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Overview of the articles

This thesis is based on the results of the DelpHi-MV study (Dementia: life- and person-centered help in Mecklenburg-Western Pomerania) and consists of three articles published in the following peer-reviewed journals:

1. Wucherer D, Eichler T, Kilimann I, Hertel J, Michalowsky B, Thyrian JR, Teipel S, Hoffmann W. Antidementia drug treatment in people screened positive for dementia in primary care. J Alzheimers Dis. 2015; 44(3):1015-21. doi: 10.3233/JAD-142064. PMID: 25391382

2. Wucherer D, Eichler T, Hertel J, Kilimann I, Richter S, Michalowsky B, Thyrian JR, Teipel S, Hoffmann W. Potentially Inappropriate Medication in Community-Dwelling Primary Care Patients who were Screened Positive for Dementia. J Alzheimers Dis. 2017; 55(2):691-701. PMID: 27716668

3. Wucherer D, Thyrian JR, Eichler T, Hertel J, Kilimann I, Richter S, Michalowsky B, Zwingmann I, Dreier-Wolfgramm A, Ritter CA, Teipel S, Hoffmann W. Drug-related problems in community-dwelling primary care patients screened positive for dementia. Int Psychogeriatr. 2017 Nov; 29(11):1857-1868. doi: 10.1017/S1041610217001442. PMID: 28780910

List of abbreviations

ABDA	Bundesvereinigung Deutscher Apothekerverbände
AchEI	acetylcholinesterase inhibitors
AD	Alzheimer's dementia
ADE	adverse drug event
ATC	Anatomisch-Therapeutisch-Chemische (ATC) Klassifikation
CI	confidence interval
DDI	drug-drug interaction
DelpHi-MV	Dementia: life- and person-centered help in Mecklenburg-Western Pomerania
DemTect	Demenz-Detektion
DphG	Deutsche Pharmazeutische Gesellschaft e.V.
DRP	drug-related problems
GDS	geriatric depression scale
GP	general practitioner
ICD-10	International statistical Classification of Diseases and related health problems
MM	medication management
MMSE	Mini-Mental State Examination
OR	odds ratio
OTC	Over-the-counter
PIE-Doc	Problem-Interventions-Ergebnis-Dokumentations-System
PIM	potentially inappropriate medications
p.r.n.	pro re nata (when necessary)
PwD	people with dementia

Contents

1. Introduction

About 1.6 million people in Germany are currently living with dementia and estimates predict that these prevalence rates will double in 2050 [1]. Approximately 75% of people with dementia (PwD) in Germany are community-dwelling patients [2]. Dementia syndromes are often complicated by frailty and multiple physical morbidities [3] accompanied by complex pharmacotherapy regimens. Cognitive impairment has a substantial impact on a patient's ability to manage their medication. Up to 41% of unplanned hospital admissions of PwD account to problems with medication [4]. Generally, unmet needs in "pharmacological treatment and care" were among the three most prevalent groups of unmet needs of PwD, together with "nursing treatment and care" and "social counseling and legal support" [5]. These areas of treatment and care of PwD are a logistical and financial challenge for the German health system, and require closer cooperation between the health care providers [6]. According to the World Alzheimer Report the provision and financing of measures that meet the long-term care needs of PwD and support for caregivers is one of the urgent political priorities [7].

Dementia is currently not curable and the pharmacotherapy of PwD pursues the following goals: deceleration of cognitive decline, avoiding/reducing of neuropsychiatric symptoms associated with dementia, management of accompanying chronic diseases, and ensuring adequate medication administration. To achieve these goals current German and international guidelines recommend psychosocial interventions and additionally an antidementia drug treatment (primarily for Alzheimer's disease) [8, 9]. However, the recommended early onset of antidementia drug treatment following the diagnosis of dementia is not always implemented [3, 10-12].

Another recommendation for the patients with cognitive impairment and dementia concerns the avoidance of potentially inappropriate medication (PIM) and reduction of drug-related problems (DRP)[13]. More than half of the inappropriate medications in the German list of PIM for the elderly, the Priscus list [14], are also declared as inappropriate for the treatment of PwD due to side effects that may worsen cognitive impairment.

Drug-related problems in PwD such as non-adherence, over/under supply with medication, adverse drug effects, or drug misuse can substantially affect the therapeutical success. The prevalence of DRP is particularly high in older multimorbid patients [15]. The incidence of

hospitalization due to at least "possible" serious outpatient DRP in Germany is estimated to be about 3.3% - of these 20.1% would be avoidable [16]. The neuropsychiatric condition leads to a decrease in mental abilities, such as memory and concentration, and impairs the patient's persistence with medication therapy [17, 18]. The research in patient populations of PwD is complicated due to mental and physical comorbidity [19], therefore little is known about the prevalence of DRP among PwD, especially in primary care. However, such knowledge is the basis for measures to improve the safety of drug therapies and the development of care concepts for PwD that could help to reduce DRP and avoid PIM.

An instrument for the improvement of drug safety is medication management (MM). According to the legislature, medication management is a process which is used to analyze the patient's entire medication (including OTC-medication) regularly with the objective to improve medication safety by identifying and resolving DRPs [20]. In its statement [21], the German Pharmaceutical Society (DPhG) has recommended a timely introduction of quality-assured medication management into pharmaceutical practice and emphasized its importance for drug therapy safety. The aim of this thesis is the investigation of pharmacotherapy of community-dwelling people screened positive for dementia and the possibilities for their optimization. The focus is on the analysis of the treatment with antidementia drugs, the identification of PIM and other DRP. Such knowledge is the basis for planning and implementing effective medication management for people with dementia in primary care.

