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BENZODIAZEPINES AND COGNITIVE FUNCTIONING IN OLDER ADULTS

With emphasis on long-term use and withdrawal

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"Rauhan ikävä on kotia, sitten synkkänä toteaa:
–Nyt minulta viedään koti, kun elän liian kauan,
minusta on vaivaa, vaivaa,
vaikka kaikkeni olen antanut.

On surullista, että me vanhat ihmiset joudumme kokemaan syyllisyyttä siitä,
että elämme liian kauan. Näin ei saisi olla."

***

"Rauha longs for her home saying blue:
–Now they take off my home as I live too long,
I cause nothing but trouble, trouble,
even if I have given everything I can.

It is sad that we old people need to feel guilty for living too old.
It should not be this way."

K.S. 2004 – from a letter by a participant of this academic thesis

To my dearest,

Maria,

Pirjo and Tapio

ABSTRACT

Juha Puustinen

BENZODIAZEPINES AND COGNITIVE FUNCTIONING IN OLDER ADULTS
With emphasis on long-term use and withdrawal

From Department of Family Medicine, Institute of Clinical Medicine, Faculty of Medicine, University of Turku; Medical Teaching and Research Health Centre, University Consortium of Pori and Faculty of Medicine, University of Turku, Pori; Division of Clinical Neuroscience, Turku University Hospital; Department of Neurology, Institute of Clinical Medicine, Faculty of Medicine, University of Turku; Pori Health Centre, Pori City Hospital, Pori; Härkätie Health Centre; Lieto; Units of Neurology and Geriatrics, Satakunta Central Hospital, Pori, Finland.

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Benzodiazepines (BZD) and benzodiazepine related drugs (RD) are the most commonly used psychotropics among the aged. The use of other psychotropics taken concomitantly with BZD/RD or their cognitive effects with BZD/RD have not been studied frequently.

The aim of this academic thesis was to describe and analyse relationships between the use of BZD/RD alone or concomitantly with antipsychotics, antidepressants, opioids, antiepileptics, opioids and anticholinergics in the aged and their health. Especially, the relationships between long-term use of BZD/RD and cognitive decline were studied. Additionally, the effect of melatonin on BZD/RD withdrawal and the cognitive effects of BZD/RD withdrawal were studied.

This study used multiple data sets: the first study (I) was based on clinical data containing aged patients (≥65 years; N=164) admitted to Pori City Hospital due to acute disease. The second data set (Studies II and III) was based on population-based data from the Lieto Study, a clinico-epidemiological longitudinal study carried out among the aged (≥65 years) in the municipality of Lieto. Follow-up data was formed by combining the cohort data collected in 1990-1991 (N=1283) and in 1998-1999 (N=1596) from those who participated in both cohorts (N=617). The third data set (Studies IV and V) was based on the Satauni Study's data. This study was performed in the City of Pori in 2009-2010. In the RCT part of the Satauni Study, ninety-two long-term users of BZD/RD were withdrawn from their drugs using melatonin against placebo. The change of their cognitive abilities was measured during and after BZD/RD withdrawal.

BZD/RD use was related to worse cognitive and functional abilities, and their use may predict worse cognitive outcomes compared with BZD/RD non-users. Hypnotic use of BZD/RD could be withdrawn with psychosocial support in motivated participants, but melatonin did not improve the withdrawal results compared to those with placebo. Cognitive abilities in psychomotor tests did not show, or showed only modest, improvements for up to six months after BZD/RD withdrawal. This suggests that the cognitive effects of BZD/RD may be long-lasting or permanent.

Keywords: Aged, benzodiazepines, benzodiazepine related drugs, cognitive decline, cognitive recovery, follow-up, elderly, older people, epidemiology, randomised controlled trial, population-based, predictors, risk factors, withdrawal

TIIVISTELMÄ

Juha Puustinen

BENTSODIATSEPIINIT JA IKÄÄNTYVIEN KOGNITIIVINEN TOIMINTAKYKY - pitkäaikaiskäyttö ja vieroitus

Yleislääketiede, kliininen laitos, lääketieteellinen tiedekunta, Turun yliopisto; Opetusterveyskeskus, Porin yliopistokeskus ja lääketieteellinen tiedekunta, Turun yliopisto; Neurotoimialue, Turun yliopistollinen keskussairaala; neurologia, kliininen laitos, lääketieteellinen tiedekunta, Turun yliopisto; Porin perusturvakeskus; Porin kaupunginsairaala; Härkätien sosiaali- ja terveyspalvelut; neurologian ja geriatrian yksiköt, Satakunnan keskussairaala, Pori, Suomi.

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Bentsodiatsepiinit ja niiden tavoin vaikuttavat lääkkeet ovat yleisimpiä iäkkäiden käyttämiä psyykenlääkkeitä. Muiden psyykenlääkkeiden tai niiden yhteiskäytön yhteyksiä bentsodiatsepiinien ja niiden tavoin vaikuttavien lääkkeiden kanssa kognitiivisten kykyjen heikkenemiseen ei ole juurikaan tutkittu.

Tämän väitöskirjatutkimuksen tavoitteena oli kuvata ja analysoida bentsodiatsepiinien ja niiden tavoin vaikuttavien lääkkeiden, psykoosilääkkeiden, masennuslääkkeiden, opioidien, epilepsialääkkeiden ja antikolinergien käytön, erityisesti pitkäaikaiskäytön, yhteyksiä terveydentilaan ja kognitiivisen toimintakyvyn heikkenemisen vaaraan iäkkäillä. Erityistä huomiota kiinnitettiin näiden lääkeryhmien samanaikaisen käytön, erityisesti pitkäkestoisen samanaikaisen käytön, yhteyksiin kognitiivisen toimintakyvyn laskun vaaraan. Lisäksi tutkittiin, voidaanko melatoniinilla helpottaa pitkäaikaisesta bentsodiatsepiinien unilääkekäytöstä vieroittumista ja vaikuttaako bentsodiatsepiinien vieroitus kognitiiviseen tai psykomotoriseen toimintakykyyn.

Tutkimuksen osa-aineistoina käytettiin useita aineistoja: Ensimmäisenä osa-aineistona (I osatutkimus) käytettiin yli 65-vuotiaita Porin kaupunginsairaalan akuuttiosastojen potilaita, jotka saapuivat äkillisen sairauden vuoksi hoitoon heinäkuussa 2004 (N=164). Toinen osa-aineisto (II ja III osatutkimukset) muodostettiin Liedon kunnassa suoritetun väestöpohjaisen kliinis-epidemiologisen pitkittäistutkimuksen perus- ja seuranta-aineistoista. Liedossa suoritettiin vuosina 1990–1991 kaikkien kunnassa asuneiden 65 vuotta täyttäneiden (N=1283) laaja terveystutkimus, jossa osallistujia oli 1196 (93 %). Seuraava poikkileikkaustutkimus suoritettiin vuosina 1998–1999, jolloin aineiston muodostivat kyseisenä ajankohtana Liedossa asuneet 65 vuotta täyttäneet henkilöt (N=1596), joista 82 % saapui tutkimuksiin (N=1260). Seuranta-aineisto kognition muutoksen suhteen muodostettiin niistä henkilöistä, jotka olivat elossa molempien poikkileikkaustutkimusten aikana ja osallistuivat niihin (N=617). Tutkimuksen kolmantena osa-aineistona (IV ja V osatutkimukset) käytettiin Porissa 2009–2010 suoritettua Satauni-tutkimusta (N=92). Tässä tutkimuksessa vieroitettiin unilääkkeiden (bentsodiatsepiinien ja niiden tavoin vaikuttavien lääkkeiden) pitkäaikaiskäyttäjiltä unilääkitys RCT-asetelmassa pitkävaikutteista melatoniinivalmistetta ja lumetta käyttäen.

Bentsodiatsepiinien tai niiden tavoin vaikuttavien lääkkeiden käyttö oli yhteydessä alentuneeseen kognitiiviseen ja toiminnalliseen toimintakykyyn ei-käyttäjiin verrattuna. Seurantatutkimus osoitti, että näiden lääkkeiden käyttö oli yhteydessä myös huonomman kognitiivisen toimintakyvyn ennusteeseen. Unilääkekäytöstä oli mahdollista vieroittaa motivoituneita pitkäaikaiskäyttäjiä psykososiaalisella tuella, mutta melatoniini ei parantanut vieroitustuloksia lumeeseen verrattuna. Kognitiiviset kyvyt eivät parantuneet tai paranivat vain hyvin vähän bentsodiatsepiinien ja niiden tavoin vaikuttavien lääkkeiden vieroituksen jälkeen. Tämä voi viitata kognitiivisten haittavaikutusten olevan hyvin hitaasti paranevia tai jopa pysyviä.

Avainsanat: Ikääntyvät ja iäkkäät henkilöt, bentsodiatsepiinit, bentsodiatsepiinien tavoin vaikuttavat lääkkeet, kognitiivinen toimintakyky, kognitiivisen toimintakyvyn lasku, kognitiivisen toimintakyvyn paraneminen, epidemiologia, satunnaistettu kontrolloitu tutkimus, seurantatutkimus, vaaratekijät, vieroitus, väestötutkimus

CONTENTS

ABBREVIATIONS

AD	Alzheimer's disease
ADL	activities of daily-living
AHFS	American Society of Health-System Pharmacists
APA	American Psychiatric Association
ATC	Anatomical Therapeutic Chemical
BPSD	behavioural and psychological symptoms of dementia
BVRT	Benton Visual Retention Test
BWSQ	Benzodiazepine Withdrawal Symptom Questionnaire
BZD	benzodiazepine
CDR	Clinical Dementia Rating
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CNS	central nervous system
COR	cumulative odds ratio
CRM	controlled-release melatonin
DDD	defined daily dose
FIMEA	Finnish Medicines Agency (*former* NAM)
GABA	gamma-aminobutyric acid
GDR	gradual dose reduction
DEPS	Depression Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
GDS	Geriatric Depression Scale
GEE	Generalized Estimating Equations
HPLC	high performance liquid chromatography
HR	hazard ratio
IADL	instrumental activities of daily-living
ICD	International Classification of Diseases
INCB	International Narcotics Control Board
IST	Isaacs Set Test
LC-MS/MS	liquid chromatography-tandem mass spectrometry method
M	men

MMSE	Mini-Mental State Examination
N	number
NAM	National Agency for Medicines (*present* FIMEA)
NMDA	N-methyl-D-aspartate
NNH	number needed to harm
NNT	number needed to treat
OR	odds ratio
P	p-value
RCT	randomized, controlled trial
RD	benzodiazepine related drug
RR	risk ratio
SD	standard deviation
SRT	Simple Reaction Time
TMT-A	Trail Making Test, form A
TMT-B	Trail Making Test, form B
W	women
WHO	World Health Organization
95 % CI	95 % confidence interval
2-CRT	Two-Choice Reaction Time
10-CRT	Ten-Choice Reaction Time

LIST OF ORIGINAL PUBLICATIONS

I Associations between use of benzodiazepines or related drugs and health, physical abilities and cognitive function: a non-randomised clinical study in the elderly. Puustinen J, Nurminen J, Kukola M, Vahlberg T, Laine K, Kivelä SL. Drugs and Aging. 2007;24(12):1045-59.

II Use of CNS medications and cognitive decline in the aged: a longitudinal population-based study. Puustinen J, Nurminen J, Löppönen M, Vahlberg T, Isoaho R, Räihä I, Kivelä SL. BMC Geriatrics. 2011;11:70. *doi: 10.1186/1471-2318-11-70.*

III CNS medications as predictors of precipitous cognitive decline in the cognitively disabled aged: a longitudinal population-based study. Puustinen J, Nurminen J, Vahlberg T, Lyles A, Isoaho R, Räihä I, Kivelä SL. Dementia and Geriatric Cognitive Disorders Extra. 2012;2(1):57-68. *doi: 10.1159/000336710.*

IV Melatonin for sedative withdrawal in older patients with primary insomnia: A randomised double-blind placebo-controlled trial. Lähteenmäki R, Puustinen J, Vahlberg T, Lyles A, Neuvonen PJ, Partinen M, Räihä I, Kivelä SL. British Journal of Clinical Pharmacology. E-published 2013 Nov 29. *doi: 10.1111/bcp.12294.*

V Effect of withdrawal from long-term use of temazepam, zopiclone or zolpidem as hypnotic agents on cognition in older adults. Puustinen J, Lähteenmäki R, Polo-Kantola P, Salo P, Vahlberg T, Lyles A, Neuvonen PJ, Partinen M, Räihä I, Kivelä SL. European Journal of Clinical Pharmacology. 2014;70(3):319-29. *doi: 10.1007/s00228-013-1613-6.*

These articles are referred to in the text by Roman numerals I-V.

1. INTRODUCTION

Cognitive abilities in the aged have a crucial influence on public health and economics. Impaired cognitive abilities decrease functional abilities of daily living and quality of life. They also increase the use of health and social services and the need for supported living arrangements.

The ageing brain undergoes many changes. Pathological ageing may lead to cognitive decline and dementia (Drag et al. 2010). Epidemiologic studies have identified many modifiable risk factors for cognitive decline and dementing diseases (Barnes et al. 2011). Among these, physical inactivity, cognitive inactivity, depression, smoking, obesity, hypertension and diabetes mellitus are well-known modifiable risk factors for cognitive decline and dementing diseases, but together these risk factors explain only about half of the incident dementia cases (Barnes et al. 2011).

Use of benzodiazepines (BZD) or related drugs (RD) in the aged has been a controversial topic. In short-term use (a few weeks), BZDs and RDs have been proven to be fairly effective as hypnotics and anxiolytics (Holbrook et al. 2000; Stevens et al. 2005). However, in the aged there is evidence for only limited benefits with high risks for adverse outcomes (Glass et al. 2005). Risks associated with the use of BZD/RD include dependency (Swift et al. 1984), tolerance (Swift et al. 1984), disabilities in activities of daily-living (ADL) (Gray et al. 2006), cognitive decline or dementia (Holbrook et al. 2000; Glass et al. 2005; de Gage et al. 2012; Gallacher et al. 2012), mobility disabilities (Gray et al. 2006), falls (Hartikainen et al. 2007), fractures (Nurminen et al. 2010), chemical restraint (Nurminen et al. 2009), traffic accidents (Smink et al. 2010; Orriols et al. 2011), pneumonia (Obiora et al. 2012), cancer (Kripke et al. 2012), abuse (O'Brien C 2005) and increased mortality (Kripke et al. 1998; Gisev et al. 2011; Kripke et al. 2012; Obiora et al. 2012).

BZD/RD are most commonly used by the aged, precisely those with the greatest risk for cognitive decline and dementing diseases (Linjakumpu et al. 2002; Hartikainen et al. 2003), and their use in Finland has been increasing during the 1990's (Linjakumpu et al. 2002) and 2000's (Jyrkkä et al. 2006). BZD/RD are often used for years despite treatment recommendations not to do so (Barnas et al. 1991; Ishigooka et al. 1998; Egan et al. 2000; Neutel 2005).

BZD/RD are central nervous system depressing drugs (Bormann 2000), and they could theoretically adversely affect neural functions and impair the brain's plasticity and, thus, impair cognitive abilities (Ashton 1991). BZD/RD among the aged are commonly used concomitantly with other medications that have central nervous system (CNS) effects (Nurminen et al. 2009; Nurminen et al. 2010). The concomitant use of BZD/RD with other CNS medications and their combined effects on the cognitive abilities in the aged have not been previously studied.

The prevalence of Alzheimer's disease (AD) and other dementing diseases is expected to triple over the next 40 years (Brookmeyer et al. 2007). Thus there is a growing need for finding other modifiable risk factors that contribute to cognitive decline and dementia to expand preventive strategies, as the current medications available for Alzheimer's

disease (AD) and other dementing diseases have limited effect sizes (O'Brien et al. 2011). Additionally, many promising new drugs have failed in clinical trials (Green et al. 2009; Quinn et al. 2010).

There is a need for data on the factors associated with BZD/RD use that would predict cognitive impairment among the aged when BZD/RD are used alone or concomitantly with other CNS medications. These patients include those with normal cognitive functioning and those experiencing cognitive decline or dementia. Additionally, knowledge on the effects of easily achievable BZD/RD withdrawal interventions on cognitive functioning is needed. Among pharmacologic therapies, there are non-pharmacologic therapies for insomnia and anxiety available, and withdrawal of BZD/RD can be achieved with varying results (Lader et al. 2009).

With this data on risk factors for cognitive decline, future trials on modifiable risk factors for preventing cognitive decline and dementing diseases can be planned. Data from these studies can be generalised to clinical decision making at the level of individuals and of public health. Family physicians, geriatricians, psychiatrists and neurologists have the main responsibility for use of medications and health maintenance in the ageing and aged, and can be leaders in guidelines and appropriate pharmacotherapy for them.

2. DEFINITIONS

2.1. Older adult, aged

Defining old age or the aged is controversial. People age with great interindividual variability and even changes in the individual's organs during biological ageing can advance at various rates. People aged 55-65 years may be referred as older adults. In most developed countries a chronological age of 65 years or higher is an accepted threshold defining an aged person. This age group has been divided into subgroups of 65-74 year-olds (the ageing, young-old), 75-84 year-olds (the aged, old-old), and 85 year-olds and older (oldest-old) (Evans 1992).

Age and ageing can also be explored from the perspectives of biological age (physical and physiological changes), personal (self-perceived age), social (roles and role expectations by the community) and subjective factors (Laslett 1991).

2.2. Cognitive abilities, cognitive functioning

Cognitive abilities are a set of functions, skills or processes produced by the activity of neuronal networks in the brain. Psychologically, cognitive functioning has been divided into functions such as receiving, processing and conveying information. In receiving, information is selected and classified through perceptional functions. Information is processed using memory and learning (encoding, retrieval, storage), thinking (or mental organisation) and reorganisation of information. For perceptional functioning, attention is needed to sustain concentration on a particular object, action or thought (Lezak 1995).

Cognitive functioning can be measured with cognitive tests, tools designed to measure the level of a subject's cognitive abilities objectively. Cognitive abilities are needed to perform activities of daily-living (ADL), such as eating, taking care of oneself or to perform instrumental activities of daily-living (IADL), such as the use of tools, cooking, driving in unfamiliar environments and managing finances (Lezak 1995).

2.3. Benzodiazepines and related drugs

Benzodiazepines (BZD) and benzodiazepine related drugs (here: related drugs, RD) are the most commonly used medications affecting the central nervous system (CNS) (Linjakumpu et al. 2002; Hartikainen et al. 2003).

In 1952, the first version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-I) by the American Psychiatric Association (APA) introduced two different medical entities: psychosis and neurosis (Lopez-Munoz et al. 2011). It was concurrently shown that conventional psychoanalysis, a non-pharmacological treatment, might worsen some patients' condition and anxiety (Eysenck 1952). Previously used drugs,

alcohol, alkaloids from opium, other narcotic plants (hyoscyamus, datura, belladonna), paraldehyde, choral hydrate, the bromides, barbiturates and meprobamate had only limited effectiveness in treating anxiety (Lopez-Munoz et al. 2011). The first sedative drug marketed specifically for anxiety since 1955 was meprobamate under the brand name of Miltown®, but it was soon replaced by benzodiazepines during the 1960's (Lopez-Munoz et al. 2011).

The first benzodiazepine, chlordiazepoxide (initially named as methaminodiazepoxide), was discovered in 1956, patented in 1958 and was marketed as Librium® since 1960 (Lader 2011; Lopez-Munoz et al. 2011). Since then numerous benzodiazepine derivatives have been synthesised (Mandrioli et al. 2010). The most commonly used BZDs in Finland are temazepam, oxazepam, diazepam, alpratzolam, lorazepam and chlordiazepoxide (Konu et al. 2010). Among RDs the most commonly used are zopiclone and zolpidem, while zaleplone use is quite rare (FIMEA 2011).

The core chemical structure of BZD is the fusion of a benzene ring and a diazepine ring. The chemical structures of RDs are different from BZDs (NICE 2004), but they both mediate their effects by enhancing the action of the depressive neurotransmitter gamma-aminobutyric acid (GABA) (Roy-Byrne 2005). GABA is an important neurotransmitter as more than a third of all CNS synapses are operated by GABA (Bormann 2000). The depressive neurotransmitter GABA has a dynamic balance with the excitatory neurotransmitter glutamate, and together these systems modulate neuronal excitability (Bormann 2000). A rise in GABA levels results in sedative, hypnotic, anxiolytic, anticonvulsant, muscle relaxant and amnesic action by acting at the limbic, thalamic and hypothalamic CNS levels (Roy-Byrne 2005; Lopez-Munoz et al. 2011). BZDs are capable of producing CNS depression ranging from mild sedation through to coma (AHFS 2002). Adverse effects are thought to be mediated by GABA-receptors distributed throughout the cerebral cortex, limbic area, cerebellum and spinal cord (Gudex 1991).

Benzodiazepine related drugs (RD) (WHO 1995) are chemically distinct medications from BZD, and they are referred to in the literature as 'benzodiazepine-like drugs' (Orriols et al. 2011), 'non-benzodiazepines' (Hajak et al. 2003; Huedo-Medina et al. 2012) or 'Z-drugs' (Siriwardena et al. 2008; Huedo-Medina et al. 2012). RDs are pharmacologically similar to BZDs, having similar benefits, side effects and risks – at least as demonstrated in short-term placebo-controlled trials when BZDs and RDs have been compared (Holbrook et al. 2000; Glass et al. 2005; Huedo-Medina et al. 2012) or when patients' perceptions are compared between BZD and RD (Siriwardena et al. 2008). Authorities regard RDs as equivalent to BZDs (NICE 2004).

Currently, benzodiazepine pharmacotherapy has been recommended to continue no longer than one to three months (Einarson 1980; NICE 2004; NIH 2005; Lader et al. 2009). In the literature, long-term BZD use has been defined as a duration of regular or daily use greater than 12 months, with variation ranging from 12 weeks to more than 5 years, and short-term use being a shorter period – use less than 12 months (Barker et al. 2003).

3. REVIEW OF THE LITERATURE

3.1. Cognitive abilities and their change with ageing

3.1.1. Ageing brain

Normal ageing is associated with several biologic, structural and functional physiological changes in the brain. These changes are reflected in changes of neuropsychological, cognitive functioning.

Neuropsychological changes

During normal ageing, many cognitive functions remain relatively intact. These include vocabulary, semantic knowledge, procedural skills and emotional memory (Dore et al. 2007). However, ageing changes cognitive abilities such as processing speed, working memory, learning and executive functions (Dore et al. 2007).

Better cognitive performance is associated with younger age and higher education in population-based samples (Elias et al. 1997; Au et al. 2004; Dore et al. 2007). Even latter generations may have higher cognitive abilities compared to their parents, but this difference is only partly explained by a higher level of education (Au et al. 2004). Gender has been shown not to predict the cognitive performance (Dore et al. 2007). In normal cognitive ageing, minor differences between genders have been shown to remain stable in longitudinal prospective studies (Aartsen et al. 2004; de Frias et al. 2006).

Structural changes

Microscopically, neurons lose a number of their spines in normal ageing, but this change is not accompanied with significant neuron death (Scheibel et al. 1975; Nakamura et al. 1985; de Brabander et al. 1998; Morrison et al. 2002). However, age-related atrophy is non-linear, it accelerates with increasing age (Raz 2005).

Biochemical changes

Ageing is related to changes in the GABAergic, cholinergic, serotonergic, dopaminergic, and glutaminergic systems (Dickstein et al. 2007). These changes make neurons vulnerable to impaired transmission, potentially leading to disruptions in corticocortical signaling pathways (Dickstein et al. 2007).

Inhibitory function in the prefrontal cortex has been reported to be increased in a study exploring the aged monkey brain (Luebke et al. 2004). This may be related to increased action potential dependent release of gamma-amino butyric acid (GABA), but this hypothesis has not been confirmed (Dickstein et al. 2007). The cholinergic system deteriorates during normal ageing (Dumas et al. 2011). It has been even hypothesised that changes in cholinergic system are responsible for cognitive changes during ageing (Bartus et al. 1982). The serotonin system declines in normal ageing (Eppinger et al.

2011). Serotonin is hypothesised to be related to reacting to aversive stimuli and its depletion is connected to lower impulse control (Eppinger et al. 2011).

Normal ageing is also accompanied by dopamine dysregulation in multiple brain areas including the striatum and the frontal cortex (Kaasinen et al. 2000; Mozley et al. 2001; Reeves et al. 2002; van Dyck et al. 2002; Stark et al. 2004). Loss of dopamine activity detected in positron emission tomography is a strong predictor of cognitive performance decline, particularly motor and executive functioning abilities, even in normal ageing (Volkow et al. 1998; Backman et al. 2000; Erixon-Lindroth et al. 2005). Cognition can be affected by fluctuations of dopamine levels, as demonstrated in experimental studies (Luciana 1992; Luciana et al. 1998). Dopamine and serotonin are thought to interact in controlling behaviour, influencing both flexible and adaptive decision making (Dayan et al. 2009). The noradrenalin mediated transporter system is another system that declines in normal ageing (Ding et al. 2010). The noradrenalin system is involved in mediating arousal, but it may also affect cognitive functions (Berridge et al. 2003). The glutaminergic system undergoes changes during ageing (Dickstein et al. 2007). The number of neurons expressing ionotropic glutamate or N-methyl-D-aspartate (NMDA) receptors decrease with ageing (Hof et al. 2002; Morrison et al. 2002).

Functional changes

Normal ageing is accompanied by decreased resting blood flow and functional blood flow, influencing the metabolic rate of oxygen consumption and vascular reactivity of cerebral vessels to various chemical modulators (Cabeza 2002; Gazzaley 2005). Age-related decreased occipitotemporal activity is coupled with increased frontal activity (Davis et al. 2008). The clinical significance of this functional posterior-anterior shift is not understood, but it has been demonstrated across multiple, diverse cognitive functions including attention, visuospatial processing and memory (Davis et al. 2008), and it has been associated with age-related changes in the cholinergic system (Dumas et al. 2011).

3.1.2. Cognitive reserve theory

High education is thought to be a proxy indicator of cognitive reserve which is defined as an ability to cope more successfully with age-related changes in the brain (Stern 2002; Corral et al. 2006; Drag et al. 2010). Cognitive reserve may be passive (e.g. the capacity of neurons) and/or active (e.g. the ability to optimise performance by recruiting alternative brain networks, brain plasticity) (Stern 2002). Cognitive reserve has been positively associated with cognitive performance in multiple domains, including attention and memory (Corral et al. 2006).

Not all findings support the cognitive reserve theory. Instead of social factors (such as education), biological factors such as visual and auditory acuity can account for a large proportion of age-related variance across cognitive tests, including those assessing processing speed, reasoning, memory and fluency (Lindenberger et al. 1994; Lindenberger et al. 1997). Sensory functions decline due to ageing (Weale 1961). It has been proposed that more cognitive resources and effort are needed to compensate for this sensory decline in stimulus identification, and thus, this compensation of cognitive

resources could be taken away from more complex, cognitive operations such as memory (Ross et al. 1997; Buckner et al. 2000).

3.1.3. Changes of sleep during ageing and relations of sleep to health

Ageing and aged persons tend to sleep less than young or middle-aged persons (Ohayon et al. 2004). Ageing is associated with qualitative changes of sleep: poor sleep quality and fragmentation of sleep increase with age (Cajochen et al. 2006). Physiological functions of sleep are not completely understood. It has been hypothesised that sleeping is essential for CNS energy metabolism, consolidation of long-term memories and learning (Donlea et al. 2009; Wamsley et al. 2011). During sleep, the CNS modifies synaptic connections between neurons, which might explain brain plasticity needed for behavioural adaptability to environment, learning and memory (Cirelli et al. 2008; Donlea et al. 2009; Gilestro et al. 2009).

Adverse health outcomes due to reduced sleep are well-known: lack of sleep can distract many functions of the CNS, increase the risk of depression and cardiovascular diseases, and cause immunological and endocrinological disturbances (Cirelli et al. 2008; van Leeuwen et al. 2009; Buxton et al. 2010; Utge et al. 2010; Kronholm et al. 2011).

3.1.4. Role of anxiety and chronic insomnia on cognitive functioning

There is controversial evidence as to whether anxiety itself has negative effects on cognitive testing (Barker et al. 2003). Cognitive testing has not been shown to be affected by anxiety disorder (Gladsjo et al. 1998) or scoring highly on test anxiety scales (Chavez et al. 1983). A controlled study comparing drug-free anxious participants with normal participants found no difference between them in cognitive functioning except for a ball-bearing test measuring motor coordination (Gorenstein et al. 1995). Conversely, anxiety may lead to reduced test performance scores on tasks such as Digit Span (Lezak 1995).

