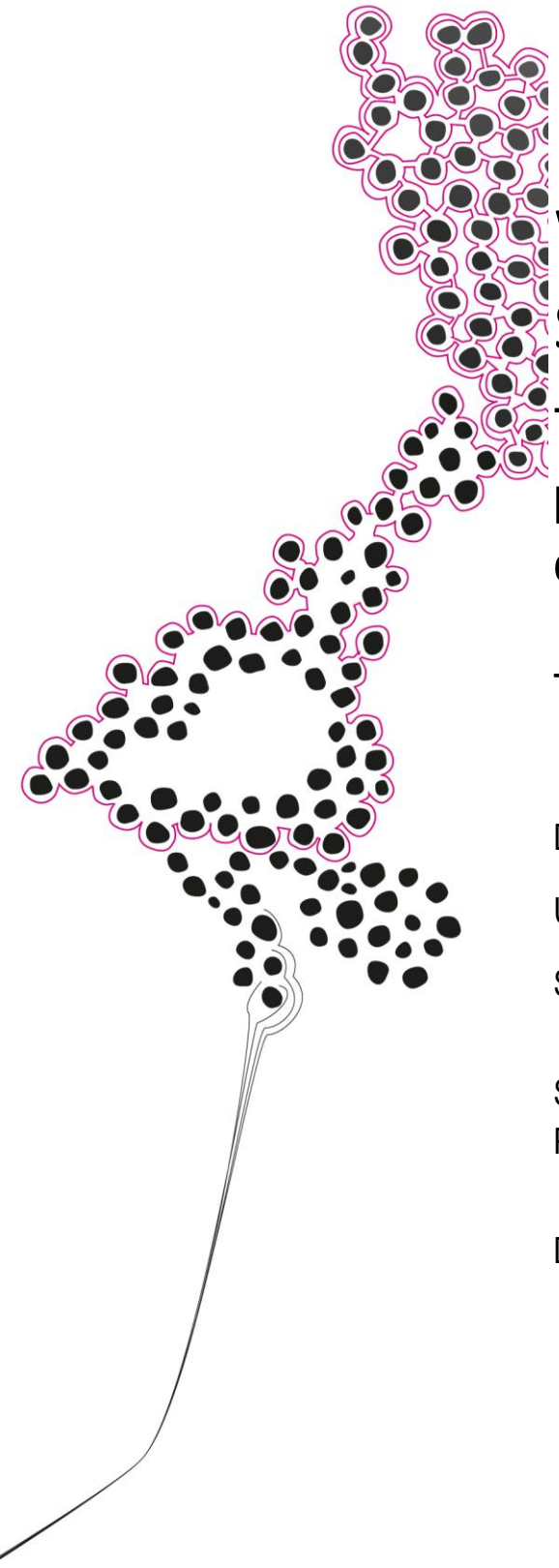

PSYCHOTROPIC MEDICATION OF PATIENTS WITH KORSAKOFF'S SYNDROME

The impact of medication reviews on psychotropic medication and possible changes in behavior

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Abstract

Korsakoff's syndrome (KS) is a degenerative neurological disorder caused by persistent vitamin B1 deficiency. In most cases this deficit is caused by chronic alcoholism. The condition is characterized by a disproportionate impairment in memory and executive functions relative to overall cognitive functioning. Primary medical treatments for cognitive, emotional and behavioral symptoms are antipsychotics, antidepressants, tranquilizers and anticonvulsants. Research on psychotropic medication of patients with KS is rare and shows mixed results for each treatment approach. Therefore, current treatment approaches should be regarded with criticism, to avoid overtreatment.

In the present study data of 64 patients with KS were analyzed, in order to evaluate the advisability of systematic medication reviews for the psychotropic treatment of KS. The psychotropic treatments of patients before and after a systematic review of their medication were compared, in order to find out if the reviews were followed by changes in psychotropic medication. Further, the effects of reduced psychotropic medication on symptoms of agitation and apathy were examined.

The most relevant conclusion of the study is that it is advisable, to review the psychotropic medications of patients with KS. Due to methodological issues this finding has to be regarded with caution. Further investigations are needed to confirm the conclusion. Furthermore, interesting associations could be discovered during the data analysis. Antipsychotic and antidepressant medications were associated with low levels of apathy. Even more interesting was the strong association found between number of psychotropic treatment categories a patient received and symptoms of apathy. Both findings could be interpreted as support for the effectiveness of psychotropic treatment for behavioral symptoms in patients with KS.

Samenvatting

Het syndroom van Korsakov, oftewel Korsakov Syndroom (KS), is een degeneratieve neurologische aandoening, veroorzaakt door een aanhoudend tekort aan vitamine B1. In de meeste gevallen wordt de deficiëntie veroorzaakt door chronisch alcoholisme. De aandoening wordt gekenmerkt door een disproportionele achteruitgang van het geheugen en executieve functies vergeleken met het algemene cognitieve functioneren. Primaire medische behandelingen voor cognitieve, emotionele en gedragsmatige symptomen zijn antipsychotica, antidepressiva, tranquilizers en anti-epileptica. Onderzoek naar psychotrope medicatie van patiënten met KS is schaars en levert gemengde resultaten op voor elke aanpak van behandeling. Daarom moeten gebruikelijke benaderingen met psychotrope medicijnen kritisch beschouwd worden om overbehandeling te voorkomen.

In deze studie werden gegevens van 64 patiënten met KS geanalyseerd om het nut van systematische medicatiebeoordelingen voor de psychotrope behandeling van KS te evalueren. De psychotrope behandelingen van patiënten voor en na een systematische beoordeling van hun medicatie werden vergeleken, om te zien of de beoordelingen gevolgd werden door veranderingen in psychotrope medicatie. Verder werden de effecten van verminderde psychotrope medicatie op agitatie en apathie onderzocht.

De meest relevante conclusie van deze studie is dat het raadzaam is om de psychotrope medicatie van patiënten met KS systematisch te beoordelen. Wegens methodologische problemen moet deze bevinding met voorzichtigheid beschouwd worden. Verder onderzoek is nodig om de conclusie te bevestigen. Voorts konden tijdens de data-analyse interessante associaties ontdekt worden. Antipsychotica en antidepressieva stonden in verband met lage niveaus van apathie. Nog interessanter was de sterke associatie die tussen het aantal psychotrope behandelingscategorieën van een patiënt en symptomen van apathie gevonden werd. Beide bevindingen zouden als steun voor de effectiviteit van psychofarmaca voor de behandeling van gedragssymptomen bij patiënten met KS kunnen worden geïnterpreteerd.