2. Objectives

Little is known about the situation with pharmacotherapy in community-dwelling PwD. Therefore, the research questions of the present work were to determine (a) the frequency and type of antidementia drug treatment, and the socio-demographic and clinical variables associated with antidementia drug treatment; (b) the prevalence of PIM according to the Priscus list, and the sociodemographic and clinical variables associated with the use of PIM; (c) the frequency and the type of DRPs, and the socio-demographic and clinical variables associated with DRPs in community-dwelling primary care patients who were screened positive for dementia.

3. Methods

3.1 Study design

The present analyses were based on data from the DelpHi-MV study (Dementia: life- and person-centered help in Mecklenburg-Western Pomerania), a GP-based, cluster-randomized, controlled intervention study to implement and evaluate an innovative concept of collaborative dementia care management in Germany designed to test the efficacy and efficiency of implementing a subsidiary support system for persons with dementia who live at home [22]. The age of the patients was 70 years or older, they lived at home, were positively screened for dementia (DemTect<9) in participating GP practices, and provided a written informed consent for participation in the study. In case a patient was unable to give a written informed consent, the form was signed on his or her behalf by his or her legal representative (as approved by the Ethical Committee of the Chamber of Physicians of Mecklenburg–Western Pomerania, registry number BB 20/11). The study was registered as clinical trial (ClinicalTrials.gov Identifier: NCT01401582). The DelpHi-MV study is described more detailed elsewhere [22].

3.2 Participants

A total of N=6,838 patients were screened for dementia in 125 general practitioner practices. Of these, n=1,166 patients (17%) were eligible for the DelpHi-MV study, n=634 patients (54%) agreed to participate and n=516 participants started the baseline assessment. There were no significant differences regarding age, sex, and the DemTect score among patients included in the analysis and those who dropped out of the study [23] . The analysis for the antidementia drug treatment was based on the preliminary data from 243 patients with complete baseline assessments regarding relevant variables on January 1, 2014 [24]. The analysis of the PIM was based on the data of 448 study participants with a complete baseline assessment [25], and the analysis of DRP was based on the data of n=446 study participants with a complete baseline assessment including medication review [26].

3.3 Data assessment and analysis

The home medication assessment examined the study participant's entire medication history (prescription drugs and over-the-counter (OTC) drugs) including compliance, adverse effects, and drug administration [27]. A community pharmacist or the pharmacist in the study center conducted the medication review for the study's participants. Active substances were coded according to the Anatomical Therapeutic Chemical (ATC) classification system (German Modification) [28, 29]. Topical agents and homeopathic medicines were not considered in this analysis. The following antidementia drugs recommended by national guideline [30] were considered: donepezil (N06AD02), rivastigmine (N06AD03), galantamine (N06AD04), and memantine (N06AX01) [29]. Potentially inappropriate medications (PIMs), the drugs for which the risk of an ADE outweighs the clinical benefit, particularly when there is an evidence in favor of a safer or more effective alternative therapy for the same condition [31], were determined using a list of PIM in the elderly (Priscus list). The German Priscus list was established in line with the international PIM lists and published in 2010, aiming to reduce the rate of ADE and to provide higher medication safety [14]. The DRPs were grouped into five main groups according to the PIE-Doc®-System [32]: inappropriate drug choice; inappropriate administration by patients/problems with administration and compliance; inappropriate dosage/problems with the dosage; problems with drug interactions; and problems with adverse drug events (ADEs). Drug interactions, drug-food interactions, and double prescriptions (of the same drugs or of drugs in the same drug class) were identified by Risk-Check tool CAVE of ABDA-Database [33].

A "traffic light system," a pragmatic system of DDI classification of the ABDA-Database, was employed to classify the drug interactions and drug–food interactions into six categories of severity: "serious consequences probable, contraindicated," "contraindicated as a precaution," "monitoring or adjustment is needed," "monitoring and adjustment is necessary in some cases," "supervise as a precaution," and "no action is normally required" [33]. The first three categories of severity were considered during medication reviews. The clinical relevance of drug–drug interactions was assessed by the pharmacists during the medication review implementation. Polypharmacy was defined here as the use of five or more prescription medications (concurrent regular medications).

To analyze the associations between the sociodemographic and clinical variables and the occurrence of antidementia drugs, PIM, and DRPs, the following factors were considered: age, sex, living situation (alone/not alone), cognitive status, functional status, depressive symptoms, visit to a specialist (neurologist/psychiatrist [yes/no]), medication, formal diagnosis of dementia, and comorbid diagnoses. The severity of cognitive impairment was assessed using the Mini-Mental State Examination (MMSE) [34]. The severity of dementia was categorized as: “no cognitive impairment” (MMSE score 27–30), “mild” (20–26), “moderate” (10–19), or “severe cognitive impairment” (0–9) [30]. Depressive symptoms were assessed using the Geriatric Depression Scale (GDS) and categorized as “no depression” (score 0–5) or “possible depression” (score 6–15) [35]. Functional status was assessed using the Bayer Activities of Daily Living Scale (B-ADL) [36]. In accordance with the International Statistical Classification of Diseases and Related Health Problems (ICD-10, German Modification) [37], the medical diagnoses of dementia were retrieved from the medical records of the treating GP, including the exact date of the initial diagnosis. Dementia diagnoses assigned on the screening day or thereafter were excluded from these analyses. The ICD-10 codes considered were: F00/G30 (dementia due to AD), F01 (vascular dementia), F02 (dementia in other diseases), F03 (unspecified dementia), and G31 (other degenerative diseases of nervous system, not otherwise classified). Diagnosis of mental and behavioral disorders refers to the ICD-10 codes F04-F69.