Chronic insomnia is not related to impaired cognitive performance or the impairment may be selective. According to a recent meta-analysis (Fortier-Brochu et al. 2012), no differences between insomniacs and non-insomniacs have been found in cognitive performance in the domains of day-time attention (alertness, complex reaction time, speed of information processing, selective attention, sustained attention/vigilance) in neuropsychological testing. However, small to moderate magnitude effects from chronic insomnia were found in episodic memory, problem solving, manipulation in working memory and retention in working memory.

3.1.5. Protective factors against cognitive decline and risk factors for cognitive decline

Education and cognitive inactivity. Level of education can account for a significant portion of the cognitive variance associated with normal ageing (Drag et al. 2010). Years of education have been associated with lower rates of cognitive decline across time (Habib et al. 2007), better performance on cognitive tasks (Ardila et al. 2000), lower

incidence of dementia (Valenzuela et al. 2006) and reduced brain atrophy (Meguro et al. 2001). Engagement in leisure activities and cognitively stimulating activities have been associated with slower rates of age-related cognitive decline (Hultsch et al. 1999; Scarmeas et al. 2003; Wilson et al. 2005; Bielak et al. 2007) and a lower rate of dementia incidence (Scarmeas et al. 2001).

Physical inactivity. Physical inactivity is estimated to increase the risk of dementia with OR 1.39 (95 % CI 1.16-1.67) (Barnes et al. 2011). Physical activity and cardiorespiratory fitness have been associated with faster reaction times (Hillman et al. 2006), better cognitive performance (Colcombe et al. 2003; Newson et al. 2006), lower rates of cognitive decline over time (Weuve et al. 2004), and a lower risk of cognitive impairment or dementia (Laurin et al. 2001).

Depression. Depression is related to increased risk of dementia with OR of 1.90 (95 % CI 1.55-2.33) according to a recent meta-analysis (Barnes et al. 2011). There is no evidence that treatment of late-life depression can lower or delay dementia incidence (Barnes et al. 2011).

Smoking. Current smoking, but not being a former smoker, is associated with a higher risk of AD with RR of 1.59 (95 % CI 1.15-2.20) according to a meta-analysis (Barnes et al. 2011).

Obesity. There is evidence of an association between midlife, but not late life, obesity and increased risk of dementia with a pooled RR estimate of 1.60 (95 % CI 1.34-1.92) according to a meta-analysis (Barnes et al. 2011).

Hypertension. Hypertension in midlife, but not late-life, is associated with an increased risk of dementia with weighed RR 1.61 (95 % CI 1.16-2.24) for AD according to a meta-analysis (Barnes et al. 2011). There is a discordance between three meta-analyses (Wang et al. 2003; Peters et al. 2008; McGuinness et al. 2009) as to whether the treatment of hypertension prevents cognitive decline or dementia (Barnes et al. 2011).

Diabetes mellitus. A significant association between diabetes and all-cause dementia has been shown using meta-analyses technique with a combined RR 1.47 (95 % CI 1.25-1.73) (Lu et al. 2009) and a pooled RR 1.54 (95 % CI 1.33-1.79) (Profenno et al. 2010).

Diet. Reduction of caloric intake improves scores on memory tests (Witte et al. 2009). The Mediterranean diet is associated with lower risk of AD (Scarmeas et al. 2006; Sofi et al. 2010).

3.1.6. Delirium – acute somatic cognitive syndrome with poor outcomes

Delirium is a multifactorial syndrome in which cognition and the level of consciousness are disturbed, and psychotic and motor symptoms may co-exist (APA 1994; Meagher 2009). Attention is the most affected domain of cognition (APA 1994; APA 1999). Unlike the long-term cognitive decline or dementia, delirium develops acutely in hours or days, and the level of symptoms usually fluctuates (Inouye 2006; Fong et al. 2009). The old age and cognitive decline or dementia predispose to delirium due to disturbances

in homeostasis, acute disease or inappropriate drugs, as these factors may cause disturbances to neurotransmission (Inouye et al. 1996; Rahkonen et al. 2000; Gleason 2003; Cole 2004). Benzodiazepines or anticholinergic drugs should be avoided as they may cause or increase disturbances of GABAergic and cholinergic neurotransmission (Inouye 2006; Fong et al. 2009).

The overall prevalence of delirium in the community is 1-2 %, but in general hospital admission, the rate increases to 14-24 % of patients (Inouye 1998). Among the most critically ill aged patients, delirium incidence can reach 70-87 % (Pisani et al. 2003). It has been estimated that 30-40 % of deliriums related to hospitalisation could be prevented (Siddiqi et al. 2006). Delirium is not always a reversible condition, and it is associated with persistent cognitive and functional adverse outcomes, precipitated rate of progression of dementia and the increased risk of institutionalisation (Levkoff et al. 1992; Murray et al. 1993; Rahkonen et al. 2001; Siddiqi et al. 2006; Fong et al. 2009; Davis et al. 2012). The mortality rates among hospitalised patients with delirium range from 22 to 76 % (APA 1999).

3.2. Measures of cognitive functioning

Several measures of cognitive functioning have been developed to distinguish normal, age-related cognitive changes from the abnormal changes. The performance of cognitive measures are related to biological and functional changes of the brain. MMSE is the most commonly used general measure of cognitive functioning, but it cannot measure time-related performance such as reaction times. After the MMSE screening, more accurate neuropsychological tests, such as CogniSpeed, CERAD, TMT, are often needed for both research and clinical purposes.

MMSE (Mini-Mental State Examination)

MMSE (Mini-Mental Status Examination) is a widely used brief assessment tool for global cognitive function in the aged (Folstein et al. 1975). The MMSE contains 30 items which measure orientation to time and place, registration, attention, recall, language and visual construction (Folstein et al. 1975). The most commonly used threshold screen for dementia suspicion is 24 points of a possible total of 30 (Drag et al. 2010). Loss of neuronal synapses correlates with lower total MMSE points (Scheff et al. 2006).

CogniSpeed

CogniSpeed is a validated, commercial automatised battery of cognitive tests (Portin 1992). CogniSpeed contains tests for reaction time, automatic visual processing, working memory, controlled processing and attention. The program is available for use on standard PC-compatible workstations.

No age-related significant differences between age groups (39-49, 50-59, 60-69, 70-82 year olds) have been detected in the normal population in the Simple Reaction Time (SRT) test, and only minor age-related changes were reported in the Two Choice Reaction

Time test (2-CRT) and the Ten Choice Reaction Time test (10-CRT). Education does not explain this minor difference between age groups, nor the observation that male participants had slightly better cognitive abilities in the simple SRT and in the motoric programming tests (Portin 1992).

Examples of other cognitive measures

The Trail Making Test, forms A and B (TMT-A and TMT-B), evaluates attention, visuomotor processing speed and mental flexibility capacities (Reitan 1958). The Benton Visual Retention Test (BVRT) is a cognitive test which evaluates immediate visual memory (Benton 1965). The Isaacs Set Test (IST) is used when semantic verbal fluency and the speed of verbal production is tested (Isaacs et al. 1973). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) is a set of cognitive tests that include the MMSE for diagnosing Alzheimer's disease (Morris et al. 1988).

3.3. Benzodiazepines and related drugs in older adults

BZDs and RDs have been widely prescribed for many clinical indications since the 1960s. However, many of their adverse effects became evident shortly after their introduction.

3.3.1. Clinical indications

The GABA agonistic properties of BZDs and RDs have been utilised in treating anxiety, insomnia, agitation, panic disorder, depression, social phobia, seizures, muscle spasms, psychotic states, obsessive-compulsive disorder, alcohol withdrawal, as a premedication for medical or dental procedures and for side-effects induced by antidepressants and neuroleptics (Pollack 1993; AHFS 2002; Stevens et al. 2005).

The first randomized double-blind placebo-controlled clinical trial addressing the treatment of anxiety with BZDs was published ten years after the beginning of BZD marketing in 1970 (Lopez-Munoz et al. 2011). In this short-term four-week-trial, the effectiveness and safety of diazepam (10 mg/d) and phenobarbital (150 mg/d) were compared in a total sample of 472 patients (Hesbacher et al. 1970). Both active drugs were more effective than placebo, but did not statistically significantly differ from each other (Hesbacher et al. 1970). In terms of adverse effects, diazepam showed fewer adverse effects and fewer patients discontinued diazepam treatment (Hesbacher et al. 1970).

Since the 1970s, dozens of RCTs have been performed to study the effects of BZD or RD on their second main indication, insomnia (Glass et al. 2005, Huedo-Medina et al. 2012).

3.3.2. Prevalence of use and predisposing factors for use

BZDs became the most widely prescribed medications in the world during the decade between 1965 and 1975 (Rickels 1978). In the mid-1970's BZDs were consumed by

10-20 % of the total population in Western countries (Balter et al. 1974). In 2010, approximately 6-10 % of American adults still used BZD/RD, and use was estimated to be even higher in some parts of Europe and especially among the aged (Verdoux et al. 2005; INCB 2011).

In Finland, BZDs and RDs have been the most commonly used psychotropics among the aged patients (Hartikainen et al. 2003; Rikala et al. 2011), and their use increased among this population during the 1990's (Linjakumpu et al. 2002). In 1990, 19 % of the aged used these medications and by the end of decade the proportion of users had increased to 22 % of the aged population (Linjakumpu et al. 2002). The trend of increasing BZD/RD use continued between 1998 and 2003 (Jyrkkä et al. 2006). The highest load of sedative drugs (which also includes sedative psychotropics other than BZDs or RDs) is concentrated in the oldest-old (Linjakumpu et al. 2004; Jyrkkä et al. 2006) and in those using multiple concomitant medications (Jyrkkä et al. 2009).

The characteristics of short- and long-term BZD users have been compared in a Dutch cross-sectional study (Zandstra et al. 2002). Long-term users were older and had a more severe history of mental health problems for which they had received more treatment; these patients used more psychotropic drugs in general and consulted hospital specialists more frequently. They also had more physical illness and reported a lower self-perceived health status.

3.3.3. Adverse outcomes

History

The first report of benzodiazepine addiction was published in 1963 (Greenblatt et al. 1978). In 1964 World Health Organization (WHO) reported that chlordiazepoxide was a drug capable of producing addiction of the barbiturate type (Barker et al. 2003). In 1980, the risk of addiction was proven to be a non-biased conclusion when low-dose diazepam that had been used for a six-year period was stopped in a cross-over double-blind design and the withdrawal syndrome developed (Winokur et al. 1980). In 1984, WHO categorised benzodiazepines as "controlled" substances due to their capacity to create dependence and depression of the central nervous system, actions which lead to distortions in motor function, behaviour and personality (Lopez-Munoz et al. 2011). In some North American states prescription of benzodiazepines was restricted and made subject to the same control measures as other drugs, including opiates, barbiturates and amphetamines, and the maximal length of BZD prescriptions was limited to 30 days (Rado 1989). Prescription use fell by 50 %, but the use of other older and more dangerous anxiolytics and hypnotics rose (Maddaloni 1990).

Associated adverse outcomes of benzodiazepine and related drug use

A longitudinal study with a follow-up of six years showed that users of BZD had a hazard rate (HR) of 1.23 (95 % CI = 1.09-1.39) for developing mobility disability and a 1.28 HR (95 % CI = 1.09-1.52) for developing ADL disability (Gray et al. 2006).

In an observational study, BZD, RD, barbiturate and sedative antihistamine users had a four times higher mortality compared to non-users, and the effect was dose-related (Kripke et al. 2012). Those aged 75 or older and using any of these hypnotics had the worst prognosis for survival compared to younger and non-users of hypnotics (Kripke et al. 2012). BZD use has been associated with an increased risk of pneumonia and increased mortality (Obiora et al. 2012).

In Finnish studies, a higher score in the sedative index of medication (Linjakumpu et al. 2003) has been associated with poor cognitive abilities, female gender, impaired instrumental activities of daily living (IADL), poor-self perceived health, loneliness, worse muscular strength and falling (Taipale et al. 2011a; Taipale et al. 2011b).

Chronic BZD treatment has been reported to lead to GABA down-regulation in the CNS (Ashton 1989; Hutchinson et al. 1996) and, thus, discontinuation of BZD may lead to reduction of GABA which then leads to a more excited CNS, resulting in an increase in irritability, myoclonus and seizures (APA 1990).

Frequently reported and well-known acute withdrawal symptoms for BZD discontinuation are anxiety, insomnia, restlessness, agitation, irritability and muscle tension (APA 1990). Withdrawal symptoms after the use of BZDs with short half-lives appear within 6 to 12 hours, peak within 2 to 4 days and subside in 1 to 3 weeks, whereas withdrawal symptoms from long half-life benzodiazepines start within 24 to 48 hours, peak in 4 to 7 days and then subside in 2 to 4 weeks (Schweizer 1995).

Other epidemiologically reported adverse outcomes related to use of BZD/RD are increased risks of fallings (Hartikainen et al. 2007), fractures (Nurminen et al. 2010; Nurminen et al. 2012), substance abuse (O'Brien C 2005), traffic accidents (Smink et al. 2010; Orriols et al. 2011), chemical restraining (Nurminen et al. 2009) and cancer incidence (Kripke et al. 2012).

3.4. Cognitive abilities and use of benzodiazepines and related drugs in the aged

Adverse effects on cognition in the aged from BZD and RD use, whether short-term or long-term, have been reported in many cross-sectional, longitudinal studies (long-term use) and experimental studies (short-term use).

3.4.1. Associations between cognitive abilities, benzodiazepines and related drugs

Use of BZD/RD was associated with the risk of dementia, according to ICD-9 criteria in a large registry based case-control study (Wu et al. 2009). This relationship with a dementia diagnosis seemed to be inversely time-dependant in the current users who had the highest risk for diagnosed dementia, and the risk decreased as the duration of BZD discontinuation lengthened (Wu et al. 2011).

3.4.2. Use of benzodiazepines and related drugs as predictors of cognitive decline

Studies among pooled adult and aged populations

The evidence of cognitive short-term and long-term effects of BZD use was summed up in a non-systematic review by Barker and co-authors (2003). Short-term cognitive negative effects reported to be related to BZD use were anterograde amnesia, decreased verbal fluency, psychomotor speed / performance, reaction time, coordination and attention, effortful processing, episodic memory, semantic memory and explicit memory (Barker et al. 2003).

The long-term adverse cognitive effects related to BZDs, reported in several studies, are self-experienced memory disturbances despite tolerance of the sedative effects in long-term use, deterioration of episodic memory, impaired non-verbal memory, and in some studies in verbal memory and verbal learning. Not all case-control studies have found memory impairments and the finding sometimes conflict (Barker et al. 2003). In terms of attention and concentration, some studies support the notion that long-term BZD use is associated with significant impairment in the domains of concentration, attention, vigilance, speed of information processing and sustained attention, but these relationships are highly conflicting (Barker et al. 2003). Data on the relation between long-term BZD use and change of visuospatial skills are also conflicted (Barker et al. 2003). Other cognitive effects (decreased arousal and psychomotor skills, conceptual tracking abilities, critical flicker fusion threshold, general intellectual ability, motor speed and fine coordination, reaction time, speed of information processing) have been reported in individual studies or by using different methods and, thus, they cannot be summed up (Barker et al. 2003).

The process of gathering data for the review by Barker and co-authors (2003) was not described and participants of all ages were included. Thus, this review cannot be generalised to ageing and aged persons even if the authors conclude that ageing and the aged form the majority of long-term users. Additionally, the authors conclude that due to dissimilar settings, populations and cognitive measures, the studies are difficult to be compared reliably.

In 2004, Barker and co-authors published a systematic review and meta-analysis of the cognitive effects of long-term BZD use. The studies included were performed among participants with a mean age of 47.6 years with a range of 21-75 years and a mean time of BZD use of 9.9 years (range 1 to 34 years). The mean numbers of BZD users (33.5 ± 28.9) and controls (27.9 ± 19.6) were quite small. Thus, this meta-analysis cannot be generalised to older adults and the aged. Despite the young mean age, long-term benzodiazepine users were consistently more impaired than controls across all cognitive categories examined, with effect sizes ranging in magnitude from –1.30 to –0.42; the mean weighted effect size was –0.74 ± 0.25.

Longitudinal, epidemiologic studies among the aged with normal cognitive abilities

A systematic review of long-term BZD use and the risk of cognitive decline in the aged was published in 2005 (Verdoux et al. 2005). Six papers containing aged general population samples (60 years or older) were identified, and they had follow-up periods

ranging between two and eight years (Dealberto et al. 1997; Fastbom et al. 1998; Hanlon et al. 1998; Lagnaoui et al. 2002; Paterniti et al. 2002; Allard et al. 2003).

Of these studies, three found an increased risk of cognitive decline (Dealberto et al. 1997; Lagnaoui et al. 2002; Paterniti et al. 2002), two found no association (Hanlon et al. 1998; Allard et al. 2003), and two reported a lower risk of cognitive decline in former or ever BZD users (Dealberto et al. 1997; Fastbom et al. 1998). Inconsistently, Dealberto with co-authors (1997) found an increased risk among ever and former users of BZD for dementia, but not for current users. The authors concluded that the discrepant findings might be due to methodological differences, especially regarding the definitions of exposure and cognitive outcome (Verdoux et al. 2005).

Since the publication of the systematic review by Verdoux and co-authors in 2005, six population-based prospective studies have been published (Bierman et al. 2007; van Vliet et al. 2009; de Gage et al. 2012; Desplenter et al. 2012; Gallacher et al. 2012; Mura et al. 2012). Thus, ten longitudinal, prospective studies of BZD/RD use and cognitive decline among the aged with normal cognitive abilities (Hanlon et al. 1998; Allard et al. 2003; Bierman et al. 2007; van Vliet et al. 2009; Desplenter et al. 2012) or dementia (Fastbom et al. 1998; Lagnaoui et al. 2002; de Gage et al. 2012; Gallacher et al. 2012; Mura et al. 2012) have been published.

Please, see the summary of these studies in Appendices 1 and 2.

Additionally, five longitudinal, prospective studies have been performed in which BZD/RD use were studied as a part of psychotropic medication among other psychotropic medications reported cognitive decline among the aged with normal cognitive abilities (Berg et al. 1996; Dealberto et al. 1997; Paterniti et al. 2002; Allard et al. 2003; Wright et al. 2009).

Please, see Appendix 3 for a summary.

Of all these longitudinal studies, five showed precipitous cognitive decline (Dealberto et al. 1997; Hanlon et al. 1998; Paterniti et al. 2002; Bierman et al. 2007; Wright et al. 2009), and three suggested higher incidence of dementia among BZD/RD users (Lagnaoui et al. 2002; de Gage et al. 2012; Gallacher et al. 2012). One study showed that chronic BZD/RD users are cognitively impaired compared to non-users, but the cognitive decline did not differ between them during the follow-up (Mura et al. 2012). However, four studies failed to show a relation between long-term use of BZD/RD and change in cognitive abilities (Dealberto et al. 1997; Allard et al. 2003; van Vliet et al. 2009; Desplenter et al. 2012), and one suggested that BZD use had protective effects against incident Alzheimer's disease (Fastbom et al. 1998). In a study reporting psychotropic use predicting cognitive decline (Berg et al. 1996), BZDs were pooled together with neuroleptics, antidepressants and sedatives in the analyses and thus the role of BZD's cannot be evaluated separately; this study was not included in the material for critical review by Verdoux and co-workers (2005).

Cognitively disabled aged or aged with dementia

Only two longitudinal studies (Ellul et al. 2007; Rosenberg et al. 2012) have been performed on the risk of precipitous cognitive decline and the use of BZD/RD among patients with Alzheimer's disease (details shown in Appendix 4), but no other longitudinal studies among the cognitively deteriorated aged have been published. Among those patients with pre-existing Alzheimer's disease, the risk of cognitive decline was nearly three-fold among those taking sedatives. The risk of precipitous decline among those with concomitant use of sedatives and antipsychotics seemed to be additive (Ellul et al. 2007). In the elderly with incident Alzheimer's disease, BZD use was associated with greater severity of dementia, more rapid decline in MMSE and the progress of dementia as measured by CDR (Clinical Dementia Rating) (Rosenberg et al. 2012).

3.4.3. Experimental studies of benzodiazepines or related drugs in older adults and the aged

A meta-analysis of randomised, controlled trials (RCTs) of BZDs or RDs among the aged showed that short-term use of sedative hypnotics has only limited advantages in the treatment of insomnia when weighing their adverse effects (Glass et al. 2005). The RCTs included in this analysis had participants with ages ranging from 57 to 98 years and were short-term studies with follow up of one week or less in 11 studies; more than one week but not more than two weeks in seven studies; more than two weeks but not more than nine weeks in only six studies. No placebo-controlled studies longer than nine weeks long have been performed in the aged.

Meta-analysis of BZDs (Glass et al. 2005) and RDs (Huedo-Medina et al. 2012) have shown very modest NNT's for improved sleep quality, total sleep time and awakenings, but common NNH and adverse events such as cognitive and psychomotor adverse effects, morning or daytime fatigue. The authors concluded that in people over 60, the benefits of BZD, RD or other sedatives in short-term use, may not justify the increased risk, particularly if the patient has additional risk factors for cognitive or psychomotor adverse events (Glass et al. 2005).

No objective neuropsychological measurements on cognition were made in the RCTs used in the meta-analysis by Glass and co-authors (2005), so the determination of cognitive adverse effects has been based on the participants' subjective or the researchers' observational reports on memory loss, confusion or desorientation. Thus, minor changes in cognition may have been unrecognised.

3.5. Means for benzodiazepine or related drug withdrawal in older adults and the aged

The acknowledged relationship between the BZD/RD use and the increase risk of adverse outcomes has led to the research of means for BZD/RD withdrawal. Several different withdrawal protocols or strategies containing non-pharmacologic or pharmacologic interventions and combinations of them have been studied.

Systematic reviews and meta-analysis

For withdrawal of long-term BZD/RD use, a Cochrane collaboration systematic review examined substitutive pharmacotherapy (Denis et al. 2006).

Two meta-analyses on alternative treatment approaches for BZD discontinuation (Voshaar et al. 2006; Parr et al. 2009) have identified different methods compared to routine care. These meta-analysis dichotomised the RCTs to minimal interventions and systematic discontinuation interventions (Voshaar et al. 2006); or to brief interventions, gradual dose reduction (GDR) and psychological interventions (Parr et al. 2009). GDR has been compared with combinations of GDR and psychosocial interventions or substitutive pharmacotherapies (Voshaar et al. 2006; Parr et al. 2009). Parr and co-authors (2009) accepted studies restricted to out-patient settings, while Vorshaar and co-authors (2006) accepted studies performed both in out- and in-patient settings.

The Cochrane collaboration systematic review by Denis and co-authors (2006) included eight RCTs with a total of 458 outpatients, with ages ranging from 18 to 70 years and mean ages ranging from 39 to 54 years. The heterogeneity of settings, designs, source and format of interventions prevented the pooling of data for a meta-analysis. Results support GDR rather than abrupt withdrawal of BZD. Progressive withdrawal (over 10 weeks) appeared preferable if compared to abrupt since the number of drop-outs was lower and withdrawal was judged more favourable by the participants. The low mean ages in the RCTs included in the review limit the generalizability of these results to the ageing and the aged.

The meta-analysis by Voshaar and co-authors (2006) gathered the evidence of different strategies for withdrawal from long-term BZD use in in- and out-patient settings. 29 articles met the inclusion criteria. The authors identified two groups of interventions: minimal intervention (e.g. giving advice in the form of a letter or meeting to a large group of people; N=3) and systematic discontinuation interventions (defined as treatment programmes led by a physician or psychologist; N=26). Mean ages in studies of minimal interventions (N=3) and systematic discontinuation alone (N=1) were higher (71 and 62 years, respectfully) than in those systematic discontinuation studies with combined psychotherapy (N=5; mean 56 years) and pharmacotherapy (N=21; mean 52 years). Both minimal and systematic interventions or pharmacotherapeutic augmentation with imipramine or carbamazepine were found to be more effective than routine care. Due to the different mean ages of participants, only the results considering minimal interventions and systematic discontinuation alone can be generalised to the ageing and the aged.

The latest meta-analysis by Parr and co-authors (2009) identified 32 RCTs of which five compared brief intervention (in these, N=3 studies, individuals were randomised; N=2, practises were randomised), gradual dose reduction (N=1), psychological treatment to routine care in out-patient settings (N=3). In 25 of 32 RCTs GDR was compared to combinations with GDR and psychological interventions (7 RCTs) and GDR with substitutive pharmacotherapy (17 RCTs). One RCT compared combinations of GRD and psychological interventions to GRD and abrupt BZD withdrawal. The mean age of participants in these RCTs varied between 38-71 years, with the mean age being 60 or

over in 10 of 32 RCTs. Despite the great variation of age within and between the RCTs, no different age groups were used in the analysis, which reduces the generalizability of the meta-analysis to the ageing and the aged. The meta-analysis showed that GDR and brief interventions provided superior BZD discontinuation rates at post-treatment compared to routine care. Psychological treatment combined with GDR was superior to both routine care and GDR alone. Substitutive pharmacotherapies did not add to the impact of GDR and abrupt substitution of BZD by other pharmacotherapy was less effective than GDR alone.

Melatonin in the withdrawal RCTs of BZDs or RDs in older adults and in the aged

Previous RCTs on BZD/RD withdrawal aided by melatonin are summarised in Appendix 5.

The effect of controlled-release melatonin (CRM) in a 2 mg dose was compared to placebo in an RCT (Garfinkel et al. 1999). The double-blind six-week trial showed that participants in the CRM group had discontinued their BZDs more often (P=0.006) and had better sleep-quality scores (P=0.04) than those in placebo group. Open follow-up until 6 months revealed that of the 24 participants who discontinued BZD and received CRM, 19 maintained good sleep quality. Results of this trial may be generalised with caution to the ageing and the aged.

Another six-week RCT compared fast release melatonin in a 3 mg dose to placebo (Cardinali et al. 2002). Forty-five participants regularly taking BZDs were assessed by the quality of morning freshness, daily alertness, sleep quality, and sleep onset and offset times. No significant modifications of sleep or wakefulness were detected after BZD withdrawal. Compared to baseline, there was a general lack of changes in the quality of wakefulness or sleep in participants taking melatonin or placebo. Sleep quality for participants taking melatonin during the first two weeks of treatment was significantly lower than that of placebo.

A third RCT compared melatonin (5 mg dose) to placebo in the discontinuation of BZD in participants with insomnia (Vissers et al. 2007). There were no differences between the melatonin and placebo groups at six weeks after withdrawal from BZD, after six months or at one year. However, about half of the participants in this trial were younger than 65, which weakens the generalizability of these results to the aged.

Register study

A retrospective analysis of a prescription database identified 512 patients who had initiated treatment with CRM 2 mg over a 10-month period (Kunz et al. 2012). A majority (74 %) of the patients were aged 55 or older. Of 112 patients who had previously used BZDs, 31 % discontinued treatment with BZDs three months after starting CRM treatment. The discontinuation rate was non-significantly higher in patients receiving two or three melatonin prescriptions compared to those who received only one prescription (42 % vs. 28 %; P=0.21).

3.6. Effect of withdrawal of benzodiazepines and related drugs on cognitive function in older adults and in the aged

Previous studies on the effects of BZD/RD withdrawal on cognition are summarised in Appendix 6.

Register study

A large registry-based case-control cohort study showed that current users of BZD have the highest risk for diagnosed dementia (cases N=8434, matched comparison subjects N=16706), but the risk for dementia diminishes as the time to discontinuation of use increases (Wu et al. 2011).

Prospective withdrawal studies

Only a few studies on the cognitive effects of BZD withdrawal in older adults and in the aged have been published (Salzman 1992; Rummans et al. 1993; Curran et al. 2003; McAndrews et al. 2003; Tsunoda et al. 2010). The minimum age for participants in these studies varied from 55 years (Rummans et al. 1993), 60 years (McAndrews et al. 2003; Tsunoda et al. 2010), to 65 years or older (Curran et al. 2003). Salzman with co-workers only reported mean ages for withdrawal (83 years) and control groups (89 years).

All of these BZD withdrawal studies had open-label designs (Salzman 1992; Rummans et al. 1993; McAndrews et al. 2003; Tsunoda et al. 2010) and in all of these studies participants have been allocated to withdrawal groups or to control groups according to their own willingness to withdraw. Only a minority of these studies had BZD-free comparison groups (Rummans et al. 1993; McAndrews et al. 2003), one study had no comparison group and participants were compared to themselves over time (Tsunoda et al. 2010). Only one of these studies (Curran et al. 2003) had a controlled double-blind design in terms of beginning BZD withdrawal. Three of these studies were performed in the community-dwelling aged (Rummans et al. 1993; Curran et al. 2003; McAndrews et al. 2003), and two in nursing home dwellers (Salzman 1992; Tsunoda et al. 2010). The majority of these studies have been performed among the healthy aged without serious psychiatric or neurological diseases (Krahn et al. 1993; Curran et al. 2003; McAndrews et al. 2003), but one study included a sample with schizophrenia, primary insomnia, dementia and bipolar disorder (Tsunoda et al. 2010). Cognitive re-assessments were performed 6-10 days (Rummans et al. 1993), 2-3 weeks (Salzman 1992), 4 weeks (McAndrews et al. 2003), 5 weeks (Tsunoda et al. 2010), or 24 and 52 weeks (Curran et al. 2003) from the discontinuation.

