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**Potential risks associated with some commonly used drugs
among older people in institutional settings – focus on proton
pump inhibitors and drugs with anticholinergic properties**

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Academic Dissertation

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To my loving father

”There are some remedies worse than the disease”

(Publilius Syrus, circa 42 B.C.)

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Abbreviations

ACBS	Anticholinergic Cognitive Burden Scale
ADE	Adverse drug events
ADL	Activities of daily living
ADR	Adverse drug reactions
ADS	Anticholinergic Drug Scale
AUC	Area under the curve
CCI	Charlson Comorbidity Index
CDI	Clostridium difficile infections
CDR	Clinical Dementia Rating
ChEIs	Acetylcholinesterase inhibitors
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
DAPs	Drugs with anticholinergic properties
DDIs	Drug-drug interactions
DDDI	D-class drug-drug interactions
HR	Hazard ratio
IADL	Instrumental activities of daily living
MMSE	Mini Mental State Examination
MNA	Mini Nutritional Assessment
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PIDs	Potentially inappropriate drugs
PPI	Proton-pump inhibitors
SAA	Serum anticholinergic activity
SD	Standard deviation

SFINX Swedish, Finnish, Interaction X-referencing database
SSRI Selective serotonin reuptake inhibitor

Definitions

Residential care	Long-term care given to older people who stay in a residential setting rather than in their own home. Room and board and varying degrees of assistance. Various options available depending on the needs of the individual with disabilities, mental health problems, or dementia. This term is often used interchangeably with assisted living facility.
Assisted living facility	Room and board and varying degrees of assistance with management of medical conditions and with activities of daily living (ADL) in physically or cognitively impaired patients. In Finland, often similar to nursing homes in their level of care.
Nursing home	Facility providing 24-hour care for people requiring assistance with ADL/Instrumental activities of daily living (IADL) and having identified health needs.
Group home	Small group homes available, e.g., for patients with dementia. They may specialize in people with mental health problems, patients with neuropsychiatric symptoms, or certain ethnic groups.
Long-term care ward, long-term care hospital	Facility providing room and board, management of chronic medical conditions, and assistance with ADLs in physically and/or cognitively impaired patients. More hospital-like setting than traditional nursing homes.
Acute geriatric ward	Provides subacute and acute care, management, and rehabilitation for multimorbid, older patients by a multidisciplinary geriatric team.

List of original publications

This thesis is based on the following original publications:

1. Teramura-Grönblad M, Hosia-Randell H, Muurinen S, Pitkala K. Use of proton-pump inhibitors and their associated risks among frail elderly nursing home residents. *Scand J Prim Health Care* 2010;28(3):154-9.
2. Teramura-Grönblad M, Bell JS, Pöysti MM, Strandberg TE, Laurila JV, Tilvis RS, Soini H, Pitkälä KH. Risk of death associated with use of proton-pump inhibitors in three cohorts of institutionalized older people in Finland. *J Am Med Dir Assoc* 2012;13(5):488.e9-13.
3. Teramura-Grönblad M, Muurinen S, Soini H, Suominen M, Pitkälä KH. Use of anticholinergic drugs and cholinesterase inhibitors and their association with psychological well-being among frail older adults in residential care facilities. *Ann Pharmacother* 2011;45(5):596-602.
4. Teramura-Grönblad M, Raivio M, Savikko N, Muurinen S, Soini H, Suominen M, Pitkälä KH. Potentially severe drug-drug interactions among older people in assisted living facilities in Finland. *Scan J Prim Health Care* 2016;34(3):250-7.

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Abstract

Background: Frail older people in institutional settings are known to suffer from comorbidities and are often administered a high number of concomitant drugs. They are therefore prone to polypharmacy, adverse drug effects, and drug-drug interactions (DDIs). Older people living in assisted living represent a particularly frail segment of the elderly population, and a large proportion of them suffer from cognitive impairment. During the last decade knowledge has accumulated on the adverse effects of drugs with anticholinergic properties (DAPs) and long-term use of proton-pump inhibitors (PPIs) among older people. Less is known about the extent and prevalence of these effects among the frailest older people in institutional settings. Residents in assisted living facilities are often taken care of by consulting primary care physicians. Therefore, they may have rare opportunities for a thorough reassessment of their medication after admission to institutional care. Thus, their use of drugs intended to be taken over a limited period is often extended.

Aims: This study explores the associations of DAPs and PPIs with adverse effects and investigates potentially severe DDIs among older residents in institutional settings. Of particular interest were adverse effects and mortality associated with the use of PPIs (Studies 1 and 2). In addition, concomitant use of DAPs and acetylcholinesterase inhibitors (ChEIs) and their association with psychological well-being (PWB) were investigated (Study 3). Finally, the prevalence of potentially severe D-class drug-drug interactions (DDDIs) and their association with mortality were clarified (Study 4).

Methods: This study consists of four substudies. Study 1 includes 1987 residents (mean age 83.7 years, 80.7% women) from a project investigating the nutrition of nursing homes in Helsinki in 2003. Study 2 consists of three samples from various institutional settings: 1389 residents in 69 assisted living facilities in 2007 (first cohort; mean age 82.7 years, 78.9% women), 1004 residents of long-term care hospitals in 2003 (second cohort; mean age 81.3 years, 75.3% women), and 425 residents in acute geriatric wards or in nursing homes in 1999-2000 (third cohort; mean age 86.1 years, 81.6% women) in Helsinki. Study 3 investigates 1475 residents (mean age 82.8 years, 77.7% women) from a project assessing nutrition in assisted living facilities in the metropolitan area of Finland. In Study 4, these same residents were followed up for mortality for 3 years. Those 1327 residents having complete follow-up data available were included (mean-age 82.7 years, 78.3% women). In all studies participants were interviewed by trained nurses. Demographics were retrieved from medical records. Drug use and medical diagnoses were confirmed from medical records, and drugs were coded with the WHO Anatomical Therapeutic Chemical Classification

System. All DAPs were classified according to the Anticholinergic Risk Scale (Study 3). Mini Nutritional Assessment (MNA) was used for evaluating nutritional status, Clinical Dementia Rating (CDR) for assessing dementia and disability, PWB scale for exploring residents' well-being, and Charlson comorbidity index (CCI) for assessing the severity and burden of diseases. Swedish, Finnish, Interaction X-referencing database (SFINX) was used to detect DDDIs (Study 4). Mortality data were retrieved from central records in Studies 2 and 4.

Results: Of nursing home residents in Study 1, 22% were administered proton-pump inhibitors (PPIs) on a daily basis. Regular PPI use was associated with diarrhoea, prior hip fracture, coronary heart disease, and lactose intolerance, indicating possible side effects or use for an inappropriate therapeutic intent.

In Study 2, the prevalence of the use of PPIs varied from 21.4% (geriatric wards and nursing homes) to 26.4% (assisted living facilities). The use of PPIs was not associated with mortality among residents in assisted living facilities. However, their use was associated with increased mortality in settings where residents experienced higher levels of disability and comorbidities (long-term hospitals, geriatric wards, and nursing homes), and thus, possible higher vulnerability to adverse drug events (ADEs) of PPIs. In the acute geriatric hospital and nursing home cohort, the risk for mortality was HR 1.90 (95% CI 1.23 to 2.94) even after adjustment for age, gender, comorbidities, delirium, and use of aspirin and selective serotonin reuptake inhibitors.

In Study 3, 41.6% of residents were administered DAPs. Of residents in assisted living facilities, 10.7% were administered ChEIs and DAPs concomitantly. DAP use was associated with use of a higher number of drugs, more severe disability, depression, psychiatric disorders, and Parkinson's disease. DAP use was associated with low psychological wellbeing even after adjustment for age, gender, education, comorbidities, and use of ChEIs.

In Study 4, 5.9% of residents in assisted living facilities were susceptible to severe DDDIs. The most common DDDIs were related to use of potassium-sparing diuretics, carbamazepine and methotrexate. Residents exposed to severe DDIs were more often exposed to polypharmacy than residents not exposed to DDIs. No significant difference in mortality emerged between residents with and without DDDIs.

Conclusions: The PPIs are common in institutionalized settings and they may expose to unexpected adverse effects such as diarrhoea and higher mortality among frail older people. Inappropriate use of DAPs and ChEIs concomitantly is common in assisted living facilities. DAP

use was associated with poorer psychological well-being. Potentially severe DDIs are relatively uncommon in these populations even with a high prevalence of polypharmacy.

Tiivistelmä

Tausta: Laitoksissa asuvien hauraiden vanhusten tiedetään olevan monisairaita ja usein käyttävän paljon samanaikaisia lääkkeitä. Monilääkityksen takia he ovat alttiita haittavaikutuksille ja lääkkeiden haitallisille yhteisvaikutuksille. He ovat haurainta osaa vanhusväestöä ja suurin osa heistä kärsii muistisairaudesta. Viimeisen kymmenen vuoden aikana tutkimustieto antikolinergisten lääkkeiden and pitkäaikaisen protonipumppuinhibiittoreiden (PPI) käytön haitoista on lisääntynyt. Vähemmän tiedetään miten nämä haitat ilmenevät kaikkein hauraimmilla laitoshoidossa asuvilla vanhuksilla. Pitkäaikaishoidossa asuvat vanhuksot ovat usein yleislääkäreiden hoidossa. He pääsevät harvoin perusteelliseen lääkehoidon arviointiin sen jälkeen kun he ovat muuttaneet pitkäaikaishoitoon. Siten sama lääkitys jatkuu usein pitkään, vaikka lääkitys olisi tarkoitettu käytettäväksi vain väliaikaisesti.

Tutkimuksen tavoitteet: Tämän tutkimuksen tarkoituksena oli arvioida antikolinergisten ja PPI lääkkeiden yhteyttä niiden mahdollisiin haittavaikutuksiin sekä lääkkeiden yhteisvaikutuksia laitoshoidossa olevilla vanhuksilla. Erityisesti arvioitiin PPI lääkkeiden haittavaikutuksia (osatutkimus 1) ja PPI käytön yhteyttä kuolemanvaaraan (osatutkimus 2). Lisäksi selvitettiin antikolinergisesti vaikuttavien lääkkeiden samanaikaista käyttöä asetyylikoliiniesteraasi-estäjien (AKE) kanssa ja niiden vaikutusta psyykkiseen hyvinvointiin (osatutkimus 3) sekä potentiaalisesti vakavien D-luokan yhteisvaikutusten yleisyyttä sekä niiden yhteyttä kuolemanvaaraan (osatutkimus 4).

Menetelmät: Väitöskirja koostuu neljästä osatutkimuksesta. Osatutkimuksen 1 aineistossa oli 1987 helsinkiläistä vanhainkotiasukasta (keski-ikä 83.7 vuotta, 80.7% naisia), joiden lääkitys tutkittiin osana asukkaiden ravitsemustilan kehittämissuunnitelmaa. Osatutkimus 2 koostui kolmesta otoksesta: 1389 asukkaasta 69 Helsingin palvelutaloista vuodelta 2007 (ensimmäinen kohortti; keski-ikä 82.7 vuotta, naisia 78.9%), 1004 asukkaasta pitkäaikaissairaaloista vuodelta 2003 (toinen kohortti; keski-ikä 81.3 vuotta, naisia 75.3%), ja 425 asukkaasta geriatrisen akuuttihoiton osastoilta tai Helsingin kaupungin vanhuskodeista vuosilta 1999-2000 (kolmas kohortti; keski-ikä 86.1 vuotta, 81.6% naisia). Osatutkimuksessa 3 aineistona oli 1475 Helsingin metropolialueen palvelutalojen asukasta (keski-ikä 82.8 vuotta, 77.7% naisia) projektissa, joka selvitti heidän ravitsemustilaansa vuonna 2007. Osatutkimus 4:ssä seurattiin näiden samojen asukkaiden kuolleisuutta kolmen vuoden ajan. Ne 1327 asukasta, joilla oli täydelliset seurantatiedot käytettävissä lääkehoidon ja ravitsemustilan osalta otettiin tutkimukseen (keski-ikä 82.7 vuotta, 78.3% naisia).

Kaikissa tutkimuksissa koulutetut hoitajat tekivät haastattelun osallistujille. Demografiset tiedot, lääkkeiden käyttö ja sairausdiagnoosit vahvistettiin sairauskertomustiedoista. Lääkkeet koodattiin käyttämällä WHO:n ATC koodeja (Anatomical Therapeutic Chemical Classification System). Kaikki antikolinergisesti vaikuttavat lääkkeet luokiteltiin Anticholinergic Risk Scale luokituksen mukaan (osatutkimus 3). Ravitsemustila määriteltiin Mini Nutritional Assessment (MNA) mittarilla, dementian vaikeusaste ja toiminnanvajeet Clinical Dementia Rating (CDR) luokituksella, asukkaiden hyvinvointi Psychological Well-being mittarilla. Charlson comorbidity indeksin avulla arvioitiin sairauksien vakavuutta ja kuormitusta. Swedish-Finnish Interaction X-referencing - tietokantaa (SFINX) käytettiin arvioitaessa lääkkeiden mahdollisia vakavia, D-luokan yhteisvaikutuksia (osatutkimus 4). Tiedot kuolleisuudesta kerättiin keskusrekistereistä (osatutkimukset 2 ja 4).

Tulokset: Osatutkimuksessa 1 vanhainkodin asukkaista 22 % sai päivittäin PPI lääkkeitä. Säännölliseen PPI käyttöön liittyviä oireita ja piirteitä olivat ripuli, aikaisempi lonkkamurtuma, sepelvaltimotauti ja laktoosi-intoleranssi viitaten PPI lääkkeiden mahdollisiin sivuvaikutuksiin tai niiden käyttöön väärällä hoitodikaatiolla.

Osatutkimuksessa 2:ssa PPI lääkkeiden käytön yleisyys vaihteli 21.4 %:sta (geriatriset osastot ja vanhainkodit) 26.4 %:iin (palvelutalot). PPI lääkkeet eivät liittyneet kuolleisuuteen palvelutalojen asukkaiden kohdalla. Sen sijaan ne liittyivät kohonneeseen kuolleisuuteen laitoksissa, joissa asukkailla oli enemmän toiminnanvajeita ja jossa he olivat monisairaita. Pitkäaikaissairaaloiden, geriatristen osastojen ja vanhainkotien asukkaat olivat alttiita PPI-lääkkeiden haittavaikutuksille. Geriatrisen akuuttihoiton osaston ja vanhainkodin kohortissa kuolleisuuden vaara oli HR 1.90 (95 % CI 1.23 - 2.94) jopa vakioitaessa ikä, sukupuoli, liitännäissairaudet, delirium, sekä ASA ja SSRI lääkkeiden käyttö.

Osatutkimuksessa 3, 41.6 % asukkaista käytti antikolinergisesti vaikuttavia lääkkeitä. Tutkittavista 10.7% käytti AKE-lääkkeitä ja antikolinergisesti vaikuttavia lääkkeitä samanaikaisesti. Antikolinergisesti vaikuttavien lääkkeiden käyttöön liittyi suurempi lääkkeiden lukumäärä, toiminnanvajeus, depressio, psykiatriset sairaudet ja Parkinsonin tauti. Antikolinergisesti vaikuttavien lääkkeiden käyttö oli yhteydessä heikompaan psyykkiseen hyvinvointiin kun ikä, sukupuoli, koulutus, monisairaus ja AKE-lääkkeiden käyttö vakioitiin.

Osatutkimuksessa 4 laitosten asukkaista 5.9 % altistui lääkkeiden vakaville D-luokan yhteisvaikutuksille. Tavallisimmat lääkkeiden yhteisvaikutukset liittyivät kaliumia säästävien diureettien, karbamatsepiinin ja metotreksaatin käyttöön. Asukkaat, jotka altistuivat lääkkeiden

vakaville yhteisvaikutuksille, käyttivät enemmän lääkkeitä ja heillä esiintyi enemmän nivelsairauksia. Ryhmien välisessä kuolleisuudessa ei ollut merkitsevää eroa.

Johtopäätökset: PPI lääkkeiden käyttö on tavallista laitoshoidossa ja niiden käyttöön mahdollisesti liittyy mahdollisesti haittavaikutuksia kuten ripulia ja lisääntynyttä kuolleisuutta laitoshoidossa olevilla kaikkein hauraimmilla vanhuksilla. Antikolinergisesti vaikuttavien lääkkeiden ja AKE-lääkkeiden yhteiskäyttö on yleistä laitoshoidossa. Antikolinergisesti vaikuttavien lääkkeiden käyttöön liittyy heikentynyt psyykkinen hyvinvointi. Lääkkeiden vakavat yhteisvaikutukset ovat suhteellisen harvinaisia näillä potilailla, vaikka monilääkitys on hyvin yleistä.

1. Introduction

Older people living in institutional care represent the frailest segment of the older population, and they suffer from multiple co-morbidities and cognitive decline and are dependent in their activities of daily living (ADL) (Elseviers et al. 2010, Onder et al. 2012). They are often administered a high number of concomitant drugs (Ramage-Morin 2009, Elseviers et al. 2010, Onder et al. 2012, Beloosesky et al. 2013). Thus, they are prone to polypharmacy, DDIs and various adverse events (Johnell and Klarin 2007, Hosia-Randell et al. 2008, Vetrano et al. 2013).

Many commonly prescribed drugs predispose patients to adverse effects, which may in fact outweigh any benefits (AGS 2012, Socialstyrelsen 2012). Several experts have defined inappropriate drugs for older people (Beers et al. 1991, Beers 1997, Fick et al. 2003, Gallagher et al. 2008, O'Mahony and Gallagher 2008, AGS 2012, Socialstyrelsen 2012, O'Mahony et al. 2015). These drug lists include, for example, psychotropic drugs, drugs with anticholinergic properties (DAPs), non-steroidal anti-inflammatory drugs (NSAIDs), and generally drugs that lack efficacy or ones that have more harms than benefits. Older people in institutional settings suffer from dementia, malnutrition, risk of falls, and frailty, which predispose them to the adverse effects of many medications. If a medication is prescribed to treat the side effect of a previous medication, a "prescribing cascade" may result. Health care personnell need to be alert to this, especially among frail older people, who are particularly susceptible to DDIs and adverse reactions (ADRs) (Resnick 1995, Rochon and Gurwitz 1997, Seymour and Routledge 1998, Delafuente 2003, Gill et al. 2005, Spinewine et al. 2007, Bell et al. 2012).

Although inappropriate drugs have been investigated for several decades, the studies have been mainly descriptive and have explored prevalence. Less is known about the side effects or prognostic validity associated with these drugs (Jano and Aparasu 2007). Furthermore, the benefits and harms of many commonly prescribed drugs have not been explored and weighted in frail older populations (Vetrano et al. 2013). For example, long-term use of PPIs has been suggested to predispose older people to *Clostridium difficile* infections (Leonard et al. 2007, Yearsley et al. 2006), community-acquired pneumonia (Laheij et al. 2004) and hip fractures (Moayyedi and Cranney 2008). However, it is not known whether the benefits of these drugs overcome these adverse effects in frail, institutionalized older people.

DAPs have been found to worsen cognitive decline among frail older people (Uusvaara et al. 2009). In institutional settings, their use is even more complicated since dementia is common and residents may concomitantly use ChEIs.

In Finland, older residents in institutional care are often taken care of by primary care physicians (Hosia-Randell et al. 2008, Rummukainen et al. 2012, Pitkälä et al. 2014). These physicians act merely as visiting consultants in institutional settings. In addition, few patients in nursing homes have opportunities for a thorough review of their medication after admission to a nursing home (Pitkälä et al. 2014). Thus, their use of those drugs intended to be taken over a limited period may often be extended.

This study focuses on risks and adverse effects, such as diarrhoea, poor psychological well-being, and mortality, related to the use of PPIs and DAPs among frail older people living in institutional settings. It also explores the prevalence and risks related to DDDIs among older people living in assisted living facilities.

2. Review of the literature

2.1. Ageing and changes in pharmacokinetics and pharmacodynamics

Ageing is known to be associated with an increased prevalence of multiple diseases, which often exposes older people to polypharmacy (Corsonello et al. 2010). The ageing process is characterized by significant changes in physiological reserve, pharmacokinetics, and pharmacodynamic responses. Age-related changes in pharmacokinetics and pharmacodynamics in conjunction with comorbidity and polypharmacy expose frail older people to higher risk of adverse drug reactions (ADRs), which in turn contribute to rising health burden and costs (Corsonello et al. 2010, Hovstadius et al. 2010).

2.1.1. Pharmacokinetics

Gastric emptying and colonic transit are usually slower in the elderly, but absorption in the intestine, particularly passive absorption, is less affected (Boparai and Korc-Grodzicki 2011, Hubbard et al. 2013). However, one in three older people suffer from atrophic gastritis and inability to secrete gastric acid, which may lead to intestinal bacterial overgrowth and decline in absorption of iron, folate, calcium, vitamin K, and vitamin B12 (Saltzman and Russell 1998). This is especially relevant among older adults administered drug therapies that affect gastric acid secretion (Ito and Jensen 2010). Medicines absorbed through the skin may undergo alterations with ageing. Drug absorption may be decreased due to reduced tissue blood perfusion related to skin atrophy in older persons (Trautinger 2001).

With ageing, loss of water content and increase of body fat content may lead to modification of the distribution of drugs, with an increased circulating concentration of water-soluble drugs and a prolonged elimination of lipid-soluble drugs (Cusack 2004, Turnheim 2004, Boparai and Korc-Grodzicki 2011, Hubbard et al. 2013). For example, the long half-life of the benzodiazepine diazepam has been considered inappropriate because of its extremely prolonged elimination in older adults (Beers 1997). This may be especially relevant among frail older people – such as the institutionalized elderly– among whom body fat is increased and lean body mass is decreased (Hubbard et al. 2013).

With frailty and ageing serum albumin level diminishes (Boparai and Korc-Grodzicki 2011, Hubbard et al. 2013). Decreased serum albumin levels, together with impaired nutritional state and

comorbidities, may predispose to increased response to drugs bound to albumin, as a consequence of an increase in the active percentage of these drugs that are highly bound to protein (Boparai and Korc-Grodzicki 2011).

There is wide inter-individual variation in hepatic drug metabolism (Cusack 2004). Age-related decline in elimination of metabolized drugs is common in older individuals with serious diseases. This particularly applies to drugs eliminated by the cytochrome enzyme system (Cusack 2004, Boparai and Korc-Grodzicki 2011). There may be a decline in liver size and liver blood flow that may influence the rate of hepatic metabolism (Boparai and Korc-Grodzicki 2011). Inhibition of drug metabolism is not altered with ageing, but induction has been shown to be reduced in some studies (Cusack 2004). Among older people, first-pass metabolism may be reduced, leading to increased bioavailability of some drugs metabolized by cytochrome P450 enzymes (Boparai and Korc-Grodzicki 2011).

With ageing diminished glomerular filtration rate, tubular secretion, and renal blood flow leads to a reduction in renal elimination of drugs, constituting the most significant pharmacokinetic change in older people that results in a decreased clearance of many drugs (Mangoni and Jackson 2004, Turnheim 2004, Boparai and Korc-Grodzicki 2011). Because of reduced muscle mass there may be normal serum creatinine levels despite a reduced glomerular filtration rate. Therefore, Cockcroft-Gault or other equations are often used to estimate the glomerular filtration rate (Boparai and Korc-Grodzicki 2011). This method has been criticized and alternative methods such as use of cystatin C levels in serum as estimates of renal function are under investigation (Hubbard et al. 2013).

Renal impairment and decreased clearance of drugs may especially be aggravated in older people with chronic medical conditions such as diabetes and heart failure (Khalil et al. 2016).

Other comorbidities may also alter pharmacokinetics. Diabetic gastroparesis, atrophic gastritis, obesity surgery or other gastrointestinal disorders may hinder drug absorption (Gubbins and Bertch 1991, Horowitz et al. 2002, Stein et al. 2014).

2.1.2. Pharmacodynamics

Old age may lead to increased drug sensitivity as a consequence of altered pharmacodynamics (Turnheim 2004). Age-related changes in pharmacodynamics may occur, for example, at the receptor level or they may be due to altered homeostatic mechanisms (Turnheim 2004).

Pharmacodynamic changes in ageing tend to be more complex than pharmacokinetic changes, and they are often drug class specific (Cho et al. 2011). For example, older adults experience an

exaggerated response to benzodiazepines due to loss of neuronal substance, decreased synaptic activity, impaired glucose metabolism in the brain, and higher penetration of drugs in the central nervous system (CNS) (Turnheim 2004, Boparai and Korc-Grodzicki 2011). Similarly, the use of anticholinergic drugs, may be related to adverse effects in the CNS such as cognitive impairment and confusion (Turnheim 2004, Boparai and Korc-Grodzicki 2011).

2.1.3. Risks in older people for adverse drug reactions

Among older people, common ADRs are often due to alterations in renal, gastrointestinal, cardiovascular, endocrine, and neurological systems. In addition, the toxicity of drug combinations may be synergistic and greater than the sum of the risk of toxicity of each agent used alone. Non-steroidal anti-inflammatory drugs (NSAIDs) can increase the risk of peptic ulcer by 4-fold in older patients, and this risk is 15-fold with concomitant use of NSAIDs and corticosteroids (Boparai and Korc-Grodzicki 2011) (Table 1)

Table 1. Examples of drugs causing common adverse effects in older people (adapted by Boparai and Korc-Grodzicki 2011)

Anticoagulants	Bleeding, increased risk for drug interactions
Drugs with anticholinergic properties	Dry mouth, constipation, urinary retention, delirium
Tricyclic antidepressants	Dry mouth, constipation, urinary retention, tachycardia, hypotension, sedation, cognitive impairment
Antihistamines	Sedation, dry mouth, cognitive impairment
Antihypertensives	Hypotension, sexual dysfunction, altered mental status
Antipsychotics	Orthostatic hypotension, confusion, sedation, weight gain, drug-induced movement disorders, changes in thermal regulation
Benzodiazepines	Sedation, impaired motor function, depression, altered mental status
Digoxin	Intoxication with nausea, vomiting, cardiac arrhythmias, altered mental status
H2-receptor antagonists	Altered mental status, depression, confusion
Narcotic analgesics	Constipation, sedation, altered mental status, falls
Non-steroidal anti-inflammatory drugs	Gastric irritation, gastrointestinal bleeding, constipation, renal dysfunction, fluid retention, altered mental status
Sedatives/hypnotics	Excessive sedation, gait disturbances, delirium, depression

2.2. Polypharmacy

Polypharmacy can be defined as the concurrent use of many different drugs. It can also be defined as the excessive use of not clinically indicated or inappropriate drugs (WHO 1997). These drugs may be prescribed as chronic, required, or short-term medication. Also over-the-counter drugs (OTC) drugs, complementary and alternative medicines, and dietary supplements need to be taken into account.

Polypharmacy is most commonly defined quantitatively by a specific number of drugs in use, but also qualitative definitions, in reference to the quality of drug treatment, are used especially in the USA. (Larsen and Martin 1999, Maher et al. 2014). In studies applying a quantitative definition, five or more different prescribed drugs is the most frequently used cutoff (Bjerrum et al. 1998, Viktil et al. 2007, Haider et al. 2008, Onder et al. 2012). Excessive polypharmacy is most commonly defined as the use of ten or more drugs (Chan et al. 2009, Haider et al. 2009, Jyrkkä et al. 2011, Onder et al. 2012). However, there is no consensus regarding the number of medications at which polypharmacy begins (Fried et al. 2014).

Older people are prone to polypharmacy due to comorbidities, lack of follow-up of evidence-based clinical practice guidelines, and multiple prescribers (Barat et al. 2000, Bergman et al. 2007, Chan et al. 2009, Sergi et al. 2011, Blanco-Reina et al. 2015). The development of drugs for old age diseases such as dementia and osteoporosis has increased the number of drugs that old people are administered (Jyrkkä et al. 2006). More than 90% of older people use prescribed medications (Jyrkkä et al. 2006, Fried et al. 2014). Home-dwelling older people use on average four to seven drugs per person (Barat et al. 2000, Jyrkkä et al. 2006, Haasum et al. 2012). Older people in institutional settings constitute the frailest group, with a higher number of prescribed drugs, on average seven to ten drugs (Jyrkkä et al. 2006, Hosia-Randell et al. 2008, Haasum et al. 2012, Onder et al. 2012).

Several studies have suggested that advanced age, living in institutions, female sex, and lower education are associated with polypharmacy (Jyrkkä et al. 2006, Haider et al. 2009). Multimorbidity (Chan et al. 2009) and use of cardiovascular drugs, analgesics, asthma drugs, psychotropics, and anti-ulcer medications have been proposed to be associated with polypharmacy (Bjerrum et al. 1998, Jyrkkä et al. 2006). Table 2 lists factors that have been associated with polypharmacy according to the literature.

Table 2. Factors associated with polypharmacy (adapted from Barat et al. 2000, Jyrkkä et al. 2006, Bergman et al. 2007, Chan et al. 2009, Haider et al. 2009, Jyrkkä et al. 2009, Hovstadius et al.2010, Boparai and Koro-Grodzicki 2011, Sergi et al. 2011)

<i>Factors related to population, health care system and physicians</i>
Enhanced life expectancy, increasing older population
Development of new therapies and technologies
Increased use of preventive strategies
Development of drugs for old age diseases
Single disease oriented treatment guidelines
Prescribing habits, multiple prescribers, physician's work load, lack of time
<i>Factors related to patients</i>
Age
Female gender
Low socioeconomic status
Low education
Impaired self-reported health status
Single diseases (cardiovascular disease, asthma/chronic obstructive pulmonary disease, chronic pain, diabetes, depression)
Multimorbidity
Impaired nutritional status
Impaired functional status
Impaired cognitive function
Non-adherence to drug treatment
Living in institution

The benefits of a medication should always outweigh potential harms for the patient. The use of multiple medications may be associated with risk of negative consequences such as ADRs, drug-drug interactions (DDIs), non-adherence to drug therapy, inappropriate prescribing, and underuse of a beneficial medication (Spinewine et al. 2007). A systematic review showed that polypharmacy is associated with falls, hospitalizations, decline in cognitive and physical functioning, and mortality (Fried et al. 2014). From the point of view of society, polypharmacy also increases healthcare costs (Masoudi et al. 2005).

Several studies have suggested an association between polypharmacy, risk of hospital admissions and mortality among older people (Alarcón et al. 1999, Espino et al. 2006, Iwata et al. 2006, Ruiz et al. 2008, Jyrkkä et al. 2009, Fried et al. 2014). However, the independent role of polypharmacy in mortality is difficult to show, as drugs may instead be markers of underlying diseases causing deaths in elderly persons. This confounding by indication has rarely been taken into account in these studies. Most studies are merely descriptive, lacking the possibility for assessment of causality.

2.2.1. Polypharmacy among older people in institutional care

Several factors may increase the use of medications among older residents in institutional care. Older people in these settings suffer from multiple comorbidities and symptoms requiring treatment (Hosia-Randell et al. 2008). In addition, strict use of evidence-based clinical practice guidelines may lead to polypharmacy and very complicated drug treatments (Boyd et al. 2005). Besides polypharmacy, underuse of necessary drugs is also common (Löppönen et al. 2006).

Many international studies have reported that institutionalization is associated with a higher number of prescribed drugs (Jyrkkä et al. 2006, Finkers et al. 2007, Hosia-Randell et al. 2008, Olsson et al. 2010, Bronskill et al. 2012, Onder et al. 2012). In a five-year follow-up study conducted in Finland, the mean number of drugs among older people who moved from home to institutional care increased from 7.8 to 11.5 ($p < 0.001$) (Jyrkkä et al. 2006). In this Finnish study, older people in assisted living received on average more cardiovascular drugs and less drugs taken when needed than community-dwelling older people (Jyrkkä et al. 2006). Poor self-reported health, female gender, high age, and specific diseases and symptoms (asthma/chronic obstructive pulmonary disease (COPD), heart disease, diabetes, depression and pain) were associated with a higher number of administered drugs. Poor health has been associated with the use of more than ten drugs, malnutrition, and functional and cognitive impairments (Jyrkkä et al. 2011). An association was present between excessive polypharmacy and mortality (Jyrkkä et al. 2009).

In the SHELTER study conducted in nursing homes in eight European countries, nearly half of the residents ($N = 4023$) used 5-9 drugs and a further 24% ten or more drugs (Onder et al. 2012). An association existed between excessive polypharmacy (>10 drugs) and chronic diseases, depression, pain, dyspnea and gastrointestinal symptoms. An inverse association was observed between excessive polypharmacy and age, decreased functional ability, and cognitive impairment (Onder et al. 2012).

Some studies suggest that elderly persons with dementia take on average more drugs than those without dementia (Lau et al. 2010). In addition, some studies have shown that specific drug categories considered inappropriate for older people, most commonly anticholinergics and sedative drugs, are prescribed more often to the elderly with poorer cognitive performance (Hanlon et al. 1998).

However, one US study reported cognitive impairments to be associated with reduced prescription drug use (Crentsil et al. 2010).

Nursing home residents with impaired cognitive status are often prescribed drugs to treat chronic conditions rather than to manage symptoms with questionable benefits to the patients (Tjia et al. 2010). Use of drugs in older adults with cognitive impairment raises several potential concerns. There is a need to avoid drugs that may affect cognition when treating patients with co-existing cognitive impairment (Huey et al. 2006). In nursing homes, an association has emerged between drugs considered potentially inappropriate (PIDs) and polypharmacy (Rancourt et al. 2004, Hosiara-Randell et al. 2008, Stafford et al. 2011).