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1. Introduction

Korsakoff's syndrome (KS) is a degenerative neurological disorder caused by a deficiency in thiamine (vitamin B1) that is characterized by a disproportionate impairment in memory and executive functions relative to overall cognitive functioning. Because alcohol consumption is the major predisposing factor for the disorder it is sometimes confused with alcohol related dementia, which is a direct consequence of chronic alcoholism. KS in contrast is assumed to be entirely caused by thiamine depletion, which is the consequence of alcoholism in most cases. Characteristic symptoms are anterograde and retrograde amnesia, impairments in executive functions like attention, planning, concept shifting, organization, monitoring and inhibition, apathy and agitation. (van Oorts & Kessels, 2009; Oscar-Berman, 2012; Kopelman 1995; Harper, Gold, Rodriguez & Perdices, 1989; Kopelman, Thomson, Guerrini & Marshall, 2009).

Besides psychosocial interventions, primary treatments for cognitive, emotional and behavioral symptoms are antipsychotics, antidepressants, tranquilizers and anticonvulsants, though no particular treatment category has been proven to be effective for this particular clientele. Research on psychotropic medication of patients with Korsakoff's syndrome is rare and shows mixed results for each treatment approach. Based on these suggestions and the notion that psychotropic medicines are associated with severe side effects, current treatment approaches should be regarded with criticism, to avoid overtreatment. (Day, Bentham, Callaghan, Kuruvilla & George, 2008; Monnelly, Ciraulo, Knapp, LoCastro & Sepulveda, 2004; O'Carrol, Moffoot, Ebmaier & Goodwin, 1994; Bains, Birks & Dening, 2009; Polycarpou, Papanikalaou, Ioannidis and Contopoulos-Ioannidis, 2008).

The objective of the present study is to compare the daily psychotropic medications of patients with Korsakoff's syndrome before and after systematic reviews of the medical treatments, in order to find out, if the reviews were followed by changes in psychotropic medication. Further, the effects of reduced psychotropic medications on symptoms of agitation and apathy were examined.

1.1 Korsakoff's syndrome

Alcohol consumption is related to a large variety of biological, especially neurological harm such as alcohol related dementia. Besides the fact that alcohol can affect and damage the brain directly, there are also medical conditions that arise from the indirect effects of alcohol consumption. The alcohol-conditioned amnestic syndrome (ICD-10: F 10.6), primarily referred to as "Korsakoff's syndrome" is one of these conditions. One of the first to describe Korsakoff's syndrome was the Russian psychiatrist and neurologist Sergei Korsakow. In 1887 his pioneering research endeavor with 18 alcoholic diseased patients delivered a crucial step to the establishment of a distinct medical condition (Kopelman et al., 2009).

Against common beliefs it is not the destruction of nerve cells, inflicted by alcohol that causes KS, but a complex interaction of indirect implications of alcohol consumption. A lack of vitamin B1 (thiamine) is responsible for the onset of the disease. Non-alcoholic etiologies that result in a thiamine depletion (e.g. Anorexia nervosa) can also be the cause of KS. However, thanks to high nutritional standards this is very uncommon. Kopelman (1995) defines Korsakoff's syndrome as "a disproportionate impairment in memory, relative to other aspects of cognitive function, resulting from a nutritional (thiamine) depletion". Thiamine is crucial for the organic maintenance of the brain. People who saturate their calorie requirement with alcoholic beverage have a lack of essential nutrients, thiamine being one of these. Further, the harm to the digestive system inflicted by alcohol consumption impairs the body's ability to absorb thiamine. The resulting thiamine depletion is responsible for a degeneration of specific brain areas; primarily the thalamus. Further, the diencephalon, mammillary bodies and gray matter in the prefrontal cortex are affected. Besides damage to distinct brain areas recent evidence points to a more intricate pattern of neurological harm. Accordingly, an interruption of complex cerebellothalamocortical and limbic circuitry has been linked to Korsakoff's syndrome (van Oorts & Kessels, 2009; Oscar-Berman, 2012).

Characteristic symptoms of Korsakoff's syndrome include anterograde and retrograde amnesia. The inability to consolidate new memories is often compensated by the integration of old memory fragments into new memories. This is also true for the integration of fantasy content into new memories (confabulations). Further characteristic symptoms include deficits in executive functions like attention, planning, concept shifting, organization, monitoring and inhibition. An impact on executive functioning has been indicated by various studies. However, it is less clear which executive functions are most severely affected (van Oorts & Kessels, 2009). Other characteristic symptoms are agitation, apathy, fatigue and mood swings (Kopelman, Thomson, Guerrini & Marshall, 2009).

The pre-stage to Korsakoff's syndrome is Wernicke's encephalopathy (WE). WE also results from a lack of thiamine and is characterized by mental status changes like confusion, sluggishness, apathy, inability to concentrate and decreased situation awareness. Further common symptoms include ocular abnormalities and motor problems, such as gait incoordination and ataxia. Untreated, WE can lead to coma and death (Sechi & Serra, 2007). The major difference between WE and KS is, that in cases of WE thiamine treatment can elicit a rapid clinical recovery. If WE is left untreated, patients can develop Korsakoff's syndrome, which is also often referred to as "Wernicke-Korsakoff-syndrome". The brain damages characteristic for KS are predominantly irreparable (Zahr, Kaufman & Harper, 2011; Day et al., 2008)

1.2 A description of the population

The actual number of patients with Korsakoff's syndrome in the Netherlands can only be estimated. Blansjaar, Horjus and Nijhuis (1987) concluded that 4.8 in 10,000 people in Den Haag have KS. Current estimations for the Netherlands assume about 8.000 people to be affected by the disease (Brandt, van Bruggen-Rufi & Kluck-Walpot, 2010). Research on international prevalence rates has been rarely published in recent years. Harper, Fornes, Duyckaerts, Lecomte and Hauw (1995) were the last researchers to publish corresponding data. Big differences in prevalence rates between various countries were found in their autopsy based study. Australia had the highest prevalence rates with 2,8% prevalence in a sample of a hospital in Perth and 2,1% in a sample of a hospital in Sydney. Prevalence rates in France ranged from 0,4% to 1,3% and in Germany from 0,3% to 0,8%. The USA had the lowest prevalence rates, ranging from 0% in Oklahoma to 1,0% in Connecticut.

