Pharmaceutical Care for Alzheimer Patients and their Caregivers

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Abstract

The main part of this thesis aimed at setting up, conducting, and evaluating a pharmaceutical care (PC) pilot study for ambulatory Alzheimer patients and their caregivers. It was designed as an open, prospective, controlled two-armed observational study lasting seven months. Whereas pharmacists in the control group provided their usual dispensing, colleagues in the intervention group offered a PC program to Alzheimer patients and their caregivers. Outcomes were compliance, *knowledge in pharmacotherapy*, satisfaction with information about medicines, health-related quality of life, feasibility, and process measures such as incidence of drug related problems. In a secondary part the forgiveness of donepezil, an antidementia drug, was characterised in a simulation study.

In total 50 patients were recruited: Thirty-one patients were recruited for the control group and 19 patients for the intervention group. The primary outcome in our PC study was compliance to antidementia drugs determined by electronic monitoring. The relative PC intervention effect was 11%. Moreover, it was half as likely to observe a non-compliant month in the intervention compared to the control group. Mean knowledge of indication increased from 73% to 78% in the intervention group whereas it slightly decreased in the control group. Surprisingly, PC could not improve patients' taking behaviour in relation to a meal. Patients/caregivers in the intervention group were very satisfied with information about medicines from their pharmacist reaching 88% of the total score on average (100% = completely satisfied). Patients were more satisfied with information about action and usage than potential problems of medication. PC did not relevantly improve health-related quality of life. Pharmacists documented approximately three drug related problems per patient on average. Median time to handle a drug related problem was 10 min. The most predominant drug related problem was inappropriate drug choice. Moreover, the median number of counselling sessions was four. Concerning the feasibility of the PC intervention four major themes were identified: image of community pharmacy, interaction with physicians, interaction with patients/caregivers, and community pharmacy setting, which are also interacting with one another. For 10 mg (5 mg) donepezil forgiveness was estimated as 80% (90%) daily compliance or two (one) dosage omissions at steady-state, respectively.

In this pilot study PC could relevantly improve several outcome measures. Future projects should pursue collaborative care approaches integrating PC into medical, nursing, and social care concepts. In addition, future approaches should involve computerised documentation systems for PC. This could facilitate the uptake of pharmaceutical care.

Zusammenfassung

Der Hauptteil dieser Arbeit beschäftigt sich mit dem Aufbau, der Durchführung und der Evaluierung einer Pilot-Studie zur Pharmazeutischen Betreuung (PB) von ambulanten Alzheimer-Patienten und ihren Angehörigen. Die Studie wurde im prospektiven, offenen, kontrollierten zweiarmigen Design über einen Zeitraum von sieben Monaten durchgeführt. Während die Apotheker in der Kontrollgruppe keine strukturierte Beratung/Betreuung für die Patienten/Angehörigen angeboten haben, wurden die Patienten/Angehörigen in der Interventionsgruppe pharmazeutisch betreut. Zielgrößen innerhalb der Studie waren Compliance, Wissen in der Arzneimitteltherapie, Zufriedenheit mit der Beratung zu Arzneimitteln, gesundheitsbezogene Lebensqualität, Durchführbarkeit und Prozesszielgrößen wie Inzidenz von arzneimittelbezogenen Problemen (ABP). In einem zweiten Teil wurde in einer Simulationsstudie die *Dosis-Auslassungs-Verzeihlichkeit* des Antidementivums Donepezil charakterisiert.

31 Patienten wurden für die Interventionsgruppe, 19 Patienten für die Kontrollgruppe rekrutiert. Primäre Zielgröße war die Compliance in der Antidementivatherapie, die mittels elektronischer Arzneimittelverbrauchsmonitore bestimmt wurde. Der relative PB-Interventionseffekt war 11 %. Es nur etwa halb so wahrscheinlich, einen nicht-therapietreuen Monat in der Interventionsgruppe im Vergleich zur Kontrollgruppe zu beobachten. Das mittlere Indikations-Wissen stieg in der Interventionsgruppe von 73 % auf 78 %, während es in der Kontrollgruppe leicht abnahm. Überraschenderweise konnte PB das Einnahme-Wissen im Bezug auf eine Mahlzeit nicht positiv beeinflussen. Patienten/Angehörige waren sehr zufrieden mit den Informationen zu Arzneimitteln durch Apotheker (im Durchschnitt 88 % vom Gesamtscore). Patienten/Angehörige waren zufriedener mit Informationen zur Anwendung des Arzneimittels als zu potenziellen ABP. PB konnte die gesundheitsbezogene Lebensqualität nicht relevant verbessern. Im Durchschnitt dokumentierten die Apotheker drei ABP. Die mediane Zeit zur Bearbeitung eines ABP war zehn Minuten. Das häufigste ABP war die Anwendung eines ungeeigneten Arzneimittels. Die mediane Anzahl an Betreuungsgesprächen pro Patient war vier. Im Bezug auf die Durchführbarkeit der PB konnten vier Hauptthemen identifiziert werden: Image der öffentlichen Apotheke, Zusammenarbeit mit Ärzten, Zusammenarbeit mit Patienten/Angehörigen und das Setting der öffentlichen Apotheke. Im zweiten Teil konnte durch PK/PD-*In-silico*-Simulationen gezeigt werden, dass die *Dosis-Auslassungs-Verzeihlichkeit* von 5 mg (10 mg) Donepezil bei 80 % (90 %) Compliance lag oder eine (zwei) Dosisauslassung(en) im Steady State.

