Psychotropic drugs:
Use and side effects in older psychiatric patients

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Abbreviations

ADR = Adverse drug reactions

MMSE = Mini mental status examination

MADRS = Montgomery and Aasberg depression rating scale

CCI = Charlson comorbidity index

OR = Odds ratio

TDM = Therapeutic drug monitoring

T1 = On admission

T2 = After four weeks of treatment

DDD = Defined daily dose

UKU = Udvalg for kliniske undersøgelser

UPLC = Ultra performance liquid chromatography

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Summary

Background

Use of psychotropic drugs is widespread for older patients in general, and more knowledge on the use and complications of use is needed for the population of geriatric psychiatric patients.

Aims

We wanted to investigate the use and unreported use of psychotropic drugs on admission to a geriatric psychiatric hospital in relation to serum concentrations. We also evaluated drug side effects by a comprehensive side effect interview and performed cognitive tests on admission and after four weeks. We further wanted to investigate whether change in cognitive function was related to the cessation of benzodiazepines.

Methods

This observational cross-sectional study was performed in the years 2006-2008, and 236 patients were included in the study. Blood samples were taken the day after admission, and in addition to routine biochemical tests, serum analyses for 56 psychotropic drugs were performed. The UKU side effect rating scale was performed on admission to hospital, as well as several cognitive tests, including the Mini Mental Status Examination, the Hopkins Verbal Learning Test, the Digit Vigilance Test and the Stroop test. Somatic comorbidity was measured using the Charlson Comorbidity Index. Severity of depression was examined with the Montgomery and Aasberg Depression Rating Scale. Psychiatric diagnoses were based on all available information, and registered on discharge.

Results

We found that most patients used psychotropic drugs on admission to a geriatric psychiatric hospital, and almost half of the patients had unreported use of

psychotropic drugs. Psychotropic polypharmacy (the use of tree or more concurrent drugs) was detected in half (47 %) of the patients. The dosages of the drugs were below 1 Defined Daily Dose (DDD) for all drug groups except for antidepressants, where the average dose was 1.2 (1.1-1.4) DDD. Supra therapeutic concentrations of all drugs were uncommon. The patients who were considered to have major side effects of psychotropic drugs were more often female patients with a diagnose of affective disorder, using a higher number of psychotropic drugs, a higher number of somatic drugs, unreported use of psychotropic drugs and having a higher score on the Charlson comorbidity index. On admission to hospital, several cognitive tests were performed. After four weeks of hospital treatment, cognitive function improved slightly, but only for one of the memory tests, improvement was related to the cessation of benzodiazepines.

Conclusions

Most of the older patients used psychotropic drugs when admitted to a geriatric psychiatric hospital, and unreported use of these drugs was common. Few patients had serum levels above reference range, and the doses of drugs were moderate. As for side effects of these drugs, clinicians should be especially aware of female patients using a high number of drugs and suffering from somatic comorbidity. The results on cognitive tests improved slightly after four weeks of inpatient treatment, but relation to the cessation of benzodiazepines was found only for one memory test.

List of papers

I. Psychotropic medication in geriatric psychiatric patients: use and unreported use in relation to serum concentrations

II. Correlates of major medication side effects interfering with daily performance: results from a cross-sectional cohort study of older psychiatric patients

III. Changes in cognitive function during psychogeriatric treatment in relation to benzodiazepine cessation

1 General introduction

1.1 Mental health in the elderly

Knowing that the number of people aged 65 and over is expected to rise during the next decades worldwide, the demographic changes will pose major challenges for health-care systems (Christensen et al., 2009). More knowledge of the health in older patients is needed as these patients often are excluded from clinical research (Bugeja et al., 1997). Although disability and disease are not inevitable consequences of aging (Freedman et al., 2002), advances in treatment of a variety of disorders have led to increased prevalence of many chronic diseases in older people (Crimmins, 2004, Crimmins and Beltran-Sanchez, 2011, Crimmins et al., 2009). Accordingly, the prevalence of mental disorders among elderly also needs to be assessed (Andreas et al., 2013). A review of mental health in old age conclude that mental disorders are common, with dementia and depression posing the biggest threats to health, but that other mental disorders in the elderly are under-researched and prevalence rates differ substantially (Riedel-Heller et al., 2006). A Swedish study based on pharmaceutical use among older patients, showed that mental disorders affect every fifteenth older person in Sweden, and that the prevalence increases with age (Martinsson et al., 2011, Borjesson-Hanson et al., 2011). A study based on interviews have on the other hand shown a higher prevalence (Skoog et al., 1993), and a French study showed a prevalence of mental disorders to be almost 20 % in people without dementia aged 65 years and older (Ritchie et al., 2004). In Australia, community dwelling elderly have been found to experience substantial rates of mental disorders associated with significant disability (Trollor et al., 2007). Also, mental illnesses, such as depression and anxiety which are often comorbid conditions (Lamers et al., 2011, Beekman et al., 2000), can be unrecognized and untreated in older patients (Djernes, 2006, Allan et al., 2014), although highly prevalent (Braam et al., 2014, Beekman et al., 1998). The prevalence of factors associated with mental disorders increase with age, such as loss of relatives, network, functional ability and health

(Palsson and Skoog, 1997), and biological factors such as brain atrophy and change in neurotransmitters may also increase patients vulnerability towards mental disorders (Blazer and Hybels, 2005). Co-occurrence of somatic and psychiatric illnesses has growing evidence. Researchers agree that persons with a serious mental disorder seem to have worse physical health than persons with no mental disorder (Rasanen et al., 2007, Miller et al., 2006, Jones et al., 2004, Harris and Barraclough, 1998), but the nature of the relationship between mental disorder and physical health remains unclear (Iacovides and Siamouli, 2008). There is however increasing attention towards the higher mortality in mental disorders, and estimates suggest that mental disorders are one of the most substantial causes of death worldwide (Walker et al., 2015), underlining this as a major global challenge. At the same time, somatic illness is often associated with psychiatric illness such as depression in heart failure (Rutledge et al., 2006), and depression after stroke with as much as a third of stroke survivors experiencing depression (Hackett et al., 2005).

1.1.1 Mood disorders in older persons

Mood disorders are a major cause of suffering in older patients (Rovner et al., 1991). Depression is the most frequent psychiatric illness in older people, with a frequency of perhaps 12-14 % (Engedal, 2000), and untreated depression is associated with increased morbidity, mortality and worsening of medical problems (Unutzer, 2007). Bipolar disorder in older patients is by far less common, with an estimated lifetime prevalence of 0.5-1 % (Sajatovic and Chen, 2011). Most bipolar patients manifest their first episode as young adults (Rasanen et al., 1998), and only a small fraction have onset in later life (Sajatovic et al., 2005).

1.1.2 Anxiety in older persons

Late-life anxiety disorders are common, but under-diagnosed and under-treated (Andreescu and Varon, 2015). The prevalence rates vary, but studies have found an overall prevalence of 10 % (Beekman et al., 1998), and as high as 28 % in clinical settings (Bryant et al., 2008). Anxiety has a clear negative impact on the functioning and well-being of older persons (de Beurs et al., 1999).