Although the major predisposing factor for the development of KS is abuse of alcohol (Harper et al., 1989), there is no obvious correlation between per capita consumption of alcohol and prevalence rates of Korsakoff's syndrome (Harper et al., 1996). Though most patients with Korsakoff's syndrome are alcoholics, it is not the amount of alcohol consumed, but the degree of thiamine depletion that predisposes an individual to the development of the disease. However, a correlation between alcohol consumption and cognitive impairment in general does exist. Remarkably, evidence suggests a J-shaped relationship between the consumption of alcohol and cognitive impairment. According to Gupta and Warner (2008) people who consume low levels of alcohol are less prone to the emergence of cognitive

impairment than people who do not consume alcohol at all. An explanation of this phenomenon or indications of a causal relationship are not provided. Kopelman, Thomson, Guerrini and Marshall (2009) concluded that some heavy drinkers may also have a genetic predisposition to the development of Korsakoff's syndrome. In a Dutch study 75% of KS patients were male (Schepers, Koopmans & Bor, 2000), which reflects the fact that men are more prone to alcohol- use and abuse than women (Hasin, Stinson, Ogburn & Grant, 2007). The same study showed that more than 50% of the patients were divorced and that the average patient had about 3 co-morbid conditions like psychological disorders, hypertonia or liver diseases at admission (most of these being due to alcoholism). Prevalence rates are higher in areas of socio-economic deprivation and in people 50-60 years of age (MacRae & Cox, 2003; Cox, Anderson & McCabe, 2004). The incidence of KS can be reduced by systematic interventions. Harper, Sheedy, Lara, Garrick, Hilton and Raisanen (1998) concluded that a significant decline in prevalence rates of KS in Australia has taken place after a nationwide program of thiamine fortification in bread flour had been implemented.

1.3 The effects of psychotropic medicine

Research on psychotropic medication of patients with Korsakoff's syndrome is scarce and neither the effectiveness nor the ineffectiveness of any particular direction of psychotropic treatment has been adequately established. While there is little known about the effects and especially the side effects of psychotropic medication of patients with Korsakoff's syndrome, sources of additional insights can be suggested by findings about psychotropic medication of patients with dementia. Though not classified as dementia, KS as an amnestic disorder is very similar to some types of dementia like Alzheimer's disease (van Oort & Kessel, 2009). Because of the congruence between symptoms of the diseases it is often even difficult to distinguish between them. Because of the high mean age of patients with KS they are often erroneously diagnosed with Alzheimer's disease (Oslin, Atkinson, Smith & Hendrie, 1998).

Besides the similarities in etiology there are also many similarities in the medical treatment of these diseases. Particularly antipsychotics are frequently prescribed to counteract symptoms of different dementia types, Korsakoff's syndrome and alcohol dependency (Day, Bentham, Callaghan, Kuruvilla & George, 2008; Monnelly et al., 2004; Nijk, Zuidema & Koopmans, 2009). A case study by Kamlana (1996) demonstrated the effectiveness of the

antipsychotic Risperidone in the reduction of psychotic symptoms in a patient with KS. Representative studies with more participants or other antipsychotics for Korsakoff's syndrome populations have not been conducted. Research on antipsychotic medications in patients with dementia has raised doubts about their effectiveness. Alltough many patients with dementia are treated with antipsychotic medicine, current findings indicate a high rate of patients who do not profit from this approach. Nijk, Zuidema and Koopmans (2009) addressed amongst others the effectiveness of antipsychotic medication for patients with dementia. They conclude that "the association with neuropsychiatric symptoms raises questions of efficacy of these drugs and the risk of chronic use". Kleijer et al. (2009) demonstrated that only a minority of 15% of the patients with dementia showed improvements in behavioral problems in response to antipsychotic medication. The study showed that the majority of patients did not gain profit on behavioral problems from antipsychotic treatment. It also showed that behavioral problems stayed stable or even improved in 58% of the patients after withdrawal from antipsychotic medicine.

Though frequently prescribed, the effectiveness of antidepressants for patients with KS is also questionable. Evidence provides a mixed picture of the usefulness of antidepressant medication. In addition to positive effects on mood, the norepinephrine reuptake inhibitor Reboxetine produced significant increases in cognitive performance in a sample of 105 patients with Korsakoff's syndrome (Reuster, Buechler, Winiecki & Oehler, 2003). Several studies indicated enhanced memory performances in patients with KS as a consequence of treatment with the selective serotonin reuptake inhibitor Fluvoxamine (Mrazek, Menges, Steffes, Thelen & Erkwoh, 1999; Martin, Adinoff, Lane, Stapleton, Bone, Weingartner, Linnoila & Eckardt, 1995). Another study demonstrated that aside from moderate positive effects on mood, Fluvoxamine was associated with impaired verbal fluency and the emergence of severe depressive episodes in some patients with KS (O'Carrol et al., 1994). Besides the few findings on antidepressant medication of patients with KS only weak support for the use of antidepressant medicine in patients with dementia is offered (Bains, Birks & Dening, 2009).

Many KS patients are treated with benzodiazepines (tranquilizers), because of their comorbid alcohol dependency. Treatment with tranquilizers is the standard practice to counteract symptoms of withdrawal in patients with alcohol dependency (Saitz & Malley, 1997; Soyka, 1995). Further, tranquilizers are frequently used in the long-term treatment of chronic alcoholism (Kissin, 2006). For Korsakoff's syndrome this practice should be handled with caution because of the congruence between symptoms of the disease and side effects of

the medication. Consumption of tranquilizers causes strong anterograde amnesia (Venault, Chapouthier, Carvalho, Simiand, Morre, Dodd & Rossier, 1986; Curran, 1991). Specific effects of tranquilizers on anterograde amnesia in KS patients have not been investigated yet. The same is true for effects on executive functioning and coordination. Both KS and comsumption of tranquilizers are responsible for a decline in attention and psychomotor tasks (Curran, 1991).

Like tranquilizers, anticonvulsants are regularly prescribed for patients with KS because of comorbid alcohol dependency. They are used to counteract symptoms of withdrawal, especially seizures. They also offer advantages over tranquilizers in the treatment of alcohol withdrawal. In contrast to tranquilizers, anticonvulsants do not have any abuse potential, minimal interactions with alcohol and may be more effective in the improvement of psychiatric symptoms of alcohol withdrawal (Myrick, Brady & Ballenger, 2001). As indicated by Johnson (2004) anticonvulsant medications are also "promising treatments for reducing drinking and preventing relapse among alcohol-dependent individuals". On the other hand, there is less promissing research on anticonvulsants in the treatment of alcohol dependency. Polycarpou et al. (2008) included 48 studies with a total of 3610 individuals in their review in order to determine the effectiveness and safety of anticonvulsants in the treatment of alcohol withdrawal. Their findings suggest that definite conclusions about the effectiveness and safety of anticonvulsant medication in alcohol withdrawal cannot been drawn from the results. In comparison to placebo conditions therapeutic success tended to be more common among patients treated with anticonvulsants. Anticonvulsants also tended to show a protective benefit against seizures, but these effects did not reach formal statistical significance.