In diesem Pilot-Projekt zur PB konnten verschiedene Zielgrößen maßgeblich verbessert werden. Zukünftige Versorgungskonzepte sollten die PB in medizinische, pflegerische und soziale Versorgungsformen integrieren. Zusätzlich sollten zukünftige Ansätze EDV-Dokumentationssysteme beinhalten. Dies könnte die Umsetzung der PB im Apothekenalltag forcieren.

Abbreviations

A	Augsburg
AAppO	Approbationsordnung für Apotheker
ABDA	Bundesvereinigung Deutscher Apothekerverbände
ACE	Angiotensin converting enzyme
AD	Alzheimer's disease
AChE	Acetylcholinesterase
ACOVE	Assessing Care of the Vulnerable Elders
ADAS-cog	Alzheimer's Disease Assessment Scale-cognitive subscale
ATC	anatomical therapeutic chemical classification
BAK	Bundesapothekerkammer (Federal Pharmacists' Chamber)
CI	confidence interval
CIBIC plus	Clinician's Interview-Based Impression of Change Plus
D	Day
DC	daily compliance
DPhG	Deutsche Pharmazeutische Gesellschaft
DRP	drug related problem
Eq.	Equation
FIP	Féderation International Pharmaceutique
GP	general practitioner
H	Hour
HDPE	high density polyethylen
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
ICC	intraclass correlation coefficient
ID	identifier
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
L	Leipzig
MCS	mental component summary
Md	missing data
MEMS®	medication event monitoring system
MGMM	measurement-guided medication management
MRC	Medical Research Council
NMDA	N-methyl-D-aspartic acid
OR	odds ratio

OS	Oliver Schwalbe (research pharmacist)
P	pharmacist
PC	Pharmaceutical care
PCNE	Pharmaceutical Care Network Europe
PCS	physical component summary
PI-Doc®	problem-intervention-documentation classification system
PK	pharmacokinetics
PD	pharmacodynamics
RBC	red blood cell
RIE	relative intervention effect
SF-12	12-item short form health survey
SIMS	satisfaction with information about medicines scale
SD	standard deviation
SE	standard error
SOP	standard operating procedure
SPC	summary of product characteristics
SPSS®	Statistical Package for the Social Sciences
SRM	standardized response mean
T_0	time point after inclusion of patients and caregivers
T_7	time point at the end of the study
TBRM	taking behaviour in relation to a meal
tid	three times a day
TTU	time with therapeutic undersupply
WHO	World Health Organisation

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1 Introduction

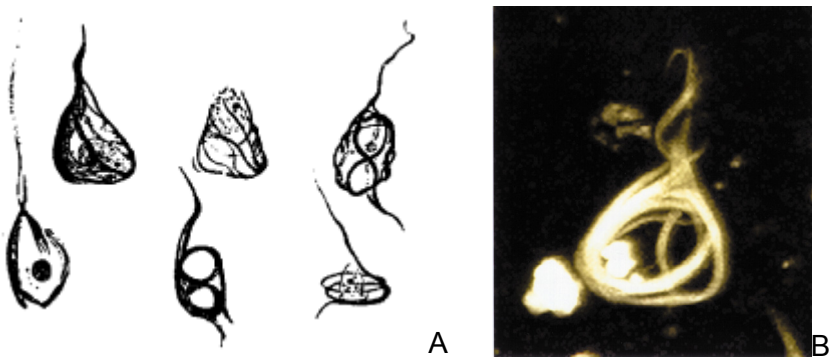
1.1 Alzheimer's disease

1.1.1 Pathology and epidemiology

Alzheimer's disease is associated with a loss of cholinergic transmission in neurons of the hippocampus and cortex starting from the nucleus basalis of Meynert [1]. Two pathologies are mainly considered to be responsible for these deficits:

- extracellular plaques composed of amyloid β
- intracellular tangles composed of the hyperphosphorylated protein tau

In 1906, at a conference, the psychiatrist Alois Alzheimer described a patient called Auguste D, a 51-year-old woman, who had shown progressive cognitive impairment, hallucinations and psychosocial incompetence. At necroscopy there were plaques, neurofibrillary tangles (Fig. 1A), and arteriosclerotic changes. Fig. 1B shows a high-resolution picture of neurofibrillary tangles.



A B

Fig. 1 Neurofibrillary tangles
A: Alzheimer's drawings based on optical microscopy [2]
B: picture by high-resolution microscopy [3]

Tau is a protein that binds to microtubules, a intracellular structure responsible for axonal transport processes. In Alzheimer's disease the equilibrium between particular kinases and phosphatases is disturbed leading to hyperphosphorylated tau is which dissociates from microtubules. This causes disassembly of microtubules and impaired axonal function which first causes neuronal dysfunction, later to transmitter deficits, and finally to neuronal death.

A central hypothesis for the cause of Alzheimer's disease is the amyloid cascade hypothesis. Amyloid plaques mainly consist of amyloid β 42 (Aβ42). This peptide,

which consists of 42 amino acids, is excised from amyloid precursor protein (APP) by secretases. Resulting peptides have different lengths. From all products Aβ42 has the lowest solubility. In addition, proteolytic cleavage is obstructed. This leads to the formation of extracellular plaques (Fig. 2). The sequence of amino acids in APP seem to be a determinant for the formation of Aβ42 [4].

