (Draganich et al. 2001). Thus, there may be differences in impacts on physical function within drug classes.

The number of studies about sedative drugs other than benzodiazepines and antidepressants is too small to make any conclusions (Table 5). A review of antiepileptic use and balance disturbances among older people concluded that some antiepileptics including primidone, phenobarbital, phenytoin and carbamazepine appear to produce a greater impairment of balance compared to newer antiepileptic drugs, but there is a considerable lack of research on the topic (Fife and Sirven 2005). Altogether, the number of studies regarding sedative drugs and decline in physical function is remarkably small when considering the variety of sedative drugs, prevalence of use among older people, and concern about possible decline in physical function related to the use of sedative drugs. Research utilizing cumulative exposure methods of sedative drug use has started to fill this gap in recent years.

Impairment of physical function related to sedative drug use may also be consequence of physical inactivity caused by these drugs. This may result in disuse atrophy (Clark 2009). Higher level of physical activity has been associated with a slower rate of mobility decline (Buchman et al. 2007). In addition, physical inactivity may result in decreased muscle strength (Rantanen et al. 1999, Goodpaster et al. 2008). Sedation caused by drugs may cause or worsen physical inactivity which may result in decline in muscle strength and thus, poorer physical function.

2.6.3 Mortality associated with the use of sedative drugs

There are three studies of mortality and sedative drug use utilizing one of the four methods to assess cumulative exposure to drugs with sedative properties (Taipale et al. 2009, Lowry et al. 2011, Wilson et al. 2012, Table 4). The study by Taipale et al. was conducted among 1004 residents of long-term care facilities in Finland, whereas Lowry et al. studied 362 older hospitalized, acutely ill patients in the UK. Wilson et al. studied mortality among 602 older people living in residential aged care facilities in Australia. All three studies have concluded that there was no association between sedative drug use and mortality.

Drug classes contributing to sedative load have been associated with an increased risk of death among older people (Table 6). Antipsychotics are the most frequently studied drug group in relation to mortality, with at least 18 original studies conducted among older people or persons with dementia. Of these 18 studies, 15 have reported an increased risk of death associated with antipsychotic use.

The first meta-analysis that led to warnings of mortality risk associated with atypical antipsychotic use was published in 2005 by Schneider et al. (Schneider et al. 2005). In the analysis of 3353 participants, older persons randomized to atypical antipsychotics were at higher risk of death compared to those prescribed placebo (meta-analysis odds ratio [OR] 1.54, CI 1.06–2.23). Subsequent studies have also demonstrated an increased mortality risk with conventional antipsychotics (Table 6). Wang et al. reported that conventional antipsychotics were associated with a significantly higher risk of death compared to atypical antipsychotics (Wang et al. 2005), and this have been also found in other studies (Schneeweiss et al. 2007, Gill et al. 2007, Setoguchi et al. 2008, Liperoti et al. 2009, Musicco et al. 2011). Two studies have reported a similar risk of death for conventional and atypical antipsychotic use (Trifiro et al. 2007, Kales et al. 2007). The studies also indicate that risk of death may be highest in the start of the treatment (Wang et al. 2005, Schneeweiss et al. 2007, Rossom et al. 2010).

A review by Mittal et al. concluded that current data indicates that the risk of death with atypical and conventional antipsychotics is greater than when compared to placebo group or nonusers of antipsychotics (Mittal et al. 2010). According to 14 reviewed studies, the risk was estimated to be 1.2 to 1.6 times higher in the antipsychotic treated group. The risk was found to similar for both atypical and conventional antipsychotics, and no one drug has been found to be safer than other. The mortality risk was estimated to be elevated in the first 30 days of treatment and possibly until 2 years.

The most recent studies have concentrated on specific antipsychotics, and associated risk of death (Rossom et al. 2010, Kales et al. 2012, Table 6). In both studies, haloperidol was associated with the highest risk of death during the first 30-180 days of treatment, HR 1.5-3.2. Rossom et al. found an increased risk of death associated with also olanzapine and risperidone use but not for quetiapine use, and Kales et al. reported similar results. Further studies with large study samples are needed to assess the risk of death associated with specific antipsychotic drugs.

Studies concerning other drug classes than antipsychotics have presented conflicting results (Table 7). In some studies of antipsychotics and mortality among participants with dementia, antipsychotic use has been associated with higher mortality rate compared to users of other psychiatric medications including antidepressants (Kales et al. 2007). In a recent study of specific antipsychotic drugs among incident users with dementia, valproic acid use was associated with a similar risk as olanzapine and risperidone (Kales et al. 2012). Thus, results of other sedative drugs in comparison to antipsychotics are inconsistent.

Of five reviewed studies regarding antidepressant use and mortality, two have not found any association (Barnett et al. 2006, McCusker et al. 2006), two have found an increased risk of death (Ryan et al. 2008, Coupland et al. 2011) and one a lower risk of death (Ried et al. 2011) (Table 7). This may be partly related to different patient characteristics in different studies. Studies have been conducted among participants with pneumonia (Barnett et al. 2006), among participants with diagnosed depression (Coupland et al. 2011), and among veterans who have had a stroke (Ried et al. 2011). Antidepressants may be used in various indications, and underlying diseases may affect the risk of death.

Studies regarding benzodiazepines and mortality among older people have been inconclusive in results, and heterogeneous when considering the definition of drugs (Table 7). Some studies included hypnotics, some included anxiolytics and hypnotics, benzodiazepines or "sleeping pills". Some studies used administrative dispensing data and other used survey based data. Four studies have not found an association (Rumble et al. 1992, Merlo et al. 2000, Vinkers et al. 2003, Gisev et al. 2011), whereas three studies have reported at least partly positive results (Merlo et al. 1996, Kripke et al. 1998, Lopez et al. 1999). In a study by Merlo et al., combined use of anxiolytic-hypnotics and analgesics was associated with all-cause mortality and with ischemic heart disease mortality (Merlo et al. 1996). Kripke et al. found an association between hypnotic use and an increased risk of death among older men but among women (Kripke et al. 1998). Lopez et al. reported an increased mortality risk among sedative-hypnotic users compared to nonuse in small sample (n=179) of participants with dementia (Lopez et al. 1999). However, hypnotic use has been associated with an increased risk of death among middle-aged persons (Kripke et al. 2012) and thus, further research is needed to establish this association among older persons.

Opioids were studied in one study among older people diagnosed with osteoarthritis or rheumatoid arthritis (Solomon et al. 2010a, Solomon et al. 2010b). Compared to use of non-steroidal anti-inflammatory drugs (NSAIDs), opioids were associated with an increased risk of death (Solomon et al. 2010a). Among opioid users, oxycodone and codeine were

associated with an increased risk of death compared to hydrocodone use after 30 days of exposure (Solomon et al. 2010b). These two studies by Solomon et al. questioned the safety of opioid use among older people. However, opioids may have been selectively prescribed to older people at higher risk of death.

There are several potential mechanisms behind sedative drugs and an increased risk of death. Antipsychotics have been associated with prolongation of QT interval and sudden cardiac deaths (Straus et al. 2004). Other possible causes of death associated with antipsychotics are cerebrovascular adverse events which may be related to orthostatic hypotension caused by antagonism of alpha-adrenergic receptors (Mittal et al. 2011). This may result in a decrease in cerebral perfusion. The risk of cerebrovascular adverse events has been shown to be similar with conventional and atypical antipsychotics, and associated with therapy lasting for more than 30 days (Mehta et al. 2010). Sedation and extrapyramidal symptoms that may contribute to swallowing problems and corresponding risk of pneumonia, have also been suggested as possible mechanisms of an increased risk of death associated with antipsychotic use among older people (Liperoti et al. 2009, Mittal et al. 2010).

Causes of deaths that have been related to hypnotic use include suicide, cancer, and confounding by indications insomnia and depression (Kripke 2009). One potential cause of death related to psychotropic drug use is an increased risk of falls and fractures which have been associated with all discussed drug classes (Cumming and Le Couteur 2003, Hartikainen et al. 2007). However, there is a lack of studies concerning mechanisms and causes of death related to sedative drug use.

In conclusion, studies regarding antipsychotics and an increased risk of death are numerous, conducted among patients with and without dementia, and the risk has been demonstrated with both conventional and atypical antipsychotics. The risk is elevated at the start of the treatment but is associated also with long-term use. Evidence related to other drugs with sedative properties does not clearly indicate whether or not use of these drugs among older people is associated with an increased risk of death. Further studies are needed to assess the possible association between sedative drug use and mortality.

Table 4. Cumulative exposure to sedative drugs and linkage to adverse events Sedative Load Model, Drug Burden Index, Sloane Model or CNS Drug Model

Study, country, study name	**N**	**Age and gender distribution**	**Setting**	**Study design**	**Method to quantify cumulative effect of sedative drugs**	**Studied outcomes**	**Association of sedative drug use with the outcomes (vs. no use)**
Hilmer et al. 2007 US, Health ABC study	3075	Age range 70–79 y, mean age 74 years, 52% women	C	CS	DBI	SPPB (modified), DSST scores	Poorer SPPB scores (p<0.001) and poorer DSST scores (p=0.01) among those exposed to DBI drugs
Cao et al. 2008 US, Womens' Health and Ageing Study	932	≥65 years, median age 78 years, 100% women	C	CS	DBI	MMSE, ADL, walking speed, mobility (self-reported), balance (full tandem stand), chair stands, upper extremity function (self-reported), grip strength	DBI: impaired grip strength OR 3.3 (1.5–7.3), mobility difficulty OR 2.4 (1.1–5.3), ± other outcomes, $DBI_{ANTICHOL}$: poorer performance in all outcomes
Gnjidic et al. 2009 Australia, Concord Health and Ageing in Men Project	1705	≥70 y, mean age 77, 100% men	C	CS	DBI	IADL, balance (sway), walking speed, narrow walk, chair stands, grip strength	DBI: poorer performance in IADL, walking speed, narrow walk, balance and grip strength (p<0.05), DBI_{SED}: poorer performance in IADL, walking speed, narrow walk, balance and grip strength (p<0.05)
Hilmer et al. 2009 US, Health ABC Study	2172	70–79 y, 52% women	C	L	DBI	Functional performance assessed with SPPB, usual walking speed and grip strength	DBI: lower SPPB scores (p=0.01), lower walking speed (p=0.004) and lower grip strength (p=0.004) after 5 years
Wilson et al. 2010 Australia	526	Mean age 86, 72% women	I	L	DBI	Physical function assessed with grip strength, reaction time, walking speed and balance	In longitudinal analysis, DBI: poorer balance (p=0.02). In cross-sectional analysis, DBI_{SED}: poor balance OR 1.57 (1.08–2.27)
Gnjidic et al. 2011 Australia	115	Mean age 82, 73% women	I	CS	DBI	SPPB and grip strength	DBI: decrease in SPPB score (p=0.04) ± grip strength

Table 4. Continued

Gnjidic et al. 2011 Finland, GeMS Study	700	Mean age 82 (all ≥75), 69% women	C	CS	DBI	Physical function assessed with walking speed, chair stands, grip strength, TUG, IADL and Barthel Index	DBI: poorer walking speed, chair stands, TUG, IADL and BI ($p<0.001$)
Wilson et al. 2011	602	Mean age 86, 71% women	I	L	DBI	Incident rate of falls during follow-up	DBI: increased risk of falls, incident rate ratio for low DBI 1.61 (1.17–2.23) and for high DBI 1.90 (1.30–2.78)
Lowry et al. 2011 UK	362	Mean age 84, 59% women	I	CS	DBI	Barthel Index, in-hospital mortality	Higher DBI: lower BI scores, length of stay in hospital HR 1.23 (1.06–1.42), ± in-hospital mortality HR 1.17 (0.72–1.90)
Wilson et al. 2012	602	Mean age 86, 71% women	I	L	DBI	One-year all-cause mortality	± mortality risk, DBI low (0–1) HR 1.13 (0.82–1.57), DBI high (≥1) HR 1.19 (0.82–1.74)
Taipale et al. 2009 Finland	1004	Mean age 81, 75% women	I	L	Sedative Load Model	All-cause mortality over 5 years	± mortality risk HR 1.01 (0.91–1.13)
Wright et al. 2009 US, Health ABC Study	2737	≥65, 53% women	C	L	CNS Drug Model	Cognitive decline during 5 years, 3MS score	Cognitive decline HR 1.37 (1.11–1.70) over 5 years
Boudreau et al. 2009 US, Health ABC Study	3055	70–79, 52% women	C	L	CNS Drug Model	Incident mobility limitation: two consecutive self-reports of any difficulty walking ¼ mile or climbing 10 steps without resting	Incident mobility limitation HR 1.28 (1.12–1.47)
Hanlon et al. 2009 US, Health ABC Study	3055	70–79 52% women	C	L	CNS Drug Model	Number of falls	Risk of falls OR 1.95 (1.35–2.81)

C=community-dwelling, I=institutional living (in nursing homes, long-term care facilities, residential aged care facilities), CS=cross-sectional study, L=longitudinal cohort study, DBI = Drug Burden Index, DBI_{SED} = sedative component of Drug Burden Index, $DBI_{ANTICHOL}$=anticholinergic component of Drug Burden Index, DSST= Digit Symbol Substitution Test, MMSE= Mini-Mental State Examination, 3MS=modified Mini-Mental State Examination, ADL = Activities of Daily Living, IADL= Instrumental Activities of Daily Living, BI=Barthel Index, TUG=Timed Up&Go test, CNS = central nervous system, HR= hazards ratio, OR = odds ratio, CI = confidence interval, Health ABC = Healthy, Aging and Body Composition.

Table 5. Associations between sedative drug use and decline in physical function

Study, country	n	Age	Pattern of use	Study design	Drug	ADLs/ IADLs	Self-reported mobility	Mobility performance	SPPB, EPESE	Balance	Muscle strength
Ried et al. 1998 US	4192	≥65	LT	L	BZD	+					
Gray et al. 2006 US	9093	≥65	LT	L	BZD, any use BZD, short-acting BZD, long-acting BZD, higher dose	+ + ± +	+ + + +				
Gray et al. 2002 USA	1519	≥65	LT	L	BZD anxiolytic use BZD hypnotic use	+ ±					
Gray et al. 2003 US	885	≥70	LT	L	BZD, any use BZD, higher dose BZD, low dose BZD, long-term use BZD, past use				+ + ± + ±		
Landi et al. 2007 Italy	364	≥80	LT	L	BZD AP	+ +		± ±	+ ±		± ±
Ebly et al. 1997 Canada	2035	≥65	LT	CS	BZD AD AP opioid	+ + ± +					
Eto et al. 1998 Japan	53	≥65	LT	CS	BZD			+		±	
Cutson et al. 1997 US	12	Mean 70	I	CO	BZD (diazepam)					+	
Lord et al. 1995 Australia	414	Mean 74	LT	CS	BZD psychotropics ≥1 AD					+ ± 	 + +
Lord et al. 1992 Australia	100	≥60	LT	CS	psychotropics					+	+
Penninx et al. 1998 US	1286	≥71	LT	L	AD (mostly amitriptyline)				±		
Draganich et al. 2001 US	12	Mean 67	I	CO	ADs, amitriptyline desipramine paroxetine	 	 	 + ± ±	 	 	

+=positive association with decline, ±= no association, (empty)= not studied or reported.
LT = long-term use, I = incident use or single dose, CO = cross-over trial, L = longitudinal study, CS = cross-sectional study, BZD = benzodiazepine, AD = antidepressant, AP = antipsychotic, ADL = Activities of Daily Living, IADL = Instrumental Activities of Daily Living, self-reported mobity = self-reported difficulty or disability in mobility, mobility performance = walking speed or cadense (steps/min) or TUG test, SPPB = short physical performance battery, EPESE = physical performance test battery developed for the Established Populations for Epidemiologic Studies of the Elderly, balance = balance test results, including postural sway measurements, muscle strength = grip strength, ankle or quadriceps strength.