A comprehensive standardized baseline assessment was conducted at the participant’s home by study nurses with a dementia specific qualification [38] and included a computer-assisted home medication assessment [27]. Standard methods of DRPs detection such as the Braun Bag Review are less appropriate for community-dwelling PwD because of impaired cognition. The medication in the DelpHi-MV study was collected at each participant´s home and medication administration was assessed by the study nurse. Standardized use of documentation forms for home medication assessment in the DelpHi-MV study was described by Fiss and colleges [27].

3.4 Descriptive and multivariate statistics

Statistical analyses in this work were performed using STATA®13 [39]. The variables for the patient sample were summarized using descriptive statistics. Metric variables were expressed by means and standard deviation, nominal variables by proportions. For

continuous variables, Welch t-tests were used in univariate analysis, comparing the individuals with antidementia drug-, or PIM prescription, or DRPs to individuals without antidementia drug-, or PIM prescription, or DRPs. For nominal variables Fisher's exact test was used. Note that the p-values must be treated with care as these tests do not take into account the stochastic dependency of patients who were recruited by the same GP.

Logistic regression models were used to evaluate which variables were associated with antidementia drugs use or PIM use (dependent variables in these models) [25]. The sociodemographic factors (age, sex, living situation (alone vs. not alone)) and the total number of drugs were used as covariates and were included to attenuate possible confounding factors, the clinical variables (cognitive status, functional status, depressive symptoms, diagnosis of dementia) were the independent variables of interest. Poisson regression models were used to evaluate which variables were associated with the total number of DRPs [26]. The regression model included the cognitive status (measured with the MMSE) as an explanatory variable. Age, sex, living situation, functional status, depressive symptoms, total number of drugs taken, documented diagnosis of dementia before screening, the number of somatic comorbidities, and diagnosis of mental and behavioral disorders were included as covariates.

4. Summary of results

4.1. Sociodemographic and clinical characteristics of the study population

A total of 6,838 patients were screened for dementia in 125 GP practices. Of these, 1,166 patients (17%) were eligible for the DelpHi-MV study, 634 patients (54%) agreed to participate. 118 patients dropped out of the study before the baseline assessment either due to withdrawal of informed consent: n = 85, because of death: n = 19, because of relocation: n = 5, or because of other reasons: n = 9, and 516 participants started the baseline assessment. A total of 70 participants was excluded from the present analysis during the period of baseline assessment due to missing data or because of other reasons (missing data: n = 46; death: n = 2; withdrawal of the informed consent: n = 18; moving away: n = 1; not assessed: n = 1; other reasons: n = 2).

The analysis of antidementia drug use is based on the data from 243 patients with complete baseline assessments regarding relevant variables on January 1, 2014 (preliminary data). The

analysis of PIM use is based on the data of 448 participants who participated in the DelpHi-MV study with a complete baseline medication assessment. The DRP analysis was based on the data of 446 participants of the DelpHi-MV study with a complete baseline medication review. The sociodemographic and clinical characteristics of the study population for the research articles of this work were also described elsewhere more detailed [24-26].

4.2 Antidementia drug use: prevalence and correlates

In the DelpHi-MV study sample of community-dwelling people who were screened positive for dementia 30% of the patients received antidementia drugs. The most frequently prescribed medications for people receiving antidementia drugs were memantine (45%), followed by donepezil (31%), rivastigmine (14%) and galantamine (11%). No cases of combination therapy with acetylcholinesterase inhibitors and memantine were found. In the group of participants receiving antidementia drug treatment, 63% had a formal diagnosis of dementia, leaving 38% being treated without a formal diagnosis. In the subgroup of study participants with a formal diagnosis of dementia 46% received antidementia medication. The analysis of antidementia drug use and specific dementia diagnosis showed that 65% of the patients with an AD diagnosis, 44% of the patients with a vascular dementia diagnosis and 47% of the patients with an unspecified dementia diagnosis were treated with antidementia drugs (note that 14 patients have more than one dementia diagnosis, retrieved from the medical records of the treating GP, double entries are therefore possible). The results of the multivariate conditional logistic regression analysis showed that the prescription for antidementia drugs was significantly associated with the severity of cognitive impairment (OR=0.84; p=0.010) and a formal dementia diagnosis (OR=2.79; p=0.034). A subsequent analysis based on the total study sample showed a prevalence of antidementia drugs use of 26%.