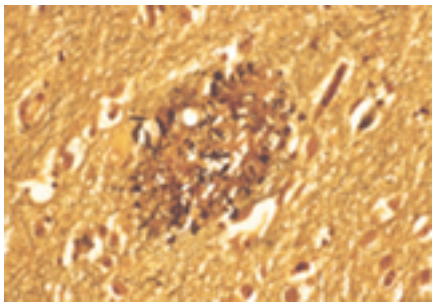


Fig. 2 Amyloid plaques (microscopic picture) [3]

Alzheimer's disease presents the most common type of dementia, accounting for 50-60% of all cases [5]. Apart from Alzheimer's disease, there exist approximately 15 other degenerative diseases of the brain that could cause dementia. Moreover, primary can be distinguished from secondary dementia. Secondary dementia constitutes approximately 10% of all cases and is caused by other diseases, e.g. vitamin B deficiencies, thyroid diseases, or brain tumours. Primary dementia can be divided into neurodegenerative dementia, vascular dementia, and mixed forms. Alzheimer's disease falls into the category of neurodegenerative dementia.

Ageing is the most obvious risk factor for dementia: The prevalence of dementia is below 1% in individuals aged 60-64 years, but almost exponentially increases with age affecting 24%-33% aged 85 years or older in the Western world [5]. In 2001, more than 24 million people worldwide were suffering from dementia, a number that is expected to double every 20 years up to 81 million in 2040 due to increase in life expectancy [5]. In 2007 about 1.07 million moderately to severely demented people lived in Germany. The prevalence of dementia exponentially grows with age (Fig. 3). Prevalence in women and men is almost equal until the age of 70. After that, prevalence is higher in women because men in the higher age groups tend to be healthier.

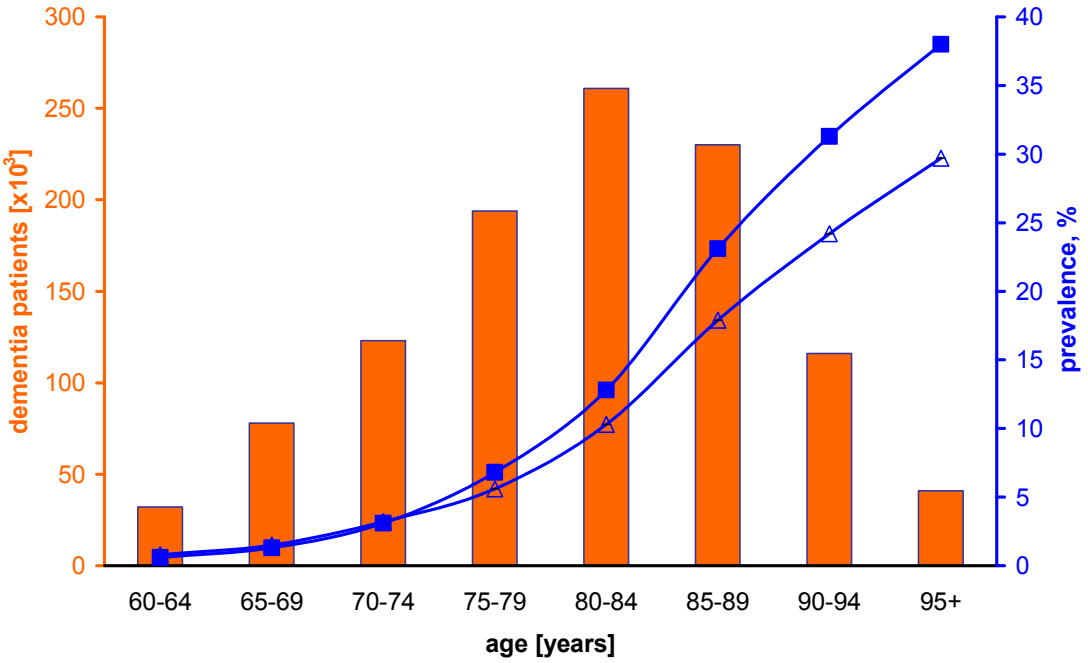


Fig. 3 Dementia patients in Germany: absolute figures (bars) and prevalence (boxes and triangles); filled boxes: women, hollow triangles: men

1.1.2 Pharmacotherapy

None of the current treatment options for Alzheimer's disease are curative or are known to directly halt or reverse the pathophysiological processes of the disorder. Therefore, the specific goals of therapy are to preserve cognitive and functional ability (activity of daily living), with maintenance of patients'/caregivers' quality of life. Secondary goals include treating the psychiatric and behavioural sequelae that occur as a result of the disease [6].

Cholinesterase inhibitors (ChEIs) have been the cornerstone of treatment for patients with Alzheimer's disease for over a decade. Currently, three drugs in this class, donepezil, galantamine, and rivastigmine are approved and recommended for the treatment of mild to moderate Alzheimer's disease. ChEIs decrease acetylcholinesterase activity in a number of brain regions in patients with AD resulting in high concentrations of acetylcholine [7]. All three drugs have demonstrated a benefit in patients with mild-to-moderate Alzheimer's disease with regard to the therapeutic goal "improvement in or maintenance of cognitive function" [8].

Memantine, a NMDA (N-methyl-D-aspartic acid) receptor antagonist, is approved for the treatment of moderate to severe AD [9]. The involvement of glutamate mediated neurotoxicity in the pathogenesis of AD is a finding for increasing scientific acceptance. Additionally, impairment of synaptic plasticity, a prerequisite for learning, may result not

only from neuronal damage per se but may also be a direct consequence of this continuous, non-contingent NMDA receptor activation. Memantine restores the homeostasis in the glutamatergic system, providing neuroprotection and reverses learning and memory process deficits [10].

Besides, the ginkgo biloba extract EGb 761 is used for the treatment of dementia. It is approved for all types of dementia. Its therapeutic effectiveness is currently controversially discussed. Especially concerning “activities of daily living” there is evidence of a benefit at a daily dose of 240 mg [11]. However, the conclusion that ginkgo has a beneficial effect is based on very heterogeneous results [11]. Consequently, no conclusion can be made on the potential effect size [11].