2.3. Potentially inappropriate drugs (PIDs)

PIDs can be defined as drugs in which the risk of adverse events exceeds the clinical benefits, or drugs used when there is a safer and more effective choice of treatment (Beers et al. 1997, O'Mahony and Gallagher 2008). PID lists were developed to prevent prescribing high-risk medications for older adults. Use of PIDs has been suggested to be associated with increased risk of adverse events involving increased risk of hospitalization or mortality among older people (Gallagher et al. 2008, Gallagher and O'Mahony 2008, Ruggiero et al. 2010, Gallagher et al. 2011). However, the use of an inappropriate drug according to the former Beers' list was not associated with other health care use or mortality among community-dwelling older people (Jano and Aparasu 2007). One study exploring nursing home patients suggested an increased risk of hospitalizations and mortality among those using any Beers' inappropriate medications compared with those not using any of these (Lau et al. 2005).

2.3.1. Criteria for PIDs

Criteria for PIDs can be divided into explicit (criterion-based) and implicit (judgement-based) criteria (O'Connor et al. 2012, Kaufmann et al. 2014). Explicit criteria are usually based on literature review or expert consensus methods (O'Connor et al. 2012). Moreover, explicit criteria are usually drug- or disease-oriented and can be applied with little or no clinical judgment (Spinewine et al. 2007). Thus, they are highly reproducible and are well suited for large-scale studies. They have been developed in various countries (USA, Canada, Australia, Ireland, France, Germany, Sweden, Norway, Italy, Austria, Thailand, and Taiwan) (Morin et al. 2015). Implicit tools are, by contrast, based on a clinician's assessment and are patient-specific. The focus is usually on the patient rather than on drugs or diseases. These approaches are potentially the most sensitive in finding patients' drug problems and can account for individual preferences of a patient (Spinewine et al. 2007). However, they are often time-consuming, are dependent on the user's knowledge and attitudes, and may have low reliability (Kaufmann et al. 2014).

The most widely used explicit criteria for PIDs have been Beers' criteria, which were originally developed for nursing home residents (Beers et al. 1991) and were later expanded to include all people of advanced age (Beers 1997). The criteria have been updated twice (Fick et al. 2003, AGS 2012). Although the Beers' criteria have been widely used and studied, the criteria before 2012 update (AGS 2012) had a low prognostic validity (Jano and Aparasu 2007). Furthermore, they included a large number of drugs unavailable in countries other than USA, thus differing from criteria that take into account local health policies, drug regimens, and clinical guidelines (Pitkälä et al. 2002). The updated version of Beers' criteria (AGS 2012) is more comprehensive than the previous ones (Beers et al. 1991, Beers et al. 1997, Fick et al. 2003). The updated version also includes, for example, antipsychotics and NSAIDs (AGS 2012). Although these criteria may be used in clinical practice, evaluation and decisions should be evaluated on a personal basis (PID use for a short period, with low dosages following patient's symptoms) (Hartikainen and Ahonen 2011).

The drugs available in different countries vary markedly (Pitkälä et al. 2002). Accordingly, many countries have developed their own PID lists to take into account, country-specific approved drugs and specific prescribing and therapeutic culture and guidelines (Table 3). It is important to consider and weigh benefits and harms of drugs in clinical assessment of an older patient. Alternative safer treatments should be chosen when available. In some cases, a limited use of PIDs may be justified (sometimes a single dose, for a short period, with low dosages or close response follow-up). It has been argued that PID lists should be used to flag older people with potential risks rather than explicitly discontinuing these drugs (Pitkälä et al. 2002). The STOPP/START criteria have been widely adopted by European experts (Gallagher et al. 2011). It has also been argued that these criteria have better prognostic validity than the Beers' criteria (O'Mahony et al. 2015).

Gallagher and colleagues (2011) developed a new screening tool for older persons' prescriptions that incorporates the criteria for PID known as STOPP (Screening Tool of Older Persons' Prescriptions) and the criteria for potentially appropriate, indicated drugs known as START (Screening Tool to Alert doctors to Right, i.e. appropriate, indicated Treatment) validated by Delphi's consensus technique. STOPP criteria includes, among others, drug–drug and drug–disease interactions, drugs that adversely affect older patients at risk of falls, and duplicate drug class prescriptions. START consists of 22 evidence-based prescribing indicators for commonly encountered diseases in older people.

Table 3. Criteria for potentially inappropriate drugs for older people (adapted from Ahonen 2011, O'Connor et al. 2012).

Study	Name of criteria, year, country	Characteristics of criteria and target population
Beers et al. 1991	Beers' criteria, 1991, USA	Explicit criteria, list based on a study among nursing home older residents (30 PIDs)
Beers 1997	Beers' criteria, 1997, USA	Explicit criteria, expanded list from Beers et al.1991, based on a population study of people ≥ 65 years (66 PIDs)
McLeod et al. 1997	McLeod's criteria, 1997, Canada	Explicit consensus criteria, drugs associated with clinically significant ADRs in older people, availability of at least one drug that has been shown to be a safer alternative (38 PIDs)
Zhan et al. 2001	Zhan's criteria, 2001, USA	Explicit criteria (11 drugs that should always be avoided in older patients, 8 drugs that are rarely appropriate, 14 drugs that have some indications, but are often misused; total 33 PIDs)
Fick et al. 2003	Beers' criteria, 2003, USA	Explicit criteria, updating of the Beers criteria, medications that should generally be avoided due to possible lack of efficacy or risk for ADRs when a safer alternative drug is available, drugs to be avoided in certain medical conditions (49 PIDs)
Laroche et al. 2007	French criteria, 2007, France	Explicit consensus criteria (29 medications or medications classes that should be avoided due to possible lack of efficacy, risk for ADRs when a safer alternative drug is available, 5 drugs to be avoided in certain medical conditions; total 34 PIDs)
Gallagher and O'Mahony 2008	STOPP/START, 2008, Ireland	Explicit consensus criteria based on indication of drug or symptoms, duration of treatment, drug interactions, dosage, duplicate drugs, including 65 PIDs (STOPP) and 22 evidence-based prescribing indicators for commonly encountered diseases in older people (START)
Basger et al. 2008	Australian Prescribing Indicators Tool, 2008, Australia	Explicit and implicit criteria based on treatment guidelines, drug-disease interactions, laboratory trackings, general warnings
Rognstad et al. 2009	NORSEP, 2008, Norway	Explicit consensus criteria, drugs, drug dosages, and drug combinations that should be avoided for older people (21 PIDs, 14 drug combinations)
Socialstyrelsen 2010	"Indikatorer för god läkemedelsterapi hos äldre" 2010, Sweden	Explicit criteria, long-term use of benzodiazepines, drugs with strong anticholinergic properties, concomitant use of at least 3 psychotropic drugs, potentially severe drug-drug interactions
Hartikainen and Ahonen 2011	"Täkkäiden lääkitöksen tietokanta", 2010, Finland	Explicit criteria based on consensus (A=drugs that can be used, B=low evidence, experience, efficacy, C=with caution, D=should be avoided)
American Geriatrics Society 2012 (Beers' Criteria Update Expert Panel)	Beers' criteria, 2012, USA	Explicit consensus criteria, update of the previous Beers' criteria, drugs to be generally avoided, in certain diseases, drugs to be used with caution in older patients (53 PIDs)
Hanlon and Schmader 2013	Medication Appropriateness Index (MAI), 1992, USA	Implicit criteria based on indication, efficacy, adequate dosage, sufficient instructions, clinically significant drug interactions, feasibility of drug treatment, availability of less expensive alternative drugs, absence of duplicate medications, adequacy of drug treatment

PID = Potentially inappropriate drug, ADR=adverse drug reaction

PID criteria in different countries have similarities but also differences (Chang and Chan 2010, O'Connor et al. 2012). Most criteria include various sedative drugs, psychotropic drugs, and anticholinergic drugs in their lists. Many also include drugs (e.g. digoxin, NSAIDs) that are harmful

for renal function (Gallagher et al. 2008, Gallagher and O'Mahony 2008, AGS 2012). Drug-disease interactions are taken into account (e.g. the use of certain calcium channel blockers in patients with chronic constipation or heart failure, theophylline as monotherapy or beta-blockers in patients with asthma or chronic obstructive pulmonary disease, long-term neuroleptics in patients with Parkinsonism) (Fick et al. 2003, Basger et al. 2008, Gallagher and O'Mahony 2008).

2.3.2. Prevalence and outcomes of PID use

Prevalence of PIDs and their associated factors have varied depending on the patient population and the criteria used (Guaraldo et al. 2011). In community settings, the prevalence of PIDs according to Beers' criteria has been in the range of 6-41% (Pitkälä et al. 2002, Fialova et al. 2005, Leikola et al. 2011), whereas the respective figure among older nursing home residents is 16-83% (Lau et al. 2005, Raivio et al. 2006, Hosia-Randell et al. 2008, Ruggiero et al. 2010, Chang and Chan 2010, Vieira de Lima et al. 2013). Even studies using the same criteria may have different findings if some drugs from the PID list are ignored (Pitkälä et al. 2002). Few studies have compared how different criteria identify PID users. In an inter-European study, STOPP/START criteria found a higher prevalence of PID users (51.3%) than the Beers' criteria (30.4%) (Gallagher et al. 2011). However, in a Malaysian study the Beers' criteria seemed to identify more PID users than the STOPP criteria (Chen et al. 2012). In a Spanish study, both Australian criteria (Basger et al. 2008) and STOPP/START criteria (Gallagher and O'Mahony 2008) found a high number of drug problems among nursing home residents (García-Gollarte et al. 2012).

PID use has been associated with higher age, female gender, and higher number of drugs (Guaraldo et al. 2011). A review argued that the use of inappropriate drugs according to the former Beers' criteria was not associated with the amount of health care use or mortality (Jano and Aparasu 2007). In a nursing home study using Beers' criteria in Finland, there was no association between PIDs and mortality or hospital admissions (Raivio et al. 2006), whereas an American study did show an association between the number of PIDs and hospitalizations and mortality (Lau et al. 2005). A Spanish study revealed that modification of medications on the basis of STOPP/START criteria may decrease falls, delirium, and use of health care services among nursing home patients (García-Gollarte et al. 2012).

2.4. Proton-pump inhibitors (PPIs)

Proton pump inhibitors (PPIs) are one of the most widely used drug classes (Masclee et al. 2014). In Finland, their consumption has increased almost exponentially; there is more than a 5-fold increase since their entry into the market in the early 1990s. In 2015, the Finnish Social Insurance Institution reported a defined daily dose (DDD) of 67.75 per 1000 inhabitants (Kela 2015).

The availability of PPIs has changed the treatment of upper gastrointestinal disorders, and, in general, they are effective and well-tolerated drugs (Arkkila 2015). PPIs are highly effective for treating gastric acid-related diseases such as gastro-oesophageal reflux, oesophagitis, and gastric and duodenal ulcers (Wolfe et al. 2000). They are also used to reduce the risk of gastrointestinal bleeding related to NSAIDs and low-dose aspirin (Pilotto et al. 2004, AGS 2012). Although there are critical indications for long-term use (e.g. Barrett's oesophagus), chronic PPI use is often not indicated (Choudhry et al. 2008). The STOPP/START criteria recommended that full dosage of PPI use should be limited to eight weeks (Gallagher and O'Mahony 2008). It has been stated that PPIs are overutilized among hospital inpatients (Heidelbaugh et al. 2006, Pham et al. 2006, Hamzat et al. 2012). Hospital patients are commonly discharged with a PPI prescription (Heidelbaugh et al. 2006, Pham et al. 2006).

The use of PPIs has increased rapidly during the past decades, especially in older people and accounts for a significant amount of drug expenses (Heidelbaugh et al. 2006, Hamzat et al. 2012). Accordingly, PPIs are the most common drugs prescribed to community-dwelling older people (Onder et al. 2016) and one of the mostly prescribed drugs for long-term care residents (de Souto Barreto et al. 2013, Vetrano et al. 2013), even without an indicated diagnosis (Patterson Burdsall et al. 2013).

PPIs are generally safe to use, and they are usually not included as PIDs for older people. For example, the Beers' criteria 2012 recommend their use when an older person with a history of gastric or duodenal ulcer is using NSAIDs or low-dose aspirin (AGS 2012). However, in recent years some unexpected adverse effects have been described in association with PPI use. Therefore, long-term use of PPIs at full dosages is considered inappropriate for older people according to STOPP & START criteria (Gallagher and O'Mahony 2008). Clinical guidelines for PPI use have been developed in some countries such as in the UK (NICE 2014) and USA (Bhatt et al. 2008, NICE 2014).

2.4.1. Pharmacokinetics of PPIs

All classes of PPIs share the same mode of action (inhibition of gastric proton pump). There are only minor pharmacokinetic differences between various PPIs. They have a half-life of about one hour and are thus unlikely to accumulate even when clearance is reduced - with increasing age. They also have similar time to achieve maximum concentration (Klotz 2000).

PPIs are exclusively metabolized by the hepatic route, by the cytochrome P450 isoform CYP2C19, for which they have a greater affinity, and by the isoform CYP3A4, which functions as an overflow pathway. CYP2C19 has two genotypes with a slow metabolizer and an extensive metabolizer phenotype. Approximately 3% of Caucasians are slow metabolizers. The effects of the genotypes vary among the PPIs, with omeprazole being most affected and rabeprazole the least since it is predominantly metabolized non-enzymatically and only minimally by CYP. The polymorphically expressed CYP2C19 contributes to a variable but significant extent to rapid hepatic elimination. Renal impairment does not affect PPI metabolism. Nevertheless, lower dosages are advisable for older people (Klotz 2000).

2.4.2. Drug-drug interactions involving PPIs

PPIs impair the absorption of many drugs since they decrease gastric acidity (Robinson and Horn 2003). Because older people are often administered a wide range of other drugs concomitantly with PPIs, there is an increased risk for DDIs (Robinson and Horn 2003). DDIs are common for drugs whose clearance involves CYP-mediated oxidative metabolism (CYP2C19 and CYP3A4) in the liver, with possible associations with the CYP phenotype of the patient. The potential for significant DDIs varies according to the class of PPIs. Special attention is warranted when PPIs are co-administered with narrow therapeutic index drugs such as phenytoin, warfarin, and theophylline. In addition, PPIs may alter the absorption of some drugs, such as digoxin and ketoconazole, by decreasing the acidity of the stomach (Robinson and Horn 2003) (Table 4).

Table 4. DDIs between PPIs and other drugs (adapted from Klotz 2000).

Drug used	Mechanism	Omeprazole	Lansoprazole	Pantoprazole	Rabeprazole
Digoxin	P-glycoprotein (?), absorption (intra-gastric pH)	increased AUC ¹	NA ²	NO ³	increased AUC ¹
Ketoconazole	Absorption (intra-gastric pH)	decreased AUC ¹	NA ²	NA ²	decreased AUC ¹
Theophylline	³ CYP1A2	NO ³	NO ³	NO ³	NO ³
Phenytoin	³ CYP2C9	decreased CL ⁴	NO ³	NO ³	NO ³
Warfarin	³ CYP2C9	NO ³	NO ³	NO ³	NO ³
Metoprolol	³ CYP2D6	NO ³	NA ²	NO ³	NA ²
Cyclosporin	³ CYP3A4	NO ³	NA ²	NO ³	NA ²
Carbamazepine	³ CYP3A4	decreased CL ⁴	NA ²	NO ³	NA ²
Nifedipine	³ CYP3A4	decreased CL ⁴	NA ²	NO ³	NA ²
Diazepam	³ CYP2C19	decreased CL ⁴	NO ²	NO ³	NO ³

¹AUC = area under the concentration-time curve; ⁴CL = systemic clearance; ³CYP = cytochrome P450; ²NA = data not available; ³NO = no significant interaction; ? = maybe involved.

2.4.3. Adverse effects associated with PPI use

Short-term use of PPIs may be associated with infrequent mild side-effects such as headache, diarrhoea, constipation, nausea and rash (Masclee et al. 2014). PPIs increase the gastric pH, impairing the absorption of many drugs (Robinson and Horn 2003). In addition, PPIs have some DDIs (Robinson and Horn 2003). In older people, long-term PPI use may be associated with risks and ADEs such as infections (Masclee et al. 2014).

Gastrointestinal infections

As a major defense mechanism against ingested pathogens, gastric acidity prevents colonization of the normally sterile upper gastrointestinal tract (Dial et al. 2005). Accordingly, PPI use and achlorhydria are associated with small bowel bacterial overgrowth (Masclee et al. 2014). Long-term PPI use may also be related to risk of *Clostridium difficile* infection (CDI) (Dial et al. 2005, Kwok et al. 2012, Masclee et al. 2014). In meta-analyses of cohort and case-control studies of >300 000 patients, the risk estimates have varied between 1.7 and 2.3 among users of PPIs compared with non-users (Janarthanan et al. 2012, Kwok et al. 2012). Compared with histamine-2-receptor antagonist users, PPI users may have a higher risk of CDI (Kwok et al. 2012). In a meta-analysis, concomitant use of PPIs and antibiotics seemed to confer a greater risk (OR 1.96) than PPI use alone (Kwok et al. 2012). Possible mechanisms may be related to increased conversion of the spore-form of *C. difficile* to its more virulent vegetative form, which is able to survive in the enteric lumen and, easily spreads between patients, especially in hospitals and nursing homes. The vegetative spores may return to a toxin-producing strain causing acute infection (Masclee et al. 2014).

Continuous PPI use also causes an elevated risk of CDI recurrence (Linsky et al. 2010, McDonald et al. 2015). Few studies have investigated the prevalence and risk factors of CDI in nursing homes, where residents are often admitted from acute care settings. Nursing home residents are predisposed to CDI due to comorbidities, decreased immune response, medications, and generally increased risk of infection. A majority of nursing home residents acquire CDI prior to entering the nursing home after a recent hospital discharge (Zarowitz et al. 2015). They are more likely to have severe underlying comorbidities and be readmitted to the hospital compared with patients with nursing home-acquired CDI (Zarowitz et al. 2015).

Decreased gastric acidity may also be related to increased risk of other bacterial enteric infections, such as Salmonella and Campylobacter infections (Leonard et al. 2007).

Pneumonia

PPIs may be associated with increased colonization of the upper gastrointestinal tract with potentially pathogenic organisms, which may increase the risk of community-acquired pneumonia in older people (Laheij et al. 2004, Sarkar et al. 2008). The risk may be especially relevant among hospitalized older patients at risk of aspiration (Masclee et al. 2014). A meta-analysis of 31 observational studies suggested a slightly increased risk of pneumonia among PPI users (OR 1.27) (Eom et al. 2011). However, a recent meta-analysis including cohort studies on new users of NSAIDs with or without PPIs suggested no risk of PPIs upon hospitalization for community-acquired pneumonia (Filion et al. 2014).

Malabsorption

B12 vitamin. While a normal diet usually contains substantially more vitamin B12 than is needed, the functional reserve is diminished in older people due to a decline in vitamin B12 absorption. A large proportion of vitamin B12 in food is bound to protein, from which it is released with the aid of acid and pepsin in the stomach, and, furthermore, bound to the intrinsic factor in order to be absorbed at the end of the small intestine (Arkkila 2015). PPIs reduce the levels of acid, which impairs the release of protein-bound vitamin B12 to its unbound state, thus leading to impaired absorption of vitamin B12 and its deficiency. Other factors, such as *Helicobacter pylori* infection (Valuck and Ruscini 2004) or bacterial overgrowth of small intestine (Masclee et al. 2014) may enhance this process. Long-term PPI treatment may also be associated with B12 vitamin deficiency by decreasing the release of intrinsic factor (Sagar et al. 1999, Masclee et al. 2014). Prolonged vitamin B12 deficiency may lead to reversible megaloblastic anaemia and demyelinating neurologic disease resulting in gait disorders and muscle weakness, and it has been linked to other aspects of neurological function such as cognitive decline and visual disturbances (Stabler 2013). Several

studies have investigated the association between PPI use and B12 vitamin deficiency with controversial findings (Valuck and Ruscin 2004, den Elzen et al. 2008, Dharmarajan et al. 2008). However, it has been concluded that long-term use of PPIs may lead to a decline in B12 concentration and in vulnerable older people also to deficiency (Arkkila 2015).

Calcium. PPIs may decrease calcium absorption by inhibiting solubilization of calcium salts and release of ionized calcium (Ito and Jensen 2010, Arkkila et al. 2015). Since calcium solubility absorption is dependent on the pH of the solution, calcium absorption has likewise been speculated to depend on the gastric pH (Hansen et al. 2010).

Magnesium. PPI treatment may be associated with hypomagnesaemia, which may lead to severe symptoms such as fatigue, tetany, cardiac arrhythmia, and concomitant secondary electrolytic disturbances (e.g. hypocalcaemia). The mechanism is seen to be a class-drug effect, possibly involving magnesium absorption (Arkkila 2015). The time of onset has varied widely (2 weeks to 14 years, mean 5.3years). Hypomagnesaemia may be resolved with withdrawal of PPI and may recur with PPI restart. Associated risk factors were comorbidity and concomitant use of diuretics (Ito and Jensen 2010, Hess et al. 2012, Arkkila 2015).

Risk of fractures

Several large-scale studies have shown an association between long-term PPI use and bone fractures (Yang et al. 2006, Roux et al. 2009, Corley et al. 2010, Ngamruengphong et al. 2011, Maggio et al. 2013b). This relationship has not been observed consistently in all studies (Targownik et al. 2008, Gray et al. 2010, Ito and Jensen 2010). According to the literature review by Masclee et al. (2014), there still seems to be inconsistent evidence concerning the association between PPIs and fractures.

Possible mechanisms have been suggested to be related to mineral density loss since PPIs may decrease intestinal calcium absorption, and this may lead to risk of fractures (Hansen et al. 2010, Ngamruengphong et al. 2011, Masclee et al. 2014). It has also been argued that PPIs may affect bone resorption, resulting in decreased bone turnover (Masclee et al. 2014). Furthermore, profound acid suppression by PPIs may indirectly cause hypergastrinaemia, stimulating parathyroid glands to increase parathyroid hormone levels (Masclee et al. 2014, Arkkila 2015).

One study suggested that the highest risk of fractures occurred among those with the highest PPI adherence, an intermediate risk among those with intermediate adherence, and the lowest risk among those with lowest adherence (Ding et al. 2014).

Cardiovascular outcomes

It has been argued that certain class of PPIs (omeprazole and esomeprazole) may attenuate the effect of aspirin on platelet aggregation and, in addition, impair conversion of clopidogrel to its active metabolite, thereby affecting platelet inhibition function (Masclee et al. 2014). Thus, PPIs may increase the risk for cardiovascular events (Wurtz et al. 2010). Several studies have explored this issue, but inconsistent evidence has emerged of an association between long-term PPI use and risk of adverse cardiovascular events (Masclee et al. 2014).

Other risks

It has been hypothesized that PPIs may increase the risk for gastrointestinal malignancies (Song et al. 2014). Long-term PPIs may lead to hypergastrinaemia (Yang et al. 2007). Gastrin has growth-promoting effects on a number of epithelial cell types, including cells located in the pancreatic, gastric, and colonic mucosa. It is possible that the trophic effects of gastrin may increase the chance of sporadic mutations in normal cells and/or enhance the proliferation and progression of neoplastic tissues or their precursors (Yang et al. 2007). However, PPIs have not been documented to increase the risk for adenocarcinomas of the stomach or colon (Williams and McColl 2006, Song et al. 2014, Arkkila 2015).

Recent studies have also suggested that PPIs may increase the risk of dementia (Haenisch et al. 2015, Gomm et al. 2016). The German Study on Ageing, Cognition, and Dementia followed up 73 679 participants free of dementia at baseline in 2004 until 2011 (Gomm et al. 2016). The patients receiving regularly PPIs (N=2950) had an increased risk of dementia during follow-up (HR 1.44; 95%CI 1.36 to 1.52). However, this study has been criticized for several reasons. The risk associated with dementia may arise from residual confounding. Furthermore, dementia diagnoses were not rigorously defined in the study (Nguen and Hur 2016).

In summary, risks related to PPI use have been found in epidemiological studies. The original randomized, controlled trials did not reveal these ADEs. Whereas most of the ADEs related to PPIs have a theoretical basis, these longitudinal studies cannot rule out user bias or residual confounding. Furthermore, some of the ADEs seems to carry fairly small risks (e.g. pneumonia) while others may include high risks (e.g. gastrointestinal infection). This emphasizes the fact that the clinician should always weigh potential benefits against potential risks (Table 5).

Table 5. Adverse effects associated with PPI use in older patients (adapted from Masclee 2014, Song et al. 2014, Arkkila 2015, Gomm et al. 2016)

Adverse event	Risk	Biological mechanism	Strength of association, consistency of evidence	Limitations of studies	Conclusions
<i>C. difficile</i> infection	22 cases per 100000 in the general population Age \geq 65 years increases the risk up to 16-fold	1. Conversion of spore-form in <i>C. difficile</i> to a vegetative form able to survive in the enteric lumen 2. Promotion of small intestinal bacterial overgrowth affecting the commensal intestinal microbiota	Moderate strength (risk estimates 2-3), inconsistent evidence	Uncontrolled confounding for severity of illness or other comorbid diseases PPIs may act as an intermediate factor for antibiotic therapy Limited data on dose and duration effects	Clinicians should test for <i>C. difficile</i> presence in older patients treated with PPIs when presenting with diarrhoea symptoms
Pneumonia	Annual incidence of 33-114 per 1000 for older people in residential care Extensively varying prevalence of vitamin B12 deficiency reported (3-40%) At least 5-15% of patients \geq 65 years affected	Possible bacterial and viral colonization by suppression of the gastric acid environment 1. Decreased gastric acidity resulting in reduced release of protein-bound vitamin B12 2. Decreased secretion of intrinsic factor 3. Bacterial overgrowth in blind loops of duodenum and jejunum	Low to moderate strength (risk estimates < 2-4), inconsistent evidence Low strength (risk estimates < 2), inconsistent evidence	No duration response observed. Possibly confounding by indication and protopathic bias No data on effect of PPIs on other sensitive measures of vitamin B12 deficiency	No significant impact on clinical practice Impaired vitamin B12 absorption aggravated by <i>H. pylori</i> infection Monitoring of vitamin B12 levels every 1-2 years during long-term PPI therapy is not recommended, but may be considered in subjects at risk
Bone fractures	Cumulative 1-year incidence of hip fractures: Women aged 70-74 years: 0.5%; 80-84 years: 1% Men aged 70-74 y: 0.3%; 80-84 y: 0.5%	1. Reduced calcium absorption 2. Impairment of microfractures regeneration 3. Elevation of PTH levels related to parathyroid hyperplasia	Low strength (risk estimates < 2), inconsistent evidence	No dose or duration responses observed Possible confounding factors involving polypharmacy and comorbidities	Fractures likely to occur in older patients who are already more prone to fractures due to comorbid diseases Clinicians should if possible lower dose and shorten PPI treatment in older patients at risk for osteoporosis

Table 5 (continued)

Hypomagnesaemia	Prevalence: 36 % of older people in long-term care facilities affected Not applicable	Poorly understood	Unknown, inconsistent evidence	Limited data	Scarce data on the association of PPIs and hypomagnesaemia
Cardiovascular outcomes (DDIs between PPIs and low-dose aspirin (LDA) /clopidogrel)		1. Decreased gastric acidity limits the lipophilicity of LDA and thereby reduces the passive absorption of LDA across the gastric mucosal membrane 2. Competitive inhibition of CYP2C19 by PPIs impairing the conversion of clopidogrel to its active substance and thereby affecting the platelet inhibition function	Low strength (risk estimates < 2), inconsistent evidence	Possible indication bias and residual confounding	No profound evidence for an interaction between LDA, clopidogrel and PPIs that allows changing guideline recommendations to avoid concomitant use of these agents
Dementia	Increased incidence of dementia in a population study (2004-2011), 2950 patients with regular PPIs (HR 1.44; 95% CI 1.36 to 1.52)	1. Enhancement of β -amyloid levels in the brains of mice by affecting the enzymes β - and γ -secretase 2. Modulation of the degradation of A β by lysosomes in microglia	Low strength, inconsistent evidence	Risk associated with dementia may be due to misclassification bias and residual confounding	No strong evidence of association between regular PPI treatment and incidence of dementia in older adults
Gastrointestinal malignancies	Systematic review, randomized controlled trials (RCTs) in adults \geq 18 years - concerning the effects of long-term PPI use on gastric mucosa changes, confirmed by endoscopy or biopsy sampling	Trophic effects of gastrin may increase the chance of sporadic mutations in normal cells and/or enhance the proliferation and progression of neoplastic tissues or their precursors	Low strength, inconsistent evidence	High risk of bias observed in the studies	Imprecise evidence that PPIs can cause or accelerate the progression of corpus gastric atrophy or intestinal metaplasia

2.4.4. PPI use and mortality

In a large UK population-based study based on general practice records, mortality of long-term users of omeprazole (N=17489, mean age 60 years, median follow-up 26 months) was compared with that of the general population. Use of omeprazole was associated with increased mortality (Bateman et al. 2003). Mortality risk was considered to be due to pre-existing illness such as pre-existing severe oesophageal disease. In this study, a significant mortality increase was seen in the first year, but it fell to population levels by the fourth year. The main mortality causes were attributed to neoplasms and circulatory, digestive, and respiratory diseases (Bateman et al. 2003). According to a follow-up study of older people discharged from hospitals (N=441, mean age 80 years, follow-up one year) in Italy, the use of high dose PPIs was independently associated with one-year mortality even after adjustment for age, sex, cognitive impairment, depression, disability, nutrition, several comorbidities, number of drugs, and use of NSAIDs or antithrombotics (Maggio et al. 2013a). In this study, PPI users (N=174) were more often cognitively impaired, received a higher number of drugs and anti-thrombotic treatment and presented more comorbidity, cardiovascular diseases, peptic ulcer, and diarrhoea compared with non-users (N=317) (Maggio et al. 2013a). In an Australian study (N=602, mean age 86 years, one year follow-up), use of PPIs was not associated with mortality among residents in intermediate level residential aged-care facilities (Wilson et al. 2011). The participants were assessed in a fall prevention study. The mortality rate among PPI users was 11.0%, compared with 9.8% among patients without PPIs (HR 1.08; 95% CI 0.63-1.86).

Scant studies exist concerning the association of PPIs and mortality. None of the randomized studies of PPIs has explored mortality as an outcome. The prospective cohort studies (Wilson et al. 2011, Maggio et al. 2013a) may not take into account all confounding factors. Thus, mortality in these studies may be due to confounding by indication. The retrospective study concerning general practice records may include even more confounders since the background general population may be healthier than the one using general practice consultations.

2.5. Drugs with anticholinergic properties (DAPs)

Drugs with anticholinergic properties (DAPs) refer to medications having antagonistic effects on the cholinergic neurotransmitter system. DAPs are commonly used, for example, to treat peripheral symptoms such as overactive bladder, COPD, gastrointestinal symptoms, or muscle spasms, but

they also have a number of CNS effects (Uusvaara et al. 2011, Salahudeen et al. 2014, Salahudeen et al. 2016).

2.5.1. Physiology of DAPs blockade

Cholinergic neurotransmission occurs through the binding of the neurotransmitter acetylcholine to either muscarinic or nicotinic receptors (Uusvaara et al. 2011, Lampela 2013). Acetylcholine is a neurotransmitter with brain-mediating effects on cognitive functions as well as on the parasympathetic nervous system, which has physiological functions in many organs of the body, including the eye, heart, lungs, blood vessels, gastrointestinal tract, and urinary bladder (Samuels 2009). The term anticholinergic activity of a drug usually refers to the antagonistic effects on muscarinic receptors (Kay et al. 2005).

The DAPs blockade on the various muscarinic receptors in the peripheral parasympathetic nervous system is taken advantage of when bronchodilatation is needed in COPD, and to treat symptoms of irritable bowel or diarrhoea as well as urinary incontinence due to overactive bladder or inactive detrusor muscle (Uusvaara 2013, Salahudeen et al. 2014). The muscarinic receptor (M-receptor) subtype distribution in various organs and the potential side-effects of their blockade are presented in Table 6.

Table 6. Distribution of M-receptors in the central nervous system (CNS) and other organs and adverse reactions (ADRs) related to DAPs (adapted from Tunc 2001, Kay et al. 2005, DeMaagd and Geibig 2006, Samuels 2009, Lampela 2013, Uusvaara 2013).

M-receptor subtype	Distribution in (CNS)	Distribution in other locations than CNS	Potential ADRs of blockade of M-receptor
M1	high levels in central cortex, hippocampus and neostriatum (about 40-50% of total acetylcholine receptors)	gastrointestinal tract, skin, salivary glands, sympathetic ganglia	- CNS ADRs ¹ (cognitive decline, mood disorders, confusion, delirium, hallucinations, slowing of psychomotor speed, ADL impairment, sleep disturbance) - Peripheral ADRs (e.g. constipation, dry mouth)
M2	high levels throughout brain	cardiac tissue, smooth muscle	- CNS ADRs ¹ (cognitive deficits) - Peripheral ADRs (tachycardia, palpitation, angina pectoris)
M3	low levels throughout brain	smooth muscle, salivary glands, eyes, blood vessels, lungs	- CNS effects? - Peripheral ADRs (bronchus dilation, vasoconstriction, dry mouth)
M4	high levels in neostriatum, cortex, and hippocampus	salivary glands	- CNS effects? - Peripheral ADRs (dry mouth, dental caries)
M5	substantia nigra and hippocampus	eye (ciliary muscle, iris)	- CNS effects? - Peripheral ADRs (blurred vision, increased risk for glaucoma)

¹CNS ADR = adverse drug reaction in the central nervous system

However, precise distribution and functions of muscarinic receptors are not well-known (Lampela 2013). Previous studies have suggested that the effects of acetylcholine, a neurotransmitter in the brain involved in cognition, are mediated by all muscarinic (M1-M5) receptors, which are distributed in varying amounts in different parts of the brain, especially in the hippocampus and cortex. Cholinergic transmission is important in the CNS in processing of memory, language, and visuospatial and perceptual functions (Kay et al. 2005, Lampela 2013) as well as orientation, concentration, attention, and psychomotor speed (Lieberman 2004, Uusvaara et al. 2011, Lampela et al. 2013). DAPs act as blockers of these receptors and if they can enter the CNS, they can cause a decreased cholinergic activity in the brain, which may be associated with cognitive decline, memory impairment, sleeping problems, attention deficit, confusion, hallucinations, and delirium (Lieberman 2004, Uusvaara et al. 2011, Lampela et al. 2013, Leaderbrand et al. 2016). The activities of M3, M4, and M5 in the brain are not completely understood. The blocking of these receptors may lead to, for example, hallucinations, sedation, and delirium (DeMaagd and Geibig 2006). These adverse effects may go unrecognized in older people, among whom memory is not re-evaluated on a routine basis (Kay et al. 2005).