4.3 Potential inadequate medication according to Priscus criteria: prevalence and correlates

Of the 448 community-dwelling patients who were screened positive for dementia, a total of 99 study participants (22%) received at least one PIM according to the Priscus list. The most commonly used active substance classes of PIMs included the following: tricyclic antidepressants (22.5% of all PIM in analysis), benzodiazepine derivatives and

benzodiazepine-related drugs (20.7%), nonsteroidal anti-inflammatory and antirheumatic drugs (15.3%), drugs for urinary frequency and incontinence (7.2%), and peripherally acting antiadrenergic agents (7.2%). The most common PIMs were amitriptyline (14.4% of all PIMs), etoricoxib (9.9%), doxazosin (7.2%), diazepam (7.2%), and solifenacin (6.3%). None of the study participants in the subgroup taking amitriptyline were diagnosed with neuropathic pain according to the medical records of the treating GP. The multivariate conditional fixed-effects logistic regression analyses (n=334 patients assigned to n=44 clusters) showed that the cognitive impairment (MMSE) was not associated with PIM use in either model. The results of the first multivariate conditional logistic regression also showed that the prescription of a PIM was significantly and positively associated with the total number of drugs taken (OR: 1.11; 95% CI: 1.00-1.24; p=0.043). In a second logistic regression model, which included the number of diagnosed mental and behavioral disorders (F04-F69) and the number of comorbidities as additional predictors, the prescription of a PIM was significantly positively associated with a diagnosis of a mental or behavioral disorder (OR: 1.59; 95% CI: 1.10-2.30; p=0.014). Accordingly, the second model reached significance (Wald $chi^2(10)=22.77$, p=0.012), underlining the predictive value of psychiatric comorbidities for the prescription of a PIM [25].

4.4 Drug-related problems: prevalence and correlates

Polypharmacy was identified in 67.3% (n=300) of the study participants. Of the 446 total patients, 414 (92.8%) had at least one DRP detected by a pharmacist or a study nurse during a home visit. A total of 1,077 DRPs were registered. Problems related to administration and compliance were the most common group of DRPs (59.9% of registered DRPs), followed by problems with drug interactions (16.7%), problems with inappropriate drug choice (14.7%), problems with the dosage (6.2%), and problems with adverse drug events (2.5%). The most frequent specific DRPs included the following problems: inadequate drug storage (43.7% of all study participants in analysis), inappropriate time of application (40.4%), inappropriate combination of drugs (34.8%), no medication list / medication list outdated (24.7%), inappropriate drugs according to the Priscus list (22.9%), and forgetting to take the drug (18.4%). 2% of the study participants took acetylcholinesterase inhibitors and anticholinergic drugs (quetiapine: n=5 cases; amitriptyline: n=3, doxepin, n=1; tolterodine, n=1) at the same time.

The results of the multivariate logistic regression analysis for the main groups of DRPs revealed that cognitive impairment (measured as MMSE) was associated with adverse drug events reported by the study participants (OR: 1.20; 95% CI: 1.06-1.36; p=0.004). The total number of drugs taken (OR: 1.26; 95% CI: 1.15-1.39; p<0.001) and support with medication (OR: 1.78; 95% CI: 1.05-3.02; p=0.033) were associated with drug interactions. The presence of a diagnosis of mental and behavioral disorders was associated with problems of inappropriate drug choice (OR: 1.66; 95% CI: 1.24-2.21; p=0.001). In the multivariate Poisson regression analysis, the total number of drugs taken (b=0.07; 95% CI: 0.05-0.09; p<0.001) and the presence of a diagnosis of mental and behavioral disorders (b=0.09; 95% CI: 0.03-0.15; p=0.003) were associated with total number of DRPs. Unlike in the multivariate logistic regression, cognitive impairment was not associated with the total number of DRPs in Poisson regression analysis.

5. Discussion

Antidementia drug treatment

Approximately 30% of primary care patients screened positive for dementia received specific antidementia drug treatment, with the most frequently prescribed antidementia agents being memantine and the acetylcholinesterase inhibitor donepezil. This is the first study to examine patients who were screened positive for dementia and therefore there are no directly comparative figures. Due to the lack of comparable data (as previously stated, most studies used a formal diagnosis as inclusion criteria), we cannot estimate whether this is a high or low rate. In the subgroup of study participants with a formal diagnosis of dementia in the present analysis, 46% received antidementia medication. This finding is comparable to the prevalence of antidementia drug utilization in nursing service-supplied outpatients in Germany (45%) [5]. In comparison to nursing home residents (15%), the rate of antidementia drug treatment was considerable higher [7]. One explanation could be that there is a high proportion (approximately 60%) of residents with severe dementia in nursing homes [26] where therapy with antidementia drugs had been terminated earlier. A possible reason for this effect is the multimorbidity of nursing home residents and the associated polypharmacy. The risk of adverse drug interactions or side effects increases with the number of different drugs and may cause non-adherence with the antidementia drug treatment. However, the

low rate of antidementia drug treatment may imply a certain degree of under-treatment of PwD in nursing homes.

In general, a formal diagnosis is important for adequate treatment and care [14]. In the group of participants receiving antidementia drug treatment, 65% had a formal diagnosis of dementia, leaving 38% being treated without a formal diagnosis. Our findings show that 43% of people receiving antidementia drug treatment have received specialist treatment (neurologist/psychiatrist) (as stated by the participants). However, our data do not deliver information about the relation between formal diagnosis and drug treatment. The question remains open: were the antidementia drugs prescribed by GPs without a dementia diagnosis? Were the antidementia drugs prescribed by the specialists, but the diagnoses were not registered by the GP in medical records? Not only cases matching with the diagnosis must be considered in the analysis of antidementia drugs, but also the cases without formal diagnosis. The highest frequency of antidementia drug taking was observed in the group of participants with AD diagnosis (65%), which also corresponds to the recommendations of the current guidelines.