In addition, Alzheimer patients are frequently suffering from non-cognitive symptoms such as aggression, anxiety, depression, or sleep disturbances. Commonly employed agents to treat these disorders are antidepressants and neuroleptics. The use of neuroleptics in Alzheimer patients should be restricted to the lowest dose and shortest period of time required since its use was associated with increased mortality in several studies [12-14].

The ACOVE (Assessing Care of Vulnerable Elders) clinical committee defined quality indicators for the care of dementia patients [15]. These give recommendations concerning e.g. clinical cognitive evaluation, laboratory testing, and caregiver support. Also the physician/pharmacist should perform a medication review to detect any medication that may be associated with mental status changes. Particularly the use of markedly anticholinergic drugs can cause cognitive deficits [16, 17].

Non-pharmacological strategies such as psychoeducation and occupational therapy are equally important. Studies demonstrated the positive effect on patients’ activity of daily living and caregiver burden [18, 19].

1.2 Pharmaceutical Care

According to the Féderation International Pharmaceutique (FIP) pharmaceutical care is "the responsible provision of pharmacotherapy for the purpose of achieving definite outcomes that improve or maintain a patient's quality of life. It is a collaborative process that aims to prevent or identify and solve medicinal product and health-related problems. This is a continuous quality improvement process for the use of medicinal products." Information and counselling of patients becomes care if the following requirements are fulfilled: systematic approach, setting a goal, patient-related documentation, and monitoring (Fig. 4) [20].

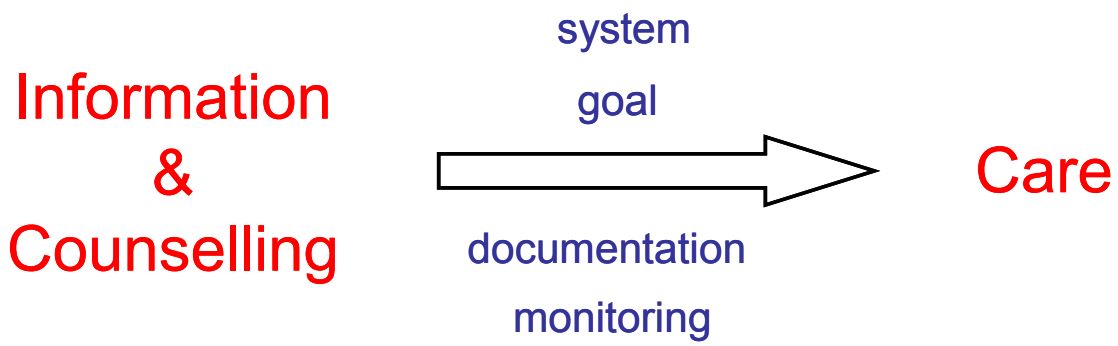


Fig. 4 Differences between information/counselling and care

Pharmaceutical care has to be implemented systematically, e.g. the pharmacist annually checks the medication profiles (i.e. consumption rate) of short-acting beta agonists in asthma patients. Subsequently, patients with particularly high prescription rates are counselled in the community pharmacy. Also, the pharmacist could check whether all Alzheimer's patients receive maintenance doses or whether some patients are still on a starting dose. Furthermore, having a "system" means that all care processes are comprehensible and undergo quality control, which increases the chances of reimbursement from health insurance companies [20]. Pharmaceutical care wants to reach a "goal" depending on the therapeutic situation, e.g. lowering blood pressure as result of increased compliance. An important tool for pharmaceutical care presents patient-related "documentation". This means that all medication data are recorded and processed in the pharmacy's computer. In addition, further information such as dosages, chronic diseases, adverse drug reactions, and drug related problems can be documented. Documentation is a prerequisite for effective quality improvement

in pharmacotherapy [20]. In addition, success and failure of pharmaceutical care should be “monitored”.

A first nationwide implementation of a pharmaceutical care model is the family pharmacy program, which is reimbursed by the statutory insurance company BARMER Ersatzkasse [21]. This contract was negotiated mainly based on positive findings from two studies investigating efficacy and effectiveness of a pharmaceutical care intervention for asthma patients [22, 23]. This concept includes direct communication between the community pharmacist and the general practitioner (GP) which is remunerated by the BARMER Ersatzkasse [21]. One weakness is that a six-hour seminar for one pharmacist per community pharmacy might not be sufficient to integrate pharmaceutical care into the daily routine. In addition, support for community pharmacists, e.g. in the format of quality circles, is missing. Furthermore, no research was implemented to see how pharmacists’ behaviour changed or if patients had any benefit out of it. It was also not investigated how this care model changed collaboration between pharmacists and GPs [20].

A new reimbursed service provided by community pharmacists deals with an intervention to improve self-monitoring of blood glucose in type 2 diabetic patients [24]. It is also a service for insurants of BARMER Ersatzkasse. Self-testing is monitored using a standardized check-list on which any error made during the performance of the test was recorded. If necessary, patients are instructed in the accurate operation of their meter. If any errors occur, a follow-up appointment can be scheduled.

Until now there exist no studies investigating the impact of pharmaceutical care for Alzheimer patients and their caregivers.

1.3 Compliance and Forgiveness

Studies investigating compliance show a variety of measures of medication usage and varying terminologies (e.g. compliance, adherence, persistence) complicating the interpretation and comparison of those studies [25]. The Medication Compliance and Persistence Work Group of the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) defined medication compliance (synonym: adherence) as “the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen” [25]. Persistence may be referred to as “the duration of time from initiation to discontinuation”. Today, no overarching term combines these two concepts [25].