1.1.3 Psychotic illness in older persons

Schizophrenia is commonly thought of as an illness of younger persons, but it can extend into and first appear in later life (Howard et al., 2000). Although symptoms are variable within this patient group, a recent study found that patients with very late onset psychosis (after 60 years of age) had more positive psychotic symptoms but did not differ on neuropsychological tests compared to younger patients groups, questioning the idea that very late onset psychosis is an expression of a degenerative condition (Hanssen et al., 2014). On the other hand, a recent study in an outpatient setting found that the most common etiology of psychotic symptoms in older age was dementia, followed by delusional disorder, schizophrenia and depression (Matsuoka et al., 2015).

1.1.4 Dementia in older persons

Dementia includes a number of organic brain disorders leading to reduced memory, loss of intellectual abilities and loss of daily functioning (Engedal, 2002), with the largest group being Alzheimer's disease (60-70 %), followed by vascular dementia and Lewy-body dementia (Engedal, 2003). Aging is the main risk factor of cognitive impairment and dementia, and the prevalence of dementia doubles with every 5-year increase in age after the age of 60 years (Ferri et al., 2005).

1.1.5 Use of alcohol and medications in older persons

Two categories of substance use problems are major concerns among older adults: alcohol and psychoactive prescription drugs (Wang and Andrade, 2013). Prescription drug use disorders have become an important and growing health problem (Holmes, 2012), and older adults who drink alcohol and take medications are at risk for a variety of harms (Moore et al., 2007). A review found that one out of ten older women misuse prescription drugs, and that nonmedical use of prescription drugs is likely to increase in the years to come (Simoni-Wastila and Yang, 2006). Long term effects of alcohol use are debated, and a recent population based study from Norway with a 27 year period of follow-up, found an increased risk of dementia in persons who drink alcohol frequently (Langballe et al., 2015). Misuse and dependency on alcohol and medications are increasing problems also in Norway, and there is a need for more clinical and research attention in this field (Lunde, 2013).

1.2 Drug use in the elderly

1.2.1 General drug use in the elderly

The elderly often suffer from several diseases and are as a consequence major recipients of medications. Polypharmacy (use of multiple drugs) is common in older adults (Qato et al., 2008, Jyrkka et al., 2006, Maher et al., 2014, Linjakumpu et al., 2002), and will be necessary due to the need for treating the various diseases. Consumption of multiple drugs increases the risk of adverse drug reactions (ADRs) (Herrlinger and Klotz, 2001, Klein-Schwartz and Oderda, 1991). ADRs are often more serious when they occur in the elderly (Cresswell et al., 2007), and have shown to be an indicator for morbidity and mortality (Jyrkka et al., 2009, Hajjar et al., 2007). Both pharmacokinetic and pharmacodynamic changes as a result of aging must be considered when prescribing for the elderly (Mangoni and Jackson, 2004, Turnheim, 2004, Burton et al., 2005, Turnheim, 1998), and although geriatric patients in general are the major recipients of drugs, they are not well represented in studies when drugs are developed (Konrat et al.,

2012, Schmucker and Vesell, 1999). A recent study of elderly psychiatric patients found that more than half of patients (63 %) reported side effects, but this was not related to the use of potentially inappropriate medications (PIMs) (Hefner et al., 2015). It is safe to claim that optimizing drug treatment in the elderly is challenging (Mallet et al., 2007, Shah and Hajjar, 2012). The pharmacological treatment of older patients with psychiatric disorders is complex, as concurrent disorders may influence symptoms and drug treatment.

Non-compliance with long-term medication has been reported to 50 % in general (Monane et al., 1994), but adherence-rates vary depending on the measuring method (Barat et al., 2001). In some studies, older patients were more compliant than younger (Monane et al., 1994, Curtin et al., 1997), some find no relationship between age and compliance (Lau et al., 1996, Vik et al., 2004) and yet another that old age was correlated to non-compliance (Slymen et al., 1996). Although non-adherence to medication is a well-known challenge in the treatment of elderly, barriers to adherence are not well described (Gellad et al., 2011). A study of actual use of drugs in the elderly in Denmark showed lack of adherence in 20-70% of cases (Barat et al., 2001). Polypharmacy, which is common in older patients, has been shown to be a risk factor of non-adherence after discharge from hospital (Pasina et al., 2014). Depression has also been shown to be a risk factor of non-compliance with medical treatment (Grenard et al., 2011, DiMatteo et al., 2000), and patients with impaired executive function and lack of awareness of illness may be at particular risk of non-adherence with treatment (Arlt et al., 2008). Although adherence to treatment with drugs is a well-known challenge, there are few studies where a broad serum-analysis of drugs has been performed. Lack of consistency between what doctors report and what patients actually use has been described for geriatric psychiatric patients for benzodiazepines (Hoiseth 2013), but not so for psychotropic drugs such as antidepressants, antipsychotics and antiepileptics. In the general population however, non-adherence has found to be high for all psychotropic drug classes (Bulloch and Patten, 2010).

1.2.2 Psychotropic drug use in the elderly

Psychotropic drug use is widespread in the elderly population, both for community dwelling elderly, and elders in nursing homes (Aparasu et al., 2003, Giron et al., 2001, Rikala et al., 2011, Ruths et al., 2013). The reasons for this are complex, and a recent study showed an association between loneliness and use of psychotropic drugs, even after adjusting for depression severity, anxiety, somatic symptom severity, gender, marital status and education (Boehlen et al., 2014). For the general population in Norway, 15.3 % received at least one prescription of a psychotropic drug during 2005, and overall drug use increased with age (Kjosavik et al., 2009). For patients with dementia in nursing homes, 75 % received one or more psychotropic drugs in a Norwegian study (Selbaek et al., 2007). Use of drugs with sedative and anticholinergic effects has been discouraged in older persons (Gallagher and O'Mahony, 2008). At the same time, use of benzodiazepines is widespread in older persons in Norway (Neutel et al., 2012), as well as in other countries in Europe (Johnell and Fastbom, 2009) and in the USA (Olfson et al., 2014). Long term use of benzodiazepines is a major health concern in this population (Donoghue and Lader, 2010), and increase the risk of impaired cognitive function (Billioti de Gage et al., 2012), reduce mobility and driving skills (Smink et al., 2010, Madhusoodanan and Bogunovic, 2004) and increase the risk of falls (Allain et al., 2005, Finkle et al., 2011, Kang et al., 2012). The indications for use of benzodiazepines are no different for elderly patients than for younger patients, it has however been suggested that benzodiazepines are prescribed to older patients for less specific symptoms (Madhusoodanan and Bogunovic, 2004). The use of psychotropic medications has been described to increase in older people over the last years (Hughes et al., 2015). In nursing homes, the trend is similar, a Norwegian study comparing psychotropic drug use in nursing homes in 1997 and 2009 conclude that prescribing of psychotropic drugs in nursing homes has increased considerably, especially regarding antidepressants, and that reasons for this need to be explored (Ruths et al., 2013). The pattern of psychopharmacological drug use is not previously well described in a population of geriatric psychiatric inpatients, except for one study from the

UK (Curran 2005) and a recent study of side effects in this population (Hefner et al., 2015).