The muscarinic receptors M1-M3 are found in the gastrointestinal tract, and therefore anticholinergic drugs may cause constipation and even impaired nutrition (DeMaagd and Geibig 2006, Uusvaara et al. 2011). M2 and M3 receptors are located in the bladder, and thus, their blockade may cause decreased contraction and urinary retention (DeMaagd and Geibig 2006, Samuels 2009). M1, M3, and M4 participate in glandular secretion in bronchi, gastrointestinal tract, and skin, whereas M3 and M5 work in ciliary muscles and in the iris during accommodation (Uusvaara et al. 2011).

DAPs can be either lipid-soluble or lipid-insoluble compounds. Lipid-soluble anticholinergics (e.g. atropine, scopolamine) may have more CNS adverse effects than lipid-insoluble anticholinergics (e.g. glycopyrrolate) (Lampela et al. 2013). Anticholinergic adverse effects are divided into peripheral and central adverse effects. Central anticholinergic adverse effects occur when an anticholinergic drug penetrates through the blood-brain barrier into the CNS. Increasing age, comorbidities, and neurological conditions (Alzheimer's disease, Parkinson's disease, cerebral stroke, head injuries) common in older people predispose to an increase in blood-brain permeability (Kay et al. 2005, Weiss et al. 2009). Individuals with apolipoprotein E4 allele, which represents a

major risk factor for Alzheimer's disease with cognitive decline, may be more susceptible to cognitive effects of DAPs (Uusvaara et al. 2009).

It has been argued that the use of several DAPs and the strength of anticholinergic activity of a DAP, i.e. anticholinergic burden, has importance when assessing the ADEs of DAPs among older patients (Carnahan et al. 2006, Rudolph et al. 2008, Lampela et al. 2013). There are several ways to measure anticholinergic activity or burden in the elderly.

Serum anticholinergic activity (SAA) assay, as measured by radioreceptor assay, reflects the cumulative binding of all drugs and their metabolites to all muscarinic receptors (M1-M5) (Tune et al. 1992). SAA has been correlated to serum levels of DAPs, anticholinergic activity in cerebral spinal fluid, and impaired cognition (Chew et al. 2008). However, there are also contradictory findings (Lampela et al. 2013). In a Finnish study, SAA was not associated with the number of DAPs used or cognition, vision, or ADL (Lampela et al. 2013). The meta-analysis suggested that RCTs using SAA had no association between use of DAPs and cognition, whereas pooled analysis of observational studies showed that elevated SAA was associated with cognitive decline (Salahudeen et al. 2016). Problems with reliability of SAA measurement has limited its clinical use. Therefore, several definitions of DAPs and drug lists have been introduced to measure anticholinergic burden.

2.5.2. Criteria to define DAPs

The serum anticholinergic activity (SAA) assay, originally developed by Tune and Coyle, has been considered the 'gold standard' for quantification of anticholinergic effect of drugs *in vivo*. However, this test has not been readily available in clinical practice, and its performance and interpretation have not been standardized. Therefore, lists that rank drugs on the basis of their anticholinergic potency have been developed from SAA measurements, the published literature, and expert opinion. In addition, several different *in vivo* methods (e.g. saliva or sweat secretion, papillary reflex, or heart rate variability) have been applied to measure anticholinergic effects. However, none of these methods are specific to cholinergic neurotransmission, and it has been recommended that they should be used together with subjective assessments of anticholinergic effects. There is no widely accepted simple, reliable, and fast method to assess anticholinergic burden in clinical practice (Lampela et al. 2013).

Over 600 drugs have been recognized to have anticholinergic activity (Durán et al. 2013). There are a number of methods and criteria for defining DAPs (Beers et al. 1997, Tune 2001, Ancelin et al.

2006, Carnahan et al. 2006, Boustani et al. 2008, Chew et al. 2008, Han et al. 2008, Rudolph et al. 2008, Carrière et al. 2009, Uusvaara et al. 2009, Ehrt et al. 2010, Sittironnarit et al. 2011). The drug lists have many drugs in common, but there is also considerable variation in defining these drugs (Durán et al. 2013). The development of some of these lists has depended on the patient population assessed. Thus, those (potentially anticholinergic) drugs not used or not available in a particular patient population were omitted from the criteria (Uusvaara et al. 2011, Durán et al. 2013) (Table 7).

Many drugs on the Beers' list, which is based on expert opinion, were considered inappropriate because of their anticholinergic side effects (Beers 1997). Tune (2001) showed that anticholinergic burden is associated with delirium. Ancelin et al. (2006) showed that DAPs have measurable effects on various cognitive functions of older people.

Carnahan et al. (2006) developed the Anticholinergic Drug Scale (ADS), in which scores vary between 0 and - 3 based on the drug's anticholinergic activity. They showed that ADS is associated with SAA activity (Carnahan et al. 2006). Lampela et al. (2013) further showed that 117 drugs on Carnahan's list that had anticholinergic activity were only moderately associated with cognitive function measured by the Mini Mental State Examination (MMSE) test.

The Anticholinergic Cognitive Burden Scale (ACBS) developed by Boustani et al. (2008) is a tool based on a systematic literature review by an expert panel of clinicians focusing on central rather than peripheral anticholinergic effects for categorizing drugs according to the severity of their cognitive effects. He suggested his ACBS scale for clinical use to evaluate the anticholinergic burden on cognition among vulnerable older people (Boustani et al. 2008).

Chew et al. (2008) measured in vitro the anticholinergic activity of 107 medications commonly used by older persons, by using pharmacokinetic data to translate the relationship between the dose and anticholinergic activity. Chew's list showed only a moderate association with cognition among older people (Lampela et al. 2013). Ehrt et al. (2010) developed the Anticholinergic Activity Scale (AAS) based on Chew's list and a previous literature review based on SAA and expert opinion in an eight-year cohort study (Ehrt et al. 2010).

Carrière et al. (2009) further developed Ancelin's list of DAPs. Their findings suggested that the continuous use of DAPs was associated with risk of incident dementia. Han et al. (2008) developed his list of DAPs by clinician-rated scores quantifying potential anticholinergic effects. Uusvaara et al. (2009) combined several expert lists of DAPs.

The Anticholinergic Risk Scale (ARS) was developed by an expert panel (Rudolph et al. 2008). It has shown the association of adverse effects with DAPs in two cohort studies. Drugs were scored from 0 to 3 according to their potential anticholinergic effects.

Hilmer and colleagues (2007) developed the Drug Burden Index (DBI), a method of evaluation of effect of overall exposure to medications with anticholinergic and sedative properties. It has been shown to be associated with poorer function among community dwelling older people. The DBI also has an electronic calculator available on the internet (Kouladjian et al. 2016).

SFINX-PHARAO is a Finnish-Swedish database presenting both DDIs and adverse effects of 1400 drugs (SFINX 2015). The adverse effects are reported in PHARAO with respect to nine central drug effects, including anticholinergic effects. With the aid of PHARAO, it is possible to analyze the adverse effect profile of a particular drug, e.g. when adding a new drug to a previous medication, or to analyse the adverse effect risks of all drugs together (medication overall assessment).

A systematic review by Salahudeen et al. (2015a) evaluated the association between anticholinergic burden, based on previous anticholinergic scales and expert opinion, with adverse outcomes in older people. Sittironmarit and colleagues (2011) measured the Anticholinergic Loading Scale (ACL) based on previous anticholinergic scales and expert opinion and evaluated the association between ACL with psychomotor speed and executive function.

These criteria differ in many ways (Uusvaara et al. 2011, Durán et al. 2013). The development of some of these lists has depended on the patient population assessed. Table 7 gives examples of some commonly used lists of drugs with anticholinergic properties.

Table 7. Examples of lists of drugs with anticholinergic properties (adapted from Viipuri 2016)

Reference	Study design, number of participants, country	Participants (N)	Grading system and methodology	Outcomes of study	Number of DAPs
Camahan et al. 2006, Anticholinergic Drug Scale (ADS)	Cross-sectional study, USA	Residents of long-term care facilities (279), mean age 86 years	Scores: 4-point scale (0 to 3) Basis: Expert opinion	Serum anticholinergic activity	117
Ancelin et al. 2006, Anticholinergic Burden Classification (ABC)	Longitudinal cohort study (2-year follow-up), France	Subjects >60 years without dementia at recruitment (372)	Scores: 4- point scale (0 to 3) Basis: serum anticholinergic activity and expert opinion	Cognitive performance and mild cognitive impairment	27
Hilmer et al. 2007, Drug Burden Index (DBI); Electronic calculator	Prospective study (1, 3, and 5 years)	Community-dwelling older people, 70-79 years	Measure of overall exposure to medications with anticholinergic and sedative properties that implements the principle of dose response to determine the effect of medication exposure	Functional performance	NA
Han et al. 2008, Clinician-rated Anticholinergic Score (CrAS)	Prospective cohort study (2-year follow-up), USA	Hypertensive men >65 years (544)	Scores: 4-point scale (0 to 3) Basis: previous published anticholinergic scale and expert opinion	Memory performance and executive function	60
Rudolph et al 2008, Anticholinergic Risk Scale (ARS)	Two cohorts: one retrospective cohort (N=132) and one prospective cohort study (N=117), USA	Men >65 years (1st cohort), patients attending primary care clinics (2 nd cohort)	Scores: 4-point scale (0 to 3) Basis: detailed literature review and expert opinion	Frequency of anticholinergic adverse effects	49
Boustani et al. 2008, Anticholinergic Cognitive Burden Scale (ACB)	Systematic review of literature, 13 longitudinal cohort and case-control studies, USA	Patients >65 years (N=3013) attending urban primary health care clinics, mean age 73 years	Scores: 4-point scale (0 to 3) Basis: previous published anticholinergic scale and expert opinion	Cognitive performance and cognitive impairment, including dementia, delirium, and MCI	60
Chew et al. 2008	Cross-sectional study, USA	Medications commonly used by older adults (total number of medications=107)	Scores: 5-point scale (0 to 4) Basis: serum anticholinergic activity	Anticholinergic activity in vitro	22

Uusvaara et al. 2009, Drugs with Anticholinergic Properties (DAPs)	Cross-sectional study, Finland	Subjects without clinical dementia but with a history of stable atherosclerotic disease (70-95 years) (N=400)	Scores: 3-point scale (0 to 2) Basis: previous anticholinergic scales	Cognitive performance and impairment, association with Apolipoprotein E allele	30
Ehrt et al. 2010, Anticholinergic Activity Scale (AAS)	Cohort study (8-year follow-up), Norway	Subjects (mean age 69 years) with diagnosis of Parkinson's disease (N=78)	Scores: 5-point scale (0 to 4) Basis: Chew et al. 2008, literature review on serum anticholinergic activity and expert opinion.	Long-term cognitive decline	99
Sitironmarit et al. 2011, Anticholinergic Loading Scale (ACL)	Cross-sectional study, Australia	Subjects >60 years Alzheimer's disease (N=211); mild cognitive impairment (N=133); healthy controls (N=768)	Scores: 5-point scale (0 to 4) Basis: previous anticholinergic scales (Chew, ARS, CrAs, ABC), expert opinion	Psychomotor speed and executive function	49
Durán et al. 2013	Systematic review of the literature, Ecuador	Seven risk scales, 225 total evaluated drugs.	Scores: 3-point scale (0 to 2) Basis: previous anticholinergic scales (ADS, ABC, Chew, ARS, CrAs, ACB, AAS, ACL)	Development of a uniform list of anticholinergic drugs differentiating anticholinergic potency	100
Salahudeen et al. 2015b	Systematic review of the literature, New Zealand	Subjects with a mean age of 65 years or older and living in primary care or nursing homes or hospitals	Scores: 4-point scale (0 to 3) Basis: SAA, ADS, CrAs, ARS, ACB, AAS, ACL, and expert opinion	Comparison of anticholinergic burden quantified by the anticholinergic risk scales and evaluated associations with adverse outcomes in older people	195

SAA=Serum anticholinergic activity

2.5.3. Prevalence of use of DAPs

Older people in long-term institutional settings are often treated with DAPs (Chatterjee et al. 2010, Haasum et al. 2012, García-Gollarte et al. 2012, Pitkälä et al. 2014). The use of anticholinergic drugs differs according to applied criteria, setting, availability of drugs, and country. Previous studies have shown that 8-26% of community dwelling older persons use DAPs (Roe et al. 2002, Lechevallier-Michel et al. 2005, Ancelin et al. 2006, Hilmer et al. 2007, Carrière et al. 2009).

Table 8. Prevalence of DAP use in institutional settings.

Study	Country, study population, n	Age, years	Method to detect DAP use	Users of DAPs
Bergman et al. 2007	Sweden, residents of nursing homes; (n=7904)	65 or older	List based on quality indicators by Swedish National Board of Health and Welfare	19.7%
Kolanowski et al. 2009	USA; residents with dementia in nursing homes (n=87)	65 or older	ACB ¹	At least one DAP 82%, two or more DAPs 56%. At least one drug with severe properties (ACB ¹ score 3) 37%
Chatterjee et al. 2010	USA, residents with dementia in nursing homes (n=509 931)	65 or older	ADS ²	Any DAPs 73.8%. DAPs with “marked anticholinergic activity” 21.3%
Olsson et al. 2010	Sweden; residents of nursing homes and special care units for dementia (n=3705)	65 or older	List based on quality indicators by Swedish National Board of Health and Welfare	20%
Kumpula et al. 2011	Finland; patients in long-term care hospitals; (n=1004)	mean age 81	ARS ³	55%
Haasum et al. 2012	Sweden; Social Services Register study; institutionalized residents (n=86721)	65 or older	List based on quality indicators by Swedish National Board of Health and Welfare	12.1%
Wawruch et al. 2012	Slovakia; patients in long-term care hospitals; (n=1636)	65 or older	List based on literature and ARS ³	14.2%
Kersten et al. 2013b	Norway; residents in nursing homes (n=1101)	73 or older	ADS ² ≥3	21%
Pylkkänen 2013	Finland; residents in assisted living and nursing homes in Helsinki and Kouvola (N=326)	65 or older	Combined Beers, ARS ³	68%
Landi et al. 2014	Italy; nursing home residents (n=1490)	65 or older	ARS ³	48%
Pitkälä et al. 2014	Finland; residents in assisted living facilities (N=227)	65 or older	Combined Beers, ARS ³	71%
Palmer et al. 2015	USA; residents with dementia in nursing homes (n=69877)	65 or older	ACB ¹	77%

¹ACB = Anticholinergic Cognitive Burden Scale (Boustani et al. 2008); ²ADS = anticholinergic drug scale (Carnahan et al. 2006); ³ARS = anticholinergic risk scale (Rudolph et al. 2008)

Among institutionalized older people, the variations in prevalence are even higher. In this population, 12-82 % have been treated with anticholinergic drugs, with the highest amounts being reported among those with dementia (Table 8). The wide variations in prevalences depend on population characteristics and the tool used to detect DAPs. In Sweden, the prevalence of residents who were administered DAPs was lower than in other countries (12.1% to 20%), due to the use of a restricted criteria, including only a potent class of DAPs (antihistamines, urinary and gastrointestinal antispasmodics, cyclic antidepressants, low-potency antipsychotics, anticholinergic antiparkinson drugs, class Ia antiarrhythmics, anticholinergic antiemetics). Clinical conditions such as neuropsychiatric symptoms associated with dementia, incontinence and sleep problems – which are often managed with DAPs are common in frail nursing home residents (Kolanowski et al. 2009). DAPs with high anticholinergic activities often prescribed to institutionalized residents include psychotropics and incontinence drugs (Pitkälä et al. 2014).

2.5.4. Adverse effects related to DAP use

DAPs are often used to treat psychiatric or neurological disorders or symptoms such as incontinence, diarrhea, or pain. However, DAPs also have side effects that can accumulate if a person uses several DAPs simultaneously (anticholinergic burden) (Tune 2001). Even medicines with minor anticholinergic properties may contribute to unwanted central and peripheral adverse events if used in combination with other agents having anticholinergic properties. Determination of anticholinergic adverse effects is difficult (Lampela et al. 2015). Older people are thought to be particularly vulnerable to central ADEs of anticholinergic drugs, possibly because of a decrease in the number of muscarinic receptors and an increase in the permeability of the blood-brain barrier due to comorbidities (diabetes, Alzheimer's disease, Parkinson's disease, cerebral stroke, head injuries) (Weiss et al. 2009). Individuals with apolipoprotein E4 allele, which represents a major risk factor for Alzheimer's disease with cognitive decline, may be more susceptible to cognitive effects of DAPs (Uusvaara et al. 2009). Clinically significant adverse events related to DAPs range from dry mouth, blurred vision, and constipation to more severe events such as urinary retention, arrhythmias, cognitive decline, and even delirium (Tune 2001).

The adverse effects associated with DAPs may often be treated with another drug (“prescribing cascade”), instead of ceasing or reducing the drug in response to the symptoms (Wawruch et al. 2012).

Cognition

DAP use is associated with impairment of cognitive function in older people (Lechevallier-Michel et al. 2005, Ancelin et al. 2006, Cao et al. 2008, Han et al. 2008, Carriere et al. 2009, Gray et al. 2010, Uusvaara et al. 2013). In some studies, the association of DAPs and cognitive decline has been dose- or burden-dependent (Hilmer et al. 2007, Lampela et al. 2013, Fox et al. 2014), whereas other studies have not found this association (Kersten et al. 2013b). While earlier studies stated that DAPs may not lead to dementia, the latest report suggests that there may be irreversible cognitive effects of strong DAPs (Gray et al. 2010). A Norwegian trial also proposed that reducing DAPs in nursing home residents may not improve their cognition (Kersten et al. 2013a). Both centrally and peripherally acting anticholinergic drugs have been associated with a decrease in cognition in older patients (Fox et al. 2011, Ruxton et al. 2015). Patients with dementia and frail residents in nursing homes are especially vulnerable to further cognitive decline (Bell et al. 2012). Cognitive impairment due to drugs in these patients may be misattributed to the disease process itself (Bell et al. 2012).

Use of medicines with anticholinergic or sedative properties may result in adverse events by increasing the overall anticholinergic or sedative load. The likelihood that medicines may produce unwanted central anticholinergic effects depends in part on age-related and individual variability in pharmacokinetic parameters, blood-brain barrier permeability, degree of cholinergic neuronal degeneration, and a patient's baseline cognitive status (Wawruth et al. 2012).

Use of DAPs among nursing home residents may also be associated with delirium, which implies a poor prognosis (Luukkanen et al. 2011, Landi et al. 2014). However, a systematic review found no such association (Fox et al. 2014). Table 9 shows the findings of the studies in this systematic review.

Table 9. Association between DAP use and delirium (adapted from Fox et al. 2014).

Study, country	Design, setting	N	Mean age, females (F, %)	Participant characteristics	Findings
Caeiro et al.2004, Portugal	Case-control study, hospital	74	62years; F=45%	Patients admitted due to cerebral infarct or haemorrhage	DAPs were associated with delirium
Gaudreau et al. 2005, Canada	Cohort study, hospital	261	60 years; F=44%	Patients with previous cancer diagnosis, no association between DAPs and delirium	No association between DAPs and delirium
Pandharipande et al. 2006, USA	Cohort study, hospital	198	56 years; F=48%	Patients admitted to intensive care units, no association between DAPs and delirium	No association between DAPs and delirium
Campbell et al. 2011, USA	Cohort study, hospital	147	77 years; F=63%	Patients with previous cognitive impairment	No association between DAPs and delirium
Luukkanen et al. 2011, Finland	Cohort study, hospital and nursing home	425	86.1y; F=81.6%	Patients with dementia in geriatric wards, nursing homes	Almost significant association between DAPs and delirium

Falls, functional impairments, and quality of life

Anticholinergic drugs may increase the risk of falls (Tune 2001, Landi et al. 2007, Berdot et al. 2009), with the risk associated with specific DAPs such as olanzapine and trazodone (Ruxton et al. 2015). It has been argued that acetylcholine is critical in communication between neurons and muscles for modulating posture and movement (Ruxton et al. 2015). DAPs may also have central side effects, such as dizziness, weakness, and lightheadedness, which may predispose to falls (Landi et al. 2007). The adverse effects of anticholinergic drugs also include impairments in physical performance (Hilmer et al. 2007) and physical functioning (Landi et al. 2007, Lampela et al. 2013, Fox et al. 2014).

Hospital admissions and mortality risk

Although there are many studies investigating the relationship between inappropriate drugs and hospitalizations (Jano and Aparasu 2007), less is known about how DAPs predict hospitalizations. In a few studies conducted on this topic, use of anticholinergic drugs has been associated with increased risk of hospital admissions (Uusvaara et al. 2011, Lönnroos et al. 2012, Salahudeen et al. 2015a). The first two Finnish studies were conducted among home-dwelling older people, whereas the last one was a large-scale register-based study (N=537387) from New Zealand exploring how various anticholinergic scales predict hospitalizations. The hospitalizations may be due to cognitive

and physical impairments, delirium, falls, and other adverse effects (Uusvaara et al. 2011, Lönnroos et al. 2012, Salahudeen et al. 2015a). None of these studies have specifically explored the causes underlying hospitalizations. One study found no significant difference in nursing home admissions among users and non-users of DAPs (Narbey et al. 2013).

Studies investigating the association of DAPs with mortality have reported mixed results. Some have suggested an increased risk for mortality (Panula et al. 2009, Fox et al. 2011, Lowry et al. 2011, Mangoni et al. 2013), whereas others have not shown an association (Kumpula et al. 2011, Luukkanen et al. 2011, Uusvaara et al. 2011, Wilson et al. 2011, Narbey et al. 2013, Kidd et al. 2014). The discrepancy in the findings may arise from the anticholinergic drug scales used in the studies or differences in the characteristics of study populations or follow-up times (Fox et al. 2014, Ruxton et al. 2015). Table 10 gives a summary of the studies investigating the associations of DAP use and mortality.

Table 10. Association of use of DAPs (drugs with anticholinergic properties) with mortality risk.

Study	Design, setting	Country	No. of participants (DAP users, %)	Age	Main results	Method to detect DAP use
Panula et al. 2009	Retrospective data on hip fracture patients, 3-month and 3-year mortality	Finland	461 (21.7%)	Mean age 83 years	Taking potent anticholinergic agents increased the risk for mortality	Own classification
Fox et al. 2011	2-year longitudinal study, community-dwelling and institutionalized patients	UK	12423 (47%)	Over 65 years, mean age 75 years	Increased risk for mortality among DAP users	² ACB
Kumpula et al. 2011	Prospective cohort study, long-term care wards, 1-year follow-up	Finland	1004 (55%)	Mean age 81 years	No association between higher ARS-load and mortality	¹ ARS
Lowry et al. 2011	Prospective study, hospitalized patients	Netherlands	362	Mean age 84 years	Those with higher ARS and hyponatraemia at risk for in-hospital mortality	¹ ARS
Luukkainen et al. 2011	Prospective 2-year follow-up study, geriatric wards, nursing homes	Finland	425 (80%)	over 70 years, mean age 86 years	In adjusted analyses no association between DAP use and mortality	¹ ARS, ² ACB, Beers criteria
Uusvaara et al. 2011	Prospective 3.3-year follow-up study, community-dwelling cardiovascular patients	Finland	400 (74%)	Mean age 80 years	In adjusted analyses, no association between DAPs and mortality	¹ ARS
Wilson et al. 2012	Multicentre cluster-randomized controlled trial, patients in residential aged care facilities	Australia	602 (33.6%)	Mean age 86 years	No association between DAPs and mortality	⁴ DBI
Mangoni et al. 2013	Cross-sectional study, hospitalized patients, 3-month and 1-year follow-ups for mortality	Netherlands	71 (56.3%)	Mean age 84 years	ARS score associated with mortality at 3months; ARS and DBI scores associated with 1-year mortality	¹ ARS, ³ ADS, ² ACB, ⁴ DBI
Narbey et al. 2013	Prospective cohort study, hospitalized patients	France	1176 (12%)	Mean age 85 years	No association between DAP use and mortality	Online database “TheSorimed”
Kidd et al. 2014	Retrospective analysis of prospective observational outcome audit, hospitalized patients. Mortality during hospitalization	U.K.	419 (61.1%)	Mean age 93 years	No association between DAPs and mortality	² ACB

Notes: ¹ARS= Anticholinergic risk scale (Rudolph et al. 2008); ²ACB = Anticholinergic Cognitive Burden Scale (Boustani et al. 2008); ³ADS = anticholinergic drug scale (Carnahan et al. 2006); ⁴ DBI = Drug burden index (Kouladjian et al. 2016)

2.6. Drug-drug interactions (DDIs)

The effect of medication may be influenced by other medications that an individual is taking. One drug may have an effect on another in two ways: pharmacokinetically or pharmacodynamically. DDIs may lead to increased toxicity or decreased efficacy of the drug, which may result in a prescribing cascade, further increasing the risk of adverse drug reactions (ADRs) (Mallet et al. 2007). The risk for DDIs increases exponentially with the number of ingested drugs (Johnell and Klarin 2007).

Older people are at high risk for DDIs due to physiological changes with ageing, polypharmacy, comorbidities, and decreased nutritional status (Mallet et al 2007). In older patients, DDIs are a common reason for preventable ADR, hospitalizations related to drug toxicity, higher health care costs, and increased risk of mortality (Juurlink et al. 2003, Moura et al. 2009).

On the other hand, some DDIs may be beneficial. DDIs can be used in clinical practice in the treatment of hypertension, for example, concomitant use of diuretics with ACE-inhibitors has a synergistic effect in lowering blood pressure (Carnasos and Stewart 1985).

The drugs most commonly involved in serious potential interactions are those used in daily clinical management of elderly patients with chronic diseases (e.g. cardiovascular and neurological disorders, chronic pain, dementia and related neuropsychiatric symptoms). Clinically relevant DDIs are more likely with drugs having a narrow therapeutic index (e.g. digoxin, phenytoin, carbamazepine, methotrexate, theophylline, and warfarin) since even small changes in the concentration of these drugs may result in significant clinical symptoms including intoxication (Delafuente 2003, Malone et al. 2005, Gagne et al. 2008) (Table 11).

In Finland, the most common potential DDIs in older patients were associated with the use of potassium-sparing diuretics, carbamazepine, and codeine (Hosia-Randell et al. 2008). In a study conducted by Aparasu et al. (2007) in the USA, the four most common DDIs accounted for 97% of all DDIs: anticoagulants/thyroxine (44%), warfarin/NSAID (40%), warfarin/fibrates (8%), and warfarin/trimethoprim (5%). In an Italian study, the four most common DDIs were the following: warfarin/NSAIDs, theophylline/ciprofloxacin or fluvoxamine, warfarin/barbiturates, and warfarin/fibrates (Gagne et al. 2008).

Table 11. Examples of clinically important DDIs in the elderly (adapted from Seymour and Routledge 1998, SFINX 2015)

Drug A	Drug B	Effect of interaction	Mechanism of interaction
ACE inhibitors	NSAIDs ¹	Hyperkalaemia, reduced renal function	Nephrotoxic effects Synergistic effect
Antihypertensives	Vasodilators, antipsychotics	Postural hypotension	Combined hypotensive effects
Beta-blockers	verapamil, diltiazem	Atrioventricular block, bradycardia and severe hypotension	Drug A can interact pharmacodynamically with drug B, exerting an additive cardiodepressive effect
Low-dose Aspirin	NSAIDs ¹	Peptic ulceration	Increases risk of gastrointestinal bleeding
Carbamazepine	Enzyme inhibitors ² , verapamil	Increased effect of drug A	Reduced clearance of A or increased clearance of B
Codeine	fluoxetine, paroxetine, duloxetine, haloperidol, bupropion, thioridazine, melperone, quinidine	Decreased effect of drug A	Codeine is a prodrug and the formation of morphine by CYP2D6 enzyme is essential for analgesia. Drug B are inhibitors of this CYP isoenzyme
Corticosteroids (oral)	NSAIDs ¹	Peptic ulceration	Gastrointestinal irritation and inhibition of ulcer healing
Donepezil	SSRIs	Increased risk for arrhythmia	Additive effects prolonging QT-time, increasing risk of Torsades de Points
Digoxin	Amiodarone, diltiazem, verapamil, clarithromycin Diuretics (loop and thiazides)	Increased effect of drug A Increased effect of drug A	Reduced clearance of A Diuretic-induced hypokalaemia
Diuretics (potassium-sparing)	ACE-inhibitors, potassium supplements)	Hyperkalemia, impaired renal function	Synergistic potassium-elevating effects
Fluoxetine	Tramadol, moclobemide, trazodone, selegiline, venlafaxine, duloxetine, citalopram, paroxetine, sertraline	Risk for serotonin effects/syndrome is increased	Unknown, possible additive inhibitory effect on serotonin re-uptake. Changes of pharmacokinetics of drug B in some cases
Lithium	NSAIDs, thiazide diuretics	Increased effect of drug A	Reduced clearance of A
SSRIs	NSAIDs	Increased risk of bleeding	Both NSAIDs and SSRIs impair platelet aggregation. SSRIs reduce the amount of serotonin in platelets and NSAIDs inhibit the synthesis of thromboxane A2. NSAIDs also impair the protective effect of prostaglandins in gastric mucosa by inhibiting COX-1 enzyme.
Theophylline	Enzyme inhibitors ³	Increased effect of drug A	Reduced clearance of A
Warfarin	NSAIDs, low-dose Aspirin Metronidazole, fibrates Antifungals, ciprofloxacin, erythromycin Cholestyramine, carbamazepine	Increased anticoagulant effect Increased anticoagulant effect Reduced anticoagulant effect	Additive effects on coagulation and haemostasis Inhibition of warfarin metabolism Impaired absorption and increased elimination of warfarin
Omeprazole	Ketoconazole Cyclosporine Diazepam Iron salts	Decreased effect of drug B Increased effect of drug B Increased effect of drug B Impaired effect of drug B	Impaired absorption of drug B Possible CYP450 inhibition Impaired elimination of drug B Impaired absorption of drug B

¹NSAIDs = non-steroidal anti-inflammatory drugs; SSRI=Selective serotonin reuptake inhibitor; ²e.g. quetiapine, risperidone, amlodipine, many antifungal medications, oxycodone, buprenorphine, tamsulosin, tamoxifen (among many others); ³e.g. ciprofloxacin, cimetidine

Identifying DDIs in older people and their management may be challenging. Physicians are often unaware of all of the drugs that their patients are taking (Langdorf et al. 2000, Mallet et al. 2007). Atypical presentation of symptoms, such as confusion, falls, and weakness, may confuse the detection of DDIs. Older patients might receive prescriptions from several physicians. This may increase the risk of polypharmacy and DDIs (Seymour and Routledge 1998).

It is likely that only a small proportion of potential interactions result in clinically significant events (Mallet et al. 2007), and, while death or serious clinical consequences are rare, mild, clinically insignificant ADRs among the elderly may be more common (Seymour and Routledge 1998). Only a few studies have examined clinical outcomes of DDIs in older populations (Juurlink et al. 2003).

2.6.1. Pharmacokinetic interactions

DDIs may be pharmacokinetic or pharmacodynamic (Mallet et al. 2007). In recent years, advanced databases have enabled clinical evaluation of pharmacokinetic interactions. Pharmacokinetic interactions result in changes in the drug concentrations involved, increasing or decreasing the pharmacological effect of these drugs (Delafuente 2003).

With pharmacokinetic DDIs, one drug affects the absorption, distribution, metabolism, or excretion of another drug (Mallet et al. 2007). Decreased liver and renal functions related to ageing may exaggerate the DDIs affecting drug metabolism and elimination, resulting in an increased risk of drug toxicity (Delafuente 2003).

The precipitant drug may alter the absorption of the object drug in different ways. Changes in gastric acidity and gastrointestinal motility may affect the absorption of certain drugs (e.g. PPIs vs. calcium, iron, vitamin B12). Absorbant drugs (e.g. cholestyramine) may inhibit absorption of certain drugs (e.g. digoxin, warfarin, levothyroxine). Drugs with anticholinergic properties and opioids will slow gastrointestinal motility, while such drugs, as metoclopramide will increase motility. Because of slowing of the gastrointestinal tract, the absorption of a drug may be delayed. However, the full extent of drug absorption is achieved and the area under the blood concentration–time curve (AUC) is unchanged. This may be important to consider when using an analgesic. Another consequence of one drug slowing the gastrointestinal transit time could be a decrease in the amount absorbed of another drug. This could potentially cause peak serum concentrations of the drug to be below the needed threshold for effect (Delafuente 2003).

A common DDI affecting drug distribution is alteration in protein binding by competitive inhibition of protein binding sites. It is clinically important only for drugs that are highly protein bound and with a narrow therapeutic index, for which even small increases in drug serum concentrations may be associated with severe drug toxicity (e.g. warfarin and aspirin interaction) (Delafuente 2003). For drugs that do not have significant toxicity associated with small increases in drug serum concentrations, DDIs involving protein binding inhibition mechanisms are less important. Although competitive inhibition will increase the free fraction of the drug, the serum concentration may not become toxic. More importantly, however, as the free fraction increases there is more unbound drug available for renal elimination or liver metabolism, keeping serum drug concentrations below a toxic level (Delafuente 2003).