In the present analysis, we found that about half of the patients with the diagnosis of unspecified dementia received antidementia drugs (47%).That finding is interesting, because the use of anti-dementia drugs for unspecified dementia is an off-label treatment, and the difficulty of treatment should be adequately considered. AD is the most common type of dementia and accounts for an estimated 60% to 80% of all cases [27]. We suspect that a majority of the people with dementia who had been diagnosed with unspecified dementia in our analysis could in fact have Alzheimer's disease. Although Alzheimer's disease is the most recognized form of dementia, the other types have distinct clinical features and are often overlooked [28].

Factors associated with antidementia drug treatment

Antidementia drug treatment is significantly associated with more severe cognitive impairment and the presence of a formal diagnosis of dementia. This is in line with the current guidelines. An interesting question, however, is whether different types of diagnosis are associated in multivariate analysis with different prescription rates reflecting the above mentioned descriptive differences. However, in this study, case-numbers for subtypes of dementia were too small to conduct adequate cluster-adjusted inferential statistical

analysis. Our results do not indicate that the visit to a neurologist or psychiatrist is associated with antidementia drug treatment. This finding is only partially consistent with previous studies. Hoffmann et al. (2011) found that contact with specialists is strongly associated with acetylcholinesterase inhibitors (AchEI) prescriptions [32] and van den Bussche (2011) describes that specialists prescribe antidementia drugs twice as often as GPs [6]. We suspect that the insufficient number of cases in our study is the reason why our results are not fully consistent with others.

Potential inadequate medication according to Priscus criteria

Approximately 22% of the patients who were screened positive for dementia received at least one PIM listed in the Priscus list. The prevalence rate of PIM prescriptions in the sample is consistent with the results from previous studies that used the Priscus list and found prevalence rates for PIM use in the general German population (≥65 years of age) between 20% and 29% [40-43]. Because of the differences between the national PIM lists, a direct international comparison of the prevalence of PIM prescriptions with our findings is difficult.
In the AgnES study, which was a community-based, prospective cohort study with home-visit patients, the prevalence of Priscus PIM prescriptions amounted to 27% in the subgroup of patients who were screened positive for dementia [44]. This prevalence rate is slightly higher compared to that in our results, despite the higher degree of comorbidity in the DelpHi-MV cohort (mean number of 12 compared to 6 comorbid diagnoses per patient). This could be explained by the fact that data collection for the Delphi-trial started after the publication of the Priscus list, and would imply that PIM use in the general population might have declined since then.
Tricyclic antidepressants with anticholinergic properties (amitriptyline, trimipramine, doxepin) were the most frequently prescribed PIMs in our analysis (23% of all PIM). This finding is in accordance with a recent Australian study that reported anticholinergics and sedatives as the most commonly prescribed PIM in community-dwelling patients of memory clinics with a diagnosis of mild cognitive impairment or dementia [45]. Amitriptyline, the most frequent active agent in our analysis (14% of all PIM), is often used to treat neuropathic pain and is inexpensive. This might explain why amitriptyline was the most frequently prescribed PIM in most studies using the Priscus list in Germany [41, 44]. However, none of the study participants using amitriptyline in our analysis had a diagnosis of

neuropathic pain by their treating GP in their medical records. It is likely that psychiatric symptoms, such as depressive mood or insomnia, were common reasons for amitriptyline prescriptions in the DelpHi-MV-cohort.

At 4% of participants, the prevalence of benzodiazepine derivatives in our study was lower than that in a previous French study that found 8.5% prevalence for long-acting benzodiazepines in older people with dementia [46]. Benzodiazepines (in our sample: diazepam, medazepam, clobazam, chlordiazepoxide, nitrazepam) and benzodiazepine-related drugs (in our sample: zolpidem, zopiclone) are often used in older adults for the treatment of insomnia, depression or anxiety. In addition, they are used often to treat behavioral symptoms of dementia, despite the lack of evidence for their effectiveness [47]. In summary, in contrast to guidelines and recommendations [30], anticholinergics and benzodiazepines were the most common PIM prescriptions in analysis. This is consistent with previous evidence suggesting that patients with cognitive impairment and dementia have a higher prevalence of anticholinergic and sedative drug prescriptions than matched controls [48, 49].

Fifteen percent of the prescribed PIMs were anti-inflammatory and antirheumatic substances from the Priscus list (etoricoxib, meloxicam, ketoprofen), which are associated with an increased risk of gastrointestinal bleeding, ulceration or perforation, and renal adverse drug effects [14]. The PIMs in this group must be carefully interpreted because, in some cases, treatment with these drugs might be the only option for the patient after considering the individual's health status, possible interactions, and other factors.

The present analysis included the complete medication history of the study participants (prescription drugs and over-the-counter drugs). The considerable percentage of over-the-counter drugs is often missing from studies based on secondary (e.g., reimbursement) data alone. In our study, the prevalence of over-the-counter PIM was 4.5% for participants who used PIM. Over-the-counter PIM included the non-prescription hypnotics (doxylamine, diphenhydramine) and antiemetics (dimenhydrinate). These antihistamines for systemic use are also potentially inappropriate for older people owing to their adverse cognitive effects [50, 51]. Patients or their caregivers rarely inform their GPs about the use of OTC; therefore, it is often difficult for physicians to monitor over-the-counter PIM and their adverse drug reactions or to estimate their risks of interactions with prescribed medication.