Compliance can be very variable. A meta-analysis comprising 569 studies elucidates compliance for several diseases [26]. Average compliance ranged from 66% to 88%. Cramer et al. concluded in their review that compliance among patients with psychiatric disorders may be lower than among patients with physical disorders [27].

Tab. 1 Mean compliance for several diseases [26]

Disease	Number of studies	Mean compliance (percent)	95% confidence intervals (percent)
HIV	8	88.3	(78.9-95.2)
Arthritis	22	81.2	(71.9-89.0)
Gastrointestinal disorders	42	80.4	(73.9-86.2)
Cancer	65	79.1	(75.9-84.2)
Cardiovascular diseases	129	76.6	(73.4-79.8)
Infectious diseases	34	74.0	(67.5-80.0)
Pulmonary diseases	41	68.8	(61.1-76.2)
Diabetes	23	67.5	(58.5-75.8)
Sleep disorders	16	65.5	(54.3-75.8)

According to WHO (World Health Organisation) compliance presents a multidimensional phenomenon that is determined by the interplay of five sets of factors:

- social and economic factors

  Some factors reported to have a significant effect on compliance are poor socioeconomic status, low level of education, unemployment, unstable living conditions, long distance from treatment centre, high cost of medication, culture and lay beliefs about illness and treatment, and family dysfunction.

- health care team and system-related factors

  These include overworked health care providers, lack of incentives and feedback on performance, short consultations, weak capacity of the system to educate patients and provide follow-up, inability to establish community support and self-management capacity, lack of knowledge on compliance and of effective interventions for improving it.

- condition-related factors

  Some strong determinants of compliance are those related to the severity of symptoms, level of disability (physical, psychological, social and vocational), and

rate of progression. Co-morbidities, such as depression (in diabetes or HIV/AIDS), are important modifiers of compliance.

- therapy-related factors

  Most notable are those related to the complexity of the medical regimen, duration of treatment, previous treatment failures, frequent changes in treatment, the immediacy of beneficial effects, side-effects, and the availability of medical support to deal with them.

- patient-related factors

  Some of the patient-related factors reported to affect compliance are: forgetfulness, anxieties about possible adverse effects, low motivation; inadequate knowledge and skill in managing, negative beliefs regarding the efficacy of the treatment, misunderstanding and nonacceptance of the disease, misunderstanding of treatment instructions, lack of acceptance of monitoring, and low attendance at follow-up.

Compliance enhancing strategies can be grouped into educational, behavioural, monitoring, and pharmacotherapeutic interventions (Tab. 2). Almost all of the interventions that were effective for long-term care were complex, including combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, manual telephone follow-up, and supportive care [28].

Tab. 2 Compliance enhancing interventions

Compliance enhancing intervention	Example
Educational intervention	Providing written and/or oral information according to counselling guidance [29]
Behavioural intervention	(Electronic) patient diary
	Weekly pill-box
Monitoring intervention	Regular monitoring of blood pressure in hypertensive patients
	Follow-up after prescription of new medication [30]
Pharmacotherapeutic intervention	Rationalisation of pharmacotherapy by medication review [31]
	Prescription of sustained release formulations

The methods available for measuring compliance can be classified into direct and indirect methods. Direct methods can prove that ingestion of drug has taken place whereas indirect methods can only assume it. Direct methods comprise directly observed therapy, which is the most accurate method [32]. This is difficult to realise in everyday practice, since it requires a lot of time and personal. Another direct method is the measurement of plasma concentrations of drugs. This method is very objective, but it only gives an impression of recent administration behaviour, depending also on the half-life of the individual drug. Indirect methods comprise e.g. patient self reports and questionnaires, pill counts, rates of prescription refills, and electronic monitoring.

Since the end of the 1970s electronic monitoring has been used to compile dose administration histories of ambulatory patients [33]. The so called medication event monitoring system (MEMS®) consists of a vial with a microprocessor in the lid which records the time (date, hour, minute) of every opening [34]. In contrast to traditional compliance assessment methods such as pill count, patient diaries or patient self-report, the method of electronic monitoring demonstrated to be a more reliable tool allowing a detailed analysis of patient medication taking behaviour over time [35]. However, actual ingestion of the medicine cannot be measured [33] and compliance may be underestimated (e.g. in the case that a weekly pill-box is used instead) [36]. Nevertheless, electronic monitoring has been recognised closest to a ‘gold standard’ for compliance measurement [34]. To our knowledge, compliance studies among Alzheimer patients using electronic monitoring have not been conducted until now. A few studies have used pill-count methodology.

The advent of electronic monitoring has also advanced research on the question “how much compliance is enough?” being closely related to the concept of forgiveness. Urquhart defined forgiveness as the “drug’s post-dose duration of action minus the prescribed interval between doses“ [33]. Researchers in the HIV area have adopted a more general definition of forgiveness as the ability of a regimen to achieve and sustain adequate pharmacological response (in this case viral suppression) despite suboptimal compliance [37]. In the present work forgiveness is used in the latter sense, specifying the former as forgiveness according to Urquhart. The crucial ‘experiment’ for measuring how much compliance is enough, presents the controlled, blinded substitution of placebo for active drug [38]. This is not always ethically possible and has only been pursued in the field of e.g. oral contraception, hypertension and depression [38, 39]. Furthermore, a correlation between compliance and clinical outcome was established in observational studies [40, 41]. In general, forgiveness of drugs is rarely investigated, not at all for antidementia drugs.