Table 6. Summary of studies related to antipsychotic use and mortality among older people

Study	Drugs	N	Setting	Age and gender distribution	Hazard ratio(s), or other risk measure
Suh et al. 2005	antipsychotics	273 with dementia	I		higher mortality among nonusers HR 1.28 (1.13–1.44) compared to AP users
Wang et al. 2005	antipsychotics, atypical vs. conventional	22 890 incident users	C and I	≥65	compared to atypical AP use, conventional AP HR 1.37 (1.27–1.49), <40 days treatment HR 1.56 (1.37–1.78), 40-79 d treatment HR 1.37 (1.19–1.59), 80-180 d treatment HR 1.27 (1.14–1.41), low dose (<median) HR 1.14 (1.04–1.49) high dose (>median) HR 1.73 (1.57–1.90)
Hartikainen et al. 2005	antipsychotics	137 participants with dementia	I and C	≥75	antipsychotic use HR 2.75 (1.46–5.19) compared to nonusers of psychotropic (adjusted for age and gender)
Barnett et al. 2006	antipsychotics (atypical, conventional vs. nonusers of APs, ADs or mood stabilizers)	14057 participants with pneumonia	I	Mean age 69 years, 97% men (veterans)	conventional AP OR 1.51 (1.04–2.19) for in-hospital mortality, atypical AP no association
Nonino et al. 2006	atypical antipsychotics	2314 participants with dementia (294 users with BPSD and 2020 nonusers as controls),	C and I	≥65, mean age 83 years, 70 % women	atypical APs HR 1.02 (0.78–1.34)
Hollis et al. 2007	antipsychotics (individual drugs)	16 634 incident users, 9831 prevalent users	C and I	≥65, subgroup of users with dementia	chlorpromazine RR 1.39 (1.15–1.67), haloperidol RR 2.26 (2.08–2.47), risperidone RR 1.23 (1.07–1.40), multiple study drugs RR 1.48 (1.10–1.98) for incident AP use compared to olanzapine use
Raivio et al. 2007	antipsychotics, atypical vs. conventional	254 with dementia	I	Mean age 86	atypical HR 0.49 (0.24–0.99) conventional HR 0.68 (0.46–1.03)

Table 6. Continued

Study	Drugs	N	Setting	Age and gender distribution	Hazard ratio(s), or other risk measure
Schneeweiss et al. 2007	antipsychotics, atypical vs. conventional	37 241 incident users (the same study sample as in Setoguchi)	C and I	≥65	Conventional vs. atypical: mortality ratio 1.32 (1.23–1.42) in 180 d, high dose mortality ratio 1.67 (1.50–1.86), during first 40 d of treatment mortality ratio 1.60 (1.42–1.80). Haloperidol mortality ratio 2.14 (1.86–2.45) compared to risperidone
Kales et al. 2007	antipsychotics vs. other psychiatric medications	10 615 incident users, with dementia	C	≥65	higher mortality rate among AP users compared to users of other psychiatric medications, compared to conventional APs; atypical APs RR 0.93 (0.75–1.16), atypical + conventional AP RR 1.33 (0.94–1.86), anticonvulsants RR 0.79 (0.51–1.24), SSRIs RR 0.49 (0.39–0.62), other 2nd gen ADs RR 0.60 (0.46–0.79)
Trifirò et al. 2007	antipsychotics, atypical vs. conventional	2385	C	≥65	Atypical APs OR 2.2 (1.2–3.9), conventional APs OR 1.7 (1.3–2.2) vs. nonusers, ± between atypical and conventional APs
Gill et al. 2007	antipsychotics (atypical vs. conventional)	27 259 matched pairs, with dementia, incident users	C and I	≥66	Atypical AP 30 d HR 1.31 (1.02–1.70) among community-dwelling persons, Atypical AP 30 d HR 1.55 (1.15–2.07) among LTC residents vs. nonuse of APs, Conventional AP 30 d HR 1.55 (1.19–2.02) among CD-persons, Conventional AP 30 d HR 1.26 (1.04–1.53) among LTC residents vs. atypical AP use
Setoguchi et al. 2008	antipsychotics, atypical vs. conventional	37 241 incident users	C and I	≥65	antipsychotic use HR 1.27 (1.18–1.37) for all non-cancer deaths during 180 d, conventional AP HR 1.23 (1.10–1.36) for cardiovascular death and HR 1.36 (1.19–1.56) for out of hospital death during 180 d vs. atypical AP use

Table 6 continues

Table 6. Continued

Study	Drugs	N	Setting	Age and gender distribution	Hazard ratio(s), or other risk measure
Ballard et al. 2009	antipsychotics, withdrawal trial (half randomized to continue APs, half to placebo)	128	I	Mean age 85 years, dementia	Cumulative probability of survival during 12 months 70% for AP group and 77% for placebo group, log-rank p=0.03
Liperoti et al. 2009	antipsychotics, conventional vs. atypical, haloperidol vs. risperidone	6524 incident atypical AP users, 1581 incident conventional AP users with dementia	I	Mean age 84, 72% women	Conventional AP HR 1.26 (1.13–1.42) vs. atypical AP use. Haloperidol HR 1.31 (1.13–1.53) vs. risperidone. Risk with all atypical AP = risperidone HR.
Simoni-Wastila et al. 2009	antipsychotics	2363	I	409 participants <65 years, others ≥65, 69% women	± mortality HR 0.83 (0.69–1.00)
Rossom et al. 2010	haloperidol, olanzapine, quetiapine, risperidone	90635 (18127 exposed to APs) with dementia	C and I	≥65, about 98% men (veterans)	haloperidol >1 mg HR 3.2 (2.2–4.5), olanzapine >2,5 mg HR 1.5 (1.1–2.0, quetiapine >50 mg no association, risperidone >1 mg HR 1.6 (1.1–2.2), during the first 30 days of drug use (no associations after 30 days)
Musicco et al. 2011	antipsychotics (conventional, atypical)	4369 with dementia		≥60, mean age 79 years, 65% women	Conventional AP HR 3.7 (2.6–5.1), atypical AP HR 2.5 (2.0–3.0) vs. nonuse of APs, Conventional vs. atypical HR 1.5 (1.1–2.1)
Kales et al. 2012	antipsychotics and valproic acid	33604 incident users with dementia	C	≥65 years	haloperidol RR 1.54 (1.38–1.73), olanzapine RR 0.99 (0.89–1.10), valproic acid RR 0.91 (0.78–1.06), vs. risperidone during first 180 d

Inclusion criteria: association between drugs with sedative properties and mortality (adjusted for covariates), older people (≥65) or persons with dementia, original studies. Hazard ratio or relative risk is reported for all-cause mortality if not otherwise indicated (with 95% confidence interval).
± = no association, + = positive association with mortality, I = institutional care (setting), C = community-dwelling (setting), HR = hazard ratio, RR = relative risk, AP=antipsychotic, AD = antidepressant, SSRI = selective serotonin reuptake inhibitor, BPSD = behavioral and psychiatric symptoms of dementia, d = days, y = years, LTC = long-term care, CD= community-dwelling.

Table 7. Summary of studies related to sedative drug use and mortality among older people

Study	Drugs	N	Setting	Age and gender distribution	Hazard ratio(s), or other risk measure
Antidepressants					
Barnett et al. 2006	tricyclic ADs, other ADs (other than tricyclics) vs. nonusers of APs, ADs or mood stabilizers)	14057 participants with pneumonia	I	Mean age 69 years, 97% men (veterans)	tricyclic AD no association, other ADs no association
McCusker et al. 2006	antidepressants	456	I	≥65	± mortality (HR 1.1 [0.77–1.58])
Ryan et al. 2008	antidepressants	7363	C	≥65	antidepressant use among men HR 2.2 (1.4–3.5), not among women
Coupland et al. 2011	antidepressants (tricyclic ADs, SSRIs and other ADs)	60 746 participants with depression	C	≥65	tricyclic ADs HR 1.16 (1.10–1.22), SSRIs HR 1.54 (1.48–1.59), other ADs HR 1.66 (1.56–1.77) compared to nonuse of antidepressants among depressed patients
Ried et al. 2011	SSRIs	870 veterans with a diagnosis of stroke		Mean age 69-71 in different exposure groups	SSRI use before and after stroke HR 0.31 (0.11–0.86), ± SSRI use before stroke only and ± SSRI after stroke only vs.nonuse of SSRIs
Anxiolytics, hypnotics					
Rumble et al. 1992	hypnotics	1042	C	≥65	± hypnotic use with mortality
Merlo et al. 1996	anxiolytic-hypnotic drugs (mainly benzodiazepines) and analgesics	500	C	68 years, 100% men	anxiolytic-hypnotic and analgesic use RR 1.8 (1.1–2.9) for all-cause mortality, RR 2.7 (1.3–6.0) for ischemic heart disease mortality ± anxiolytic-hypnotic use and all-cause mortality (RR 1.0 [0.6–1.8])
Kripke et al. 1998	hypnotics	427 328	C	≥60 years	60-69 y men using 1–29 pills/ month HR 1.14 (1.02–1.27), 60-69 y men using ≥30 pills/month HR 1.32 (1.12–1.56), ≥70 y men using ≥30 pills/month HR 1.17 (1.01–1.35)
Lopez et al. 1999	sedatives/ hypnotics, antipsychotics, antidepressants	179 with dementia	C		mortality RR 1.96 for sedative/ hypnotics, ± antidepressants and antipsychotics for mortality

Table 7 continues

Table 7. Continued

Study	Drugs	N	Setting	Age and gender distribution	Hazard ratio(s), or other risk measure
Merlo et al. 2000	anxiolytic-hypnotics	491	C	68 years, 100% men	± mortality (HR 1.2 [0.8–1.7]), men with low level of psychosocial coping resources had increased risk of death regardless of anxiolytic-hypnotic use
Vinkers et al. 2003	benzodiazepines	599	C	≥85	± mortality (RR 0.77 [0.51–1.17])
Gisev et al. 2011	benzodiazepines and related drugs	2224	C	≥65	± mortality (HR 1.01 [0.84–1.21])
Opioids					
Solomon et al. 2010a	opioids	12 840 with osteoarthritis or rheumatoid arthritis		Mean age 80, 85% women	Opioids HR 1.87 (1.39–2.53) compared to use of NSAIDs
Solomon et al. 2010b	opioids: hydrocodone, codeine, oxycodone, propoxyphene, tramadol	6275 opioid users		Mean age 78-79 years between drug user groups	Oxycodone RR 2.43 (1.47–4.00), codeine RR 2.05 (1.22–3.45) compared to hydrocodone users after 30 days of exposure

Inclusion criteria: association between drugs with sedative properties and mortality (adjusted for covariates), older people, original studies. Hazard ratio or relative risk is reported for all-cause mortality if not otherwise indicated (with 95% confidence interval).
± =no association with mortality, I = institutional care, C = community-dwelling, HR = hazard ratio, RR = relative risk, AD = antidepressant, SSRI = selective serotonin reuptake inhibitor, NSAIDs = non-steroidal anti-inflammatory drugs.

3 Aims of the thesis

The overall aim of this thesis was to investigate the association between sedative load and adverse events among community-dwelling people aged 75 years and older.

The specific aims of this study were to investigate the:

1. prevalence of sedative load among community-dwelling older people and determine factors associated with sedative load;
2. association between the sedative load and objective measures of balance and mobility;
3. association between sedative load and objective measures of muscle strength; and
4. evolution of sedative load over the study period and the corresponding risk of death.

4 Materials and methods

4.1 STUDY POPULATION

Studies presented in the thesis utilized data collected as a part of Geriatric Multidisciplinary Strategy for Good Care of the Elderly (GeMS) Study. The GeMS Study was a randomized comparative study that evaluated a model for geriatric assessment, care and rehabilitation. A random sample of 1000 people aged 75 years and older (born before November 1, 1928) and inhabitants of city of Kuopio, Finland, were invited to participate. In the beginning of 2004, the city of Kuopio had a population of 88,253 inhabitants, 5,615 of whom were aged ≥75 years.

In the GeMS Study, 500 persons were randomized to an intervention group and 500 to a comparison group. Of 1000 people, 781 provided written informed consent to participate, 162 refused participation, 2 relocated and 55 died before the baseline examination. Participants living in institutional care (n=81) were excluded from the analyses and thus, 700 community-dwelling participants were included at the baseline (Figure 1).

The baseline examination took place in 2004 followed by annual examinations until 2007. In Studies I–III, only baseline data were analyzed. In Study IV, the evolution of sedative load was analyzed utilizing data from all examinations.

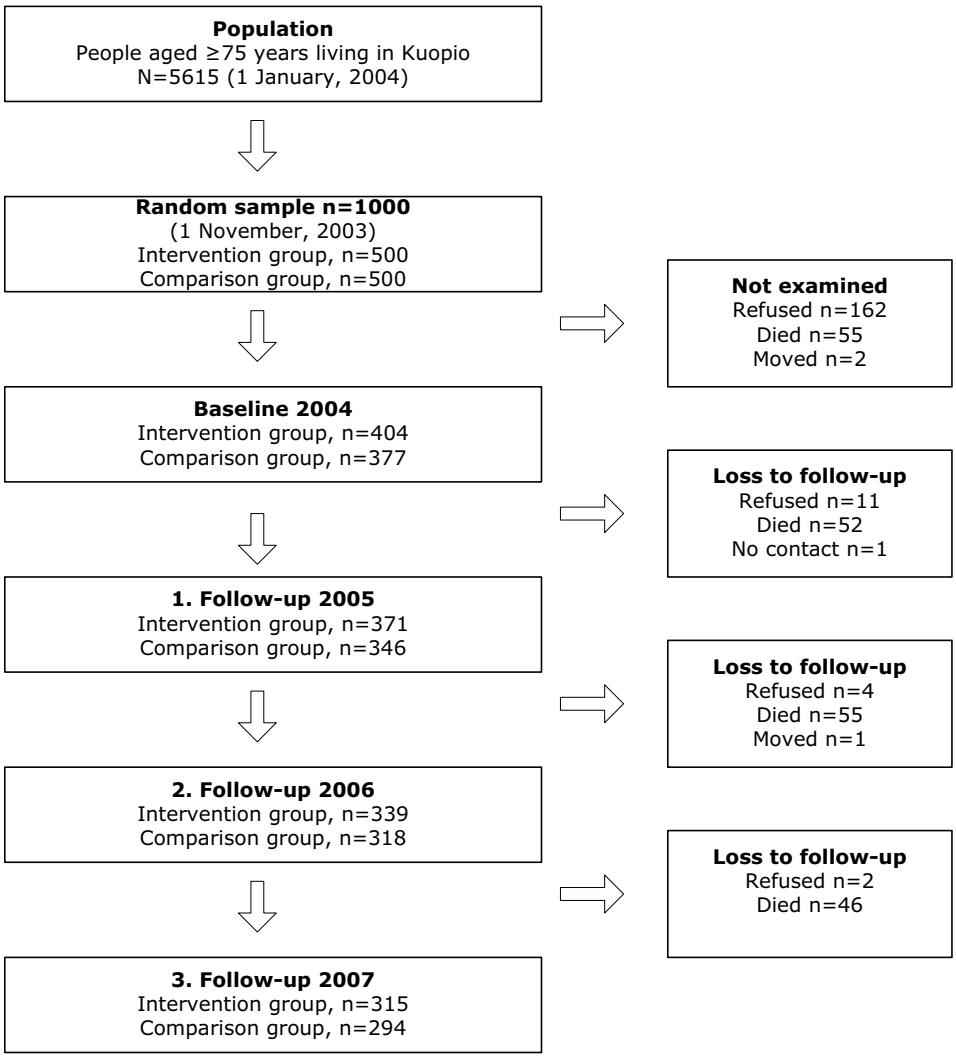

Figure 1. The flow chart of the GeMS Study

4.2 DATA COLLECTION

One of three trained nurses conducted annual, structured interviews for each participant to assess sociodemographic factors, health status and drug use. Sociodemographic factors included living situation (alone versus with someone else), years of education, and use of home-nursing services or other help. Health status included diagnosed diseases, self-rated health, and tests including the Mini-Mental State Examination (MMSE), the Geriatric Depression Scale (GDS15), and IADL scale. Participant self-reported diagnoses were verified from medical records from municipal health centers, home nursing service, local hospitals and the Kuopio University Hospital.

4.2.1 Medication exposure assessment

During the annual interviews by study nurses, participants were asked which prescription and over-the-counter drugs they used over a two-week period. Participants were asked to bring their prescription forms and drug packages to the interview. Patterns of drug use were also assessed in terms of regular and when-required drug use. A regular pattern of drug use was defined as a drug taken daily or at regular intervals. Drug use was defined as regular if participant took the drug ≥4 times a week. For long-acting intramuscular antipsychotics, regular use was considered when drug was taken at regular intervals from once-a-week to once-a-month. Drug use was considered when-required if there was an irregular pattern of use according to the participant's self-report. If a participant had a prescription from, drug package or medical record that suggested they took a drug that they did not self-report, then the nurse interviewer specifically asked about the use of this drug over the previous two weeks. Thus, medical records were used as one data source and as a basis for discussion with a participant on his or her actual drug use patterns.

4.2.2 Physical function tests

Physical function tests and interview about physical activity were conducted by two trained physiotherapists, and performed one-to-two weeks after each participant's nurse interview. The interview by the physiotherapist included an assessment of current physical activity (for example, Grimby scale), and problems in mobility. Medical records were also one data source in physiotherapist interview. The physical function testing was conducted in the outpatient clinic at the municipal health centre. The tests included mobility and balance tests, postural sway and muscle strength testing. If the participant was unable to visit the outpatient clinic, the measurements took place in the participant's home. In-home testing included only the grip strength test, and chair stands if a participant had a standard chair for the testing. Other tests were only conducted in the outpatient clinic to ensure a standard environment and reliability and validity of measurements.

4.2.3 Intervention and Comprehensive Geriatric Assessment

The intervention conducted by a multidisciplinary team was aimed at preventing disability among participants, and the CGA was an integral part of the intervention. The intervention was individually tailored, and consisted of a medical and a physical activity component. The medical component of the intervention included a structured clinical examination and medication assessment conducted by two physicians who were trainees in geriatrics. The physical activity component consisted of individually tailored physical activity counseling and an opportunity to participate in group-based muscle strength and balance training once a week at a gym that was supervised by physiotherapists. Participants in the intervention group also received advice from the other members of CGA team including dentists, ophthalmologist (only in 2006) and a nutritionist (Lampela et al. 2007, Rikala et al. 2011). The intervention focused on health and physical function related problems that a

participant had, including medical problems, medication-related problems, malnutrition, declined cognition, and declined physical health (Lihavainen et al. 2011).

One objective of the intervention was to identify and address the use of potentially inappropriate drugs, adverse drug events and drug-drug interactions (Lampela et al. 2011, Rikala et al. 2011). The assessment and optimization of medications was conducted by study physicians. Psychotropic drug use was one focus area of the medication review in the CGA (Rikala et al. 2011). The particular focus areas were: determination if there was current indication for psychotropic drug use, use of antipsychotics among participants with dementia but without current psychotic symptoms or aggression, sub-optimal use of antidepressants among those with depressive symptoms, regular and long-term benzodiazepine use, concomitant use of two or more psychotropic drugs, inappropriate doses, and potentially inappropriate use of specific drugs (tricyclic antidepressants for depression and use of long-acting benzodiazepines). In the intervention group, nurses acted as case managers organizing care and services, and giving counseling and support for family members.

Participants in both groups received standard care during the study. However, physicians referred participants in the intervention group to special health care if they identified a need for this. Thus, it is possible that after the baseline, the intervention group may have had more accurately diagnosed diseases than the comparison group.

In Study IV, the intervention and comparison groups were analyzed together. This was because the intervention did not impact the evolution of psychotropic drugs, and no differences in psychotropic drug utilization were observed between the intervention and comparison groups (Rikala et al. 2011). In addition, tests were conducted to observe the possible differences in the utilization patterns of sedative drugs during the study but none were found. Mortality rates between the groups were also similar. For these reasons, both intervention and comparison groups were analyzed together.

4.3 SEDATIVE LOAD

4.3.1 Calculation of sedative load

Sedative load was calculated according to the previously published Sedative Load Model (Linjakumpu et al. 2003, Linjakumpu et al. 2004). The Sedative Load Model considers four groups of drugs with sedative properties but only two groups are considered when assigning sedative ratings to drugs and calculating sedative load. The model was created by categorizing all drugs marketed in Finland between 1998 and 2001 according to their sedative potential. The categorization was based on consensus between a psychogeriatrician, a geriatrician and a physician specialized in pharmacoepidemiology. The basis of categorization was manufacturers' summaries of product characteristics.