In addition to the doubts about the effectiveness of psychotropic treatment there is also a wide range of side effects that have to be considered. There are very few studies on psychotropic medication of patients with Korsakoff's syndrome available and very little is known about side effects of psychotropic drugs for this particular group of patients. In dementia, agitation and apathy are very common, especially in those patients who are treated with antipsychotics. It is difficult to infer causality from these data, because antipsychotics are both prescribed to counteract these symptoms as well as suspected to cause them (Pitkala, Laurila, Strandberg & Tilvis, 2004; Wetzels, Zuidema, de Jonghe, Verhey & Koopmans, 2010; Nijk, Zuidema & Koopmans, 2009; Zuidema, Derksen, Verhey & Koopmans, 2007). Findings about patients with dementia cannot be generalized to patients with KS. In order to gain insights about the impact of psychotropic medication on patients with KS more research with this particular target population is needed. Especially systematic medication reviews in

which the current medications of individual patients are assessed, adequately adapted and documented could deliver useful sources of information about the effectiveness of psychotropic treatment.

1.4 The present study

The aim of the present study is to investigate if systematic medication reviews for patients with Korsakoff's syndrome lead to changes in psychotropic medical prescriptions and if these changes in turn lead to behavioral changes. As indicated by the evidence, effects of psychotropic medication in the treatment of dementia and alcoholism range from reduced symptoms and behavioral improvements to non-effectiveness and negative side effects. These findings do not allow solid conclusions about patients with Korsakoff's syndrome and the impact of their medication on behavioral symptoms. For the present study data of patients with Korsakoff's syndrome were gathered, in order to assess if a systematic review of their psychotropic medication led to an adaptation of it. Further, the relation between adapted medications and subsequent agitation and apathy levels was explored. Demographic data were collected, in order to explore differences between groups.

Three sources of information were used. The first is a patient record of the regular daily medications. The second is a measure of agitation symptoms. And the third is a measure of apathy symptoms. Health care professionals were responsible for the observation of patients' behavior and the corresponding documentation of it with the behavioral measures. All information was gathered at two points in time, 6 months apart. The collected data will be used to answer the following research questions:

1. *Does a systematic review of the psychotropic medication of patients with Korsakoff's syndrome lead to adapted medical prescriptions?*

2. *If so, in how far are adapted psychotropic medications associated with changes in agitation and apathy symptoms?*

2. Methods

2.1 Participants

For the present study, data of 64 patients of the ZorgAccent nursing home in Hellendoorn were used. All patients were diagnosed with Korsakoff's syndrome. 48 patients were male and 16 female. Patients were between 44 and 77 years of age with a mean age of 60 years when the first set of data was assessed in December 2012. The second set of data was assessed in June 2013. The systematic medication reviews were executed and documented by the patients' physician in charge. Measures of agitation and apathy symptoms were gathered by patients' primary caregivers.

2.2 Record of the daily medication

The first source of information was the record of a patient's daily psychotropic medication. The substances and dosages of patients' medications with emphasis on antipsychotics, antidepressants, tranquilizers and anticonvulsants were documented at the same two points in time as the behavioral measures. The records contained detailed documentations of all prescribed medications. For the present study only prescriptions of psychotropic substances were included in the analysis, because of their controversial usefulness for patients with KS and their impact on patients' behaviors. All substances were registered with frequency, time and dosage of daily administration. For the statistical analysis specific substances were grouped into antipsychotics, antidepressants, tranquilizers or anticonvulsants. For practical reasons, the dosages of substances were expressed in percentaged changes between the first and the second measure. For instance, the alteration from a daily administration of 4x10mg Diazepam to a daily administration of 2x5mg Diazepam was expressed as 75% reduction in tranquilizers. This approach could be applied without concern, because relative changes in medication and not absolute dosages of substances were of interest for this study.

2.3 Instruments

In order to assess symptoms of agitation and apathy among patients in this study, the Cohen-Mansfield Agitation Inventory (CMAI) and the Apathy Evaluation scale (AES) were used. The CMAI was developed by Jiska Cohen-Mansfield to systematically assess agitation. Cohen-Mansfield and Billing (1986) define agitation as "inappropriate verbal, vocal, or motor activity that is not judged by an outside observer to result directly from the needs or confusion of the agitated individual. Agitation is not a diagnostic term, but rather a term used by clinicians for a group of symptoms that may reflect an underlying disorder". The 29 item scale was designed to be filled in by primary caregivers of elderly patients, but can also be applied to other patients who exhibit agitated behaviors. Items like "Hitting", "Spitting", "Screaming" and "Negativism" are rated on a 7 point scale of frequency, ranging from (1) "Never", to (2) "Less than once a week", (3) "Once or twice a week", (4) "Several times a week", (5) "Once or twice a day", (6) "Several times a day" and (7) "Several times an hour". Test scores range from 0 to 230. High scores indicate high levels of agitation. Ratings pertain to two weeks preceding the administration of the test. The instrument is restricted to frequency and does not assess severity of behavior (Cohen-Mansfield, 1991). The instrument demonstrated high coefficients of inter-rater reliability ranging from 0.88 to 0.92 (Whall, Black, Yankou, Groh, Kupferschmid, Foster & Little, 1991). Reliability coefficients for internal consistency (Cronbach's alpha) were between 0.86 and 0.91. High correlations between the CMAI and the Behavioral Pathology in Alzheimer's Disease (Behave-AD) and the Behavioral Syndromes Scale for Dementia (BSSD), which are also validated measures of agitation, indicate a high convergent validity of the instrument (Finkel, Lyons & Anderson, 1992). Through factor analysis, three different clusters of agitation could be isolated. These are: aggressive behavior, physically nonaggressive behavior and verbally agitated behavior (Cohen-Mansfield, 1991). Only total scores were examined for the present study, in order to analyze overall changes in agitation.