Despite the heterogeneity of settings, methods and populations, all BZD withdrawal studies performed in the aged have concordantly supported the hypothesis that withdrawing is beneficial for producing at least partial cognitive recovery in the aged. In all of these studies, BZD withdrawal did not cause increased symptoms. However, further concern for potential cognitive long-term or permanent residual effects of BZDs was raised (Salzman 1992; Rummans et al. 1993; Curran et al. 2003; McAndrews et al. 2003; Tsunoda et al. 2010).

In the withdrawal study with the highest methodological quality and the largest sample size (Curran et al. 2003), BZDs were withdrawn in 104 BZD long-term users aged 65 or older using double-blinded cross-over design, and compared to 35 long-term users not willing to withdraw. The first group of withdrawers were double-blindly tapered from the first week of the trial, with the second group from the twelfth week. All participants were assessed at 0, 12 and 24 weeks and 50 % were reassessed at 52 weeks. 80 % of withdrawers remained BZD free for 24 weeks. There was little difference between the two withdrawer groups, but performance of the withdrawers improved on several cognitive / psychomotor tasks at 24 or 52 weeks. Withdrawers and continuers did not differ in sleep or BZD withdrawal symptoms. The authors conclude that withdrawal from BZDs produces some subtle cognitive advantages for older people without withdrawal symptoms or emergent sleeping difficulties. The results suggest that long-term use of BZD does not aid sleep.

In a non-systematic review of the short-term and long-term effects of BZD use, Barker and co-authors (2003) summed up the evidence of potential improvements of cognitive deficits after discontinuation of chronic benzodiazepine use. They identified nine studies of which four suggested cognitive recovery, two partial and three showed no recovery after long-term BZD use. The authors were concerned about the possibility that long-term BZD use may lead to persisting or residual cognitive deficits long after the drugs have been withdrawn (Barker et al. 2003), but the this review was not limited to the ageing and aged thus possessing a problem for generalizability to these age groups.

A meta-analysis on persistence of the cognitive effects of BZDs has been published by the same authors (Barker et al. 2004). A literature search in MEDLINE, PsychINFO and the Cochrane Controlled Trials Register of publications between 1980 and 2000 identified 10 studies. The mean age of participants was 47.1 years with a range of 21-75 years. The mean duration of BZD use was 10 years and the median length of time between initial and post-withdrawal assessment was 3 months (range 1-65). All 12 cognitive domains improved after withdrawal of long-term BZD use, but of these, visuospatial, attention / concentration, problem solving, general intelligence, psychomotor speed had statistically significant improvement. Previous long-term BZD users performed more poorly across 11 of 12 cognitive categories assessed at follow-up, with the exception being sensory processing. The authors concluded there may be some permanent deficits or deficits related to long-term BZD use that takes longer than 6 months to recover completely. These results cannot be generalised to the ageing and aged population due to young mean age of participants.

3.7. Summary of the literature review

The normal ageing brain undergoes several biological structural and functional changes. However, knowledge of normal brain ageing is limited and diffuse. Cognitive changes are related to these biologic neuronal changes, but the relationships between biologic and cognitive changes are neither well known nor understood.

No data on the effects of medications, especially BZD/RD, on biologic neuronal ageing has been published. The mechanisms by which BZD/RD use may change normal ageing of the brain or may be involved in precipitous cognitive decline are unknown. It can be hypothesised that the CNS depressive properties of BZD and RD may change the counts and distributions of receptors, decrease plasticity and formation of new synapses in the brain.

Many modifiable risk factors for cognitive decline and dementia have been identified. However, knowledge on exposure to medications and associated cognitive changes is limited. A majority of the longitudinal studies suggest that use of BZD/RD in the aged is related to a greater risk of cognitive decline or dementia. The knowledge of concomitant BZD/RD use with other CNS medications is very limited: no previous studies have been published on the concomitant use of CNS medications in the cognitively normal aged and change of their cognitive abilities. Only two studies have been published previously on concomitant use of CNS medications and cognitive decline among the aged with pre-existing Alzheimer's disease.

No research on concomitant BZD/RD use with other medications among the aged with normal cognitive abilities has been published previously. There is no previously published data on precipitous cognitive decline associated with BZD/RD use in patients with cognitive deterioration for any reason or for reasons other than dementia apart from Alzheimer's disease.

Only a few controlled BZD/RD withdrawal studies have been published, and they used samples with poor generalizability to populations of older adults and the aged. BZD/RD withdrawal studies with follow-up of cognitive abilities have been published in very small numbers. These studies suggest that the cognitive decline caused by long-term BZD/RD use may be long-lasting or permanent.

A very large proportion of adult and aged populations are exposed to BZDs or RDs worldwide. This combined with the potential negative effects of BZDs and RDs on cognitive abilities may possess a major public health concern, but also a potentially preventable risk factor for cognitive decline and dementia.

4. AIMS

In detail, the aims of this academic thesis were to describe and analyse:

1. The associations between cognitive abilities and the use of benzodiazepines or related drugs in the aged.

2. The use of benzodiazepines or related drugs as a predictor of cognitive decline among the cognitively normal aged.

3. The use of benzodiazepines or related drugs as a predictor of cognitive decline among the aged with pre-existing cognitive decline.

4. The effects of benzodiazepines or related drugs withdrawal intervention in primary care among older adults and in the aged.

5. The relationships between withdrawal of benzodiazepines or related drugs and changes in cognitive abilities in older adults and in the aged.

5. MATERIALS AND METHODS

5.1. Study settings and populations

The five studies in this academic thesis included three separate samples (Figure 1).

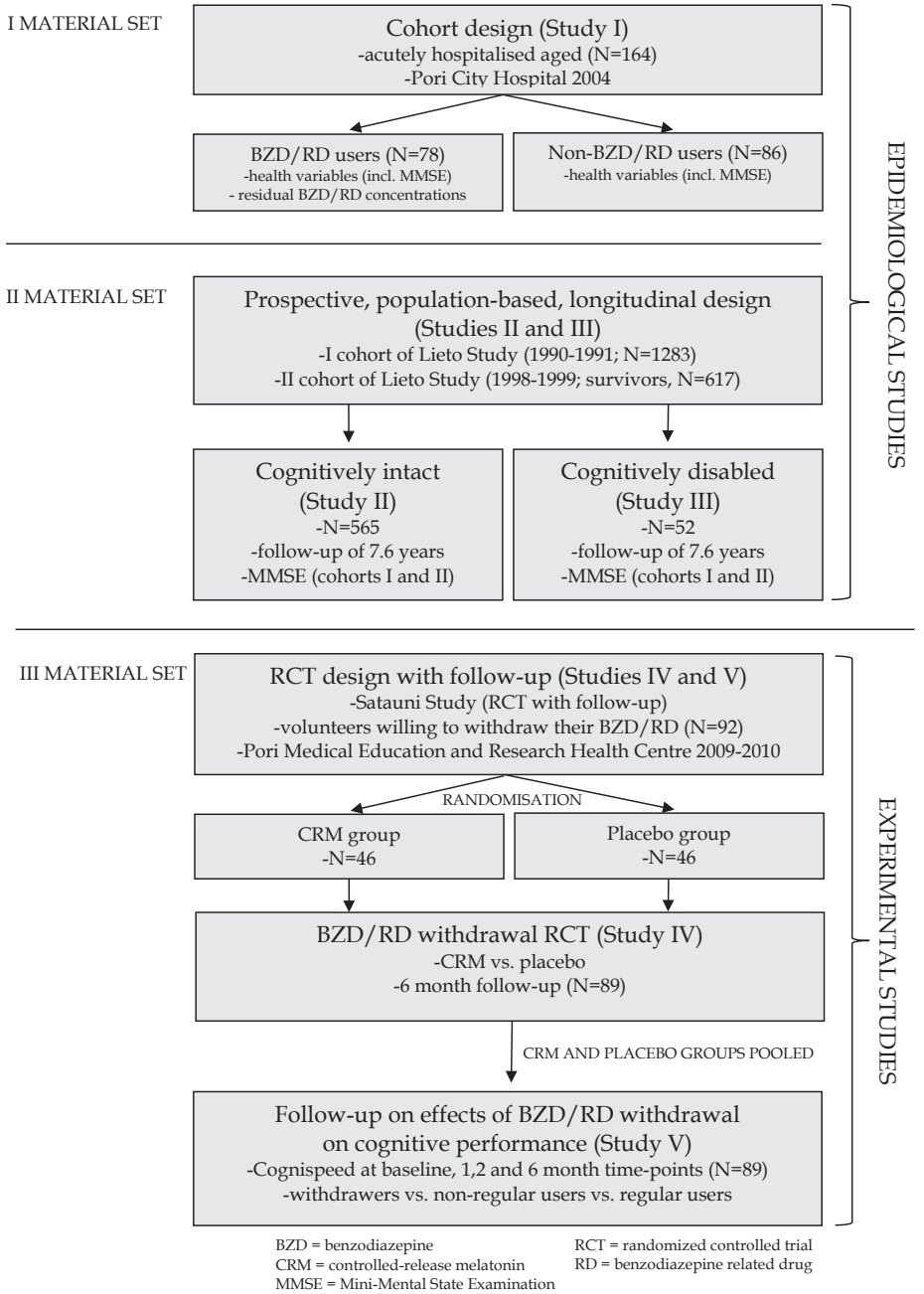


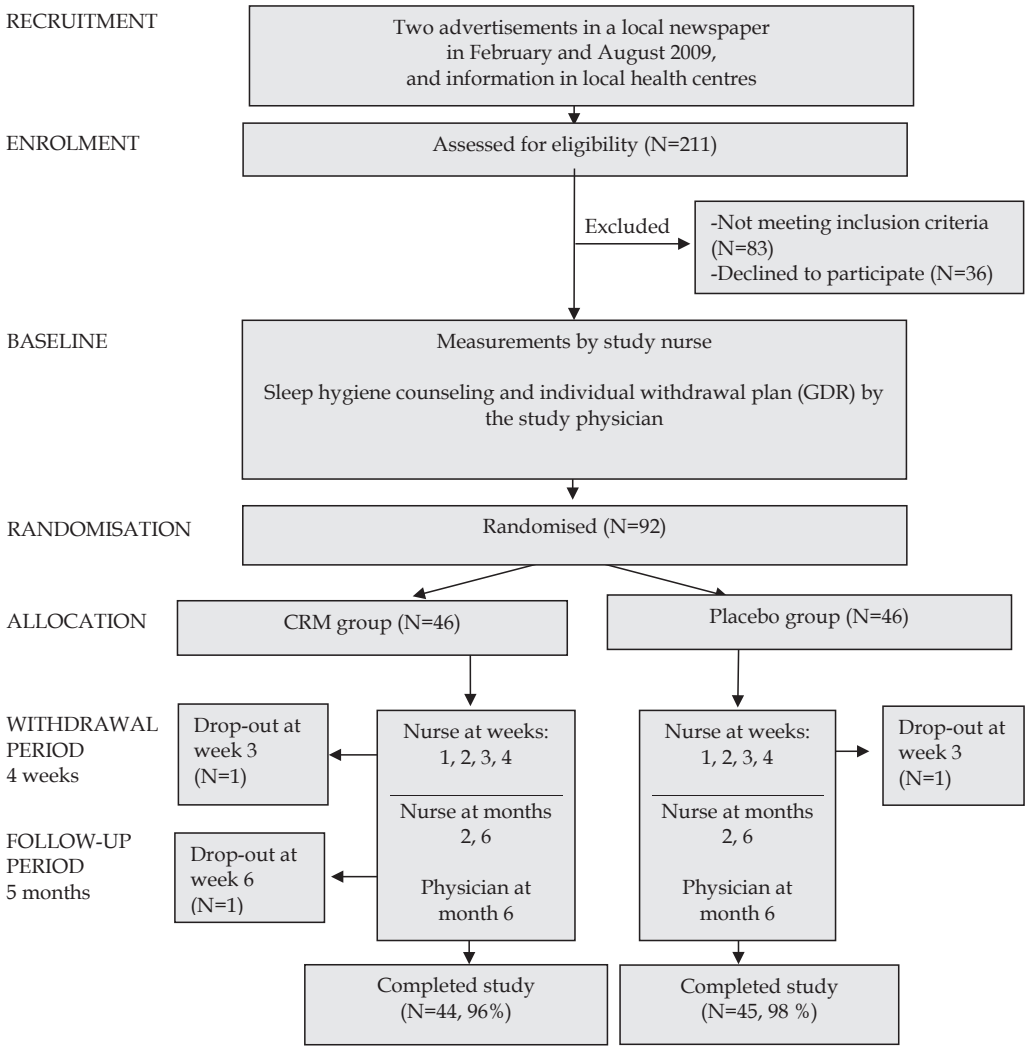
Figure 1. Hierarchy and design of Studies I-V.

Study I consisted of 188 consecutive patients who were admitted to the Pori City Hospital, Finland, due to acute illness. The aim of this observational cross-sectional study was to describe the relationships between BZD/RD use and health, functional abilities and cognitive functioning. Aged patients (≥65 years; N=164) who were born in 1939 or earlier were included. The data collection for Study I occurred between 1 June to 30 June 2004.

Studies II and III were a part of a large, longitudinal population-based study conducted in the municipality of Lieto, South-Western Finland (Isoaho et al. 1994; Löppönen et al. 2003). The first phase of the Lieto Study was conducted between 1 October 1990 and 31 December 1991, and the second phase between 1 March 1998 and 31 September 1999. The population of the first phase consisted of residents who were born in 1926 or earlier (N = 1,283). Of these, 1,196 (93 %, 488 men and 708 women) participated. The population of the second phase consisted of residents born in 1933 or earlier (N = 1,533), of whom 1,260 (82 %) participated.

The populations between Studies II and III differ by the level of baseline cognitive abilities. The sample of Study II comprised the participants of the first phase of who had scored 24 to 30 total points in the Mini-Mental State Examination (MMSE) and who were alive and participated in the second phase of the longitudinal Lieto Study (N=565; 227 men and 338 women). The population for longitudinal Study III was formed from those who participated in the first cohort and scored 0-23 total score in the MMSE, indicating pre-existing deteriorated cognitive functioning and who were alive and participated in the second cohort. The realised sample for the Study III population consisted of 52 residents (17 men and 35 women). The mean follow-up times were 7.6 ± 0.5 years in the both studies.

Studies IV and V were part of the Satauni Study, which was a single-centre, randomised, placebo-controlled double-blind study. The Satauni Study was primarily targeted to assess the effect of melatonin use in relation to withdrawal from long-term BZD/RD use (Study IV). Altogether 211 volunteer individuals were assessed for eligibility. Eighty-three of them (39 %) did not meet the inclusion criteria and 36 (17 %) declined to participate, leaving 92 eligible participants to be randomised to the controlled-release melatonin (CRM) (N=46) and placebo groups (N=46) (Figure 2). In Study IV, participants received either 2 mg of oral controlled-release melatonin (CRM) or placebo, counselling in sleep hygiene, information about possible withdrawal symptoms and psychosocial support, while the BZD/RD was withdrawn. Recruitment took place between 16 February 2009 and 14 January 2010 and follow-up lasted until 23 July 2010. Participants were primary health care outpatients living in the Province of Satakunta, in western Finland. Persons aged 55 years or over using temazepam, zopiclone or zolpidem on a regular long-term basis (prior 30 days of daily use or longer) due to primary insomnia according to DSM-IV criteria (APA 1994) were included in the study. At the beginning, 92 participants (62 women and 30 men) met the inclusion criteria. In total, 89 participants (60 women and 29 men) completed the study.



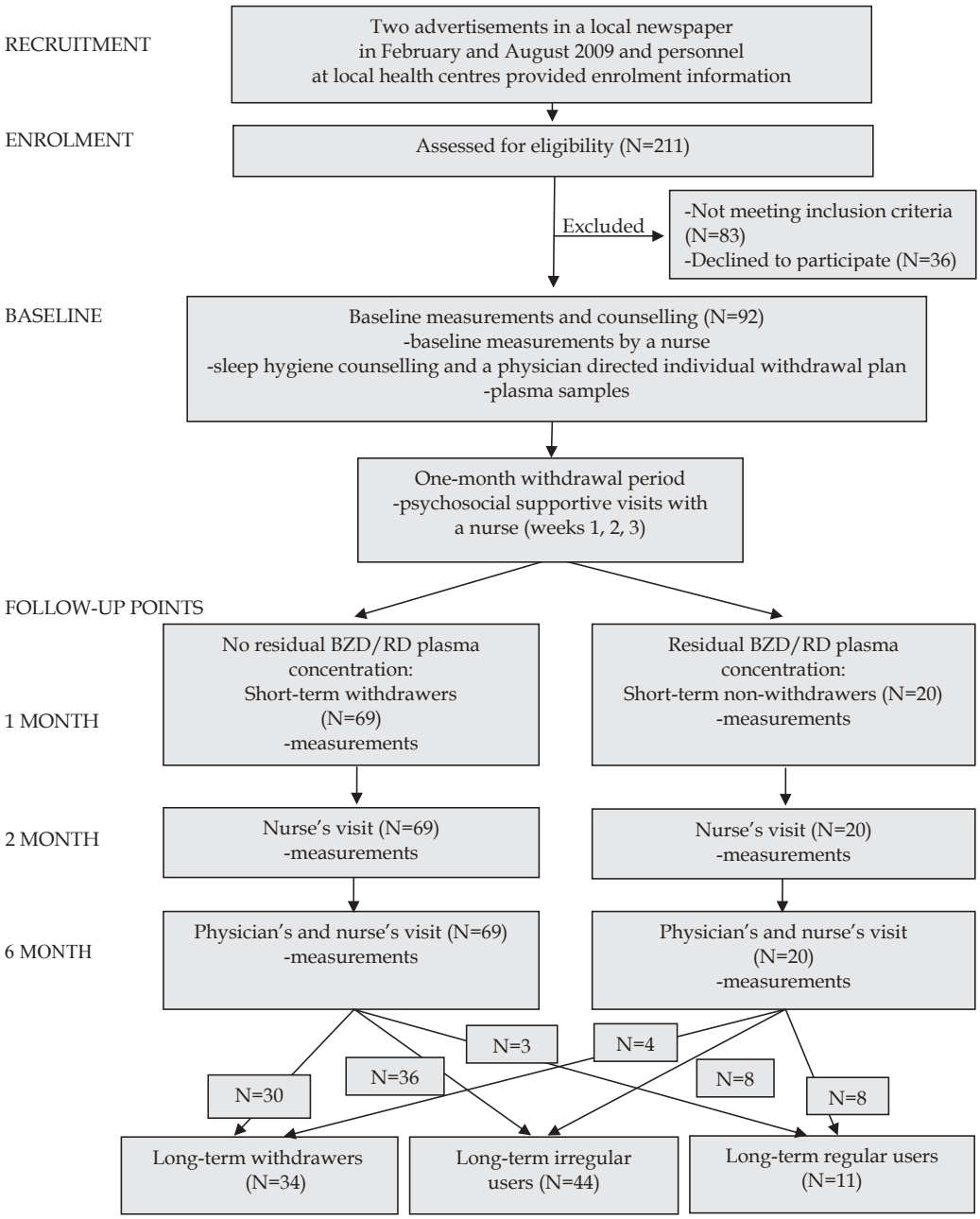
GDR = gradual dose reduction
CRM = controlled-release melatonin

Figure 2. Flow of participants (Study IV).

In Study V, participants of Study IV were categorised according to the success of their withdrawal of BZD/RD during the follow-up. Short-term and long-term BZD/RD withdrawers' cognitive performances were compared to those of controls at baseline and at the follow-up points of 1, 2 and 6 months. A control group was formed from a Finnish cohort of women (N=101) aged 55 years and over who had been previously tested and reported BZD/RD-free (Alhola et al. 2006; Karakorpi et al. 2006; Alhola et al. 2010).

In Study V, participants with no measurable plasma concentrations of temazepam, zopiclone, zolpidem or other BZDs after the one-month withdrawal period formed

the short-term withdrawers' group (N=69, 78 %) and those with measurable plasma concentrations formed the short-term non-withdrawers' group (N=20, 22 %) (Figure 3).



There were two drop outs at week 3 and one at week 6 (N shown per protocol).

Nurse's visit = A participant's visit at the Medical Teaching and Research Health Centre for individual psychosocial support and follow-up measurements performed by the nurse.

Figure 3. Flow of participants (Study V).

For Study V, long-term BZD/RD withdrawal was judged by interviewing participants and by having the physician to check their medical records and prescriptions for the six months since withdrawal began. Participants who did not use any BZD/RD at the six-month follow-up point formed the long-term withdrawers' group (N=34, 38 %) and those who had used any BZD/RD during that period formed the long-term non-withdrawers' group (N=55, 62 %). At the six-month follow-up, participants were further classified into one of three groups according to their BZD use: i) long-term withdrawers (N=34, 38 %), ii) long-term irregular users (N=44, 49 %, using medication more often than once a month, but not every evening) or iii) long-term regular users (N=11, 12 %, daily use) (Figure 3).

5.2. Ethical approvals and informed consents

Study I was approved by the Ethics Committee of Satakunta Central Hospital, Hospital District of Satakunta and the Medical Director of Pori City Hospital.

The collections of the first and second Lieto Study cohorts (Studies II, III) were approved by the Joint Ethical Committee of University of Turku and Turku University Hospital, Hospital District of Southwest Finland.

The study protocol of Satauni Study (Studies IV and V) was approved by the Ethics Committee for the Satakunta Hospital District and the National Agency for Medicines of Finland and registered as EudraCT 2008-0006795-30.

Written informed consents were obtained for all studies (Studies I-V).

5.3. Data collection

5.3.1. Background characteristics

In Study I, the participants were interviewed on their health, symptoms, functional abilities and cognitive functioning during the week prior to hospital admission. Depressive symptoms during the hospital treatment were assessed with the Depression Scale (DEPS) (Salokangas et al. 1994). All discharge diagnoses related to current treatment period according to ICD-10 classification (WHO 1999) were collected for all patients from the hospital records. The residual serum levels of the three most commonly prescribed BZDs or RDs in Finland (oxazepam, temazepam and zopiclone) (NAM 2004) were analysed in patients regularly using the corresponding drug.

In Studies II and III, detailed data concerning, for example, participants' education, socio-demographic, health behaviour diseases, cognitive and functional abilities were collected in the both phases of Lieto Study by interviews, measurements, tests and clinical examinations (Isoaho et al. 1994; Löppönen et al. 2003). When the participants could not be interviewed, proxies (relatives or caregivers) of the participants were interviewed.

In Studies IV and V, background characteristics (gender, age, marital status, education and occupation) and data concerning health behaviour, diseases, sleep behaviour, and especially medication use, were collected at baseline. Clinical examinations were performed on each patient. Information on cognitive performance, mood and quality of life were measured and recorded.

5.3.2. Cognitive measures

In Study I, cognitive abilities were assessed using the Mini-Mental State Examination (MMSE) (Folstein et al. 1975) on the first or second day of the patient's hospital stay.

In Studies II and III, a trained nurse administered the MMSE (Folstein et al. 1975) to all participants from both cohorts in 1990-1991 and 1998-1999 of Lieto Study.

In study V, a trained nurse assessed each patient's cognitive performance using a computerised test battery of attention, vigilance, and controlled psychomotor processing (CogniSpeed®, version 1.2) (Portin 1992) at baseline and at one, two and six months. Attentional performance and psychomotor performance were measured by the Simple Reaction Time (SRT) test and the Two-Choice Reaction Time (2-CRT) test, while sustained attention was assessed by the Vigilance test. The six-month follow-up study began with a one-month BZD withdrawal period and consisted of three follow-up points, i.e., at one, two and six months.

5.3.3. Medication data and classification of medications

In Study I, the author of this thesis interviewed the patients and checked their prescriptions and medical records on arrival at the hospital. Data on current medications used at home were collected for all patients, including the names, dosages and frequencies of dosing of all regular and irregular medications (given on an as-needed basis). Each medication was classified using the Anatomical Therapeutic Chemical (ATC) classification system (NAM 2004).

In Studies II and III, participants and their proxies had been requested to bring all of their prescription forms and drugs with them to the interview so that actual medication use could be confirmed. All regularly or irregularly taken prescription drugs and non-prescribed drugs (e.g. vitamins) taken during the seven days prior to the interview were recorded. Drugs were defined by using the Anatomical Therapeutic Chemical (ATC) Classification (NAM 1991). The groups of drugs defined as having a CNS effect and therefore included in the analyses are shown in Appendix 7. Eight variables describing the categories of CNS medications were then formed: BZD/RD, antipsychotics, antidepressants, any psychotropic (including BZD/RD, antipsychotics or antidepressants), opioids, anticholinergics, antiepileptics and any CNS medications (including BZD/RD, antipsychotics, antidepressants, opioids, anticholinergics or antiepileptics). Finally, 21 variables describing all combinations of the CNS medications were formed.

In Studies IV and V, a physician ascertained the use of BZD/RD and other medications by interviews and self-reports were confirmed by checking data on filled prescriptions, medical records and visual inspection of pill boxes. Participants' use of BZD/RD was re-established by interviews at one and six months, and their use of all medications at the one month follow up. Interviews and measurements were performed at baseline, during the one-month withdrawal period and at month 6 after withdrawal initiation in order to assess the intervention's effects on BZD withdrawal, withdrawal symptoms and adverse events (Figure 2).

5.3.4. Laboratory testing

Studies I, IV and V included laboratory testing of BZD/RD residual concentrations.

In Study I, residual BZD/RD concentration testing was used to establish correlations between concentrations and cognitive abilities. The residual serum levels of oxazepam, temazepam and zopiclone were analysed in patients regularly using the corresponding drug. Laboratory assistants took venous blood samples between 7 and 8 a.m. in the morning following admission. Altogether 51 samples were taken, and 10 oxazepam, 13 temazepam and 28 zopiclone residual serum concentration analyses were performed. The patients whose residual serum concentrations were analysed formed the material for analysing the relationships between residual serum concentration of specific BZD/RD and health, functional and cognitive abilities. The analyses were performed utilising high performance liquid chromatography (HPLC).

In Studies IV and V, residual concentrations were used to ensure the withdrawal of benzodiazepines or related drugs after the withdrawal period. Venous blood samples were drawn from all participants between 10 a.m. and 3 p.m. to determine plasma BZD concentrations at baseline and after one month from the beginning of withdrawal. The concentrations of temazepam, zopiclone, zolpidem, diazepam, desmetyldiazepam and oxazepam could be determined using a liquid chromatography-tandem mass spectrometry method (LC-MS/MS).

5.3.5. Withdrawal intervention and follow-up of changes in cognitive performance

Study IV combined melatonin augmented placebo-controlled benzodiazepine or a related drug withdrawal trial with psychosocial support.

At baseline, a physician provided individual sleep hygiene counselling, including discussions with participants about regular sleep rhythm and the influence of the following on sleep: normal changes in sleep patterns related to ageing, conditions of the bedroom and bed, exercise, eating and alcohol use, coffee and stimulants prior to sleeping, deep and calm breathing, and psychic and physical relaxation in bed and, if anxieties arise, advice to write them on paper. The physician performed a clinical examination of each participant and, in agreement with the participant, determined an individual withdrawal schedule. Most often the recommended reduction from the initial BZD daily dose was usually 50 % per week. Furthermore, the physician informed participants about possible withdrawal symptoms.

Participants in the randomised placebo-controlled study received either oral melatonin 2 mg or placebo at 7-8 p.m. for one month, while their BZD dose was gradually decreased each week during that month. The intervention included the possibility of weekly psychosocial support during the first month and at two and six months (Figure 2).

Participants visited a physician twice and a nurse seven times over the following six months. These visits consisted of a nurse's assessments; the physician's examinations; decision(s) about an individualised withdrawal plan and sleep hygiene counselling; individual psychosocial support and nurse interviews regarding symptoms during the withdrawal month (one week, two, three weeks and at the end of one month); follow-up assessments with a nurse (at two and six months); and follow-up examinations with a physician (at six months).

The data for Study V was derived from IV. As melatonin did not improve withdrawal symptoms in Study IV and the previous literature shows no cognitive effects related to melatonin (CRM 2 mg) (Otmani et al. 2008), data from the melatonin and placebo groups were pooled together and the data analysed according to the success of BZD/RD withdrawal during the follow-up (Figures 2 and 3). Analytically Study V consisted two parts. In the first part, data derived from the Study IV was used to examine cognitive performance before and after BZD/RD withdrawal from long-term hypnotic use. In the second part, the cognitive test results from the first part were compared to those from a previous study of non-insomniacs who were not using BZD/RD hypnotics. These participants belonged to a Finnish female cohort (N=101) who did not use BZD/RD and who had been tested previously using CogniSpeed (Alhola et al. 2006; Karakorpi et al. 2006; Alhola et al. 2010).