The term psychotropic polypharmacy has been defined in several ways, and one definition used is the concurrent use of three or more psychotropic drugs (Lesen 2009), and this definition is used in this thesis. The use of more than one psychotropic drug at the same time has been an increasing trend (Centorrino et al., 2002), and has been associated with an increased risk of side effects (Centorrino et al., 2004).

1.3 Adverse drug reactions

Adverse drug reactions (ADR) have been defined as undesired side effects or toxicity caused by administration of a drug (Slee et al., 1996), although determining causality with a suspected drug can be difficult (Naranjo et al., 1992). ADRs are often divided into ”side effects” – which are more or less expected and unavoidable and drug complications, which are more unexpected. The distinction is not well defined, and in this paper the terms ”side effects” and ADR are used synonymously.

1.3.1 Aging and side effects

In older patients, most drugs are less efficiently metabolized, compared with those in younger patients, due to altered pharmacokinetics (Burton et al., 2005). Older people also have a decreased ability to maintain homeostasis, and they may have an increased CNS-sensitivity for drugs (Mangoni and Jackson, 2004), resulting in altered pharmacodynamics. The complexity of the interactions between polypharmacy, comorbidity, altered pharmacodynamic sensitivity, and even modest changes in pharmacokinetics in elderly necessitate due caution in drug treatment (ElDesoky, 2007).

1.3.2 Aging and side effects from psychotropic drugs

Elderly female patients have been found to be especially at risk of drug-related harm from psychotropic drugs (Nyborg et al., 2012). Women have been found to differ not just in frequency, but also in presentation of side effects of psychotropic drugs (Haack et al., 2009). Using antidepressants, older women have a higher serum level than younger patients and men when corrected for dose (Bogwald et al., 2012). Female gender has also been found to be an important determining factor for subjective tolerability of antipsychotic drugs (Barbui et al., 2005), and these drugs may induce more neurotoxicity in female patients than men (Bonelli et al., 2005), although the clinical implications remain unclear (Aichhorn et al., 2006). Although age is most commonly seen as a risk factor of side effects, a Swiss study found that for psychiatric inpatients, the risk of severe ADRs was reduced with increasing age (Greil et al., 2013), but the doses of drugs were also lower in this group, and some adverse effects have for psychotropic drugs shown to be dose-related (Simon et al., 2009, Angelo and Lee, 2013). A clinical prospective study of the prescribing of psychotropic drugs in patients of 65 years and older in Denmark found that side effects were few and mild, perhaps due to cautious introduction and low dose of the medications (Olsen et al., 1990). Also important to remember, is that distinguishing between symptoms of psychiatric disorders and side effects of psychotropic drugs can be difficult (Mihanovic et al., 2009). Some of the psychoactive drugs, such as the selective serotonin reuptake inhibitors (SSRIs) have been regarded as safe for older people, but recent research indicate an increased risk of hip fractures and increased mortality (Coupland et al., 2011, van den Brand et al., 2009). In 2005 and 2008, the US Food and Drug administration issued Black Box warning about atypical and conventional antipsychotic drugs, and after the warning there has been a slight decline in the use of antipsychotics in dementia (Desai et al., 2012). For patients receiving domiciliary care in Norway, a study found that patients with dementia were more likely than patients without dementia to receive antidepressants and antipsychotics (Wergeland et al., 2013), and a recent Norwegian study found that use of antipsychotics in dementia outpatients increased short- and long-term

mortality risk (Langballe et al., 2014). Antipsychotics are known to increase the risk of adverse effects such as orthostatism, sedation and extrapyramidal in older patients (Byerly et al., 2001). A study in the USA of visits to the emergency department due to ADRs and psychiatric medications found that sedatives and anxiolytics caused the most visits in patients 65 years and older, with altered mental status and disturbances in consciousness being the most frequent ADRs, and higher age was associated with an increased risk of hospitalization. Zolpidem, often considered a safer alternative for older patients, counted alone for a fifth of the visits to the emergency department in this age group (Hampton et al., 2014).

1.4 Cognitive function

1.4.1 Cognitive function in the elderly

There are four major classes of cognitive function: Receptive function (abilities to select, acquire, classify and integrate information), memory and learning (information storage and retrieval), thinking (mental organization and reorganization of information) and expressive functions (the means through which information is communicated or acted upon) (Lezak and Lezak, 2004). Cognitive function is important to consider in geriatric patients, and can be influenced by psychiatric conditions, somatic comorbidities, medications and the development of neurodegenerative diseases (Engedal, 2003). Also, normal aging influences cognitive function, and cognitive function declines with age in patients without a diagnosis of dementia (Cullum et al., 2000). Mental disorders play a role, and patients with late-life depression are often found to have cognitive impairment, maybe for as many as half of patients (Butters et al., 2004, Bhalla et al., 2009). A Norwegian study found reduced executive function to be the core neurocognitive deficit in late-life depression (Dybedal et al., 2013), and cognitive impairment is also a well-known major feature of schizophrenia (Harvey, 2001) and bipolar disorders (Gildengers et al., 2014), although the latter is recently debated (Strejilevich et al., 2015). Anxiety and cognitive impairment are often comorbid conditions in older patients, but there are indications towards a

reciprocal relationship (Beaudreau and O'Hara, 2008). Alcohol abuse is known to have effect on cognitive and executive function, and some patients develop widespread cognitive deterioration called alcoholic dementia (Lezak and Lezak, 2004). In dementia, the pattern of cognitive impairment depend on the type of dementia, with memory- and orientation problems being common in Alzheimer's disease, as well as reduced verbal function and apraxia (Engedal, 2000). The symptoms of vascular dementia depend on the localization of the vascular lesions, and reduced memory and disorientation are common symptoms (Engedal, 2000). In frontotemporal dementia, executive functions are often reduced, with patients showing lack of initiative but the most marked symptoms are often change in social behavior and personality (Lezak and Lezak, 2004). In Lewy-body dementia, the fluctuating attention is a central symptom (Engedal, 2000).