The Apathy Evaluation Scale (AES) was developed by Robert S. Marin and serves to quantify apathy in adults and elderly individuals. It was not specifically designed for patients with KS but is frequently used for patients with dementia (Marin, Biedrzycki & Firinciogullari, 1991). Marin, Biedrzycki & Firinciogullari (1991) define apathy as "lack of motivation not attributable to diminished level of consciousness, cognitive impairment, or emotional distress". They further describe it as "a psychological dimension defined by simultaneous deficits in the overt behavioral, cognitive, and emotional concomitants of goal-directed behavior". The recognition of apathy depends on identification of specific changes in

three distinct areas: observable (overt) activity, thought content and emotional responsiveness. The 18 items of the AES were chosen in order to evaluate diminished goal-directed behavior, cognitive evidence of apathy and emotional evidence of apathy on a four-point scale of correctness, ranging from "Not at all" to "Slightly", "Somewhat" and "A Lot". Scores for the AES range from 18 to 72 with low scores indicating high levels of apathy. Satisfactory coefficients of reliability for the AES could be assessed. Coefficients for internal consistency reliability ranged between 0.86 and 0.94. Test-retest reliability varied from 0.76 to 0.94. Further an intraclass correlation coefficient of 0.94, indicating high interrater reliability, was found. The validity of the instrument was also shown to be satisfactory. Through measures of correlation the convergent and discriminant validity of the AES were assessed. A significant Pearson product moment correlation of 0.35 between the AES and the anxiety score of the Neuropsychiatric Inventory (NPI) were found, indicating satisfactory convergent validity. Further, negative Pearson product moment correlations between the AES and the euphoria score of the NPI (-0.46) and the Mini Mental State Examination (MMSE) (-0.48) were found, indicating satisfactory discriminant validity. These results were based on data of 123 patients with different medical backgrounds including strokes, Alzheimer's disease, major depression and absence of mental illness. The authors recommend the use of own norms for this instrument because of differences between medical conditions (Marin, Biedrzycki & Firinciogullari, 1991).

2.4 Procedure

The first step for the execution of the study was the documentation of the patients' medications. At the same time the first sets of behavioral measures were assessed. These measures were completed by primary health care professionals of the patients. Thereafter a systematic review of the patient's medications was conducted by the physician in charge. Six months after the documentation of medications and behavioral symptoms these data were documented for the second time. Behavioral measures were completed by the same health care professionals as for the first measure.

In June 2012, six months before the systematic review of the patients' medications a first systematic review of the patients' medications was conducted by the treating physician. Unfortunately, medical adaptations after this initial review were not documented and behavioral measures were not assessed. This constitutes a significant weakness of the study.

All registered changes in medication and behavior in this study might thus in fact be underestimations of the actual impact of medication reviews. This issue will be examined in more detail in the discussion section.

In short the procedure can be summarized as follows: Before the beginning of the present study a systematic review of the patients' medications (Review A) with medical adaptations took place. Six months later the actual study began. The first step was the documentation of the patients' medications and scores on behavioral measures. These baseline data were probably already affected by Review A. Another six months later, the second step was the execution of a second systematic review (Review B). The last step was the second documentation of the patients' medications and scores on behavioral measures.

2.5 Data analysis

For the data analysis SPSS was used. In order to find an answer to the first research question and to generate a global overview of the patients' baseline characteristics, descriptive statistics with corresponding graphs for medications and changes in medications were computed. To find an answer to the second research question independent samples t-tests and paired samples t-tests were performed. The first step was to use independent samples t-tests in order to find out, if the consumption of psychotropic medication in general and the consumption of specific psychotropic medication categories were related to symptoms of agitation and apathy. Subsequently, paired samples t-tests were performed, to test if the subgroup of patients who received adapted medications scored systematically higher or lower on measures of apathy or agitation after the alteration in prescribed medicines.

Besides the illumination of the research questions additional computations were executed, in order to explore characteristics of the population regarding gender, age, test scores and medications. Aside from descriptive statistics and further significance tests for differences between various groups, correlation tables were generated, to reveal relationships between number of different prescribed medication categories, test scores and age. Finally analyses of variance were conducted in order to examine cumulative effects between medication categories on test scores. Both moments of measurement were independently included for these analyses.