5.4. Statistical analyses

Associations between benzodiazepine and related drug use and health variables (Study I)

The Chi-square test or Fisher's exact test was used to test the differences in categorical background variables between BZD/RD users and the non-users (comparison group), and between the single BZD/RD users, concomitant users of two or more BZ/RD and the non-users of these drugs. Testing for normalities of continuous variables utilised the Shapiro-Wilk test. The differences in continuous background variables between the groups were tested using the two-sample t-test, one-way analysis of variance, Mann-Whitney U test or Kruskall-Wallis test.

The cognitively intact users of at least one CNS medication were first compared to those using no CNS medications. The second comparison group consisted of the non-users of CNS medications examined. The differences between the treatment and comparison groups in categorical variables describing health, and functional and cognitive abilities were analysed using binary or cumulative logistic regression analyses. Cumulative logistic models were used for ordinal-type dependent variables consisting of three

categories. Results of logistic regression were quantified by calculating odds ratios (OR) and cumulative odds ratios (COR) with 95 % confidence intervals (95 % CI). The two sample t-test and analysis of variance were used to test the differences in continuous variables describing health and functional and cognitive variables between the groups.

In the second phase, these analyses were adjusted for possible confounding variables (age, gender, number of all medications excluding BZD/RD, number of medications with CNS effects excluding BZD/RD and diagnosed diseases) found to differ between treatment and control groups in analysing the background characteristics. Positively skewed variables were log(x+1)-transformed and negatively skewed MMSE sum scores were $(x+1)^2$-transformed for adjusted analyses.

Spearman's correlation coefficients were calculated to analyse the associations between residual concentrations and DEPS or MMSE total points. These analyses were also performed by adjusting for possible confounding variables by calculating Spearman's partial correlation coefficients.

Benzodiazepine and related drug use and their concomitant use of them with other CNS medications as predictors of cognitive decline (Studies II and III)

The strategies for statistical analyses were identical in Studies II and III. Participants in these studies were differentiated at baseline according their MMSE sum scores. Study II was performed among those who scored in the range of 24-30 MMSE sum score at baseline (cognitively intact) and Study III among those who scored in the range of 0-23 MMSE sum score (pre-existing cognitive decline).

Statistical analyses were performed on the total sample and separately by gender and age group (younger = 65-74 yrs and older ≥75 yrs). Participants using one CNS medication at the beginning of the follow-up were compared i) with participants who did not use any of these medications at baseline and ii) with participants not using that specific medication. Participants using a combination of two or more of the CNS medications were compared with participants using none of the individual CNS medications or their combinations.

Chi-square and Fisher exact tests were used to test differences between genders and age groups, and between medication users and control groups at baseline and during the follow-up examination. The statistical significance of differences in the use of medications between baseline and follow-up examination were analysed with McNemar's test for every group of medications. The significance of changes in MMSE total scores during the follow-up in the total population and in all subgroups were tested with the Wilcoxon signed rank test. Differences between mean MMSE total scores and the changes of mean MMSE total scores between the groups were tested with the Mann-Whitney U test. Associations between the use of a specific group of CNS medications or the use of a combination of CNS medications and the risk of cognitive decline were analysed by the Mann-Whitney U test. Significance of differences in cognitive functioning changes during the follow-up between the users of a certain group of CNS medications or the users of a combination of CNS medications and the corresponding control group of

nonusers were tested with the Mann-Whitney U test. As these are nonparametric tests, the analyses conservatively estimate realised P-values.

After these analyses, adjusted analyses using analysis of covariance were performed for those groups in which the associations between the use of a certain CNS medication or the concomitant use of certain CNS medications and the risk for cognitive decline were either significant ($P<0.050$) or tending toward significant ($0.050<P<0.100$) in the bivariate analyses. Associations between probable confounding variables (age, gender, education, hypertension, atrial fibrillation or flutter, diabetes mellitus, congestive heart disease, and smoking at baseline) and the decline in MMSE sum scores were analysed in the total population.

In Study II, only the variables that were significantly associated with decline (higher age, $P<0.001$, and congestive heart disease, $P=0.002$) were used as adjustments in the analyses of covariance.

In Study III, higher age ($P<0.001$) was associated with a statistically significant decline in MMSE total scores, and this variable was controlled as a confounding variable in the analyses of covariance.

Effects of benzodiazepines and related drugs withdrawal and cognitive performance (Studies IV and V)

Categorical variables are described as counts and frequencies, continuous variables by means and standard deviations or medians and ranges. Differences in continuous variables between the CRM and the placebo groups were tested by Student's two-sample t-test or by the Mann-Whitney U-test, when appropriate. Variables measured with ordinal or nominal scales between the CRM group and the placebo group were tested using a Chi-square or Fisher's exact test. For selected variables 95 % confidence intervals (CI) were calculated, and Intention-To-Treat and Per Protocol analyses were included. The following defined daily doses (DDD) were used to compare BZD use: i) for participants <70 years of age, zolpidem 10 mg, zopiclone 7.5 mg and temazepam 20 mg, and ii) for those ≥70 years, temazepam 10 mg. DDDs were categorised into five groups (0, 0.01-0.20, 0.21-0.99, 1 and >1) for statistical analyses. The differences in changes between and within the DDD groups were analysed by cumulative logistic regression using Generalized Estimating Equations (GEE) with an independent correlation structure. The results are described as Cumulative Odds Ratios (COR) with 95 % CI. The sum of withdrawal symptoms was determined according to the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ), a self-report scale of 20 items (typical withdrawal symptoms) and additional 4 items for self-perceived symptoms (open questions) with a sum point ranging from 0 to 40 (or to 48, if there are also additional self-perceived symptoms) (Tyrer et al. 1990). BWSQ sum points were analysed using repeated measures analysis of variance using a compound symmetry covariance structure. The group was used as a fixed effect and time as a repeated effect. The symptom sums were log-transformed for statistical analysis due to their being positively skewed.

Concerning Study V, CRM was not superior to placebo in managing BZD/RD withdrawal; the withdrawal symptoms were similar in both groups (Study IV). Furthermore, previous literature shows that there have been no cognitive effects related to melatonin (CRM 2 mg) (Otmani et al. 2008). Therefore, the CRM and placebo groups of Study IV were pooled together in further analysis and re-categorised into short-term withdrawers and non-withdrawers, and long-term withdrawers, irregular users and non-withdrawers according to the use of BZD/RD at the follow-up points (Figure 3; Study V).

In Study V, differences in baseline measurements between short-term withdrawers and non-withdrawers were tested by chi-square and Fisher exact tests in variables measured with nominal or ordinal scales, and by the Mann-Whitney U test or two-sample t-test for normally distributed continuous variables. Differences in reaction times in the SRT, 2-CRT, and Vigilance tests between the three groups based on BZD/RD use duration were tested by the Kruskal-Wallis test. Negative binomial regression was used to test for differences in the number of errors in the 2-CRT test, and to test the relative error proportion in the Vigilance test results between groups classified according to the duration of the BZD/RD use at baseline.

Cognitive performance (median reaction times in ms on the SRT, 2-CRT, and Vigilance tests) between short-term BZD/RD withdrawers and non-withdrawers was compared at baseline and during follow-ups at one, two, and six months. Analysis employed repeated measures analysis of variance with unstructured covariance where the group served as a fixed factor, and time as a repeated factor. Dunnett's method was used for further comparison of follow-up measurements to those made at baseline. Reaction times in the SRT, 2-CRT, and Vigilance tests were log-transformed for repeated measures analysis of variance due to their positively skewed distributions. Negative binomial regression with Generalized Estimating Equations (GEE) with an independent working correlation structure was used in a longitudinal analysis of the number of errors in 2-CRT and the relative error proportion in the Vigilance test.

In the second part of the Study V, demographic data and reaction times in the SRT, 2-CRT, and Vigilance tests were compared between women and men in the withdrawal study sample at baseline, and at one, two, and six months. To evaluate gender differences in cognitive functioning in the Study V, women (N=59) were compared to men (N=30). Women did not differ from men in age; the number of participants with a higher number of depressive symptoms; the number of medications; reaction times in the SRT, 2-CRT, and in Vigilance tests the number of errors in the 2-CRT; relative error proportion in the Vigilance test; duration of BZD use; smoking; use of alcohol; satisfaction with life; self-reported health; expected health a year after the interview; marital status; or education. Since there were essentially no differences by gender, the entire group of withdrawal study participants were compared to the Finnish BZD-free female cohort (Alhola et al. 2006; Karakorpi et al. 2006; Alhola et al. 2010). Variables measured with nominal or ordinal scales were tested by chi-square and Fisher exact tests and continuous variables by the Mann-Whitney U-test.

Definition of statistical significance and statistical programs

In Studies I-V, P-values less than 0.05 were considered statistically significant. P-values between 0.05 and 0.10 were considered as tendencies toward statistical significance.

The statistical analyses were performed using SAS© version 9.2 and SAS Enterprise Guide© version 4.1.

6. RESULTS

6.1. Background characteristics in different study materials

6.1.1. Associations between benzodiazepine and related drug use and health variables (Study I)

Background characteristics

In Study I, altogether 188 consecutive patients were admitted during the study period. Of these patients, 164 were 65 years or older, forming the material for Study I. Their mean age was 81.6 ± 6.8 years. The MMSE total points of the 119 patients (73 %) were available for the analyses. Eighty-two (82) patients scored 20 or more MMSE total points, and 79 of them were willing to be interviewed further (Table 1). Altogether 51 blood samples were taken, of which 10 oxazepam, 13 temazepam and 28 zopiclone residual serum concentration analyses were performed.

Table 1. Gender, age, diagnoses and place of discharge of patients in BZD/RD and comparison groups and differences between the groups (Study I).

	Patients with MMSE data (N=119)					**Patients scoring ≥20 in MMSE and with interview data (N=79)**				
	BZD/RD (N=64)		**Comparison (N=55)**		**P**	**BZD/RD (N=37)**		**Comparison (N=42)**		**P**
	N	**%**	**N**	**%**		**N**	**%**	**N**	**%**	
Women	54	84	37	62	0.028	31	84	26	62	0.030
Admitted from other hospitals	17	27	16	29	0.759	11	30	10	24	0.552
Discharged to										
Home	56	88	50	91		33	89	39	93	
Long-term institution	6	9	1	2	0.237	3	8	0	0	0.207
Other hospital	1	2	2	4		1	3	2	5	
Dead	1	2	2	4		0	0	1	2	
Diagnoses potentially related to cognitive disturbances										
All neurological disorders	19	30	10	18	0.145	5	14	4	10	0.727
Dementias	10	16	3	5	0.076	2	5	0	0	0.216
Other neurological	11	17	7	13	0.498	3	8	4	10	1.000
Psychiatric disorders	6	9	1	2	0.121	2	5	1	2	0.597
Depression	6	9	1	2	0.121	2	5	1	2	0.597
Infective diseases	11	17	13	24	0.382	4	11	8	19	0.309
Alcohol related diseases	4	6	1	2	0.372	1	3	1	2	1.000
Abuse	3	5	1	2	0.623	0	0	1	2	1.000
	Mean ± SD		**Mean ± SD**		**P**	**Mean ± SD**		**Mean ± SD**		**P**
Age (years)	82.1	6.8	81.0	6.6	0.365	79.9	5.3	80.0	6.0	0.981
Number of discharge diagnoses	4.4	1.9	4.1	1.5	0.426	4.3	1.7	4.0	1.6	0.441

MMSE = Mini-Mental State Examination
SD = standard deviation

Two sets of patients were used in the analyses of potential relationships between the use of BZD/RD and health, functional abilities and cognitive functioning (Table 1). i) The first set consisted of the patients with data on MMSE sum scores (N=119). In this population, 64 patients were users of BZD/RD and 55 patients were non-users (comparison group). ii) The second set of material was comprised of patients scoring ≥20 MMSE total points and participating in the interviews (N=79). In this set, 37 patients were users of BZD/RD (treatment group) and 42 patients were non-users (comparison group). The length of the use of BZD/RD was assessed by interviewing this latter population. The mean length of use was 7.0 ± 7.0 years (range 1 to 37).

There were more women among the BZD/RD users than in the comparison group both among the patients with MMSE data and among the patients scoring 20 MMSE total points or more and having been interviewed (patients with interview data). Otherwise there were no differences in background characteristics, age or discharge diagnoses that might have implications for cognitive effects between BZD/RD users and the comparison group (Table 1).

6.1.2. Benzodiazepine and related drug use, concomitant use with other CNS medications as predictors of cognitive decline (Studies II and III)

Background characteristics

In Studies II and III, the cognitively intact (MMSE total points ≥24-30) and pre-existing cognitively deteriorated populations at baseline of the Lieto Study were younger and had a smaller number of medications than did the hospitalised sample in Study I (Tables 1 and 2).

In Study II, the majority (N=439; 78 %) of the participants who completed follow-up were aged 65 to 74 years at baseline and 126 (22 %) were 75 years or older. The mean age was 70.5 years (range 65 to 89). There were 338 women and 227 men. Users of any CNS medications were more often women, living alone and less mobile than non-users. They also more often had diagnosed depression, hypertension and a history of transient ischaemic attacks (TIA) than did non-users. Users of CNS medications were older and used a greater number of medications compared to non-users of CNS medications (Table 2).

In Study III, 52 persons who participated in both cohorts of the Lieto Study had subnormal MMSE total points between 0-23 at baseline, indicating pre-existing deteriorated cognitive functioning. Of these, 15 (29 %) were men and 37 (71 %) women. The material for Study III was older than that in Study II: the majority (N=30; 58 %) were 75 years of age or older at the beginning of the follow-up and 22 (42 %) were 65-74 years old. The mean age ± SD was 75.9 ± 7.2 years; ages ranged from 65 to 92. The users of CNS medications had a greater number of medications than did those not using CNS medications, but otherwise there were no differences in background characteristics between users of CNS medications and non-users (Table 3).

Table 2. Background data compared between users and non-users of CNS medications, at baseline (Study II).

Cognitively intact participants (baseline MMSE 24-30, N=565)					
	CNS medication users (N=171)		CNS medication non-users (N=394)		
	N	%	N	%	P
Gender (woman)	120	70.2	218	55.3	<0.001
Marital status					
Married	15	8.8	46	11.7	
Unmarried or divorced	101	59.1	256	65.0	0.076
Widowed	55	32.2	92	23.4	
Place of living					
At home alone	64	37.4	105	26.6	
At home with other person	105	61.4	288	73.1	0.007
In institution or nursing home	2	1.2	1	0.3	
Education					
Less than basic	13	7.6	19	4.8	
Basic	144	84.2	340	86.3	0.423
More than basic	14	8.2	35	8.9	
Ability to walk					
Independent	148	86.5	375	95.2	
With tools	22	12.9	18	4.6	<0.001
Needs to be assisted	0	0	1	0.3	
Diagnoses *(all related to current treatment period)*					
Depression	38	22.2	25	6.4	<0.001
Alcohol related disease	1	0.6	5	1.3	0.673
Hypertension	59	34.5	100	25.4	0.027
Hypercholesterolemia	32	18.7	60	15.2	0.303
Diabetes mellitus (type I or II)	7	4.1	25	6.3	0.288
TIA	8	4.7	3	0.8	0.004
Cerebral infarct	1	0.6	3	0.8	1.000
Cerebral haemorrage	1	0.6	1	0.3	0.514
Cerebral trauma	2	1.2	4	1.0	1.000
Malignant tumour or cancer	5	0.3	17	4.3	0.432
HIV, lues or borreliosis	0	0	0	0	1.000
Dementia (all types)	2	1.2	0	0	0.091

	Mean ± SD	Mean ± SD	P
Age	71.9 ± 5.7	69.9 ± 4.9	<0.001
Number of all medications	4.5 ± 2.7	1.6 ± 1.9	<0.001
Number of regularly taken medications	3.3 ± 2.5	1.3 ± 1.7	<0.001
Number of medications taken as needed	1.2 ± 1.2	0.3 ± 0.7	<0.001
Number of all medications excluding CNS medications	3.2 ± 2.5	1.6 ± 1.9	<0.001
Number of regularly taken medications excluding CNS medications	2.4 ± 2.1	1.3 ± 1.7	<0.001
Number of medications taken as needed excluding CNS medications	0.8 ± 1.0	0.3 ± 0.7	<0.001

CNS = central nervous system
SD = standard deviation
HIV= human immunodeficiency virus
TIA = transient ischaemic attack

Table 3. Background data on the use of medications with CNS effects and significance of the differences between users of these drugs and non-users at baseline (Study III).

Cognitively disabled participants (baseline MMSE 0-23, N=52)					
	CNS medications users (N=24)		CNS medication non-users (N=28)		
	N	%	N	%	P
Gender (woman)	5	21	10	36	0.238
Marital status					
Married	4	17	5	18	
Unmarried or divorced	8	33	15	54	0.250
Widowed	12	50	8	29	
Place of living					
At home alone	7	29	8	29	
At home with other person	13	54	20	71	0.077
In institution or nursing home	4	17	0	0	
Education					
Less than basic	7	29	8	29	
Basic	8	67	20	71	0.870
More than basic	1	4	0	0	
Ability to walk					
Independently	15	65	24	86	
With assisting device	6	26	4	14	0.119
With help of another person	2	9	0	0	
Diagnosed diseases					
Depression	5	21	1	4	0.084
Alcohol related disease	0	0	1	4	1.000
Hypertension	10	42	10	36	0.660
Hypercholesterolaemia	0	0	3	11	0.240
Diabetes mellitus (type I or II)	5	21	2	7	0.227
TIA	4	17	2	7	0.397
Cerebral infarct	1	4	0	0	0.462
Cerebral haemorrhage	1	4	0	0	0.462
Cerebral trauma	0	0	1	4	1.000
Malignant tumour or cancer	1	4	0	0	0.462
HIV, lues or borreliosis	0	0	0	0	1.000
Dementia (all types)	1	4	0	0	0.462
	Mean ± SD		Mean ± SD		P
Age	77.8 ± 6.6		74.4 ± 7.5		0.114
Number of all medications	5.4 ± 3.2		2.1 ± 2.1		<0.001
Number of regularly taken medications	4.2 ± 2.4		1.7 ± 1.6		<0.001
Number of medications taken as needed	1.2 ± 1.4		0.4 ± 0.7		0.016
Number of all medications excluding CNS medications	3.9 ± 2.9		2.1 ± 2.1		0.021
Number of regularly taken medications excluding CNS medications	3.1 ± 2.2		1.7 ± 1.6		0.017
Number of medications taken as needed excluding CNS medications	0.8 ± 1.2		0.4 ± 0.7		0.262

HIV= human immunodeficiency virus
MMSE = Mini-Mental State Examination
SD = standard deviation
TIA = transient ischaemic attack

6.1.3. Effects of benzodiazepines and related drugs withdrawal and cognitive performance (Studies IV and V)

In Study IV, there were no differences in socio-demographic characteristics between the randomised CRM and placebo groups (Table 4).

Table 4. Socio-demographic characteristics and health habits of the participants at baseline according to randomisation to the melatonin (CRM) or the placebo group, and statistical comparisons between the groups (Study IV).

	CRM group (N=46)		Placebo group (N=46)		P
	Median	(IQR) [Range]	Median	(IQR) [Range]	
Age (years)	66.5	(11) [55-89]	65.0	(10) [56-91]	0.959
Body mass index (kg/m²)	27.3	(3.8) [21.3-41.6]	26.4	(6.4) [18.8-37.1]	0.312
Doses of alcohol per week	1.3	(5.5) [0-39.5]	1.1	(4) [0-13.3]	0.602
	N	%	N	%	
Women	27	59	34	74	0.123
Exercise (hours) in a week					
< half an hour	5	11	2	4	
½-3 hours	38	83	44	96	0.106
≥3 hours	3	6	0	0	
Smokers	6	13	1	2	0.111
Persons living alone	13	28	14	30	0.819
Education					
Basic	22	49	18	39	
Professional training	18	40	23	50	0.607
University or college	5	11	5	11	
Occupation					
Retired	37	80	36	78	
Daytime work	6	13	8	18	0.854
Shift work	3	7	2	4	
Persons having a driving licence	39	85	41	89	0.536
Duration of regular benzodiazepine use					
<5 years	9	20	5	11	
5-10 years	17	37	27	59	0.107
≥10 years	20	43	14	30	
Range of use	2 - 26 years		1.5 months - 35 years		

IQR = Interquartile Range

Short-term and long-term BZD/RD withdrawers' cognitive performances were compared to those of controls at baseline and at the follow-up points of 1, 2 and 6 months. A comparison group was formed from a Finnish BZD-free cohort of women (N=101) aged 55 years and over (the enrolment and study details are described in: Alhola et al. 2006; Karakorpi et al. 2006; Alhola et al. 2010).

In Study V, there were fewer smokers among short-term BZD withdrawers compared to non-withdrawers (Table 5). Short-term withdrawers also tended to perceive their current

health and satisfaction with life better and were more optimistic than non-withdrawers concerning their expected states of health a year later. There was no difference between BZD/RD short-term withdrawers and non-withdrawers in diagnosed psychiatric, neurological or other diseases (Table 5).

Table 5. Demographic data at baseline: BZD/RD short-term withdrawers versus non-withdrawers according to 1 month withdrawal results (Study V).

	Short-term withdrawers[1] (N=69) Mean ± SD		**Short-term non-withdrawers[2] (N=20) Mean ± SD**		**P**
Age (years)	66.7 ± 7.2		66.9 ± 6.0		0.908
	Median [LQ, UQ]		**Median [LQ, UQ]**		
Number of medications	4.0 [3.0, 5.0]		4.0 [3.0, 5.5]		0.701
	N	**%**	**N**	**%**	**P**
Duration of benzodiazepine use as a hypnotic					
Less than 5 years	12	17	2	10	
5 to 10 years	34	49	8	40	0.371
10 years or longer	23	33	10	50	
Depression					
Not depressed (GDS-15 sum score <6)	63	93	16	80	0.201
Depressed (GDS-15 sum score ≥6)	5	7	4	20	
Smoking					
Non-smoker	67	97	16	80	0.022
Smoker	2	3	4	20	
Use of alcohol					
Non-user	16	24	1	5	
Once a month or more seldom	25	37	6	32	0.169
2-4 times a month	17	25	9	47	
2 times a week or more often	10	15	3	16	
Satisfaction with life					
Very satisfied	11	16	2	10	
Quite satisfied	42	61	7	35	0.053
Not satisfied, but not unhappy	13	19	9	45	
Quite unhappy	3	4	2	10	
Self-reported health					
Good	17	25	1	5	
Fair	44	64	14	70	0.069
Poor	8	12	5	25	
Expected health a year later					
Healthier than now	19	28	3	15	
No change	44	64	11	55	0.056
A bit worse than now	6	9	6	30	

[1]Participants with measurable amounts of BZD/RD in their blood, one month from initiating withdrawal

[2]Participants without measurable amounts of BZD/RD in their blood, one month from initiating withdrawal

LQ = Lower quartile

UQ= Upper quartile

Material for Studies IV and V did not contain non-users of BZD/RD. Thus, external reference material (Finnish BZD-free cohort) (Alhola et al. 2006; Karakorpi et al. 2006; Alhola et al. 2010) was used for comparisons between BZD/RD users and non-users'

cognitive performance as measured by CogniSpeed (Portin 1992). When the background variables of participants in the Satauni Study (Study V) were compared to the Finnish BZD/RD-free cohort of women (Alhola et al. 2006; Karakorpi et al. 2006; Alhola et al. 2010), the mean age in the Satauni Study sample was slightly greater than that in the BZD/RD-free cohort (66.7 ± 6.9 vs. 63.0 ± 4.1 years; P<0.001); in the withdrawal study sample participants used alcohol more often (more often than once a month; 45 %) but were also more often abstinent (20 %) compared to the BZD-free cohort (29 % and 7 %, respectively; P<0.001); participants in the withdrawal study sample were less satisfied with their lives (P=0.002) and perceived their state of health to be poorer (P=0.005). Fewer participants in the withdrawal study sample had the highest level of education (11 % vs. 18 %) or the lowest level of education (45 % vs. 65 %), resulting in their having a greater proportion of participants with the medium level of education (43 % vs. 17 %) compared to the BZD/RD-free cohort (P<0.001). There was no difference between the withdrawal study sample and the BZD/RD-free cohort in participants with a high number of depressive symptoms (P=0.941), smoking (P=0.849), or marital status (P=0.493).

6.2. Prevalence of benzodiazepine and related drug use and their concomitant use with other CNS medications (Studies I-III)

6.2.1. Use of BZD/RD in acutely hospitalised patients (Study I)

Among acutely hospitalised patients in Study I, users of BZD/RD used more medications overall than the comparison group did (Table 6). Concomitant use of two or three BZD/RD was common (Table 7).

Table 6. Medication use in BZD/RD and comparison groups and differences between the acutely hospitalized patients (Study I).

	Patients with MMSE data (N=119)			Patients scoring ≥20 MMSE sum points and with interview data (N=79)		
	BZD/RD (N=64) Mean ± SD	Comparison (N=55) Mean ± SD	P	BZD/RD (N=37) Mean ± SD	Comparison (N= 42) Mean ± SD	P
Number of medications						
All	11.0 ± 4.5	7.6 ± 3.3	<0.001	11.3 ± 4.5	7.3 ± 3.3	<0.001
Regular	9.1 ± 3.5	6.7 ± 3.0	<0.001	9.3 ± 3.5	6.5 ± 3.0	<0.001
Irregular	1.9 ± 1.6	0.8 ± 1.0	<0.001	2.0 ± 1.8	0.8 ± 0.9	0.001
Number of medications excluding benzodiazepines or related drugs or combination preparations with benzodiazepines						
All	9.6 ± 4.3	7.6 ± 3.3	0.015	9.9 ± 4.3	7.3 ± 3.3	0.009
Regular	8.3 ± 3.6	6.7 ± 3.0	0.020	8.5 ± 3.5	6.5 ± 3.0	0.011
Irregular	1.3 ± 1.4	0.8 ± 1.0	0.057	1.4 ± 1.5	0.8 ± 0.9	0.089
Number of medications with CNS effects						
All	2.6 ± 1.3	0.7 ± 0.8	<0.001	2.4 ± 1.4	0.6 ± 0.8	<0.001
Regular	1.7 ± 1.3	0.6 ± 0.8	<0.001	1.4 ± 1.3	0.5 ± 0.7	<0.001
Irregular	0.9 ± 1.0	0.1 ± 0.3	<0.001	1.1 ± 1.2	0.1 ± 0.4	<0.001

CNS = central nervous system
MMSE = Mini-Mental State Examination
SD = standard deviation

Table 7. Concomitant use of BZD/RD in acutely hospitalized patients (Study I).

	Patients with MMSE data (N=64)						Patients scoring ≥20 MMSE sum points and with interview data (N=37)					
	Regular use		Irregular use		Regular or irregular use		Regular use		Irregular use		Regular or irregular use	
	N	%	N	%	N	%	N	%	N	%	N	%
One BZD/RD	32	50	30	47	44	69	14	38	18	49	26	70
Two or three BZD/RDs	11	17	2	3	20	31	7	19	2	5	11	30

BZD = benzodiazepine
MMSE = Mini-Mental State Examination
RD = benzodiazepine related drug

6.2.2. Medication use in a cognitively intact population at baseline and during follow-up (Study II)

At Study II's baseline among population-based cohort, BZD/RD were the most commonly used CNS medications. Their use remained long-term most often (Table 8). The use of combinations of the CNS medications included in this analysis was not common at baseline (Table 9). The most common combinations were BZD/RD and anticholinergics, and also BZDs/RD and any CNS medications.

Table 8. Participants using CNS medication at the baseline and follow-up examinations and number of participants using these medications both at baseline and during follow-up (Study II).

Cognitively intact participants (baseline MMSE 24-30, N=565)						
Medication	**Number of users**					
	Baseline		**Follow-up**		**Both baseline and follow-up**	
	N	**%**	**N**	**%**	**N**	**% of users at baseline**
Opioids	9	2	43	7	3	33
Anticholinergics	78	14	104	18	37	47
Antiepileptics	7	1	7	1	3	43
Benzodiazepines and related drugs	115	20	181	32	84	73
Antipsychotics	28	5	36	6	11	39
Antidepressants	19	3	71	13	14	74
At least one CNS medication	171	30	262	46	133	78

CNS = central nervous system
MMSE = Mini-Mental State Examination

Table 9. Number and proportion of participants using a combination of CNS medications at baseline, by gender and age (Study II).