1.4.2 Cognitive function and psychotropic drugs

It is well known that use of benzodiazepines influence cognitive function, particularly learning and memory (Roache and Griffiths, 1985, Evans et al., 1990, Golombok et al., 1988). Effects of acute administration are sedation, impairment of learning, psychomotor slowing and anterograde amnesia (Stewart, 2005). Although some tolerance to these effects develop after some time, a meta-analysis comparing long-term users of benzodiazepines to non-users found users to be significantly impaired in all the cognitive domains which were tested (Barker et al., 2004), whereas other studies find that sedation and impaired attention seem to wane (Buffett-Jerrott and Stewart, 2002, Lucki et al., 1986). Studies of cognitive effects of benzodiazepines in older patients have shown contradictory results. Some studies have found small or no differences between users and non-users (Allard et al., 2003, Lagnaoui et al., 2009, Pat McAndrews et al., 2003, Puustinen et al., 2011, Puustinen et al., 2007, Verdoux et al., 2005), and although some of these studies used simple tests as the mini mental status examination, studies using more comprehensive cognitive testing also failed to document cognitive impairment related to benzodiazepines (van Vliet et al., 2009, Bierman et al.,

2007). On the other hand, studies have found decreased cognitive function in older persons using benzodiazepines (Paterniti et al., 2002, Foy et al., 1995, Hanlon et al., 1998), and a recent case-control study found that benzodiazepine use was associated with an increased risk of Alzheimer's disease (Billioti de Gage et al., 2014). There is growing evidence that antipsychotics can cause cognitive side effects in some elderly patients through effects on dopaminergic, cholinergic and histaminergic neurochemical systems (Byerly et al., 2001). Anticholinergic drugs have a risk of central adverse effects and should be used with caution in older patients (Lam and Cheung, 2012), and antidepressants with anticholinergic effects, such as tricyclic antidepressants are often avoided in older patients for that reason (Sultana et al., 2015).

2 Aims

2.1 General aims

The overall aim of the study was to gain more knowledge on the use of and side effects from psychotropic drugs in geriatric psychiatric patients.

2.2 Specific aims

The specific aims were:

1. To describe the use and unreported use of psychotropic drugs on admission to a geriatric psychiatric hospital, in relation to serum concentrations.
2. To describe side effects of psychotropic drugs in geriatric psychiatric patients, and to characterize the patients with major side effects.
3. To investigate the change in cognitive function during inpatient treatment, and whether the cease of use of benzodiazepines was related to change.

3 Methods

3.1 Subjects

This cross-sectional study included all patients admitted to the Department of Geriatric Psychiatry at Diakonhjemmet Hospital in Oslo, Norway, during the study period between the 6th of December 2006 and the 24th of October 2008. The department admits patients aged 60 years and above from a catchment area of approximately 250 000 inhabitants, requiring hospital admission due to psychiatric illnesses, irrespective of cognitive function and whether the illness is age-related or not. The patients are admitted to one of three wards, treating affective disorders, psychotic disorders, and psychiatric and behavioral symptoms of dementia, respectively. In Norway, psychiatric services are publically funded. The department does not serve as an emergency ward, and all admissions are planned. Patients are referred from their general practitioner, nursing home doctors or other parts of the specialist service such as acute psychiatric wards or geriatric departments in somatic hospitals.

All patients admitted during the time period were asked to take part in the present study. Exclusion criteria were as follows: patients admitted for planned electroconvulsive treatment; patients with a short expected stay in the department; and patients and the next of kin being unable to sign the informed consent form required for participation.

A total of 372 patients were eligible for inclusion. Of the total, 57 did not consent to participation, 28 were deemed not liable to give their informed consent and had either no relatives or no way of getting in contact with their relatives. In addition, 40 patients withdrew their consent or were admitted to another department in the

hospital during the study. For 11 patients data were lacking, leaving 236 (63%) patients to be included in the study.

3.2 Serum analyses

The referring doctors´ information on patient drug use was registered on admission. Serum samples were collected in the morning on the day after admission, before any drug was given. Drug regimens were not changed before serum samples were collected. The serum samples were analyzed at the Center for Psychopharmacology, Diakonhjemmet Hospital, in Oslo, with the analysis including all antidepressants and antipsychotics with market authorization in Norway, as well as the most commonly prescribed anticonvulsants and benzodiazepines, totaling 56 drugs. An ultra-performance liquid chromatography-mass spectrometry (UPLC-MS/MS) method, developed for routine therapeutic drug monitoring (TDM) at the Center for Psychopharmacology, was applied for the analyses of all drugs, except for that of Lithium. Lithium was analyzed using an ion-selective electrode measurement. Validation parameters for imprecision and inaccuracy were < 15 % for all analyses. All of the analytical assays had been validated and certified for routine TDM. The laboratory has been accredited since 2007, NS-EN ISO 15189 Medical laboratories, Particular requirements for quality and competence. The reference range for each psychotropic drug was derived in the laboratory, based on the laboratory's extensive database and experience, and in cooperation with other Norwegian laboratories.

3.3 Clinical assessments

The diagnoses of the patients were recorded on discharge. Diagnoses were set by the physician that was responsible for the patient during the hospital stay and were based on all of the available information obtained during the stay. The assessments were conducted by the treating physician or trained research nurses. A set of cognitive tests was performed on admission to hospital and after four

weeks. Whenever possible, new words and numbers were used at the second test to diminish the effect of learning.

3.3.1 The UKU side-effect rating scale

In 1960, the Scandinavian College of Neuropsychopharmacology (SCNP) was established (Ravn, 1961), and one of the major goals was the standardization of clinical trials with psychotropic drugs. In 1969, a subcomittee of SCNP – the Committee on Clinical Investigations (Udvalg for kliniske undersøgelser, UKU) was established. The most widely known UKU contribution is the UKU side effect rating scale (Lingjaerde et al., 1987). The goal was to develop a comprehensive side effect scale with well-defined items to be used in both clinical drug trials and routine clinical practice. The version used in this study was the Norwegian version, 1986.

The scoring should be based on all relevant information available, that is, both on what the patient reports, the doctor's observations during the interview and reports from other health personnel in contact with the patient. Several of the symptoms, such as concentration difficulties, may be part of the illness as such rather than a drug effect. The scoring steps are defined for each symptom, generally following the principle: 0 = not or doubtfully present, 1 = present to a mild degree, 2 = present to a moderate degree, 3 = present to a severe degree. All symptoms are then classified as to their supposed connection to psychotropic drugs with the three alternatives "improbable", "possible" and "probable". The classification is based on previous knowledge of the patient and clinical judgment. The use of rating scales is difficult in elderly due to somatic comorbidities. Separating symptoms of psychiatric disorders, somatic disorders, side effects and normal aging is challenging. The essential requirement for a rater is experience in interviewing psychiatric patients, and the technique should be as close to that of the common psychiatric interview as possible. The scale can be used of other

health workers than doctors. In our study, the interview was performed by the physician responsible for the patient.

The single symptom rating scale cannot be used for deriving a meaningful total side effect score. A total side effect evaluation is of interest, and for that reason the global assessment was included in the scale. A four point rating is used: 0= No side effects, 1= Mild side effects that do not interfere with the patient's daily performance, 2 = Side effects that interfere moderately with the patient's daily performance, and 3 = Side effects that interfere markedly with the patient's performance.

3.3.2 Hopkins Verbal Learning

The Hopkins verbal learning test (HVLT) (Brandt and Benedict, 2001)is a three-trial list learning and recall task comprising 12 words, four words from each of three semantic categories. The test has six equivalent alternate forms, and is particularly appropriate for serial testing as part of longitudinal studies. It is used to provide a brief assessment of verbal learning and memory, and can be given to individuals from 13 years to 80 years and above. The test was intended for use with even moderately demented patients. It is relatively brief and appears well suited for use with difficult-to-test or more severely impaired patients, and at the same time does not appear to have a ceiling effect, and may therefore be useful in patients with high premorbid function (Frank and Byrne, 2000, Hogervorst et al., 2002).