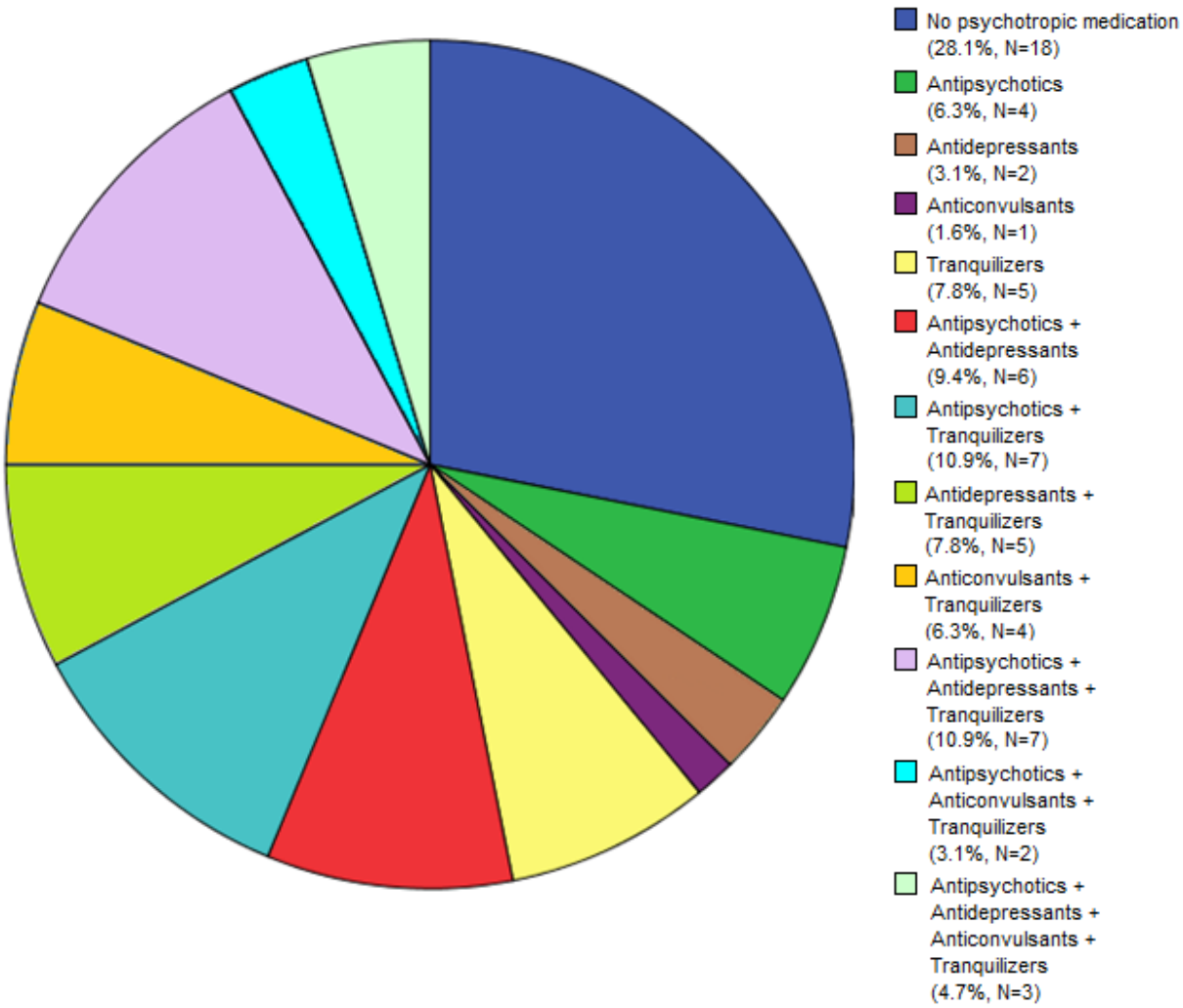
3 Results

3.1 Baseline characteristics

Frequency tables regarding consumption of psychotropic medicine revealed the following results: when the first measures were assessed, 46 (71.9%) of the 64 patients were treated with psychotropic medication. 4 (6.3%) were exclusively treated with antipsychotics, 2 (3.1%) with antidepressants, 5 (7.8%) with tranquilizers and 1 patient (1.6%) with anticonvulsants. 6 (9.4%) received a combination of antipsychotic and antidepressant medication, 7 (10.9%) received antipsychotics and tranquilizers, 5 (7.8%) antidepressants and tranquilizers, 4 (6.3%) tranquilizers and anticonvulsants. 7 (10.9%) were treated with a combination of antipsychotics, antidepressants and tranquilizers, 2 (3.1%) with antipsychotics, anticonvulsants and tranquilizers and 3 (4.7%) received all four categories of medication. Thus, more than half of the patients (N=34, 53.1%) were treated with multiple categories of psychotropic medication. A graphical representation of these data can be seen in Figure 1. On average patients received 1.5 medication categories. The mean scores for the first behavioral measures were 40.2 for the Cohen-Mansfield agitation inventory with a standard deviation of 9.3 and 52.6 for the Apathy evaluation scale with a standard deviation of 13.9. Consumption of antipsychotic medicine was significantly more frequent among male patients (54.2%) when compared to female patients (18.8%) ($t=-2.85$, $df=31.90$ $p<0.008$).

Figure 1

Distribution of Medication Categories of 64 hospitalized Patients with Korsakoff's Syndrome



3.2 Adaptations in psychotropic medications

After Review B six patients (9.4%) received adapted psychotropic treatments. 5 patients received reduced medications and one patient received increased medication. For one patient antidepressant medication was entirely disposed, for one patient antipsychotic medication was reduced by 50% and for three patients medications with tranquilizers were reduced by 66.7%, 25% and 15%. The patient with increased medication received a 25% increase in anticonvulsant medicine. Adaptations in psychotropic medications are summarized in Table 1.

Table 1

Changes in daily psychotropic Medication of 64 hospitalized Patients with Korsakoff's Syndrome

	Reduced medication	Increased medication	No change in medication
Antipsychotics (N=29)	3.45% (N=1)	0%	96.55% (N=28)
Antidepressants (N=23)	4.35% (N=1)	0%	95.65 (N=22)
Tranquilizers (N=33)	9.09% (N=3)	0%	90.91% (N=30)
Anticonvulsants (N=11)	0%	9.09% (N=1)	90.91% (N=10)
Total (N=96)	5.21% (N=5)	1.04 (N=1)	93.75 (N=90)

3.3 Changes in behavioral symptoms

Through tests of significance differences between groups were examined. Patients who consumed antipsychotics had a mean score of 62.4 on the first measure of the AES (N=29) and 63.6 on the second measure (N=28), while patients who did not consume antipsychotics had mean scores of 44.6 on the first (N=35) and 46.7 on the second measure (N=36). Independent samples t-tests revealed that these differences were significant both for the first ($t=6.58$, $df=62$, $p<0.000$) and the second measure ($t=7.19$, $df=58$, $p<0.000$). So, patients who consumed antipsychotics tended to exhibit less symptoms of apathy than patients who did not consume antipsychotics. The same is also true for the consumption of antidepressants and apathy symptoms. Patients who consumed antidepressants (N=23) had a mean score of 60.6 on the first measure of the AES and 60.7 on the second measure, while patients who did not consume antidepressants (N=41) had mean scores of 48.2 on the first and 50.8 on the second measure. These differences were significant for the first ($t=3.75$, $df=62$, $p<0.000$) and the second measure ($t= 3.20$, $df=58$, $p<0.002$). In summary, patients who consumed antipsychotic or antidepressant medicines showed significantly less symptoms of apathy than patients who did not consume these medications. Other treatment approaches were not related to higher or lower scores of apathy symptoms. No category of psychotropic treatment was related to higher or lower scores of agitation.

Patients with adapted psychotropic medications (N=6) had mean scores of 61.4 for the first and 61.2 for the second measure of agitation and 47.8 for the first and 47.3 for the second measure of apathy. Paired samples t-tests showed that both for agitation ($t=0.75$, $df=6$, $p<0.486$) and for apathy ($t=-1.14$, $df=6$, $p<0.320$) no significant differences between measurement moments could be found. With regard to the second research question, patients with adapted medications did not score systematically higher or lower on behavioral measures after the medical alteration.

3.4 Extended explorations of the population

Additional computations were executed in order to explore further characteristics of the target population. The following noteworthy findings were obtained: Positive correlations between AES and CMAI scores were found, indicating a negative association between symptoms of agitation and symptoms of apathy. So, patients with high levels of agitation tended to exhibit low levels of apathy and vice versa. This association was stronger at the second moment of measurement. Further, strong positive correlations between AES scores and number of psychotropic medication categories could be demonstrated, indicating a negative association between number of psychotropic medication categories and apathy symptoms. Accordingly, high quantities of different medication categories were associated with low levels of apathy. All correlations found in the sample are summarized in Table 2.

Analyses of variance indicate that there is a cumulative effect between the consumption of antipsychotics, antidepressants and tranquilizers on scores on the first measure of agitation symptoms ($F=9.17$, $df=1$, $p<0.004$). The combination of these three medication categories was associated with high levels of agitation symptoms for the first measure. This finding did not apply to the second measure of agitation symptoms.

Table 2

Correlations between Measures of Behavior and Number of psychotropic Treatment Categories of 64 hospitalized Patients with Korsakoff's Syndrome

	Apathy Evaluation Scale - Measure 1	Apathy Evaluation Scale - Measure 2	Cohen-Mansfield Agitation Inventory - Measure 1	Cohen-Mansfield Agitation Inventory - Measure 2
Apathy Evaluation Scale - Measure 2	**0.84** **p< 0.000**			
Cohen-Mansfield Agitation Inventory - Measure 1	0.13 p< 0.326	**0.39** **p< 0.003**		
Cohen-Mansfield Agitation Inventory - Measure 2	**0.42** **p< 0.001**	**0.28** **p< 0.037**	0.21 p< 0.139	
Number of psychotropic medication categories	**0.50** **p< 0.000**	**0.51** **p< 0.000**	0.16 p< 0.216	0.18 p< 0.198

3.5 The initial medication review – A report of the physician in charge

The lack of data preceding Review A constitutes a significant deficit of the study. Due to this shortcoming the present data are difficult to interpret. In order to compensate for this deficiency a report of the treating physician was assessed. Accordingly psychotropic treatment with antipsychotics or tranquilizers was reduced for at least 10 patients after Review A was conducted. For one patient the reduction was canceled because of an increase in agitation and anxiety. For the remaining nine (or more) patients the reduction proved to be adequate. Health care professionals reported a considerable decline in apathy symptoms among the patients with reduced medications. There was no overlap between these patients and the five patients who received reduced medications after Review B.