The most clinically important types of pharmacokinetic DDIs are those altering a drug's metabolism. Drugs that are substrates, inhibitors, or inducers of CYP isoenzymes may inhibit or induce the pharmacokinetics of other drugs, particularly those that are extensively metabolized by the hepatic cytochrome P450 system (Delafuente 2003). With ageing, more common and potentially more significant are DDIs that affect renal function due to a decrease in glomerular filtration rates (Delafuente 2003).

2.6.2. Pharmacodynamic interactions

When pharmacodynamic DDIs occur, two drugs have additive (synergistic) or antagonistic pharmacological effects, which may result in increased toxicity or decreased efficacy of the involved drugs (Delafuente 2003). When two or more drugs with similar pharmacodynamic effects are taken, the additive effects may result in excessive response and toxicity (e.g. combination of NSAIDs and corticosteroids) (Seymour and Routledge 1998). Drugs with opposing pharmacodynamic effects may reduce the response to one or both drugs (e.g. combination of ChEIs and anticholinergic drugs) (Delafuente 2003).

Pharmacodynamic interactions are common in older people, who are often sensitive to these due to reduced homeostatic mechanisms (Seymour and Routledge 1998, Delafuente 2003). The additive effects of DDIs may be particularly important when they compromise the already impaired physiological functions among older patients. Combinations of drugs causing additive sedative effects, anticholinergic effects, and hypotension and use of drugs with a narrow therapeutic index should receive special attention when prescribing drugs for older people (Seymour and Routledge 1998).

Software database systems have been developed and implemented in clinical practice for detection and prevention of adverse drug events related to DDIs. A study comparing a summary of DDI information with several interaction databases revealed that information is neither complete nor consistent among various software database systems (Böttiger et al. 2009). Many programmes have not been updated with the evolving knowledge of these interactions and do not take into consideration important factors needed to optimize drug treatment in older patients (Mallet et al. 2007). Methods such as computerized physician order entry (CPOE), computerized drug interaction software, and computerized decision support systems (CDSS) that detect and alert the physician and pharmacist to potentially serious outcomes can decrease the risk of drug errors. Systems that proactively screen for interactions at the time of electronic prescribing should be developed to prevent adverse drug events related to DDIs (Mallet et al. 2007).

Databases for DDIs do not usually include information concerning pharmacodynamic interactions in older patients. For example, antipsychotics that block alpha1-adrenergic receptors augment the effects of antihypertensives, causing orthostatic hypotension and increasing the risk of falls (Delafuente 2003). The load of several sedatives or DAPs may be considered as examples of pharmacodynamic interactions that have additive adverse effects among older people.

2.6.3. Prevalence of DDIs according to study populations

Prevalence rates of DDIs have varied greatly between populations, settings, countries, and methods used in studies. The prevalence especially depends on the DDIs included by the researchers. Some have included only potentially serious drug interactions (DDIs) (Hosia-Randell et al. 2008), whereas others have included also potentially mild or moderate DDIs (Johnell and Klarin 2007, Becker et al. 2008, Teixeira et al. 2012). Potential DDIs should be distinguished from proven DDIs (Mallet et al. 2007).

Prevalence of DDIs has varied according to the study populations: 5-12% in nursing home settings (Bergman et al. 2007, Hosia-Randell et al. 2008), 3-16% in register-based studies (Johnell and Klarin 2007, Becker et al. 2008, Nobili et al. 2009), and 3-12% in community settings (Björkman et al. 2002, Jokinen et al. 2009, Teixeira et al. 2012) (Table 12).

Table 12. Prevalence of DDIs in older patients in different settings.

Study	Country, study population, n	Age, years	Method to detect DDIs	Results
Population based studies				
Bjerrum et al. 2003	Denmark, drug register study (60-79y: n=49278) (>79y: n=18509)	≥60	Hansten et al ¹ (USA 2002) Any type of DDIs (major, moderate, minor)	25% DDIs (60-79 years) 36% DDIs (≥80 years)
Johnell and Klarin 2007	Sweden, register study (n=630743)	≥75	FASS ² Type C: clinically relevant DDIs and type D: potentially serious DDDIs	26% DDIs 5% DDDIs
Becker et al. 2008	Netherlands, population study (n=3728)	≥70	Royal Dutch Association for the Advancement of Pharmacy ³ Any DDI or potentially life-threatening DDDI	11% DDIs, 2% DDDIs (1992) 19% DDIs, 3% DDDIs (2005)
Nobili et al. 2009	Italy, register study (n=58800)	≥65	Italian drug interaction database ⁴	16% DDDIs
Secoli et al. 2010	Brazil, community-dwelling residents (n=2143)	≥60	Micromedex ⁵ Any DDIs	27% DDIs
Home-dwelling older people				
Björkman et al. 2002	Six European countries, home-dwelling residents (n=1601)	≥65	FASS ²	46% DDIs 10% DDDIs
Jokinen et al. 2009	Finland, home care residents (n=389)	≥75	SFINX ⁶ C-class clinically relevant DDI; D-class DDDIs	72% DDIs 3% DDDIs
Teixeira et al. 2012	Brazil, primary-care patients (n=827)	Mean age 64	Micromedex ⁵ Any DDI (contraindicated, severe, moderate, minor) Severe DDDIs	63% DDIs 12% DDDIs
Nursing home residents				
Bergman et al. 2007	Sweden, residents of nursing homes (n=7904)	≥65	FASS ¹	45% DDIs 12% DDDIs
Hosia-Randell et al. 2008	Finland, residents of nursing homes (n=1987)	≥65	SFINX ⁶	5% DDDIs
Liao et al. 2008	Taiwan, residents of nursing homes (n=323)	Mean age 75	DDIs Database Information System ⁷	25% DDIs

Notes: ¹ Hansten, Horn: Drugs interactions & Updates, USA 2002; ² FASS: Drug Interactions developed by Sjöqvist. Potential DDIs are categorized A to D (A and B minor, C and D clinically significant); ³ The Royal Dutch Association for the Advancement of Pharmacy categorizes both evidence and the potential clinical relevance of DDIs; ⁴ Italian interaction database classifies clinical relevance (severe, moderate, minor) of DDIs; ⁵ Computerized medication interaction information system (USA); SFINX = Swedish, Finnish, Interaction X-referencing database; ⁷ Database Information System constructed by the Department of Health, Executive Yuan, Taiwan.

2.6.4. Factors associated with risks of DDIs

The number of drugs used (Juurlink et al. 2003, Lindblad et al. 2005, Zhan et al. 2005, Cruciol-Souza and Thomson 2006, Johnell and Klarin 2007, Gagne et al. 2008, Nobili et al. 2009, Secoli et

al. 2010, Lin et al. 2011, Teixeira et al. 2012), cardiovascular diseases (Secoli et al. 2010), comorbidities (Lindblad et al. 2005, Gagne et al. 2008), and number of prescribers have been associated with increased risk of DDIs (Cruciol-Souza and Thomson 2006). There are contradictory findings concerning the association of gender (Juurlink et al. 2003, Zhan et al. 2005, Cruciol-Souza and Thomson 2006, Johnell and Klarin 2007, Gagne et al. 2008) and age with DDIs (Lindblad et al. 2005, Malone et al. 2005, Cruciol-Souza and Thomson 2006, Johnell and Klarin 2007, Gagne et al. 2008, Hosia-Randell et al. 2008, Nobili et al. 2009, Lin et al. 2011).

Generally, the DDIs leading to hospital admissions occur after administration of drugs with well-known side effects, e.g. digoxin, warfarin, ACE-inhibitors, and antidiabetic drugs (Juurlink et al. 2003). The most dependent, institutionalized patients are prone to DDIs due to polypharmacy, comorbidities, and physiological changes associated with ageing such as altered pharmacokinetics and pharmacodynamics (Liao et al. 2008).

2.6.5. Concomitant use of DAPs and cholinesterase inhibitors (ChEIs)

ChEIs and DAPs are in pharmacological opposition and their concomitant use leads to decreased therapeutic effect of both drugs (Sink et al. 2008, Boudreau et al. 2011). DAPs often block muscarinic receptors in the brain, resulting in lower acetylcholine levels, whereas ChEIs act to increase acetylcholine levels in brain synapses by inhibiting the enzyme acetylcholinesterase, which breaks down acetylcholine in the synaptic clefts (Defilippi and Crismon 2003). Thus, concomitant use of DAPs may reduce the therapeutic effect of ChEIs (Modi et al. 2009, Palmer et al. 2015).

Dementia patients treated with ChEIs have an increased risk of subsequently being treated with DAPs (Roe et al. 2002, Carnahan et al. 2004, Gill 2005, Johnell and Fastbom 2008, Modi et al. 2009, Palmer et al. 2015), especially to manage e.g. urinary incontinence (Sink et al. 2008). Urinary antispasmodics, antidepressants, antihistamines, and antipsychotics are among the DAPs administered most often concomitantly with ChEIs (Roe et al. 2002, Gill et al. 2005, Johnell and Fastbom 2008). Concomitant use of DAPs and ChEIs is often seen in older people in institutional settings, where dementia and multiple medical conditions are common (Sink et al. 2008, Modi et al. 2009). Concomitant use of DAPs and ChEIs has not been associated with a higher risk of nursing home placement or death (Boudreau et al. 2011).

Administration of multiple DAP is common among patients concomitantly receiving ChEIs and DAPs (Roe et al. 2002). The prevalence of concomitant use of DAPs and ChEIs has varied from

11% to - 47% in nursing home settings and depends on the DAP criteria used and prevalence of ChEIs (Table 13).

Table 13. Epidemiology of concomitant use of DAPs and ChEIs in nursing home populations

Study	Type of study, study population	Users of ChEIs (n, %), age	Concomitant use of DAPs and ChEIs (n, %)	DAPs examined	Factors associated with concomitant ChEI and DAP use
Sink et al. 2008 USA	Prospective cohort study	3536 (100%), ≥65 years	376 (11%);	oxybutynin or tolterodine;	Excess decline in ADL function in residents with higher levels of functioning
Modi et al. 2009 USA	Cross-sectional survey (N=3251)	3251 (100%), ≥65 years	1519 (47% of ChEI users)	Carnahan criteria ¹	Higher comorbidity (Charlson Comorbidity Index > 2)
Olsson et al. 2010 Sweden	Cross-sectional register study (N=3705)	219 (6%), Mean age 85 years	32 (15% of ChEI users)	antihistamines, antispasmodics, incontinence drugs, cyclic antidepressants, low-potency antipsychotics, anticholinergic antiparkinson drugs, class Ia antiarrhythmics, anticholinergic antiemetics	Not applicable
Palmer et al. 2015 USA	Retrospective analysis, people with dementia (N=69877)	Not stated, Mean age 84 years	25% of residents used concomitantly DAPs and ChEIs	ACBS	Aggressive behaviour, male gender, lower age, and lower cognitive impairment

¹Carnahan et al. 2006; ²Anticholinergic Cognitive Burden Scale (Boustani et al. 2008)

2.7. Summary of the literature

Older people in institutional settings are at special risk for ADRs due to changes in pharmacokinetics and pharmacodynamics, comorbidities, polypharmacy, and frequent use of PIDs (Jyrkkä et al. 2006, Hosia-Randell et al. 2008). Long-term use of PPIs is very common among the elderly in institutional settings (de Souto Barreto et al. 2013, Vetrano et al. 2013).

Although PPIs have been shown to be generally safe, their long-term use may be associated with adverse events such as gastrointestinal infections (Dial et al. 2005), -pneumonia (Laheij et al. 2004), malabsorption of calcium and vitamin B12 (Arkkila 2015), and increased risk of fractures (Yang et al. 2006). Use of PPIs may be associated with adverse side effects such as diarrhoea, which reduces the quality of life among frail older people in residential care. Diarrhoea associated

with PPIs may be due to *Clostridium difficile* infections or bacterial overgrowth both associated with complications (Yearsley et al. 2006, Arkkila 2015). Previous studies have shown contradictory results regarding the association between long-term use of PPIs and mortality, with pre-existing illnesses, disabilities, and comorbidities considered as possible predisposing factors (Bateman et al. 2003, Maggio et al. 2013a). There are only three studies exploring the association between the use of PPIs and mortality (Bateman et al. 2003, Wilson et al. 2011, Maggio et al. 2013a).

Use of DAPs is common among older people in institutional settings (Bergman et al. 2007, Kumpula et al. 2011), especially to treat clinical conditions related to dementia (Kolanowski et al. 2009). Use of DAPs is associated with side-effects possibly affecting cognition, functional activities, and quality of life (Ancelin et al. 2006, Landi et al. 2007, Kolanowski et al. 2009). However, there are no previous studies exploring the association of use of DAPs with psychological well-being.

A few studies have shown that the concomitant use of ChEIs and DAPs is common among older residents in institutional settings (Sink et al. 2008, Modi et al. 2009). The therapeutic efficacy of ChEIs may be diminished with concomitant use of DAPs (Modi et al. 2009, Palmer et al. 2015). The concomitant use of these drugs may be associated with reduced functional abilities, decline in cognitive function, behavioural symptoms, and comorbidities (Sink et al. 2008, Modi et al. 2009, Palmer et al. 2015).

Older people are susceptible to adverse events related to DDIs (Mallet et al. 2007). Factors associated with increased risk for DDDIs include polypharmacy and comorbidities (Mallet et al. 2007). The recognition and management of DDDIs may be challenging among older people due to pre-existing vague symptoms that can mask the DDDIs (Seymour and Routledge 1998). The prevalence of DDIs is not well documented (Mallet et al. 2007). Examples of drugs leading to DDIs are digoxin, warfarin, carbamazepine, and potassium-sparing diuretics (Juurlink et al. 2003, Hosia-Randell et al. 2008). Institutionalized older people are commonly prescribed a high number of drugs due to chronic diseases, and they present altered physiology due to ageing, and thus, are highly vulnerable to DDIs (Delafuente 2003).

3. Aims of the study

The general aim of this study was to investigate the prevalence and potential risks associated with PPIs, DAPs, and DDDIs among older people in institutional settings. Specific aims were as follows:

1. to assess the prevalence of PPIs and to identify their associated factors and risks among nursing home residents (Studies 1 and 2)
2. to explore the risk of death associated with use of PPIs in three institutionalized populations. (Study 2)
3. to assess the prevalence of the use of DAPs and their association with psychological well-being (Study 3)
4. to determine the concomitant use of DAPs and ChEIs in assisted living facilities (Study 3)
5. to assess potentially severe DDDIs and risks for mortality among residents in assisted living facilities (Study 4)

4. Materials and methods

4.1. Study samples

The data for this study were gathered among institutionalized older people who are known to be prone to polypharmacy and adverse drug events. Participants were all living in places where their daily needs for help could be fulfilled – in assisted living facilities, nursing homes, acute geriatric wards, and long-term hospital wards. The study samples are shown in Figures 1, 2, and 3.

Study 1 comprised cross-sectional data collected during February 2003 from all nursing homes in Helsinki, Finland as part of a nutritional care study project (Muurinen et al. 2003). There were in total 2424 residents (1088 residents from 4 public nursing homes and 1336 residents from 16 private nursing homes). Inclusion criteria for the study were long-term residency, accessibility of information concerning demographic factors, medication data available, willingness to participate, and age ≥ 65 years. Of all residents, 1987 (response rate 82.0%) were eligible for the study.

The samples for Study 2 were obtained from three previous studies. The first cohort was a cross-sectional sample collected in March 2007 as part of a larger project investigating nutritional care in assisted living facilities in the cities of Helsinki (n=36) and Espoo (n=33), Finland (Jekkonen et al. 2007). There were in all 2188 residents, and 1389 (response rate 63.5%) participated. The inclusion criteria for the study were long-term residency, accessibility of information concerning demographic factors, medication data available, willingness to participate, and age ≥ 65 years (Study 2, first cohort). The second cohort of Study 2 included 1444 residents from long-term care hospital wards in Helsinki (n=53), Finland, in September 2003, as part of a project investigating their nutritional care (Soini et al. 2004). The inclusion criteria for the study were accessibility of information concerning demographic factors, medication, mortality, and readiness to participate. Of these residents, 1004 were eligible for the study after exclusion of 357 refusals, 35 residents with incomplete medication data, and 48 residents without follow-up mortality data (response rate 69.5%). The third cohort of Study 2 included 425 consecutive patients in acute geriatric wards (n=230, Kivelä and Laakso Hospitals in Helsinki) and residents in nursing homes (n=195) in Helsinki, Finland, during 1999-2000, primarily assessed for delirium (Pitkälä et al. 2005). The exclusion criteria for the study were age ≤ 70 years and coma.

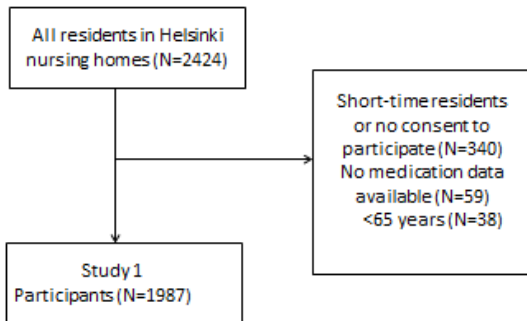


Figure 1. Flow chart of Study 1.

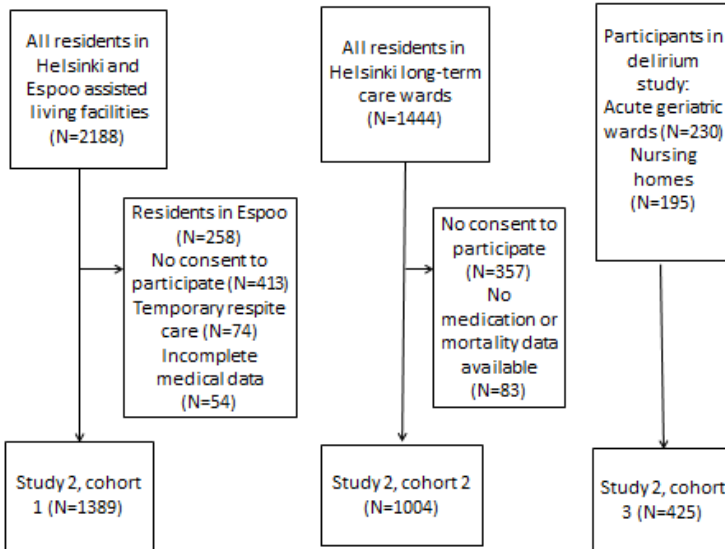


Figure 2. Flow chart of Study 2.

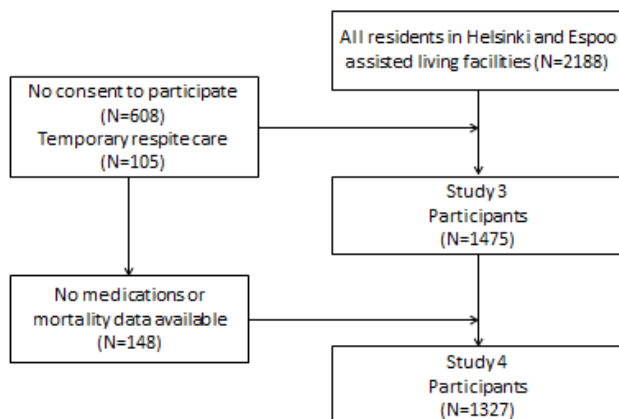


Figure 3. Flow chart of Studies 3 and 4.

In Studies 3 and 4, the data were gathered for all residents in Helsinki and Espoo assisted living facilities in 2007. Of the 2188 residents in these facilities, 713 were excluded (608 due to refusal, 105 due to temporary respite care), leaving 1475 residents (Study 3). In Study 4, 148 participants were further excluded due to insufficient availability of medication or mortality data, leaving 1327 residents eligible for the study.

4.2. Methods

4.2.1. Background data

All data were gathered by trained nursing home staff by using structured questionnaires (Appendix 1), except in Study 2 (third cohort), in which the information in acute geriatric wards was gathered by two geriatricians.

All demographic data (including age, gender, marital status, education, and place of residence) were retrieved from medical records. In addition, education and current medical diagnoses were gathered from residents' medical charts. CCI was computed as described elsewhere. Briefly, the CCI was constructed to predict a one-year mortality for a patient who may have a range of comorbid conditions, such as heart disease, dementia, or cancer (a total of 22 conditions). Each condition is

assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one. For example, stroke and cancer give 2 points, whereas dementia and myocardial infarction give one point. The scores are summed to provide a total score. CCI was used to evaluate burden of comorbidities (Charlson et al. 1987).

Mini-Nutritional Assessment (MNA) was used to evaluate residents' nutritional status (Guigoz et al. 2002) in Studies 1, 2 and 4. The MNA scores (range 0 to 30) distinguish older people as malnourished (less than 17 points), at risk for malnutrition (17-23.5 points) or as well-nourished (>23.5 points). Some MNA items were used to evaluate, for example, residents' mobility status (bed- or chair-bound / able to get out of bed but does not go out / goes out) or fluid intake (less than 3 cups per day/ 3 to 5 cups per day/ more than 5 cups per day). Their weight and height were measured, and body mass index was calculated accordingly (weight in kg/height in m²; kg/m²). If the resident was unable to stand, the height was evaluated from knee height (Soini et al. 2004) (Appendix 1).

Memory problems and dependence in activities of daily living (ADL) were assessed by items from the Clinical Dementia Rating Scale (CDR) (Hughes et al. 1982) in Studies III and IV. CDR "memory class" 1 or higher was used as a cut-off point for significant memory problems (0=No memory loss or slight inconsistent forgetfulness/ 0.5= Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness/ 1=Moderate memory loss; more marked for recent events; defect interferes with everyday activities/ 2= Severe memory loss; only highly learned material retained; new material rapidly lost/ 3= Severe memory loss; only fragments remain). CDR "personal care" higher than 1 was used as a cut-off point to define significant need for help in ADL (0-0.5= Fully capable of self-care/ 1= Needs prompting/ 2= Requires assistance in dressing, hygiene, keeping of personal effects/ 3= Requires much help with personal care; frequent incontinence) (Appendix 2).

Some gastrointestinal symptoms were retrieved from the study questionnaire in Study 2. The questionnaire item was "Does the resident have the following symptoms: constipation (yes/no), diarrhoea (yes/no), vomiting (yes/no). Furthermore, celiac disease (yes/no) and lactose intolerance (yes/no) were inquired about in the questionnaire (Study 2). The presence of delirium was determined according to the operationalized DSM-IV criteria (Study 2, third cohort) (Appendix 3).

The Psychological Well-Being Scale was used to assess the well-being of residents (Studies 3 and 4) (Routasalo et al.2009). This scale shows good test-retest reliability (Routasalo et al.2009), statistically significant prognostic validity (Pitkälä et al. 2004), and good validity for areas relevant

in psychological well-being (WHO 2003). This scale comprises dimensions important in older people's psychological, emotional, and social well-being (WHO 2004).

The Psychological Well-Being Scale is constructed according to responses to six questions. These six questions show good test-retest reliability and prognostic validity concerning mortality. These questions inquire about life satisfaction (yes/no), feeling needed (yes/no), having plans for the future (yes/no), having zest for life (yes/no), feeling depressed (seldom or never/sometimes/ often or always), and suffering from loneliness (seldom or never/sometimes/often or always). Responses "no" in questions 1-4 and "often or always" in question 5 or 6 yield 0 point. Responses "sometimes" in question 5 or 6 yield 0.5 point. Responses "yes" in questions 1-4 and "seldom or never" in question 5 or 6 yield 1 point. The Psychological Well-Being Score is then calculated by dividing the sum total of points by the number of questions that the participant has answered. A score of 1 represents the best and 0 the poorest well-being (Routasalo 2009). Participants were invited to evaluate their self-rated health (Study 3), which was categorized as good (healthy/quite healthy) or poor (quite unhealthy/unhealthy).

4.2.2. Medication use

In all samples, drug use was retrieved from medical records and assessed as the point prevalence on the day of assessment. Only drugs and vitamins administered on a regular basis were taken into account. Participants were classified as regular users if their medical charts indicated a regular sequence of dosage. All drugs were categorized according to the Anatomical Therapeutic Chemical classification system (World Health Organization 2010). The total number of regularly used drugs was calculated for each resident.

Proton-pump inhibitors

This study investigated the use of the following proton-pump inhibitors (PPIs; ATC codes A02BC): omeprazole, pantoprazole, esomeprazole, lansoprazole (Studies 1 and 2) and rabeprazole (Study 2).

To assess the potential indications of PPIs, such as gastro-intestinal (GI) protection for non-steroidal anti-inflammatory drugs (NSAIDs), drugs causing potential GI-bleeding were also categorized. The NSAIDs included all drugs with the ATC code B01AC06 (acetylsalicylic acid, including low-dose acetylsalicylic acid ≤ 250 mg), and drugs with the ATC code M01A (anti-inflammatory and antirheumatic drugs), excluding coxibs M01AH (diclofenac, etodolac, ibuprofen, indomethacin, ketoprofen, mefenamic acid, nabumetone, naproxen, piroxicam, tolfenamic acid).

Only oral formulations of NSAIDs were included in the analyses. Furthermore, use of selective serotonin reuptake inhibitors (ATC code N06AB: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) was assessed for the same reason.

Furthermore, in Study 1, drugs associated with possible GI side effects, thus confounding the adverse effects of PPIs, were also assessed. These drugs included laxatives (bulk laxative ATC code A06AC, osmotic agents A06AD, stimulant laxatives A06AB, neuromuscular agents such as cisapride, metoclopramide, carbamylcholine, pyridostigmine, distigmine), cholinesterase inhibitors (ChEIs; ATC code N06DA), and constipation-inducing-drugs such as iron supplements (ATC code B03A), antibiotics (ATC code J01), and metformin (ATC code A10BA02).

Calcium (ATC code A12A) and vitamin D (ATC code A11CC) were also categorized. In previous reports, PPIs were suggested to have an effect on the absorption of calcium and associated with hip fractures.

Drugs with anticholinergic properties (DAPs)

In Study 3, DAPs were categorized according to the anticholinergic risk scale (Rudolph et al. 2008) (Table 14). The Rudolph scale includes commonly used DAPs and classifies them according to their potential anticholinergic effects. The drugs having high potential anticholinergic effects receive three points, whereas those with moderate anticholinergic effects receive two points and those with mild effects one point. The list in its current form accurately identifies the ADRs of these drugs with respect to their anticholinergic adverse effects. The Rudolph scale is simple and easy to use and allows international comparisons (Rudolph et al. 2008, Salahudeen et al. 2015b). According to the original study, higher ARS scores were associated with higher risk of anticholinergic side effects (Rudolph et al. 2008).

Because DAPs may counteract the effects of ChEIs, the cholinesterase inhibitors (donepezil, galantamine, rivastigmine; ATC code N06DA) were categorized in the data.

Drug-drug interactions (DDIs)

The Swedish, Finnish, Interaction X-referencing database (SFINX), a computerized database system (Böttiger et al. 2009), was used to assess severe, D-class drug-drug interactions (DDIs) (Study 4).

SFINX is a commercial medical DDI database introduced in Finland in 2005 (SFINX 2015). It is updated four times a year by Medbase Ltd. in Turku, Finland, the Karolinska Institute Department

of Clinical Pharmacology in Stockholm, Sweden and the Stockholm County Council in Stockholm, Sweden. Interactions are classified according to their clinical significance (A-D) and documentation level (0-4), where A indicates a clinically insignificant interaction and D a clinically significant interaction that should be avoided. This study investigates the prevalence of DDDIs among older people in residential care facilities in Helsinki and Espoo, Finland (Study 4).

Table 14. Drugs available in Finland at the time of Study 3 and included in the Anticholinergic Risk Scale (Rudolph et al. 2008). 3 points = drugs with high anticholinergic properties, 2 points = drugs with moderate anticholinergic properties, 1 point = drugs with low anticholinergic properties.

3 Points	2 Points	1 Point
Amitriptyline hydrochloride	Amantadine hydrochloride	Carbidopa-levodopa
Atropine products	Baclofen	Entacapone
Carisoprodol	Cetirizine hydrochloride	Haloperidol
Chlorpromazine hydrochloride	Clozapine	Metoclopramide hydrochloride
Diphenhydramine hydrochloride	Loperamide hydrochloride	Mirtazapine
Fluphenazine hydrochloride	Loratadine	Paroxetine hydrochloride
Hydroxyzine hydrochloride and hydroxyzine pamoate	Nortriptyline hydrochloride	Pramipexole dihydrochloride
Hyoscyamine products	Olanzapine	Quetiapine fumarate
Oxybutynin chloride	Prochlorperazine maleate	Ranitidine hydrochloride
Perphenazine	Tolterodine tartrate	Risperidone
Thioridazine hydrochloride		Selegiline hydrochloride
Tizanidine hydrochloride		Trazodone hydrochloride

4.2.3. Mortality data

Mortality data were obtained from national registers (Studies 2 and 4). Mortality rates were followed for one year in Study 2 and for three years in Study 4.

4.3. Ethical considerations

All study procedures were planned in accordance with the Helsinki declaration. All studies were approved by the Helsinki University Central Hospital Ethics Committee. Informed consent was acquired from each participant, or from their closest proxies in case of poor cognition.

4.4. Statistical analyses

The data were coded with either Microsoft ACCESS or Microsoft Excel programs and analyzed with the NCSS (Number Cruncher Statistical System) and SPSS 12.0.1. (SPSS Inc., Chicago, IL, USA) software programs.

In all studies, the participants were divided for the analyses according to the use of potentially harmful medications (PPIs, DAPs, DDDIs), and users and non-users of the index drugs were compared. In Study 1, the participants were also dichotomized into groups having or not having diarrhoea, and these two groups were compared. In Study 3, the participants were also divided into four groups for the analyses: those using only DAPs, those using DAPs and ChEIs concomitantly, those using only ChEIs, and those using none of these. At baseline the groups were compared for categorical variables using χ^2 tests or Fisher's exact test. Differences between non-normally distributed continuous variables were assessed using Mann-Whitney U-tests when comparing two groups and Kruskal-Wallis test when comparing four groups.

Logistic regression models were used to evaluate the association of the variables (PPIs, DAPs, ChEIs) with outcomes (diarrhoea, psychological well-being). In Study 2, the analysis was adjusted for age, gender, fluid intake, comorbidities, lactose intolerance, celiac disease, chronic inflammatory bowel disease, constipation, use of laxatives, calcium supplements, and SSRIs, when assessing the association of PPIs with diarrhoea. In Study 3, the analysis was adjusted for age, gender, educational level, comorbidities, Parkinson disease, psychiatric disorder, and use of ChEIs, when assessing the association of DAPs with PWB.

Cox regression analysis was used to explore the prognostic value of PPI use and DDIs for mortality in Studies 2 and 4, respectively. The covariates were age, gender, CCI, and use of SSRI and/or Aspirin. Cohorts 1 and 2 were further adjusted for malnutrition and cohort III for delirium. Kaplan-Meier curves were constructed and log-rank tests were performed.

The results were considered significant at the level $p < 0.05$.

5. Results

5.1.Characteristics of samples

There were four large samples of institutionalized frail older people in these studies. The sample sizes ranged from 425 to 1987. The mean ages ranged from 81 to 86, and females comprised the majority of participants in all samples. Dementia was common in all samples (range 59% to 74%). In assisted living facilities, about 15% of participants were immobile, whereas in the nursing home sample about 30% were unable to move independently, and the respective figure in the long-term care wards was 86% (Table 15).

Table 15. Characteristics of participants in study samples.

Variable	Helsinki nursing homes in 2003	Geriatric wards and nursing homes in 1999	Helsinki long-term care wards in 2003	Helsinki / Espoo assisted living facilities in 2007		
				2	3	4
Study	1	2	2	2	3	4
No. of participants	1987	425	1004	1389	1475	1327
Mean age, range	84 (65 to 105)	86 (69 to 104)	81 (23 to 104)	83 (55 to 99)	83 (55 to 99)	83 (55 to 99)
Females, % (n)	80.7 (1603)	81.6 (347)	75.2 (755)	78.2 (1086)	77.7 (1146)	78.3 (1039)
Unable to move independently, % (n)	30.3 (602)	n.a.	85.9 (862)	14.6 (202)	14.6 (215)	15.0 (199)
MNA<17points, % (n)	28.4 (565)	n.a.	60.0 (602)	13.2 (183)	13.4 (197)	12.7 (169)
Dementia, % (n)	69.5 (1380)	60.0 (255)	74.3 (746)	59.0 (819)	58.9 (869)	58.9 (781)
Charlson Comorbidity Index, mean, range	2.1 (0 to 8)	2.2 (0 to 7)	2.5 (0 to 9)	2.9 (0 to 8)	2.9 (0 to 8)	2.9 (0 to 8)
Drugs, mean (range)	8.0 (0 to 21)	8.4 (0 to 18)	7.1 (0 to 20)	8.0 (0 to 21)	8.1 (0 to 21)	8.0 (0 to 21)
Polypharmacy:						
Patients with 6-9 drugs, % (n)	51.8 (1029)	51.3 (218)	53.0 (532)	47.4 (659)	47.2 (697)	49.7 (659)
Patients with >10 drugs, % (n)	30.6 (608)	37.2 (158)	23.7 (238)	31.9 (443)	31.7 (467)	33.5 (445)

MNA= Mini Nutritional Assessment (Guigoz et al. 2002); Charlson Comorbidity Index (Charlson et al. 1987), n.a. = not applicable

Malnutrition was also common. In assisted living facilities, 13% of residents were malnourished, in nursing homes 28%, and in long-term care wards 60%, predisposing them to adverse effects of drugs. Participants suffered from a high number of comorbidities (CCI range 2.1 to 2.9), which corresponds to a moderate risk for one-year mortality. Participants were also administered a high number of drugs, mean range from 7.1 to 8.4. Of residents, 79-88% had polypharmacy and 24-37% excessive polypharmacy.

5.2. Proton-pump inhibitors

5.2.1. Adverse effects associated with PPI use

In Study 1, the participants were old (mean age 84 years), mostly female (81%), and frail. Of participants, 30% were unable to move independently. One in three had suffered from a prior stroke (30%), and coronary heart disease was also common in this sample (38%).