3.3.3 Stroop test

The Stroop effect, a demonstration on interference in the reaction time of a task, was first described in 1935 (Stroop, 1935). When the name of a color is printed in a color not denoted by the name, naming the color of the word takes longer and is

more prone to errors than when the color of the ink matches the name of the color. Knowledge of this effect has led to the development of the Stroop test, which measures a person's selective attention capacity and skills, as well as their processing speed ability (Lamers et al., 2010). The utility of the Stroop test to identify dementia has been studied, and an American study found that the test was able to discriminate persons with healthy aging from those with early Alzheimer's disease (Hutchison et al., 2010).

3.3.4 Digit Vigilance Test

The Digit Vigilance Test (DVT) (Lewis, 1995) measures sustained attention and psychomotor speed. Respondents are asked to find and cross out either sixes or nines, which appear randomly within 59 rows of single digits on two separate pages. The test has been used to study the effect on attention and speed of psychotropic interventions, such as diazepam (Kelland and Lewis, 1996).

3.3.5 Mini Mental Status Examination

The Mini Mental Status Examination (MMSE) (Folstein et al., 1975) is a widely used cognitive test in clinical practice. The test was originally designed to screen for dementia, and includes measures of memory, attention, formation and other cognitive domains. It is brief, easily administered and easily scored. The version for adults should not be given unless the person has at least an eight-grade education level. The memory task consists of three words, which are repeated immediately after presentation and are recalled after two additional tasks. The MMSE also includes orientation items, figure copying, reading and writing, and the maximum score is 30. Attempts have been made to identify optimal cut-offs, based on demographic factors such as age and education, but there remains a lack of uniform clinical guidelines (Lacy et al., 2015). Recent studies have found that the test offers modest accuracy with best value for ruling out dementia in a setting of primary or community care (Mitchell, 2009, Ismail et al., 2010), with an

abnormal score of <26/30 remaining an important signal that investigations are needed (Ismail et al., 2010), but there is a lack of clarity as to what score indicates impairment and for whom (Lacy et al., 2015). It is indeed, although rare, possible to achieve the highest score while suffering from a dementing illness (Shiroky et al., 2007), underscoring the fact that it is not a diagnostic test.

3.3.6 The Montgomery and Aasberg depression rating scale

The Montgomery and Aasberg depression rating scale (MADRS) (Montgomery and Asberg, 1979) is a semi-structured clinician-rated interview commonly used in clinical practice as well as in research, and was performed by the treating physician when patients were admitted. The scale consists of ten items, with a maximum score of 60, where a higher score indicates more severe symptoms of depression. The scale has undergone a considerable amount of psychometric studying and is considered a valid standard for measurement of illness severity in depression, and different cut-offs have been used to indicate remission (Zimmerman et al., 2004). Also, older patients have been shown to report different sets of symptoms of depression than younger patients, and use of subscales have been suggested to measure outcome in older patients (Parker et al., 2003).

3.3.7 Charlson Comorbidity Index

The Charlson Comorbidity Index was developed as a prospectively applicable method for classifying comorbid conditions for use in longitudinal studies (Charlson et al., 1987). This is a weighted index that takes into account the number and the seriousness of comorbid disease. Each condition is assigned a score of 1, 2, 3 or 6, depending on the risk of dying associated with each one. Scores are summed and a total score predicts mortality.

4 Statistics

IBM SPSS® Software version 22.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. The significance level was set to 0.05. Mean values and 95 % confidence intervals (CIs) were reported for the continuous variables and the frequency distributions were reported for the categorical variables. For the comparison between groups, the independent Student's t test was used for the continuous variables, and for the categorical variables, Pearson's chi-squared test or Fisher's exact test was used. In paper II a direct multiple logistic regression was performed for the comparison of characteristics between the patients suffering from major (defined as moderate to severe) or minor (defined as mild or none) side effects, odds ratio (OR) and 95 % CI of the OR were reported. In paper III, test performances on admission (T1) compared to results after four weeks (T2) were compared using paired samples t-test for the whole group. The changes from T1 to T2 were compared between benzodiazepine "quitters" and "continuers" using a multiple linear regression, and standardized β coefficients with p-values were reported.

5 Ethical considerations

The study was conducted in accordance with the Helsinki Declaration. The Regional Committee for Ethics in Medical Research approved the study.

The present study was observational, and not considered to have any harmful effects, but it might have represented an extra effort for some patients. There is a lack of studies in older psychiatric patients, and we believe the contribution to the study offset the possible tiredness associated with the assessments.

For patients who were not able to give an informed consent due to cognitive impairment or severity of psychiatric disease, next of kin was asked.

Patients with mental disorders must be considered to be particularly vulnerable, and due caution when asking for consent is important, but our experience when performing this study was that both patients and their next of kin found contributing to research both important and meaningful.

6 Summaries of results

6.1 Paper I

What is the use and unreported use of psychotropic drugs in older patients when admitted to a psychiatric hospital?

We found that nine out of ten patients (88 %) used one or more psychotropic drug on admission to hospital, with the use of a drug defined as present in blood sample taken the morning after admission before any drug regimen was changed. Concomitant use of two or more psychotropic drugs was found in 159 (68 %) of patients, and psychotropic polypharmacy (the use of three or more drugs) was detected in half of the patients (47 %). The mean dose was below 1 Defined Daily Dose (DDD) for all drug groups, except for the antidepressants, where the average daily dose was 1.2 (1.1-1.4) DDD. When combining all psychotropic drugs, the mean dosage was 1.5 (1.4-1.7) DDD per patient. After four weeks, there were no differences in drug use for any class except for benzodiazepines, where the number of users was significantly reduced from 159 to 107 patients ($p<0.001$). Unreported use of drugs was detected in 100 (43 %) of patients. Benzodiazepines were the most common drug group detected in blood with no report of use, and antipsychotics often used ”on demand”, chlorprotixene and levomepromazine were the most frequent antipsychotics used unreported. For 25 of the patients (11 %), drugs reported used were not detected in serum analyses. These patients were significantly younger with a mean age of 75 years (72.1-77.9), compared to the rest ($p=0.037$). They also had a higher score on the MMSE with a mean of 27.3 (26.1-28.5) compared to the rest with a mean of 23.8 (22.9-24.7) ($p=0.008$). The patients showing unreported use were significantly younger compared with the remaining group of patients ($p=0.003$). A total of 24 patients lived in nursing homes. Of these, ten patients revealed unreported use of drugs and three patients had reported drug use not detected in serum analyses. These findings were no different from the findings among the home-dwelling patients, whether they received home services or not. The patients using the highest

number of drugs were patients with an affective disorder, compared with patients with a main diagnoses of dementia (p=0.010) and with the patients with a main diagnose of psychosis (p= 0.044). Only 37 patients (15.9 %) of the total group had serum levels above reference values. In conclusion, psychotropic drugs are commonly used among older psychiatric patients on admission to hospital. Psychotropic polypharmacy is a major concern with this group of patients. Unreported drug use was frequent, and a low threshold for serum analyses of psychotropic drugs, and perhaps benzodiazepines in particular, seems indicated.