Drugs in group one included primary sedatives and were assigned a sedative rating of 2 (Table 8). Drugs in group two included drugs with sedation as prominent side effect and preparations with a sedating component, and were assigned a sedative rating of 1. Group three included drugs with sedation as a potential side effect (e.g. acetyl-cholinesterase inhibitors, second generation antihistamines). Group-four included all other drugs with no known sedative properties. In Studies II–IV, only regularly used drugs were considered when sedative load was calculated. In Study I, two different sedative loads were calculated; regular sedative load (considering sedative ratings from regularly used drugs only), and total sedative load (considering both sedative ratings of regular and when-required drugs). In Study I, when-required drugs were assigned with a sedative rating of 0.5 regardless of whether they were group 1 or 2 sedative drugs. In addition, regular sedative load of the population was defined as the sum of sedative ratings at a population level considering regularly used drugs.

Sedative load was assessed in annual examinations during 2004-2007. For Studies I-III, only baseline sedative load was considered. In Study IV, exposure to drugs with sedative properties was defined as time-varying sedative load to take account on possible changes in drug use in each examination year.

Table 8. Drugs contributing to sedative load, according to the Sedative Load Model

Drug group	Examples
Group 1. Primary sedatives (sedative rating 2)	
Conventional antipsychotics (N05A)	phenothiazines, butyrophenones, thioxanthenes, sulpride, lithium
Anxiolytics (N05B)	benzodiazepines, hydroxyzine
Hypnotics and sedatives (N05C)	benzodiazepines, zopiclone, zolpidem, zaleplon, valerian, clometiazole
Antidepressants (N06AA, N06C)	
- tricyclic antidepressants, non-selective monoamine reuptake inhibitors	clomipramine, trimipramine, nortriptyline, doxepin, amitriptyline
- second generation antidepressants	mianserin
- combinations	amitriptyline with chlordiazepoxide or perphenazine
Group 2. Drugs with sedation as a prominent side effect or preparations with a sedating component (sedative rating 1)	
CNS (N)	
- opioids (N02A)	morphine, oxycodone, codeine, buprenorphine, tramadol, fentanyl, paracetamol with codeine
- antiepileptics (N03A)	hydantoin derivatives, carbamazepine and derivatives, valproic acid, gabapentin, clonazepam, lacosamide, lamotrigine, levetiracetam, pregabaline, tiagabine, topiramate, zonisamide
- anticholinergic anti-parkinson drugs	biperiden
- atypical antipsychotics	clozapine, olanzapine, quetiapine, risperidone, aripiprazole, ziprasidone
- SSRIs (N06AB)	fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram
- other second generation antidepressants	trazodone, nefazodone, mirtazapine, venlafaxine, milnacipran, duloxetine
- dopamine agonists (N04BC)	pramipexole, ropinirole, rotigotine, pergolide
- drugs for migraine, incl. psychotropics	meprobamate with ergot alkaloid, metoclopramide with ASA, triptans
Alimentary (A)	
- propulsives, antiemetics	metoclopramide, scopolamine
- antispasmodics with psychotropics	diazepam with glycopyrronium, chlordiazepoxide with klidin, oxazepam with ambutonium
Genito-urinary (G)	
- drugs for erection disturbances incl. psychotropics	meprobamate with testosterone and yohimbine (not on market anymore)
Musculo-skeletal (M)	
- NSAIDs	indometacin (with ethylmorphine), ibuprofen with codeine
- centrally acting muscle relaxants, incl. psychotropics	meprobamate or diazepam with kinin, orphenadrine, baclofen, tizanidine
Respiratory (R)	
- old antihistamines (in combinations)	cinnarizine or carbinoxamine with systemic nasal decongestants
- xanthenes	theophylline and its combinations
- antitussives with sedating components	bromhexine, ethylmorphine, codeine
- antiemetics or drugs for dizziness, incl. psychotropics	cyclizine (with diazepam), meclozine
Ophthalmologicals (S)	
- anticholinergic drops for eyes	scopolamine

CNS = central nervous system, SSRIs = selective serotonin reuptake inhibitor, NSAIDs = non-steroidal anti-inflammatory drugs, ASA = acetyl salisylic acid.
Adapted according to Linjakumpu et al. 2003, with additions made in Taipale et al. 2011 Drugs Aging

Sedative load was calculated by summing the sedative ratings for all drugs used by the participants according to the formula:

$$\text{Sedative load} = \sum_{k=1}^{n} SR_k$$

Where n stands for the number of drugs and SR_k indicates the sedative rating for drug k.

The Sedative Load Model was updated in Study I to include drugs that were marketed in Finland since the development of the original model. To update the model one clinical pharmacist reviewed the summary of product characteristics (SPCs) and research literature for all new drugs marketed in Finland from 2001 until the end of 2009. Based on these data a geriatrician, a geriatrician specialized in geriatric pharmacotherapy and two clinical pharmacists independently assigned sedative ratings for each new drug. The four member expert panel then met and any discrepancies were resolved through discussion. All new drugs were categorized using their Anatomical Therapeutic Chemical (ATC) code. As a result of this update, 15 new drugs were added to Group-two of the sedative load model: aripiprazole, ziprasidone, duloxetine, pramipexole, ropinirole, rotigotine, pergolide, clonazepam, lacosamide, lamotrigine, levetiracetam, pregabaline, tiagabine, topiramate and zonisamide (Table 8).

4.3.2 Drug classification

All drugs used by the participants were classified using the ATC classification system recommended by the World Health Organization (WHO). The ATC classification system is a hierarchical classification based on the organ or system on which they act and their therapeutic, pharmacological and chemical properties. The classification includes five different levels, from the organ or system (main group) to pharmacological/ therapeutic subgroups, and towards the chemical substance (fifth level).

For the purpose of calculating sedative load, the following definitions were made. 'Atypical antipsychotics' were defined as clozapine, quetiapine, olanzapine, risperidone, ziprasidone and aripiprazole. 'Conventional antipsychotics' were deemed to include all other drugs in ATC group N05A excluding lithium. 'Tricyclic antidepressants' were defined as ATC class, N06AA, 'SSRIs' as N06AB, and 'other antidepressants' as moclobemide and N06AX.

4.4 OUTCOME MEASURES

4.4.1 Balance and mobility tests (II)

Maximal walking speed (m/s) was measured over a 10 m distance. In all timed tests, time was taken using a stopwatch. Participants were allowed three meters for acceleration before the start line and then they were encouraged to walk as fast as possible within the confines of their current health. Participants wore their regular footwear and were allowed to use a walking aid in the walking speed and in the TUG test.

The TUG Test was used to assess both balance and basic mobility (Podsiadlo et al. 1991). The participants were instructed to stand up from a chair, walk for a distance of 3 m at maximal speed, turn, walk back, and sit down on the chair. The chair was a standard chair with armrests, and participants were allowed to use their arms for support and to assist in rising if needed. The time taken was used as a measure of performance.

The Berg Balance Scale is a test of balance rated by an observer (Berg et al. 1992). The BBS consists of 14 different balance tasks related to standing, reaching, bending, turning and transferring abilities. Each of the 14 items was scored on scale from 0 (incapable) to 4 (safe and independent) by physiotherapist. The overall test score from the BBS ranged from 0

(severely impaired) to 56 points (excellent balance). The score reflects a participant's ability to accomplish specific movements and the length of time each of the positions are held.

In the interview conducted by one of the study nurses, participants were asked to evaluate their ability to walk 400 meters on a four-point scale with the following options; "no", "not without help", "yes with difficulty but without help", or "yes". For the purposes of the analyses, the categories "not being able" and "not without help" were combined to be "no" and others were combined to "yes". Thus, the variable was treated as self-reported ability to walk independently 400 meters (yes/no).

4.4.2 Muscle strength tests (III)

Grip strength was measured using a Saehan dynamometer (Saehan Corporation, South Korea). Participants were allowed to make one maximal effort with both hands and the best result of these attempts was used in analyses. Grip strength was measured in kilograms.

Knee extension strength was measured using an adjustable dynamometer chair (Good Strength, Metitur Oy, Palokka Finland). Participants were tested on both legs and allowed to make three maximal efforts with both legs, and the best result of these six attempts was used in the analyses. Knee extension strength was measured in newtons.

The chair stands test was a modified version of Five Chair Rise test (Guralnik et al. 1994). The test assessed the ability to perform sit-to-stand and stand-to-sit transfer. Participants were instructed to stand up and sit down five times as fast as possible starting in the sitting position and stopping after the fifth rise. As a modification of the original test, hands were held free on the sides and participants were allowed to help with their hands if needed. Performance in the chair stands test was measured as the time taken to complete the test in seconds.

4.4.3 Mortality (IV)

Mortality data were obtained from the Social Insurance Institution of Finland. The SII registers are updated daily using the Population Information System maintained by the Population Register Centre of Finland. The date of death for each participant who died during the follow-up period was ascertained.

4.5 COVARIATES AND OTHER MEASURES

4.5.1 Sociodemographic characteristics

Self-reported years of education were categorized into two groups (0–6 and >6 years). Marital status was grouped as married, widowed, divorced or never-married. Loneliness was defined by asking that "how often do you feel lonely" (never, sometimes, often).

Alcohol use was defined using two different items; "do you use alcohol" (yes or no), and "do you use alcohol for medicinal purposes" (yes or no). A participant was considered an alcohol user if they answered yes to either question.

4.5.2 Health-related characteristics

Physical activity was assessed using a modified version of the Grimby scale (Grimby 1986). Participants were categorized as inactive (no other exercise, light walking 1–2 times a week), moderately active (light walking or other light exercise ≥3 times a week or moderate exercise 1–2 times a week), or active (moderate to vigorous exercise several times a week).

Self-rated health was determined with 5-point scale (from very poor to very good). For the purpose of the analysis, the categories "very poor" and "poor" were combined as "poor" and other categories were combined under single category "average or good".

The Mini-Mental State Examination was utilized to evaluate cognitive function (Folstein et al. 1975, Crum et al. 1993). MMSE scores <25 were considered indicative of cognitive impairment (Dahl et al. 2007).

Each participants' comorbidities were scored according to a modified version of the Functional Comorbidity Index (FCI) (Groll et al. 2005) which was developed to predict physical function in older people. The diagnoses that were included in the FCI were arthritis (rheumatoid arthritis and other connective tissue disorders), osteoporosis, asthma/ COPD, coronary artery disease, congestive heart failure, myocardial infarction, Parkinson's disease, stroke, diabetes mellitus, depressive symptoms (assessed using the Geriatric Depression Scale (Yesavage et al. 1983) with GDS scores ≥5 considered indicative of depressive symptoms), visual impairment, hearing impairment, and obesity (body mass index >30). For the purposes of the analyses, FCI was classified into 3 groups: 0, 1–2 and ≥3.

Dementia was diagnosed as Alzheimer's disease, vascular dementia or dementia due to other general medical conditions according to DSM-IV criteria (American Psychiatric Association 1994). Dementia with Lewy bodies was clinically diagnosed according to the core criteria published by McKeith et al (McKeith et al. 1996)

Performance in the IADLs was assessed by the 8-item scale developed by Lawton and Brody (Lawton and Brody 1969). The IADL scale includes activities such as using a telephone, shopping, making food, housekeeping activities, and ability to take responsibility for own medications and finance. For the purpose of the thesis, participants with IADL scores of 0–6 were defined as having impaired IADL whereas participants with scores of 7–8 were defined as having normal function.

4.6 STATISTICAL ANALYSIS

Data analyses were performed using SAS software (version 9.2, SAS Institute, Cary, NC, USA), and SPSS software version 17.0 (SPPS Inc, Chicago, Illinois, USA).

Characteristics of the study sample were summarized using means, percentages and standard deviations (SDs). Characteristics of participants were compared with chi-square test for categorical variables and analysis of variance (ANOVA) for continuous variables.

For Studies II–IV, sedative load was categorized as nonusers of sedatives (sedative load=0), those having a sedative load of 1–2 and those with a sedative load of ≥3. In Studies II and IV, subgroup analysis were conducted between nonusers of sedatives (sedative load=0) and users of sedatives (sedative load >0). In Study I, comparisons were made between those with sedative load ≥2 and those with sedative load from 0 to 1.

For Study I, logistic regression models were used to investigate the univariate and multivariate associations between sociodemographic and diagnostic characteristics and sedative load. Sociodemographic and health-related factors that were included in the multivariate analyses were age, gender, alcohol use, self-rated health, IADL, dementia, loneliness, and cardiovascular disease. These factors were selected based on previous research on factors associated with psychotropic drug use, and because of being significantly associated with sedative load of ≥2 in the univariate analysis. Two logistic regression models were computed: one with regular sedative load and another with total sedative load. The results of these models were expressed as ORs with 95% confidence intervals (CI).

For Studies II and III, unadjusted and adjusted analysis of covariance (ANCOVA) were performed to compare physical function outcome variables between nonusers of sedatives (sedative load=0) with those having a sedative load of 1–2 and those with a sedative load of ≥3. Models were adjusted for clinically important covariates that may influence the relationship between increasing sedative load and physical performance measures. These covariates were age (75–79, 80–84, ≥85 years), gender, education (0–6, >6 years), Grimby Scale, comorbidities using the modified FCI (0, 1–2, ≥3) and cognitive impairment (MMSE <25). A log 10 transformation was performed to improve the normality of the chair stands test distribution. For the chair stands test, the values presented are the back-transformed.

For Study II, unadjusted and adjusted logistic regression analyses were used to test the ability to walk independently 400 meters (yes, no) between nonusers of sedatives (sedative load=0) and users of sedatives (sedative load >0). Logistic regression analyses were reported using ORs and 95% CIs. Adjustments were made the same covariates as in the ANCOVA models.

For Study IV, differences in sedative drug use between intervention and control groups were measured using Mann-Whitney U test and calculating 95% confidence intervals for mean sedative loads in both groups. Both tests showed that there were no differences between the groups. A Wilcoxon signed rank test was used to show that among users of sedatives, the mean sedative load increased significantly from 2004 to 2007 in both groups. Thus, group status was not included in the Cox models.

For Study IV, Cox proportional hazards analysis was used to study sedative load and the corresponding risk of death. Sedative load was entered as time-dependent variable in the model. Individual exposure times were calculated for each participant according to their annual examination dates. The model was adjusted for the following covariates measured at the baseline: age (75–79, 80–84, ≥85 years), sex, FCI score (0, 1–2, ≥3), dementia, education (0–6, >6 years), and IADL score (0–6, 7–8). Deaths were ascertained from the SII until December 31, 2008 after which the analyses were censored. Participants were censored at the end of next year from their last examination so that they had the maximum possibility to participate in the following examination. The results of these models were expressed as hazard ratios (HRs) with 95% CIs.

4.7 ETHICAL CONSIDERATIONS

All participants or their proxies gave written informed consent to participate in the study. The study was approved by the Research Ethics Committee of the Northern Savo Hospital District, Kuopio, Finland. The study was conducted in accordance with World Medical Association Declaration of Helsinki (World Medical Association). Data collected in the GeMS Study was stored in a secure and locked file. Data analyses were performed using de-identified data only and all researchers signed data usage agreements with the University of Eastern Finland. Reports include only grouped data so that no individual participant can be identified.

5 Results

5.1 PREVALENCE OF SEDATIVE LOAD IN THE BASELINE

5.1.1 Description of the study sample

The majority of the participants were women (69%, n=486) (Table 9). The mean age of the 700 participants was 81.3 (SD 4.6) years (Table 10). The prevalence of cognitive impairment was 25%, and 36% had difficulties in IADL.

Table 9. Characteristics of the study participants according to sedative load groups in the baseline of the GeMS Study

	All % (n)	**Sedative load 0** % (n)	**Sedative load 1–2** % (n)	**Sedative load ≥3** % (n)	**p-value**[a]
Age					0.004
75–79 y	49 (346)	54 (267)	38 (56)	40 (23)	
80–84 y	31 (215)	29 (142)	35 (51)	38 (22)	
≥85 y	20 (139)	17 (86)	27 (40)	22 (13)	
Women	69 (486)	66 (324)	80 (118)	76 (44)	0.002
Education ≤6 y	51 (346)	50 (240)	50 (72)	63 (34)	0.173
IADL score ≤6	36 (252)	30 (146)	46 (67)	67 (39)	<0.001
Poor self-rated health	15 (103)	10 (51)	24 (35)	30 (17)	<0.001
Loneliness					<0.001
Often	4 (32)	3 (13)	8 (11)	14 (8)	
Sometimes	32 (225)	28 (138)	41 (60)	47 (27)	
Never	63 (441)	69 (343)	52 (76)	39 (22)	
Physical activity					<0.001
Inactive	36 (245)	31 (150)	44 (62)	60 (33)	
Moderate or active	64 (429)	69 (328)	56 (79)	40 (22)	
MMSE <25	25 (170)	20 (99)	30 (44)	47 (27)	<0.001
GDS ≥5	8 (55)	5 (25)	12 (18)	21 (12)	<0.001
FCI					0.001
0–1	11 (77)	13 (66)	5 (7)	7 (4)	
2	45 (318)	47 (230)	48 (70)	31 (18)	
≥3	44 (305)	40 (199)	48 (70)	62 (36)	
Dementia	16 (109)	12 (61)	20 (30)	31 (18)	<0.001
Unable to walk independently 400m	46 (324)	46 (229)	47 (69)	45 (26)	0.963

[a] Categorical variables were tested with chi square test, comparison between sedative load groups 0, 1–2 and ≥3.