Cognitively intact participants (baseline MMSE 24-30)										
			Gender				Age			
	Both (N = 565)		Men (N = 227)		Women (N = 338)		65-74 (N = 439)		75+ (N = 126)	
Combinations of medications	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Opioid **and**										
anticholinergic	1	0.2	0	0	1	0.3	1	0.2	0	0
antiepileptic	0	0	0	0	0	0	0	0	0	0
benzodiazepine or related drug	4	0.7	0	0	4	1.2	1	0.2	3	2.4
antipsychotic	2	0.4	0	0	2	0.6	2	0.5	0	0
antidepressant	1	0.2	0	0	1	0.3	1	0.2	0	0
any of the above drugs	6	1.1	0	0	6	1.8	3	0.7	3	2.3
Anticholinergic **and**										
antiepileptic	1	0.2	1	0.4	0	0	0	0	1	0.8
benzodiazepine or related drug	32	5.7	11	4.8	21	6.2	19	4.3	13	10.3
antipsychotic	22	3.9	6	2.6	16	4.7	13	3.0	9	7.1
antidepressant	9	1.6	3	1.3	6	1.8	8	1.8	1	0.8
any of the above drugs	48	8.5	15	6.6	33	9.8	31	7.1	17	13.5
Antiepileptic **and**										
antidepressant	0	0	0	0	0	0	0	0	0	0
benzodiazepine or related drug	3	0.5	3	1.3	0	0	2	4.6	1	0.8
antipsychotic	1	0.2	1	0.4	0	0	0	0	1	0.8
any of the above drugs	3	0.5	3	1.3	0	0	2	0.5	1	0.8
Benzodiazepine or related drug **and**										
antipsychotic	13	2.3	5	2.2	8	2.4	7	1.6	6	4.8
antidepressant	12	2.1	2	0.9	10	3.0	9	2.1	3	2.4
any of the above drugs	46	8.1	14	6.2	32	9.5	28	6.4	18	14.3
Antipsychotic **and**										
antidepressant	5	0.9	1	0.4	4	1.2	3	0.7	2	1.6
any of the above drugs	28	5.0	7	3.1	21	6.2	17	3.9	11	8.7
Antidepressant **and**										
any of the above drugs	19	3.4	4	1.8	15	4.4	15	3.4	4	3.2

CNS = central nervous system
MMSE = Mini-Mental State Examination

6.2.3. Medication use in a cognitively disabled population at baseline and during follow-up (Study III)

At baseline, BZD/RD or anticholinergics were used by approximately every fifth participant (Table 10). Half of the participants used at least one drug with effects on the CNS. Benzodiazepine or related drugs were concomitantly used with other CNS medications by every tenth participant (Table 11).

Table 10. Single and concomitant use of drugs with CNS effects at baseline, at follow-up examination and at both times in a population with MMSE 0-23 (Study III).

Cognitively disabled participants (baseline MMSE 0-23)						
	Baseline (N=52)		Follow-up (N=52)		Both at baseline and follow-up (N=52)	
	N	%	N	%	N	%
Opioids	6	12	6	12	2	4
Anticholinergics	12	23	14	27	8	15
Antipsychotics	6	12	8	15	4	8
Antidepressants	5	10	9	17	4	8
Benzodiazepines or related drugs	11	21	15	29	7	13
Antiepileptics	1	2	2	4	1	2
At least one of the above drugs	24	46	29	56	8	15

CNS = central nervous system
MMSE = Mini-Mental State Examination

Table 11. Concomitant use of drugs with CNS effects by drug combinations in a population aged ≥65 years of age at baseline with preexisting cognitive decline (MMSE 0-23) (Study III).

Cognitively disabled participants (baseline MMSE 0-23, N=52)		
Combinations of medications	**N**	**%**
Opioid **and**		
anticholinergic	2	4
antiepileptic	0	0
benzodiazepine or related drug	1	2
antipsychotic	2	4
antidepressant	2	3
any of the above drugs	4	8
Anticholinergic **and**		
antiepileptic	0	0
benzodiazepine or related drug	3	6
antipsychotic	4	8
antidepressant	2	3
any of the above drugs	9	17
Antiepileptic **and**		
antidepressant	0	0
benzodiazepine or related drug	0	0
antipsychotic	0	0
any of the above drugs	0	0
Benzodiazepine or related drug **and**		
antipsychotic	1	2
antidepressant	3	6
any of the above drugs	5	10
Antipsychotic **and**		
antidepressant	2	4
any of the above drugs	6	12
Antidepressant **and**		
any of the above drugs	5	10

CNS = central nervous system
MMSE = Mini-Mental State Examination

6.3. Associations between use of benzodiazepines or related drugs, cognitive abilities and health

6.3.1. Associations between use of BZD/RD, cognition, health and functional abilities (Study I)

All participants

In Study I, the data about health, functional and cognitive abilities were available only for the patients with MMSE. The mean MMSE total point was significantly lower in the BZD/RD group (Table 12). However, after adjusting for confounding variables identified through analysing the background characteristics (gender, number of medications excluding BZD/RD or number of medications with CNS effects excluding BZD/RD and diagnosed dementia), the difference did not remain significant.

Table 12. Cognitive functioning (as measured by MMSE sum score) of patients in the BZD/RD and comparison groups among the group with MMSE data (N=119) and the differences between these groups by adjusting confounding variables (Study I).

	BZD/RD		Comparison		
	N	Mean ± SD	N	Mean ± SD	P
Non-adjusted	64	20.8 ± 5.4	55	22.9 ± 5.4	0.018
Adjusted for gender and number of medications excluding BZD/RD	64	22.7 ± 5.7	55	24.5 ± 5.6	0.052[1]
Adjusted for gender and number of medications with CNS effects excluding BZD/RD	64	22.8 ± 5.6	55	24.3 ± 5.5	0.090[1]
Adjusted for gender, number of medications excluding BZD/RD and diagnosed dementia	64	20.7 ± 6.1	55	22.1 ± 6.3	0.146[1]
Adjusted for gender, number of medications with CNS effects excluding BZD/RD and diagnosed dementia	64	20.9 ± 6.1	55	22.2 ± 6.3	0.172[1]

BZD/RD = benzodiazepine or benzodiazepine related drug
CNS = central nervous system
MMSE = Mini-Mental State Examination
[1]Analysis of covariance. Sum scores of MMSE were square transformed $(x+1)^2$ due to negatively skewed distribution before analysis.

Participants with MMSE total points ≥20

Without adjustment, the use of BZD/RD was significantly associated with poor self-perceived health, reduced walking abilities, dizziness, inability to sleep after awakening during nights, morning fatigue and stronger depressive symptoms (Tables 13 and 14). The use tended to be associated with shorter night time sleep duration and diminished abilities to manage shopping, bank and pharmacy affairs.

After adjusting for gender and the number of all medications (excluding BZD/RD), the use of BZD/RD remained significantly associated with poor ability to sleep after

awakening during nights, tiredness in mornings and stronger depressive symptoms (Tables 13 and 14).

Table 13. Health, functional abilities and cognitive functioning of patients during the week prior to admission to the hospital in the BZD/RD and comparison groups among the group scoring ≥20 MMSE sum points and with interview data and differences between the groups by adjusting confounding variables (Study I).

	BZD/RD N = 37		Comparison N = 42		P	Adjusted for gender and N medications with CNS effects excluding BZD/RD	
	N	%	N	%		OR (95 % CI)	P
Self-perceived health							
Good or fair	28	76	39	93	0.034	3.1 (0.7-13.1)	0.120
Poor	9	24	3	7			
Ability to walk							
Independently	15	41	27	64	0.035	2.3 (0.9-6.1)	0.084
Needs assistance	22	59	15	36			
Ability to manage shopping, bank and pharmacy affairs							
Independently	14	38	25	60	0.054	2.0 (0.8-5.3)	0.158
With assistance unable	23	62	17	40			
Self-perceived memory							
Normal to age	19	51	29	69	0.108	1.9 (0.7-5.1)	0.176
Deteriorated	18	49	13	31			
Frequency of forgetting							
Often	12	32	9	21	0.269	1.6 (0.6-4.7)	0.388
Rarely	25	68	33	79			
Feelings of dizziness							
Often	13	35	4	10	0.022	2.9[1] (1.1-7.3)	0.025
Sometimes	7	19	12	29			
Never	17	46	26	62			
Tendency to fall							
Often	9	24	4	10	0.157	2.0[1] (0.8-5.1)	0.145
Sometimes	9	24	9	21			
Never	19	51	29	69			
Day-time tiredness							
Often	10	27	11	26	0.202	1.37 (0.6-3.3)	0.486
Sometimes	15	41	10	24			
Never	12	32	21	50			
Ability to sleep after awakenings							
Yes	17	46	32	76	0.006	3.8 (1.4-10.7)	0.012
No	20	54	10	24			
Feeling of freshness in the morning							
Usually	21	57	32	76	0.039	3.1[1] (1.1-8.6)	0.027
Seldom	9	24	9	21			
Never	7	19	1	2			

[1]Cumulative OR

Table 14. Health, functional abilities and cognitive functioning of acutely hospitalized patients in the BZD/RD and comparison groups among the group scoring ≥20 MMSE sum points and with interview data and differences between the groups by adjusting confounding variables (Study I).

						Adjusted for gender and N medications with CNS effects excluding BZD/RD		
	N	BZD/RD Mean ± SD	N	Comparison Mean ± SD	P	BZD/RD Mean ± SD	Comparison Mean ± SD	P[3]
Sum score of MMSE[2]	37	24.8 ± 2.2	42	25.2 ± 2.5	0.320	25.7 ± 4.7	26.1 ± 4.4	0.448
Sum score of depressive symptoms[2]	37	8.1 ± 5.1	42	4.1 ± 3.6	<0.001	7.6 ± 0.8	4.0 ± 0.7	0.001
Duration of sleep during night (hours)[1]	37	6.1 ± 1.9	42	6.9 ± 1.9	0.064	6.3 ± 0.3	7.1 ± 0.3	0.060
Duration of sleep during day-time (hours)[1]	37	0.4 ± 0.8	40	0.6 ± 1.2	0.286	0.2 ± 0.1	0.3 ± 0.1	0.211
Number of awakenings during night (hours)[1]	37	1.7 ± 1.5	42	1.7 ± 1.1	0.671	0.8 ± 0.1	0.9 ± 0.1	0.645

BZD/RD = benzodiazepine or benzodiazepine related drug
MMSE = Mini-Mental State Examination
OR = odds ratio
95 % CI = 95 % confidence interval
[1]Describes health status during the week prior to admission to hospital
[2]Assessed during the hospital treatment
[3]Analysis of covariance. Sum scores of MMSE were square transformed $(x+1)^2$ due to negatively skewed distribution and duration of sleep during day-time and number of awakenings during night were log(x+1)-transformed due to positively skewed distribution before analysis.

After adjusting for gender and the number of medications with effects on the CNS (excluding BZD/RD), the use of BZD/RD showed significant associations with dizziness, inability to sleep after awakening during nights, morning fatigue and stronger depressive symptoms. The use tended to be associated with a reduced ability to walk and shorter night time sleep (Tables 13 and 14).

In the patients with MMSE data, the only difference in background variables (age, gender, number of medications with effects on the CNS excluding BZD/RD, diagnosed dementia, diagnosed neurological disease, diagnosed depression) was found for the number of medications with effects on the CNS excluding BZD/RD between the non-users of BZD/RD, users of one BZD/RD and users of two or three BZD/RD. The use of non-BZD/RD drugs with CNS effects was less common in patients taking two or three BZDs/RDs than in non-users or the patients using only one BZD/RD (P=0.035).

In the patients with MMSE data, their sum score of MMSE was related to concomitant use of BZD/RD (P=0.034). After adjusting for the number of medications with effects on the CNS excluding BZD/RD, no significant association was found (P=0.113).

In patients scoring ≥20 MMSE total points with interview data, no significant differences were found between the concomitant use of BZD/RD and the background variables used as possible confounding variables.

Self-perceived health (P=0.013), ability to sleep after awakening during night (P=0.016), feelings of freshness in mornings (P<0.001) and the sum score of depressive symptoms (P<0.001) were related to the number of BZD/RD drugs used. In addition, dizziness (P=0.056), ability to manage shopping, bank and pharmacy affairs (P=0.066) and a tendency to fall (P=0.076) tended to be related to the number of BZD/RD drugs used.

6.3.2. Correlations between residual serum concentrations, health and functional and cognitive abilities (Study I)

The residual concentrations of oxazepam, temazepam or zopiclone were not associated with physical functional abilities. The residual serum concentration of oxazepam had a positive correlation with the total score of MMSE and the residual serum concentration of temazepam correlated negatively with the MMSE total score (Table 15).

Table 15. Correlations between residual BZD/RD serum concentrations, cognitive functioning and depressive symptoms (Study I).

	N		Unadjusted Spearman correlation coefficient	P	Adjusted Spearman partial correlation coefficient	P
Oxazepam	10	MMSE	0.838	0.003	0.636[1]	0.125
	7	DEPS	-0.407	0.364	0.045[2]	0.955
Temazepam	12	MMSE	-0.590	0.044	-0.679[1]	0.045
	2	DEPS	*		*	
Zopiclone	25	MMSE	0.238	0.252	0.213[1]	0.341
	18	DEPS	0.027	0.916	-0.010[2]	0.971

MMSE = Mini-Mental State Examination
DEPS = Depression Scale
[1]Adjusted for age, diagnosed dementia and number of medications with CNS effects excluding BZD/RD
[2]Adjusted for gender, diagnosed depression and number of medications with CNS effects excluding BZD/RD
*Cannot be calculated due to small N

After adjusting for age, diagnosed dementia and the number of medications with CNS effects excluding BZD/RD, the correlation between oxazepam concentration and MMSE sum score did not remain significant. The negative correlation between temazepam concentration and MMSE sum score remained significant even after adjusting for these confounding variables.

6.4. Benzodiazepines or related drugs as predictors of cognitive decline

6.4.1. Changes in cognitive functioning during follow-up (Studies II, III)

During the follow-up period of Study II, cognitive functioning declined significantly in the total cognitively intact population as well as in all the subgroups (Table 16). Also in Study III, cognitive functioning tended to decline in the total cognitively impaired population and in all subgroups during the follow-up period, but the change was statistically significant only in the older age group (Table 17).

Table 16. Cognitive functioning as measured by the Mini-Mental State Examination (MMSE) at baseline and after a 7.6-year follow-up, by gender and age (Study II).

Cognitively intact participants (baseline MMSE 24-30)			
	MMSE sum score		
	At baseline	After 7.6-year follow-up	
	Mean ± SD	Mean ± SD	P
Total population (N = 565)	28.1 ± 1.9	26.1 ± 4.8	<0.001
Men (N = 227)	28.3 ± 1.7	26.7 ± 3.4	<0.001
Women (N = 338)	27.9 ± 2.0	25.7 ± 3.6	<0.001
65-74 yrs (N = 439)	28.2 ± 1.8	26.9 ± 3.6	<0.001
≥75 yrs (N = 126)	27.5 ± 2.0	23.3 ± 6.7	<0.001

MMSE = Mini-Mental State Examination
SD = standard deviation

Table 17. Cognitive functioning measured by MMSE (Mini-Mental State Examination) at baseline and at a 7.6-year follow-up, by gender and age (Study III).

Cognitively disabled participants (baseline MMSE 0-23, N=52)			
	MMSE sum score		
	At baseline	During follow-up	
	Mean ± SD	Mean ± SD	P
Total population	20.0 ± 5.5	17.9 ± 8.8	0.129
Men	19.3 ± 6.3	15.7 ± 7.5	0.102
Women	20.4 ± 5.2	18.8 ± 9.2	0.406
65-74 yrs	21.9 ± 2.4	22.3 ± 7.8	0.341
≥75 yrs	18.7 ± 6.6	14.7 ± 8.2	0.003

MMSE = Mini-Mental State Examination
SD = standard deviation

6.4.2. CNS medications and their concomitant use as predictors of cognitive decline (Studies II, III)

At least one CNS medication as a predictor of cognitive decline among those cognitively intact at baseline (Study II)

The use of any kind of CNS medication at baseline was associated with cognitive decline in the bivariate analysis (P=0.041), but the relationship did not remain significant after adjusting for control variables. The baseline use of opioids in all and the use of anticholinergics in men were associated with cognitive decline (Table 18). These relationships were observable even after adjusting for control variables.

Table 18. Significant associations between the use of at least one CNS medication or their combinations and change in cognitive functioning (MMSE) among the cognitively intact participants during the follow-up of 7.6 years (1990-1999), by gender (Study II).

Cognitively intact participants (baseline MMSE 24-30, N=565)													
Medication	**Gender**	**Baseline MMSE**					**MMSE during follow-up**			**Change in MMSE**			
		Users		**Controls**			**Users**	**Controls**		**Users**	**Controls**		
		N	**Mean ± SD**	**N**	**Mean ± SD**	**P[1]**	**Mean ± SD[2]**	**Mean ± SD[2]**	**P[2]**	**Mean± SD**	**Mean± SD**	**P for diff**	**adjusted P**
Opioids[a]	M+W	9	27.7 ± 1.8	384	28.2 ± 1.8	0.276	21.2 ± 7.8	26.5 ± 4.5	0.011	-6.4 ± 7.3	-1.7 ± 4.3	0.007	0.032
Opioids[b]	M+W	9	27.7 ± 1.8	556	28.1 ± 1.9	0.372	21.2 ± 7.8	26.2 ± 4.7	0.018	-6.4 ± 7.3	-1.9 ± 4.4	0.009	0.021
Anticholinergics[b]	M	29	28.2 ± 1.8	198	28.3 ± 1.7	0.938	25.0 ± 4.4	27.0 ± 3.2	0.015	-3.2 ± 4.0	-1.3 ± 2.9	0.021	0.002
Opioid **and**													
any other CNS medication[a]	M+W	6	27.3 ± 2.0	384	28.2 ± 1.8	0.020	18.8 ± 8.7	26.5 ± 4.5	0.010	-8.5 ± 8.0	-1.7 ± 4.3	0.004	0.007
Benzodiazepine or related drug **and**													
opioid[a]	M+W	4	26.5 ± 1.7	384	28.2 ± 1.8	0.052	15.8 ± 8.7	26.5 ± 4.5	0.004	-10.8 ± 9.0	-1.7 ± 4.3	0.006	0.002
opioid[a]	W	4	26.5 ± 1.7	210	28.0 ± 2.0	0.097	15.8 ± 8.7	26.0 ± 5.2	0.007	-10.8 ± 9.0	-2.0 ± 5.1	0.010	0.024

M=men
W=women
MMSE = Mini-Mental State Examination
SD = standard deviation
P[1]=significance of difference in MMSE at baseline between users and controls
P[2]=significance of difference in MMSE during follow-up examination between users and control
P for diff=significance of difference of change in MMSE between users and controls
adjusted p=p-value for difference of change in MMSE between users and controls adjusted for control factors, analysis of covariance
[a]control group: no medication with effects on the central nervous system
[b]control group: non-users of corresponding medications

Table 19. Significant associations between the use of psychotropics or other drugs with CNS effects in cognitively disabled at baseline and change in cognitive functioning (MMSE) among cognitively disabled participants during a 7.6-year follow-up, by gender and age (Study III).

	Cognitively disabled participants (baseline MMSE 0-23, N=52)											
		Baseline MMSE					MMSE in follow-up		Change in MMSE			
		Users		Controls			Users	Controls	Users	Controls		
	Age	N	Mean ± SD	N	Mean ± SD	P	Mean ± SD	Mean ± SD			P for diff	adjusted P
Benzodiazepine or related drug[a]	75+	8	20.9 ± 2.8	11	21.1 ± 3.3	0.729	12.3 ± 7.6	17.8 ±5.6	-8.6 ± 7.0	-3.3 ± 5.6	0.116	0.015
Benzodiazepine or related drug[b]	75+	8	20.9 ± 2.8	22	17.9 ± 7.5	0.532	12.3 ± 7.6	15.6 ± 8.4	-8.6 ± 7.0	-2.3 ± 5.9	0.027	0.002
Any psychotropic drug[b] (AP, BZD/RD), AD)	75+	12	16.9 ± 8.0	18	19.9 ± 5.5	0.318	11.0 ±8.7	17.2 ± 7.0	-5.9 ± 7.0	-2.7 ± 6.4	0.309	0.037
Benzodiazepine or related drug **and**												
antipsychotic[a]	65+	1	23	27	21.5 ± 2.9	0.415	7	20.1 ± 7.2	-16	-1.4 ± 7.8	0.137	0.038
antidepressant[a]	75+	3	18.7 ± 3.8	11	21.1 ± 3.3	0.371	8.0 ± 1.7	17.8 ± 5.6	-10.7 ± 4.7	-3.2 ± 5.6	0.085	0.021
any drug with CNS effects[a]	65+	5	20.0 ± 3.3	27	21.5 ± 2.9	0.329	10.4 ± 10.5	20.1 ± 7.2	-9.6 ± 9.9	-1.4 ± 7.8	0.101	0.038
anticholinergic drug[a]	75+	2	18.6 ± 3.5	11	21.1 ± 3.3	0.184	3.5 ± 4.9	17.8 ± 5.6	-15.0 ± 8.5	-3.3 ± 5.6	0.059	0.042
any drug with CNS effects[a]	75+	4	19.3 ± 3.3	11	21.1 ± 3.3	0.279	6.0 ± 4.4	17.8 ± 5.6	-13.3 ± 6.5	-3.3 ± 5.6	0.031	0.003
any drug with CNS effects[b]	65+	5	20.0 ± 3.3	47	20.0 ± 5.7	0.603	10.4 ± 10.5	18.7 ± 8.3	-9.6 ± 9.9	-1.3 ± 7.2	0.064	0.045
any drug with CNS effects[b]	75+	4	19.3 ± 3.3	26	18.6 ± 7.0	0.573	6.0 ± 4.4	16.0 ± 7.8	-13.3 ± 6.5	-2.6 ±5.6	0.009	0.001

MMSE = Mini-Mental State Examination
BZD/RD = benzodiazepine or related drug
AP = antipsychotic
AD = antidepressant
CNS = central nervous system
SD = standard deviation
P = P-value for difference in MMSE at baseline between users and controls
P for diff = P-value for difference of change in MMSE between users and controls
Adjusted P = P-value for difference of change in MMSE between users and controls adjusted for control variables (age)
[a]control group: no medication with effects on CNS
[b]control group: non-users of corresponding medications

Concomitant use of two or more CNS medications as predictors of cognitive decline among those cognitively intact at baseline (Study II)

The combination of BZD/RD and opioids was associated with cognitive decline among cognitively intact participants (Table 18). The association remained significant after adjusting for control variables. The combination of opioids and any CNS medication was associated with cognitive decline among all participants. The association remained significant after adjusting for control variables.

At least one CNS medication as a predictor of cognitive among cognitively disabled at baseline (Study III)

After adjusting for control variables, the use of BZD/RD or any psychotropic drug was associated with the risk of cognitive decline in older (≥ 75 yrs) patients (Table 19).

Concomitant use of two or more drugs as a predictor of cognitive decline among those cognitively disabled at baseline (Study III)

After adjusting for the control variables, concomitant use of BZD/RD with antipsychotics or any drug with CNS effects was still associated with cognitive decline in the total population (Table 19). Concomitant use of BZD/RD and antidepressants or anticholinergics or any drugs with CNS effects were associated with cognitive decline in the older population (≥75 yrs). These associations remained statistically significant after adjusting for control variables.

6.5. Withdrawal of benzodiazepines or related drugs

6.5.1. Effects of withdrawal intervention on benzodiazepine or related drug use (Study IV)

Discontinuations during the withdrawal period and follow-up

Of the 92 participants willing to withdraw their BZD/RD, 89 completed the one-month withdrawal and were followed up to six months after the initiation of withdrawal. There were two drop-outs in the controlled-release melatonin (CRM) group and one in the placebo group (Figure 2).

Efficacy of CRM compared to placebo for BZD/RD withdrawal

Efficacy end points at the end of a one-month withdrawal period were determined by plasma concentrations. After a one-month withdrawal period, there were 31 [ITT 67 % (95 % CI 54-81), Per Protocol 69 % (CI 55-82)] complete short-term withdrawers in the CRM group and 39 [85 % (CI 74-95), Per Protocol 87 % (CI 77-97)] complete short-term withdrawers in the placebo group, according to plasma concentrations (between the groups: ITT analysis P=0.051; Per Protocol analysis P=0.043) (Table 20). Plasma BZD/RD concentrations decreased by at least half of the baseline level among all non-withdrawers after the one-month withdrawal period (Table 20).

Table 20. Residual BZD/RD plasma concentrations in the melatonin (CRM) and placebo groups, at the baseline and at month 1 (Study IV).

	Residual concentrations (ng/ml)							
	Baseline (N=92)				Month 1 (N=90)			
	N	%	Median	[Range]	N	%	Median	[Range]
CRM group	46				45			
Nonusers	0	0	0.0		31	69	0.0	
Temazepam	9	20	1070	[438-2160]	5	11	517	[24.0-1210]
Zopiclone	23	50	97.8	[5.2-1030]	6	13	32.4	[1.5-169]
Zolpidem	14	30	13.6	[1.1-40.0]	3	7	3.2	[1.0-56.1]
Placebo group	46				45			
Nonusers	0	0	0.0		39	87	0.0	
Temazepam	5	11	704	[0-968]	1	2	15.1	[15.1-15.1]
Zopiclone	29	63	138	[0-518]	4	9	19.5	[6.0-296]
Zolpidem	12	26	17.3	[5.2-46.1]	1	2	12.3	[12.3-12.3]

Efficacy end points at the end of a one-month withdrawal period by DDD. The change in DDD between CRM and placebo groups approached borderline significance (P=0.052, Table 21). After a one-month withdrawal period, there were 36 complete withdrawers in the CRM group and 41 in the placebo group (P=0.134; Per Protocol analysis) (Table 21). There were no differences between the CRM and placebo groups in the number of complete withdrawers (primary end point) or dose-reducers (secondary end point) by DDD category (COR=2.6, 95 % CI 0.7-9.2, P=0.136).

Table 21. BZD/RD use categorized as levels of Defined Daily Dose (DDD) in the CRM and in the placebo groups at the baseline, and at months 1 and 6 (Study IV).

DDD	Baseline (N=92)		Month 1 (N=90)		Month 6 (N=89)		P	P	P
	N	%	N	%	N	%	Month 1 vs. baseline	Month 6 vs. baseline	Month 6 vs. month 1
CRM group	46		45		44				
0	0	0	36	80	14	32			
0.01-0.20	0	0	6	13	16	36			
0.21-0.99	24	52	1	2	12	27	<0.001	<0.001	<0.001
1	15	33	2	4	1	2			
>1	7	15	0	0	1	2			
Placebo group	46		45		45				
0	0	0	41	91	20	44			
0.01-0.20	0	0	3	7	22	49			
0.21-0.99	18	39	1	2	2	4	<0.001	<0.001	<0.001
1	25	54	0	0	1	2			
>1	3	7	0	0	0	0			

Interaction between time and groups: P = 0.052; cumulative logistic regression using GEE estimation
DDD-values used: For zopiclone 7.5 mg/night, for zolpidem 10mg/night and for temazepam 20 mg/night in participants aged under 70 years and temazepam 10 mg/night in subjects aged ≥70 years.

Efficacy end points at month 6. At month 6 after withdrawal initiation, there were 14 (32 %) complete withdrawers in the CRM and 20 (44 %) in the placebo group (P=0.220; Per Protocol analysis). There was more BZD usage by DDD in the CRM group compared to the placebo group (COR=2.5, 95 %, CI 1.1-5.5, P=0.025) (Table 21).

Withdrawal symptoms and safety during withdrawal and follow-up

The occurrence of withdrawal symptoms assessed with the BWSQ (Tyrer et al. 1990) did not differ between the CRM and placebo groups at week 1 or at months 1 and 6 (Table 22). There was no serious adverse outcome in either group during the withdrawal period or at follow-up.

Table 22. Comparison of the sums of withdrawal symptoms according to BWSQ between the melatonin (CRM) and the placebo groups at week 1, month 1 and month 6 (Study IV).

Sun of withdrawal symptoms	Week 1 N	Week 1 Median (IQR) [Range]	Month 1 N	Month 1 Median (IQR) [Range]	Month 6 N	Month 6 Median (IQR) [Range]	P[1]	P[2]	P[3]
CRM group	46	4.1 (3.6) [0-14]	43	3.2 (2.9) [0-13]	44	3.6 (3.0) [0-14]	0.886	0.323	0.198
Placebo group	46	4.0 (4.9) [0-22]	42	3.2 (3.8) [0-13]	43	3.1 (2.8) [0-10]			

IQR = interquartile range

P[1] = Statistical significance for group x time interaction effect; repeated measures analysis of variance.

P[2] = Statistical significance for group effect; adjusted for group; repeated measures analysis of variance.