Factors associated with use of potentially inadequate medication according to Priscus criteria

The results of the multivariate conditional logistic regression analysis showed that the diagnosis of mental or behavioral disorder was significantly associated with PIM use in community-dwelling people who were screened positive for dementia. This can be explained by the fact that many psychotropic substances used to treat mental and behavioral disorders are included in the PIM lists. This is in line with the study of Mann et al. conducted in Austrian nursing home residents, in which neuropsychiatric symptoms were described as a risk factor for PIM use and which suggested that neuropsychiatric symptoms rather than cognitive impairments provoked PIM prescriptions [52]. The severity of cognitive impairment (measured by the MMSE score) was not associated with the risk of taking a Priscus PIM in our analysis. This result agrees with previous German and international studies that also failed to find associations between cognitive impairments or dementia and PIM use [49]. In the present univariate model, there were equally significant associations between female sex, having a formal diagnosis of dementia, polypharmacy, and PIM use. However, these results were not found in the final multivariate model, thus suggesting confounding by other factors in the model. In contrast, German studies on PIM use in the general population aged over 65 years found that female sex, age, depression, and the number of drugs taken (polypharmacy) were risk factors for PIM use [40, 53, 54]. Female sex and polypharmacy were identified as risk factors for PIM use in community-dwelling elders with dementia in Germany, as well as internationally [44, 46].

Drug-related problems

Approximately 93% of the study participants in the present analysis had at least one DRP. The present findings fall in the upper range of prevalence rates found in previous studies of community-dwelling older adults with dementia (45%-73%) [55, 56]. This finding is in line with a Swedish randomized controlled clinical trial assessing patients aged ≥75 years living in nursing homes or the community and receiving municipal health care. They reported the same DRP prevalence of 93% for 182 patients [57] as in the DelpHi-MV study. Present results for the polypharmacy subgroup (67% of the DelpHi-MV study participants with five or more prescription medications) are comparable to the 95% prevalence of at least one DRP

observed in a recent analysis of participants from senior centers and residential facilities in the USA aged 60 years and older (mean age 75.9 ± 8.5) taking five or more medications [58]. A high number of drugs taken increases the number of DRPs in persons both with dementia and without dementia, as has been shown in previous studies [59-61]. The majority of the study participants (67%) in the present analysis were patients with polypharmacy (using ≥5 prescribed drugs). This prevalence rate is higher compared to the prevalence in a geriatric ambulatory care population in Germany (27%) [62] and worldwide (29%-59%) [63].

The majority of DRPs were related to administration and compliance (59% of all detected DRPs). Some of these DRPs (inadequate storage, multiple drug taking, or no medication plan) can only be found by visiting the patients´ home, for example, 41% of the study participants stored their medication inadequately. The inappropriate storage of medication was most common in patients with polypharmacy. Present findings strongly support the notion that home-based medication review is required to identify a high number of administration- and compliance-related drug problems. In our cohort, 18% of the participants reported in the structured interview that they "often" forget to take their medications; 5% of the participants indicated that they took their medication more often than necessary. This is in line with the results by Elliott where 14% of elderly Australian patients admitted to regularly forgetting to take medication [64]. In this analysis, 25% of study participants had no medication list or the medication list was outdated according to the assessment of the study nurse. It can not be estimated if this rate is high or low because in German studies, the rate of elderly patients with polypharmacy who do not have a medication list differs greatly between 10 to 75% [65]. Nevertheless, our findings are relevant because the study participants took six prescribed drugs on average.

Problems with potential drug interactions were the second most common category (17% of all detected DRPs), which reflects the high number of drugs taken – on average, each participant took 6.4 prescribed drugs regularly. Accordingly, the total number of drugs was significantly associated with drug interactions in the multivariate analysis. Furthermore, support with medication intake from a caregiver or professional care service was significantly associated with more drug interactions. A possible interpretation of this finding is that support for medication intake could be more frequent in people with diseases that are treated with medications with high interaction potential. More than one-third (35%) of the DelpHi-MV study participants used at least one drug combination that could potentially lead to a drug interaction of moderate severity. This is in line with the results by Oesterhus

et al. where 36% of community-dwelling people with mild dementia in Norway [56] had drug interactions. Another analysis with the elderly general population in six European countries showed a higher proportion of drug interactions: 46% of the patients had at least one potential drug interaction [66]. With increasing number of diseases to treat, the likelihood of drug interaction must be weighed against the necessity to treat a given disease. The information about drug interactions should be used for careful monitoring in this vulnerable population, and to consider a reduction of polypharmacy where possible. In this analysis, a potential clinically relevant drug interaction was detected in 3% of the study participants; this rate is slightly higher than the results of Oesterhus *et al.* (less as 2%) [56].

2% of the study participants in the DelpHi-MV study took acetylcholinesterase inhibitors and anticholinergic drugs at the same time. Antidementia drugs should not be coadministrated with anticholinergic drugs due to the risk of effect elimination. GPs should avoid this combination, and people with dementia and their caregivers should be sensitized for the use of drugs with anticholinergic properties.