IADL=Instrumental Activities of Daily Living, MMSE=Mini-Mental State Examination score, GDS=Geriatric Depression Scale score, FCI=Functional Comorbidity Index score, y=years

Table 10. Characteristics of the study participants according to sedative load groups in the baseline of the GeMS Study

	All	**Sedative load 0**	**Sedative load 1-2**	**Sedative load ≥3**	**p-value[a]**
	Mean value ±SD	Mean value ±SD	Mean value ±SD	Mean value ±SD	
Mean age	81.3 (4.6)	80.8 (4.4)	82.4 (4.7)	82.5 (5.6)	<0.001
FCI mean	2.6 (1.7)	2.5 (1.7)	2.9 (1.8)	3.4 (1.7)	<0.001
Mean umber of drugs	4.9 (3.2)	4.1 (2.7)	6.4 (3.1)	8.6 (3.6)	<0.001
Mean TUG time, s	13.9 (9.3)	12.5 (8.7)	16.9 (10.2)	17.6 (9.4)	<0.001
Mean walking speed, m/s	1.3 (0.4)	1.3 (0.4)	1.1 (0.4)	1.0 (0.4)	<0.001
Berg Balance Scale, mean points	47.9 (9.1)	49.2 (8.5)	45.1 (9.5)	43.5 (10.9)	<0.001
Mean grip strength, kg	20.0 (10.2)	21.3 (10.4)	17.5 (9.1)	14.9 (8.7)	<0.001
Mean knee extension strength, N	297.6 (110.3)	310.6 (111.5)	257.2 (95.6)	267.2 (104.5)	<0.001
Mean chair stands test time, s	16.7 (7.8)	15.8 (6.6)	19.3 (10.8)	19.6 (7.0)	<0.001

[a] Continuous variables were tested with analysis of variance, and are presented as means (±SD), comparison between sedative load groups 0, 1–2 and ≥3.
N=Newtons, TUG=Timed Up&Go test, FCI=Functional Comorbidity Index score.

5.1.2 Use of drugs with sedative properties

Of 700 participants, 29% were users of drugs with sedative properties. Sedative load of 1–2 was present in 21% (n=147) of the participants, and 8% (n=58) had a sedative load of ≥3 at the baseline of the study.

Users of drugs with sedative properties were older, more likely to be women, to have depressive symptoms, and have cognitive impairment than nonusers of drugs with sedative properties (Table 9). They also had higher number of comorbidities, poor self-rated health status, and felt themselves more often lonely.

Mobility and balance test results were poorer among those having a sedative load of 1–2 and ≥3 (Table 10). They also had lower muscle strength test results compared to nonusers of sedative drugs.

The most frequently used primary sedatives (group 1) were hypnotics (15%) and conventional antipsychotics (3%) (Table 11). SSRIs (5%) and other antidepressants (3%), mainly mirtazapine, were most frequently used drugs with sedation as a prominent side effect (group 2). Of the participants, 21% used one or more group 1 drugs, and 14% used at least one group 2 drug.

Table 11. Drug classes contributing to sedative load at the baseline of the GeMS Study. Cross-sectional point prevalence of sedative drug use in 2004 (n=700) and in 2007 (n=581)

Drug group	**Users 2004 % (n)**	**Users 2007 % (n)**	**Change in %**
Conventional antipsychotics	3.4 (24)	0.9 (5)	-68
Tricyclic antidepressants	1.7 (12)	1.2 (7)	-29
Anxiolytics	3.3 (23)	3.4 (20)	+3
Hypnotics	14.6 (102)	14.1 (82)	-3
Atypical antipsychotics	2.6 (18)	4.7 (27)	+80
SSRIs	4.6 (32)	4.1 (24)	-11
Other antidepressants	3.4 (24)	6.9 (40)	+103
Antiepileptics	2.1 (15)	2.1 (12)	0
Opioids	1.9 (13)	3.3 (19)	+74

SSRIs=selective serotonin reuptake inhibitors

5.2 FACTORS ASSOCIATED WITH USE OF DRUGS WITH SEDATIVE PROPERTIES (I)

Factors associated with sedative load were investigated in two models; one with regular sedative load (only from regularly used drugs) and total sedative load (including regular and when-required drugs). In the multivariate analyses, factors associated with a regular sedative load of ≥2 were female sex (OR 1.65 [CI 1.02–2.67]), poor self-rated health (OR 2.06 [CI 1.25–3.38], and impaired IADL (OR 1.89 [CI 1.18–3.01]). Regular sedative load ≥2 was also associated with loneliness, and strongest association was found between sedative load and often feeling lonely ('sometimes lonely' OR 1.77 [CI 1.17–2.68], 'often lonely' OR 4.72 [CI 2.15–10.4]) (Table 12).

The same factors were significantly associated with having a total sedative load of ≥2 after inclusion of when-required drugs in the model (Study I).

Table 12. Factors associated with regular sedative load among the GeMS Study participants

	Unadjusted OR (95% CI)	Adjusted OR (95%CI)
Age, years		
75–79	1.00	1.00
80–84	1.60 (1.06–2.42)	1.37 (0.87–2.15)
≥85	2.21 (1.40–3.47)	1.26 (0.74–2.13)
Gender		
Male	1.00	1.00
Female	1.73 (1.14–2.63)	1.65 (1.02–2.67)
Alcohol use		
No	1.00	1.00
Yes	0.68 (0.47–0.98)	0.88 (0.59–1.32)
Self-perceived health		
Average or good	1.00	1.00
Poor	3.02 (1.94–4.70)	2.06 (1.25–3.38)
IADL		
7–8	1.00	1.00
0–6	2.27 (1.58–3.26)	1.89 (1.18–3.01)
Dementia		
Not diagnosed	1.00	1.00
Diagnosed	1.80 (1.15–2.82)	1.11 (0.64–1.93)
Loneliness		
Never	1.00	1.00
Sometimes	2.26 (1.54–3.31)	1.77 (1.17–2.68)
Often	6.70 (3.19–14.09)	4.72 (2.15–10.40)
Cardiovascular disease		
No	1.00	1.00
Yes	1.79 (1.09–2.93)	1.50 (0.87–2.56)

Factors included in the adjusted analyses were age, gender, alcohol use, self-perceived health, IADL, dementia, loneliness and cardiovascular disease. Total number of participants in the models was 674. OR=odds ratio, CI=confidence interval, IADL=Instrumental Activities of Daily Living, COPD=chronic obstructive pulmonary disease

5.3 PHYSICAL FUNCTION MEASURES ASSOCIATED WITH THE USE (II, III)

5.3.1 Mobility and balance (II)

Poor performance in all balance and mobility outcomes were significantly associated with higher sedative load ($p<0.05$) in the unadjusted analyses. The unadjusted mean scores for walking speed, TUG and BBS were poorer among women than among men (Table 13). In the unadjusted logistic regression model, self-reported ability to walk independently 400 m was associated with sedative load >0 (OR 2.85 [CI 1.58-5.15].

In the adjusted analyses, participants with a sedative load of >0 had poorer performances on walking speed, TUG and Berg Balance scale compared to participants with sedative load=0 (Figure 2). None of the outcome measures was able to differentiate between those with sedative load of 1-2 and those with sedative load ≥3. After adjusting for covariates, the association between sedative load of >0 and self-reported ability to walk independently 400 meters was no longer significant (OR 1.47 [CI 0.71–2.06]).

Table 13. Unadjusted outcome means across sedative load groups by gender

Outcomes	**SL=0**	**SL=1–2**	**SL≥3**	**p-value**
Walking speed				
men (n=177)	1.50±0.04	1.28±0.09	1.15±0.14	0.007
women (n=396)	1.25±0.02	1.02±0.04	0.93±0.07	<0.0001
TUG				
men (n=191)	11.0±0.64	15.8±1.45	15.5±2.36	0.004
women (n=438)	13.3±0.55	17.20±0.91	18.20±1.60	0.0001
Berg balance test				
men (n=193)	50.20±0.64	45.14±1.50	46.6±2.39	0.005
women (n=446)	48.61±0.53	45.04±0.89	42.61±1.50	<0.0001

Outcomes are presented as mean ± standard error.
TUG=Timed Up&Go test, SL=sedative load

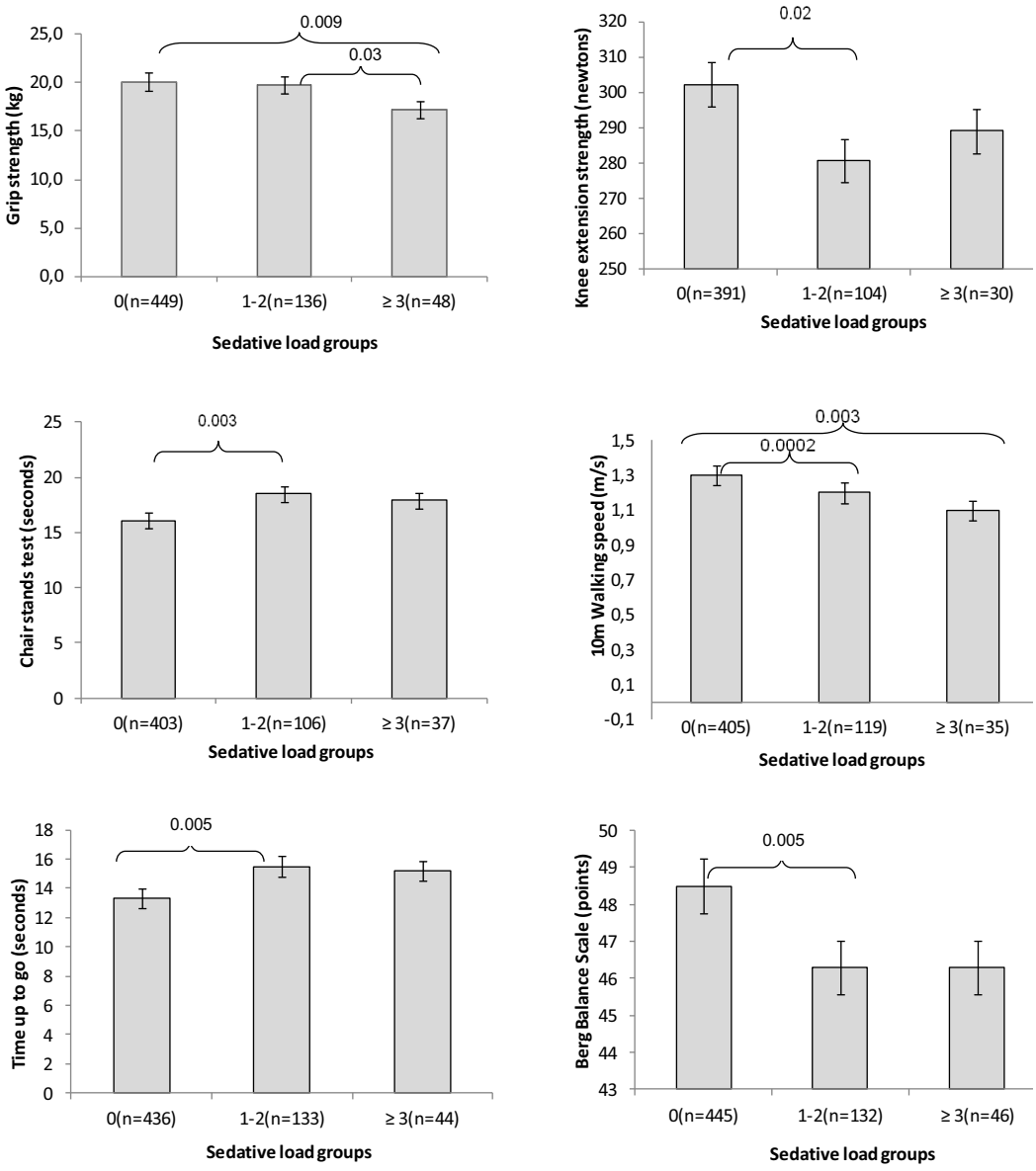

Figure 2. Adjusted means of balance, mobility and muscle strength measures according to sedative load groups. Models are adjusted for age, sex, education, cognitive impairment, FCI, and physical activity. Error bars represent SE. Parenthesis drawn from sedative load (SL)=0 to SL ≥3 represent difference between those two groups

5.3.2 Muscle strength (III)

In the unadjusted analyses, grip strength, knee extension strength and chair stands test results were associated with sedative load >0 (Table 14).

Participants with a sedative load >0 had poorer performance in grip strength and chair stands test compared to participants with sedative load=0 ($p<0.05$) in the adjusted analyses (Table 14, Figure 2). In the knee extension strength, significant difference was observed between people with sedative load of 1–2 compared to nonusers of drugs with sedative properties ($p=0.02$). In the adjusted analyses, grip strength was the only outcome measure that differentiated between those with sedative load of 1–2 and those with sedative load ≥3 ($p=0.03$).

Table 14. Unadjusted and adjusted analysis of covariance to compare means of muscle strength measures with the exposure to the drugs contributing to sedative load (SL). Means with 95% confidence intervals are displayed

Outcomes	SL=0	SL= 1–2	SL≥3	p-value
Grip strength (kg)				
unadjusted	21.3 (20.4, 22.2)	17.5 (15.9, 19.2)	14.9 (12.2, 17.7)	<0.001
adjusted	20.1 (19.5, 20.8)	19.8 (18.5, 21.0)	17.2 (15.1, 19.3)	0.03
Knee extension strength (newtons)				
unadjusted	310.6 (300.0, 321.3)	257.2 (236.3, 278.0)	267.2 (229.6, 304.8)	<0.001
adjusted	302.2 (294.1, 310.2)	280.7 (264.9, 296.5)	289.1 (259.6, 318.5)	0.06
Chair stands test (seconds)*				
unadjusted	14.9 (14.3, 15.3)	17.5 (16.4, 18.7)	16.6 (17.2, 20.7)	<0.001
adjusted	15.2 (14.7, 15.6)	16.8 (15.8, 17.8)	16.9 (15.3, 18.7)	0.003

*Variable log10 transformed after analysis.

5.4 LONGITUDINAL SEDATIVE LOAD (IV)

From baseline examination to the final examination in 2007, the sample decreased from 700 persons to 581 persons (Table 15). The prevalence of sedative drug use increased during the study years, from 29% to 36%.

Table 15. Sedative use during years 2004 to 2007 in the GeMS Study population, home-dwelling (n=700) at the baseline

	2004 n=700		**2005** n=656		**2006** n=621		**2007** n=581	
	%	n	%	n	%	n	%	n
Nonusers of sedatives	70.7	495	70.0	459	66.3	412	63.9	371
Users of sedatives	29.3	205	30.0	197	33.7	209	36.1	210
1–2	21.0	147	22.1	145	24.3	151	24.4	142
≥3	8.3	58	7.9	52	9.3	58	11.7	68
Women using sedatives	33.3	162	33.7	155	37.4	162	38.8	158
Men using sedatives	20.1	43	21.4	42	25.0	47	29.9	52
Age groups using sedatives								
75–79	22.8	79	21.6	72	26.5	86	29.7	92
80–84	34.0	73	36.4	72	39.5	73	39.9	69
≥85	38.1	53	42.4	53	44.6	50	50.0	49

Drug utilization patterns changed during the follow-up (Table 11). The proportion of hypnotic and anxiolytic use remained the same in 2004 and 2007. Conventional antipsychotic use decreased from 3% to 1%, and atypical antipsychotic use increased from 3% to 5%. Use of other second generation antidepressants (mainly mirtazapine) increased from 3% to 7%. The proportion of opioid users increased from 2% to 3%.

The mean sedative load among the study participants increased from 0.67 to 0.83 during the follow-up period (Study IV). Women and older age groups used sedative drugs more frequently than men or younger age groups (Table 15). The largest increase in the proportion of sedative users during the study period was among men (from 20% to 30%) and among persons aged 85 years or more (from 38% to 50%).

5.5 SEDATIVE LOAD AND MORTALITY (IV)

There were 159 (22.7%) baseline participants who died prior to December 31, 2008. The unadjusted HR for risk of death associated with time-dependent sedative load were 1.40 (CI 0.98–2.01) for sedative load 1–2 and 1.88 (CI 1.20–2.95) for sedative load ≥3.

When adjusting for age and gender, sedative load was no longer associated with increased mortality (sedative load 1–2 HR 1.23 [CI 0.87–1.81], sedative load ≥3 HR 1.53 [CI 0.96–2.41]). In the fully adjusted model, sedative load was not associated with risk of death (sedative load 1–2 HR 1.12 [CI 0.76–1.64], sedative load ≥3 HR 0.92 [CI 0.55–1.56]) (Table 16). In this adjusted model, only age and IADL score 0–6 were associated with a risk of death. The main factors that mediated the association between sedative load and death were the IADL score, diagnosis of a dementia, and older age.

Table 16. Sedative load and adjusted risk of death

Variable	HR	95% CI
Sedative load, time-dependent[a]		
0	ref	
1–2	1.12	0.76–1.64
≥3	0.92	0.55–1.56
Age, y		
75–79	ref	
80–84	1.66	1.10–2.51
≥85	2.55	1.65–3.97
Gender		
women	ref	
men	1.13	0.78–1.64
Education, y		
>6	ref	
0–6	0.93	0.67–1.30
IADL score		
7–8	ref	
0–6	2.01	1.35–2.98
FCI		
0	ref	
1–2	0.77	0.42–1.44
≥3	1.30	0.71–2.37
Dementia		
no	ref	
yes	1.45	0.96–2.20

[a] Time-dependent sedative load, other covariates are measured at the baseline.
FCI= Functional Comorbidity Index, IADL= Instrumental Activities of Daily Living, y=years

6 Discussion

6.1 STUDY POPULATION AND DATA COLLECTION

6.1.1 Study population

This thesis is based on data collected as part of the GeMS Study which was a randomized population-based study. The use of random population-based sample meant that it was likely to be representative of the target population. Thus, the results are likely to be generalizable to older people in the municipality of Kuopio, Finland. The results are also likely to have a high degree of generalizability to older people in Finland because of drug reimbursement system that is the same for all people across the country (Bell et al. 2007, Furu et al. 2010). In addition, Finland is ethnically homogenous and health care provided by municipalities is organized according to a national framework (Ministry of Social Affairs and Health 2008). The study may have limited generalizability to countries with different patterns of prescribing and primary health care systems.

The response rate (78%) in the GeMS Study can be considered good. Analyses also suggested that the characteristics of participants and non-participants were similar. For those persons who refused or were unable to participate to the study, the mean age and gender distribution matched well with participants. These factors support the generalizability of the results. In clinical studies, response rates over 70% are traditionally considered good (Jesson 2001).

In the thesis, persons living in institutional care were excluded. The main reasons were that persons in institutional care typically have higher exposure to drugs with sedative properties, different determinants of drug use, and different predictors of functional disability compared to those living in community-based settings (Rigler et al. 2004, Van Rensbergen & Nawrot 2010, Haasum et al. 2012).