P[3] = Statistical significance for time effect; adjusted for time; repeated measures analysis of variance.

6.5.2. Relationships between benzodiazepine or related drug withdrawal and changes in cognitive abilities (Study V)

Cognitive performance by length of previous BZD/RD use at baseline

SRT, 2-CRT and Vigilance test performances were not related to the duration of BZD/RD use before baseline (Table 23).

Table 23. Cognitive functioning: comparisons by duration of prior BZD/RD use at baseline (Study V). Medians and lower and upper quartiles, numbers of errors in 2-CRT, proportion of errors in the Vigilance test (as measured by CogniSpeed in milliseconds).

	Duration of benzodiazepine use						
	Less than 5 years (N=14)		5-10 years (N=42)		More than 10 years (N=33)		P
Test		[LQ, UQ]		[LQ, UQ]		[LQ, UQ]	
SRT							
Median (ms)	335	[317, 356]	324	[299, 342]	323	[296, 355]	0.564
2-CRT							
Median (ms)	541	[508, 579]	528	[491, 588]	566	[497, 614]	0.516
Median of errors (number)	1	[0, 2]	1	[0, 2]	0	[0, 1]	0.212
Vigilance test							
Median (ms)	535	[515, 574]	531	[491, 545]	525	[499, 563]	0.487
Median of errors (%)	0.429	[0.215, 1.066]	0.638	[0.216, 1.066]	0.632	[0.212, 1.080]	0.583

ms = Milliseconds

LQ = Lower quartile

UQ = Upper quartile

SRT = Simple Reaction Time

2-CRT = Two-Choice Reaction Time

P = Statistical significance of the difference between the durations of prior benzodiazepine use ascertained at baseline

Table 24. Baseline and follow-up cognitive functioning: comparisons of SRT, 2-CRT and Vigilance Test results by short-term (1 mo.) withdrawal status (Study V). Reaction times of SRT, 2-CRT and Vigilance tests measured by CogniSpeed at baseline and at follow-up (mo).

	Follow-up point										
	Baseline		1 mo		2 mo		6 mo				
	Median (ms)	[LQ, UQ] (ms)	Median (ms)	[LQ, UQ] (ms)	Median (ms)	[LQ, UQ] (ms)	Median (ms)	[LQ, UQ] (ms)	P[1] (inter-action)	P[2] (group)	P[3] (time)
SRT											
Short-term withdrawers (N=69)	324	[302, 342]	305	[293, 330]	309	[297, 335]	320	[296, 341]	0.218	0.636	<0.001
Short-term non-withdrawers (N=20)	326	[292, 356]	313	[276, 343]	317	[292, 343]	328	[298, 382]			
2-CRT											
Short-term withdrawers (N=69)	539	[493, 600]	528	[484, 589]	538	[485, 600]	540	[486, 598]	0.376	0.341	0.915
Short-term non-withdrawers (N=20)	549	[517, 619]	558	[525, 655]	552	[509, 591]	556	[523, 605]			
Vigilance test											
Short-term withdrawers (N=69)	526	[504, 547]	517	[498, 544]	513	[491, 556]	510	[488, 546]	0.679	0.506	0.051
Short-term non-withdrawers (N=20)	542	[495, 566]	527	[495, 562]	533	[480, 567]	524	[483, 571]			

ms = milliseconds
LQ = Lower quartile
UQ = Upper quartile
SD = Standard deviation
P[1] = Statistical significance for group x time interaction effect; repeated measures analysis of variance.
P[2] = Statistical significance for group effect; repeated measures analysis of variance.
P[3] = Statistical significance for time effect; repeated measures analysis of variance. SRT values were significantly lower at 1 month compared to baseline after adjustment for group (P=0.002).

Comparisons of short-term BZD/RD withdrawers and non-withdrawers

Between short-term withdrawers and non-withdrawers, reaction time changes did not differ for the SRT, 2-CRT or Vigilance tests (Table 24). Reaction times on the SRT, 2-CRT or Vigilance tests did not differ between short-term withdrawers and non-withdrawers, though SRT values were lower at 1 month compared to baseline (P=0.002). The change in the number of errors in 2-CRT or relative error proportion in the Vigilance test during follow-up did not differ between the two groups (Table 25). Nor were group differences in the number of errors in the 2-CRT or relative error proportion significant. The number of errors in the 2-CRT and relative error proportion in the Vigilance test decreased during the withdrawal follow-up (P=0.029 and P<0.001, respectively).

Comparisons of long-term BZD/RD withdrawers, irregular users and regular users

No difference in SRT, 2-CRT or Vigilance test reaction time changes was detected between long-term withdrawers, irregular users and regular BZD users during follow-up (Table 26). Reaction times of SRT, 2-CRT or Vigilance tests did not differ between long-term withdrawers, irregular users and regular BZD users. However, SRT values were lower at 1 month compared to baseline (P=0.002). No differences in changes in the number of errors in the 2-CRT test or the relative error proportion in the Vigilance test were detected between long-term withdrawers, irregular users or regular users during any follow-up period (Table 27). Group differences in the number of errors in the 2-CRT or relative error proportion were not significant. Comparing follow-up to baseline cognitive functioning, the number of errors in the 2-CRT and relative error proportion in the Vigilance test decreased during follow-up (P=0.035 and P<0.001, respectively).

Comparison of BZD/RD withdrawers to the BZD/RD-free cohort

Compared to a BZD/RD-free cohort, reaction times were slower in BZD/RD users at baseline (Table 28). The reaction times of BZD withdrawers in SRT or 2-CRT tests during follow-up did not reach those of the BZD-free cohort, but the difference in Vigilance test scores between these groups disappeared.

Comparison of reaction times: the Satauni study sample and the BZD/RD-free cohort

At baseline, participants in the withdrawal study sample had longer reaction times in the SRT (median; 325, lower and upper quartile; [302, 348] ms vs. 268 [254, 295] ms; P<0.001), 2-CRT (542 [493, 602] ms vs. 466 [433, 534] ms; P<0.001) and Vigilance tests (528 [499, 553] ms vs. 499 [465, 542] ms; P=0.002) compared to the BZD/RD-free cohort.

Comparison of reaction times: the Satauni study sample and the BZD/RD-free cohort at baseline and follow-up

At baseline, both short-term withdrawers and short-term non-withdrawers had longer reaction times in the SRT (P<0.001, P<0.001, respectively) and 2-CRT (both P<0.001) compared to the BZD/RD-free cohort, and they did not reach the baseline reaction times of the BZD/RD-free cohort at any follow-up point up to six months (at each follow-up point, P<0.001; 1 mo, P=0.001, 2 mo P<0.001 and 6 mo P<0.001, respectively; Table 28 for short-term withdrawers). In the Vigilance test, both short-term withdrawers and

Table 25. Baseline and follow-up cognitive functioning: comparisons of the 2-CRT, number of errors by short-term (1 mo) withdrawal status (Study V). Number of errors in the 2-CRT and the relative error proportion in the Vigilance test (CogniSpeed) at baseline and at follow-up (mo).

	Baseline		1 mo		2 mo		6 mo				
2-CRT, Number of errors											
	Median	**[LQ, UQ]**	**Median**	**[LQ, UQ]**	**Median**	**[LQ, UQ]**	**Median**	**[LQ, UQ]**	**P[1] (interaction)**	**P[2] (group)**	**P[3] (time)**
Short-term withdrawers (N=69)	1	[0, 2]	1	[0, 2]	1	[0, 2]	0	[0, 2]	0.132	0.873	0.029
Short-term non-withdrawers (N=20)	1	[0, 2]	1	[0.5, 2]	0	[0, 1]	0	[0, 1]			
Vigilance test, Relative error proportion (%)											
Short-term withdrawers (N=69)	0.632	[0.215, 1.066]	0.426	[0.000, 0.648]	0.421	[0.000, 0.637]	0.424	[0.212, 0.833]	0.870	0.630	<0.001
Short-term non-withdrawers (N=20)	0.532	[0.214, 0.963]	0.426	[0.211, 0.736]	0.216	[0.000, 0.634]	0.425	[0.211, 0.640]			

LQ = Lower quartile
UQ = Upper quartile
P[1] = Statistical significance for group x time interaction effect; negative binomial regression using GEE estimation.
P[2] = Statistical significance for group effect; negative binomial regression using GEE estimation
P[3] = Statistical significance for time effect; negative binomial regression using GEE estimation. Number of errors was significantly lower at 6 month compared to baseline after adjustment for group (P=0.014) among non-withdrawers. Relative error proportion was lower at 1 month compared to baseline (P=0.0026), 2 month compared to baseline (P<0.001) and 6 month compared to baseline (p<0.0001) after adjustment for group

Table 26. Baseline and follow-up cognitive functioning: comparisons on the SRT, 2-CRT and Vigilance Tests by long-term (6 mo.) withdrawal status (Study V). Medians (milliseconds, ms) and lower and upper quartiles of SRT, 2-CRT and Vigilance tests measured by CogniSpeed at baseline and at follow-up (mo).

	Follow-up point										
	Baseline		1 mo		2 mo		6 mo				
	Median (ms)	[LQ, UQ] (ms)	Median (ms)	[LQ, UQ] (ms)	Median (ms)	[LQ, UQ] (ms)	Median (ms)	[LQ, UQ] (ms)	P[1] (interaction)	P[2] (group)	P[3] (time)
SRT											
Long-term withdrawers (N=34)	320	[298, 350]	314	[291, 334]	309	[294, 338]	319	[294, 335]			
Long-term irregular users (N=44)	327	[303, 348]	305	[294, 330]	311	[295, 336]	326	[294, 367]	0.302	0.733	<0.001
Long-term regular users (N=11)	322	[290, 348]	298	[265, 344]	311	[292, 356]	320	[300, 367]			
2-CRT											
Long-term withdrawers (N=34)	550	[516, 602]	533	[496, 589]	539	[492, 600]	547	[516, 625]			
Long-term irregular users (N=44)	543	[486, 610]	550	[478, 606]	550	[484, 651]	548	[484, 601]	0.406	0.708	0.915
Long-term regular users (N=11)	527	[516, 588]	547	[517, 599]	535	[504, 542]	525	[493, 558]			
Vigilance test											
Long-term withdrawers (N=34)	530	[513, 557]	524	[501, 546]	518	[495, 555]	518	[504, 541]			
Long-term irregular users (N=44)	521	[481, 546]	513	[489, 545]	512	[484, 557]	506	[482, 540]	0.844	0.143	0.051
Long-term regular users (N=11)	551	[503, 594]	536	[508, 590]	543	[478, 591]	555	[477, 582]			

ms = Milliseconds
LQ = Lower quartile
UQ = Upper quartile
SD = Standard deviation
P[1] = Statistical significance for group x time interaction effect; repeated measures analysis of variance.
P[2] = Statistical significance for group effect; repeated measures analysis of variance.
P[3] = Statistical significance for time effect; repeated measures analysis of variance. SRT values were significantly lower at 1 month compared to baseline after adjustment for group (P=0.002).

Table 27. Baseline and follow-up cognitive functioning: comparing groups defined by long-term withdrawal (6 mo) on 2-CRT, number of errors (Study V). Medians of errors and lower and upper quartiles of 2-CRT and Vigilance tests and proportions of noticed stimuli of Vigilance test measured by CogniSpeed at baseline and at follow-up (mo)

	Follow-up point										
	Baseline		1 mo		2 mo		6 mo		P[1] (interaction)	P[2] (group)	P[3] (time)
2-CRT, Number of errors											
	Median	**[LQ, UQ]**	**Median**	**[LQ, UQ]**	**Median**	**[LQ, UQ]**	**Median**	**[LQ, UQ]**			
Long-term withdrawers (N=34)	1	[0, 2]	1	[1, 2]	1	[0, 2]	1	[0, 1]			
Long-term irregular users (N=44)	1	[0, 2]	1	[0, 2]	1	[0, 1]	0	[0, 1.5]	0.335	0.365	0.035
Long-term regular users (N=11)	2	[1, 4]	2	[1, 2]	0	[0, 2]	1	[0, 1]			
Vigilance test, Relative error proportion (%)											
Long-term withdrawers (N=34)	0.634	[0.215, 1.050]	0.421	[0, 0.642]	0.213	[0, 0.429]	0.321	[0.212, 0.634]			
Long-term irregular users (N=44)	0.634	[0.213, 1.385]	0.426	[0.212, 0.846]	0.426	[0.212, 0.647]	0.425	[0.213, 0.851]	0.170	0.222	<0.001
Long-term regular users (N=11)	0.433	[0, 1.068]	0.426	[0, 0.837]	0.212	[0, 0.870]	0.214	[0, 0.629]			

LQ = lower quartile
UQ = upper quartile
P[1] = Statistical significance for group x time interaction effect; negative binomial regression using GEE estimation.
P[2] = Statistical significance for group effect; negative binomial regression using GEE estimation
P[3] = Statistical significance for time effect; negative binomial regression using GEE estimation. Number of errors was significantly lower at 6 month compared to baseline after adjustment for group (P=0.016). Relative error proportion was lower at 1 month compared to baseline (P=0.006), 2 month compared to baseline (P<0.001) and 6 month compared to baseline (P<0.001) after adjustment for group.

Table 28. Comparison of BZD/RD short-term withdrawers to BZD/RD-free female cohort (Alhola et al. 2006, Karakorpi et al. 2006, Alhola et al. 2010) (Study V).

	Reaction time											
	Baseline			1 mo			2 mo			6 mo		
SRT	Median (ms)	[LQ, UQ]	P	Median (ms)	[LQ, UQ]	P	Median (ms)	[LQ, UQ]	P	Median (ms)	[LQ, UQ]	P
Short-term withdrawers (N=69)	324	[302, 342]	<0.001	305	[293, 330]	<0.001	309	[297, 335]	<0.001	320	[296, 341]	<0.001
Female BZD/RD-free cohort (N=101)	268*	[254, 295]		268*	[254, 295]		268*	[254, 295]		268*	[254, 295]	
2-CRT												
Short-term withdrawers (N=69)	539	[493, 600]	<0.001	528	[484, 589]	<0.001	538	[485, 600]	<0.001	540	[486, 598]	<0.001
Female BZD/RD-free cohort (N=101)	466*	[433, 534]		466*	[433, 535]		466*	[433, 534]		466*	[433, 534]	
Vigilance test												
Short-term withdrawers (N=69)	526	[504, 547]	0.006	517	[498, 544]	0.024	513	[491, 556]	0.045	510	[488, 546]	0.149
Female BZD/RD-free cohort (N=101)	499*	[465, 542]		499*	[433, 535]		499*	[465, 542]		499*	[465, 542]	

* = baseline measures compared at all time points

short-term non-withdrawers had longer reaction times compared to the BZD/RD-free cohort at baseline (P=0.006, P=0.040, respectively), at one-month (P=0.024, P=0.074, respectively) and two-month follow-ups (P=0.045, P=0.074, respectively). However, at the six-month follow-up, reaction times did not differ (P=0.149, P=0.077, respectively; Table 28 for short-term withdrawers).

Comparison of long-term BZD/RD withdrawers and regular BZD/RD users to the BZD/RD-free cohort at baseline and during the follow-up

At baseline, the long-term withdrawers and long-term regular users had longer SRT reaction times compared to the BZD/RD-free cohort (P<0.001, P=0.017, respectively), and on the 2-CRT (P<0.001, P=0.007, respectively). Further, neither group reached the baseline reaction times of the BZD/RD-free cohort at any follow-up point up to six months. In the Vigilance test, reaction times were longer both in long-term withdrawers and in long-term regular users compared to the BZD/RD-free cohort at baseline (P=0.005, P=0.040, respectively). At the one-month follow-up, reaction times were longer for long-term withdrawers (P=0.020), but not for long-term regular users (P=0.067). The difference for long-term withdrawers compared to the BZD/RD-free cohort was not significant at two-months (P=0.057) or at six-months (P=0.091). For long-term regular users, the difference with the BZD/RD-free cohort remained significant at both the two-month (P=0.046) and six-month follow-up points (P=0.028).

7. DISCUSSION

The results of this academic thesis showed that BZD/RD use was related to poor self-perceived health and functional abilities (Study I), and BZD/RD use may predict worse cognitive outcomes among cognitively intact (Study II) and cognitively deteriorated aged (Study III), especially, when combined to other CNS active drugs. Hypnotic use of BZD/RD could be withdrawn with psychosocial support in motivated participants, but melatonin did not improve the withdrawal results compared to those with placebo (Study IV). Cognitive abilities in psychomotor tests did not show, or showed only modest, improvement for up to six months after BZD/RD withdrawal (Study V). This suggests that the cognitive effects of BZD/RD may be long-lasting or permanent.

7.1. Study limitations and strengths

7.1.1. Study settings and populations

Three different samples were needed due to different study methods and designs needed to answer the study questions of this academic thesis (Figure 1): Study I was a cross-sectional cohort study, Studies II and III longitudinal, prospective, population-based follow-ups and Studies IV and V prospective intervention studies, of which Study IV was also an RCT.

The aim of Study I was to describe associations between BZD/RD use, health, self-perceived symptoms and cognitive functioning in the aged admitted to Finnish acute care hospital internal medicine and geriatric wards. The realised sample consisted of 188 patients, of whom 164 patients were 65 years old or older and comprised a small sized cross-sectional cohort. The study sample is likely comparable to other acute care hospitals with fragile older adults in Finland and in other countries.

The population-based data used in Studies II and III have been the basis of a large number of earlier studies published in peer-reviewed international scientific papers (Isoaho et al. 1994; Linjakumpu et al. 2002; Linjakumpu et al. 2003; Löppönen et al. 2003; Linjakumpu et al. 2004; Nurminen et al. 2010; Nurminen et al. 2012). This large Lieto Study had a high participation rate (93 %; N=1283) among the residents in the municipality of Lieto, Finland (Isoaho et al. 1994). The Lieto Study is a representative longitudinal population-based sample of a Finnish semi-rural municipality. Studies II and III utilised the MMSE data of 565 cognitively intact and 52 cognitively disabled participants included in the Lieto Study, who survived and participated in both cohorts of the Lieto Study in 1990-1991 and in 1998-1999. The complete 7.6 year follow-up data for Studies II and III were obtained for 617 participants and this longitudinal material may be considered as a large-sized study with a long follow-up time. The longitudinal population-based design and a high participation rate are major methodological strengths of Studies II and III.

In Studies IV and V (Satauni Study), the completion rate was exceptionally high as 97 % of 92 participants completed the withdrawal protocol and follow-up. It may be

suggested that this was due to frequent visits and positive psychosocial support that they were provided as well as to the gradual dose reduction (GRD) of BZDs/RDs. All of these 89 participants were users of BZD/RD and had no other psychiatric or neurologic disease than primary insomnia. The sample consisted of volunteer participants who contacted study personnel themselves and expressed their motivation to reduce their use of BZD/RD. Thus, the population of Studies IV and V were not randomly selected.

For cognitive comparisons in Study V, an external comparison group of a volunteer BZD/RD-free female cohort was acquired. They had been previously tested (CogniSpeed) and followed using the same cognitive measures (Portin 1992; Alhola et al. 2006; Karakorpi et al. 2006; Alhola et al. 2010). As the main outcome of adjuvant melatonin use to assist BZD/RD withdrawal in the Satauni Study was not proven to have statistically significant positive effects in the withdrawal process (Study IV), the only intervention was the reduction of BZD/RD. Additionally, a previous study had not detected any cognitive effects related to melatonin use (Otmani et al. 2008). Therefore, it was possible to study the persons who participated in the Study IV as one group in Study V.

7.1.2. Data collection

Background characteristics and medications

Clinical background characteristics and medication history were reliably recorded in Studies I-V.

In study I, interviews concerning health and functional abilities were limited to the patients scoring 20 or more total points in the MMSE to ensure the reliability of the answers. Thus, the results regarding relationships between drug use and interview data about health and functional and cognitive abilities represent those patients with normal or slightly lowered cognitive abilities.

Data on current medications used at home were collected for all patients including the names, dosages and frequencies of dosing of all regular and irregular (given as-needed) medications by interviewing the patients and checking their prescriptions on arrival to the hospital. These data were recorded in the medical records and the medical records were then used in collecting data for this study. Each medication was classified using the Anatomical Therapeutic Chemical (ATC) classification system (NAM 2004).

According to the Study I protocol, no changes in prescriptions of BZD/RD were made before collecting the data on medications from medical records and before taking blood samples for determining drug concentrations. There was no suspicion of intoxication of these drugs in any patient. Thus, the results of the use of these drugs describe their use before the patient's arrival at this acute hospital. Altogether 51 venous blood samples were obtained in order to examine the associations between BZD/RD concentrations and cognitive abilities. The interviews of the patients showed that BZD/RD use had lasted for years, the shortest length being one year. The BZD/RD group consisted of long-term users of BZD/RD.

In Studies II and III, the large pool of background data and measurements has permitted analyses of confounder factors are part of the Lieto Study (Isoaho et al. 1994).

The medication data collected for study material in Studies II and III relied on multiple sources. Trained nurses interviewed participants about their medication use, participants were asked to bring all their prescriptions with them. Medical records and pill boxes were also utilised. This method is considered to be reliable. The CNS medications used in the analyses were classified according their ATC-classification (NAM 1991). The definition of anticholinergic drugs was not based on a set of single criteria, but rather a combination of information gained from multiple sources (Appendix 7; Basu et al. 2003; Fick et al. 2003; Socialstyrelsen 2003; Pharmaceutical Information Centre 2004; Ancelin et al. 2006; Bottiggi et al. 2006; Han et al. 2008; Carriere et al. 2009).

The BZD/RD treatment indications and length of use were obtained from interviews in Studies I, IV and V. No data on the indications or the length of BZD/RD use was collected in Studies II and III, and thus, the use of BZD/RD may have been continuous or intermittent between Lieto Study cohorts. However, BZD/RD seemed to be the most commonly used by the same participants even during the follow-up period of nearly eight years. Additionally, Study V showed that potential cognitive decrements related to BZD/RD use may last long-term or be even permanent.

The data collected in Studies IV and V comprised a wide variety of background variables. Data collection was performed using methods similar to those of the Lieto Study (Studies II and III), with exception that, instead of paper medical records, electronic medical records were available for the Satauni Study (Studies IV and V).

Venous blood samples for all participants were drawn twice to determine plasma concentration of BZD/RD at baseline and at the one–month time point for confirming the withdrawal success (Studies IV and V). The evaluation of participants' BZD/RD withdrawal success at the six month time point, however, was determined through interviews and checking intervening filled prescription forms. This inconsistency may have affected the results. In addition to determining BZD use through careful interviews that elicited the precise nature and extent of BZD use, plasma concentrations were measured by a sensitive method at baseline and at the one-month follow-up. Since the risk for relapse into BZD/RD use is possible after withdrawal, this possibility was explored at the six months follow up by interview questions and responses were subsequently verified by the physician and audits of their medical records and pill boxes.

In Study IV, the preparations (CRM and placebo) given to participants had an identical appearance, ensuring the double-blinding. Not all participants could remember when they had started to use BZD/RD as a hypnotic. By checking prescriptions from each participant's health centre and hospital documents and by consulting with the participant's physician, the duration could be estimated by classifying use as less than 5 years of BZD use, from 5 to 10 years and 10 or more years of BZD use. There were only two participants who had used BZD/RD for less than 1 year. Thus, the material for Study IV represents ageing and older long-term BZD/RD hypnotic users selected by self-willingness to withdraw from their use of BZDs/RDs.

Cognitive measures

The measurements for cognitive functioning by Mini-Mental State Examination (MMSE) (Folstein et al. 1975) were used in Studies I-III. MMSE measures general, global cognitive abilities. MMSE is not a diagnostic test for dementia, and it does not distinguish dementia from e.g. delirium, depression, or cognitive disturbances caused by inappropriate medication, but it is a widely used clinical test for follow-up of individual cognitive abilities.

The most commonly used threshold screen for dementia suspicion is 24 points of a total possible 30 points (Drag et al. 2010). The MMSE cut off point 23/24 provides a sensitivity of 69 % and a specificity of 99 % for dementia (Tangalos et al. 1996). Thus, this threshold value was selected for Studies II and III to categorise the aged population to cognitively intact and cognitively pre-existing disabled. In Study I, a lower MMSE threshold value of 19/20 was used to extend the material from cognitively intact to those patients who had minimally sub-normal global cognitive functioning as measured by the MMSE. Patients with lower than 20 MMSE total points were considered unreliable for interviews and they were not further interviewed.

In Study I, MMSE tests were made on the first or the second day after hospital admission. Acute illnesses leading to the hospitalisation or delirium may have lowered cognitive abilities in this aged population, which must be kept in mind when interpreting the results between BZD/RD use or their concentrations and cognitive abilities. It is also possible, that the BZD/RD users were more seriously cognitively affected by acute illness than the non-users. Additionally, the use of BZD/RD might lower delirium threshold. Results based on interview data represent patients' feelings within one week prior to admission. Thus, they describe the situation before the acute illness.

In Studies II and III, MMSE tests represent the participants' global cognitive abilities in their normal health status. MMSE tests were performed for both cohorts of the Lieto Study (Isoaho et al. 1994; Löppönen et al. 2003). Only the baseline data on CNS medication use was used in the analysis of cognitive change during follow-up.

In Studies IV and V, CogniSpeed was used instead of MMSE to ensure greater sensitivity for small cognitive changes. The sensitivity and specificity of CogniSpeed have been confirmed previously (Revonsuo et al. 1993; Kujala et al. 1994; Kujala et al. 1995; Lilja et al. 2001). Repetitive computerised patterns of neuropsychological tests were administered by a trained study nurse at baseline, during the withdrawal and follow-up periods.

Attentional functioning and psychomotor speed, which were measured by reaction time tests (CRT and 2-CRT) and a sustained attention test (Vigilance), are important for a variety of cognitive tasks and every day functioning. They are all impaired by long-term BZD/RD use (Barker et al. 2004). Computerised testing eliminates the possibility of human error or changes in the testing method's calibration during follow-up. The SRT, 2-CRT and Vigilance tests that are used are not very susceptible to a learning effect and they measure reliably and validly the speed and accuracy of the entire cognitive psychomotor process from perception of the stimuli, to processing and producing sensible muscular outputs while maintaining attention (Portin et al. 1999; Alhola et al.

2006). Thus, lack of performance improvement in non-withdrawers during the follow-up course suggests that the minor improvement in long-term withdrawers was not explainable as a learning effect. Furthermore, none of the Satauni Study participants (Studies IV and V) suffered from a systemic progressive disease (active cancer or dementing disorder), serious psychiatric or cognitive disorder which could explain their inferior cognitive performance.

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

7.1.3. Statistical analyses

Summary of study designs for the basis of statistical analyses is shown in Figure 1.

In Study I, an observational, cross-sectional cohort design was used. Due to the lack of a time dimension in the cross-sectional design, temporal relationships between associations cannot be proved. This study type is susceptible to biases even with adjustments; causal-relations between associations cannot be estimated in cross-sectional study type.

The designs of Studies II, III and V were prospective, longitudinal and observational. Many potential risk factors for cognitive decline such as age, gender, education, hypertension, atrial fibrillation or flutter, diabetes mellitus, congestive heart disease and smoking at baseline could be adjusted for as control factors. The use of alcohol was not measured during the first phase; therefore, this could not be used as a control variable. Studies about the use of alcohol among older Finns in the late 1980s have shown that use diminishes with increasing age, and few older people, mainly men, are heavy users of alcohol (Kivelä et al. 1988).

In Studies II and III, CNS medication use was not common and the concomitant use of several CNS medications was quite rare. These facts have affected the strength of the statistical tests, especially when analysing the data by gender and age. Previous results have shown that psychotropics, especially benzodiazepines, are commonly used for years (Study I, Linjakumpu et al. 2002). In Studies II and III, from one-third to two-thirds of those using a particular CNS medication at baseline used a similar medication at the time of the follow-up examination. Most often BZD/RD was used by both cohorts. This supports the hypothesis that quite a few participants used these medications during the whole follow-up period and were real long-term users.

In Studies II and III, the number of participants using two or more medications with CNS effects concomitantly was low. This poses statistical limitations. Negative associations may be caused by the small sample sizes and the small number of users. Due to a lack of statistical power, the results do not prove that medications with CNS effects have no effect on cognition. Positive results, especially measured by the quite insensitive MMSE, however, show strong associations in this population-based sample.

In Study IV, CRM was compared to placebo in a randomized, double-blind, controlled design (RCT). RCTs allow one to determine causalities between interventions and outcomes. Randomisation and double-blinding were successful in Study IV, so the CRM and placebo groups are comparable from baseline until the end of follow-up. Re-categorisation of the data according to success of BZD/RD withdrawal in Study V poses a risk for selection bias. Background characteristics between short-term withdrawers and non-withdrawers did not differ substantially, and the results were identical according to different categorisations of withdrawal success at time-points of 1 or 6 months.