In this analysis, for 8% of the patients, the dosage of drugs was too high according to the current recommendations and guidelines. This prevalence might be overestimated, because a high dosage (beyond the recommendations of the guidelines) could be therapeutically justified. In 5% of the participants, the medication review provided evidence that the dosage may be too low. This was particularly the case for antidementia drugs, such as acetylcholinesterase inhibitors and memantine. However, a final judgment of these numbers is not possible since the medication review had no information on the tolerance of antidementia drugs for the individual patient which may have been clinically justified. The effective doses of antidementia drugs are known (16-24mg/24h of galantamine, 10mg/24h of donepezil, 6-12mg/24h of rivastigmine or 9.5mg/24h of rivastigmine patch, 20mg/h of memantine). The assessment of dosage is an important part of a comprehensive medication review to identify inappropriate dosing.

In the present analysis, 6% of the study participants reported adverse drug events (ADEs) related to a prescribed medication. This finding is in line with a previous study of Gurwitz *et al.*, who reported a 5% frequency of ADEs in a population of outpatients aged 60 and older [67]. The proportion of outpatients with at least one ADE ranged from 5% to 35% in previous studies [64, 68, 69], this results were in the lower range. The number of self-reported ADEs in the present analysis can be underestimated because patients with moderate and severe cognitive impairment (22% and 2% of participants in our study, respectively) had difficulties

in communicating their ADEs more frequently [19]. This assumption was supported by the results of our multivariate logistic regression analysis for different groups of DRPs. The results show that the study participants who had better cognitive status reported ADEs more frequently. Therefore the validity of self-reported ADE's during the home medication assessment is problematic. It is also possible that some ADEs were not recognized or documented by the study nurses. The recent Australian study showed, that 16% of the hospitalized population had a confirmed ADE, half the ADEs were detected after the patient had been admitted and the most ADEs were detected by the medical practitioners [70]. In the present analysis the lack of GP evaluations of ADEs should be taken into account in the interpretation of the results.

Factors associated with total numbers of drug-related problems

The results of the multivariate regression analysis confirmed a strong association of the total number of drugs taken with the occurrence of DRPs. The results of the multivariate logistic regression analysis for different main groups of DRPs revealed that degree of cognitive impairment (MMSE defined) was associated with ADEs reported by the study participants. The total number of drugs taken and support with medication were associated with drug interactions. The presence of a diagnosis of mental and behavioral disorders was associated with problems of inappropriate drug choice. In the multivariate Poisson regression analysis, the total number of drugs taken and the presence of a diagnosis of mental and behavioral disorders were associated with total number of DRPs. Cognitive impairment was not associated with the total number of DRPs.

6. Limitations

In the analysis of antidementia drug use 44 observations had to be excluded from the logistic regression model. These are the patients of those general physicians who generally prescribe antidementia drugs either for all or for none of study participants. In the group of these excluded patients the prevalence of antidementia drug use was significant lower compared to the observations included in the model (16% vs. 33%). This could restrict the transferability of the logistic regression results.

The prevalence of PIM use was analyzed as yes/no, regardless of the frequency of PIM use

(fixed schedule or p.r.n., without dosage specifications). Therefore, the PIM prevalence might have been somewhat overestimated in this analysis. Patients who were excluded from the analyses due to missing data had more severe cognitive impairment than the patients that were included, as determined by the DemTect score. This might have biased the results. The PIM prevalence was higher in patients included in the regression analysis compared to those excluded due to invariance in the outcome variables in their respective cluster. Therefore, patients with a lower PIM rate were somewhat under-represented in the regression analysis. Because the DelpHi-MV cohort included mostly patients with mild dementia and just a few patients with severe dementia, the effect of severe dementia on the prescription rates of PIM might have been represented insufficiently.

The number of DRPs may be underrepresented in present analysis in case the pharmacists did not detect all possible DRPs. Another limitation is the study´s dependence on self-reported medication administration and ADEs. There was no additional monitoring of drug administration or comparison of self-reported ADEs with the physician records; thus, our results may underestimate the actual numbers. Accordingly, the present study included mostly patients with mild dementia and only a few patients with severe dementia. Effects of severe dementia on DRPs might be underrepresented. That is, the results might have been distorted and should be interpreted with caution.

7. Conclusion

The present thesis reviews the pharmacotherapy of people screened positive for dementia in German primary care. The results of this work can be used as a basis for the improvement of the drug safety of PwD by state of the art medication management.

On one hand, there is a considerable number of people treated with antidementia drugs without beeing formally diagnosed by their treating GP. On the other hand more than half (54%) of the formally diagnosed PWD do not receive any antidementia drug treatment. Antidementia drug treatment should be based on a differential dementia diagnosis as well as an individual assessment of risks and benefits. GPs should be informed about the benefits and risks of pharmacotherapy for patients with dementia. Likewise, education about options and criteria for antidementia drug treatment should be offered to PwD and their caregivers.

The results of the present analyses show that the prevalence of PIM prescriptions in community-dwelling primary care patients who were screened positive for dementia was

comparable to the prevalence in the general older population in Germany. The presence of a diagnosis of a mental or behavioral disorder in this patient group was the only factor associated with increased PIM use in a multivariate model. One should investigate whether mental / behavioral disorders could be treated with non-PIM medications. Cognitive impairment was not a risk factor for a PIM prescription. Certainly, the individual therapeutic decision of the treating physician may differ from the recommendations of the Priscus list because of other factors that need to be considered, such as the patient's anamnesis, comorbidities, prognostic estimates, individual needs, and prescriptions of co-treating physicians. Nevertheless, there is a clear potential for an enhanced medication management of PwD that could reduce PIM prescriptions, especially regarding drugs with anticholinergic properties and long-acting benzodiazepines for chronic use.