Of assessed residents in study 1 (N=1987), one in five (21.8%) were treated with regular PPIs. No differences existed in age, gender, or nutritional status between users and non-users of PPIs. The factors associated with PPI regular treatment were poorer functional status (inability to move independently) (35.5% vs. 28.9%, $p=0.009$), higher CCI score [2.3 (1.3) vs. 2.1 (1.2), $p<0.001$], and higher number of medications [10.5 (3.4) vs. 7.2 (3.2), $p<0.001$]. Use of calcium supplements (40.1% vs. 24.9%, $p<0.001$), vitamin D supplements (37.7% vs. 29.5%, $p=0.001$), and SSRIs (32.8% vs. 24.9%, $p=0.001$) was also associated with regular PPI treatment. Other factors associated with regular PPI use were prior ventricular or duodenal ulcer (15% vs. 3.1%, $p<0.001$), cancer (15.1% vs. 10.3%, $p=0.008$), coronary heart disease (47.4% vs. 34.9%, $p<0.001$) and lactose intolerance (15.1% vs. 7.8%, $p<0.001$). PPI users suffered less often from dementia (56.8% vs. 73%, $p=0.001$).

PPI use was associated with diarrhoea (19.7% vs. 12.9%, $p<0.001$) and frequent vomiting (8.2% vs. 3.7%, $p<0.001$). PPI users had more often a prior history of hip fracture (28.5% vs. 19.4%, $p<0.001$) than those without PPI. No significant association was present between low-dose aspirin or NSAID administration and regular PPI treatment.

Among PPI users, those suffering from diarrhoea were older [84.9 years (7.2) vs. 83.5 years (7.7), $p=0.003$], had more comorbidities (2.3 (1.2) vs. 2.1 (1.2), $p=0.001$), were administered a higher number of medications [8.6 (3.6) vs. 7.8 (3.5), $p<0.001$], and suffered more often from frequent vomiting (9.2% vs. 3.7%, $p<0.001$). Diabetes (21.7% vs. 16.6%, $p=0.047$), celiac disease (1.5% vs. 0.3%, $p=0.009$), lactose intolerance (28.1% vs. 6.4%, $p<0.001$), prior ventricular or duodenal ulcer

(9.0% vs. 4.8%, $p=0.007$), and coronary heart disease (44.3% vs. 36.1%, $p=0.0013$) were also associated with diarrhoea. Residents suffering from diarrhoea used less often laxatives (46.2% vs. 56.6%, $p=0.001$), but were administered more often SSRIs (31.8% vs. 25.9%, $p=0.041$) than their peers without diarrhoea.

In logistic regression analysis, PPI use showed an independent association with diarrhoea (OR 1.60, 95% CI 1.20-2.15; $p=0.002$) even after adjustment for age, gender, fluid intake, CCI, lactose intolerance, celiac disease, chronic inflammatory bowel disease, constipation, use of laxatives, calcium supplements, and SSRIs. Other factors associated with diarrhoea were CCI (OR 1.16, 95% CI 1.05-1.28; $p=0.005$) and age (OR 1.02, 95% CI 1.00-1.04; $p=0.008$).

5.2.2.PPI use and mortality

Study 2 contained three cohorts. Of the residents in assisted living facilities ($n=1389$; the first cohort of Study 2), 25% suffered from prior stroke and 13 % had prior myocardial infarction. Of residents, 22% were treated regularly with SSRIs, 45% with low-dose Aspirin, and 3% with NSAIDs. In addition, 26% were using PPIs.

Among residents in assisted living, no association existed between 12-month all-cause mortality and use of PPIs (20.2% vs. 20.4%, $p=0.94$). There was no increased risk of death associated with the use of PPIs (HR 1.06; 95% CI 0.77–1.46) in the Cox proportional hazards model adjusted for age, gender, CCI, immobility, and use of SSRIs. A positive association emerged between age (83.6 vs. 82.4, $p=0.011$), mean number of drugs (8.8 vs. 7.6, $p<0.001$), use of SSRIs (27.5% vs. 20.6%, $p=0.007$), and immobility (18.0% vs. 13.3%, $p=0.030$) and use of PPIs. There were no associations with use of PPIs and comorbidities or the use of NSAIDs or Aspirin.

Of residents in long-term care hospital units ($n= 1004$; the second cohort of Study 2), 38% had had a previous stroke, 36% were treated with low-dose Aspirin, 28% were treated with regular SSRIs and 3% with regular NSAIDs. Of this sample, 23% were administered PPIs.

In long-term care hospital patients ($n = 1004$), mortality was higher among PPI-users than non-users (33.3% vs. 26.6%, $p=0.048$). In the Cox proportional hazard model adjusted for age, sex, CCI, use of SSRIs, and malnutrition, there was an increased risk of mortality associated with the use of PPIs (HR 1.36; 95% CI 1.04-1.77). PPI-users had a higher mean number of drugs than non-users (9.3 vs. 6.4, $p<0.001$), higher use of SSRIs (38.1% vs. 24.7%, $p<0.001$), and higher level of comorbidity evaluated with CCI (2.7 vs. 2.5, $p=0.042$). PPI-users were diagnosed less with dementia (63.1% vs. 80.0 %, $p<0.001$). PPI users presented more often a previous history of

myocardial infarction (16.8% vs. 9.8%, $p=0.010$) and duodenal/ventricular ulcer (12.6% vs. 2.2%, $p<0.001$). No difference existed between users and non-users of PPIs concerning immobility, previous stroke, or use of NSAIDs or low-dose Aspirin.

Of participants in acute geriatric hospitals and nursing homes ($n = 425$; the third cohort of Study 2), 25% suffered from acute delirium. Of the sample, 25% had suffered from previous stroke and 76% were dependent in their ADL according to CDR. In this sample, 48% received regular low-dose Aspirin, 8% regular NSAIDs, and 27% regular SSRIs. Of the whole sample, 21% were on PPIs. Of participants using concomitantly low-dose Aspirin or NSAID with SSRI ($n=67$, 15.8%), only six (9.0%) were on PPIs.

In patients in acute geriatric hospitals and nursing homes ($n = 425$), mortality was higher among users than non-users of PPIs (36.3% vs. 21.9%, $p=0.005$). In the Cox proportional hazard model adjusted for age, gender, CCI, delirium, and use of Aspirin and SSRIs, there was an increased risk of mortality associated with the use of PPIs (HR 1.90; 95% CI, 1.23-2.94). Users of PPIs had a higher level of comorbidity (2.5 vs. 2.1, $p=0.046$), were administered a higher number of drugs [10.7 vs. 7.8, $p<0.001$] and were less dependent in ADL activities (62.6% vs. 79.6%, $p<0.001$) than non-users. Compared with non-users, PPI-users were also found to use less Aspirin (34.1% vs. 52.4%, $p=0.002$) and SSRIs (15.4% vs. 29.9%, $p=0.005$), to suffer less from dementia (46.2% vs. 63.8%, $p=0.002$), and to present more often with previous history of duodenal/ventricular ulcer (11.0% vs. 2.4%, $p<0.001$). No difference emerged in age, gender, or use of NSAIDs among users and non-users of PPIs.

5.3. Use of DAPs and ChEIs

Among the participants assessed in assisted living facilities in Study 3 ($n=1475$), 26% suffered from previous stroke, 21% from depression, 10% from other psychiatric disorders, and 5% from Parkinson's disease. Of residents, 81% were dependent in ADL according to CDR "personal care". Of the sample, 59% had a diagnosis of dementia and 52% scored one or more in the CDR "memory" item, indicating moderate or severe dementia (Hugher et al. 1982). In this sample, 42% were administered DAPs according to the ARS (Rudolph et al. 2008).

Among the participants in residential care facilities ($n = 1475$), 41.6% ($n = 613$) were users of DAPs according to ARS. The most commonly used DAPs, with low to moderate anticholinergic activity (1-2 points according to Anticholinergic Risk Scale), were mirtazapine (30.3%), risperidone (29.4%), quetiapine (16.2%), levodopa (11.4%), and olanzapine (9.6%).

The participants were divided according to ChEI and DAP drug treatment into 4 groups: 1) residents receiving both ChEIs and DAPs (10.7%), 2) residents receiving ChEIs but not DAPs (11.7%), 3) residents receiving DAPs but not ChEIs (30.8%), and 4) residents receiving neither ChEIs nor DAPs (46.7%) (see Study 3, Table 4).

The residents receiving DAPs but not ChEIs were the youngest group (mean age 81.5 years), whereas those receiving ChEIs but not DAPs were the oldest group (mean age 84.2 years). The ChEI users had a higher educational level, lower stages of cognition according to the CDR memory class, and more dependence on ADL according to the CDR personal care class than non-users of ChEIs. No significant difference emerged regarding gender distribution or mean CCI among the four groups studied.

The residents administered DAPs were more often administered a higher number of drugs (8.8 (SD 3.4) vs 7.5 (SD 3.3), $p < 0.001$) and were more often treated with ChEIs or memantine (34.6% vs. 26.9%, $p = 0.0016$). DAP use was associated significantly with lower psychological well-being (0.66 [0.25] vs. 0.69 [0.23], $p = 0.010$). Low PWB (score < 0.50) was used as a response variable. In logistic regression analysis, use of DAPs was associated with low psychological well-being (OR 1.40, 95% CI 1.00 to 1.94, $p = 0.048$) even after adjustment for covariates (age, sex, education, CCI, psychiatric illnesses, Parkinson's disease, and use of ChEIs). The effect of anticholinergic burden, defined by the anticholinergic risk scale (ARS), on psychological well-being was also examined. Proportions of poor psychological well-being among those having scores of 0, 1, 2, or 3 or more were 14.2%, 19.2%, 25.0%, and 12.0%, respectively ($p = 0.030$ for trend).

Users of DAPs presented more disabilities (CDR, personal care > 1) (85% vs. 78%, $p < 0.001$) than non-users of DAPs. No significant difference was present between use of DAPs and CCI. DAP users suffered more often from depression (26.4% vs. 16.4%, $p < 0.001$), psychiatric disorders (18.4% vs. 4.8%, $p < 0.001$), and Parkinson's disease (10.0% vs. 1.3%, $p < 0.001$) than non-users. No significant difference between users and non-users of DAPs regarding cognition (CDR, memory class > 0.5) was seen (54.6% vs. 50.6%, $p = 0.12$).

Residents with concomitant use of DAPs and ChEIs suffered more from depression (29.9%), and had less frequently a previous history of stroke (17.2%) or coronary disease (22.4%) than the other groups.

5.4. Potentially serious drug-drug interactions (DDDI)

Of participants assessed in Study 4 (n = 1327), one in five had had a prior stroke, and 18% presented with diabetes mellitus. Over half of the residents suffered from significant cognitive decline according to CDR scale (memory class >0.5) (55%), and 68% were dependent in ADL (CDR personal care >1). Of this sample, 6% were exposed to potentially serious DDIs.

Of the assessed participants in assisted living and having drug data available (n = 1327), 78 (5.9%) were found to have DDDIs according to SFINX, with a total of 86 interactions. Eight residents were susceptible to two DDDIs (Table 16).

Compared with other residents, those exposed to DDDIs had been prescribed a higher number of drugs (10.8 (SD 3.8) vs. 7.9 (SD 3.7), $p < 0.001$) and more often had rheumatoid or osteoarthritis (24.7% vs. 15.4%, $p = 0.030$). DDDIs were not associated with age, gender, marital status, education, common medical conditions, functioning, nutrition, or psychological well-being. A larger portion of residents with DDDIs suffered from cardiovascular diseases (37.7% vs. 28%, $p = 0.070$).

The most common DDDIs were related to concomitant use of potassium with either amiloride (n=12) or spironolactone (n=12). However, 12 residents concomitantly using potassium and potassium-sparing diuretics were also administered furosemide. There were 13 DDDIs related to the concomitant use of carbamazepine and risperidone (N=5), felodipine (N=2), cyclosporin (N=1), quetiapine (N=1), estriol (N=1), oxycodone (N=1), tolterodine (N=1), or lercanidipine (N=1). There were 9 participants concomitantly receiving methotrexate and pantoprazole (N=4), omeprazole (N=2), esomeprazole (N=2), or lansoprazole (N=1). However, methotrexate was not administered in high dosages, thus, not predisposing these patients to DDDIs. The concomitant use of a calcium-channel and beta-blockers was observed in 10 residents. Only three DDDI cases presented with concomitant use of NSAIDs and warfarin.

There was no significant difference between three-year all-cause mortality among those with and without DDDIs (46.2% vs. 44.4%, $p = 0.76$).

Table 16. Potentially severe drug interactions in residents of assisted living in Helsinki and Espoo, Finland.

Drug	Interacting drug	Number of residents exposed to severe DDIs	Concern
Warfarin	Aspirin, celecoxib, tramadol	5	Increased risk of bleedings, if combined
Verpamil	Digoxin, timolol, bisoprolol	4	Increased risk of additive cardio-depressive effect
Diltiazem	Metoprolol, atenolol, timolol, propranolol	6	Increased risk of additive cardio-depressive effect
Clopidogrel	Esomeprazole, omeprazole	3	Loss of clopidogrel efficacy
Carbamazepine	Risperidone, quetiapine, felodipine, ciclosporine, estriol, oxycodone, tolterodine, lercanidipine	13	Loss of therapeutic effect of the interacting drug
Ferrous sulphate	Doxycycline, norfloxacin	2	Reduced absorption of the interacting drug
Colestyramine	Furosemide	1	Reduced absorption of furosemide
Potassium	Spirolactone, amiloride, triamterene	26	Increased risk for hyperkalemia
Calcium	Norfloxacin, ciprofloxacin	3	Reduced absorption of the interacting drug
Methotrexate	Lansoprazole, pantoprazole, omeprazole, esomeprazole	9	Increased risk for methotrexate intoxication with high doses of methotrexate
Oxycodone	Rifampicin	1	Loss of oxycodone efficacy
Magnesium	Norfloxacin	1	Loss of therapeutic effect of norfloxacin
Periciazine	Levodopa, cabergoline	2	Loss of therapeutic effect of both drug and interacting drug
Amlodipine	Rifampicin	1	Loss of amlodipin efficacy
Fenytoin	Tamsulosin	1	Loss of therapeutic effect of the interacting drug
Tramadol	Duloxetine	1	Increased risk for serotonin syndrome
Felodipine	Itraconazole	1	Increased felodipine therapeutic effect
Timolol	Acetazolamide	5	Increased risk for dyspnoea and acidosis in patients with pulmonary obstruction or emphysema
Duloxetine	Codeine	1	Loss of therapeutic effect of codeine

6. Discussion

In these studies, 21-26% of residents were administered PPIs on a daily basis. Regular PPI use was associated with diarrhoea and prior hip fracture, indicating possible side effects. The use of PPIs was not associated with mortality among residents in assisted living facilities. However, their use was associated with increased mortality in settings where residents experienced higher levels of disability and comorbidities (long-term hospitals, geriatric wards, and nursing homes), indicating the higher vulnerability of these individuals to adverse events of PPIs. Of residents in assisted living facilities, 10.7% were administered ChEIs and DAPs concomitantly. DAP use was associated with use of a higher number of drugs, more severe disability, depression, psychiatric disorders, and Parkinson's disease. DAP use was associated with low psychological well-being even after adjustment for age, gender, education, comorbidities, and use of ChEIs. Use of PPIs and DAPs was associated with polypharmacy.

Potentially serious DDIs according to SFINX were observed in 5.9% of residents in assisted living facilities. Use of higher number of drugs and rheumatoid/osteoarthritis were associated with DDDIs. The most frequent DDDIs were related to the concomitant use of potassium with amiloride or spironolactone. Carbamazepine was also associated with more frequent DDDIs. No difference in mortality was observed between residents exposed to DDDIs and those not exposed to DDDIs.

6.1. Methodological considerations

6.1.1. Study populations

This study consisted of a large number (N=4891) of older people in the metropolitan area of Finland living in various institutional settings such as assisted living facilities, nursing homes, long-term care wards and acute geriatric wards. They represent a wide range of frail older people with polypharmacy, and a high number of comorbidities and disabilities. Thus, they represent the frailest part of the older population prone to adverse events related to drug use. The original studies aimed to examine all institutionalized residents and the exclusion criteria were thus kept low. The study samples had satisfactory response rates ranging from 63% to 82%. The exclusion criteria were age younger than 65 years (Studies 1-4; only cohorts 1 and 2 in Study 2) and 70 years (Study 2, cohort 3), short-term residency, refusal to participate, insufficient information on drug use or demographic data, and coma (Study 2, cohort 3). In Studies 2 and 4, exclusion criteria also concerned patients

with insufficient information on social security codes. The only limiting factor was obtaining informed consent from all residents and – in cases of dementia – from their closest proxies. Thus, the populations may be considered to represent fairly well their respective background populations.

The data were collected between the years 1999 and 2007. The population in institutional settings has undergone a significant change from those times, since the number of nursing home beds has been constantly decreasing in the last decade, whereas the number of beds in assisted living facilities has significantly increased (Pitkälä et al. 2015). The institutionalized population in Finland is significantly older and more disabled today than ten years ago. In addition, they have a higher number of comorbidities and dementia is more prevalent. Furthermore, in assisted living facilities polypharmacy has increased between 2007 and 2011 (Pitkälä et al. 2015). However, the population in assisted living facilities today resembles that of nursing homes in 2003 (Pitkälä et al. 2015).

The mean age of patients varied from 81 years (Study 2, long-term care wards) to 86 years (study 2, geriatric wards and nursing homes). In European nursing homes, the mean age has ranged from 83 to 86 years (Kersten et al. 2013b, Onder et al. 2012, Haasum et al. 2012), and in the USA the respective figure was 84 years (Palmer et al. 2015). In line with previous studies in institutional settings, nearly four of five of the participants were females (Kersten et al. 2013b, Onder et al. 2012, Haasum et al. 2012, Palmer et al. 2015). The proportion of malnourished participants varied from 13% (Study 2, assisted living facilities) to 60% (Study 2, long-term care hospital wards), which is similar to previous studies (Guigoz 2006). The CCI varied from 2.1 (Study 1, nursing homes) to 2.9 (Study 2, assisted living facilities, Studies 3 and 4), which is in line with previous studies from institutional settings and indicates a high number of comorbid conditions (Onder et al. 2012). Consistent with previous studies, the mean number of drugs ranged from 7.1 (study 2, long-term care hospital wards) to 8.4 (study 2, geriatric wards and nursing homes) (Haasum et al. 2012). The prevalence of dementia varied from 59% (study 2, assisted living facilities, studies 3 and 4) to 74% (study 2, long-term care wards). In an inter-European study, the prevalence of cognitive decline was 69% (Onder et al. 2012).

6.1.2. Study design and data collection

All of the studies here used a cross-sectional design with follow-up of mortality data. The drug use and other characteristics were assessed as a point prevalence at baseline. Thus, it is not known how the drug use changed during the follow-up period, which is a limitation of the studies.

The data were collected by trained registered nurses who knew the residents from their wards well. All nurses received at least half a day of training for data collection and assessments. The demographic data, current diagnoses, and drug lists were retrieved from medical records, ensuring the reliability of data. Thus, data on current drug use were comprehensive. Mortality data were retrieved from central registers, and it was 100% complete among those who had the correct social security code.

Furthermore, the studies used the same questionnaire throughout the years enabling comparisons between studies. The questionnaires were embedded with well-validated scales such as MNA (Guigoz et al. 2002), CCI (Charlson et al. 1987), CDR (Hughes et al. 1982), and the Psychological Well-Being Scale (Routasalo et al. 2009).

6.1.3. Strengths of the study

The main strength of this study is the large representative samples of frail older people in institutional care with well-characterized cohorts (assisted living facilities, nursing homes, long-term care hospitals, acute geriatric wards). Clinical data on demographic factors were collected by well-trained nurses familiar with the residents, increasing the reliability of the results. Medical diagnoses and use of medications were gathered from medical records and mortality data from central registers, which are reliable and accurate in Finland. The drugs were classified with ATC codes, an international classification system that allows comparisons (World Health Organization 2015). Structured questionnaires were retrieved from validated measures (CDR, MNA, psychological well-being, CCI). To minimize data coding errors, a researcher compared the participants' medication lists in the questionnaire with the electronic version of the list.

6.1.4. Limitations of the study

This study had a cross-sectional design. Thus, it is not possible to draw any definite conclusions concerning causal relationships or trends between the factors associated with mortality or psychological well-being and drug use. Factors restricting the interpretation of the findings included unavailability of prescription sequence, limited number of variables, and limited information on specific medical conditions and aetiologies. The original studies did not include information on variables such as *Clostridium difficile* infections, pneumonias, B-12 vitamin deficiency, or oesophageal reflux disease, which would have been important confounders to explore in the PPI studies. Diarrhoea was only inquired about with a yes/no question, thus limiting the interpretation of the relationship between symptoms and use of PPIs. Similarly, the DAP study

did not include variables affecting psychological well-being such as mood, social relationships, or social activities. Unfortunately, the typical AEs of DAPs, such as cognitive decline or falls, were not assessed in our study. One additional limitation is the possibility of potential confounding factors among older people with multiple morbidities. As usually seen in observational studies, the associations observed here may have been due to residual confounding.

Only residents with regular drug administration were considered as drug users. Drugs used on an as needed basis were not included here. This may have influenced the results concerning drug prevalences, but ensures the reliability of the results. There is no standardized, reliable, and practical method to assess anticholinergic burden in clinical practice (Lampela et al. 2013). The rating of anticholinergic activity for medicines in various rating scales is inconsistent. The same drug is rated with varying degrees for anticholinergic activities according to different lists (Salahudeen et al. 2015a). Drug lists vary according to different criteria (Viipuri 2016). The DAP classification used in this study (ARS, Rudolph et al. 2008) may be criticized. There are a number of DAP classifications available in the literature (see Table 7). The ARS includes 49 drugs as DAPs, thus representing a medium-sized list. Some of the drugs on the ARS list are not associated with central adverse effects, and other drugs on the list do not present potentially anticholinergic properties (Rudolph et al. 2008). In Finland, 32 drugs are available according to the ARS list. However, the ARS is one of the most used DAP lists, allowing international comparisons.

It might have been interesting to explore the mortality causes for the samples. However, these data were not available.

One limitation with SFINX is that it only considers interactions between two drugs. Thus, in a population prone to polypharmacy, the true prevalence of potentially serious interactions is probably much higher than the figures presented here. Furthermore, another limitation of SFINX is that it does not usually include information concerning pharmacodynamic interactions in older patients.

6.2. Proton-pump inhibitors

6.2.1. Adverse effects associated with PPI use

About one-fifth of nursing home residents received PPIs regularly. The prevalence of use of PPIs in nursing homes in Helsinki was lower to that reported in many recent studies, in which figures have

ranged from 37.2% to 79.7% (de Souto Barreto et al. 2013, Patterson et al. 2013, Vetrano et al. 2013, Pitkälä et al. 2014). Thus, the use of PPIs seems to have increased during the past decade. This may be due to the guidelines recommending the use of PPIs not only for anti-ulcer treatment but also for gastrointestinal protection with concomitant use of NSAIDs or anti-platelet treatment (Bhatt et al. 2008). According to the Fimea and Kela statistics, PPIs as an individual drug class are among those drugs with the highest costs to their users and to society (Fimea and Kela 2016). In 2015, there were 638 943 users receiving financial compensation for PPIs and more than 41 million euros were spent on PPIs in Finland. The number of users of PPIs has more than tripled from 2003 to 2015 (Fimea and Kela 2016)

Differences in gender or nutrition were not associated with use of PPIs. In line with previous studies, PPI use was associated with poorer functional status (Corsonello et al. 2014), increased number of comorbidities, higher number of medications, use of calcium supplements, SSRI use, and previous history of peptic ulcer or coronary heart disease (de Souto Barreto et al. 2013). Consistent with de Souto Barreto's study, PPI use was lower in residents with dementia.

In some earlier studies, PPIs were administered to reduce the risk of gastrointestinal bleeding related to use of NSAIDs and low-dose Aspirin (de Souto Barreto 2013). In the present study, users of NSAIDs and Aspirin were not more often administered PPIs, except in cohort 3 of Study 2 (patients in nursing home and acute geriatric wards), in which the users of low-dose Aspirin were more often on PPIs. Furthermore, no consistent relationship between use of PPIs and prior ulcer diagnoses was seen in residents in assisted living facilities, possibly indicating PPI use without clear therapeutic indications. Among SSRI users, the use of PPIs was significantly higher in all cohorts. SSRI users are considered to be at risk for GI-bleeding, especially when they concomitantly use NSAIDs (Böttiger et al. 2009).

In this study, use of PPIs was associated with prior hip fracture. Previous studies have reported an association between PPI use and increased risk of fractures among older people with risk factors for osteoporosis, possibly due to malabsorption of calcium (Masclée et al. 2014, Arkkila 2015). In the present study, PPI users more frequently received calcium and vitamin D supplementation, probably for secondary prevention of fractures.

In multivariate logistic regression analysis, the use of PPIs along with CCI and age were independently associated with diarrhoea. About half of PPI users with diarrhoea were administered laxatives. This may be inappropriate. However, some of these patients may suffer intermittently from constipation and diarrhoea. Diarrhoea was logically associated with lactose intolerance, celiac

disease, and use of SSRIs, but not with use of ChEIs. The latter group of drugs is considered to have gastrointestinal side effects (Nordberg and Svensson 1998).

The association between use of PPIs and symptoms of diarrhoea could be attributed to an increased risk of *Clostridium difficile* infection. Long-term acid suppression may cause small bowel bacterial overgrowth, which is further enhanced by age, antibiotic exposure, and prior hospitalization as risk factors for *C. difficile* infection (Laheij et al. 2004, Kwok et al. 2012, Masclee et al. 2014, Zarowitz et al. 2015). Unfortunately, in this study it was not possible to get information regarding possible aetiologies of diarrhoea in the population.

There are a few studies investigating CDI prevalence in nursing home residents (Simor et al. 2002, Laffan et al. 2006, Zarowitz et al. 2015). Predisposing factors to CDI in this population include, underlying diseases, such as diabetes and heart disease, and treatment with PPI, as reported by Zarowitz et al. (2015). In line with this study, residents using PPI and suffering from diarrhoea suffered more from diabetes and heart disease.

Residents in institutional care facilities, prone to recurrent episodes of hospitalizations, are often prescribed PPIs for routine prophylaxis. Use of PPIs is continued without a specific indication after discharge (Amaral et al. 2010). In this population, diarrhoea may reduce the quality of life, therefore deserving special attention. The benefits and possible risks associated with long-term PPI use in frail older people should be evaluated on a regular basis, avoiding unnecessary long-term treatment without clear therapeutic purposes.

6.2.2.PPI use and mortality

Use of PPIs was associated with increased mortality in cohorts of frail older people with high levels of comorbidities (long-term care hospitals, nursing homes, and acute geriatric wards). Among residents with better function in ADL-activities in assisted living facilities, no excess mortality associated with PPI use was observed.

There are few studies investigating the association of PPIs with mortality risk among older people. According to an Italian study, use of PPIs in an older population discharged from hospitals was associated with increased mortality risk in previously hospitalized older people. Predictive factors for mortality were age, hypoalbuminaemia, being dependent in ADL-activities, and comorbidity (Maggio et al.2013a). However, in an Australian study, use of PPIs was not associated with mortality among residents in intermediate-level residential aged-care facilities (Wilson et al. 2011).

There may be several reasons for the association between PPIs and mortality. It might be accounted for by confounding by indication. However, the analyses were adjusted for CCI. Previous studies have reported an association between use of PPIs, bacterial overgrowth, *C. difficile* infections (Laheij et al. 2004), pneumonia (Yearsley et al. 2006), hip fractures (Yang et al. 2006), cardiovascular adverse outcomes (Masclee et al. 2014), and gastrointestinal cancer (Arkkila 2015). In line with Wilson and colleagues (2011), in the present study PPI use among residents in assisted living was not associated with increased mortality risk. Differences in risk of increased mortality among the cohorts could be explained by the residents in assisted living being less frail, presenting with better nutritional status, and having less disability than patients in long-term care hospitals, nursing homes, or acute geriatric wards, who would be more vulnerable to complications such as infections, hip fractures, and strokes. However, the association between PPIs and mortality could be due to residual confounding, and further studies are needed to confirm the finding in the frailest populations.

6.3. Concomitant use of ChEIs and DAPs

In our study sample, DAPs were commonly used among these frail elderly residents in residential care facilities; 41.6% of those in this study were receiving these drugs, which falls between the figures of 2.5% and 48% reported previously (Johnell and Fastbom 2008, Landi et al. 2014). The prevalence of DAP use has varied widely (Carnahan et al. 2004, Gill et al. 2005, Johnell and Fastbom 2008, Sink et al. 2008, Modi et al. 2009, Landi et al. 2014) depending on the patient population as well as the definition of DAPs. In the present study, DAP users suffered more from medical conditions requiring DAP treatment (depression, psychiatric disorders, Parkinson's disease).

Among the residents, 15.7% were administered ChEIs. The ChEI users were more often cognitively impaired and disabled, but had better subjective health. In accord with previous studies, there were significantly more users of DAPs among the users of ChEIs than among the non-users (Carnahan et al. 2004, Gill et al. 2005, Johnell and Fastbom 2008, Sink et al. 2008, Modi et al. 2009). DAPs may be used to treat the adverse effects of ChEIs, such as urinary incontinence and gastrointestinal problems, resulting in a prescribing cascade in which misattribution of an ADE leads to inappropriate use of a second drug. In general, patients with dementia are more prone to receive DAPs than patients without dementia. The concurrent use of DAPs and ChEIs is not clinically indicated because they antagonize each other and DAPs further impair cognition among patients with dementia (Defilippi and Crismon 2003, Johnell and Fastbom 2008).

Anticholinergic drugs may impair cognition and also have several other adverse effects in older people (Ancelin et al. 2006, Rudolph et al. 2008, Uusvaara et al. 2009). Studies investigating the association of use of ChEIs and DAPs with psychological well-being have been scarce.

In multivariate logistic regression analysis, after adjusting for age, sex, education, CCI, psychiatric illnesses, Parkinson's disease, and use of ChEIs, DAPs was associated with poor psychological well-being. Use of DAPs exposes patients to various adverse effects, which may in turn explain the poor psychological well-being of their users. DAPs may also be markers of underlying disease (e.g. urinary incontinence, depression, Parkinson's disease), which is the true risk factor for poor psychological well-being (Miu et al. 2010).

In the present study, the effect of anticholinergic burden according to the ARS scale (Rudolph et al. 2008) was evaluated, and higher burden was associated with lower psychological well-being. Although the original Rudolph list includes drugs without significant anticholinergic properties, it does not include some common DAPs. Despite the fact that many drugs on the original Rudolph list are not available in Finland, the scale is simple, easy to use, and allows international comparisons.

A limitation of this study is that the burden of various DAPs (dosage or potency) could not be measured reliably. Exploring anticholinergic burden is difficult in older people for many reasons (e.g. variability in blood-brain barrier and anticholinergic tolerance between patients, unavailability of information about anticholinergic burden and SAA of some drugs). In addition, the detailed mechanism of DAPs affecting psychological well-being could not be evaluated and adjustment for the severity of medical conditions could not be performed, which could be due to residual confounding.

6.4. Drug-drug interactions

About 6% of residents in assisted living facilities were predisposed to potentially severe drug-drug interactions (DDIs). Those participants vulnerable to DDIs were treated with a higher number of drugs and were more likely to suffer from rheumatoid arthritis or osteoarthritis. There was also a trend with respect to cardiovascular diseases.

Almost half of the DDIs detected in this study were associated with risk of loss of therapeutic effect of the interacting drugs. About one fifth of DDIs was associated with an increased risk for hyperkalemia. One of ten DDIs was associated with increased risks for cardio-depressive effect. The most frequent DDIs were potassium with potassium-sparing diuretics, carbamazepine with various drugs, and calcium-channel blockers with beta-blockers. The DDI of methotrexate with

proton-pump inhibitors cannot be confirmed since the risk of DDDI between these drugs is highest among patients receiving methotrexate in high doses for cancer. The indications for methotrexate could not be confirmed. The patients in this study were likely to receive methotrexate mostly for treatment of auto-immune diseases such as rheumatoid arthritis. DDDIs were not associated with risk of higher mortality.

In addition to polypharmacy, comorbidities and decreased nutritional status may increase the risk for DDIs in older people (Mallet et al. 2007). In the present study, with respect to potentially severe DDIs (DDDIs), common medical conditions and nutritional status were not associated with increased risk for DDDIs.

In previous studies, the range of DDDIs has varied from 0.7% to 16% between different populations, countries, and settings (Johnell and Klarin 2007, Hosia-Randell et al. 2008, Nobili et al. 2009, Teixeira et al. 2012). In the present study, the prevalence of DDDIs (5.9%) compared quite well with that observed in earlier studies, particularly when the same criteria (SFINX) were used (Johnell and Klarin 2007, Hosia-Randell et al. 2008). However, the prevalence rates are not directly comparable since SFINX has been regularly updated.

In this study, dementia was not associated with increased risk for DDDIs, contrary to a previous study conducted in nursing homes in Finland (Hosia-Randell et al. 2008). In line with earlier findings, there was an association between a higher number of drugs and an increased risk of DDDIs (Bjerrum et al. 2003, Zhan et al. 2005, Cruciol-Souza et al. 2006, Johnell and Klarin 2007, Hosia-Randell et al. 2008, Nobili et al. 2009, Secoli et al. 2010, Lin et al. 2011). Only a few previous studies have assessed adverse outcomes of DDDIs, and they have suggested an association between DDDIs and hospitalizations (Juurlink et al. 2003, Moura et al. 2009). Unfortunately, it was not possible to study hospitalizations. However, no difference with respect to DDDIs was observed for 1-year or 3-year mortality.