7.2. Results

7.2.1. Prevalence of benzodiazepine or related drug use (Studies I-III)

Increasing polypharmacy and psychotropic drug use among adults 65 years of age and older have been reported (Linjakumpu et al. 2002; Hartikainen et al. 2003; Jyrkkä et al. 2006). BZD/RD are reported to be the most common group of CNS medications in the aged (Linjakumpu et al. 2002; Hartikainen et al. 2003; Nurminen et al. 2009).

In Study I, the use of BZD/RD, even concomitantly with several other BZD/RDs, was common and long-term in this frail population. Nearly every second patient in this aged, acutely hospitalised sample used BZD/RD. This figure is higher than that found in the general aged Finnish population in the Lieto Study or in other studies (Linjakumpu et al. 2002; Hartikainen et al. 2003; Jyrkkä et al. 2006). The use of BZD/RD seem to be concentrated in the most frail and vulnerable aged. The prevalence of psychotropics is even higher in long-term care (Pitkälä et al. 2004; Nurminen et al. 2009).

Concomitant use of CNS medications in the Lieto Study (Studies II and III) was minor. The Lieto Study was a population-based sample of all residents living in the municipality of Lieto. When the Lieto Study was conducted in the 1990s, many of the pharmaceuticals that appeared in Study I were not yet approved for marketing or their use had not yet been established clinically. For instance, no medications for Alzheimer's disease, the newest antidepressants, antipsychotics or antiepileptics were in clinical use during the data collection period of the Lieto Study.

7.2.2. Cognitive abilities and symptoms associated with benzodiazepine or related drug use (Study I)

In Study I, use of BZD/RD was not associated with worse MMSE total points after adjusting for age and use of other CNS medications. Conversely, the BZD/RD was concentrated in the oldest group with the heaviest CNS polypharmacy. BZD/RD users had more other symptoms (dizziness, worse abilities to fall-asleep after waking up during night, tiredness in mornings) than those who did not use these drugs.

After adjusting for control variables, the use of BZD/RD was not associated with changes in or levels of cognitive functioning as measured by MMSE, but it was associated with dizziness, inability to sleep after awaking during nights and morning fatigue during

the week prior to admission and with stronger depressive symptoms measured at the beginning of the hospital stay. Their use tended to be associated with a reduced ability to walk and with shorter night-time sleep during the week prior to admission. Higher residual serum concentration of temazepam correlated with a lower MMSE sum score after adjusting for confounding variables. Tiredness and muscle relaxation are among the pharmacological CNS depressive effects of BZD/RD. These effects may be experienced as dizziness.

BZD/RD had been used by study participants for many years. However, causality between drug use and poor health or poor functional and cognitive abilities cannot be determined by a cohort study. The results from multivariate analyses that statistically adjust for control variables showed that BZD/RD use was associated with a higher occurrence of dizziness, sleeping problems, tiredness and depressive symptoms. Whether these symptoms were secondary to BZD/RD use, or preceded the use of these medications, cannot be determined.

The users of BZD/RD could not fall back to sleep easily after waking up during nights, and they felt themselves to be tired on awakening in the morning. This supports the previous findings suggesting that the long-term use of BZD/RD does not normalise sleep in aged patients with insomnia (Byles et al. 2003). Self-perceived insomnia is a common problem in the aged (Christer et al. 2002). Insomnia may be incorrectly considered as an independent disorder and treated with BZD/RD without behavioural or other non-pharmacological treatments, and this may lead to long-term BZD/RD use. Insomnia may sometimes be a symptom of depression (Nielsen et al. 1998). Normal ageing is related to shortening of slow wave sleep, to lengthening of light sleep and to an increase in short awakenings (Morgan 1996; Nielsen et al. 1998; Neubauer 1999).

The use of BZD/RD was also related to strong depressive symptoms. Patients using these drugs may suffer from undiagnosed depression, the symptoms of which are inadequately treated with BZD/RD. Antidepressants and non-pharmacological treatments should be provided instead of long-term BZD/RD prescriptions.

Analyses regarding associations between the concomitant use of two or more BZD/RD supported earlier findings of significant relationships between the use of these drugs and high occurrences of dizziness, sleeping problems, morning fatigue and depressive symptoms. In addition to these findings, more patients using two or three BZD/RD felt their health to be poor compared to the patients using only one BZD/RD.

The aim behind measuring the residual serum concentrations of the three most commonly used BZD/RD was to discover whether higher concentrations are related to poor self-perceived health, physical functional abilities and/or cognitive functioning. These kinds of correlations have not been studied earlier.

No significant correlations between worse functional abilities or stronger depressive symptoms and higher residual concentrations were found for any drug concentration measured here. Only a high residual concentration of temazepam correlated with declined cognitive abilities and the correlation was significant even after adjusting for control variables. The findings do not justify the recommendation of routine clinical

measurement of serum concentration of BZD/RD to help to identify the patients who would have the greatest benefits from withdrawal of BZD/RD.

7.2.3. Benzodiazepines or related drugs as predictors of cognitive decline (Studies II and III)

Cognitively intact aged at baseline

Study II was performed among the aged with normal cognitive abilities at baseline. The results showed that opioids and the combined use of opioids and BZD/RD or any CNS medications predicted cognitive decline. In addition, the use of anticholinergic medications was discovered to predict the risk of cognitive decline in men.

The single use of a BZD/RD, antidepressants or antipsychotics was not related to the risk of cognitive decline. These relationships are previously studied mainly for the use of BZDs, and the results are controversial (Berg et. al. 1996; Dealberto et al. 1997; Fastbom et al. 1998; Hanlon et al. 1998; Lagnaoui et al. 2002; Paterniti et al. 2002; Allard et al. 2003; Bierman et al. 2007; van Vliet et al. 2009; Wright et al. 2009; de Gage et al. 2012; Desplenter et al. 2012; Gallacher et al. 2012; Mura et al. 2012).

In Study II, the combination of a BZD/RD or any CNS medication and opioids predicted cognitive decline. Also the use of opioids alone predicted cognitive decline during the follow-up period. No previous studies on possible long-term effects of opioids on cognitive functioning in the aged were found. Diagnoses of the opioid users showed that these medications were used for painful arthrotic diseases. Nobody was diagnosed as suffering from cancer pain. These findings support the idea that use of a psychotropic medication alone does not inevitably effect cognitive functioning, but combining this kind of a medication with opioids may be harmful.

Anticholinergic use was related to the risk of cognitive decline in men. Here the results are in concordance with the results of previous studies about the use of anticholinergics as a risk factor for cognitive decline among unselected cognitively intact older persons (Basu et al. 2003; Ancelin et al. 2006; Bottiggi et al. 2006; Han et al. 2008; Carriere et al. 2009). In the Study II sample, more men than women used anticholinergic psychotropics with a high CNS affinity (Todorova et al. 2001), while women used more commonly urge incontinence medications that were targeted to have peripheral effects (Todorova et al. 2001). The blood-brain barrier permeability of alternative anticholinergic medications may differ between molecules (Todorova et al. 2001), age (Pakulski et al. 2000) or disease states (Starr et al. 2003), which might explain why the risk of cognitive deterioration was detected only among men.

Cognitively disabled aged at baseline

Study III was performed among the aged with pre-existing cognitive decline at baseline. This was the first longitudinal, population-based study describing and analysing associations between concomitant use of drugs with effects on the CNS and the long-term risk of cognitive decline among cognitively disabled aged persons. The finding that BZD/RD use predicts precipitous cognitive decline in a population with

pre-existing cognitive decrements could be replicated (Ellul et al. 2007; Rosenberg et al. 2012).

Concomitant use of a BZD/RD with an antidepressant, anticholinergic, antipsychotic or any drug with CNS effects predicted cognitive decline. This is in line with the previous finding (Ellul et al. 2007) that concomitant use of a BZD/RD and an antipsychotic is associated with precipitous cognitive decline. Only one study (Ellul et al. 2007) has explored the effect of concomitant use of medications having CNS effects on cognitive function in a cognitively disabled sample. That study, however, had a short follow-up period (12 months) and only included patients diagnosed with Alzheimer's disease, excluding patient groups with cognitive decline caused by other disorders. The material for Study III was a population-based sample with 7.6 years' follow-up of those with pre-existing cognitive decline for any reason. Rosenberg and co-authors (2012) had shorter follow-up time (3.7 years), but larger sample-size (N=230).

It is evident that the CNS medications in Study III were used to treat the behavioural and psychological symptoms connected to declined cognition (Wragg et al. 1988; Stern et al. 1991; Lemke 1995; Semla et al. 1995; Finkel et al. 1996; Burke et al. 1997; Porsteinsson et al. 1997; Tariot et al. 1998). The important question is whether the precipitous cognitive decline among those cognitively disabled patients receiving CNS medications was directly caused by the medications or is it the proxy-result of a more aggressive dementing disorder with more difficult behavioural and psychological symptoms of dementia (BPSD) requiring medical treatment. However, in the Study III sample only one participant was diagnosed with dementia and the other diagnosed conditions were not themselves cognitively progressive. It is possible that the change in MMSE was caused directly by the medications.

In the literature, reports on negative effects on cognition caused by medications in the aged with dementia have been published for other CNS medications, but not for BZD/RD. An RCT (Ballard et al. 2005) supports the idea that antipsychotic use (in this study quetiapine, an atypical antipsychotic with some anticholinergic properties) increases the risk of hastened cognitive decline among patients with Alzheimer's disease, but it does not assess this risk with concomitant use of other drugs. Another RCT found a risk of additional cognitive decline when Alzheimer patients with BPSD were treated with atypical antipsychotics (risperidone, quetiapine, olanzapine) compared to placebo (Vigen et al. 2011). The association between use of an anticholinergic and cognitive decline has been previously shown in longitudinal epidemiologic studies among the aged (Knegtering et al. 1994; Ancelin et al. 2006; Bottiggi et al. 2006), but no such results have been published for a population with pre-existing cognitive decline at baseline. Only tricyclic antidepressants and conventional antipsychotics were used in the population of Study III in the beginning of the 1990s, and the strong anticholinergic properties of these medications, combined with the CNS depressing GABAergic properties of BZD/RDs may have mediated the detected adverse cognitive effects.

7.2.4. Withdrawal of benzodiazepines or related drugs (Study IV)

In Study IV, effects of controlled-release melatonin (CRM) were compared against placebo in an RCT design with BZD/RD long-term users. The main outcome of including psychosocial support in the intervention with gradual dose reduction (GRD) of BZD/RD was the success of BZD/RD withdrawal. Also BZD/RD withdrawal symptoms were observed.

CRM given during the one-month BZD/RD withdrawal period for participants with primary insomnia and long-term BZD/RD use showed no superiority over placebo. Neither complete short-term BZD/RD withdrawal nor BZD/RD reduction rates favoured the CRM group over placebo group. By month 6 after withdrawal initiation, BZD/RD use increased in both groups but, unexpectedly, there were even more withdrawers and greater BZD/RD reduction rates in the placebo group participants than in the CRM group. BZD/RD withdrawal symptoms in CRM users were similar to those in the placebo group.

BZD/RD withdrawal results were good (67-85 %) in both groups in the short-term, though only moderate (30-43 %) in the long-term. The results suggest that success in BZD/RD withdrawal or dose reduction can be achieved in primary care in motivated patients when sufficient psychosocial support and counselling are provided.

In previous BZD withdrawal trials (Denis et al. 2006) the drop-out rate varied between 18 and 73 %. In an open trial (Lemoine et al. 2011) assessing the efficacy of CRM, only 96 of the 244 (43 %) participants completed the 12 month-follow-up. Previous studies that combined GDR and cognitive behavioural therapy (CBT) reported drop-out rates from 3 to 28 %, while withdrawal studies with GDR alone had drop-out rates between 12 to 22 % (Voshaar et al. 2006; Parr et al. 2009) (Appendix 5). The trial (Study IV) had a minimal number of drop-outs compared to the combination CDR and CBT studies.

It can be suggested that this high rate of retention is due to providing psychosocial support during the withdrawal period and to participants' high motivation for BZD/RD withdrawal. Participants had received the offer of counselling and support by phoning the nurse or making extra visit to the nurse. Once a week appointments with the nurse appeared to be sufficiently supportive during the withdrawal period, but it is possible that most participants might have required even more support after the withdrawal period to accomplish healthier sleep patterns without BZD/RD. It is speculative but reasonable to infer that if psychosocial support had been provided during the follow-up period, long-term persistence and withdrawal rates may have been higher.

Two methods were used to determine the change in BZD/RD use. BZD/RD concentrations were drawn at baseline and at the end of withdrawal period. Additionally, BZD/RD use was assessed via interview and converted to DDD at baseline, 1 and 6 months. According to the BZD plasma concentrations, five participants in the CRM group and two in the placebo group had misrepresented their discontinuation of BZDs. This phenomenon has been reported previously (Vissers et al. 2007). Additionally, it is possible that very small residual concentrations may not have been detected or that plasma concentrations have varied due to different sampling times. These can explain

the minor differences in results between the two methods for determining BZD use at baseline and after completion of the withdrawal period. The reliability of long-term BZD withdrawal persistence results would have been improved if the concentrations had been drawn at follow-up months 2 and 6 also.

Results of Study IV agree with two previous RCTs (Cardinali et al. 2002; Vissers et al. 2007) which showed no significant difference between melatonin and placebo in short-term BZD withdrawal outcomes. In contrast to the results of Study IV, a previous RCT (Garfinkel et al. 1999) using CRM 2 mg nightly for 6 weeks reported significantly better BZD discontinuation than did placebo (see Appendix 5 for the details of previous studies). The intervention in Study IV showed only moderate, long-term BZD withdrawal rates. Garfinkel and co-authors (1999) reported a very high (78 %) persistence of BZD withdrawal in the CRM group. In that study, however, study participants received open label CRM for up to six months, while the participants in Study IV received CRM only during the one-month withdrawal period. This longer CRM use may partly explain the difference in outcomes.

Comparisons of results from Study IV to previously published RCTs (Garfinkel et al. 1999; Cardinali et al. 2002; Vissers et al. 2007) must be made with caution due to subtle but meaningful methodological differences in design, length of melatonin treatment, use of melatonin during follow-up and measures reported. Previous RCTs have been performed with small samples, ranging from 34 to 45 participants, without reporting power calculations for those sample sizes and the difference (Vissers et al. 2007) in preparations as some trials have studied controlled-release (Garfinkel et al. 1999), some fast-release (Cardinali et al. 2002; Vissers et al. 2007) preparations and different doses of melatonin ranging from 2, 3 to 5 mg (Garfinkel et al. 1999; Cardinali et al. 2002; Vissers et al. 2007). Furthermore, those samples have included participants younger than 55 (Garfinkel et al. 1999; Cardinali et al. 2002; Vissers et al. 2007) and/or they have not reported the age range or inclusion criteria concerning the younger age group (Cardinali et al. 2002) (see Appendix 5 for details). GDR has been shown to be useful in BZD withdrawal (Denis et al. 2006; Voshaar et al. 2006; Parr et al. 2009). Some of the previous melatonin RCTs and Study IV combined GDR with melatonin treatment during the withdrawal phase. Short-term withdrawal results in Study IV were good in both the CRM and placebo groups. It may be suggested that these results are explained by including intensive psychosocial support during the withdrawal period.

Study IV cannot explain why CRM was not superior to placebo. Long-term BZD dependence may be more adverse for sleep quality than the compensatory effects of a 2 mg dose of CRM are for sleep improvement. Paradoxically, a previous RCT (Cardinali et al. 2002) found sleep quality to be worse in the CRM group compared to placebo during the first weeks of BZD withdrawal, while in other studies sleep quality was improved by using CRM in BZD users (Garfinkel et al. 1995; Garfinkel et al. 1997). A placebo effect may be operating both in the use of BZD for insomnia and in BZD withdrawal (Huedo-Medina et al. 2012). However, the present RCT design in Study IV did not allow us to study the possible significance of a placebo effect in BZD withdrawal: there was no internal control group with only a pharmacological or a psychosocial intervention. Therefore medication effects cannot be distinguished from

those due to psychosocial support (Macedo et al. 2003; Shorter 2011). However, it can be suggested, for patients, a tablet provides psychological benefit when withdrawing from long-term BZD use.

7.2.5. Change of cognitive performance related to BZD/RD withdrawal (Study V)

Study V showed that despite discontinuation of BZD/RD as a hypnotic, cognitive performance did not improve after a one-month withdrawal period or even in a longer-term (up to 6 months) follow-up and that long-term BZD/RD use is related to impairment in cognitive performance.

Performance in attentional functioning and psychomotor speed was worse in BZD/RD users compared to BZD/RD-free subjects. Despite successful BZD/RD withdrawal, patients' cognitive performance did not have a clinically meaningful change during the six month study period. Cognitive performance at baseline and at follow-up is not related to the duration of previous BZD/RD use. Only long-term BZD/RD withdrawers showed even minor improvement in Vigilance test measurements at two-month and six-month follow-ups when compared to BZD/RD-free subjects. These results support the conclusion that cognitive performance deteriorates with long-term BZD/RD use and that this decline is long-lasting, potentially even permanent.

Since reaction times in the cognitive tests were longer at baseline in the withdrawal study sample compared to the BZD/RD-free cohort, it can be interpreted as deterioration of cognitive performance with long-term BZD/RD use, a finding that is consistent with prior research (Paterniti et al. 2002; Barker et al. 2003; Barker et al. 2004; Stewart 2005; Bierman et al. 2007). Further, the results of Study V are consistent with previous findings that cognitive recovery after long-term BZD use may be incomplete and may persist even after BZD withdrawal (Salzman 1992; Rummans et al. 1993; Barker et al. 2004; Barker et al. 2005). Due to the six-month follow-up period, it cannot be said exactly how long this deterioration may persist or if it is permanent. In the majority of tests, the cognitive performance of withdrawers did not reach the comparison group's level in six months. Only Vigilance test performance, which is more discriminating, showed even minor improvement in long-term withdrawers compared to BZD/RD-free subjects. Thus, six months' follow-up seemed not to be long enough for complete neural system recovery after regular benzodiazepine use spanning many years. In some studies, however, small improvements in withdrawers' cognitive performance have been reported after follow-ups (Curran et al. 2003; McAndrews et al. 2003; Tsunoda et al. 2010) ranging from one week to 12 months. These discordant research results may be due to differences in study designs, follow-up duration, demographics, confounders, BZD types and doses, indications for BZD, as well as differences in cognitive measurements and domains.

BZD/RDs may influence cognitive performance, especially attentional functioning (Barker et al. 2004), via their CNS depressive properties (Roy-Byrne 2005; Lopez-Munoz et al. 2011). Attentional functioning and psychomotor speed, which were measured by reaction time tests (CRT and 2-CRT) and a sustained attention test (Vigilance),

are important for a variety of cognitive tasks and every day functioning. They are all impaired by long-term BZD use (Barker et al. 2004).

Withdrawer and non-withdrawer groups were formed according to BZD/RD plasma samples' results at one month. However, some participants' relapse into BZD/RD use and their not successfully withdrawing until after the one-month withdrawal period might have affected the long-term comparisons (Figure 3). In order to exclude this potential bias, participants were classified into long-term withdrawers, irregular users, and regular users. The results were, however, similar despite alternate group classifications, using either the one-month plasma concentration data (short-term withdrawal) or the six-month interview data (long-term withdrawal) (Figure 3).

The Satauni Study sample of women and men consisted only of long-term BZD/RD users at baseline. To evaluate whether BZD/RD users have poorer cognitive performance as a function of drug use, data from a previously reported Finnish BZD/RD-free cohort of women was used (Alhola et al. 2006; Karakorpi et al. 2006; Alhola et al. 2010). The BZD/RD-free female cohort had had similar inclusion and exclusion criteria as in the Satauni Study. Since the demographic data and performance in CogniSpeed did not differ between female and male participants in the withdrawal study, the entire group was compared to the BZD/RD-free cohort of women. Additionally, when the cognitive results of the female participants of the withdrawal study were compared in a sub-analysis with those of the BZD-free cohort of women, the results were essentially the same as when compared with the whole group (men and women). The mean age of withdrawal study participants (66.7 ± 6.9 years) was greater than that of the BZD/RD-free cohort (63.0 ± 4.1 years). However, no age related differences in SRT, regardless of educational attainment, have been detected in various age groups within a healthy population, and only minor age-related changes were observed in the 2-CRT (Portin 1992). In addition, it has been previously shown in a pre-post study that ageing by as much as six more years is not related to a change in cognitive performance using CogniSpeed (Alhola et al. 2006).

Results for the BZD/RD withdrawal's effects can be generalised to relatively healthy older (≥ 55 years) out-patients who have primary insomnia with long-term BZD/RD use. However, it can be hypothesised that the withdrawal study sample and the BZD/RD-free cohort could have been selected in ways that produce study subjects who differed by their sleep quality background and possible underlying anxiety disorders. These differences, if they existed, could cause the insomnia and, thus, lead to long-term BZD/RD use. It is worthy of notice that the BZD/RD-free cohort did not have diagnoses of insomnia. Thus, it is possible that selection bias by chronic insomnia could explain the difference between the groups in cognitive performance at baseline, although insomnia as such was not associated with attention or psychomotor performance in a recent meta-analysis (Fortier-Brochu et al. 2012). Nor is anxiety disorder associated with worse performance in psychomotor or neuropsychological tests (Chavez et al. 1983; Gladsjo et al. 1998). Thus, differences in cognitive performance between BZD/RD users and BZD/RD-free subjects cannot be explained solely by underlying psychological factors and selection bias, but is more likely a consequence of long-term BZD/RD use.

7.3. Implications for future studies and clinical practise

The finding that BZD/RD use is associated with cognitive decline among older adults is harmonious with the majority of literature. It is suggested that the use of BZD/RD may increase the risk of cognitive decline, but stronger evidence in longitudinal studies is required to confirm this causal relationship. Specifically, more evidence is needed concerning the concomitant use of BZD/RD with other CNS medications and their risk of cognitive decline. This is important since the concomitant use of several medications affecting the CNS is increasing in clinical practice. Larger controlled BZD/RD withdrawal studies and other CNS medications with a larger spectrum of cognitive domains measured and with longer follow-ups are needed to show whether the relationships between BZD/RD use and cognitive functioning are reversible or not.

In addition to the studies documenting cognitive decline related to CNS medication use, the underlying mechanisms by which this effect occurs should be identified as well. This requires basic research that would reveal phenomena at the cellular and molecular level through which the harmful effects of the medications are mediated to neurons as individual cells and neural networks or to CNS plasticity.

Evidence-based disease-specific recommendations and guidelines are useful tools in clinical practice, but as the number of diseases that an older individual can have increase with age, consequently the combination of different guidelines often result in an extensive list of medications. These guidelines do not take a comprehensive view and consequential polypharmacy increases the risk of medication interactions and side-effects.

In general, indications for medication use should be carefully evaluated before starting BZD/RD or other CNS medication. Furthermore, the evaluation of the balance between potential adverse effects and efficacy of the already prescribed drugs should be taken seriously. Non-pharmacological treatments for insomnia and anxiety should not be forgotten or disregarded.

8. CONCLUSIONS

The following major findings and conclusions were made:

1. Long-term use of benzodiazepines or related drugs and the concomitant use of these drugs with other psychotropics are common in aged, hospitalised patients. In the aged general population, these drugs and their concomitant use is less common. Long-term use of benzodiazepines or related drugs is associated with poor self-perceived health, including a high occurrence of dizziness, sleeping problems, morning fatigue and depressive symptoms. These common symptoms may at least partly be side effects in users of these drugs.

2. In the cognitively intact aged, concomitant use of benzodiazepines or related drugs and opioids, or the concomitant use of opioids with any psychotropic medication or any CNS medication, or the use of anticholinergics and opioids alone predict precipitous cognitive decline.

3. In the cognitively disabled aged, use of benzodiazepines or related drugs, or any psychotropic medications may be a potential risk factor for further cognitive decline. The concomitant use of a benzodiazepine and an antipsychotic, an antidepressant, an anticholinergic or any CNS affecting medication predicts a higher risk of precipitous cognitive decline.

4. Benzodiazepine or related drug withdrawal is feasible in a primary care setting with psychosocial support where withdrawal and sustained abstinence are controlled. Melatonin does not improve withdrawal outcomes against placebo.

5. Long-term hypnotic benzodiazepine or related drug use is related to impairment in cognitive performance compared to a benzodiazepine or related drug-free cohort. Despite discontinuation of benzodiazepine or related drug as a hypnotic, cognitive performance does not improve after a one-month withdrawal period or even in a longer-term follow-up until six months. These results suggest that the negative effect of chronic hypnotic benzodiazepine or related drug use on cognitive performance is long-lasting or even irreversible.

9. RECOMMENDATIONS

1. Physicians and caregivers should recognise benzodiazepines or related drugs, and their concomitant use with other CNS medications, as an associated factor for many symptoms and as a potential risk factor for cognitive decline.

2. Physicians and other health care professionals should recommend gradual dose reductions for long-term users of benzodiazepines or related drugs and support the withdrawers psychosocially.

3. The possibly causal relationship between cognitive decline and benzodiazepines or related drugs and CNS medications needs to be explored in further population-based prospective and experimental studies.

4. The current therapeutic approach of keeping benzodiazepine or related drug treatment periods as short as possible is consistent both with patient safety and with risk management.

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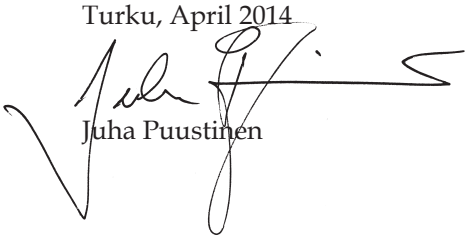

Juha Puustinen

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12. APPENDICES

Appendix 1. Longitudinal studies on the use of BZD/RD and the risk of cognitive decline in the aged.

Authors, year of publication, country, N, proportion of gender, mean age ± SD, range at baseline	Population, study design, follow-up	Source of medication data, frequency of updating the medication data	Medications studied, data on medication	Source of data on cognitive ability, Cognitive measures	Statistic analyses (covariates)	Results
Hanlon et al. 1998, United States, N=2765, NA ± NA, 65 -105	Community dwelling, prospective, longitudinal, 3 years (cohorts 1986-1987 and 1989-1990)	A trained interviewer visited the homes and asked to show the all the medications prescribed by a doctor or any other medications used during the previous 2 weeks, strength, whether the participants name was on label, regularly or as needed, at every cohort	BZDs, dose, half-life, duration, converted to standardised daily dose	By a trained interviewer, SPMSQ, OMCT	Multivariate analyses, race, gender, age, education in years, health status (Rosow-Breslau scale), chronic disease status, depressive symptoms (CES-D), use of thyroid medications, trouble falling asleep, smoking, alcohol use	After control for covariates, current users made more errors on the memory test (beta coefficient, 0.35; 95 % confidence interval [CI], 0.10 to 0.61) than nonusers. Further assessment of the negative effects on memory among current users suggested a dose response in which users taking the recommended or higher dose made more errors (beta coefficient, 0.57; 95 % CI, 0.26 to 0.88) and a duration response in which long-term users made more errors (beta coefficient, 0.39; 95 % CI, 0.05 to 0.73) than nonusers. Users of agents with long half-lives and users of agents with short half-lives both had increased memory impairment (beta coefficient, 0.32; 95 % CI, 0.01 to 0.64 and beta coefficient, 0.38; 95 % CI, 0.02 to 0.75, respectively) relative to nonusers. Previous benzodiazepine use was unrelated to memory problems, and current and previous benzodiazepine use was unrelated to level of cognitive functioning as measured with the other 4 tests.
Bierman et al. 2007, Netherlands, N=2105, 47.5 % male, 69.19 ± 8.5, 62-NA	Community dwelling, prospective longitudinal study, 9 years (examination every three years, four cohorts)	Interviews at the homes by specially trained and supervised interviewer: self-report and compared with information on the drug containers, every three years	BZD or RD, type, dosage, frequency, duration of use, recalculated in diazepam equivalent units	Measurements performed every three years, MMSE, CT, RCPM, AVLT	Multilevel analyses, socio-demographic (age, gender, level of education), number of diseases (0-8), alcohol consumption, anxiety symptoms, depressive symptoms	A negative effect of BZD use on cognitive performance was found. Higher doses of BZDs correlated with worse cognitive performance. This effect was significant for all cognitive performance tests expect the MMSE and the AVLT learning. After adjusting for confounding variables, the negative relationship remained significant for the RCPM and AVLT retention. Association between the cumulative exposure to BZDs and the cognitive performance tests found significant negative effects on all cognitive performance test scores. After adjusting for confounding variables, the negative association remained for the MMSE, the RCPM and the AVLT delayed recall and retention. However, the effect sizes were very small.

van Vliet et al. 2009, Belgium, N=486, 34.6 % male, NA ± NA, 85	Community dwelling and institutionalised, prospective, longitudinal study, 5 years	Interviewed and tested at home, the performer of the interviews and tests not reported, for home-dwellers, data obtained from pharmacist records and from a questionnaire filled out by the treating physician from institutionalised participants	BZD on a daily basis in the 2 months before and 2 months after their 85th birthday were defined as BZD users (users) and compared to non-users, irregular were excluded	Global cognitive abilities: MMSE (for all participants); attention: Stroop Test, processing speed: LDT, immediate and delayed recall memory: PLT (for participants scoring 19 more higher score in MMSE)	Robust linear regression analysis, no adjustments for cognitive analysis.	Benzodiazepine use at baseline was not associated with cognitive impairment. Discontinued BZD users had a 4.0 point lower MMSE score than continued users (95 % CI: 1.31–6.73, P=0.004).
Desplenter et al. 2012, Finland, N=449 (of whom 139 users and 310 non-users), 31.2 % male, 81.7±4.7 (users), 79.9±3.8 (non-users), 75-NA	Community dwelling, prospective, longitudinal study, 4 years	Trained nurses conducted annual interviews at outpatient study clinic or at home, participants were interviewed four times between 2004 and 2007	BZD or RD (ATC classes N05 and N05C) according to each participant's actual pattern of use according to interviews	Annual MMSE's (participants with score lower than 24 or dementia according to DSM-IV were excluded)	The mixed model was adjusted for the covariates as sociodemographic factors (gender, age, education), depressive symptoms, study group allocation and concomitant antipsychotic drug use)	The association between use of sedative drugs and incident cognitive decline was not statistically significant when assessed using MMSE scores collected from 2005 to 2007 (P=0.051). However, in secondary analyses conducted using only those MMSE scores obtained in 2005 and 2007, use of sedative drugs was associated with statistically significant cognitive decline (P=0.019).
Mura et al. 2012, France, 5195 of whom 969 chronic BZD users (73 % women; mean age 74.6 ± 5.4 years) and 4226 non-users (56 % women, mean age 73.2 ± 5.0), 65-NA	Population based study with follow-up for 7 years (baseline, 2, 4, 7 years)	Face to face interviews at health centre or at home	BZD or RD	Trained psychologist performed MMSE, IST, BVRT and TMT (A and B)	Nonlinear multivariate mixed model with a latent process. Analyses were adjusted for age, centre, gender, education, socio-professional status, depression, insomnia, high blood pressure, hypercholesterolemia, alcohol, tobacco consumption and physical activity.	Chronic use was significantly associated with a lower latent cognitive level (β=-1.79 SE=0.25 P=<0.001), but no association was found between chronic use and an acceleration of cognitive decline, neither on the latent cognitive process (β×time=0.010 SE=0.04 P=0.81), nor on specific neuropsychological tests.