The capacity for forgiveness of drugs may differ substantially, depending on their pharmacokinetic (PK, i.e. the drug exposition) and pharmacodynamic (PD, i.e. the drug effect) properties, e.g. half-life and steepness of concentration-effect relationship. Thus, given a known pharmacokinetic/pharmacodynamic (PK/PD) relationship, *in silico* studies were also suggested for the characterisation of forgiveness [42, 43]. In the case of donepezil, inhibition of peripheral cholinesterase can serve as a PD biomarker [44]. To avoid therapeutic undersupply, the daily dosages of cholinesterase inhibitors to achieve a consistent cholinesterase inhibition of at least 40% corresponded to those causing improvements in ADAS-cog and functional activity scores [45].

1.4 Objectives

The present study aims at setting up, conducting, and evaluating a pharmaceutical care model for Alzheimer patients and their caregivers in the ambulatory setting. To our knowledge there has been no prior research performed in this field worldwide. A pharmaceutical care intervention had to be developed as well as an appropriate study design, outcomes, and infrastructure.

Primary outcome within the study was compliance with antidementia drugs determined by electronic monitoring. Further outcomes were *knowledge in pharmacotherapy*, satisfaction with information about medicines, health-related quality of life, drug related problems, and feasibility of this pharmaceutical care intervention for pharmacists.

It was the aim of the accompanying cross-sectional study to determine Alzheimer's caregivers' satisfaction with information about medicines from their pharmacist.

A further objective was to characterise the forgiveness of the antidementia drug donepezil by pharmacokinetic/pharmacodynamic *in silico* simulations.

2 Patients and Methods

2.1 Pharmaceutical care pilot study: study protocol

A pilot study investigating pharmaceutical care for Alzheimer patients and their caregivers was performed from 2006 to 2008.

2.1.1 Study design

The present study was a multicentre, prospective, open, controlled, two-armed cohort study (Fig. 5). We chose a pre-test post-test non-equivalent group design (quasi-experimental design) [46].

Two groups of patients were compared with each other:

- a control group, in which outcomes were determined without pharmaceutical care
- an intervention group, which included a pharmaceutical care program in addition to outcome measurement

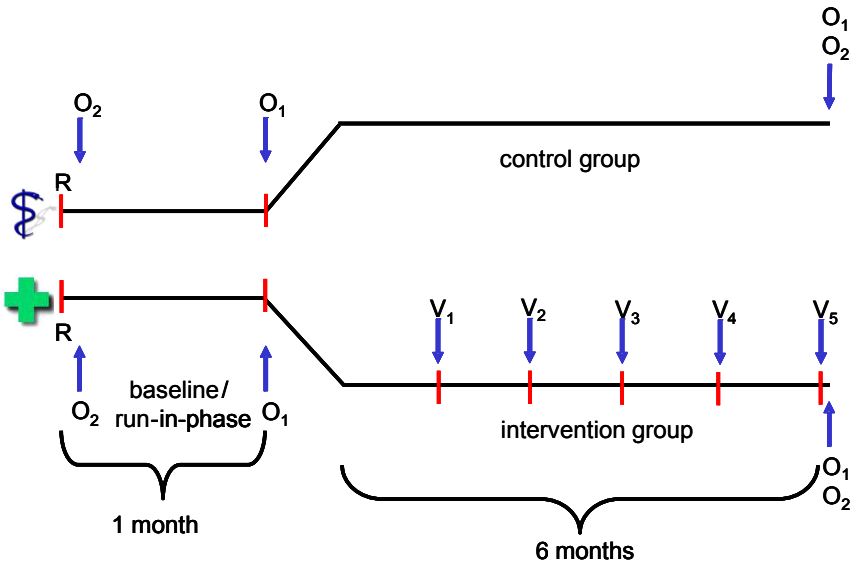


Fig. 5 Study design; = clinic, = community pharmacy, O_1 = primary outcome, O_2 = secondary outcome, R = recruitment, V = visit in community pharmacy, individualised counselling session (up to five)

Details of the study course will be given in 2.1.5.

2.1.2 Patient population

We defined the following inclusion criteria for patients (and caregivers, where applicable):

- diagnosis of Alzheimer's disease
- prescription of an antidementia drug (ATC code: N06D)
- patient lives in ambulatory setting
- ability to communicate in German (patient and caregiver)
- ability to consent (patient)
- written and informed consent (patient and caregiver)
- minimum age of 18 years (patient and caregiver)
- willingness to accept a regular community pharmacy at least for the duration of the study

The following exclusion criteria were applied

- patient lives in a nursing home
- intention to move outside Greater Berlin within study period

2.1.3 Study centres and collaboration partners

The study was implemented involving the Gerontopsychiatric Clinic of Charité University Hospital as well as cooperating community pharmacies. Patients and caregivers of the control group were recruited in the gerontopsychiatric clinic. Moreover, pharmaceutical care was provided by community pharmacists in participating study centres. A survey over all study centres is given in Tab. 3.

Tab. 3 Participating study centres

	Name
Gerontopsychiatric Clinic	Charité – Universitätsmedizin Berlin Department of Psychiatry and Psychotherapy
Community pharmacies	Apotheke an der Vogelweide, Halle Carée-Apotheke, Berlin Curtius-Apotheke, Berlin Elsen-Apotheke*, Berlin Fortunatus-Apotheke Berlin Löwen-Apotheke*, Berlin Prenz'l-Apotheke*, Berlin Taut-Apotheke*, Berlin Tulpen-Apotheke*, Berlin Ludgeri-Apotheke*, Billerbeck Glashütter-Apotheke*, Norderstedt

* One pharmacist in this community pharmacy is member of the quality circle Alzheimer organised by the Department of Clinical Pharmacy and Pharmacists' Chamber Berlin.

Data collection and analysis was performed in the Department of Clinical Pharmacy, Freie Universität Berlin/Martin-Luther-Universität Halle-Wittenberg. During the course of the pilot project we identified further study centres, but in these no patient recruitment could be realised.