6.2 Paper II

What characterizes the patients with major side effects from psychotropic drugs?

In this study, the UKU side-effect rating scale was performed on admission to hospital. Among the 206 patient included in the analysis, 70 (34%) had major side effects. The most frequent side effects were asthenia (31 %), reduced salivation (31 %), concentration difficulties (28 %), memory impairment (24 %) and orthostatic dizziness (18%). The significant characteristics which predicted major side effects were female gender (OR 2.4, 95 % CI 1.1-5.5), main diagnosis of affective disorder (OR 4.3, 95 % CI 1.5-12.3), unreported use of psychotropic medications (OR 2.0, 95 % CI 1.0-4.1), a higher number of reported psychotropic medications (OR 1.7, 95 % CI 1.2-2.3), a higher number of reported medications for physical disorders (OR 1.2, 95 % CI 1.1-1.5) and higher score on the Charlson comorbidity index (OR 1.2, 95 % CI 1.0-1.4). There were no differences in the routine biochemical test performed on admission between the patients with major side effects and patient with no or minor side effects. In conclusion, clinicians working with older psychiatric patients should be especially aware of side effects in female patients with affective disorders, higher drug use and somatic comorbidity.

6.3 Paper III

Does cognitive function in older psychiatric patients improve after four weeks of treatment, and are changes related to the cessation or the continuation of benzodiazepine use?

Out of the 236 patients included in this study, 165 (69.9%) used benzodiazepines on admission. In this observational study, patients received treatment in accordance with their psychiatric disorders during the hospital stay, and there were no changes in medical treatment as a consequence of the study. Out of the patients using benzodiazepines, 69 patients (41.8 %) quit the use of benzodiazepines during the four weeks hospital stay. Cognitive tests, including the Hopkins verbal learning test, the Stroop test, the Digit vigilance test and Mini mental status examination (MMSE) were performed on admission and after four weeks. For all patients, improved performances were observed in 10 out of 12 cognitive tests, and significant improvements were seen in 4 out of 12 tests. Benzodiazepine ”quitters” improved significantly more than ”continuers” ($p=0.027$) only on the Hopkins verbal learning test, delayed recall performance. For the MMSE, no significant differences between the two groups were found, nor in the MADRS-score. The patients who were continuers were more often depressed ($p<0.001$) and prior admissions to a psychiatric hospital were more commonly observed in this group ($p=0.020$). The patients with a diagnosis of dementia were more likely to quit the use of benzodiazepines ($p=0.018$). In conclusion, the total group of older psychiatric patients had somewhat improved results on cognitive tests after four weeks of hospital treatment, but only on the Hopkins verbal learning (delayed recall) was the improvement related to benzodiazepine cessation.

7 General discussion

This thesis presents three papers elucidating different aspects of psychopharmacological treatment in older psychiatric patients. Firstly, the use and unreported use in relation to serum concentrations are described. Thereafter the major side effects of psychotropic drugs and the related patient characteristics are studied. Finally, in the last paper the performances on cognitive tests after four weeks of treatment are analyzed, in relation to cessation of benzodiazepines.

Older psychiatric patients in need of inpatient treatment are a smaller group of patients, but at the same time challenging patients to treat, as they suffer not only from serious mental disorders, but also medical comorbidity and use many drugs. This is a group of patients who has not been exposed to much research or attention, neither from the clinical field or the research community. These older patients are vulnerable, as they often have sparse relations to family and friends, and they are in need of substantial health and community services. More knowledge of treatment with psychotropic drugs in this population is of value for patients, clinicians, care providers and health care planners.

7.1 The use and unreported use of psychotropic drugs

In the first paper, the use and unreported use of psychotropic drugs are described. Performing serum analyses of all psychotropic drugs available for analysis is a major strength of the study. Such a comprehensive screening, thereby providing information of unreported use, has to the best of our knowledge not previously been performed. The serum levels of main drug have been used when studying adherence (Jonsdottir et al., 2010, Scott and Pope, 2002), and descriptions of drug use are most commonly based on information provided by patients, doctors or

larger prescription registers. Accurate information of drug use just before admission to hospital might shed light on reasons for admission.

Adherence to medication is generally described as the extent to which patients take medications as prescribed, and non-adherence is known to cause worsening of diseases and increased health care costs (Osterberg and Blaschke, 2005). As for mental disorders, non-adherence to medications have shown to increase the risk of hospitalization (Sullivan et al., 1995), and this has also been shown for specific diagnoses such as schizophrenia (Law et al., 2008, Rittmannsberger et al., 2004) and affective disorders (Schumann et al., 1999). In our study, we did not study adherence as such, and serum analyses do not provide us with the one correct answer when it comes to measuring adherence. Collecting the blood samples the morning after admission may both overestimate and underestimate the use of psychotropic drugs. Drugs with a short half-life may be underestimated, and for drugs with a longer half-life, the use may be overestimated. Also, a cross sectional view gives us only information from the day of the analyses, whilst what is more clinically important when taking medication is following medical advice for doses, intervals and remembering to take the drugs every day. The serum analyses cannot provide information of the larger picture. On the other hand, traditional methods for assessing adherence may be unreliable in older patients (MacLaughlin et al., 2005), and there is a need for standardizing measurements of adherence in an older population (Gellad et al., 2011). In our study, only one out of ten patients had a negative serum sample for drugs reported from the referring doctor, which indicates that in this population, non-adherence is not an important factor contributing to hospitalization. This is in contrast to what has previously been published for other populations. The fact that these patients also were younger and had a higher score on the MMSE compared to the rest of the patients, indicates that forgetting medication due to cognitive impairment is not the main or only explanation.

Drug related problems are also a well-known cause of admissions to hospital (Bergman and Wiholm, 1981, Chan et al., 2001, Hallas et al., 1992, Marcum et al., 2012). High serum concentrations of drugs and levels above reference range may increase the risk of adverse reactions in older patients with altered pharmacodynamics and pharmacokinetics due to age-related changes (Turnheim, 2004). Reference ranges are developed based on results from both adults and elderly patients, and there are indications that elderly patients have higher serum levels after correcting for dose (Waade et al., 2012, Aichhorn et al., 2005, Unterecker et al., 2013). The recommended serum levels for the whole population may not be directly transferable to the older population. In our study, 15.9 % of patients had serum levels above reference range. This group of patients might deserve special attention when it comes to side effects, knowing that the ranges are not age-specific, even though we did not find any correlation between major side effects and serum levels above reference range in our study.