6.1.2 Study protocol

Studies I–III were cross-sectional whereas Study IV was longitudinal. Cross-sectional data do not allow determination of causality. The results of the cross-sectional studies should be interpreted cautiously. Drugs with sedative properties may have been selectively prescribed to participants at higher risk of impaired balance, mobility and muscle strength. Adjustments were made for confounders that were considered clinically important but the possibility of residual confounding cannot be excluded

The study protocol was based on interviews conducted by three trained nurses. It was designed to assess drugs that participants were actually using rather than drugs intended for use. The use of nurse interviews to assess drug use, therefore, represented an advantage over the use of prescribing or dispensing records (Lau et al. 1997, Rikala et al. 2010). During the interview, medical records of each participant were available to study nurse and drug use recorded in the medical record but not self-reported by the participant was specifically enquired about. Recall bias was minimized by asking participants to take drug packages and prescription forms to the interview. In the interview, it was also possible to distinguish between drugs that were taken regularly and drugs that were taken on when-required basis. This was especially important in case of psychotropic drugs which are often prescribed on when-required basis but may actually be used regularly (Baker and Oleen 1988). However, if a participant was unwilling to report use of a drug and it was prescribed by a private practitioner, it was not possible to determine its use.

The GeMS Study was a randomized comparative study and included an intervention, namely Comprehensive Geriatric Assessment. The intervention included an examination by two physicians who were trainees in geriatrics, and thus, there may be some differences

between intervention and comparison groups in terms of diagnosed diseases. This was because physicians referred participants randomized to the intervention group to special health care if they identified a need for this. In addition, study nurses acted as case managers for participants and their families in the intervention group, and provided counseling and support. However, regardless of their study group allocation, all participants continued to receive standard care during the GeMS Study. Although one aim of the medication assessment was to review psychotropic drug use the intervention did not have effect on the utilization of psychotropic drugs (Rikala et al. 2011). The intervention was effective in terms of optimizing physical function (Lihavainen et al. 2011) but only baseline data were used in Studies II and III in this thesis. These data were collected before the intervention began. The interventions targeted at improving physical function and reducing inappropriate drug use could have potentially impacted mortality of the intervention group. However, mortality between the groups was found to be similar. This may have been because the annual examination of the comparison group also served as a form of intervention. If the need for immediate care was identified during the annual examinations, then a participant in the comparison group was guided to appropriate health services.

6.2 SEDATIVE LOAD MODEL

The Sedative Load Model is a comprehensive and previously published classification of drugs with sedative properties (Linjakumpu et al. 2003, Linjakumpu et al. 2004). The model was developed in Finland, and before Study I, it was updated with drugs that came onto the market after the publication of the original model. These updates were published in Study I of this thesis. Thus, the model can be considered comprehensive in terms of the drugs used by the GeMS Study participants. Furthermore, the model took into account the use of multiple drugs with sedative properties. This was important because in 'real-life' settings older people often use multiple drugs with sedative properties (Linjakumpu et al. 2004, Jyrkkä et al. 2006, Hilmer et al. 2007, Hanlon et al. 2009)

Compared to other metrics that measure the cumulative effect of taking multiple drugs with sedative properties, the Sedative Load Model is most comprehensive in terms of the drugs and drug classes that are included (Taipale et al. 2010, Table 1). The Sedative Load Model also includes drugs for somatic disorders. Besides the drug classes considered, the cumulative methods differ in terms of sedative ratings assigned to each drug, the inclusion or exclusion of drug dose in the model and each model's likely ease of use in clinical practice. In these models, sedative ratings are assigned by consensus, and were not previously validated which is a limitation of the Sedative Load Model.

One possible limitation of the model is that it does not include doses of drugs. The presence of dose-response relationship is commonly regarded as evidence for causality of an ADR (Naranjo et al. 1981). However, there is a lack of evidence from clinical trials to inform appropriate drug dosing in people aged 75 years and older including sedative drugs (Hilmer et al. 2011). Thus, choosing "reference doses" for metrics that assess the cumulative effect of drug burden is problematic. Furthermore, different indications may be treated with different doses of a drug, and this is a difficult factor to incorporate into the metrics. Interestingly, a study utilizing the Drug Burden Index found similar associations with impairments in physical function as was found with sedative load among the GeMS Study participants (Gnjidic et al. 2011). The Drug Burden Index also includes doses of drugs. It is not known to what extent the similarities in findings between DBI and sedative load extend to other study samples.

In this thesis, when-required drugs were not considered when calculating sedative load in Studies II–IV. In Study I, factors associated with the use of drugs with sedative properties did not change when including when-required drugs in the analyses. Similarly,

in the development of DBI the inclusion of when-required drugs in the analyses had only minimal effect on the associations between DBI and physical and cognitive function, and thus, DBI does not consider when-required drugs (Hilmer et al. 2007). In the GeMS Study, the specific frequency of when-required drug use was not known, or it was less than four times a week. Thus, inclusion of when-required drugs might have produced an overestimation of sedative effects of drugs and associations towards the null. For these reasons, when-required drugs were not considered in Studies II–IV. As a consequence, sedative loads reported in the thesis may be underestimation of total drug use.

In this thesis, sedation is defined as subjective feelings of drowsiness and sleepiness, and decreased psychomotor functioning. Psychomotor functioning includes speed of processing in the CNS, and also aspects of attention and memory. These are also related to each other, because poor attention decreases speed of processing or increases mistakes. SSRIs are often considered as non-sedating, but they have been shown to impair cognitive and psychomotor processing although to a lesser extent than benzodiazepines (Hindmarch 2009). In addition, Hindmarch analyzed cognitive toxicity of different psychotropic drugs, and found that SSRIs possessed the largest intraclass variation.

The Sedative Load Model does not include past use of sedative drugs. This may be a limitation although the importance of past use of sedative drugs on physical function has not been widely studied. In a study by Gray and coworkers, long-term benzodiazepine use was associated with decline in physical function but past use was not (Gray et al. 2003). Impaired cognition associated with benzodiazepines has been shown to resolve after withdrawal of these drugs but some impairments remain in comparison to never-users (Barker et al. 2004). Past use of sedative drugs might have an impact on physical function decline if sedative drug use caused physical inactivity. Physical inactivity has been associated with decreased muscle strength (Rantanen et al. 1999, Goodpaster et al. 2008). It is possible to regain muscle strength but it requires regular muscle strength training or other physical activity. Thus, without an increase in physical activity after ceasing sedative drugs, the impairments in muscle strength may persist. In the GeMS Study, there were no data on duration of drug use or past use of drugs at the baseline.

Study IV included prevalent users of sedative drugs without knowledge of the duration of drug use. This introduces the possibility that the study sample comprised a group of survivors. If these drugs would have an impact on mortality at the start of the treatment, then this study design may not reveal an increased risk of death. However, there are also problems in alternative data sources, i.e. prescription registers, in terms of classification of exposure to sedative drugs. Using prescription registers, incident use could be determined according to the day that a drug was first dispensed. However, this could lead to misclassification because use of the drug may not have been started at that day, or started at all (Pit et al. 2008, Noize et al. 2009). Prescription registers do not include data on non-adherence to drug use. Furthermore, prescription registers typically include limited data on comorbidities that analyses regarding mortality hazard should be adjusted for (Furu et al. 2010). Interview data verified from medical records has an advantage over prescription registers due to knowledge about which drugs are actually used and which diagnosed diseases participants actually have. In addition, in the GeMS Study the group of sedative never-users decreased during the study period which indicates that all users were not long-term users.

One limitation of the Sedative Load Model is that drug groups included and rated with sedative rating have intraclass variation in regard to sedative potential. Intraclass variation of SSRIs was discussed above, but there is also variation in sedative potential of conventional and atypical antipsychotics. In future studies, the possibility to define subgroups within the major drug groups should be considered. Another possibility could be to use a measure to rate individual drugs based on their sedative potential. This could be done utilizing proportional impairment ratios (PIRs) to summarize data from placebo-controlled psychometric tests with several aspects of cognitive and psychomotor function

(Hindmarch 2009). The PIR method has been used to rate sedative potential and cognitive toxicity of psychotropic drugs and antihistamines among healthy young volunteers (McDonald et al. 2008, Hindmarch 2009). It would be worth studying the correlation between impairment ratios in younger and older people. Furthermore, the impact of comorbidities on sedative potential could be investigated. One future objective could be to investigate does subjective or objective sedation test results correlate with sedative load of a participant.

6.3 DEFINITIONS AND MEASUREMENTS

6.3.1 Comorbidities and mortality

Participant self-reported diagnoses were complemented with data obtained from the Finnish National Prescription and Special Reimbursement Registers maintained by the Social Insurance Institution of Finland (SII) (Furu et al. 2010). The Finnish Prescription Register is a nationwide claims database which includes information on all reimbursed drug purchases in Finnish community pharmacies. The Special Reimbursement Register includes people who are entitled to receive reimbursements above the basic refund level. Receiving a higher level of refund is based on diagnoses and a certificate from a physician fulfilling explicit criteria established by the SII. In the GeMS Study, medical records were present at the nurse interview, physiotherapist interview, and examination by physician. By combining these data sources it was ensured that diagnostic data were complete.

To adjust for comorbid diseases in Studies II–IV, the Functional Comorbidity Index was utilized (Groll et al. 2005). The FCI is a previously validated index that takes into account medical conditions that have been shown to predict physical function in older persons. However, other comorbidities not included in the FCI and undiagnosed diseases may also have impacted the association between sedative load and physical function. In Study IV, other diseases affecting mortality were considered. As a result, dementia was included in the Cox proportional hazards models but there were a too small number of cases with active cancer to be included in the analysis. One limitation with the FCI is that it does not take into account disease severity which may also affect the associations. Thus, confounding by indication cannot be ruled out.

6.3.2 Physical function measures

Physical function tests were conducted by one of two trained physiotherapists. Balance and mobility tests included walking speed, TUG and Berg Balance scale which have been previously utilized and validated among older people (Podsiadlo et al. 1991, Berg et al. 1992, Montero-Odasso et al. 2005). Measurements were performed in standardized circumstances, and by two trained physiotherapists who encouraged participants to do their best in the tests.

The participation rate in balance, mobility and muscle strength tests varied from 75% to 90%. When considering persons aged 75 years and older, these participation rates can be considered good. Reasons for nonparticipation in physical function testing were mainly related to difficulties in mobility and transporting to health centre to attend the testing. Most of the performance-based tests (walking speed, TUG, BBS and knee extension strength) could not be performed in the participant's home.

Muscle strength tests utilized in Study III were grip strength, knee extension strength and chair stands test which also includes aspects of mobility and balance. Of these tests, grip strength is the most widely used muscle strength tests among older people, and it has been shown to predict numerous functional outcomes, including an increased risk of fractures and cognitive decline (Cooper et al. 2011). Knee extension strength and chair stands test both describe function of lower extremities which is important in mobility and

balance, and in active independent living. In addition, muscle strength tests were conducted by two trained physiotherapists which is strength of the study.

6.4 DISCUSSION OF THE RESULTS

6.4.1 Prevalence of use of drugs with sedative properties (I)

At the baseline of the GeMS Study, 29% of the participants used one or more drugs with sedative properties. When considering when-required drugs, the prevalence was 45%. In a study by Linjakumpu and coworkers in 1998–1999, 40% of community-dwelling older people aged ≥64 years used ≥1 drugs with sedative properties (Linjakumpu et al. 2004). In that study, when-required drug use was also included and thus, prevalence is comparable to Study I. There are no other studies of sedative load conducted among community-dwelling persons to compare these current results.

Studies among older people living in residential aged care and long-term care facilities have reported higher prevalences of sedative drug use compared the GeMS Study (Taipale et al. 2009, Parsons et al. 2011). In Northern Ireland, the prevalence of sedative drug use was 67% among persons with dementia (Parsons et al. 2011). In Finland, 85% of residents of long-term care facilities in Helsinki were reported to use at least one drug with sedative properties (Taipale et al. 2009). It is somewhat controversial because often the frailest older people live in the care facilities. There may also be differences between countries and treatment cultures but the lack of studies prevents international comparison.

The prevalence of sedative drug use measured with other methods to quantify cumulative exposure to drugs with sedative properties has reported lower utilization rates among community-dwelling older people. The prevalence of the sedative component of the DBI was 13–16% of community-dwelling participants (Table 2). Sedative drug use according to CNS drug model was 14% of the participants. The differences may be explained by fewer drug classes included in these models. However, the prevalence of sedative drug use in the GeMS Study is higher compared to studies with DBI and CNS drug model because the prevalence of hypnotic users was 15%. Psychotropic drug use has been reported to be higher in Finland compared to other Nordic countries among community-dwelling persons (Linjakumpu et al. 2002).

The most frequently used drugs with sedative properties were hypnotics. These were used by 15% of the participants were using. This was a similar prevalence to that reported by Linjakumpu et al. (Linjakumpu et al. 2002) although in Linjakumpu's study when-required drug use was also included. Use of hypnotics among community-dwelling Finns did not decrease between the studies in 1998-99 (Linjakumpu et al. 2002) and 2004 (Study I).

The prevalence of anxiolytic use was 3% at the baseline of the GeMS Study whereas it was reported to be 10% among community-dwelling participants in Lieto in 1998–99 including when-required drug use (Linjakumpu et al. 2002). The difference may be related to decreased use of anxiolytics among community-dwelling older people or variations in local treatment cultures (Lieto compared to Kuopio). However, the difference is most likely explained by the inclusion of when-required anxiolytic use in the study by Linjakumpu et al. because anxiolytics are often used on when-required basis rather than regularly. In long-term care facilities anxiolytics were the most prevalent sedative drug class in 2003 (Taipale et al. 2009), whereas hypnotics were the most common drugs among community-dwelling samples (Study I, Linjakumpu et al. 2002).

Factors associated with sedative load in the multivariate analyses included female gender. Linjakumpu et al. reported a similar finding in their study. This may reflect gender differences in healthcare utilization behavior and prescribing patterns which has been reported for psychotropic drug use (Gleason et al. 1998, Voyer et al. 2004). However, sedative load was not associated with age in the adjusted model which is in contrast to the previous study by Linjakumpu et al. In the adjusted model, IADL and gender had the most

prominent impact on the association between sedative load and age. This provides an explanation for the lack of association between sedative load and age.

Impaired IADL was associated with use of drugs with sedative properties. Linjakumpu et al. did not measure IADL in their study but they reported that sedative load was associated with difficulties or dependence in mobility (Linjakumpu et al. 2004). The association between IADL and sedative load could reflect acute sedation experienced by the participants which infers their attention, psychomotor function and reaction time which are important in complex tasks of daily living like shopping and taking care of financial issues. However, it is also possible that the association reflects drug channeling bias.

Loneliness was strongly associated with sedative load in Study I. Loneliness may be associated with depressive symptoms, and in the previous study of sedative load, the association between sedative load and depressive symptoms was reported (Linjakumpu et al. 2004). In both Study I and in Linjakumpu's study, loneliness and depressive symptoms were variables with the highest adjusted odds ratios in the multivariate models. Use of benzodiazepines and also other psychotropic drugs have been associated with depressive symptoms in several studies (Dealberto et al. 1997, Blazer et al. 2000, Carrasco-Garrido et al. 2007). Benzodiazepine use has also been reported to be a marker of untreated depression (Assem-Hilger et al. 2009). The subjective feeling of loneliness may also directly influence on use of drugs with sedative properties. Loneliness may reflect social isolation and these drugs may be used to escape these feelings. It is notable that in this study, loneliness was assessed as a subjective feeling of being lonely and it was strongly associated with sedative load. However, living alone was not associated with sedative load. Previous studies that have investigated the association between loneliness and psychotropic drug use have been inconclusive, although this may be partly due to the difficulty of operationalizing the concept of loneliness (Voyer et al. 2004).

Poor self-rated health was associated with sedative load in Study I. This finding was consistent with the previous study by Linjakumpu et al. The relationship may be multidimensional; the poor perceptions of health may negatively impact mental health leading older people to seek help for sleep problems and psychological symptoms. Alternatively, drugs with sedative properties may lower mood and physical performance, and lead to poorer perceptions of health (Voyer et al. 2004). Participants' self-rated health may also accurately reflect actual health status, and describe the increasing number of comorbidities which are treated with an increasing number of sedative drugs.

6.4.2 Association between sedative load and physical function (II, III)

In Studies II and III, sedative load was found to be associated with poorer performance in balance, mobility and muscle strength tests. Various aspects of physical function were measured and all showed impairments in performance among users of sedative drugs.

Sedative load and physical function has not been studied before and thus, Studies II and III in thesis are the first studies to report this association. Declines in physical function have been reported with sedative drug use measured with other cumulative exposure methods (Table 4). The Drug Burden Index has been associated with declines in physical function measured with grip strength, chair stands, walking speed, self-reported physical function measures, TUG and Berg Balance scale. DBI has also been investigated among the GeMS Study participants and similar impairments were reported in physical function measures compared to the results of Studies II and III (Gnjidic et al. 2011a). Although DBI also includes anticholinergic drugs without sedative properties, sedative load and DBI were associated with similar impairments in physical function. Thus, these indices may be useful in indicating inappropriate drug use patterns which are associated with impairments in clinically important physical function.

In contrast, the CNS drug model has not been studied with performance based physical function measures. Use of sedative drugs according to CNS drug model has been associated with an increased risk of falls (Hanlon et al. 2009). DBI have been investigated in

relation to risk of falls only in one study among older people living in residential aged care facilities (Wilson et al. 2011). Falls are an important future outcome for research also among community-dwelling older people. Falls are particularly dangerous among older people because of the risk of fractures. Drug classes included in the sedative load have been associated with an increased risk of falls (Hartikainen et al. 2007) and thus, it could be expected that cumulative exposure to sedative drugs would be associated with an increased risk of falls.

Previous studies of drug classes contributing to sedative load and impaired physical function support findings of Studies II and III. Benzodiazepines are the most frequently studied drug group, and have been associated with impairments in ADLs and IADLs in several studies (Ried et al. 1998, Ebly et al. 1997, Gray et al. 2006, Landi et al. 2007). Benzodiazepine use has been associated with self-reported mobility difficulty, (Gray et al. 2006), lower scores on short physical performance battery (Landi et al. 2007), and decreased walking speed (Eto et al. 1998). Use of antipsychotics and opioids has also been associated with impairments in ADL functions (Lord et al. 1995, Ebly et al. 1997). However, there is a lack of studies concerning use of sedative drugs and performance-based physical function tests. Measuring drug use with indices of cumulative exposure to sedative drugs offers an advantage over studies of single drug classes. Older people often use multiple drugs with sedative properties which may impact with associations studied with a single drug class or lead to exclusion of persons using multiple drugs with sedative properties.