Beyond study centres further cooperation partners contributed to the pilot project:

- Institute of Clinical Epidemiology, Medical Faculty of the Martin-Luther-Universität Halle-Wittenberg (study design and data analysis)
- Berlin Institute of Technology, Clinical and Health Psychology, Developmental Psychology (psychometric issues)
- Clinical Pharmacology and Pharmacoepidemiology, and General Practice and Health Services Research, University Hospital Heidelberg (German version of the satisfaction with information about medicines questionnaire, see 2.2.3)
- Pharmacists' Chamber Berlin (administration of quality circle Alzheimer)

2.1.4 Informed consent

Patients and caregivers were informed about the study either by a research pharmacist (control group) or a community pharmacist (intervention group). A patient information leaflet (Appendix A) was given to all patients/caregivers summarising important study facts. In the control group the research pharmacist was present during consultations in

the clinic. Whenever the physician identified possibly suitable patients, they were referred to the research pharmacist who explained the study background and the procedures. Ability to consent was confirmed on site. By contrast, for the intervention group informing patients/caregivers occurred in collaborating community pharmacies. Subsequently, the pharmacist contacted the prescribing physician (directly or by phone/fax) to confirm ability to consent. To give consent, patients/caregivers signed two copies of the consent form. One copy was retained by the patient; the other was filed in the Department of Clinical Pharmacy. If patients did not want to participate there was the possibility of completing a short non-participant questionnaire. SOPs of the recruitment into intervention and control group can be found in Appendix A.

2.1.5 Study course

2.1.5.1 Study timeframe

The study period comprised a one month baseline phase followed by a main phase lasting six months (Fig. 6). During the full study period we measured compliance of antidementia drugs by electronic monitoring (2.2.1). After written informed consent an appointment was scheduled where the research pharmacist visited the patient and caregiver at home. During this first visit the research pharmacist deblistered patient's antidementia drug and subsequently filled the MEMS®. We informed patients/caregivers about the features of MEMS® (i.e. patients knew that we monitored their compliance). For the duration of the study patients/caregivers were advised to use the MEMS® container for storage and withdrawal of antidementia drug only. We illustrated the correct usage of MEMS® by an information sheet (Appendix A).

After inclusion and at the end of the study the research pharmacist performed a medical and social anamnesis (Fig. 6) [Appendix B]. In addition, patient reported outcomes were determined such as compliance (Morisky score), health-related quality of life (HRQOL), and satisfaction with information about medicines (Appendix B). *Knowledge in pharmacotherapy* was determined by a structured interview (Appendix B). Moreover, pharmacists in the intervention group documented drug related problems. Additionally, in both groups, we instructed patient's regular community pharmacy how to implement the MEMS® refill (SOPs in Appendix A).

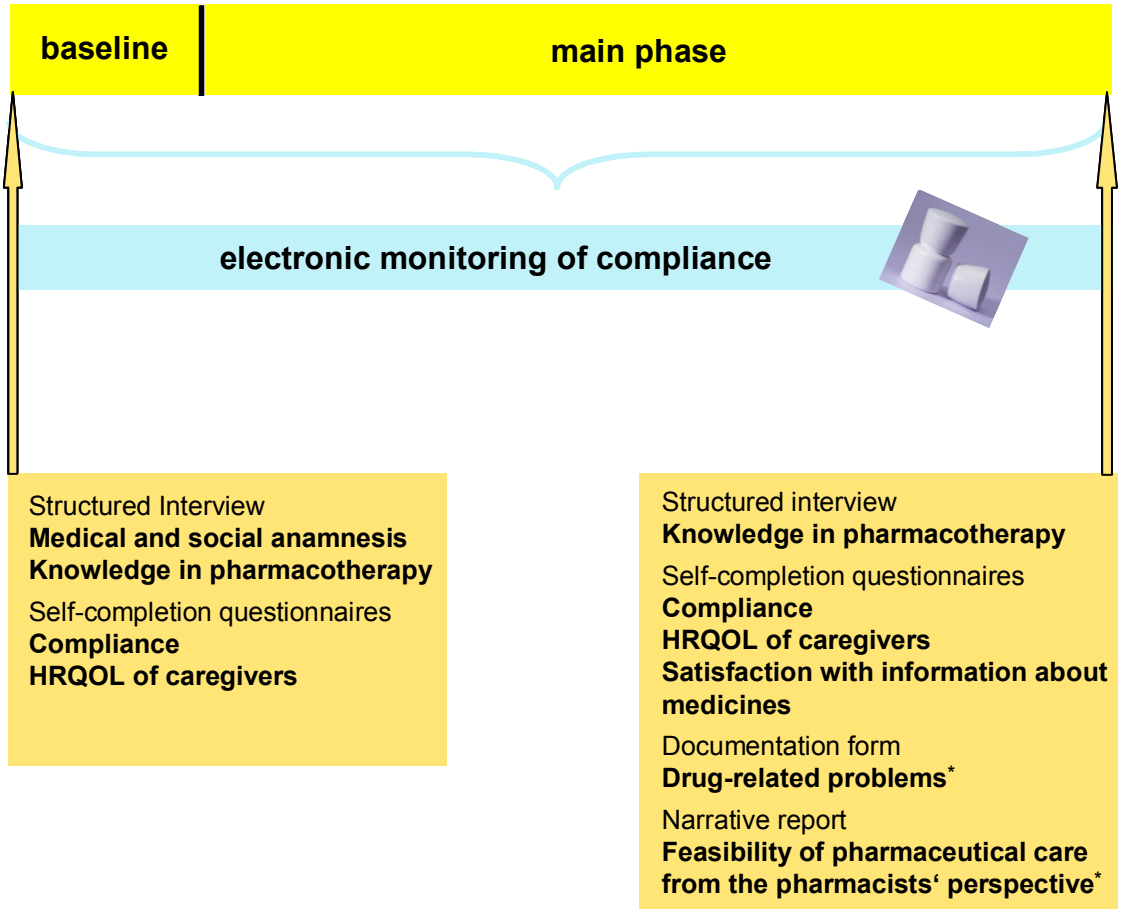


Fig. 6 Measurement of outcomes during the study; HRQOL = health-related quality of life; * intervention group only