In line with another Finnish study, the most common DDDIs were related to concomitant use of potassium with potassium-sparing diuretics and concomitant use of carbamazepine with other drugs (Hosia-Randell et al. 2008). However, 12 residents concomitantly using potassium and potassium-sparing diuretics were also administered furosemide, which may lower the risk of hyperkalemia. Only three DDDI cases caused by concomitant use of NSAIDs and warfarin were found.

In a Swedish study investigating older people in six European countries, the most common DDDIs were associated with a combination of bromide- and B2-agonists (29% of total DDDIs), potassium

and potassium-sparing agents (18% of total DDDIs), and antithrombotic agents combined with NSAIDs or acetylsalicylic acid (18% of total DDDIs) (Björkman et al. 2002).

Although DDDIs are seldom life-threatening, they should be avoided. DDDIs are associated with loss of therapeutic effect of the interacting drug, increased risk of hyperkalemia, cardio-depressive effects, increased bleeding risk, and as suggested by a few previous studies – risk of hospitalizations (Juurlink et al. 2003, Moura et al. 2009). Physicians in charge of older people's care in institutional settings should place a major emphasis on drug lists and check for possible serious interactions using the available databases. Special care should, however, be taken when drugs with narrow therapeutic indices are administered (Delafuente 2003). The impaired physiological functions of older patients augment additive DDDIs (Seymour and Routledge 1998) and it should be borne in mind that the altered pharmacokinetics and pharmacodynamics of older people increase risks of DDDIs (Mallet et al. 2007).

7. Conclusions

The use of PPIs and DAPs is common among institutionalized residents. Use of PPIs was associated with diarrhoea and prior hip fracture in older residents in nursing homes. PPIs were also associated with increased all-cause mortality in older people in long-term care hospitals, acute geriatric wards, and nursing homes. In assisted living facilities, PPIs were not associated with increased mortality.

The use of DAPs according to the ARS was very high, with four of ten patients on DAPs. The use of DAPs was associated with low psychological well-being. Concomitant use of DAPs and ChEIs was common among older adults in assisted living facilities.

About 6% of older people in residential care facilities were exposed to DDDIs. The exposure was associated with a higher number of medications, but not with all-cause mortality.

8. Implications for future studies

Further investigations are needed to improve the recommendations concerning PPI indications, duration, and discontinuation of therapy among frail older people in institutional care settings. Prospective intervention trials and larger observational studies should investigate the possible risks between PPI use and adverse effects in this population segment.

Future research should aim to improve knowledge of DAP use among the elderly and clarify these risks. Physicians need to consider how DAP use affects the overall risk and well-being of each patient.

Another area requiring research is the clinical applications of computerized database systems for DDDIs among older people in institutional care living facilities.

It is important for clinicians to regularly evaluate the medications of older patients in institutional care settings. Clinicians should if possible avoid long-term use of PPIs and DAPs unless their benefits clearly exceed their risks. Clinicians should regularly use SFINX-PHARAO databases and other databases to avoid DDDIs and possible adverse effects of anticholinergic drugs.

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10. References

- AGS. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2012;60:616-31.
- Ahonen J. Iäkkäiden lääkehoito. Vältettävät lääkkeet ja yhteisvaikutukset. Publications of the University of Eastern Finland. Dissertations in Health Sciences 66. Farmasian laitos, Terveystieteiden Tiedekunta, Itä-Suomen Yliopisto, Kuopio 2011.
- Alarcón T, Bárcena A, González-Montalvo J, Penãlosa C, Salgado A. Factors predictive of outcome on admission to an acute geriatric ward. *Age Ageing* 1999;28:429-32.
- Amaral MC, Favas C, Alves JD, et al. Stress-related mucosal disease: incidence of bleeding and the role of omeprazole in its prophylaxis. *Eur J Intern Med* 2010;21:386-8.
- Ancelin ML, Artero S, Portet F, Dupuy AM, Touchon J, Ritchie K. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *BMJ* 2006;332:455-9.
- Aparasu R, Baer R, Aparasu A. Clinically important potential drug-drug interactions in outpatient settings. *Res Social Adm Pharm* 2007;3:426-37.
- Arkkila P. Protonipumpun estäjien pitkäaikaisen käytön haitat. *Suom Lääkäril* 2015;18:1235-40.
- Barat I, Andreassen F, Damsgaard EM. The consumption of drugs by 75-year-old individuals living in their own homes. *Eur J Clin Pharmacol* 2000;56:501-9.
- Basger BJ, Chen TF, Moles RJ. Inappropriate medication use and prescribing indicators in elderly Australians: development of a prescribing indicators tool. *Drugs Aging* 2008;25:777-93.
- Bateman DN, Colin-Jones D, Hartz S, et al. Mortality study of 18 000 patients treated with omeprazole. *Gut* 2003;52:942-6.
- Becker ML, Visser LE, van Gelder D, Hofman A, Stricker BH. Increasing exposure to drug-drug interactions between 1992 and 2005 in people aged > or = 55 years. *Drugs Aging* 2008; 25: 145-52.
- Beers MH, Ouslander JG, Rollinger I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. *Arch Intern Med* 1991;151:1825-32.
- Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch Intern Med* 1997;157:1531-6.
- Bell JS, Mezrani C, Blacker N, et al. Anticholinergic and sedative medicines - prescribing considerations for people with dementia. *Aust Fam Physician* 2012;41:45-9.

Beloosesky Y, Nenaydenko O, Gross Nevo RF, Adunsky A, Weiss A. Rates, variability, and associated factors of polypharmacy in nursing home patients. *Clin Interv Aging* 2013;8:1585-90.

Berdot S, Bertrand M, Dartigues JF, et al. Inappropriate medication use and risk of falls--a prospective study in a large community-dwelling elderly cohort. *BMC Geriatr* 2009;9:30.

Bergman A, Olsson J, Carlsten A, Waern M, Fastbom J. Evaluation of the quality of drug therapy among elderly patients in nursing homes. *Scand J Prim Health Care* 2007;25:9-14.

Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* 2008;118:1894-909.

Bjerrum L, Søgaard J, Hallas J, Kragstrup J. Polypharmacy: correlations with sex, age and drug regimen. A prescription database study. *Eur J Clin Pharmacol* 1998;54:197-202.

Bjerrum L, Andersen M, Petersen G, Kragstrup J. Exposure to potential drug interactions in primary health care. *Scand J Prim Health Care* 2003;21:153-8.

Björkman IK, Fastbom J, Schmidt IK, Bernsten CB. Pharmaceutical care of the elderly in Europe research (PEER) group. Drug-drug interactions in the elderly. *Ann Pharmacother* 2002;36:1675-81.

Blanco-Reina E, Ariza-Zafra G, Ocaña-Riola R, León-Ortíz M, Bellido-Estévez I. Optimizing elderly pharmacotherapy: polypharmacy vs. undertreatment. Are these two concepts related? *Eur J Clin Pharmacol* 2015;71:199-207.

Boparai MK, Korc-Grodzicki B. Prescribing for older adults. *Mt Sinai J Med* 2011;78:613-26.

Boudreau DM, Yu O, Gray SL, Raebel MA, Johnson J, Larson EB. Concomitant use of cholinesterase inhibitors and anticholinergics: prevalence and outcomes. *J Am Geriatr Soc* 2011;59:2069-76.

Boustani M, Campbell N, Munger S, Maidment I, Fox C. Impact of anticholinergics on the aging brain: a review and practical application. *Aging Health* 2008; 4: 311-20.

Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA* 2005;294:716-24.

Bronskill SE, Gill SS, Paterson JM, Bell CM, Anderson GM, Rochon PA. Exploring variation in rates of polypharmacy across long term care homes. *J Am Med Dir Assoc* 2012;13:309.e15-21.

Böttiger Y, Laine K, Andersson ML, et al. SFINX-a drug-drug interaction database designed for clinical decision support systems. *Eur J Clin Pharmacol* 2009;65:627-33.

- Caeiro L, Ferro JM, Claro MI, Coelho J, Albuquerque R, Figueira ML. Delirium in acute stroke: a preliminary study of the role of anticholinergic medications. *Eur J Neurol* 2004;11:699-704.
- Campbell N, Perkins A, Hui S, Khan B, Boustani M. Association between prescribing of anticholinergic medications and incident delirium: a cohort study. *J Am Geriatr Soc*. 2011;59 Suppl 2:S277-81.
- Cao YJ, Mager DE, Simonsick EM, et al. Physical and cognitive performance and burden of anticholinergics, sedatives, and ACE inhibitors in older women. *Clin Pharmacol Ther* 2008;83:422-9.
- Carnahan RM, Lund BC, Perry PJ, Chrischilles EA. The concurrent use of anticholinergics and cholinesterase inhibitors: rare event or common practice? *J Am Geriatr Soc* 2004;52:2082-7.
- Carnahan RM, Lund BC, Perry PJ, et al. The Anticholinergic Drug Scale as a measure of drug related anticholinergic burden: associations with serum anticholinergic activity. *J Clin Pharmacol* 2006;46:1481-6.
- Carnasos GJ, Stewart RB. Clinically desirable drug interactions. *Ann Rev Pharmacol Toxicol* 1985;25:67-95.
- Carrière I, Fourrier-Reglat A, Dartigues JF, et al. Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. *Arch Intern Med* 2009;169:1317-24.
- Chan DC, Hao YT, Wu SC. Polypharmacy among disabled Taiwanese elderly: a longitudinal observational study. *Drugs Aging* 2009;26:345-54.
- Chang CB, Chan DC. Comparison of published explicit criteria for potentially inappropriate medications in older adults. *Drugs Aging* 2010;27:947-57.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-83.
- Chatterjee S, Mehta S, Sherer JT, Aparasu RR. Prevalence and predictors of anticholinergic medication use in elderly nursing home residents with dementia: analysis of data from the 2004 National Nursing Home Survey. *Drugs Aging* 2010;27:987-97.
- Chen LL, Tangiisuran B, Shafie AA, Hassali MA. Evaluation of potentially inappropriate medications among older residents of Malaysian nursing homes. *Int J Clin Pharm* 2012;34:596-603.
- Chew ML, Mulsant BH, Pollock BG, et al. Anticholinergic activity of 107 medications commonly used by older adults. *J Am Geriatr Soc* 2008; 56: 1333-41.
- Cho S, Lau SW, Tandon V, Kumi K, Pfuma E, Abernethy DR. Geriatric drug evaluation: where are we now and where should we be in the future? *Arch Intern Med* 2011;171:937-40.

Choudhry MN, Soran H, Ziglam HM. Overuse and inappropriate prescribing of proton pump inhibitors in patients with *Clostridium difficile*-associated disease. *QJM* 2008;101:445-8.

Corley DA, Kubo A, Zhao W, Quesenberry C. Proton pump inhibitors and histamine-2 receptor antagonists are associated with hip fractures among at-risk patients. *Gastroenterology* 2010;139:93-101.

Corsonello A, Pedone C, Incalzi RA. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. *Curr Med Chem* 2010;17:571-84.

Corsonello A, Maggio M, Fusco S, et al. Proton pump inhibitors and functional decline in older adults discharged from acute care hospitals. *J Am Geriatr Soc* 2014;62:1110-5.

Crentsil V, Ricks MO, Xue QL, Fried LP. A pharmacoepidemiologic study of community-dwelling, disabled older women: Factors associated with medication use. *Am J Geriatr Pharmacother* 2010;8:215-24.

Cruciol-Souza JM, Thomson JC. Prevalence of potential drug-drug interactions and its associated factors in a Brazilian teaching hospital. *J Pharm Pharm Sci* 2006;9:427-33.

Cusack BJ. Pharmacokinetics in older persons. *Am J Geriatr Pharmacother* 2004;2:274-302.

Defilippi JL, Crismon ML. Drug interactions with cholinesterase inhibitors. *Drugs Aging* 2003;20:437-44.

Delafuente JC. Understanding and preventing drug interactions in elderly patients. *Crit Rev Oncol Hematol* 2003;48:133-43.

DeMaagd G, Geibig J. An overview of overactive bladder and its pharmacological management with a focus on anticholinergic drugs. *P&T* 2006;31:462-71.

de Souto Barreto P, Lapeyre-Mestre M, Mathieu C, et al. Prevalence and associations of the use of proton-pump inhibitors in nursing homes: a cross-sectional study. *J Am Med Dir Assoc* 2013;14:265-9.

den Elzen WP, Groeneveld Y, de Ruijter W, et al. Long-term use of proton pump inhibitors and vitamin B12 status in elderly individuals. *Aliment Pharmacol Ther* 2008;27:491-7.

Dharmarajan TS, Kanagala MR, Murakonda P, Lebelt AS, Norkus EP. Do acid-lowering agents affect vitamin B12 status in older adults? *J Am Med Dir Assoc* 2008;9:162-7.

Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. *JAMA* 2005;294:2989-95.

Ding J, Heller DA, Ahern FM, Brown TV. The relationship between proton pump inhibitor adherence and fracture risk in the elderly. *Calcif Tissue Int* 2014;94:597-607.

Durán CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. *Eur J Clin Pharmacol* 2013;69:1485-96.

- Ehrt U, Broich K, Larsen JP, Ballard C, Aarsland D. Use of drugs with anticholinergic effect and impact on cognition in Parkinson's disease: a cohort study. *J Neurol Neurosurg Psychiatry* 2010;81:160-5
- Elseviers MM, Vander Stichele RR, Van Bortel L. Drug utilization in Belgian nursing homes: impact of residents' and institutional characteristics. *Pharmacoepidemiol Drug Saf* 2010;19:1041-8.
- Eom CS, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. *CMAJ* 2011;183:310-19.
- Espino DV, Bazaldua OV, Palmer RF, et al. Suboptimal medication use and mortality in an older adult community-based cohort: results from the Hispanic EPESE Study. *J Gerontol A Biol Sci Med Sci* 2006;61:170-5.
- FASS (Pharmaceutical Specialities in Sweden). Stockholm: LINFO Läkemedelsinformation AB (Drug information), 1997. Available from:URL:<http://www.fass.se> (in Swedish).
- Fialova D, Topinkova E, Gambassi G, et al. Potentially inappropriate medication use among elderly home care patients in Europe. *JAMA* 2005;293:1348–58.
- Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Arch Intern Med* 2003; 163:2716–24.
- Filion KB, Chateu D, Targownik LE, et al. Proton pump inhibitors and the risk of hospitalisation for community-acquired pneumonia: replicated cohort studies with meta-analysis. *Gut* 2014;63:552–8.
- Fimea, Kela. Finnish Medicines Agency Fimea and Social Insurance Institution. Finnish Statistics on Medicines 2015 . Erweko Oy. Helsinki 2016
- Finkers F, Maring JG, Boersma F, Taxis K. A study of medication reviews to identify drug-related problems of polypharmacy patients in the Dutch nursing home setting. *J Clin Pharm Ther* 2007;32:469-76.
- Fox C, Richardson K, Maidment ID, et al. Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. *J Am Geriatr Soc* 2011;59:1477-83.
- Fox C, Smith T, Maidment I, et al. Effect of medications with anti-cholinergic properties on cognitive function, delirium, physical function and mortality: a systematic review. *Age Ageing* 2014;43:604-15.
- Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. *J Am Geriatr Soc* 2014;62:2261-72.
- Gagne JJ, Maio V, Rabinowitz C. Prevalence and predictors of potential drug-drug interactions in Regione Emilia-Romagna, Italy. *J Clin Pharm Ther* 2008;33:141-51.

Gallagher PF, Barry PJ, Ryan C, Hartigan I, O'Mahony D. Inappropriate prescribing in an acutely ill population of elderly patients as determined by Beers' Criteria. *Age Ageing* 2008;37:96-101.

Gallagher P, O'Mahony D. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. *Age Ageing* 2008;37:673-9.

Gallagher P, Lang PO, Cherubini A, et al. Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. *Eur J Clin Pharmacol* 2011;67:1175-88.

García-Gollarte F, Baleriola-Júlvez J, Ferrero-López I, Cruz-Jentoft AJ. Inappropriate drug prescription at nursing home admission. *J Am Med Dir Assoc* 2012;13:83.e9-15.

Gaudreau JD, Gagnon P, Harel F, Roy MA, Tremblay A. Psychoactive medications and risk of delirium in hospitalized cancer patients. *J Clin Oncol* 2005;23:6712-8.

Gill SS, Mamdani M, Naglie G, et al. A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. *Arch Int Med* 2005;165:808-13.

Gomm W, von Holt K, Thomé F, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. *JAMA Neurol* 2016;73:410-6.

Gray SL, LaCroix AZ, Larson J, et al. Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative. *Arch Intern Med* 2010;170:765-71.

Guaraldo L, Cano FG, Damasceno GS, Rozenfeld S. Inappropriate medication use among the elderly: a systematic review of administrative databases. *BMC Geriatr* 2011;11:79.

Gubbins PO, Bertch KE. Drug absorption in gastrointestinal disease and surgery. *Clinical pharmacokinetic and therapeutic implications*. *Clin Pharmacokinet*. 1991;21:431-47.

Guigoz Y, Lauque S, Vellas BJ. Identifying the elderly at risk for malnutrition. The Mini Nutritional Assessment. *Clin Geriatr Med* 2002;18:737-57.

Guigoz Y. The Mini Nutritional Assessment (MNA) review of the literature--What does it tell us? *J Nutr Health Aging* 2006;10:466-85.

Haasum Y, Fastbom J, Johnell K. Institutionalization as a risk factor for inappropriate drug use in the elderly: a Swedish nationwide register-based study. *Ann Pharmacother* 2012;46:339-46.

Haenisch B, von Holt K, Wiese B, et al. Risk of dementia in elderly patients with the use of proton pump inhibitors. *Eur Arch Psychiatry Clin Neurosci* 2015;265:419-28.

Haider SI, Johnell K, Thorslund M, Fastbom J. Analysis of the association between polypharmacy and socioeconomic position among elderly aged > or =77 years in Sweden. *Clin Ther* 2008;30:419-27.

- Haider S, Johnell K, Weitoft GR, Thorslund M, Fastbom J. The influence of educational level on polypharmacy and inappropriate drug use: a register-based study of more than 600,000 older people. *J Am Geriatr Soc* 2009;57:62-9.
- Hamzat H, Sun H, Ford JC, Macleod J, Soiza RL, Mangoni AA. Inappropriate prescribing of proton pump inhibitors in older patients: effects of an educational strategy. *Drugs Aging* 2012;29:681-90.
- Han L, Agostini JV, Allore HG. Cumulative anticholinergic exposure is associated with poor memory and executive function in older men. *J Am Geriatr Soc* 2008;56:2203-10.
- Hanlon JT, Horner RD, Schmader KE, et al. Benzodiazepine use and cognitive function among community-dwelling elderly. *Clin Pharmacol Ther* 1998;64:684-92.
- Hanlon JT, Schmader KE. The medication appropriateness index at 20: where it started, where it has been, and where it may be going. *Drugs Aging* 2013;30:893-900.
- Hansen KE, Jones AN, Lindstrom MJ, et al. Do proton pump inhibitors decrease calcium absorption? *J Bone Miner Res* 2010;25:2786-95.
- Hansten PD, Horn JR, Hazlet TK. ORCA: OpeRational ClassificAtion of drug interactions. *J Am Pharm Assoc (Wash)* 2001;4:161-5.
- Hartikainen S, Ahonen J. Iäkkäiden lääkityksen tietokanta tukee lääkevalintoja. *SIC* 2011;1:4-9.
- Heidelbaugh JJ, Inadomi JM. Magnitude and economic impact of inappropriate use of stress ulcer prophylaxis in non-ICU hospitalized patients. *Am J Gastroenterol* 2006;101:2200-5.
- Hess MW, Hoenderop JG, Bindels RJ, Drenth JP. Systematic review: hypomagnesaemia induced by proton pump inhibition. *Aliment Pharmacol Ther* 2012;36:405-13.
- Hilmer SN, Mager DE, Simonsick EM, Cao Y. A drug burden index to define the functional burden of medications in older people. *Arch Intern Med* 2007; 23;167:781-7.
- Horowitz M, O'Donovan D, Jones KI, Feinle C, Rayner CK, Samson M. Gastric emptying in diabetes: clinical significance and treatment. *Diabet Med* 2002;19:177-94.
- Hosia-Randell HM, Muurinen SM, Pitkälä KH. Exposure to potentially inappropriate drugs and drug-drug interactions in elderly nursing home residents in Helsinki, Finland: a cross-sectional study. *Drugs Aging* 2008;25:683-92.
- Hovstadius B, Hovstadius K, Astrand B, Petersson G. Increasing polypharmacy – an individual-based study of the Swedish population 2005-2008. *BMC Clin Pharmacol* 2010;10:16.
- Hubbard RE, O'Mahony MS, Woodhouse KW. Medication prescribing in frail older people. *Eur J Clin Pharmacol* 2013;69:319-26.
- Huey ED, Taylor JL, Luu P, Oehlert J, Tinklenberg JR. Factors associated with use of medications with potential to impair cognition or cholinesterase inhibitors among Alzheimer's disease patients. *Alzheimers Dement* 2006;2:314–21.

Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry* 1982;140:566-72.

Ito T, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B12, iron, and magnesium. *Curr Gastroenterol Rep* 2010;12:448-57.

Iwata M, Kuzuya M, Kitagawa Y, Suzuki Y, Iguchi A. Underappreciated predictors for postdischarge mortality in acute hospitalized oldest-old patients. *Gerontology* 2006;52:92-8.

Janarthanan S, Ditah I, Adler DG, Ehrinpreis MN. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. *Am J Gastroenterol* 2012;107:1001-10.

Jano E, Aparasu RR. Healthcare outcomes associated with beers' criteria: a systematic review. *Ann Pharmacother* 2007;41:438-47.

Jekkonen T, Muurinen S, Soini H, Suominen M, Suur-Uski I, Pitkälä K. Helsinkiläisten iäkkäiden palveluasumisen asukkaiden ravitsemustila 2007. Helsingin kaupungin sosiaaliviraston tutkimuksia. 2008:2.

Johnell K, Klarin I. The relationship between number of drugs and potential drug-drug interactions in the elderly: a study of over 600,000 elderly patients from the Swedish Prescribed Drug Register. *Drug Saf* 2007;30:911-8.

Johnell K, Fastbom J. Concurrent use of anticholinergic drugs and cholinesterase inhibitors: register-based study of over 700,000 elderly patients. *Drugs Aging* 2008;25:871-7.

Jokinen T, Vanakoski J, Skippari L, Iso-Aho M, Simoila R. Iäkkäiden potilaiden kokonaislääkitystä on syytä arvioida säännöllisesti kotihoidossa. *Suom Lääkäril* 2009;19:1772-6.

Juurink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA* 2003;289:1652-8.

Jyrkkä J, Vartiainen L, Hartikainen S, Sulkava R, Enlund H. Increasing use of medicines in elderly persons: a five-year follow-up of the Kuopio 75+ Study. *Eur J Clin Pharmacol* 2006;62:151-8.

Jyrkkä J, Enlund H, Korhonen MJ, Sulkava R, Hartikainen S. Polypharmacy status as an indicator of mortality in an elderly population. *Drugs Aging* 2009;26:1039-48.

Jyrkkä J, Enlund H, Lavikainen P, Sulkava R, Hartikainen S. Association of polypharmacy with nutritional status, functional ability and cognitive capacity over a three-year period in an elderly population. *Pharmacoepidemiol Drug Saf* 2011;20:514-22.

Kaufmann CP, Tremp R, Hersberger KE, Lampert ML. Inappropriate prescribing: a systematic overview of published assessment tools. *Eur J Clin Pharmacol* 2014;70:1-11.

Kay GG, Abou-Donia MB, Messer WS Jr, Murphy DG, Tsao JW. Antimuscarinic drugs for overactive bladder and their potential effects on cognitive function in older patients. *J Am Geriatr Soc* 2005;53:2195-201.

Kersten H, Molden E, Tolo IK, Skovlund E, Engedal K, Wyller TB. Cognitive effects of reducing anticholinergic drug burden in a frail elderly population: a randomized controlled trial. *J Gerontol A Biol Sci Med Sci* 2013a;68:271-8.

Kersten H, Molden E, Willumsen T, Engedal K, Bruun Wyller T. Higher anticholinergic drug scale (ADS) scores are associated with peripheral but not cognitive markers of cholinergic blockade. Cross sectional data from 21 Norwegian nursing homes. *Br J Clin Pharmacol* 2013b;75:842-9.

Khalil H. Diabetes microvascular complications – A clinical update. *Diabetes Metab Syndr*. 2016; Dec 13. pii: S1871-4021(16)30264-8. [Epub ahead of print]

Kidd AC, Musonda P, Soiza RL et al: The relationship between total anticholinergic burden (ACB) and early in-patient hospital mortality and length of stay in the oldest old aged 90 years and over admitted with an acute illness. *Arch Gerontol Geriatr* 2014;59:155-61.

Klotz U. Pharmacokinetic considerations in the eradication of *Helicobacter pylori*. *Clin Pharmacokinet* 2000;38:243-70.

Kolanowski A, Fick DM, Campbell J, Litaker M, Boustani M. A preliminary study of anticholinergic burden and relationship to a quality of life indicator, engagement in activities, in nursing home residents with dementia. *J Am Med Dir Assoc* 2009;10:252-7.

Kouladjian L, Gnjjidic D, Chen TF, Hilmer SN. Development, validation and evaluation of an electronic pharmacological tool: The Drug Burden Index Calculator©. *Res Social Adm Pharm* 2016;12:865-75.

Kumpula EK, Bell JS, Soini H, Pitkälä KH. Anticholinergic drug use and mortality among residents of long-term care facilities: a prospective cohort study. *J Clin Pharmacol* 2011;51:256-63.

Kwok CS, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, Loke YK. Risk of *Clostridium difficile* infection with acid suppressing drugs and antibiotics: meta-analysis. *Am J Gastroenterol* 2012;107:1011–9.

Laffan AM, Bellantoni MF, Greenough WB 3rd, Zenilman JM. Burden of *Clostridium difficile*-associated diarrhea in a long-term care facility. *J Am Geriatr Soc* 2006;54:1068-73.

Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004;292:1955-60.

Lampela P, Lavikainen P, Garcia-Horsman JA, Bell JS, Huupponen R, Hartikainen S. Anticholinergic drug use, serum anticholinergic activity, and adverse drug events among older people: a population-based study. *Drugs Aging* 2013;30:321-30.

Lampela P. Improving pharmacotherapy in older people, a clinical approach. Dissertation in Health Sciences. University of Eastern Finland, 2013. http://publications.uef.fi/pub/urn_isbn_978-952-61-1124-7/urn_isbn_978-952-61-1124-7.pdf, accessed 27th August 2016.

Landi F, Russo A, Liperoti R, et al. Anticholinergic drugs and physical function among frail elderly population. *Clin Pharmacol Ther* 2007;81:235-41.

Landi F, Dell'Aquila G, Collamati A, et al. Anticholinergic drug use and negative outcomes among the frail elderly population living in a nursing home. *J Am Med Dir Assoc* 2014;15:825-9.

Langdorf M, Fox JC, Marwah RS, Montague BJ, Hart MM. Physician versus computer knowledge of potential drug interactions in the emergency department. *Acad Emerg Med* 2000;7:1321-9.

Laroche ML, Charmes JP, Merle L. Potentially inappropriate medications in the elderly: a French consensus panel list. *Eur J Clin Pharmacol* 2007;63:725-31.

Larsen PD, Martin JL. Polypharmacy and elderly patients. *AORN J* 1999;69:619-22, 625, 627-8.

Lau DT, Kasper JD, Potter DE, Lyles A, Bennett RG. Hospitalization and death associated with potentially inappropriate medication prescriptions among elderly nursing home residents. *Arch Intern Med* 2005;165:68-74.

Lau DT, Mercaldo ND, Harris AT, Trittschuh E, Shega J, Weintraub S. Polypharmacy and potentially inappropriate medication use among community-dwelling elders with dementia. *Alzheimer Dis Assoc Disord* 2010;24:56-63.

Leaderbrand K, Chen HJ, Corcoran KA, Guedea AL, Jovasevic V, Wess J, Radulovic J. Muscarinic acetylcholine receptors act in synergy to facilitate learning and memory. *Learn Mem* 2016;23:631-8.

Lechevallier-Michel N, Molimard M, Dartigues JF, Fabrigoule C, Fourier-Réglat A. Drugs with anticholinergic properties and cognitive performance in the elderly: results from the PAQUID Study. *Br J Clin Pharmacol* 2005;59:143-51.

Leikola S, Dimitrow M, Lyles A, Pitkälä K, Airaksinen M. Potentially inappropriate medication use among Finnish non-institutionalized people aged ≥ 65 years: a register-based, cross-sectional, national study. *Drugs Aging* 2011;28:227-36.

Leonard J, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. *Am J Gastroenterol* 2007;102:2047-56.

Liao HL, Chen JT, Ma TC, Chang YS. Analysis of drug-drug interactions (DDIs) in nursing homes in Central Taiwan. *Arch Gerontol Geriatr* 2008;47:99-107.

Lieberman JA 3rd. Managing anticholinergic side effects. *Prim Care Companion J Clin Psychiatry* 2004;6:20-3.

Lin CF, Wang CY, Bai CH. Polypharmacy, aging and potential drug-drug interactions in outpatients in Taiwan: a retrospective computerized screening study. *Drugs Aging* 2011;28:219-25.

Lindblad CI, Artz MB, Pieper CF, et al. Potential drug-disease interactions in frail, hospitalized elderly veterans. *Ann Pharmacother* 2005;39:412-7.

- Linsky A, Gupta K, Lawler EV, Fonda JR, Hermos JA. Proton pump inhibitors and risk for recurrent *Clostridium difficile* infection. *Arch Intern Med* 2010;170:772-8.
- Lowry E, Woodman RJ, Soiza RL, Mangoni AA. Associations between the anticholinergic risk scale score and physical function: potential implications for adverse outcomes in older hospitalized patients. *J Am Med Dir Assoc* 2011;12:565-72.
- Luukkanen MJ, Uusvaara J, Laurila JV, et al. Anticholinergic drugs and their effects on delirium and mortality in the elderly. *Dement Geriatr Cogn Dis Extra* 2011;1:43-50.
- Lönroos E, Gnjjidic D, Hilmer SN, et al. Drug Burden Index and hospitalization among community-dwelling older people. *Drugs Aging* 2012;29:395-404.
- Löppönen M, Rähä I, Isoaho R, Vahlberg T, Puolijoki H, Kivelä SL. Dementia associates with undermedication of cardiovascular diseases in the elderly: a population-based study. *Dement Geriatr Cogn Disord* 2006;22:132-41.
- Maggio M, Corsonello A, Ceda , et al. Proton pump inhibitors and risk of 1-year mortality and rehospitalization in older patients discharged from acute care hospitals. *JAMA Intern Med* 2013a;173:518-23.
- Maggio M, Lauretani F, Ceda GP, et al. Use of proton pump inhibitors is associated with lower trabecular bone density in older individuals. *Bone* 2013b;57:437-42.
- Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf* 2014;13:57-65.
- Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. *Lancet* 2007;370:185-91.
- Malone DC, Hutchins DS, Hauptert H, et al. Assessment of potential drug-drug interactions with a prescription claims database. *Am J Health Syst Pharm* 2005;62:1983-91.
- Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004;57:6-14.
- Mangoni AA, van Munster BC, Woodman RJ, de Rooij SE. Measures of anticholinergic drug exposure, serum anticholinergic activity, and all-cause postdischarge mortality in older hospitalized patients with hip fractures. *Am J Geriatr Psychiatry* 2013;21:785-93.
- Masclee GM, Sturkenboom MC, Kuipers EJ. A benefit-risk assessment of the use of proton pump inhibitors in the elderly. *Drugs Aging* 2014;31:263-82.

Masoudi FA, Baillie CA, Wang Y, et al. The complexity and cost of drug regimens of older patients hospitalized with heart failure in the United States, 1998-2001. *Arch Intern Med* 2005;165:2069-76.

McDonald EG, Milligan J, Frenette C, Lee TC. Continuous proton pump inhibitor therapy and the associated risk of recurrent *Clostridium difficile* infection. *JAMA Intern Med* 2015;175:784-91.

McLeod PJ, Huang AR, Tamblyn RM, Gayton DC. Defining inappropriate practices in prescribing for elderly people: a national consensus panel. *CMAJ* 1997;156:385-91.

Miu DK, Lau S, Szeto SS. Etiology and predictors of urinary incontinence and its effect on quality of life. *Geriatr Gerontol Int* 2010;10:177-82.

Moayyedi P, Cranney A. Hip fracture and proton pump inhibitor therapy: balancing the evidence for benefit and harm. *Am J Gastroenterol* 2008;103:2428-31.

Modi A, Weiner M, Craig BA, Sands LP, Rosenman MB, Thomas J 3rd. Concomitant use of anticholinergics with acetylcholinesterase inhibitors in Medicaid recipients with dementia and residing in nursing homes. *J Am Geriatr Soc* 2009;57:1238-44.

Morin L, Fastbom J, Laroche ML, Johnell K. Potentially inappropriate drug use in older people: a nationwide comparison of different explicit criteria for population-based estimates. *Br J Clin Pharmacol* 2015;80:315-24.

Moura CS, Acurcio FA, Belo NO. Drug-drug interactions associated with length of stay and cost of hospitalization. *J Pharm Pharm Sci* 2009;12:266-72.

Muurinen S. Hoitotyö ja hoitohenkilöstön rakenne vanhusten lyhytaikaisessa laitoshoidossa. Akateeminen väitöskirja, Tampereen yliopisto, 6.6.2003.

Narbey D, Jolly D, Mahmoudi R, et al. Relationship between anticholinergic drug use and one-year outcome among elderly people hospitalised in medical wards via emergency department: the SAFES cohort study. *J Nutr Health Aging* 2013; 17:766-71.

Ngamruengphong S, Leontiadis GI, Radhi S, Dentino A, Nugent K. Proton pump inhibitors and risk of fracture: a systematic review and meta-analysis of observational studies. *Am J Gastroenterol* 2011;106:1209-18.