Impairments in muscle strength have been reported in users of benzodiazepines and other psychotropic drugs. Diazepam has been shown to delay activation of muscles (Cutson et al. 1997), and use of psychotropic drugs has been associated with decreased quadriceps and ankle muscle strength (Lord et al. 1995). Benzodiazepine use has been associated with poorer balance measures among older people (Lord et al. 1995) although benzodiazepines have been shown to impair balance and postural sway among healthy volunteers (McClelland 1989). Thus, it can be concluded that results of Studies II and III are consistent with the results of the previous studies.

Although previous studies support the association between sedative drug use and impaired physical function, Studies II and III utilized cross-sectional data, and causal relationship cannot be concluded. DBI and physical function has also been studied in longitudinal studies (Hilmer et al. 2009, Wilson et al. 2010), as well as CNS drug use and falls and mobility limitation (Hanlon et al. 2009, Boudreau et al. 2009). It cannot be ruled out that the associations between physical function measures and sedative load were caused by residual confounding by indication. Unmeasured comorbidities or varying severity of diseases could have caused the associations. Sedative load and physical function measures should be studied in longitudinal design to be able to determine if changes in physical function are more pronounced among sedative drug users compared to nonusers. Another possibility is to investigate physical function among incident users of sedative drugs before and after the start of the treatment.

Physical function tests utilized in Studies II and III have been widely used among older people and these tests are shown to predict important outcomes. Slower walking speed has been associated with hospitalizations (Cesari et al. 2005, Montero-Odasso et al. 2005). Poor performance in various tests including walking speed, TUG, Berg Balance scale, grip strength and knee extension strength has been associated with an increased risk of falling (Shumway-Cook et al. 2000, Lajoie et al. 2002, Montero-Odasso et al. 2005, Morris et al. 2007, Pijnappels et al. 2008). Weaker grip has also been associated with an increased risk of fractures (Cooper et al. 2010). Most of these tests are also predictors of mortality. Poor performance in walking speed, grip strength, knee extension strength and chair stands test have been associated with an increased risk of death (Rantanen et al. 2003, Newman et al. 2006, Morris et al. 2007, Cesari et al. 2009). Physical functioning is also important for active and independent living in older people. Decline in muscle strength typically occurs first, followed by impairments in mobility because muscle strength is crucial for mobility

functions (Rantanen et al. 1999). Declines in muscle strength are hazardous for independent living, for example weakness in lower extremities may result in inability to rise from a chair, or lifting up an object from the floor. Independent living is very challenging and requires intensive help from home-nursing services if muscle strength of lower extremities limits these functions.

Differences in physical function test results between users and nonusers of sedative drugs in Studies II and III were clinically relevant. The mean difference in adjusted walking speed between those with SL=0 and SL≥3 was 0.2 m/s which is considered clinically relevant (Gill 2010). In Study II, the time taken to complete the TUG test was 15.2 seconds for those with SL≥3 compared to 13.3 seconds for those with SL=0. This is clinically important as older adults who take longer than 14.0 seconds to complete the TUG have been shown to be at higher risk of falling (Shumway-Cook et al. 2000). Clinically relevant change was also observed in grip strength in Study III. Compared to nonusers of sedatives, those with sedative load ≥3 had 2.9 kg lower grip strength after adjustments for covariates (20.1 kg vs. 17.2 kg). In a previous study, it was demonstrated that a 2.0 kg decline in grip strength among men and women aged 59–73 years was equivalent to five years of chronological ageing (Ashfield et al. 2010). In Study III, participants with a sedative load >0 took more than 17.1 seconds to perform five chair stands. Previous studies have demonstrated that this length of time was predictive of adverse outcomes (Cesari et al. 2009). In a study conducted by Cesari et al., older people who took ≥17.1 seconds to complete five chair stands were at higher risk of developing persistent severe lower extremity limitation, and a higher risk of death during follow-up.

The pharmacological mechanisms behind the association between sedative drug use and impaired physical function are not clear. It is likely that mechanisms leading to mobility limitation are multidimensional, and may be due to drug related cognitive impairment, impaired psychomotor performance, overall sedation, slowing of neuromuscular processing in the CNS, and muscle-relaxants effects and reduced muscle function (Davidoff 1985, Cutson et al. 1997, Young-McCaughan et al. 2001, Buffett-Jerrott et al. 2002, Turner et al. 2006, Wezenberg et al. 2007, Hindmarch 2009). Psychomotor slowing, as indicated by prolonged reaction times, delays in muscle activation and impaired attention, is likely to be the main factor behind the association between use of sedative drugs and impaired physical function. All sedative drug classes have the potential to cause psychomotor slowing (Hindmarch 1980). Sedative drugs also have muscle-relaxant properties due to various pharmacological mechanisms (Davidoff 1985). However, it is notable that muscle-relaxant effects of benzodiazepines occur at higher doses than the anxiolytic effects based on required receptor occupancies (Möhler et al. 2002), although the clinical relevance of the difference has not been studied among older users. In addition, aging has been associated with changes in GABA-A receptors and their subtypes (Turnheim 2003) and thus, muscle-relaxant effects of benzodiazepines are not fully known among older people.

In addition to these direct drug-related mechanisms, the association between sedative drug use and impairments in physical function may be related to physical inactivity, and thus, disuse atrophy caused by decrease in physical activity. Another possibility is that sedative drugs are more often prescribed to persons with impairments in physical function. Sedatives are often prescribed to persons with cognitive impairment, and cognitive impairment has been associated with impaired muscle strength (Atkinson et al. 2010). However, the analyses in Studies II and III were adjusted for physical activity level and cognitive impairment.

In Studies II and III, there was a lack of dose-response relationship between increasing sedative load and performance in physical function tests. The presence of a dose-response relationship is considered indicative of causality for ADRs (Naranjo 1981). Among the GeMS Study participants, there was relatively small sample size of participants with a sedative load of ≥3 (n=58), and all of them did not participate in the physical function

testing. Thus, the possible dose-response relationship between sedative load and physical function tests requires further investigation in studies with larger sample sizes.

6.4.3 Longitudinal sedative load (IV)

One of the main findings of the Study IV was that the prevalence of any regular sedative drug use increased during the 3-year follow-up. This reflects the tendency to initiate sedative drug use with increasing age. The proportion of all user categories (i.e. those with sedative load of 1–2 and those with ≥3) increased whereas proportion of nonusers decreased.

The proportion of those with sedative load of ≥1 increased from 29% in 2004 to 36% in 2007. There are few previous longitudinal studies of sedative or psychotropic drug use among the same community-dwelling older people. In a study by Hanlon et al., use of CNS drugs (i.e. antipsychotics, antidepressants, benzodiazepines, and opioids) increased during a 5 year follow-up period (Hanlon et al. 2009). The proportion of those using one or more of these drugs increased from 14% to 18%. In the Kuopio 75+ Study, the prevalence of psycholeptic use (i.e. antipsychotics, anxiolytics and sedative-hypnotics) increased from 31% in 1998 to 43% in 2003 among persons aged 75 years or older and living in community at the baseline (Jyrkkä et al. 2006). The higher prevalence compared to the current study may partly be explained by inclusion of when-required drug use in the analyses.

During the follow-up, changes in drug classes contributing to sedative load occurred. In 2007, atypical antipsychotic use (5%) was more prevalent than conventional antipsychotic use (1%) whereas in 2004, the opposite was found. Among antidepressants, other second generation antidepressants were the most frequently used antidepressants in 2007 whereas in 2004, SSRIs were the most frequently used. The most common drug in the class of other antidepressants was mirtazapine which may also be used to treat insomnia.

The prevalence of sedative drug use increased with age, and increased within age groups during the follow-up. There was a marked increase in sedative drug use among those aged ≥85 years; from 38% in 2004 to 50% in 2007. This means that in 2007, half of all persons aged 88 years or older used drugs with sedative properties. A notable increase in the prevalence of sedative drug use was seen among men, from 20% to 30% during the 3-year follow-up period.

6.4.4 Association between sedative load and mortality (IV)

Sedative load was associated with an increased risk of death in the unadjusted analyses, but the association was no longer significant after adjusting for covariates. These results were consistent with a previous study of long-term care facility residents that found no association between baseline sedative load and mortality (Taipale et al. 2009). Similar results have been reported with Drug Burden Index. The DBI was not associated with in-hospital mortality among older hospitalized patients in the United Kingdom (UK) (Lowry et al. 2011), and among older people in residential aged care facilities in Australia (Wilson et al. 2012). The results of Study IV suggest that impaired cognition and IADL have a greater impact on mortality than use of drugs with sedative properties. However, cognitive impairment may increase the susceptibility to ADEs associated with sedative drugs. In addition, in Study I, an association between sedative load and impaired in IADL was identified.

The cumulative exposure to sedative drugs has been associated with impaired physical function. However, Study IV and above mentioned three studies with sedative load and DBI have concluded that there is no association between sedative drug use and mortality. This implies that these cumulative exposure measures are more predictive of functional abilities than mortality. However, it is possible that study samples (from 362 to 1004) have been under powered in the mortality studies because older people have various competing causes of death.

In previous studies, antipsychotic use has been associated with an increased risk of death whereas studies on benzodiazepines have reported conflicting results (Kripke et al. 2012). The majority of sedative load in the GeMS Study sample consisted of hypnotic and anxiolytic use (55%) and antipsychotic use was not common. Our results may reflect the differential risk of death associated with different drug groups. Solomon and coworkers found that opioid users had an increased risk of death compared to NSAID users (Solomon et al. 2011a). They also found that opioid use was associated with an elevated risk of falls and fractures. However, in the GeMS Study the proportion of opioid users was low throughout the follow-up period.

Studies regarding use of antidepressants and mortality have identified both an increased and decreased risk of death (Coupland et al. 2011, Ried et al. 2011). These discrepancies may reflect differences in patient populations. Coupland and coworkers analyzed persons diagnosed with depression whereas Ried et al. studied patients who had suffered a stroke. Antidepressants are prescribed for a variety of indications, including depression, anxiety and neuropathic pain, and observational studies of antidepressant use may be subject to confounding by indication. Similarly, antidepressant use is itself a risk factor for stroke and it is difficult to assess if increased risk of stroke is caused by antidepressant use or underlying depression (Smoller 2011).

In Study IV, time-dependent sedative load was utilized to take into account the changes in sedative drug use during follow-up period. Previous studies have utilized cross-sectional assessments of drug use at the baseline only (Merlo et al. 2000, Taipale et al. 2009, Gisev et al. 2011, Lowry et al. 2011). In Study IV, the mean sedative load of baseline sedative users decreased while the mean sedative load of baseline nonusers increased. This indicates that baseline users decreased or ceased use of sedative drugs and new users started drug use. In the GeMS Study, drug use was reassessed at yearly intervals and thus, the actual timing of starting or stopping drugs was not known. This may partly explain the negative result because previous studies on antipsychotics and opioids have concluded that the risk of death is greatest at the start of treatment (Wang et al. 2005, Solomon et al. 2010b).

7 Conclusions

This thesis investigated the association between sedative load and adverse drug events among community-dwelling people aged 75 years and older. Conclusions based on the four studies included in the thesis are as follows:

1. Nearly every third older person had a sedative load ≥1 when only regularly used drugs were considered. Sociodemographic and health-related factors associated with having a higher sedative load were female sex, poor self-rated health and impaired IADL. The strongest association was found between sedative load and subjective feelings of loneliness.

2. Sedative load was associated with impaired balance and mobility among community-dwelling older people. Although causality cannot be inferred from results of cross-sectional studies, the findings suggest that clinicians should pay special attention to the possibility of impaired physical function associated with the use of multiple sedative drugs.

3. Sedative load was associated with impaired muscle strength, and higher sedative load was associated with poorer grip strength. This is important because maintenance of adequate muscle strength is a crucial factor enabling independence and living at home for older people.

4. The prevalence of sedative load increased during the 3-year follow-up. At the end of study, 36% of participants used sedative drugs, and half of persons aged 88 years and older used one or more sedative drugs. Sedative load was not associated with an increased risk of death. Frequent and increasing use of sedative drugs with increasing age highlights the importance of developing strategies to optimize and rationalize use of these drugs among older people.

8 Implications for the future

Implications for practice

1. Clinicians should pay special attention to the frequent use of sedative drugs. Older persons may also seek or be prescribed sedative drugs for unapproved indications for which social interventions should be recommended. When prescribing, dispensing or administering sedative drugs, clinicians should monitor treatment and ADEs, ensure appropriate indication, and prevent intermittent and short-term treatments from evolving into regular and long-term use.

2. The association between sedative load and impaired physical function provides additional evidence that sedative load may have serious consequences for older people. Clinicians should monitor ADEs and changes in physical function when re-assessing sedative drug use. The maintenance of adequate muscle strength and mobility is important for independence of older people.

3. High sedative load can be considered as a risk indicator that a person may have or be at risk of having impaired physical function. Thus, the Sedative Load Model could be utilized to identify older persons who are in need for interventions such as medication assessment, withdrawal of sedative drugs and improvement of physical function.

4. Older people who are using sedative drugs may not attribute the ADEs they experience to their drug therapy. Information and education of patients and family members about ADEs should be considered to be able to impact on prevalence of sedative drug use. In addition, all sedative users should receive advice and support to gradually reduce their use of sedative drugs.

5. The societal impact of frequent sedative drug use and corresponding ADEs should be considered in terms of current healthcare systems and policy to support independent living of older people. The current objective is to maintain physical function and independence and thus, sedative drug use should be recognized as one important factor that may counteract these objectives. There is a need for regular assessment of drugs used by older people and this should be done systematically and annually with special focus on ADEs. There is also a need for evidence-based treatment guidelines for older people.

Implications for research

1. The prevalence of sedative load should be assessed in different patient populations and countries with different healthcare systems and prescribing practices. Longitudinal studies are needed to assess how different drugs contribute to increasing sedative load, and if similar factors are associated with the use.

2. The association between sedative load and impaired physical function should be further investigated. Prospective, longitudinal studies should be conducted to observe if functional decline is more severe among sedative users compared to nonusers. In addition, it is also important to assess if the association is caused by the direct effects of sedative drugs on muscles or slowing of processing information in the CNS, or indirect effects in terms of decreased physical activity and disuse atrophy.

3. The predictive validity of the Sedative Load Model with regard to being able to predict declines in physical function should be assessed. In addition, the Sedative Load Model should be further updated to include new drugs. Further evidence is needed to inform the allocation of sedative ratings to specific drugs.

4. One future objective is to conduct further studies to assess the possible association between sedative load and mortality. While antipsychotic use has been associated with an increased risk of death in various studies, findings in relation to the risk of death associated with other sedative drugs are mixed. For mortality studies, larger samples of older people are needed. Where possible, future studies should utilize incident use cohorts of sedative users rather than prevalent use cohorts to overcome possible survivor bias.

5. Further studies are also needed to assess the possible association between sedative load and a range of other ADEs not studied in this thesis. These include impaired cognition, psychomotor performance, incident frailty, admission to institutions, and risk of falls and fractures.

9 References

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), 4th ed. Washington, DC: American Psychiatric Association, 1994

Aniansson A, Rundgren A, Sperling L: Evaluation of functional capacity in activities of daily living in 70-year-old men and women. Scand J Rehabil Med 12: 145–154, 1980

Ashfield TA, Syddall HE, Martin HJ, Dennison EM, Cooper C, Aihie Sayer A: Grip strength and cardiovascular drug use in older people: findings from the Hertfordshire Cohort Study. Age Ageing 39: 185–191, 2010

Assem-Hilger E, Jungwirth S, Weissgram S, Kirchmeyr W, Fischer P, Barnas C: Benzodiazepine use in the elderly: an indicator for inappropriate treated geriatric depression? Int J Geriatr Psychiatry 24: 563–569, 2009

Atkinson HH, Rapp SR, Williamson JD, et al.: The relationship between cognitive function and physical performance in older women: results from the Women's Health Initiative Memory Study. J Gerontol A Biol Sci Med Sci 65A: 300–306, 2010

Baker MI, Oleen MA: The use of benzodiazepine hypnotics in the elderly. Pharmacother 8: 241–247, 1988

Ballard C, Hanney ML, Theodoulou M, et al.: The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. Lancet Neurol 8: 151–157, 2009

Barak Y, Wagenaar RC, Holt KG: Gait characteristics of elderly people with a history of falls: a dynamic approach. Phys Ther 86: 1501–1510, 2006

Barker MJ, Greenwood KM, Jackson M, Crowe SF: Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: a meta-analysis. Arch Clin Neuropsychol 19: 437–454, 2004

Barnett MJ, Perry PJ, Alexander B, Kaboli PJ: Risk of mortality associated with antipsychotic and other neuropsychiatric drugs in pneumonia patients. J Clin Psychopharmacol 26: 182–187, 2006

Bell JS, Väänänen M, Ovaskainen H, Närhi U, Airaksinen MS: Providing patient care in community pharmacies: practice and research in Finland. Ann Pharmacother 41: 1039–1046, 2007

Bell JS, Taipale HT, Soini H, Pitkälä KH: Sedative load among long-term care facility residents with and without dementia. Clin Drug Investig 30: 63–70, 2010

Berg KO, Maki BE, Williams JI, Holliday PJ, Wood-Dauphinee SL: Clinical and laboratory measures of postural balance in an elderly population. Arch Phys Med Rehabil 73: 1073–1080, 1992

Blazer D, Hybels C, Simonsick E, Hanlon JT: Sedative, hypnotic and antianxiety medication use in aging cohort over ten years: a racial comparison. J Am Geriatr Soc 48: 1073–1079, 2000

Bleicher K, Cumming RG, Naganathan V, et al.: The role of fat and lean mass in bone loss in older men: findings from the CHAMP study. Bone 49: 1299–1305, 2011

Boudreau RM, Hanlon JT, Roumani YF et al.: Central nervous system medication use and incident mobility limitation in community elders: the Health, Aging and Body Composition Study. Pharmacoepidemiol Drug Saf 18: 916–922, 2009

Bourin M, Briley M: Sedation, an unpleasant, undesirable and potentially dangerous side-effect of many psychotropic drugs. Hum Psychopharmacol 19: 135–139, 2004

Bowie MW, Slattum PW: Pharmacodynamics in older adults: A review. Am J Geriatr Pharmacother 5: 263–303, 2007

Brown RE, Stevans DR, Haas HL: The physiology of brain histamine. Prog Neurobiol 63: 637–672, 2001

Buchman AS, Wilson RS, Boyle PA, Tang Y, Fleischman DA, Bennett DA: Physical activity and leg strength predict decline in mobility performance in older persons. J Am Geriatr Soc 55: 1618–1623, 2007

Buffett-Jerrott SE, Stewart SH: Cognitive and sedative effects of benzodiazepine use. Curr Pharm Des 8: 45–58, 2002

Cao YJ, Mager DE, Simonsick EM, et al.: Physical and cognitive performance and burden of anticholinergics, sedatives, and ACE inhibitors in older women. Clin Pharmacol Ther 83: 422–429, 2008

Carrasco-Garrido P, Jimenez-Garcia R, Astasio-Arbiza P, Ortega-Molina P, de Miguel AG: Psychotropics use in the Spanish elderly: predictors and evolution between years 1993 and 2003. Pharmacoepidemiol Drug Safety 16: 449–457, 2007

Castelino RL, Hilmer SN, Bajorek BV, Nishtala P, Chen TF: Drug Burden Index and potentially inappropriate medications in community-dwelling older people: The Impact of Home Medicines Review. Drugs Aging 27: 135–148, 2010

Cesari M, Kritchevsky SB, Penninx BW, et al.: Prognostic value of usual gait speed in well-functioning older people-results from the Health, Aging, and Body Composition Study. J Am Geriatr Soc 53: 1675–1680, 2005

Cesari M, Kritchevsky SB, Newman AB, et al.: Added value of physical performance measures is predicting adverse health-related events: results from the Health, Aging and Body Composition Study. J Am Geriatr Soc 57: 251−259, 2009

Clark BC: In vivo alterations in skeletal muscle form and function after disuse atrophy. Med Sci Sports Exerc 41: 1869−1875, 2009

Cook JM, Blyanova T, Masci C, Coyne JC: Older patient perspectives on long-term anxiolytic benzodiazepine use and discontinuation: a qualitative study. J Gen Intern Med 22: 1094−1100, 2007

Cooper R, Kuh D, Hardy R: Objectively measured physical capability levels and mortality: systematic review and meta-analysis. BMJ 341: c4467, 2010

Cooper R, Kuh D, Cooper C, et al.: Objective measures of physical capability and subsequent health: a systematic review. Age Ageing 40: 14−23, 2011

Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J: Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ 2011; epub ahead of print Aug 2.