4. Discussion

4.1 Conclusions

These results leave ample space for interpretations. In order to interpret the results, first of all the most important findings will be summarized: Most of the 64 patients were treated with psychotropic medicine and the majority received a combination of different psychotropic treatments. Five patients received reduced medications and one patient received increased medication after Review B. No significant differences regarding behavioral symptoms between patients with adapted psychotropic medications and other patients were found. Patients who consumed antipsychotics or antidepressants tended to exhibit significantly less symptoms of apathy. Further, a negative association between number of prescribed psychotropic medication categories and symptoms of apathy was found. According to the report of the physician in charge about Review A, about 10 patients were already treated with reduced psychotropic medications before Review B was conducted. As observed by health care professionals, these patients experienced considerable decreases in apathy symptoms. It should also be mentioned that in 2012 (before the first medication review) a comparison between nursing homes for patients with Korsakoff's syndrome regarding prescriptions of psychotropic medicine was assessed. Interestingly, among 11 nursing homes the ZorgAccent nursing home was on the third place of the lowest rate of psychotropic prescriptions. So, before the realization of any systematic review patients of the ZorgAccent nursing home were already treated with low rates of psychotropic medication compared to other nursing homes for patients with KS.

The first research question was if a systematic review of the psychotropic medication of patients with KS would lead to adapted medical prescriptions. Considering the results of the present study and the report of the physician in charge about Review A, the answer to this question seems to be "yes". Unfortunately, no solid conclusion regarding the question can be based on the findings of the present study. However, a tendency towards medication reduction appeared. Five patients received reduced medications, whereas only one patient received increased medication. For all other patients psychotropic treatments remained unchanged after Review B. It should be noticed, that an initial review had taken place, before the present study was conducted. The impact of this review was not accurately documented, but the resulting impression clearly points to reduced psychotropic medications following Review A. Both reviews combined led to reduced psychotropic prescriptions for at least 15 patients, which is

more than 20% of the whole sample. Given the fact that the ZorgAccent nursing home was known for low rates of psychotropic prescriptions before the realization of medication reviews, it might be suggested that systematic medication reviews in other institutions for patients with KS could result in even more extensive adaptations of psychotropic treatments.

The second research question "If so, in how far are adapted psychotropic medications associated with changes in agitation and apathy symptoms?" cannot be answered with certainty based upon the present results. Tests of significance demonstrated that patients who underwent a change in psychotropic medicine did not score systematically higher or lower on measures of agitation or apathy after the adaptation was implemented. The lack of significant differences implies that altered medications did not have any influence on symptoms of agitation or apathy. But this is not necessarily true. Given the small amount of individuals with adapted medications, differences in scores between the two moments of measurement would have to be consistent or quite big in order to be significant. Furthermore, according to the primary caregivers of the 10 patients who received reduced psychotropic medications after Review A, these patients exhibited considerable declines in apathy symptoms. No certain answer to the second research question can be based upon the results of the present study. An impact of adapted psychotropic prescriptions on agitation or apathy cannot be ruled out based on the present findings.

Besides answers to the research questions there was more information gathered during the data analysis that require an interpretation. One finding was that patients who consumed antipsychotics or antidepressants exhibited significantly lower levels of apathy symptoms than patients who did not consume these medicines. One plausible explanation for these results is that antipsychotics and antidepressants counteract apathy symptoms and that patients experience a decline in apathy as a result of antipsychotic and antidepressant treatment. Contrary to the findings of Kleijer et al. (2009) and Nijk, Zuidema and Koopmans (2009) antipsychotics could thus be effective at least in the treatment of behavioral symptoms.
Concerns about the effectiveness of antidepressants (Bains, Birks & Dening, 2009) could also not be confirmed in this study. However, it is also possible, that the subgroups of patients who were treated with antipsychotics or antidepressants scored low on symptoms of apathy before their medical treatment.

The negative correlation between number of different psychotropic treatment categories a patient received and symptoms of apathy deserves special attention, because of its magnitude. This correlation was found for both measures of apathy symptoms and was quite strong. Furthermore, it had very high levels of statistical significance. Unfortunately we

are left with this statistical snap-shot. There is no information available about the level of behavioral symptoms of patients before they received psychotropic treatment. So, it is not known if the correlative association is based on causality. Causality assumed, the association could be interpreted as further support for the effectiveness of psychotropic treatment in the reduction of apathy symptoms. Patients could have experienced a decline in apathy symptoms as a result of treatment with multiple medication categories. It is unlikely that the mere number of treatment categories is related to low levels of apathy. The combination of certain substances or at least of certain medication categories is more likely to be responsible for a decline in apathy symptoms. Direct causality is one possible explanation. But other interpretations have to be considered, too. Patients could have exhibited low levels of apathy before the prescription of their psychotropic treatment. In this scenario a superordinated variable could be the cause of both high numbers of treatment categories and low levels of apathy. Degree of alcohol dependency for example is a variable that could explain the association of the two underlying variables. A high degree of alcohol dependency could be a reason for the prescription of multiple medication categories, in order to counteract symptoms of withdrawal. Especially in the early stadium of alcohol withdrawal patients exhibit high levels of agitation (Addolorato et al., 2006) which in turn is associated with low levels of apathy. The negative association between agitation and apathy could also be demonstrated in the present study. In order to get beyond these speculations, further research on the correlation between number of psychotropic treatment categories and symptoms of apathy is needed.

Analyses of variance indicated a cumulative effect of antipsychotics, antidepressants and tranquilizers on symptoms of agitation. The three substance categories by themselves were not related to symptoms of agitation. The combination of all three however, seems to have caused a rise in agitation symptoms. An alternative explanation would be that patients who exhibit high levels of agitation frequently receive a combination of antipsychotics, antidepressants and tranquilizers in order to counteract agitation symptoms. For this particular finding the first approach seems to be the better explanation, because no single treatment category was associated with agitation. Finally the fact that the correlation between AES and CMAI scores changed over time, requires an interpretation. A possible explanation could be that some patients experienced changes in behavior between the two moments of measurement. This seems likely, given the fact that symptoms of withdrawal decrease over time. Thus, it could have been expected that patients who were new in the institution exhibited changes in behavior during their first weeks. Another explanation could be that the instruments are not as reliable as expected.