Nguien L, Hur C. Proton Pump Inhibitors and Dementia Incidence. *JAMA Neurol* 2016; 73:1027-8.

NICE. National Institute for Health and Care Excellence. Dyspepsia and gastro-oesophageal reflux disease. Investigation and management of dyspepsia, symptoms suggestive of gastro-oesophageal reflux disease, or both. Issued September 2014 last modified November 2014.

<https://www.nice.org.uk/guidance/cg184/resources/gastrooesophageal-reflux-disease-and-dyspepsia-in-adults-investigation-and-management-35109812699845>. Accessed 28th August, 2016.

Nobili A, Pasina L, Tettamanti M, et al. Potentially severe drug interactions in elderly outpatients: results of an observational study of an administrative prescription database. *J Clin Pharm Ther* 2009;34:377-86.

- Nordberg A, Svensson AL. Cholinesterase inhibitors in the treatment of Alzheimer's disease: a comparison of tolerability and pharmacology. *Drug Saf* 1998;19:465-80.
- O'Connor MN, Gallagher P, O'Mahony D. Inappropriate prescribing: criteria, detection and prevention. *Drugs Aging* 2012;29:437-52.
- Olsson J, Bergman A, Carlsten A et al. Quality of drug prescribing in elderly people in nursing homes and special care units for dementia: a cross-sectional computerized pharmacy register analysis. *Clin Drug Investig* 2010;30:289-300.
- O'Mahony D, Gallagher PF. Inappropriate prescribing in the older population: need for new criteria. *Age Ageing* 2008;37:138-41.
- O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015;44:213-8
- Onder G, Liperoti R, Fialova D, et al. SHELTER Project. Polypharmacy in nursing home in Europe: results from the SHELTER study. *J Gerontol A Biol Sci Med Sci* 2012;67:698-704.
- Onder G, Marengoni A, Russo, et al. Geriatrics Working Group of the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA); Medicines Utilization Monitoring Center Health Database Network. Advanced age and medication prescription: more years, less medications? A nationwide report from the Italian medicines agency. *J Am Med Dir Assoc* 2016;17:168-72.
- Palmer JB, Albrecht JS, Park Y, et al. Use of drugs with anticholinergic properties among nursing home residents with dementia: a national analysis of Medicare beneficiaries from 2007 to 2008. *Drugs Aging* 2015;32:79-86.
- Pandharipande P, Shintani A, Peterson J et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006;104:21-6.
- Panula J, Puustinen J, Jaatinen P, Vahlberg T, Kivela SL. Effects of potent anticholinergics, sedatives and antipsychotics on postoperative mortality in elderly patients with hip fracture: a retrospective, population-based study. *Drugs Aging* 2009;26:963-71.
- Patterson Burdsall D, Flores HC, Krueger J, et al. Use of proton pump inhibitors with lack of diagnostic indications in 22 Midwestern US skilled nursing facilities. *J Am Med Dir Assoc* 2013;14:429-32.
- Pham CQ, Regal RE, Bostwick TR, Knauf KS. Acid suppressive therapy use on an inpatient internal medicine service. *Ann Pharmacother* 2006;40:1261-6.
- Pilotto A, Franceschi M, Leandro G, et al. Proton-pump inhibitors reduce the risk of uncomplicated peptic ulcer in elderly either acute or chronic users of aspirin/non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther* 2004;20:1091-7.
- Pitkälä KH, Strandberg TE, Tilvis RS. Inappropriate drug prescribing in home-dwelling, elderly patients: a population-based survey. *Arch Intern Med* 2002;162:1707-12.

Pitkälä KH, Laakkonen ML, Strandberg TE, Tilvis RS. Positive life orientation as a predictor of 10-year outcome in aged population. *J Clin Epidemiol* 2004;57, 409-14.

Pitkälä KH, Laurila JV, Strandberg TE, Tilvis RS. Prognostic significance of delirium in frail older people. *Dement Geriatr Cogn Disord* 2005;19:158-63.

Pitkälä KH, Juola AL, Kautiainen H, et al. Education to reduce potentially harmful medication use among residents of assisted living facilities: a randomized controlled trial. *J Am Med Dir Assoc* 2014;15:892-8.

Pitkälä KH, Juola AL, Hosia-Randell H, et al. Eight-year trends in the use of opioids, other analgesics, and psychotropic medications among institutionalized older people in Finland. *J Am Med Dir Assoc* 2015;16:973-8.

Pylkkänen S. Potentiaalisesti haitallisten lääkkeiden kasautuminen ympärivuorokautisessa hoidossa olevilla iäkkäillä Helsingissä ja Kouvolassa. Pro gradu tutkielma. Farmasian tiedekunta, Sosiaalfarmasian osasto, Helsingin yliopisto. Marraskuu 2013.

Raivio MM, Laurila JV, Strandberg TE, Tilvis RS, Pitkälä KH. Use of inappropriate medications and their prognostic significance among in-hospital and nursing home patients with and without dementia in Finland. *Drugs Aging* 2006;23:333-43.

Ramage-Morin PL. Medication use among senior Canadians. *Health Rep* 2009;20:37-44.

Rancourt C, Moisan J, Baillargeon L, Verreault R, Laurin D, Grégoire JP. Potentially inappropriate prescriptions for older patients in long-term care. *BMC Geriatr* 2004;4:9.

Resnick NM. Urinary incontinence. *Lancet* 1995;346:94-9.

Robinson M, Horn J. Clinical pharmacology of proton pump inhibitors: what the practising physician needs to know. *Drugs* 2003;63:2739-54.

Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. *BMJ* 1997;315:1096-9.

Roe CM, Anderson MJ, Spivack B. Use of anticholinergic medications by older adults with dementia. *J Am Geriatr Soc* 2002;50:836-42.

Rognstad S, Brekke M, Fetveit A, Spigset O, Wyller TB, Straand J. The Norwegian General Practice (NORGE) criteria for assessing potentially inappropriate prescriptions to elderly patients. A modified Delphi study. *Scand J Prim Health Care* 2009;27:153-9.

Routasalo PE, Tilvis RS, Kautiainen H, Pitkälä KH. Effects of psychosocial group rehabilitation on social functioning, loneliness and well-being of lonely, older people: randomized controlled trial. *J Adv Nurs* 2009;65:297-305.

Roux C, Briot K, Gossec L, et al. Increase in vertebral fracture risk in postmenopausal women using omeprazole. *Calcif Tissue Int* 2009;84:13-9.

- Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. *Arch Intern Med* 2008;168:508-13.
- Ruggiero C, Dell'Aquila G, Gasperini B, et al. Potentially inappropriate drug prescriptions and risk of hospitalization among older, Italian, nursing home residents: the ULISSE project. *Drugs Aging* 2010;27:747-58.
- Ruiz B, García M, Aguirre U, Aguirre C. Factors predicting hospital readmissions related to adverse drug reactions. *Eur J Clin Pharmacol* 2008;64:715-22.
- Rummukainen ML, Jakobsson A, Matsinen M et al. Reduction in inappropriate prevention of urinary tract infections in long-term care facilities. *Am J Infect Control* 2012;40:711-4.
- Ruxton K, Woodman RJ, Mangoni AA. Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: A systematic review and meta-analysis. *Br J Clin Pharmacol* 2015;80:209-20.
- Sagar M, Janczewska I, Ljungdahl A, Bertilsson L, Seensalu R. Effect of CYP2C19 polymorphism on serum levels of vitamin B12 in patients on long-term omeprazole treatment. *Aliment Pharmacol Ther* 1999;13:453-8.
- Salahudeen MS, Duffull SB, Nishtala PS. Impact of anticholinergic discontinuation on cognitive outcomes in older people: a systematic review. *Drugs Aging*. 2014;31:185-92.
- Salahudeen MS, Hilmer SN, Nishtala PS. Comparison of anticholinergic risk scales and associations with adverse health outcomes in older people. *J Am Geriatr Soc* 2015a;63:83-90.
- Salahudeen MS, Hilmer SN, Nishtala PS. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. *BMC Geriatr* 2015b;15:31.
- Salahudeen MS, Chyou TY, Nsihtala PS. Serum anticholinergic activity and cognitive and functional adverse outcome in older people: a systematic review and meta-analysis of the literature. *PLoS One* 2016;11:e0151084.
- Saltzman JR, Russell RM. The aging gut. Nutritional issues. *Gastroenterol Clin North Am* 1998;27:309-24.
- Samuels L. Pharmacotherapy update: hyoscine butyrbromide in the treatment of abdominal spasms. *Clinical Medicine: Therapeutics* 2009:1647-655.
- Sarkar M, Hennessy S, Yang YX. Proton-pump inhibitor use and the risk for community-acquired pneumonia. *Ann Intern Med* 2008;149:391-8.
- Secoli SR, Figueras A, Lebrão ML, de Lima FD, Santos JL. Risk of potential drug-drug interactions among Brazilian elderly: a population-based, cross-sectional study. *Drugs Aging* 2010;27:759-70.

Sergi G, De Rui M, Sarti S, Manzato E. Polypharmacy in the elderly: can comprehensive geriatric assessment reduce inappropriate medication use? *Drugs Aging* 2011;28:509-18.

Seymour RM, Routledge PA. Important drug-drug interactions in the elderly. *Drugs Aging* 1998;12:485-94.

SFINX. Swedish, Finnish, INteraction X-referencing. Kustannus Oy Duodecim. 2015. In: <http://www.terveysportti.fi/libproxy.helsinki.fi/terveysportti/sfinx.koti>. Accessed Sept 2nd, 2016.

Simor AE, Bradley SF, Strausbaugh LJ, Crossley K, Nicolle LE; SHEA Long-Term-Care Committee. Clostridium difficile in long-term-care facilities for the elderly. *Infect Control Hosp Epidemiol* 2002;23:696-703.

Sink KM, Thomas J 3rd, Xu H, Craig B, Kritchevsky S, Sands LP. Dual use of bladder anticholinergics and cholinesterase inhibitors: long-term functional and cognitive outcomes. *J Am Geriatr Soc* 2008;56:847-53.

Sittironnarit G, Ames D, Bush AI et al. Effects of anticholinergic drugs on cognitive function in older Australians: results from the AIBL study. *Dement Geriatr Cogn Disord* 2011;31:173-8

Socialstyrelsen. Indikatorer för god läkemedelsterapi hos äldre, 2010. In: <http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/18085/2010-6-29.pdf>. Accessed 27th August, 2016.

Socialstyrelsen. Äldre med regelbunden medicinering -antalet läkemedel som riskmarkör. 2012. Artikelnummer 2012-6-18. In: <http://www.socialstyrelsen.se/publikationer2012/2012-6-18>. Accessed 2nd September, 2016.

Soini H, Juntunen S, Routasalo P, et al. Pitkäaikaispotilaiden ravitsemustila. Helsingin kaupungin terveystieteiden tutkimuksia 2004:1. Sosiaali- ja terveydenhuollon tietopalvelu. Helsingin kaupunki. 2004.

Song H, Zhu J, Lu D. Long-term proton pump inhibitor (PPI) use and the development of gastric pre-malignant lesions. *Cochrane Database Syst Rev* 2014 Dec 2;12:CD010623.

Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet* 2007;370:173-84.

Stabler SP. Clinical practice. Vitamin B12 deficiency. *N Engl J Med* 2013;368:149-60.

Stafford AC, Alswayan MS, Tenni PC. Inappropriate prescribing in older residents of Australian care homes. *J Clin Pharm Ther* 2011;36:33-44.

Stein J, Stier C, Raab H, Weiner R. Review article: The nutritional and pharmacological consequences of obesity surgery. *Aliment Pharmacol Ther* 2014;40:582-609.

Targownik LE, Lix LM, Metge CJ, Prior HJ, Leung S, Leslie WD. Use of proton pump inhibitors and risk of osteoporosis-related fractures. *CMAJ* 2008;179:319-26.

- Teixeira JJ, Crozatti MT, dos Santos CA, Romano-Lieber NS. Potential drug-drug interactions in prescriptions to patients over 45 years of age in primary care, southern Brazil. *PLoS One* 2012;7:e47062.
- Tjia J, Rothman MR, Kiely DK, et al. Daily medication use in nursing home residents with advanced dementia. *J Am Geriatr Soc* 2010;58:880-8.
- Trautinger F. Mechanisms of photodamage of the skin and its functional consequences for skin ageing. *Clin Exp Dermatol.* 2001;26:573-7.
- Tune L, Carr S, Hoag E, Cooper T. Anticholinergic effects of drugs commonly prescribed for the elderly: potential means for assessing risk of delirium. *Am J Psychiatry* 1992;149:1393-4.
- Tune LE. Anticholinergic effects of medication in elderly patients. *J Clin Psychiatry* 2001;62 (Suppl 21):11-14.
- Turnheim K. Drug therapy in the elderly. *Exp Gerontol* 2004;39:1731-8.
- Uusvaara J, Pitkälä KH, Tienari PJ, Kautiainen H, Tilvis RS, Strandberg TE. Association between anticholinergic drugs and apolipoprotein E epsilon4 allele and poorer cognitive function in older cardiovascular patients: a cross-sectional study. *J Am Geriatr Soc* 2009;57:427-31
- Uusvaara J, Pitkälä KH, Kautiainen H, Tilvis RS, Strandberg TE. Association of anticholinergic drugs with hospitalization and mortality among older cardiovascular patients: A prospective study. *Drugs Aging* 2011;28:131-8.
- Uusvaara J, Pitkälä KH, Kautiainen H, Tilvis RS, Strandberg TE. Detailed cognitive function and use of drugs with anticholinergic properties in older people: a community-based cross-sectional study. *Drugs Aging* 2013;30:177-82.
- Uusvaara J. Adverse events among older people associated with use of drugs with anticholinergic properties. Academic dissertation. University of Helsinki, 2013.
- Valuck RJ, Ruscin JM. A case-control study on adverse effects: H2 blocker or proton pump inhibitor use and risk of vitamin B12 deficiency in older adults. *J Clin Epidemiol* 2004;57:422-8.
- Vetrano DL, Tosato M, Colloca G, et al. Polypharmacy in nursing home residents with severe cognitive impairment: results from the SHELTER Study. *Alzheimers Dement* 2013;9:587-93.
- Vieira de Lima TJ, Garbin CA, Garbin AJ, Sumida DH, Saliba O. Potentially inappropriate medication used by the elderly: prevalence and risk factors in Brazilian care homes. *BMC Geriatr* 2013;13:52.
- Viipuri L. Antikolinergisten lääkkeiden käyttöön liittyvät tekijät helsinkiläisillä ympärivuorokautisen hoidon asiakkailta. Tutkielma. Helsingin Yliopisto, Yleislääketieteen osasto. 16.10.2016
- Viktik KK, Blix HS, Moger TA, Reikvam A. Polypharmacy as commonly defined is an indicator of limited value in the assessment of drug-related problems. *Br J Clin Pharmacol* 2007;63:187-95.

Wawruch M, Macugova A, Kostkova L, et al. The use of medications with anticholinergic properties and risk factors for their use in hospitalised elderly patients. *Pharmacoepidemiol Drug Saf* 2012;21:170-6.

Weiss N, Miller F, Cazaubon S, Couraud PO. The blood-brain barrier in brain homeostasis and neurological diseases. *Biochim Biophys Acta* 2009;1788:842-57.

WHO. World Health Organization. *Drugs for the Elderly*. WHO Regional Publications, European Series, No. 71, 2nd edition. Ed. Offerhaus L, WHO Regional Office for Europe, Copenhagen 1997.

WHO. WHOQOL – BREF introduction, administration, scoring and generic version of the assessment. Field Trial Version December 1996. In *Quality of Life Research. A Critical Introduction*. Ed. Rapley M. Sage Publications, London 2003, pp. 229–248.

WHO Collaborating Centre for Drug Statistics Methodology. *The Anatomical Therapeutic Chemical Classification System*. WHO Collaborating Centre for Drug Statistics Methodology. Norwegian Institute of Public Health. http://www.whocc.no/atc_ddd_index/. Accessed Aug 21st, 2016.

Williams C, McColl KE. Review article: proton pump inhibitors and bacterial overgrowth. *Aliment Pharmacol Ther* 2006;23:3-10.

Wilson N, Gnjidic D, March L et al. Use of PPIs are not associated with mortality in institutionalized older people. *Arch Intern Med* 2011;171:866.

Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. *Gastroenterology* 2000;118:9-31.

Wurtz M, Grove EL, Kristensen SD, Hvas AM. The antiplatelet effect of aspirin is reduced by proton pump inhibitors in patients with coronary artery disease. *Heart* 2010;96:368–71.

Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006;296:2947-53.

Yang YX, Hennessy S, Probert K, Hwang WT, Sedarat A, Lewis JD. Chronic proton pump inhibitor therapy and the risk of colorectal cancer. *Gastroenterology* 2007;133:748-54.

Yearsley KA, Gilby LJ, Ramadas AV, Kubiak EM, Fone DL, Allison MC. Proton pump inhibitor therapy is a risk factor for *Clostridium difficile*-associated diarrhoea. *Aliment Pharmacol Ther* 2006;24:613-9.

Zarowitz BJ, Allen C, O'Shea T, Strauss ME. Risk factors, clinical characteristics, and treatment differences between residents with and without nursing home- and non-nursing home-acquired *Clostridium difficile* infection. *J Manag Care Spec Pharm* 2015;21:585-95.

Zhan C, Sangl J, Bierman AS, et al. Potentially inappropriate medication use in the community-dwelling elderly: findings from the 1996 Medical Expenditure Panel Survey. *JAMA* 2001;286:2823-9.

Zhan C, Correa-de-Araujo R, Bierman AS, et al. Suboptimal prescribing in elderly outpatients: potentially harmful drug-drug and drug-disease combinations. *J Am Geriatr Soc* 2005;53:262-7.

11. Appendices

Appendix 1. ASUKKAAN RAVITSEMUSTILAN ARVIOINNIN TUTKIMUSLOMAKE

Kirjaa tiedot asianomaiseen kohtaan tai merkitse rasti

Lomakkeen täyttöpäivämäärä: _____

Asukkaan sukunimi, etunimi _____

Asukkaan sosiaaliturvatunnus _____

Talon nimi: _____

Talon tutkimusnumero (ohjeesta): _____

Ryhmäkodin/osaston nimi: _____

Ryhmäkodin/osaston tutkimusnumero (ohjeesta): _____

Asukas on pitkäaikaisasukas ___ tai arviointi- ja kuntoutusjakson asiakas ___ (rasti oikeaan kohtaan)

Asukas asuu (merkitse rasti)

- 1 Yhden hengen huoneessa osastolla/ryhmäkodissa
- 2 Kahden hengen huoneessa osastolla/ryhmäkodissa
- 3 Useamman hengen huoneessa osastolla/ryhmäkodissa
- 4 Yksin erillisessä palvelutaloasunnossa
- 5 Erillisessä palvelutaloasunnossa toisen henkilön kanssa
- 6 Muu asumismuoto tai huonejärjestely, mikä? _____

Asukkaan pituus _____ cm (katso ohje MNA-testin käyttöoppaasta kysymys 6.)

Paino nyt (kk sisällä punnittu) _____ kg

Paino keväällä 2011 (noin 6 kk aiemmin) _____ kg Tietoa ei ole ___ (laita rasti).

Kauanko hoitajakso on kestänyt tässä ryhmäkodissa/osastolla/palveluasunnossa?

___ vuotta ___ kuukautta _____ päivää

Seuraavissa kysymyksissä ympyröi yksi vastausvaihtoehdoista ja kirjaa ympyröimäsi numero kysymyksen oikealla puolella olevaan ruutuun.

MNA SEULONTA

1. Onko ravinnonsaanti vähentynyt viimeisen kolmen kuukauden aikana ruokahaluttomuuden, ruoansulatusongelmien, puremis- tai nielemisvaikeuksien takia?

0 = Kyllä, ravinnonsaanti on vähentynyt huomattavasti

1 = Kyllä, ravinnonsaanti on vähentynyt hieman

2 = Ei muutoksia

3 =

2. Painonpudotus kolmen viime kuukauden aikana?
 0 = Painonpudotus yli 3 kg
 1 = Ei tiedä
 2 = Painonpudotus 1-3 kg
 3 = Ei painonpudotusta
3. Liikkuminen?
 0 = Vuode- tai pyörätuolipotilas
 1 = Pääsee ylös sängystä, mutta ei käy ulkona
 2 = Liikkuu ulkona
4. Onko viimeisen kolmen kuukauden aikana ollut psyykkistä stressiä tai akuutti sairaus?
 0 = Kyllä
 1 = Ei
5. Neuropsykologiset ongelmat?
 0 = Dementia tai masennus
 1 = Lievä dementia, depressio tai neuropsykologinen ongelma
 2 = Ei ongelmia
6. Painoindeksi eli BMI (=paino / (pituus)² kg/m²)
 0 = BMI on alle 19
 1 = BMI on 19 tai yli, mutta alle 21
 2 = BMI on 21 tai yli, mutta alle 23
 3 = BMI on 23 tai enemmän

Pisteet yhteensä (kohdat 1-6)

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MNA ARVIOINTI

7. Asuuko haastateltava kotona (**kaikille vastataan 0 = Ei**)
 1 = Kyllä
 0 = Ei
8. Onko päivittäisessä käytössä enemmän kuin 3 reseptilääkettä?
 0 = Kyllä
 1 = Ei
9. Painehaavaumia tai muita haavoja iholla?
 0 = Kyllä
 1 = Ei
10. Päivittaiset lämpimät ateriat (sisältää puurot ja vellit)?
 0 = 1 ateria
 1 = 2 ateraa
 2 = 3 ateraa
11. Sisältääkö ruokavalio vähintään
- | | <u>Ei</u> | <u>Kyllä</u> |
|--|-----------|--------------|
| • Yhden annoksen maitovalmisteita (maito, juusto, piimä, viili) | _____ | _____ |
| • Kaksi annosta tai enemmän kananmunia viikossa (myös ruuissa, esim. laatikot) | _____ | _____ |

- Lihaa, kalaa tai linnun lihaa joka päivä _____
- 0.0 = Jos 0 tai 1 kyllä -vastausta
- 0.5 = Jos 2 kyllä -vastausta
- 1.0 = Jos 3 kyllä -vastausta

12. Kuuluuko päivittäiseen ruokavalioon kaksi tai useampia annoksia hedelmiä tai kasviksia?

- 0 = Ei
- 1 = Kyllä

13. Päivittäinen nesteen juonti?

- 0 = Alle 3 lasillista
- 0.5 = 3-5 lasillista
- 1 = Enemmän kuin 5 lasillista

14. Ruokailu

- 0 = Tarvitsee paljon apua tai on syötettävä
- 1 = Syö itse, mutta tarvitsee hieman apua
- 2 = Syö itse ongelmitta

15. Oma näkemys ravitsemustilasta

- 0 = Vaikea virhe- tai aliravitseminen
- 1 = Ei tiedä tai lievä virhe- tai aliravitseminen
- 2 = Ei ravitsemuksellisia ongelmia

16. Oma näkemys terveydentilasta verrattuna muihin samanikäisiin

- 0 = Ei yhtä hyvä
- 0.5 = Ei tiedä
- 1 = Yhtä hyvä
- 2 = Parempi

17. Olkavarren keskikohdan ympärysmitta (OVY cm)

- 0 = OVY on alle 21 cm
- 0.5 = OVY on 21-22 cm
- 1.0 = OVY on yli 22 cm

18. Pohkeen ympärysmitta (PYM cm)

- 1 = PYM on alle 31 cm
- 2 = PYM on 31 cm tai enemmän

Pisteet yhteensä (kohdat 7-18)

Pisteet yhteensä (kohdat 1-6)

MNA Kokonaispistemäärä

ASUKKAAN TAUSTATIEDOT

Kysymyksen vastausvaihtoehdoista ympäröidään sopivin numero (vain yksi) tai kirjoitetaan puuttuva tieto.

19. Ikä: _____ vuotta

20. Sukupuoli?

1 = Nainen

2 = Mies

21. Siviilisääty?

1 = Naimaton

2 = Leski

3 = Eronnut

4 = Avio- tai avoliitossa

22. Koulutus?

1 = Kansakoulu tai vähemmän

2 = Keskikoulu, ammattikoulu, lukio, muu ammattitutkinto

3 = Korkeakoulu

23. Syökö asukas yleensä pääateriansa yksin

1 = Ei

2 = Kyllä

24. Missä asukas syö yleensä pääaterian/pääateriat

1 = Talon ruokasalissa

2 = Ryhmäkodin ruokasalissa

3 = Ruoka viedään palvelutalossa asukkaan kotiin

4 = Ruoka tulee kotiateriapalvelusta asukkaan kotiin

5 = Asukas hoitaa itse ateriansa

6 = Muu, mikä _____

25. Asukkaan mahdollisuus valita annoksen koko ja ruokalaji

1 = Ruoka on valmiiksi annosteltuina asukkaalle

2 = Asukas voi itse tai avustettuna annostella ruokansa, ei vaihtoehtoja pääruokalajista

3 = Asukas voi itse tai avustettuna annostella ruokansa, ainakin kaksi vaihtoehtoa pääruokalajista

26. Millainen on asukkaan ruoan rakenne?

1 = Nestemäinen

2 = Sosemainen

3 = Pehmeä

4 = Kiinteä (normaali)

27. Kuinka paljon asukas syö tavallisesti pääaterioilla?

1 = vähän

2 = melko vähän

3 = normaalisti

4 = melko paljon

5 = paljon

28. Syökö asukas välipaloja?

1 = Ei

2 = Kyllä

29. Käyttääkö asukas täydennysravintovalmisteita (esim. Nutridrink, Resource)?
1 = Ei
2 = Kyllä
30. Käyttääkö asukas tehostettua ruokavaliota (energia- ja/tai proteiinitiheä ruokavalio)?
1 = Ei
2 = Kyllä
31. Käyttääkö asukas kalsiumvalmistetta?
1 = Ei
2 = Kyllä
31. Käyttääkö asukas D-vitamiinivalmistetta
1 = Ei
2 = Kyllä
32. Seurataanko asukkaan painoa säännöllisesti?
1 = Ei koskaan
2 = Kerran vuodessa tai harvemmin
3 = Kahdesti - kuudesti vuodessa
4 = Yli kuusi kertaa vuodessa
33. Onko asukkaalla seuraavia ruokailuun ja suuhun sekä ruoansulatuselimistöön liittyviä ongelmia? (voi valita useita vaihtoehtoja)
- | | <u>Ei</u> | <u>Kyllä</u> | |
|--------------------------------|-----------|--------------|---|
| 1 = Puresmisongelmia | 1 | 2 | |
| 2 = Kuiva suu | 1 | 2 | |
| 3 = Kipua suussa | 1 | 2 | |
| 4 = Nielemisongelmia | 1 | 2 | |
| 5 = Ummetusta | 1 | 2 | |
| 6 = Ripulia | 1 | 2 | |
| 7 = Oksentelua | 1 | 2 | |
| 8 = Muita ongelmia, mitä _____ | 1 | | 2 |
34. Mikä on asukkaan hampaiston tila?
1 = Hampaaton, ei proteesia
2 = Kokoproteesi sekä ylä- että alaleuassa
3 = Hampaaton, mutta joko ylä- tai alaleuan kokoproteesi ja/tai muita osaproteeseja
4 = Omia hampaita ja yksi tai useampia proteeseja
5 = Vain omia hampaita
35. Peseekö asukas hampaansa/puhdistaa proteesinsa päivittäin (itse tai avustettuna)?
1 = Ei
2 = Kyllä
36. Koska hammaslääkäri tai suuhygienisti on tarkastanut asukkaan hampaat/suun viimeksi?
1 = alle vuosi
2 = yhdestä kolmeen vuoteen
3 = yli kolme vuotta sitten
4 =
37. Onko asukkaalla seuraavia sairauksia tai onko hän sairastanut jonkin niistä aikaisemmin?
- | | <u>Ei</u> | <u>Kyllä</u> |
|---------------------------------------|-----------|--------------|
| 1 = Diabetes (sokeritauti) | 1 | 2 |
| 2 = Sepelvaltimotauti | 1 | 2 |
| 3 = Sydänveritulppa eli sydäninfarkti | 1 | 2 |

4 =	Aivohalvaus tai aivoverenkiertohäiriöitä	1 2
5 =	Dementia	1 2
6 =	Depressio	1 2
7 =	Muu psykiatrinen sairaus	1 2
8 =	Parkinsonin tauti	1 2
9 =	MS, ALS, muu neurologinen sairaus	1 2
10 =	Nivelkulumat, reuma	1 2
11 =	Krooninen keuhkoputkentulehdus (COPD), astma tai muu keuhkosairaus	1 2
12 =	Maha- tai pohjukaissuolen haavauma	1 2
13 =	Muu krooninen suolistosairaus	1 2
	• Jos on, mikä _____	
14 =	Lonkkamurtuma	1 2
15 =	Syöpä	1 2
	• Jos on, mikä _____	
16 =	Pitkäaikainen tulehdus	1 2
	• Jos on, mikä _____	
17 =	Jokin muu pitkäaikainen sairaus	1 2
	• Jos on, mikä _____	

Kysytään asukkaalta itseltään:

38. Oletteko tyytyväinen elämäänne?
 1. en
 2. kyllä
 3. asukas ei pysty vastaamaan
39. Tunnetteko itsenne tarpeelliseksi?
 1. en
 2. kyllä
 3. asukas ei pysty vastaamaan
40. Onko Teillä tulevaisuudensuunnitelmia?
 1. ei
 2. kyllä
 3. asukas ei pysty vastaamaan
41. Onko Teillä elämänhalua?
 1. ei
 2. kyllä
 3. asukas ei pysty vastaamaan.
42. Oletteko masentunut? (jos asukas ei kykene vastaamaan, hoitajan arvio)
 1 = harvoin tai ei koskaan
 2 = toisinaan
 3 = usein tai aina
43. Kärsittekö yksinäisyydestä? (jos asukas ei kykene vastaamaan, hoitajan arvio)
 1 = harvoin tai ei koskaan
 2 = toisinaan
 3 = usein tai aina
44. Millaiseksi arvioitte oman terveydentilanne tällä hetkellä?
 1 = Pidän itseäni terveenä
 2 = Pidän itseäni melko terveenä
 3 = Pidän itseäni sairaana
 4 = Pidän itseäni hyvin sairaana

Hoitajan arvio asukkaan tilanteesta:

45. Millainen on asukkaan muisti (kognitiiviset toiminnot)?
- 1 = Ei muistin huonontumista tai pientä muistamattomuutta toisinaan
 - 2 = Lievää jatkuvaa muistamattomuutta, tapahtumien osittaista muistamista, ”hyvänlaatuista” muistamattomuutta
 - 3 = kohtalaista muistin huonontumista, selvempänä koskien viimeaikaisia tapahtumia, vaikuttaa jokapäiväisiin toimintoihin
 - 4 = Vaikea muistihäiriö, vain hyvin opittu aines säilynyt, uusi aines unohtuu pian
 - 5 = Vaikea muistihäiriö, vain pirstaleita säilynyt
46. Miten asukas huolehtii päivittäisistä toiminnoistaan (itsestä huolehtiminen)
- 1 = Täysin kykenevä huolehtimaan itsestään
 - 2 = Tarvitsee kehotuksia ja muistutuksia
 - 3 = Tarvitsee apua pukeutumisessa, henkilökohtaisessa hygieniassa ja henkilökohtaisten tavaroidensa hoidossa
 - 4 = Tarvitsee paljon apua itsestään huolehtimisessa, usein inkontinentti (virtsan tai ulosteen pidätyskyvyttömyys)
47. Pystyykö asukas vaivatta liikkumaan sisällä?
- 1 = Kyllä
 - 2 = Ei, hän tarvitsee kepin tai rollaattorin
 - 3 = Ei, hän tarvitsee toisen henkilön apua
 - 4 = Ei, hän ei pysty kävelemään
 - 5 =
48. Pystyykö asukas vaivatta liikkumaan ulkona?
- 1 = Kyllä
 - 2 = Ei, hän tarvitsee kepin tai rollaattorin
 - 3 = Ei, hän tarvitsee toisen henkilön apua
 - 4 = Ei, hän ei pysty kävelemään
49. Näkeekö asukas lukea?
- 1 = Ei
 - 2 = Kyllä
50. Kuuleeko hän tavallista puhetta?
- 1 = Ei
 - 2 = Kyllä
51. Tiedot taustatietolomakkeeseen antoi
- 1 = asukas pääosin itse
 - 2 = hoitaja

Lääkkeet**52. Tulosta tai kopioi asukkaan voimassa oleva lääkelista ja niittaa se tähän kyselylomakkeeseen liitteeksi.**

Tarkista vielä, että kaikki kohdat tulivat täytettyä. Kiitos!