Crum RM, Anthony JC, Bassett SS, Folstein MF: Population-based norms for the Mini-Mental State Examination by age and education level. JAMA 269: 2386−2391, 1993

Davidoff RA: Antispasticity drugs: mechanisms of action. Ann Neurol 17: 107−116, 1985

Cumming RG, Le Couteur DG: Benzodiazepines and risk of hip fractures in older people: a review of the evidence. CNS Drugs 17: 825−837, 2003

Cutson TM, Gray SL, Hughes MA, Carson SW, Hanlon JT: Effect of a single dose of diazepam on balance measures in older people. J Am Geriatr Soc 45: 435−440, 1997

Dahl A, Berg S, Nilsson SE: Identification of dementia in epidemiological research: a study on the usefulness of various data sources. Aging Clin Exp Res 19: 381−90, 2007

Davidoff RA: Antispasticity drugs: mechanisms of action. Ann Neurol 17: 107−116, 1985

Dealberto MJ, Seeman T, McAvay GJ, Berkman L: Factors related to current and subsequent psychotropic drug use in an elderly cohort. J Clin Epidemiol 50: 357−364, 1997

Dorsey ER, Rabbani A, Gallagher SA, Conti RM, Alexander C: Impact of FDA black box advisory on antipsychotic medication use. Arch Intern Med 170: 93−103, 2010

Draganich LF, Zacny J, Klafta J, Karrison T: The effects of antidepressants on obstructed and unobstructed gait in healthy elderly people. J Gerontol A Biol Sci Med Sci 56: M36−M41, 2001

Dunn JE, Furner SE, Miles TP: Do falls predict institutionalization in older persons? An analysis of data from the Longitudinal Study of Aging. J Aging Health 5: 194–207, 1993

Ebly E, Hogan DB, Fung TS: Potential adverse outcomes of psychotropic and narcotic drug use in Canadian seniors. J Clin Epidemiol 50: 857–863, 1997

Echizenya M, Mishima K, Satoh K, Kusanagi H, Ohkubo T, Shimizu T: Dissociation between objective psychomotor impairment and subjective sleepiness after diazepam administration in the aged people. Hum Psychopharmacol 22: 365–372, 2007

Eto F, Saotome I, Furuichi T, Ogasawara M: Effects of long-term use of benzodiazepines on gait and standing balance in the elderly. Ann N Y Acad Sci 860: 543–545, 1998

Evans WJ, Campbell WW: Sarcopenia and age-related changes in body composition and functional capacity. J Nutr 123: 465–468, 1993

Fife TD, Sirven J: Antiepileptic drugs and their impact on balance. Aging Health 1:147–155, 2005

Folstein MF, Folstein SE, McHugh PR: "Mini-Mental State" A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12: 189–198, 1975

Frankfort SV, Tulner LR, van Campen JP, Koks CH, Beijnen JH: Evaluation of pharmacotherapy in geriatric patients after performing complete geriatric assessment at a diagnostic day clinic. Clin Drug Invest 26: 169–174, 2006

Fried LP, Young Y, Rubin G, Bandeen-Roche K & WHAS II Collaborative Research Group: Self-reported preclinical disability identifies older women with early declines in performance and early disease. J Clin Epidemiol 54: 889–901, 2001

Furu K, Wettermark B, Andersson M, Martikainen JE, Almasdottir AB, Sorensen HT: The Nordic countries as a cohort for pharmacoepidemiological research. Basic Clin Pharmacol Toxicol 106: 86–94, 2010

Giampaoli S, Ferrucci L, Cecchi F, et al.: Hand-grip strength predicts incident disability in non-disabled older men. Age Ageing 28: 283–288, 1999

Gill SS, Bronskill SE, Normand SL, et al.: Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med 146: 775–786, 2007

Gill TM, Williams CS, Richardson ED, Tinetti ME: Impairments in physical performance and cognitive status as predisposing factors for functional dependence among nondisabled older persons. J Gerontol A Biol Sci Med Sci 51A: M283–M288, 1995

Gill TM: Assessment of function and disability in longitudinal studies. J Am Geriatr Soc 58: 5308−5312, 2010

Gisev N, Hartikainen S, Chen TF, Korhonen M, Bell JS: Mortality associated with benzodiazepines and benzodiazepine-related drugs among community-dwelling older people in Finland: a population-based retrospective cohort study. Can J Psychiatry 56: 377−381, 2011

Gleason PP, Schulz R, Smith NL et al.: Correlates and prevalence of benzodiazepine use in community-dwelling elderly. J Gen Intern Med 13: 243–250, 1998

Gnjidic D, Cumming RG, Le Couteur DG, et al.: Drug burden index and physical function in older Australian men. Br J Clin Pharmacol 68: 97–105, 2009

Gnjidic D, Le Couteur DG, Abernetrhy DR, Hilmer SN: A pilot randomized clinical trial utilizing the drug burden index to reduce exposure to anticholinergic and sedative medications in older people. Ann Pharmacother 44: 1725–1732, 2010

Gnjidic D, Bell JS, Hilmer SN, Lönnroos E, Sulkava R, Hartikainen S: Drug Burden Index associated with function in community-dwelling older people in Finland: a cross-sectional study. Ann Med 2011a; epub ahead of print Apr 15

Gnjidic D, Le Couteur D, Abernethy DR, Hilmer SN: Drug burden index and Beers criteria: impact on functional outcomes in older people living in self-care retirement villages. J Clin Pharmacol 2011b, epub ahead of print

Gnjidic D, Hilmer SN, Blyth FM, et al.: High-risk prescribing and incidence of frailty among older community-dwelling men. Clin Pharmacol Ther 2012, epub ahead of print Feb 1

Goodpaster BH, Chomentowski P, Ward BK, et al.: Effects of physical activity on strength and skeletal muscle fat infiltration in older adults: a randomized controlled trial. J Appl Physiol 105: 1498–1503, 2008

Gray SL, LaCroix AZ, Blough DK, Wagner EH, Koepsell TD, Buchner D.: Is the use of benzodiazepines associated with incident disability? J Am Geriatr Soc 50: 1012–1018, 2002

Gray SL, Penninx BW, Blough DK, et al.: Benzodiazepine use and physical performance in community-dwelling older women. J Am Geriatr Soc 51: 1563–1570, 2003

Gray SL, LaCroix AZ, Hanlon JT, et al.: Benzodiazepine use and physical disability in community-dwelling older adults. J Am Geriatr Soc 54: 224–230, 2006

Grimby G: Physical activity and muscle training in the elderly. Acta Med Scand Suppl. 711: 233–237, 1986

Groll DL, To T, Bombardier C, Wright JG: The development of a comorbidity index with physical function as the outcome. J Clin Epidemiol. 58: 595–602, 2005

Guralnik JM, Simonsick EM, Ferrucci L, et al.: A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 49: M85–94, 1994

Guralnik JM, Ferrucci L, Pieper CF, et al.: Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. J Gerontol Med Sci 55A: M221–M231, 2000

Haasum Y, Fastbom J, Johnell K: Institutionalization as a risk factor for inappropriate drug use in the elderly: a Swedish nationwide register-based study. Ann Pharmacother Feb 7, epub ahead of print, 2012

Hairi NN, Cumming RG, Naganathan V, et al.: Loss of muscle strength, mass (sarcopenia), and quality (specific force) and its relationship with functional limitation and physical disability: the Concord Health and Ageing in Men Project. J Am Geriatr Soc 58: 2055–2062, 2010

Hanlon JT, Boudreau RM, Roumani YF, et al.: Number and dosage of central nervous system medications on recurrent falls in community elders: the Health, Aging and Body Composition study. J Gerontol A Biol Sci Med Sci 64: 492−498, 2009

Hartikainen S, Rahkonen T, Kautiainen H, Sulkava R: The use of psychotropics and survival in demented elderly individuals. Int Clin Psychopharmacol 20: 227−231, 2005

Hartikainen S, Lönnroos E, Louhivuori K: Medication as a risk factor for falls: critical systematic review. J Gerontol A Biol Sci Med Sci 62: 1172−1181, 2007

Hege SG, Ellinwood EH Jr, Wilson WH, Helligers CA, Graham SM: Dissociations in the expression of the sedative effects of triazolam. Psychopharmacology 131: 101−7, 1997

Hilmer SN, Mager DE, Simonsick EM, et al.: A drug burden index to define the functional burden of medications in older people. Arch Intern Med 167: 781−787, 2007

Hilmer SN, Mager DE, Simonsick EM, et al.: Drug Burden Index score and functional decline in older people. Am J Med 122: 1142−1149, 2009a

Hilmer SN, Gnjidic D: The effects of polypharmacy in older adults. Clin Pharmacol Ther 85: 86–88, 2009b

Hilmer SN, Gnjidic D, Abernetrhy DR: Pharmacoepidemiology in the postmarketing assessment of the safety and efficacy of drugs in older adults. J Gerontol A Biol Sci Med Sci 67: 181−188, 2012

Hindmarch I: Psychomotor function and psychoactive drugs. Br J Clin Pharmacol 10: 189–209, 1980

Hindmarch I: Cognitive toxicity of pharmacotherapeutic agents used in social anxiety disorder. Int J Clin Pract 63: 1085−1094, 2009

Holland R, Desborough J, Goodyer L, Hall S, Wright D, Look YK: Does pharmacist-led medication review help to reduce hospital admissions and death in older people? A systematic review and meta-analysis. Br J Clin Pharmacol 65: 303–319, 2008

Hollis J, Grayson D, Forrester L, Brodaty H, Touyz S, Cumming R: Antipsychotic medication dispensing and risk of death in veterans and war widows 65 years and older. Am J Geriatr Psychiatry 15: 932–941, 2007

Horak FB: Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? Age Ageing 35(Suppl 2): ii7−ii11, 2006

Iliffe S, Curran HV, Collins R, Yuen Kee SC, Fletcher S, Woods B: Attitudes to long-term use of benzodiazepine hypnotics by older people in general practice: finding from interviews with service users and providers. Aging Mental Health 8: 242−248, 2004

Iyer S, Naganathan V, McLachlan AJ, Le Couteur DG: Medication withdrawal trials in people aged 65 years and older. Drugs Aging 25: 1021−1031, 2008

Jesson J: Cross-sectional studies in prescribing research. J Clin Pharm Ther 26: 397−403, 2001

Jyrkkä J, Vartiainen L, Hartikainen S, Sulkava R, Enlund H: Increasing use of medicines in elderly persons: a five-year follow-up of the Kuopio 75+ Study. Eur J Clin Pharmacol 62: 151−158, 2006

Kales HC, Valenstein M, Kim HM, et al.: Mortality risk in patients with dementia treated with antipsychotics versus other psychiatric medications. Am J Psychiatry 164: 1568−1576, 2007

Kales HC, Kim HM, Zivin K et al.: Risk of mortality among individual antipsychotics in patients with dementia. Am J Psychiatry 169: 71−79, 2012

Kannus P, Sievänen H, Palvanen M, Järvinen T, Parkkari J: Prevention of falls and consequent injuries in elderly people. Lancet 366: 1885−1893, 2005

Kripke DF, Klauber MR, Wingard DL, Fell RL, Assmus JD, Garfinkel L: Mortality hazard associated with prescription hypnotics. Biol Psychiatry 43: 687−693, 1998

Kripke DF: Do hypnotics cause death and cancer? The burden of proof. Sleep Med 10: 275−276, 2009

Kripke DF, Langer RD, Kline LE: Hypnotics' association with mortality or cancer: a matched cohort study. BMJ Open Feb 27: 2, 2012

Kyle UG, Genton L, Hans D, et al.: Total body mass, fat mass, fat-free mass, and skeletal muscle in older people: cross-sectional differences in 60 year-old persons. J Am Geriatr Soc 49: 1633−1640, 2001

Lajoie Y, Girard A, Guay M: Comparison of the reaction time, the Berg Balance Scale and the ABC in non-fallers and fallers. Arch Gerontol Geriatr 35: 215−225, 2002

Lampela P, Hartikainen S, Sulkava R, Huupponen R: Adverse drug effects in elderly people-a disparity between clinical examination and adverse effects self-reported by the patient. Eur J Clin Pharmacol 63: 509−515, 2007

Landi F, Russo A, Liperoti R, et al.: Anticholinergic drugs and physical function among frail elderly population. Clin Pharmacol Ther 81: 235−241, 2007

Latham NK, Mehta V, Nguyen AM, et al.: Performance-based or self-report measures of physical function: which should be used in clinical trials of hip fracture patients? Arch Phys Med Rehabil 89: 2146−2155, 2008

Lau HS, de Boer A, Beuning KS, Porsius A: Validation of pharmacy records in drug exposure assessment. J Clin Epidemiol 50: 619–625, 1997

Lawton MP, Brody EM: Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 9: 179–186, 1969

Lihavainen K, Sipilä S, Rantanen T, Kauppinen M, Sulkava R, Hartikainen S: Effects of comprehensive geriatric assessment and targeted intervention on mobility in persons aged 75 years and over: a randomized controlled trial. Clin Rehabil 2011, epub ahead of print Oct 17

Linjakumpu T, Hartikainen S, Klaukka T, Koponen H, Kivelä SL, Isoaho R: Psychotropics among the home-dwelling elderly- increasing trends. Int J Geriatr Psychiatry 17: 874–883, 2002

Linjakumpu T, Hartikainen S, Klaukka T, Koponen H, Kivelä SL, Isoaho R: A model to classify the sedative load of drugs. Int J Geriatr Psychiatry 18: 542–544, 2003

Linjakumpu TA, Hartikainen SA, Klaukka TJ, et al.: Sedative drug use in the home-dwelling elderly. Ann Pharmacother 38: 2017–2022, 2004

Liperoti R, Onder G, Landi F, et al.: All-cause mortality associated with atypical and conventional antipsychotics among nursing home residents with dementia: a retrospective cohort study. J Clin Psychiatry 70: 1340–1347, 2009

Lopez OL, Wisniewski SR, Becker JT, Boller F, DeKosky ST: Psychiatric medication and abnormal behavior as predictors of progression in probable Alzheimer disease. Arch Neurol 56: 1266–72, 1999

Lord SR, McLean D, Stathers G: Physiological factors associated with injurious falls in older people living in the community. Gerontology 38: 338–346, 1992

Lord SR, Anstey KJ, Williams P, Ward JA: Psychoactive medication use, sensori-motor function and falls in older women. Br J Clin Pharmacol 39: 227–234, 1995

Lowry E, Woodman RJ, Soiza RL, Hilmer SN, Mangoni AA: Drug burden index, physical function and adverse outcomes in older hospitalized patients. J Clin Pharmacol 2011, published ahead of print

Majeroni BA, Hess A: The pharmacologic treatment of depression. J Am Board Fam Pract 11: 127–139, 1998

Maki BE, Zecevic A, Bateni H, Kirshenbaum N, McIlroy WE: Cognitive demands of executing postural reactions: does aging impede attention switching? Neuroreport 12: 3583–3587, 2001

McClelland: Body sway and the effects of psychoactive drugs – a review. Human Psychopharmacol 4: 3–14, 1989

McCusker J, Cole M, Ciampi A, Latimer E, Windholz S, Belzile E: Does depression in older medical inpatients predict mortality? J Gerontol A Biol Sci Med Sci 61: 975–981, 2006

McDonald K, Trick L, Boyle J: Sedation and antihistamines: an update. Review of inter-drug differences using proportional impairment ratios. Hum Psychopharmacol 23: 555–570, 2008

McKeith IG, Galasko D, Kosaka K, et al.: Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 47: 1113–1124, 1996

McLachlan AJ, Hilmer SN, Le Couteur DG: Variability in response to medicines in older adults: phenotypic and genotypic factors. Clin Pharmacol Ther 85: 431–435, 2009