The most important finding in the study we believe to be the high number of unreported drugs compared to the information from the referring doctors. This was a rather surprising finding, although discrepancies between reported drug use on admission to hospital and actual drug use is well known (Vira et al., 2006, Rognstad and Straand, 2004). Unreported use was most common for benzodiazepines, as reports in previous studies also support (Hoiseth et al., 2013a, Spagnoli et al., 1989). Knowledge of unreported use of other psychotropic drugs is of clinical importance, but benzodiazepines were by far most common in this study sample, and thereby probably represent the most significant clinical challenge. Many older patients have used benzodiazepines for longer periods of time (Neutel et al., 2012), in contrast to what guidelines recommend, although there is no lack of explicit criteria for inappropriate prescription for elderly people (Rognstad et al., 2009, Gallagher and O'Mahony, 2008, Davidoff et al., 2015). The fact that many patients had unreported use of benzodiazepines is important, as symptoms of withdrawal can be protracted, severe and cause delay in the

correct diagnoses and treatment of psychiatric disorders, when the underlying factor of some symptoms is unrecognized. Withdrawal symptoms can include anxiety, insomnia, memory and concentration impairments and muscle spasms as well as the more rare but serious reactions of fits and psychosis (Lader, 2012).

7.2 Evaluating side effects of psychotropic drugs

In the second paper, a comprehensive consideration of side effects from psychotropic drugs is performed. The use of multiple drugs increase the risk of drug interactions and side effects (Herrlinger and Klotz, 2001), and our patients used a mean number of 2.8 psychotropic drugs based on serum analyses, and use of other drugs was widespread, with a mean of 4.5 somatic drugs. Polypharmacy is inevitable for many older patients, but research has established a strong relationship between polypharmacy and negative clinical outcomes (Maher et al., 2014), and this must be considered when prescribing for the elderly (Steinman and Hanlon, 2010).

When side effects of psychotropic drugs are considered in the population of geriatric psychiatric patients, studies compare drugs (Navarro et al., 2001, Katona et al., 1999, Kyle et al., 1998, Allard et al., 2004) or evaluate side effects of drug groups such as antidepressants in elderly (Mottram et al., 2006). In the naturalistic setting, at least for geriatric psychiatric inpatients, psychotropic polypharmacy is common, and knowledge of side effects in this population is limited. In the second paper, we aim to characterize the patients with major side effects when admitted to hospital. The significant characteristics predicting major side effects were female gender, main diagnose of affective disorder, unreported use of psychotropic medications, a higher number of reported psychotropic medications, a higher number of reported medications for somatic disorders and a higher score on the Charlson comorbidity index. Patients with these characteristics might deserve some extra attention when it comes to evaluating side effects, as these are not always spontaneously reported.

Studying side effects, one must also take into account that placebo medication is known to produce side effects. One of the first reviews of side effects reported in patients receiving placebo (Pogge, 1963) found that these patients reported many common side effects such as drowsiness, vertigo and dry mouth. The reasons for placebo effects in psychiatry are not well known, a recent review concluded that low symptom severity at baseline and a modern trial design were most strongly associated with increased placebo effect (Weimer et al., 2015). The question of reasons for placebo side effects remain unanswered.

In our study, the five most common symptoms considered to be side effects were asthenia (31 %), reduced salivation (31 %), concentration difficulties (28%), memory impairment (24 %) and orthostatic dizziness (18 %). When the UKU side effect rating scale was developed, they found that both failing memory, concentration difficulties and orthostatic dizziness were more frequent above 80 years old, but reduced salivation did not increase with age. Asthenia was increasing in higher age, but at the highest frequency in the lower age groups. Normal symptoms of aging can be difficult to distinguish from side effects, and must be considered. When the scale was developed, they also found an increasing percentage of patients with severe side effects above the age of 50 years. Also, there was a tendency for more side effects with increasing severity of illness.

Why is it important to characterize what recognizes patients more likely to experience major side effects? Older patients are at risk of polypharmacy with associated increased risk of side effects, interactions and non-adherence (Shah and Hajjar, 2012). There is a need for more personalized medicine, and increased awareness on use and side effects of psychotropic drugs is one reason for authors finding it important to write articles such as ”ten commandments” and ”seven sins” of psychopharmacology (Solberg and Refsum, 2015, Salzman et al., 2010).

7.3 Cognitive effects of benzodiazepines

The relation between benzodiazepines and risk of dementia has been debated the recent years. Several studies have found that benzodiazepines may play a role in the development of dementia (Wu et al., 2009, Wu et al., 2011, Lagnaoui et al., 2002, Gallacher et al., 2012, Billioti de Gage et al., 2012), and a recent case-control study found a stronger association for long term exposure indicating a causative relationship (Billioti de Gage et al., 2014). These results are not necessarily transferable to an older population with severe psychiatric disorders and probably more marginal cognitive function, and in a population of geriatric psychiatric patients – no differences in cognitive performances were found on admission to a psychiatric hospital when benzodiazepine users were compared to non-users (Hoiseth et al., 2013b). Elderly of poor mental and physical health are at increased risk of long-term benzodiazepine use (Luijendijk et al., 2008). Although our study was not able to identify a relation between performance on cognitive tests and cessation of benzodiazepines, other side effects of benzodiazepines in older patients, such as risk of falls (Glass et al., 2005, van Strien et al., 2013, Woolcott et al., 2009, Bloch et al., 2011) and fractures (Cumming and Le Couteur, 2003, Allain et al., 2005, Finkle et al., 2011, Kang et al., 2012, Nurminen et al., 2010, Xing et al., 2013) are well known. Although there is an increased awareness of side effects from long-term use, a change in use is yet to be seen (Cunningham et al., 2010), and more focus on harm reduction is warranted (Lader, 2012, Moore et al., 2014).

It should be noted that the patients included in the present study used low doses of benzodiazepines. Previous studies documenting impaired cognitive function of benzodiazepines after long-term use includes users of higher doses, with the average daily dose in a meta-analysis being as much as 17.2 mg (diazepam equivalent) (Barker et al., 2004). The lack of relation between use of benzodiazepines and cognitive function in the present study indicate both that the

effect of benzodiazepines is more difficult to reveal in a population of more marginal cognitive function, but also that the long-term impairment of cognitive function seen in low-dose users might be more limited. Studies of a relationship between dementia and benzodiazepines have not looked at the daily dose, but use or period of exposure. When debating the problem of a large number of benzodiazepine users in the society, it should be kept in mind that most of these persons use a low dose, which probably is comparable to the patients in the present study. Most elderly people taking benzodiazepine anxiolytics took less than 4 DDD per week on average in a Norwegian study (Neutel et al., 2012). So is dose important in benzodiazepine use and risk of dementia? Billioti de Gage et al found a higher risk associated with long acting benzodiazepines indicating a dose-response, (Billioti de Gage et al., 2014), but this question is yet to be answered, and it is a question asked by the patients as well as clinicians and health care planners.

7.4 Methodological considerations

7.4.1 Study group and design

The current thesis has some limitations. The study is cross-sectional, as many clinical studies in the field of psychiatry, and this limits the discussion of causality. In the study of benzodiazepines and cognitive test results, a longitudinal part was added, but the follow-up was after only four weeks, and further measurements would have added valuable information.