Lomakkeet kootaan talossa ja palautetaan vanhusten palvelujen vastualueelle 31/10/2007
 mennessä: **Helena Soini, PL 8555, 00099 Helsingin kaupunk**

Appendix 2. Clinical Dementia Rating

Subject Initials _____

CLINICAL DEMENTIA RATING (CDR)

CLINICAL DEMENTIA RATING (CDR):	0	0.5	1	2	3
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	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

Appendix 3. Delirium tutkimuksen kyselylomake

Potilaan perustiedot: (pyydä yhteystiedot: osoite, puh.nro, tai käytä TARRAA)

Täydennä tai rengasta:

1. Potilaan nimi _____ Tutkija: _____

2. Potilaan sotu: _____ - _____

3. Potilaan numero : _____

4. Tutkimuspäivä: _____ / klo: _____

5. Tutkimuspaikka: _____

1. geriatrinen akuuttiosasto
2. kuntoutusosasto
3. vanhainkoti
4. psykiatriosasto

6. Tutkimusmaa 1. Suomi 2. Ruotsi 3. Englanti

7. Potilaan koulutustaso 1. Vähemmän kuin kansakoulu
2. Kansakoulu
3. Keskikoulu
4. Lukio
5. Korkeakoulu

8. Missä työssä potilas on ollut eniten elämänsä aikana

1. Maanviljelys, karjanhoito, metsätyö, emäntä
2. Tehdas, kaivos, rakennus tms työ
3. Toimistotyö, palvelutyö, henkinen työ
4. Kotirouva, perheenemäntä
5. muu, mikä? _____

9. Siviilisääty:

1. Naimisissa tai avoliitossa
2. Naimaton
3. Asumuserossa tai eronnut
4. Leski

10 .Missä potilas asuu:1. Kotona

2. Pysyvästi kodinomaisissa olosuhteissa, missä: _____

3. Pysyvästi vanhainkodissa, missä: _____

4. Pysyvästi sairaosastolla, missä : _____

11. Tupakointi:

1. Ei ollenkaan
2. alle 10 tupakkaa /vrk
3. Yli 10 tupakkaa/vrk

12. Alkoholin käyttö

1. Ei ollenkaan
2. harvemmin kuin kerran viikossa
3. Kerran viikossa tai useammin

13.Potilaan perussairauksien diagnoosit:1. _____ 2. _____

3. _____ 4. _____ 5. _____

6. _____ 7. _____ 8. _____

muuta: _____

14. Potilaan käyttämä lääkitys: 1. _____ 2. _____

3. _____ 4. _____ 5. _____

6. _____ 7. _____ 8. _____

muuta: _____

15. RR _____ / _____ 16. Pulssi _____ /min

16. Sairaalaan tulon syy: _____

KYSYMYSKAAVAKE

Ohje kaavakkeen täyttäjälle:

Voit keskustella potilaan kanssa aluksi täysin vapaamuotoisesti, jotta hän tuntisi olonsa mukavaksi. Potilaalle tulee kertoa, mistä tutkimuksessa on kyse (oheinen potilastiedote). Lisäksi voit sanoa esim: "Tutkimme iäkkäillä sairaalapotilailla yleisiä ilmeneviä sekavuusoireyhtymän oireita, jonka vuoksi tulemme haastattelussa testaamaan muistia, keskittymistä, päättelykykyä sekä teidän itsenne kokemia oireita sairaalassaoloaikana / viime aikoina vanhainkodissa. Osa kysymyksistä on helppoja, osa hieman vaikeampia, eikä teidän tarvitse huolestua, mikäli kaikkiin ei löydy vastausta."

Kun vastaat kysymyskaavakkeen tutkijan täydettävään osaan, tulee sinun osissa: **3. Havainnoinnin häiriöt 6. Uni 7. Psykomotoriikan aktiivisuus (osin) 10. Alku ja kesto 11. Vaihtelu 12. Sundowning 13. Tunteet 14. Etiologia 15. Dementia - ottaa huomioon potilaan oireet ainakin viimeisten viikkojen ajalta.** Saat siis käyttää potilaspapereita, tietoja omaisilta tai potilasta hoitavilta apunasi.

Sen sijaan osiot: **2. Tajunnantaso ja tarkkaavaisuus 3. Abstrakti ajattelu ja yleinen käsityskyky 5. Puhe 8. orientaatio, 9. muisti, 16. muut oireet** sinun tulisi päätellä potilaasta saamasi vaikutelman perusteella.

Täytä oheinen KYLLÄ / EI / En tiedä -lista seuraavasti: mikäli potilas vastaa oikein tai hyvin lähelle oikeaa vastausta, täytä KYLLÄ. Samoin mikäli näkemyksesi väittämästä tai kysymyksen vastauksesta on myönteinen tai lähellä sitä, vastaa KYLLÄ. Mikäli potilas vastaa väärin, tai hänellä ei ole ko oiretta tai potilaan status ei vastaa väitettä, vastaa EI. Mikäli olet täysin epävarma, vastaa "en tiedä".

OSA 1. Potilaan haastattelu:

Jos potilas vastaa oikein tai lähelle oikea vastaus, ruksaa KYLLÄ, muutoin EI. Pyri välttämään vaihtoehtoa "en tiedä". Kysymyksiin 1.8 – 1.19 sekä 1.45 – 1.47 suoraan potilaan mielipide/vastaus.

	kyllä	ei	en tiedä
1.1. Mikä teidän nimenne on (etu- ja sukunimi)?			
1.2. Kuinka vanha te olette?			
1.3. Miksi olette joutunut sairaalaan (tietääkö potilas?)			
1.4. Oletteko naimisissa?			
1.5. Onko teillä perhettä?			
1.6. Kuinka monta lasta teillä on?			
1.7. Mitä olette tehnyt aikaisemmin ammatiksenne?			
1.8. Oletteko tunteneet itsessänne outoa sekavuutta viime päivinä?			
1.9. Onko teillä ollut ongelmia nukkumisen kanssa viime päivinä?			
1.10. Onko teillä ollut vaikeuksia nukahtaa viime päivinä?			
1.11. Onko teillä ollut päiväaikaista väsymystä?			
1.12. Onko teillä ollut kipuja tai meteliä, jotka ovat vaikeuttaneet nukkumista?			
1.13. Onko teillä ollut ikäviä painajaisia viime päivinä?			
1.14. Onko teillä ollut vaikeuksia muistaa asioita viime päivinä?			
1.15. Oletteko nähnyt viime päivinä ihmisiä, asioita tai esineitä joita ei oikeasti ole olemassa?			
1.16. Oletteko viime päivinä kuullut ääniä tai puhetta joiden todellisuutta epäilette?			
1.17. Oletteko kokenut näitä asioita täällä sairaalassa ollessa vai myös aiemmin kotona?			
1.18. Onko teillä ollut outoa kokemusta että esineet liikkuvat, ovat liian pieniä tai suuria?.			
1.19. Entä onko oma kehonne muoto tai koko tuntunut oudolta?			
1.21. Mikä vuosi nyt on?			
1.23. Mikä vuodenaika? (kevät, kesä, syksy, talvi)			
1.20. Monesko päivä tänään on? (+/- yksi päivä)			
1.24. Mikä viikonpäivä nyt on?			
1.22. Mikä kuukausi?			
1.25. Paljonko kello on? (suurinpiirtein, +/- kaksi tuntia)			
1.25.1 Missä maassa me olemme?			
1.26. Tiedättekö mikä tämä paikka on?			
1.26.1 Missä kerroksessa me olemme?			
1.27. Tietääkö potilas olevansa sairaalassa/vanhainkodissa, vaikka ei muistaisikaan sen nimeä ?			
1.28. Minä vuonna olette syntyneet?			
1.29. Mikä on teidän osoitteenne (tai puhelinnumeronne)?			
1.30. Muistatteko äitinne tyttönimen?			
1.31. Kuka on Suomen presidentti tällä hetkellä?			
1.32. Kuka oli edellinen presidentti?			
1.33. Seuraavassa pyydän teitä painamaan mieleenne kolme pientä sanaa, jotka teidän tulisi painaa mieleenne. Heti kun olen sanonut ne, voitteko toistaa ne perässäni: PAITA, RUSKEA, VILKAS. (montako oikein: _____)			
1.34. Seuraavassa keskittymistä mittaavassa tehtävässä pyytäisin Teitä luettelemaan sanan PUTKI kirjaimet lopusta alkuun. (vaihtoehtoisesti 1.37)			

1.35. Voisitteko nimetä viikonpäivät takaperin			
1.36. Muistatteko ne kolme pientä sanaa, jotka aiemmin toistitte perässäni?(kuinka monta meni oikein: _____)			
1.37 Voisitteko vähentää luvusta 100 7? Ja edelleen miinus 7? Ja edelleen miinus 7? Jne. Kuinka monta meni oikein (nollaan saakka): _____			
1.37.1 Vähentäkää luvusta 20 3. Ja edelleen 3, jne (nollaan saakka): Oikein _____			
1.37.1 Nyt luen teille lauseen. Pyytäisin teitä toistamaan sen: OPPILAS RATKAISI MONIMUTKAISEN TEHTÄVÄN			
1.37.2.1 Seuraavassa annan teille paperin ja pyydän teitä tekemään sille jotain. Annetaan paperi: ottakaa paperi oikeaan käteenne (ottaa paperin oikeaan käteen)			
1.37.2.2. taittakaa se keskeltä kahtia _____ (taittaa sen)			
1.37.2.3. ja laittakaa se polvienne päälle _____ (laittaa polviensa päälle)			
1.37.3. Nyt näytän teille tekstin. Pyytäisin teitä lukemaan sen ääneen ja noudattamaan kehotusta (viimeinen sivu)			
1.37.4. Tässä on kynä ja paperia. Kirjoittaisitteko jonkin itse keksimänne lauseen.			
1.37.5. Voisitteko piirtää tämän alapuolelle samanlaisen kuvion (viimeinen sivu)			
1.37.6. Digit span etuperin: pt toistaa _____ numeroa			
1.37.7. Digit span takaperin: pt toistaa _____ numeroa			
1.38 Mitä tekisitte, jos löytäisitte kadulta kirjekuoren, jossa on osoite ja leimaamaton postimerkki päällä?			
1.39. Miksi pitää pysyä erossa huonosta seurasta?			
1.40 Voitteko selittää, miksi junassa on veturi?			
1.41. Miksi maksetaan veroja?			
1.42. Mitä tarkoittaa sananlasku "On taottava kun rauta on kuumaa"?			
1.43. Mitä tarkoittaa sananlasku "Tyhjä tynnyrit kolisevat eniten"?			
1.44. Mitä tekisitte, jos eksyisitte metsään päiväsaikaan?			
1.45. Oletteko tunteneet itsenne masentuneeksi viime aikoina?(kysy erikseen kysymyksen 13.1. kaikki oireet potilaalta)			
1.46. Oletteko tunteneet itsenne ahdistuneeksi tai hermostuneeksi viime aikoina? (kysy erikseen kysymyksen 13.3 kaikki oireet potilaalta)			
1.47. Oletteko pelännyt viime aikoina?			
1.48. Tunnistaako potilas rannekellon JA kynän?			
1.49. Pystyykö potilas kooperaamaan testauksessa ?			
1.50. Kieltäytyykö potilas testistä kesken testauksen?			

OSA 2. Tutkijan täydennettävä:**2. Tajunnantaso ja tarkkaavaisuus****TÄYTÄ HAASTATELUSSA SAAMASI VAIKUTELMAN PERUSTEELLA**

	kyllä	ei	en tiedä
2.1.1. Onko potilaalla tietoisuuden hämärtymistä /"sumenemista" (heikentynyt tietoisuus ympäristöstä)?			
VALITSE SEURAAVISTA 2.1.2 – 2.1.7 VAIN YKSI VAIHTOEHTO:			
2.1.2. Onko potilaalla muuta tajunnantason häiriötä?			
2.1.3. Onko potilaan tajunnatase normaali (valpas)?			
2.1.4. Onko potilaan tajunnatase ylivalpas (säpsähtelevä)?			
2.1.5. Onko potilas unelias (helposti herätettävissä)?			
2.1.6. Onko potilas erittäin unelias (vaikeasti heätettävissä)?			
2.2.1. Onko potilalla alentunut kyky kohdistaa tarkkaavaisuuttaan (esim keskustelun aloituksessa haastattelijan kanssa)?			
2.2.2. Onko potilaalla alentunut kyky keskittyä (esim ongelmia tavatessaan sana "PUTKI" lopusta alkuun 1.34 tai laskiessaan 1.37 tai 1.37.1)?			
2.2.3. Onko potilaalla alentunut kyky ylläpitää tarkkaavaisuuttaan (esim luettellessaan viikonpäiviä takaperin)?			
2.2.4. Onko potilaalla vaikeutta siirtää huomiotaan (esim. kyselyn aihepiiriin vaihtuessa uuteen)?			
2.2.5. Jääkö potilas herkästi keskustelun aikana tuijottelemaan kaukaisuuteen kykenemättä seuraamaan ympäristönsä tapahtumia?			
2.2.6. Onko potilalla toistuvia ajatuksia/pakkomielteitä, jotka estävät häntä reagoimasta asianmukaisesti ympäristöön (esim. etsii kadonnutta omaisuuttaan tai on oikeissa lähteä jonnekin)?			
2.2.7. Onko potilaan tarkkaavaisuudessa vaihtelua (esim. vastaus alkaa asianmukaisesti, mutta hiipuu kesken lauseen)?			
2.2.8. Onko kysymyksen toisto tai asiaan palauttaminen tarpeen enemmän kuin kerran?			
2.2.9. Puhuuko potilas asiaankuulumattomia (esim vaihtaa puheenaihetta yllättävästi tai kertoo asiaankuulumattoman tarinan)?			
2.2.10. Onko tarkkaamattomuuteen mahdollisesti syynä vaikea kipu, heikotus, masennus, kiihtymys...?			

3. Abstrakti ajattelu ja ymmäry**TÄYTÄ HAASTATELUSSA SAAMASI VAIKUTELMAN PERUSTEELLA**

	kyllä	ei	en tiedä
3.1. Onko potilaalla kyky johdonmukaiseen päättelyyn? (esim. vastaa oikein kysymyksiin 1.40 TAI 1.41)			
3.2. Onko potilaalla kyky abstraktiin ajatteluun? (esim. kykenee vastaamaan oikein ainakin yhteen kysymyksistä 1.42. tai 1.43)			
3.3. Onko potilaalla arvostelukykyä? (esim. vastaa oikein yhteen kysymyksistä 1.38 tai 1.39)			
3.4. Onko potilaalla kyky suunnitelmalliseen toimintaan? (esim. vastaa oikein kysymykseen 1.44)			
3.5. Kyseleekö potilas epäasianmukaisia kysymyksiä?			
3.6. Voikomatalan henkisen suorituskyvyn selittää vähäisellä koulutuksella tai aikaisemmalla henkisellä vajaakykyisyydellä?			

4. Havainnoinnin häiriö

TÄYTÄ OTTAEN HUOMIOON POTILAAN OIREET VIIKKOJEN AJALTA

	kyllä	ei	en tiedä
4.1. Onko potilaalla väärintulkintoja , aistihairahduksia(=aistiärsykkeen väärintulkinta) tai aistiharhoja (= sisäisiä todellisilta tuntuvia aistimuksia, esim näkö tai kuuloharha)?			
4.3. Onko potilaalla muita havainnoinnin häiriöitä? Mitä?			
4.4. Onko potilaalla harhaluuloja (virhepäätelmiä ulkoisesta todellisuudesta)?			
4.5. Onko potilas nähnyt sellaista (esim. esineitä, asioita, ihmisiä) joita ei oikeasti ole? (näköharhoja)			
4.6. Onko potilas nähnyt esineitä tai muita objekteja liian pienenä, suurena tai useana?			
4.7. Onko potilas tunnistanut näkemänsä esineet väärin (esim. virtsannut roskakoriin tai syönyt kukkia tai kysymys 1.48)?			
4.8. Onko potilas kuullut puhetta tai muita ääniä, joita ei ole olemassa (mahdollista olemassaolevaa korvien soimista ei oteta huomioon) (kuuloharhoja) ?			
4.9. Onko potilas tulkinnut kuulemiaan ääniä väärin (esim. luullut huutavaa huonetooveriaan itkeväksi lapseksi)?			
4.10. Onko potilaalla tuntoaistimuksia (joku koskettaa, satuttaa, ryömii iholla) joita ei voi selittää?			
4.11. Onko potilaalla tunne liikkumisesta (esim putoamisesta) ollessaan paikoillaan?			
4.12. Onko potilaalla vainoharhaisia ajatuksia (esim. myrkytetyksi tai ryöstetyksi tulemisesta tai jonkin pahan tapahtumisesta kotonaan)?			
4.13. Onko potilaalla delusionaalista väärintulkintaa (esim. uskoo tutkijan/hoitajan olevan hänen puolisonsa)?			
4.14. Onko potilaalla merkittävästi heikentynyt kuulo (vaikeus kuulla kovaa puhetta korvan vierestä - mahdollisen kuulolaitteensaakaan avulla)?			
4.15. Onko potilaan näkö merkittävästi heikentynyt (kyvyttömyys lukea apuvälineidenkään avulla)?			

5. Puhe**TÄYTÄ HAASTATELUSSA SAAMASI VAIKUTELMAN PERUSTEELLA**

	kyllä	ei	en tiedä
5.1. Onko potilas kyvytön puhumaan? (ei puhu lainkaan)			
5.2. Onko potilaan puhe hajanaista? (esim. toistuvaa syrjähtelyä puhutusta asiasta tai epäjohdonmukaisuutta)			
5.3. Onko potilaan puhe epätarkoituksenmukaista? (esim. sopimatonta tai aihepiiriin kuulumatonta)			
5.4. Onko potilaan puhe harhailevaa? (esim .toistuvaa rönsyilyä aihepiiristä toiseen)			
5.5. Onko potilaalla elimellinen puhehäiriö (dysfasia tai dysartria, esim. aivohalvauksen jälkitilana)?			
5.6. Onko potilaalla muu puheen häiriö? Mikä? _____			
5.7. Onko potilaan puhe epätavallisen nopeutunutta?			
5.8. Onko potilaan puhe epätavallisen hidastunutta?			
5.9. Onko potilas epätavallisen toistelevaa (esim. juuttuu vastaukseen uudelleen ja uudelleen)?			
5.10. Onko potilaan puhe epätavallisen äänestä?			

5.11. Puhuuko tai laulaako potilas itsekseen? OTA HUOMIOON OIRE VIIMEISTEN VIIKKOJEN AJALTA			
5.12. Käyttääkö potilas asiaan liittymättömiä sanoja tai fraaseja ?			
5.13. Onko potilaalla järjestäytymätöntä ajattelua , joka ilmenee harhailevana, epätarkoituksenmukaisena tai epäjohdonmukaisena puheena?			

6. Uni

TÄYTÄ OTTAEN HUOMIOON POTILAAN OIREET VIIKKOJEN AJALTA

	kyllä	ei	en tiedä
6.1. Onko potilaalla unettomuutta?			
6.2. Onko potilaalla päiväaikaista väsymystä?			
6.3. Onko potilaalla uni-valverytmin häiriö?			
6.5. Kärsiikö potilas täydellisestä unen puutteesta?			
6.6. Onko potilas valveilla enemmän kuin 3 tuntia yössä (klo 24 - 06)?			
6.8. Nukkuuko potilas enemmän kuin 3 tuntia päivisin (klo 9 - 20)?			
6.9. Onko potilaalla ilmeinen syy uni-valverytmin häiriöön (esim.kipu, huutava huonetoveri, ym.)?			
6.10. Nukahtelee potilas ennakoimattomasti (esim. kesken lauseen, ruokailun tai WC-käynnin)?			
6.11. Onko potilaan uni-valverytmi käänteinen (nukkuu suurimman osan päivää ja valvoo suurimman osan yötä)?			
6.12. Kärsiikö potilas häiritsevistä unista tai painajaisista?			
6.13. Onko potilaalla vaikeutta erottaa unet todellisuudesta (esim. unilla on taipumus jatkua heräämisen jälkeen harhanäkyinä)?			

7. Psykomotorinen aktiivisuus

TÄYTÄ OTTAEN HUOMIOON POTILAAN OIREET VIIKKOJEN AJALTA

	kyllä	ei	en tiedä
7.1. Onko potilaalla lisääntynyt psykomotorinen aktiivisuus(esim. puuhailee puhuessaan, yrittää lähteä jonnekin, kipeää laitojen yli, kiskoo letkuja ja katetreita, repii vuodevaatteita, riisuutuu ym.)?			
7.2. Onko potilaalla vähentynyt psykomotorinen aktiivisuus (esim. liikkumattomuus, taipumus olla paikoillaan)?			
7.3. Onko potilaan reaktioaika pidentynyt (kestääkö epätavallisen kauan ennen kuin potilas seuraa ohjeita tai vastaa kysymyksiin)? VAIKUTELMA HAASTATELUSSA			
7.4. Onko osoitettavissa autonomisen, erityisesti sympaattisen, hermoston aktivoitumista (nopea pulssi, laajentuneet pupillit, punakat kasvot, hikoilevat kämmenet)? VAIKUTELMA HAASTATELUSSA			
7.5. Kärsiikö potilas uutena oireena virtsa-tai ulosteinkontinenssista?			
7.7. Onko potilas helposti säpsähtelevä tai pelokas? VAIKUTELMA HAASTATELUSSA			
7.8. Vaihtelee potilaan psykomotorinen aktiivisuus ennakoimattomasti hitaudesta/uneliaisuudesta kiihtyneeseen?			
7.9. Onko potilasta jouduttu sitomaan lepositeisiin viimeisen viikon aikana? (Sänkyyn tai esim G-tuoliin pöydän avulla)			

8. Orientaatio

TÄYTÄ HAASTATELUSSA SAAMASI VAIKUTELMAN PERUSTEELLA

	kyllä	ei	en tiedä
8.1. Onko potilas orientoitunut aikaan? (kysymykset 1.21 - 1.24 kaikki oikein, yksi virhe sallitaan)			
8.2. Onko potilas orientoitunut paikkaan? (kysymykset 1.26 TAI 1.27 oikein)			
8.3. Onko potilas orientoitunut henkilöön?			

9. Muisti

TÄYTÄ HAASTATELUS SAAMASI VAIKUTELMAN PERUSTEELLA

	kyllä	ei	en tiedä
9.1. Onko potilaalla vaikeutta välittömässä mieleenpalauttamisessa (esim. kysymys 1.33)?			
9.2. Onko potilaalla vaikeutta muistaa viimeaikaisia tapahtumia (esim sairaalaan tulon syy, jonkin merkittävä tapahtuma viime viikoilta)?			
9.3. Onko potilaalla vaikeutta muistaa varhaisia asioita (esim. kysymys 1.6,1.7 tai 1.32)?			
9.4. Onko potilaalla vaikeutta pitää mielessään juuri puhuttuja asioita (kysymys 1.36)?			
9.5. Onko potilaalla vaikeutta muistaa juuri tapahtuneita asioita (esim. sairaalassa olonsa syy, omaisten vierailut, päiväohjelma, ateriat, ym., kts kysymys 1.3)?			
9.6. Onko potilaalla vaikeutta muistaa oma henkilöhistoriansa (esim. siviilisääty, lasten lukumäärä, aiempi ammatti, ym., esim. kysymys 1.5-1.7)?			
9.7. Johtuuko muistinmenetyks edeltävästä dementiaasta?			
9.8. Onko Alzheimerin taudista selvää näyttöä? (pään CT)			
9.9. Verisuoniperäisestä eli ns. vaskulaaridementiaasta? (- " -)			
9.10. Sekatyypisestä dementiaasta? (- " -)			
9.11. Lewyn kappale dementiaasta? (- " -)			
9.12. Muusta dementoivasta sairaudesta? Mistä?: _____			
9.13. Onko potilaan muistia testattu ennen häiriötä? (Testi, päivämäärä, tulos? _____).			
9.14. Onko potilaan muistia testattu häiriön aikana? (Testi, päivämäärä, tulos? _____).			
9.15. Mikä on oma vaikutelmasi: Onko potilaalla muistihäiriö?			
9.16. Onko potilaalla mielestäsi sekavuusoireyhtymä eli delirium?			
9.17. Mikä on vaikutelmasi: onko potilaalla tilapäisiä sekavuusoireita?			

10. Oireiden alku ja kesto

MIKÄLI POTILAS ON MIELESTÄSI SEKAVA TAI HÄNELLÄ ESIINTYY JOITAKIN EM. 2. – 7. KYSYMYSRYHMIEN OIREITA, TÄYTÄ SEURAAVA KYSYMYKSISSÄ TARKOITETAAN SEKAVUUTEEN LIITTYVIÄ TILAPÄISIÄ UUSIA OIREITA (ESIM VUOSIA JATKUNEITA DEMENTIAN MUISTIOIREITA EI OTETA HUOMIOON, ELLEI UUTTA ÄKILLISTÄ MUUTOSTA OLE TAPAHTUNUT

	kyllä	ei	en tiedä
10.1. Ovatko häiriön kliiniset oireet (sekavuus) kehittyneet lyhyen ajan kuluessa (yleensä tuntien, päivien aikana)?			
10.2. Onko häiriö kestänyt vähemmän kuin 6 kuukautta?			
10.5. Ovatko kliiniset piirteet kehittyneet muutaman viikon kuluessa?			
10.6. Ovatko kliiniset piirteet kestäneet yli kaksi viikkoa?			

10.7. Onko häiriö kestänyt yli 6 kuukutta?			
10.9. Mitä käytit tietolähteenä vastatessasi näihin kysymyksiin (10.1.-10.9.)? (potilas itse, omainen, henkilökunta, potilasasiakirjat?)(alleviivaa oikea vaihtoehto)			

11. Oireiden vaihtelevuus

MIKÄLI POTILAS ON MIELESTÄSI SEKAVA TAI HÄNELLÄ ESIINTYY JOITAKIN EM. 2. – 7. KYSYMYSRYHMIEN OIREITA, TÄYTÄ SEURAAVA

	kyllä	ei	en tiedä
11.1. Vaihtelevatko kysymysryhmien 2. – 9. kliiniset oireet (onko niillä taipumus lisääntyä tai vähentyä voimakkuudeltaan) minuuttien kuluessa (esim. keskustelun aikana)? Tuntien kuluessa, päivän kuluessa, viikkojen kuluessa?(alleviivaa oikea vaihtoehto)			

12. Oireiden ajankohta

MIKÄLI POTILAS ON MIELESTÄSI SEKAVA TAI HÄNELLÄ ESIINTYY JOITAKIN EM. 2. – 7. KYSYMYSRYHMIEN OIREITA, TÄYTÄ SEURAAVA

	kyllä	ei	en tiedä
12.1. Mihin vuorokauden aikaan kliiniset oireet (kysymysryhmien 2. – 9.) ovat pahimmillaan? Yöaikaan?			
12.2. illalla?			
12.3. aamulla?			
12.4. päiväsaikaan?			
12.5. Milloin potilaan sekavuusoireet ovat ilmenneet viimeisen vuorokauden aikana (alleviivaa oikeat): a. aamulla b. päivällä c. illalla d. yöllä			

13. Tunneoireet

TÄYTÄ OTTAEN HUOMIOON POTILAAN OIREET VIIKKOJEN AJALTA

	kyllä	ei	en tiedä
13.1. Onko potilaalla kliinisesti masennus/masentunutta mielialaa esim. alakuloisuutta, kiinnostuksen puutetta, epätavallista itkuisuutta, kuoleman toiveita, tarpeettomuuden tunteita, apatiaa, arvottomuuden tunteita, itsesyytöksiä tai somaattisia depression oireita)? (Alleviivaa potilaan oireet). Muita, Mitä: _____			
13.2. Onko potilaalle tehty jokin depressiotesti? (Testi, päivämäärä, tulos? _____)			
13.3. Onko potilaalla ahdistustata (esim.pelkoja, keskittymisvaikeutta, motorista levottomuutta, epätavallista kyvyttömyyttä odottamiseen, hermostuneisuutta tai ahdistuksen somaattisia ilmentymiä kuten rintatuntemusta, vapinaa, hikoilua, punakkuutta, ym.)? (Alleviivaa potilaan oireet). Muita, mitä: _____			
13.4. Onko potilaalla pelkoa (esim pelko olevansa korkeassa paikassa tai pimeässä/ suljetussa tilassa, epätavallisen voimakasta uskomusta jonkin pahan tapahtumisesta itselleen/muulle)? Mitä: _____			
13.5 Onko potilaalla ärtyisyyttä (epätavallista närkästystä kosketuksesta, puheesta, ym.)?			
13.6.Onko potilaalla euforiaa (esim. epätavallista hyväntuulisuutta, hymyä ja naurua, vastoinkäymisten kieltämistä)?			
13.7. Onko potilaalla apaattisuutta (esim. epätavallisen heikkoja tunnereaktioita, välinpitämättömyyttä vastoinkäymisiä kohtaan)?			
13.8. Onko potilaalla ihmettelevää hämmennystä (esim. yllättymistä, epätietoisuutta, kiusaantuneisuutta)?			
13.9. Onko potilaalla joku muu ilmeinen tunne-elämän häiriö?			

Mikä? _____			
13.10. Onko potilaalla selvä vaikeus pidätellä tunteitaan (esim. raivoa, epäsovivaa naureskelua tai itkua)?			
13.11. Onko potilaalla tilanteeseen selvästi sopimattomia mielialan vaihteluita (esim. tunteiden nopeaa muuttumista)?			
13.14. Onko potilas ollut aggressiivinen tai väkivaltainen?			
13.15. Onko potilas huutanut vihaisesti?			
13.16. Onko potilaalla ollut pyrkimystä harhailla tai karata osastolta?			
13.17. Onko potilas herkästi kiihtyvä?			
13.18. Onko potilas levoton?			

14. Aiheuttaja

MIKÄLI POTILAS ON MIELESTÄSI SEKAVA TAI HÄNELLÄ ESIINTYY JOITAKIN EM. 2. – 7. KYSYMYSRYHMIEN OIREITA, TÄYTÄ SEURAAVA (14.1 –14.3 ovat vaihtoehtoja toisilleen)

	kyllä	ei	en tiedä
14.1. Onko potilaalla selvä osoitettavissa oleva orgaaninen syy/syyt, joka on aiheuttanut häiriön (sekavuuden)?			
14.2. Onko potilaalla todennäköinen orgaaninen syy/syyt, joka on aiheuttanut häiriön?			
14.3. Onko potilaalla mahdollinen orgaaninen syy/syyt, joka on aiheuttanut häiriön?			
14.4. Mikä on paras arviosi häiriön aiheuttamasta syystä/syistä? 1. _____ 2. _____ 3. _____ 4. _____ Näyttö: _____			
14.5. Oliko häiriön syy/syyt mahdollista määrittää yksinomaan potilaan kliinisen tutkimuksen perusteella?			
14.6. Mitä muita lähteitä oli käytössäsi selvittäessäsi häiriön syytä/syitä (omainen, henkilökunta, potilasasiakirjat, kliininen tutkimus, laboratoriotutkimukset, röntgentutkimukset, muita, mitä: _____)? (alleviivaa oikeat vaihtoehdot)			
14.7. Onko potilaalle tehty häiriön aikana EEG-tutkimus? Tulos? _____)			
14.8. Onko näyttöä määritettävissä olevasta lääketieteellisestä sairaudesta tai häiriöstä (somaattisesta?) (specific medical condition)?			
14.9. Onko näyttöä lääkeaineen/nautintoaineen haittavaikutuksesta joka aiheuttaa sekavuuden tai sen liikkäytöstä (substance intoxication)?			
14.10. Onko näyttöä lääkeaineen/nautintoaineen äkillisestä lopettamisesta (substance withdrawal)?			
14.11. Onko näyttöä muista aiheuttajista?			
14.12. Onko näyttöä aistitoimintojen virikkeettömydestä (sensorinen deprivatio)?			

15. Dementia

TÄYTÄ SEN PERUSTEELLA MIKÄ ON OLLUT POTILAAN KOGNITIIVNEN

SUORITUSKYKY SAIRAUTTA /SEKAVUUSTILAA EDELTÄVÄSTI TAI VIIMEISTÄÄN KAKSI KUUKAUTTA SITTEN

	kyllä	ei	en tiedä
15.1. Onko potilaalla aiempi dementia?			
15.2. Perustuuko sen diagnoosi neurologin/geriatrin/psykiatrin arvioon?			
15.3. Onko potilaalle tehty pään tietokonekuvaus? Tulos: _____ Milloin: _____			
15.4. Ovatko omaiset tai hoitajat havainneet potilaan muistin tai henkisen suorituskyvyn heikentyneen jo ennen tätä sairastumisjaksoa?			
15.5. Onko potilaalla ollut apraxiaa? (vaikeutta hallita liikkeitään)			
15.6. Onko potilaalla ollut agnosiaa? (vaikeutta tunnistaa/nimetä esineitä normaaleista aisteista huolimatta)?			
15.7. Onko potilaalla ollut vaikeutta suorittaa suunnitelmallista, lopputulokseen tähtäävää toimintaa (esim. suunnitella, organisoida, analysoida, ajatella abstraktioita)?			
15.8. Onko muistin heikkous ja 15.5 - 15.7. aiheuttanut merkittävää puutetta sosiaalisessa kanssakäymisessä ja onko häiriö pitkällä aikavälillä lisääntynyt aiemmasta tasostaan?			
15.9. Onko tämä häiriö alkanut hiipivästi ja onko henkisen suorituskyky hitaasti heikkenemässä?			
15.10. Onko potilaalla mitään seuraavista diagnooseista: aivoverenkierron häiriö, Parkinsonin tauti, Huntingtonin tauti, subduraalihakematoma, normaalipaineinen hydrokephalus tai aivokasvain? Mikä: _____			
15.11. Onko potilaalla mitään seuraavista demencian aiheuttajista: kilpirauhasen vajaatoiminta, B12-vitamiinin tai foolihapon tai niasiinin puute, hyperkalsemia, neurosyphilis or HIV-infektio? Mikä: _____			
15.12. Onko häiriön syy joku kemiallinen tekijä (esim. alkoholi)?			
15.13. Onko häiriö mahdollisesti depression tai skitsofrenian aiheuttama? Alleviivaa			

16. Muut oireet

TÄYTÄ HAASTATELUS SAAMASI VAIKUTELMAN PERUSTEELLA

	kyllä	ei	en tiedä
16.1. Onko potilaalla vapinaa?			
16.2. Tunnistaako potilas olevansa sairas?			
16.3. Onko potilaan persoonallisuudessa tapahtunut äkillinen muutos viimeisen kuukauden aikana? (AIEMPI TILANNE)			

17. CDR –luokitus

TÄYTÄ LUOKITUS SILLÄ PERUSTEELLA MIKÄ HÄNEN SUORITUSKYKYNsä ON OLLUT PARI KUUKAUTTA SITTEN / ENNEN NYKYISTÄ SAIRASTUMISJAKSOA

Täytä oheinen kaavake ja sillä perusteella luokitus on: _____

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