Mehta S, Johnson ML, Chen H, Aparasu RR: Risk of cerebrovascular adverse events in older adults using antipsychotic agents: a propensity-matched retrospective cohort study. J Clin Psychiatry 71: 689–698, 2010

Merlo J, Hedblad B, Ogren M, et al.: Increased risk of ischaemic heart disease mortality in elderly men using anxiolytics-hypnotics and analgesics. Results of the 10-year follow-up of the prospective population study "Men born in 1914", Malmo, Sweden. Eur J Clin Pharmacol 49: 261–265, 1996

Merlo J, Ostergren PO, Mansson NO, et al.: Mortality in elderly men with low psychosocial coping resources using anxiolytic-hypnotic drugs. Scand J Public Health 28: 294–297, 2000

Ministry of Social Affairs and Health: National Framework for High-Quality Services for Older People. Ministry of Social Affairs and Health; Helsinki, Finland, Report No:5, 2008. Available at:
http://www.stm.fi/c/document_library/get_file?folderId=39503&name=DLFE-6710.pdf
[Accessed Feb 13 2012]

Mittal V, Kurup L, Williamson D, Muralee S, Tampi RR: Review: risk of cerebrovascular adverse events and death in elderly patients with dementia when treated with antipsychotic medications: a literature review of evidence. Am J Alzheimers Dis Other Demen 26: 10–28, 2011

Montero-Odasso M, Schapira M, Soriano ER, et al.: Gait velocity as a single predictor of adverse events in healthy seniors aged 75 years and older. J Gerontol A Biol Sci Med Sci 60A: 1304–1309, 2005

Moreland JD, Richardson JA, Goldsmith CH, Clase CM: Muscle weakness and falls in older adults: a systematic review and meta-analysis. J Am Geriatr Soc 52: 1121–1129, 2004

Morris R, Harwood RH, Baker R, Sahota O, Armstrong S, Masud T: A comparison of different balance tests in the prediction of falls in older women with vertebral fractures: a cohort study. Age Ageing 36: 78–83, 2007

Musicco M, Palmer K, Russo A, et al.: Association between prescription of conventional or atypical antipsychotic drugs and mortality in older persons with Alzheimer's disease. Dement Geriatr Cogn Disord 31: 218–224, 2011

Möhler H, Fritschy JM, Rudolph U: A new benzodiazepine pharmacology. J Pharmacol Exp Ther 300: 2–8, 2002

Naranjo CA, Busto U, Sellers EM et al.: A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30: 239−245, 1981

Newman AB, Kupelian V, Visser M, et al.: Strength, but not muscle mass, is associated with mortality in Health, Aging and Body Composition Study Cohort. J Gerontol A Biol Sci Med Sci 61A: 72−77, 2006

Nishtala PS, McLachlan AJ, Bell JS, Chen TF: Psychotropic prescribing in long-term care facilities: impact of medication reviews and educational interventions. Am J Geriatr Psychiatry 16: 621−632, 2008

Nishtala PS, Hilmer SN, McLachlan AJ, Hannan PJ, Chen TF: Impact of residential medication management reviews on drug burden index in aged-care homes: A retrospective analysis. Drugs Aging 26: 677–686, 2009

Noize P, Bazin F, Dufouil C, et al.: Comparison of health insurance claims and patient interviews in assessing drug use: data from the Three-City (3C) Study. Pharmacoepidemiol Drug Saf 18: 310−319, 2009

Nonino F, De Girolamo G, Gamberini L, Goldoni CA; Modena Work Groups for Antipsychotics in Dementia: Survival among elderly Italian patients with dementia treated with atypical antipsychotics: observational study. Neurol Sci 27: 375−380, 2006

Parr JM, Kavanagh DJ, Cahill H, Mitchell G, McD Young R: Effectiveness of current treatment approaches for benzodiazepine discontinuation: a meta-analysis. Addiction 104: 13−24, 2009

Parsons C, Haydock J, Mathie E, et al.: Sedative load of medications prescribed for older people with dementia in care homes. BMC Geriatrics 11: 56, 2011

Paterniti S, Dufouil C, Alpérovitch A: Long-term benzodiazepine use and cognitive decline in the elderly: the Epidemiology of Vascular Aging Study. J Clin Psychopharmacol 22: 285−293, 2002

Penninx BW, Guralnik JM, Ferrucci L, Simonsick EM, Deeg DJ, Wallace RB: Depressive symptoms and physical decline in community-dwelling older persons. JAMA 279: 1720−1726, 1998

Penninx BW, Ferrucci L, Leveille SG, Rantanen T, Pahor M, Guralnik JM: Lower extremity performance in nondisabled older persons as a predictor of subsequent hospitalization. J Gerontol Med Sci 55A: M691−M697, 2000

Pijnappels M, van der Burg PJ, Reeves ND, van Dieën JH: Identification of elderly fallers by muscle strength measures. Eur J Appl Physiol 102: 585−592, 2008

Pimlott NJ, Hux JE, Wilson LM, Kahan M, Li C, Rosser WW: Educating physicians to reduce benzodiazepine use by elderly patients: a randomized controlled trial. CMAJ 168: 835–839, 2003

Pit SW, Byles JE, Henry DA, Holt L, Hansen V, Bowman DA: A quality use of medicines program for general practitioners and older people: a cluster randomised controlled trial. Med J Austr 187: 23–30, 2007

Pit SW, Byles JE, Cockburn J: Accuracy of telephone self-report of drug use in older people and agreement with pharmaceutical claims data. Drugs Aging 25: 71–80, 2008

Podsiadlo D, Richardson S: The timed "Up and Go" : a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 39: 142–148, 1991

Raivio MM, Laurila JV, Strandberg TE, Tilvis RS, Pitkälä KH: Neither atypical nor conventional antipsychotics increase mortality or hospital admissions among elderly patients with dementia: a two-year prospective study. Am J Geriatr Psychiatry 15: 416–424, 2007

Ramaekers JG, Muntjewerff ND, van Veggel LMA, Uiterwijk MMC, O'Hanlon JF: Effects of nocturnal doses of mirtazapine and mianserin on sleep and on daytime psychomotor and driving performance in young, healthy volunteers. Hum Psychopharmacol 13: S87–S97, 1998

Rantanen T, Era P, Kauppinen M, Heikkinen E: Maximal isometric muscle strength and socio-economic status, health and physical activity in 75-year-old persons. J Aging Phys Activity 2: 206–220, 1994

Rantanen T, Guralnik JM, Sakari-Rantala R, et al.: Disability, physical activity and muscle strength in older women: the Women's Health and Aging Study. Arch Phys Med Rehabil 80: 130–135, 1999

Rantanen T, Volpato S, Ferrucci L, Heikkinen E, Fried LP, Guralnik JM: Handgrip strength and cause-spesific and total mortality in older disabled women: exploring the mechanism. J Am Geriatr Soc 51: 636–641, 2003a

Rantanen T: Muscle strength, disability and mortality. Scand J Med Sci Sports 13: 3–8, 2003b

Reynolds GP: Receptor mechanisms in the treatment of schizophrenia. J Psychopharmacol 18: 340–345, 2004

Ried LD, Johnson RE, Gettman DA: Benzodiazepine exposure and functional status in older people. J Am Geriatr Soc 46: 71–76, 1998

Ried LD, Jua H, Feng H, et al.: Selective serotonin reuptake inhibitor treatment and depression are associated with poststroke mortality. Ann Pharmacother 45: 888–897, 2011

Rigler SK, Perera S, Jachna C, Shireman TI, Eng M: Comparison of the association between disease burden and inappropriate medication use across three cohorts of older adults. Am J Geriatr Pharmacother 2: 239–247, 2004

Rikala M, Hartikainen S, Sulkava R, Korhonen MJ: Validity of the Finnish Prescription Register for measuring psychotropic drug exposures among elderly finns: a population-based intervention study. Drugs Aging 27: 337–349, 2010

Rikala M, Korhonen MJ, Sulkava R, Hartikainen S: The effects of medication assessment on psychotropic drug use in the community-dwelling elderly. Int Psychogeriatr 23: 473–484, 2011

Rossom RC, Rector TS, Lederle FA, Dysken MW: Are all commonly prescribed antipsychotics associated with greater mortality in elderly male veterans with dementia? J Am Geriatr Soc 58: 1027–1034, 2010

Rubenstein LZ: Geriatric imperative: geriatric assessment programs. J Med Soc N J 81: 651–654, 1984

Rumble R, Morgan K: Hypnotics, sleep and mortality in elderly people. J Am Geriatr Soc 40: 787–791, 1992

Ryan J, Carriere I, Ritchie K, et al.: Late-life depression and mortality: influence of gender and antidepressant use. Br J Psychiatry 192: 12–18, 2008

Salonoja M, Salminen M, Aarnio P, Vahlberg T, Kivelä SL: One-time counselling decreases the use of benzodiazepines and related drugs among community-dwelling older persons. Age Ageing 39: 313–319, 2010

Sayers SP, Brach JS, Newman AB, Heeren TC, Guralnik JM, Fielding RA: Use of self-report to predict ability to walk 400 meters in mobility-limited older adults. J Am Geriatr Soc 52: 2099–2103, 2004

Schneider LS, Dagerman KS, Insel P: Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 294: 1934–43, 2005

Schmader KE, Hanlon JT, Pieper CF, et al.: Effects of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly. Am J Med 116: 394–401, 2004

Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C, Wang PS: Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. CMAJ 176: 627–632, 2007

See S, Ginzburg R: Skeletal muscle relaxants. Pharmacother 28: 207–213, 2008

Semla TP, Beizer JL, Higbee MD, et al.: Geriatric Dosage Handbook: Including clinical recommendations and monitoring guidelines. 12th ed. Hudson, OH: Lexi-Comp, 2007

Setoguchi S, Wang PS, Brookhart A, Canning CF, Kaci L, Schneeweiss S: Potential Causes of Higher Mortality in Elderly Users of Conventional and Atypical Antipsychotic Medications J Am Geriatr Soc 56: 1644−1650, 2008

Shumway-Cook A, Brauer S, Woollacott M: Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go test. Phys Ther 80: 896−903, 2000

Simoni-Wastila L, Ryder PT, Qian J, Zuckerman IH, Shaffer T, Zhao L: Association of antipsychotic use with hospital events and mortality among medicare beneficiaries residing in long-term care facilities. Am J Geriatr Psychiatry 17: 417−427, 2009

Simonsick EM, Newman AB, Nevitt MC, et al.: Measuring higher level physical function in well-functioning older adults: expanding familiar approaches in the Health ABC Study. J Gerontol A Biol Sci Med Sci 56A: M644−M649, 2001

Sloane P, Ivey J, Roth M, Roederer M, Williams CS: Accounting for the sedative and analgesic effects of medication changes during patient participation in clinical research studies: measurement development and application to a sample of institutionalized geriatric patients. Contemp Clin Trials 29: 140−148, 2008

Smith AJ, Tett SE: Improving the use of benzodiazepines-is it possible? A non-systematic review of interventions tried in the last 20 years. BMC Health Serv Res 10: 321, 2010

Smoller JW: Do antidepressants raise the risk of stroke? Am J Psychiatry 168: 457−459, 2011

Snijders AH, Verstappen CC, Munneke M, Bloem BR: Assessing the interplay between cognition and gait in clinical setting. J Neural Transm 114: 1315−1321, 2007

Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S: The comparative safety of analgesics in older adults with arthritis. Arch Intern Med 170: 1968−1978, 2010a

Solomon DH, Rassen JA, Glynn RJ, et al.: The comparative safety of opioids for nonmalignant pain in older adults. Arch Intern Med 170: 1979−1986, 2010b

Statistics Finland: Population by age 1900−2060 (years 2010 to 2060: projection). Population Statistics, 2009. Available at:
http://www.stat.fi/til/vaenn/2009/vaenn_2009_2009-09-30_tau_001_en.html [Accessed at Feb 15 2012]

Steffen TM, Hacker TA, Mollinger L: Age- and gender-related test performance in community-dwelling elderly people: six-minute walk test, Berg Balance Scale, Timed Up & Go Test, and gait speeds. Phys Ther 82: 128−137, 2002

Straus SM, Bleumink GS, Dieleman JP, et al.: Antipsychotics and the risk of sudden cardiac death. Arch Intern Med 164: 1293−1297, 2004

Suh GH, Shah A: Effect of antipsychotics on mortality in elderly patients with dementia: a 1-year prospective study in a nursing home. Int Psychogeriatr 17: 429−441, 2005

Taipale HT, Bell JS, Soini H, Pitkälä KH: Sedative load and mortality among residents of long-term care facilities. A prospective cohort study. Drugs Aging 26: 1−11, 2009

Taipale HT, Hartikainen S, Bell JS: A comparison of four methods to quantify the cumulative effect of taking multiple drugs with sedative properties. Am J Geriatr Pharmacother 8: 460−471, 2010

Tiedemann A, Sherrington C, Lord SR: Physiological and psychological predictors of walking speed in older community-dwelling people. Gerontology 51: 390−395, 2005

Tiligada E, Kyriakidis K, Chazot PL, Passani B: Histamine pharmacology and new CNS drug targets. CNS Neurosci Ther 17: 620−628, 2011

Timmerman H: Why are non-sedating antihistamines non-sedating? Clin Exp Allergy 29 (suppl 3): 13−18, 1999

Toornvliet R, van Berckel BN, Luurtsema G et al.: Effect of age on functional P-glycoprotein in the blood-brain barrier measured by use of (R)-[(11)C]verapamil and positron emission tomography. Clin Pharmacol Ther 79: 540−548, 2006

Trifiro G, Verhamme KM, Ziere G, Caputi AP, Ch Stricker BH, Sturkenboom MC: All-cause mortality associated with atypical and typical antipsychotics in demented outpatients. Pharmacoepidemiol Drug Saf 16: 538−544, 2007

Tulner LR, van Campen JP, Frankfort SV, et al.: Changes in under-treatment after Comprehensive Geriatric Assessment. An observational study. Drugs Aging 27: 831−843, 2010

Turner C, Handford ADF, Nicholson AN: Sedation and memory: studies with a histamine H-1 receptor antagonist. J Psychopharmacol 20: 506−517, 2006

Turnheim K: When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. Exp Gerontol 38: 843−853, 2003

Van Craen K, Braes T, Wellens N, et al.: The effectiveness of inapatient geriatric evaluation and management units: a systematic review and meta-analysis. J Am Geriatr Soc 58: 83−92, 2010

Van Rensbergen G, Nawrot T: Medical conditions of nursing home admissions. BMC Geriatr 10: 46, 2010

Verster JC, Volkerts ER, Spence DW, Alford C, Pandi-Perumal SR: Effects of sleep medications on cognition, psychomotor skills, memory and driving performance in the elderly. Cur Psychiatry Rev 3: 281−292, 2007

Vinkers DJ, Gussekloo J, van der Mast RC, Zitman FG, Westendorp RG: Benzodiazepine use and risk of mortality in individuals aged 85 years or older. JAMA 290: 2942−2943, 2003

Visser M, Rubin SM, Harris TB, Pahor M: Prognostic value of usual gait speed in well-functioning older people-results from the Health, Aging and Body Composition Study. J Am Geriatr Soc 53: 1675−1680, 2005

Voshaar RC, Gorgels WJ, Mol AJ et al.: Tapering off long-term benzodiazepine use with or without group cognitive-behavioural therapy: three-condition, randomised controlled trial. Br J Psychiatry 182: 498−504, 2003

Voyer P, Cohen D, Lauzon S, Collin J: Factors associated with psychotropic drug use among community dwelling older persons: a review of empirical studies. BMC Nurs 3: 3, 2004

Wang PS, Schneeweiss S, Avorn J, et al.: Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 353: 2335−2341, 2005

Weingartner HJ, Sirocco K, Rawlings R, Joyce E, Hommer D: Dissociations in the expression of the sedative effects of triazolam. Psychopharmacol 119: 27−33, 1995

Wezenberg E, Sabbe BG, Hulstijn W, Ruigt GS, Verkes RJ: The role of sedation tests in identifying sedative drug effects in healthy volunteers and their power to dissociate sedative-related impairments from memory dysfunctions. J Psychopharmacol 21: 579−587, 2007

Wilson NM, Hilmer SN, March LM, et al.: Associations between drug burden index and physical function in older people in residential aged care facilities. Age Ageing 39: 503−507, 2010

Wilson NM, Hilmer SN, March LM, et al.: Associations between drug burden index and falls in older people in residential aged care. J Am Geriatr Soc 59: 875−880, 2011

Wilson NM, Hilmer SN, March LM et al.: Associations between Drug Burden Index and mortality in older people in residential aged care facilities. Drugs Aging 29: 157−165, 2012

WHO Collaborating Centre for Drug Statistics Methodology: The anatomical therapeutic chemical classification system 2010 [online]. Available from URL:
http://www.whocc.no/atcddd/ [Accessed 2010 Nov 24]

Wittenborn JR: Effects of benzodiazepines on psychomotor performance. Br J Clin Pharmacol 7: 61S−67S, 1979

World Medical Association: Declaration of Helsinki. Ethical principles for medical research involving human subjects. Available from URL: http://www.wma.net/en/30publications/10policies/b3/17c.pdf [Accessed 2012 Feb 13]

Woollacott M, Shumway-Cook A: Attention and the control of posture and gait: a review of an emerging area of research. Gait Posture 16: 1−14, 2002

Wright RM, Roumani YF, Boudreau R, et al.: Effect of central nervous system medication use on decline in cognition in community-dwelling older adults: Findings from the Health, Aging and Body Composition Study. J Am Geriatr Soc 57: 243–250, 2009

Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 17: 37–49, 1982−1983

Young-McCaughan S, Miaskowski C: Definition of and mechanism for opioid-induced sedation. Pain Manag Nurs 2: 84−97, 2001

Zermansky AG, Alldred DP, Petty DR, et al.: Clinical medication reviw by a pharmacist of elderly people living in care homes-randomised controlled trial. Age Ageing 35: 586−591, 2006

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Sedative Load and Adverse Events Among Community-Dwelling Older People

Older people are frequent users of drugs with sedative properties although they are susceptible to adverse drug events. Sedative load refers to cumulative exposure to multiple drugs with sedative properties. This thesis investigated sedative load and adverse drug events including impaired mobility and muscle strength, and an increased risk of death among community-dwelling older people aged 75 years and older.

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