The study population were patients admitted to a geriatric psychiatric hospital, and of the 372 eligible patients, 57 patients did not consent. We do not have data on which patients chose not participate, but the impression from the clinical practice was that patients with psychotic diseases more often were not willing to participate in the study. Also 28 patients were not capable of giving consent and

had no next of kin, and it is probable that these patients had more severe dementia. Also, 40 patients withdrew consent or were moved to another department. The patients transferred to another department would be so for somatic reasons, and thereby it is probable that some of the most severely somatic ill patients did not participate. The population studied is therefore probably representative of most older patients in need of psychiatric inpatient treatment, but perhaps not completely so for patients with more severe dementia and more severe somatic illness.

7.4.2 Diagnostic criteria and cognitive tests

All patients were diagnosed by their treating clinician, and the diagnoses registered at discharge were used in our study. Using a diagnostic interview in all patients could have strengthened the diagnostic process, although clinical evaluation and observations over a longer period of time are thorough and naturalistic methods, and diagnostic challenges were discussed in weekly meetings with all treating clinicians present.

The MADRS was performed by the treating clinician. One must keep in mind that this rating scale is not a diagnostic instrument, but a method of comprehensively surveying the type and magnitude of symptom burden present. As this rating scale is commonly used in clinical practice, most doctors would gain much experience with the use of this scale, but the inter-rater reliability was not formally tested.

As for the cognitive tests, MMSE-scores are related to premorbid intelligence and educational attainment, and IQ has a stronger relation to the MMSE than education (Strauss et al., 2006). It has also been found that in patients with probable Alzheimer's disease retested within two weeks, slight improvement is

noted, implying that clinicians monitoring change should be cautious in interpreting small changes (Strauss et al., 2006). In our study, the MMSE was performed by several doctors and nurses, and scoring of some items is somewhat subjective, also there is no time limit for any item. When performing the Stroop test, education shows a modest relation to the score in adults and IQ shows a stronger relation to the test score. Aging appears to be linked with a slowing in color naming. Studies of aging and Stroop results have been somewhat contradictory (Troyer et al., 2006), but experience with the test affect performance (Strauss et al., 2006). For Hopkins Verbal Learning Test, age has the largest effect on every variable, accounting for much of the variance, but education and IQ also have some effect (Brandt and Benedict, 2001). Practice effects did emerge when normal individuals were given the same form after a two week interval, but when alternate forms were used, as was in our study, practice effects were minimal (Barr, 2003).

Another weakness of the study is that symptoms of withdrawal were not specifically registered, as they can sometimes be protracted (Ashton, 1991). Also, improvement of cognitive function has been seen after a longer time period from withdrawal (Curran et al., 2003), and a follow up some time after discharge would have provided more information on this subject.

7.4.3 Analytical methods

The serum analyses of a comprehensive repertoire of psychotropic drugs were a strength of the present study. As for the analytical method of serum analyses, validation parameters for imprecision and inaccuracy were < 15 % for all analytes in the laboratory performing the analyses. In our study, the biggest source of inaccuracy is therefore probably not the serum analyses, but the information provided by the referring doctor, information well known to be less than optimal (Baena Parejo et al., 2015). Supplying this information with other sources, such

as relatives, home services and pharmacy contacts would have given a more complete list, and if adherence were to be studied as such – that would have been key, and would have added valuable data in our study as well.

7.4.4 Assessment of side effects

The present study had available data on complete UKU side effect rating scale assessments of all patients, a strength compared to previous studies. When performing a cross-sectional study on side effects of drugs, a main weakness is the uncertainty with regard to assessing the drug-relatedness of symptoms. There is also a risk of bias in the assessment of drug-relatedness in the direction of expected connections between psychotropic drugs and side effects. In a naturalistic setting, many patients use more than one psychotropic drug, and many have somatic comorbidity, leading to additional medication, making the relation between psychotropic drugs and side effects even more complicated. Also, and especially with older patients, there is the possibility that the choice of ongoing medication has been influenced by previous side effects. The results of cross-sectional studies must therefore be interpreted with caution. Another methodological weakness is also the fact that the grading scale was performed by several clinicians, and the fact that inter-rater-reliability was not formally tested.

Grading the somatic comorbidity, the Charlson comorbidity index was used. A more thorough consideration of frailty would perhaps have given more clinically important knowledge of which patients are more prone to side effects, and would have strengthened this study in that important aspect, as somatic health in mental disorders deserves more attention in all age groups. Also, although predicting mortality is an important aspect, the index have not been shown to predict health care utilization (Yurkovich et al., 2015), which is important in health care planning.

8 Generalizability and further research

8.1 Generalizability of the current results

The patients in this study are included from the catchment area of the department of Geriatric psychiatry at Diakonhjemmet Hospital. The study has the advantage of a rather large sample size for this particular group of patients, and it could be assumed that the results are generalizable to other clinical samples of patients with the same diagnoses within this age group. In Norway, however, psychiatric services for older patients are organized in different ways, and whether you receive treatment in a geriatric psychiatric department or a general psychiatric ward for adults depend on where the patients live. In the catchment area of this study, age is the only factor deciding whether a patient in need of inpatient treatment is admitted to the department of geriatric psychiatry. The selection of the patients contributing to research is probably slightly better functioning patients than those not wishing to contribute, and this is a general problem in clinical studies with informed consent.

8.2 Implications for further research

This was a cross-sectional, observational study and the results must be interpreted in that context. Performing serum-analyses of psychotropic medications gave valuable information on unreported use of drugs, and performing benzodiazepine screening and paying attention to the significance of use and unreported use of this drug group in particular seems indicated. Knowledge of the actual use of benzodiazepines is of importance for a larger group of patients, as use of these drugs is widespread (Olfson et al., 2014), and research point towards more and serious risks associated with benzodiazepine use (Billioti de Gage et al., 2014). Older patients with psychiatric disorders and somatic comorbidity suffer almost inevitably from polypharmacy, making the evaluation of side effects from drugs a harder task than in younger patients. A longitudinal design, where side effects are

registered at several time points and over a longer period of time might give more solid information on what the true side effects are and shed more light on which patients are most at risk of side effects.

As for the results of cognitive tests in relation to benzodiazepine cessation, a naturalistic study gives important information on the patients as they present in a hospital setting and the treatment as usual, but an intervention study with benzodiazepine cessation and a longer follow-up period could provide more knowledge on the importance of such interventions in this group of patients, and perhaps elderly patients in general.

9 Conclusions

The thesis aimed to increase the knowledge on use of and side-effects from psychotropic drugs in geriatric psychiatric patients. The major conclusions we can make are as follows:

1. Patients admitted to a geriatric psychiatric hospital used on average 2.8 psychotropic drugs. Unreported drug use of particularly benzodiazepines was common. Serum levels above reference range were not so common, and this was also the case for finding a negative serum analysis of a reported drug. These findings indicate that polypharmacy and unreported drug use are clinical issues that need to be assessed.
2. A third of the patients were considered to have major side effects. The most important patient characteristics correlated to this finding were female gender, main diagnosis of affective disorder, unreported use of psychotropic medication, a higher number of psychotropic or somatic medications and a higher score on the Charlson comorbidity index.
3. For all patients, improved performances on cognitive tests were seen after four weeks of treatment. Benzodiazepine ”quitters” improved significantly more than ”continuers” only on one test (Hopkins verbal learning test, delayed recall).

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