ATC = Anatomical Therapeutic Chemical
AVLT = Auditory Verbal Learning Test
BZD = benzodiazepine
BVRT = Benton Visual Retention Test
CES-D = The Center for Epidemiologic Studies Depression Scale
CI = confidence interval
CT = Coding task
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, version IV
LDT = Letter Digit Coding Test
MMSE = Mini-Mental State Examination
NA= not available
PLT = Picture Learning Test
OMCT = Orientation-Memory-Concentration Test
OR = odds ratio PLT-I and PLT-d = 12 Picture Learning Test
RCPM = Raven's Coloured Progressive Matrices
RD = benzodiazepine related drug
SD = standard deviation
SPMSQ = Short Portable Mental Status Questionnaire
TMT (A and B) = Trail Making Test, forms A and B

Appendix 2. Longitudinal studies on the use of BZD/RD and the risk of any dementia in the aged.

Authors, year of publication, country, N, proportion of gender, mean age ± SD, range at baseline	Population, study design, follow-up	Source of medication data, frequency of updating the medication data	Medications studied, data on medication	Source of data on cognitive ability, Cognitive measures	Statistic analyses (covariates)	Results
Fastbom et al. 1998, Sweden, N=668 (MMSE 23 or under, N=314, and 24 or higher, N=354), 75 – NA	Longitudinal case-control study, 3-year follow-up	Data on drug used during previous two weeks were collected by nurses. Examinations performed at research centre or at home.	BZDs, drug information confirmed by proxy as needed and drug containers inspected.	Dementia according to DSM-III-R criteria, assessments using cognitive battery, data collected by nurses and diagnoses made by a physician and confirmed by a senior colleague as needed.	Logistic regression analysis to analyse associations between BZD use and incidence of dementia controlling for age, gender, level of education, use of NSAIDs and oestrogens.	There was a significantly lower incidence of Alzheimer disease in the BZD positive group than in the BZD negative group. This negative association remained significant after controlling for potential confounders.
Lagnaoui et al. 2002, France, N=3643, 79+ 6 (cases, N=150), NA , 74 ± 6 (controls, 3519), 65-NA	Epidemiological survey of a representative non-institutional-ised sample, prospective, longitudinal, 8 years (cohorts at baseline, 1, 3 5, 8 years later)	Face-to-face interviews in the subject's home by a trained neuropsychologist: participants were asked to show prescription and non-prescription drugs used in the past 2 weeks, 1) spontaneous reporting, 2) visual inspection of patient's medicine chest to validate the oral information.	BZDs, information obtained by face-to-face interview and visual assessment of patient's medicine chest by a trained neuropsychologist	By a trained neuropsychologist at every cohort, dementia diagnosed according to DSM-III-R	Bivariate analyses and unconditional logistic regression. Adjusted for age, gender, education level, living alone, wine consumption, psychiatric history and depressive symptomatology	After controlling for confounding factors, ever use of benzodiazepines was associated with a significantly increased risk of dementia [adjusted odds ratio (OR), 1.7; 95 % confidence interval, 1.2-2.4]. Former use was associated with a significantly increased risk of dementia (adjusted OR, 2.3; 95 % CI,1.2-4.5). No association was found between dementia and the current use of benzodiazepines (adjusted OR, 1.0; 95 % CI, 0.6-1.6).

Gallacher et al. 2012, United Kingdom, N=1134 men, of whom 103 taking BZD regularly (of these, 41 only one phase of the study and 62 more than one phase), BZD users 61.7 (4.6) and never-users 61.2 (4.4) years old	Representative population sample of men born between 1920 and 1939 first examined between 1979 and 1983 and survivors re-examined on four occasions between 1983 and 2004, mean follow-up time 22 (19-24) years	Complete list of drugs taken regularly at each examination	BZD use reported 1) at phase of the study, 2) and only one at only one examination (4 years or less) and those reported use at two or more examinations (>4 years)	At age 55-74, cognitive tests AH4 for fluid intelligence, NART for crystallised intelligence, four choice reaction time task, MMSE, and CAMCOG for global impairment. At age 65-84, tests were repeated. Subjects failing in CAMCOG were clinically assessed and categorised to vascular (NINCDS-AIREN criteria) and non-vascular dementia (DSM-IV criteria) and to cognitively impaired with no dementia.	Logistic regression model adjusted for age, social class, education, smoking, cardiovascular disease and at later phase for a number of cognitive tests as factors that may determine both risk of dementia and use of BZD. Three further models were adjusted for psychological distress, trait anxiety and daytime sleepiness.	Men taking BZD regularly at one or more phase sowed an increased incidence of dementia (OR=3.5, 95 % CI 1.57-7.79), which persisted despite adjustments. Men exposed in earlier phases showed a greater association than more recent exposure. No dose-response effects with drug duration could be shown.
de Gage et al. 2012, France, N=1063 BZD non-users at baseline, 95 new BZD users (57 % women) and 968 BZD non-users (49 % women) in which 253 cases of dementia (24 %) of which 20 (32 %) in new BZD users and 223 (23 %) in non-users, 78.2 + NA years, 65-NA years	Representative sample of community dwelling people, prospective longitudinal, nested case-control study design, follow-up up to the 20 year with median of 6.2 [2.6, 12.3] years	Follow-up visits every two or three years by a trained neuropsychologists	BZDs and RDs, detailed information on drug use during face to face interviews by a trained neuropsychologist using standardised questionnaire at each follow-up visit	By a trained neuropsychogist at every cohort, dementia diagnosed according to DSM-III-R	Multivariable adjusted Cox proportional hazards models and adjusted for age, gender, education, marital status, wine consumption, use of antidiabetics, antihypertensives, statins, platelet inhibitors, change of cognitive measures, and observed before the start of BZD (MMSE, BVRT, Isaacs set test), depressive symptoms (CES-D)	New use of BZD was associated with an increased risk of dementia (multivariable adjusted hazard ratio 1.60, 95 % CI 1.08-2.43). A secondary analysis pooled cohorts of participants who started BZDs during follow-up and evaluated the association with incident dementia. The pooled hazard ratio across the five cohorts of new BZD users was 1.46 (1.10-1.95). The results of a complementary nested-case study showed that ever user of BZDs was associated with 50 % increase in the risk of dementia (adjusted OR 1.55, 1.24-1.96) compared with never users. The results were similar in past users (OR 1.56, 1.23-1.98) and recent users (1.48, 0.83-2.63) but reached significance only for past users.

AH4 = Alice Heim 4
BZD = benzodiazepine
CAMCOG = Cambridge Cognitive Examination
CES-D = Center for Epidemiologic Studies Depression Scale
CI = confidence interval
DSM-III-R = Third revision of the Diagnostic and Statistical Manual of Mental Disorders
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, version IV
NA= not available
NART = National Adult Reading Test
NINCDS-AIREN = National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences
NSAID = non-steroidal anti-inflammatory drug
OR = odds ratio
RD = benzodiazepine related drug
SD = standard deviation

Appendix 3. Longitudinal studies on the use of BZD/RD and unspecified and concomitant use of psychotropics and the risk of cognitive decline in the aged.

Authors, year of publication, country, N, proportion of gender, mean age ± SD, range at baseline	Population, study design, follow-up	Source of medication data, frequency of updating the medication data	Medications studied, data on medication	Source of data on cognitive ability, Cognitive measures	Statistic analyses (covariates)	Results
Berg et al. 1996, Sweden, 743 elderly persons, population based representative sample, proportion of women NA	Longitudinal cohort study of three cohorts: at age of 70, 75, and 79	Home interview by a registered nurse and one-day examination at the outpatient clinic of a geriatric hospital	Psychotropics: neuroleptics, antidepressants, anxiolytics and sedative/hypnotics	Psychological tests performed at out-patient clinic, Series of items by Dureman and Sälde (verbal meaning, spatial ability, perceptual speed), Thurstone Memory Test, Digit Span of WAIS	Bivariate models. No adjustments.	Data on medication use revealed that the use of psychoactive agents increased with age, and was greater for females. A cross-sectional analysis showed that those using psychoactive medicines had lower cognitive test scores compared with those who did not receive such drugs. Repeated measures analysis of variance demonstrated that psychotropics had a negative and cumulative effect on cognition, with the function of subjects who received psychoactive agents consistently poorer than those who did not. The magnitude of this effect is relatively small and for several cognitive tests subjects who received these drugs averaged only a few points lower than individuals not using psychoactive medicines.
Dealberto et al. 1997, United States, N=1200, 65.4 % women, aged 65 and over in 1982	Representative sample (N=2800) of aged non-institutionalised persons of whom cognitively intact at baseline were followed for 6 years (cohorts 1982 and 1988)	Home interviews by a trained examiner, medications used in the past 2 weeks (prescribed and non-prescribed)	BZD (anxiolytics, hypnotics) and non-BZD psychotropics (sedatives, antidepressants, neuroleptics) (all medications were recorded)	Structural tests by trained examiners, SPMSQ	Multivariate logistic regression. Covariates in different models: cognitive performance at baseline, depressive symptoms (CES-D)	Cognitive decline differed according to class of psychotropic drugs and pattern of use: BZD use was not significantly associated with cognitive decline (P=0.131); the most striking change was the decrease of the odds ratio associated with temporary use of BZD in 1982, which was almost significantly below 1 (OR=0:23; P=0.056); the risk associated with continuous use became negligible (OR=1.18; P=0.848); the higher risk associated with new use remained almost unchanged (OR=1.96 P=0.248) BZD temporary users exhibited a lower risk compared with never users (OR=0.23, P=0.056), non-BZD new users a higher risk (OR=5.02, P<0.001).

Paterniti et al. 2002, France, N=1176, 58.9 % women, 65.0 ± 3.0 (users N=159), 65.3 ± 2.9 (controls N= 1017), 60-70	Community dwelling, prospective longitudinal, 4 years (0, 2, 4 year examinations)	Data on drug use were collected at baseline and at each follow-up evaluation.	anxiolytics, hypnotics, sedatives, neuroleptics, antidepressants, normothymics, doses and then classified to benzodiazepines, duration at the 2-year examination	A trained psychologist administered cognitive tests at baseline, 2-year and 4-year evaluations, MMSE, DSST, TMT-B, AVLT, FTT	Random effect linear models adjusted for gender, alcohol intake, Spielberger and CES-D scores, cognitive performance, age, education, coronary heart disease, hypertension, diabetes, hyperlipidemia	Chronic users of benzodiazepines had higher risk of cognitive decline in Mini-Mental State Examination, 1.9 (1.0-3.5), Digit Symbol Substitution test, 2.7 (1.6-4.7), Trail Making test, part B, 2.1 (1.2-3.7). Episodic and recurrent users had lower cognitive score than non-users, but differences were not statistically significant.
Allard et al. 2003, France, 372 (71 % women) of whom 225 were non-consumers of psychotropics, 75.7 years (consumers of psychotropics 77.1 and non-consumers 74.2), range of age NA	Representative sample in regional general practitioner network, prospective, longitudinal, three examinations annually	Medication use was established by the home visitor by inspection of medications by the subject or care-giver and prescriptions	benzodiazepines, antidepressants, normothymics, neuroleptics, psychostimulants	A computerised cognitive test battery developed for the study containing tests for attention, working, episodic, semantic and implicit memory, visuospatial analysis and linguistic abilities	Logistic regression model adjusted for age, gender education, co-morbidity (depression), hospitalisation, prodromal dementia	No effect was found for benzodiazepines. A significant positive effect in chronic psychotropic consumers was found on tests of secondary memory (delayed verbal recall: OR=1.22; 95% CI [1.04–1.43]; P=0.013) and this effect is principally attributable to antidepressants with significant effects being shown for both verbal (OR=1.59; 95 % CI [1.18–2.14]; P=0.002) and visual recall (OR=1.51; 95 %CI [1.05–2.16]; P=0.025).
Wright et al. 2009, United States, N=2737 (women 52.5 %), 73.6 ± 2.9, aged 70 to 79 at baseline	Healthy adults, longitudinal cohort study (at least 4 years)	Participants were asked to bring their clinic visits all medications they had taken in the previous 2 weeks, trained interviewers obtained medication data at baseline and two follow-up cohorts following in 2 year intervals	CNS medications (opioid receptor agonists and psychotropics), strength, dosage form, use as routinely or as-needed, duration of use	Tested by study personnel at each cohort (baseline, 3 and 5 years), 3MS	To detect an association between exposure to CNS medications and incident cognitive impairment or change in cognitive function, separate multivariable interval-censored survival analyses were conducted while adjusting for demographics, health-related behaviour, health status, indications for CNS medications	By Year 5, 7.7 % of subjects had incident cognitive impairment; 25.2 % demonstrated cognitive decline. CNS medication use increased from 13.9 % at baseline to 15.3% and 17.1% at Years 3 and 5, respectively. It was not associated with incident cognitive impairment (adjusted hazard ratio (adj HR)=1.11, 95 % confidence interval (CI)=0.73-1.69) but was associated with cognitive decline (adj HR 1.37, 95 % CI=1.11-1.70). Longer duration (adj HR=1.39, CI=1.08-1.79) and higher doses (>3 standardised daily doses) (adj HR=1.87, 95 % CI=1.25-2.79) of CNS medications suggested greater risk of cognitive decline than with nonusers.

3MS = Modified Mini-Mental State Examination
AVLT = Auditory Verbal Learning Test BZD = benzodiazepine
CES-D = Center for Epidemiologic Studies-Depression Scale
CI = confidence interval
CNS = central nervous system
DSST = Digit Symbol Substitution Test
FTT = Finger Tapping Test
MMSE = Mini-Mental State Examination
NA= not available
OR = odds ratio
RD = benzodiazepine related drug
SD = standard deviation
SPMSQ = Short Portable Mental Status Questionnaire
TMT-B = Trail-Making Test, part B
WAIS = Wechsler Adult Intelligence Score

Appendix 4. Longitudinal studies on the use of BZD/RD and the risk of precipitous cognitive decline in the aged with dementia.

Authors, year of publication, country, N, proportion of gender, mean age ± SD, range at baseline	Population, study design, follow-up	Source of medication data, frequency of updating the medication data	Medications studied	Source of data on cognitive ability, Cognitive measures	Statistic analyses (covariates)	Results
Ellul et al. 2007, United Kingdom, N=224, 73 % women, 82.3 ± 6.5 years, 65-NA	Representative group of patients with Alzheimer's disease from the community, follow-up of 12 months	Patients or their caregivers were asked to show the medications they were actually taking, medication data was recorded at both phases	BZD, RD, antipsychotics, drugs for dementia, renin-angiotensin system affecting drugs, statins	Diagnosis of Alzheimer's disease was made according to NINCDS-ARDRA criteria, cognitive decline was measured using GDS by trained researchers	Logistic regression analysis adjusted for presence of delusions, hallucinations, aggressive behaviour, extrapyramidal signs	Patients who were taking antipsychotic drugs and sedatives had a significantly higher risk of deterioration than those who were taking none [ORs 2.74 (95 % confidence interval (CI) 1.17 to 6.41] and 2.77 (95 % CI 1.14 to 6.73), respectively). Higher risk of deterioration was observed in those who were taking both antipsychotic and sedative drugs together [OR 3.86 (95 % CI 1.28 to 11.7].
Rosenberg et al. 2012, United States, N=230, 72.4 % females at baseline, 62.4 % females during follow-up, 85.1 ± 6.1, 65-NA	Longitudinal, population-based, follow-up with a mean of 3.7 years visits varying from 6 to 18 months	Visual inspection of all available medications at each follow-up. When institutionalised participants, information was obtained from nursing home records. Data collected at each follow-up. Summary measure to quantify medication exposure was used (PI)	BZD, antidepressants, antipsychotics	Diagnosis of dementia was made according to DSM-III-R criteria and diagnosis for Alzheimer's disease by a consensus panel consisting of neurologists, geropsychiatrists, neuropsychologists, and a cognitive neuroscientist according to NINCDS-ARDRA criteria. MMSE, CDR-Sum, NPI	Mixed-effect model adjusted for age, gender, education, estimated duration of dementia prior to baseline visit, GMHR, APOE eta4 alleles, baseline NPI-Total	At baseline, psychotropic medication use was associated with greater severity of dementia and poorer medical status. Higher Persistency Index (PI) for all medication classes was associated with a more rapid decline in MMSE. For antidepressant, SSRI, BZD, and typical antipsychotic use, a higher PI was associated with a more rapid increase in CDR-Sum.

APOE = apolipoprotein E
BZD = benzodiazepine
CDR-Sum = Clinical Dementia Rating, Sum of Boxes
CI = confidence interval
CNS = central nervous system
DSM-III-R = Third revision of the Diagnostic and Statistical Manual of Mental Disorders
GDS = Global Deterioration Scale
GMHR = General Medical Health Rating
MMSE = Mini-Mental State Examination
NA= not available
NINCDS-ARDRA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NPI = Neuropsychiatric Inventory
OR = odds ratio
PI = Persistency Index
RD = benzodiazepine related drug
SD = standard deviation
SSRI = selective serotonin re-uptake inhibitor

Appendix 5. Melatonin in the withdrawal RCTs of BZD/RD in older adults and in the aged.

Authors, year of publication, country, N, proportion of gender, mean age ± SD, range at baseline	Population, study design, follow-up	Source of medication data, frequency of updating the medication data	Medications studied	Results
Garfinkel et al. 1999, Israel, N=34 (25 women), 68 ± 13 years, 40-90 years	Independently living volunteers using BZD daily for over 6 months and willing to withdraw. RCT with double-blind placebo-controlled (part 1: 1-6 weeks) and single-blind parts (part 2: 7-12 weeks), BZD were withdrawn gradually during part 1 and those who could not withdraw were encouraged to withdraw gradually during part 2. Following the parts 1 and 2, all were given possibility to use same dosage of melatonin every evening openly and followed up to 6 months.	BZD consumption was reported daily by all patients using a questionnaire.	Melatonin 2 mg in controlled-release formulation against placebo given 2 hours before bedtime. Subjects were informed that they were receiving at least 1 period of active treatment during the study, but they were unaware of whether they were receiving melatonin or placebo during each of these periods.	By the end of period 1, 14 of 18 (78 %) who had received melatonin, but only 4 of 16 (25 %) in the placebo group, discontinued BZD therapy (P=0.006). Sleep-quality score were higher in the melatonin group (P=0.04). Six additional subjects in the placebo group discontinued BZD therapy when given single-blindly melatonin in part 2. The 6-month follow-up assessment showed that of the 24 patients who discontinued BZD and received melatonin therapy openly, 19 maintained good sleep quality.
Cardinali et al. 2002, Argentina, N=45 (36 women), 70.5 ± 13.1 years, range NA	Volunteers taking regularly (not defined) BZD and willing to withdraw. Six-week RCT comparing melatonin to placebo. All were given placebo for 7 days before the active treatment. Those participants who showed more than 30 percent improvement in sleep quality with placebo before BZD withdrawal (7 days) or could not withdraw BZD as prospectively decided (day 14: BZD dose; day 28: BZD withdrawn) were excluded. Assessed by quality of morning freshness, daily alertness, sleep quality and sleep onset and offset times.	Clinical interviews by physician at days 1, 14, 28 and 42.	Melatonin 3 mg in fast-release formulation against placebo 30 mins before sleeping time.	No significant modifications of sleep of wakefulness were detected after BZD withdrawal. Compared to baseline, there were no changes in quality of wakefulness or sleep in participants taking melatonin or placebo. Sleep quality of participants taking melatonin during the first two weeks of treatment was significantly lower than that of placebo, but after then the significance disappeared. Melatonin advanced sleep onset by 27.9 ± 11.9 min (P=0.0001) and decreased significantly variability of sleep onset time (P=0.03).
Vissers et al. 2007, the Netherlands, N=38 (22 women), mean age NA, 6 participants younger than 50, 6 participants 50-59 and 26 participants aged 60 or older, range NA	Volunteers long-term users of BZD (more than three months more than three days per week) willing to withdraw in nine general practices. BZD were gradually withdrawn by lowering the dose by 25 of the original dose every two weeks. RCT with six-week withdrawal period of benzodiazepines and follow-up until 1 year.	Four questionnaires (baseline, 18, 26 weeks and 1 year) and three urine samples (baseline, six weeks and 1 year) confirming the withdrawal of BZD.	Melatonin 5 mg in fast-release formulation against placebo four hours before going to bed.	No differences between melatonin and placebo groups were found. 21 participants (55 %) discontinued the use of BZD after the withdrawal period: 12 (60 %) in melatonin group and 9 (50 %) in placebo group. After one year, 15 (40 %) had stopped their BZD use both in the intervention group on melatonin and in the placebo control group (8/20, 40 %, in melatonin group and 7/18, 39 %, in placebo group, respectively).

BZD = benzodiazepine
NA= not available
SD = standard deviation
RCT = randomized controlled trial

Appendix 6. Effect of withdrawal interventions of benzodiazepines and related drugs on cognitive function in older adults and in the aged.

Authors, year of publication, country, N, proportion of gender, mean age ± SD, range at baseline	Population	Study design, follow-up, benzodiazepine withdrawal	Controls	Cognitive measures, re-assessments	Results
Salzman 1992, United States, N=25, 80 % women, 86.0 ± NA	Nursing home dwellers taking BZDs at least one month, those willing to withdraw (N=13) were withdrawn, and those who continued BZDs (N=12) were used as controls,	Single blind case-control longitudinal withdrawal study, researchers were blinded for discontinuation two-week withdrawal period	BZD users who were not willing to withdraw or physician did not recommend withdrawing due to poor health state were used as controls for withdrawers	Digit span, vigilance test paradigm re-assessments at 2-3 weeks	BZD withdrawers compared to non-withdrawers had an improvement in total memory, immediate recall and total digits. There was also a trend in improvement in delayed recall. Clinically, withdrawers appeared more alert and less forgetful to nursing staff and family members. One year BZD discontinuation rate was 60 %.
Rummans et al. 1993, United States, N=62, 66 ±7.4, 55- NA years	20 community-dwelling BZD-users (withdrawn in 7-10 days) compared to 20 alcohol users (withdrawn in 5-7 days) and 22 BZD-free and alcohol-free community dwellers, all groups without neurological or other psychiatric diseases but substance addiction	Matched case-control cohort study (by age, gender, IQ)	Alcohol-dependent and BZD-free and alcohol-free controls	WAIS-R (for matching the participants by intelligence), AVLT performed after the participants had completely withdrawn their addictive substance, cognitive testing performed in a mean of 6-7 days for BZD users and 10 days for alcohol users after the last dose of BZD or alcohol	After withdrawal of BZDs, previous BZD users had more difficulty with tests of learning and short-term and delayed recall compared to age, gender and IQ matched previous alcohol-dependant or BZD-free and alcohol-free control group. The difference was significant between previous BZD users and controls.
Curran et al. 2003, United Kingdom, N=192, 71 % women, 77 ± 6.9, 65-93	192 community-dwelling long-term users of BZD hypnotics without neurological or psychiatric diseases from 25 general practices, those with neurological or psychiatric diseases were excluded	Double-blind RCT (the beginning of the BZD withdrawal in cross-over design), group A (N=55) double blindly withdrew BZDs in 8 or 9 weeks, group B (N=49) double blindly continued BZD for three months and then withdrew in 8 or 9 weeks, and group C (N=34) openly continued their normal BZD use, 52-week follow-up and urine samples at baseline and 52 week from 27 participants	Those not willing to withdraw benzodiazepines	Spot the Word task, Speed of Comprehension Test, Prose recall, Map location task, Digit span, Speed of information processing task, simple reaction time, tapping speed baseline measures and re-assessments at 24 (100 % of participants) and 52 weeks (50 %)	Of all patients beginning the trial, 80 % had successfully withdrawn 6 months later. There was little difference in cognitive testing between groups A and B, but these groups differed from continuers (C) in that the performance of the withdrawers on several cognitive/psychomotor tasks showed relative improvements at 24 or 52 weeks.

McAndrews et al. 2003, Canada, N=51) BZD-users 61.7 ± 9.3 and controls 62.7 ± 9.1, 47 % women, 50 years - NA	25 community-dwelling unselected BZD users (at least for 6 months) and 26 healthy control subjects both groups without neurological or psychiatric diseases	Case-control longitudinal withdrawal study, average withdrawal period 10 ± 9.7 weeks	Benzodiazepine-free controls	Digit span, animal fluency, Stroop test (reading, colour naming and colour–word conditions), the trail-making test, digit-symbol substitution test, finger tapping and bead-sorting, immediate and delayed tests of story and design, recall of digit-symbol pairs, and three measures from the CERAD 10-item list-learning test. Selected subtests from the WAIS-R (information, vocabulary, comprehension, similarities) were administered at baseline to assess intellectual functioning to ensure matching between groups on this factor, re-assessments at 4 weeks	25 BZD users completed the study, 27 could not withdraw BZDs. There were no significant group differences in cognitive performance between BZD users and controls after adjusting for affective status. BZD users who withdrew showed greater improvements on tests of attention and speed of processing at repeat testing compared with controls. This improvement was not attributable to a change in affective status.
Tsunoda et al. 2010, Japan, 30, 43 % women, 79.1 ± 8.9, 60-77	Nursing home-dwellers using benzodiazepines at least for 2 months with diagnosed schizophrenia, primary insomnia, dementia and bipolar disorder,	Open-label longitudinal study, benzodiazepines gradually withdrawn in 3 weeks, 8-week follow-up	No control group, participants were compared to themselves in time	CFF, RBANS, re-assessments at 5 weeks	26/30 completed the study, 24 were completely discontinuing BZDs as two reduced by 50 and 67 %. Significant improvements were observed in the CFF and RBANS immediate memory, language and attention index scores.

AVLT = Auditory Verbal Learning test
BZD = benzodiazepine
CERAD = Consortium to establish a registry for Alzheimer's disease
CFF = Critical Flicker Fusion Test
IQ = intelligence quotient
MMSE = Mini Mental State Examination
RBANS = Repeatable Battery for the Assessment of Neuropsychological Status
RCT = randomized controlled trial
RD = benzodiazepine related drug
WAIS-R = Revised Wechsler Adult Intelligence Score

Appendix 7. Generic names of medications used in the analyses of Studies II and III.

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