4.2 Critical reflection

For a number of reasons the discussed findings must be considered with caution. The most significant weakness of the study is the fact that all results could be affected by the medication review that has been conducted prior to the present study. For this weakness was compensated by the integration of a report about the impact of this initial review by the physician in charge. Although the report offers valuable insights into the role of Review A, it has by far not the same scientific value as an accurate documentation of the actual impact of the initial medication review.

Another point of critique is the use of percentaged changes in psychotropic medicines. Because relative changes in medication were of interest for this study, this practice offered a simple method for the statistical ascertainment of relevant medication data. Another option would have been the transformation of medication dosages into defined daily doses, which are generally accepted standard dosages of specific substances, established by the World Health Organization (WHO) (Maxwell, Heaney, Howie & Noble, 1993). The inclusion of defined daily doses into the statistical analysis would have enabled more elaborate examination of the baseline characteristics of patients. The comparison of defined daily doses and actual prescriptions of patients would have allowed further insights into the intensity of psychotropic treatments.

Further, the size of the sample was relatively small, given the large amount of subgroups. For instance the subgroup of people who received reduced medications consisted of 5 people. Statistical analyses with such small groups impeded the establishment of reliable and valid results. Future research endeavors with more participants and a control condition could deliver more differentiated results with more solid conclusions and answers to the research questions.

4.3 Implications

The results of this study provide insights into the role of psychotropic medication of patients with Korsakoff's syndrome. Valid conclusions could offer new perspectives on clinical practices and interventions relating to KS. But these could hardly be gained. Based on the results of this study the impact of systematic medication reviews on prescription of psychotropic medications could not be clarified with certainty. The findings do not prove a connection between these practices. However, the findings do strengthen the assumption that

medication reviews are associated with reductions in psychotropic medicine among patients with KS. The attained insights could serve as an outline for prospective studies that aim at the clarification of this issue. In order to gain solid answers to the research questions of this study, several aspects should be considered. First of all a proper research design with patients who were not already involved in medication reviews should be realized. In this study a preceding medication review certainly had an influence on the results and complicated the achievement of conclusions. Further, big quantities of participants should allow for more certainty regarding answers to the research questions and more differentiation between medication categories, dosages and combinations. In the present study many aspects could not be adequately analyzed because of small subgroups. The inclusion of a control condition in the research design could assist in the attempt to find a solid answer to the first research question. One group of patients with KS could undergo a medication review, while another group could function as a control group. The analysis of subsequent changes in psychotropic medication of the two groups should provide a certain answer to the question if medication reviews lead to adapted medical prescriptions.

The second research question, if adaptations in psychotropic medications would be followed by changes in behavioral symptoms, could not be answered because of the shortcomings that already impeded the formation of an answer to the first research question. Due to Review A, some patients were already treated with adapted psychotropic medications. Therefore, the number of patients with adapted medications after Review B was rather small. The comparison of this small group and the other patients regarding behavioral symptoms did not provide significant differences. The use of bigger sample sizes would probably not even be necessary for the execution of prospective studies on these research questions, if the formation of samples with adequate baseline characteristics could be realized. One important baseline characteristic would be the absence of any prior medication review. Under these circumstances a much higher rate of patients with adapted psychotropic medications after a systematic review and a bigger corresponding subgroup could be expected. In order to conduct deeper analyses regarding different medication categories and substances, bigger sample sizes would still be beneficial.

Aside from answers to the research questions the study provided some interesting findings and a variety of different explanations for phenomena that could stimulate prospective research endeavors. Especially the association between number of psychotropic treatment categories and symptoms of apathy requires further investigation. Considering the acquired insights and points of critique of the present study, a compendium of the design of a

prospective study could look like as follows: Next to the research questions of the present study, the third research question “In how far is the number of psychotropic medication categories a patient receives associated with symptoms of apathy?” would be included. For the clarification of these questions a sample size of about 150 patients with Korsakoff’s syndrome would be advantageous. With this sample size a control condition could be included, in order to compare patients who undergo medication reviews with patients who do not undergo medication reviews. Furthermore, the formation of adequate subgroup sizes could be achieved. The mentioned ranking of nursing homes regarding prescriptions of psychotropic medications or similar rankings should be considered for the generation of an adequate sample. Nursing homes with average prescription practices should be included in the study, in order to find participants who represent the target population as adequate as possible. Further, multiple nursing homes should be included, to create a sample with diversity. Hereby differences between nursing homes could be compensated for. For the rest of the study a similar procedure as for the present study could be applied. With this design solid answers to the research questions should be obtained and further characteristics of the population regarding different medications and their impact on behavior could be explored.

4.4 Final remark

The most important conclusion of this study is that it is advisable, to review the psychotropic medications of patients with Korsakoff’s syndrome. Though, the institution in which the patients of this study were hospitalized was known for low rates of psychotropic prescriptions, there was still a total of at least 15 of 64 patients who received reduced psychotropic medications. Unfortunately, this conclusion is based on information that has to be formulated with terms such as “though”, “still” and “at least”. Due to methodological shortcomings, the conclusion has to be stated conditionally. Further investigation with proper research design is necessary to achieve absolute certainty on this issue. The same methodological shortcomings impeded the formation of a group of patients who received reduced psychotropic medications in this study, which in turn impeded the statistical analysis, necessary for the clarification of the second research question. Again, further investigation with proper research design is required to obtain the desired insights.

In addition to these findings some unexpected results appeared. Antipsychotic and antidepressant medication was associated with low levels of apathy. A possible explanation for this finding is that antipsychotics and antidepressants counteract symptoms of apathy. Contrary to skepticism about the effectiveness of psychotropic treatment for behavioral symptoms (Kleijer et al., 2009; Nijk, Zuidema & Koopmans, 2009), these results could be interpreted as support for the effectiveness of antipsychotic and antidepressant treatments. Data on behavioral symptoms preceding psychotropic prescriptions was not available. Thus, other interpretations have to be considered, too. Even more interesting was the association found between number of psychotropic treatment categories a patient received and symptoms of apathy. This strong association could also be interpreted as support for the effectiveness of psychotropic treatment for behavioral symptoms. The combination of certain substances could lead to a significant decline in symptoms of apathy. Again, other explanations cannot be ruled out, because of the lack of data on behavioral symptoms prior to the medical treatment. Prospective research endeavors could focus on these issues, to enrich the present state of knowledge on psychotropic medication for patients with Korsakoff's syndrome, alcohol dependency and dementia.

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