Presented results confirm a high prevalence of DRPs in community-dwelling primary care patients who screened positive for dementia. Even if cognitive impairment was not identified as a risk factor for an increased number of DRPs, the total number of drugs taken was crucial. A home medication review by trained nurses could be effective for PwD with polypharmacy, because it gives comprehensive information on the actual medications taken, including OTC drugs, nutritional factors, patient storage and errors on medication intake. Many DRPs at the patient level are more reliably detected during a home visit, such as having no or an outdated medication list, inadequate medication storage, inappropriate application time, no intake due to forgetfulness, and self-omission of the drug by the patient. Consistent with a range of previous studies, the present data underline the necessity of a comprehensive medication review of people with polypharmacy as a part of routine care to avoid harm to patients and to reduce the costs incurred by DRPs in health care systems. Future analyses and further research questions will examine whether medication management can reduce PIM and DRPs.

Studies from Europe and US identified significant effects of medication management on various therapeutic outcomes (e.g., reduction of dosing errors, reduction in the frequency of drug-related problems, reduction of polypharmacy, increase in patient satisfaction) in primary care [71-74]. The recent German cluster randomized WestGem study has shown that medication management in the context of an interprofessional work of pharmacists, physicians and nursing staff improves the therapy of multimorbid patients with polypharmacy. In the study population of a total of 142 study participants aged 65 and older, the number of DRP decreased significantly, and the effects were stronger the longer the

patients were treated by the interprofessional team [75]. Patients with dementia were not included in the WestGem study. The interventions for this patient group have some special features due to the disease and need additional specification. The integration of the MM concept into the German health care system is currently in progress. The ARMIN project is running at the federal level [76], and several local projects were carried out [77]. Most of these projects have multimorbid patients with polypharmacy as target population and are not focusing on PwD. Such pharmacoepidemiological analyses can be used for the assessment of pharmacotherapeutic needs, planning support systems and care measures.

Summary

People with dementia (PwD) are often multimorbid and have complex pharmacotherapy regimens associated with an increased number of drug-related problems. This can lead to a reduction in the quality of life and increased hospitalization rates for PwD, and high costs for the national health system. Therefore, it is important to take the prevention of DRP into account when planning care programs for PwD. Previous medication safety and care studies mainly concentrated on institutionalized PwD. Little is known about the situation in community-dwelling PwD. The objectives of this thesis are to determine: (a) the frequency and type of antidementia drug treatment and associated socio-demographic and clinical variables (b) the prevalence of PIM according to the Priscus list and associated sociodemographic and clinical variables associated (c) the frequency and the type of DRPs and associated socio-demographic and clinical variables in community-dwelling primary care patients who were screened positive for dementia. The analyses are based on the data from the DelpHi-MV study, a cluster-randomized, controlled intervention trial to implement and evaluate an innovative concept of collaborative dementia care management in Germany. The data of N=448 study participants (≥70 years, living at home) screened positive for dementia (DemTect<9) with a complete baseline medication assessment were included in the analysis.

The results showed that 30% of community-dwelling people who were screened positive for dementia received antidementia drugs, 63% of these had a formal diagnosis of dementia. In the subgroup of study participants with a formal diagnosis of dementia 46% received antidementia medication. The prescription for antidementia drugs was significantly associated with the severity of cognitive impairment and a formal dementia diagnosis. 38% of patients without diagnosis receive antidementia drugs. 22% of study participants received at least one PIM according to the Priscus list. The cognitive impairment was not associated with PIM use. The prescription of a PIM was significantly associated with the total number of drugs taken, and with a diagnosis of a mental or behavioral disorder. Polypharmacy, defined as the chronical use of five or more medications, was identified in 67% of the study participants, 93% had at least one DRP detected by a pharmacist or a study nurse during a home visit. A total 1,077 DRPs were registered. Problems related to administration and compliance were the most common group of DRPs, followed by problems with drug interactions, problems with inappropriate drug choice, problems with the dosage, and

problems with adverse drug events. Cognitive impairment was not associated with the total number of DRPs. The total number of drugs taken and the presence of a diagnosis of mental and behavioral disorders were associated with total number of DRPs.

The thesis provides an overview of the complete medication and DRPs of PwD in primary care. Among others, the problems of antidementia drug treatment and intake of the PIMs were discussed. The thesis suggests that medication management based on home medication assessment is important for PwD, because such a review ensures the availability of comprehensive information on the actual complete medication, nutritional factors, and real drug administration. The thesis thus provides a basis for the improvement of medication safety and the development of innovative care concepts for PwD. The high prevalence of DRPs in this population underlines the importance of including a systematic medication management into dementia treatment and care programs. Identified risk factors for DRPs can help to allocate medication management to the patient groups that are at the highest risk.

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Appendix 1

Article 1: **Antidementia Drug Treatment in People Screened Positive for Dementia in Primary Care**

Appendix 2

Article 2: **Potentially Inappropriate Medication in Community-Dwelling Primary Care Patients who were Screened Positive for Dementia**

Appendix 3

Article 3: **Drug-related problems in community-dwelling primary care patients screened positive for dementia**