2.1.5.2 Control group

Patients in the control group received standard care. Standard care denoted community pharmacists provided their usual dispensing service which included appropriate drug information and advice for patients according to the Ordinance on the Operation of Pharmacies [47]. No defined compliance enhancing intervention or pharmaceutical care program was offered. In the case of asking a research pharmacist a question, patient and caregiver were referred to respective physician or pharmacist. If questions were very urgent, patient and caregiver were briefly counselled. Contact to the research pharmacist was limited to two face-to-face interviews - at the beginning and at the end – and one intermediate download of MEMS® data, usually after the end of the baseline phase.

2.1.5.3 Intervention group

To initially train community pharmacists for the provision of pharmaceutical care and to accompany the study, an Alzheimer quality circle was founded in cooperation with the Pharmacists' Chamber of Berlin. Quality circles are small groups of health professionals, based on voluntary participation and concerned with activities aimed at assessing and continuously improving the quality of patient care [48]. Important features are patient and practice orientation, confrontation of new information or recommendation with daily practice, and consideration of implementation [48]. The Alzheimer quality circle, which the author of this dissertation moderated, met bimonthly from September 2006 until July 2008 (Tab. 4): Individual sessions lasted 2.5 hours. Sessions comprised a workshop preparing community pharmacists for pharmaceutical care. Furthermore, several sessions dealt with presentation and discussion of drug related problems in individual Alzheimer patients.

Tab. 4 Meetings of the Alzheimer quality circle

Individual meeting	Key contents
1	workshop: pharmacotherapy and pharmaceutical care for Alzheimer's patients and their Caregivers (I)
2	workshop: pharmacotherapy and pharmaceutical care for Alzheimer's patients and their caregivers (II)
3	communication in pharmaceutical care (with physicians and patients)
4	facilitating recruitment: arguments for patients/caregivers and physicians
5	non-cognitive disorders of Alzheimer patients
6	development of individualised patient information leaflets for common antidementia drugs
7	presentation and discussion of a study patient
8	presentation and discussion of a study patient (medication review, detection and solution of drug related problems) [I] Alzheimer and self-medication
9	presentation and discussion of a study patient (medication review, detection and solution of drug related problems) [II] Beers criteria development of a care algorithm for Aricept®
10	presentation and discussion of a study patient (medication review, detection and solution of drug related problems) [III]
11	short lecture: atrial fibrillation presentation and discussion of a case example from literature [49]
12	discussion of results from a mystery customer project [50]

Originally only pharmacists who attended the Alzheimer quality circle were supposed to recruit and care for Alzheimer patients and their caregivers. Due to low recruitment rate further community pharmacists were also trained in pharmacotherapy and pharmaceutical care of Alzheimer patients. Here, the author of this thesis implemented an in-house seminar lasting 1.5 hours.

Patients in the intervention group received a complex pharmaceutical care program including up to five scheduled counselling sessions (Fig. 5). Materials used for this intervention are listed in Appendix C. The first visit comprised thorough medication history taking [51]. For this purpose patients or caregivers were advised to bring all medication (prescription, non-prescription, food supplements etc.) to the community pharmacy ("brown bag"). Based on this information the pharmacist composed a medication plan which was regularly updated and distributed to the patient/caregiver during the course of the study (Appendix C) [52]. After the first visit, the pharmacist took notes on patient's medication experience [51] (Appendix C). Subsequently, a medication review was performed using a structured approach (Appendix C). Here, as well as throughout the whole study drug related problems were identified, documented, and solved (2.2.5) (Appendix C) [53]. Tools to facilitate medication review were a German translation and adaptation of the Beers criteria [54] and a list with markedly anticholinergic drugs (anticholinergic drug scale level 3) [55]. Additionally, all pharmacists received a chart with commonly occurring drug-drug interactions and recommended actions [56]. Visits two to five offered structured counselling according to an extended guidance of the German Federal Pharmacists' Chamber (Appendix C) [29]. Moreover, visits three to five included measurement guided medication management (MGMM) [57], i.e. an individual MEMS® compliance report was printed and discussed with the patient to improve medication taking behaviour (Appendix C).

2.1.6 Ethical approval

The Department of Clinical Pharmacy applied for a review of the pilot study at the Ethics Committee of the Charité. The study was denoted as a medicinal scientific research project (no clinical drug trial). We submitted all requested materials on 23 November 2005. A hearing was scheduled on 1 December 2005. On 14 December the Ethics Committee expressed there were no ethical objections to the study. Nevertheless, they recommended a few modifications of the study design. On 19 January 2006 the Department of Clinical Pharmacy commented these recommendations. On 25 January 2006 the Ethics Committee expressed its full approval.

2.2 Pharmaceutical care pilot study: outcomes

2.2.1 Compliance

We determined compliance with antidementia drugs by electronic monitoring. The Medication Event Monitoring System (Aardex® Ltd., Zug, Switzerland) consists of a medication container with a microprocessor in the lid (Fig. 7). All devices were delivered in "sleep mode". Before use we activated them by the software called MEMS® WakeUp (Aardex® Ltd., Zug, Switzerland).

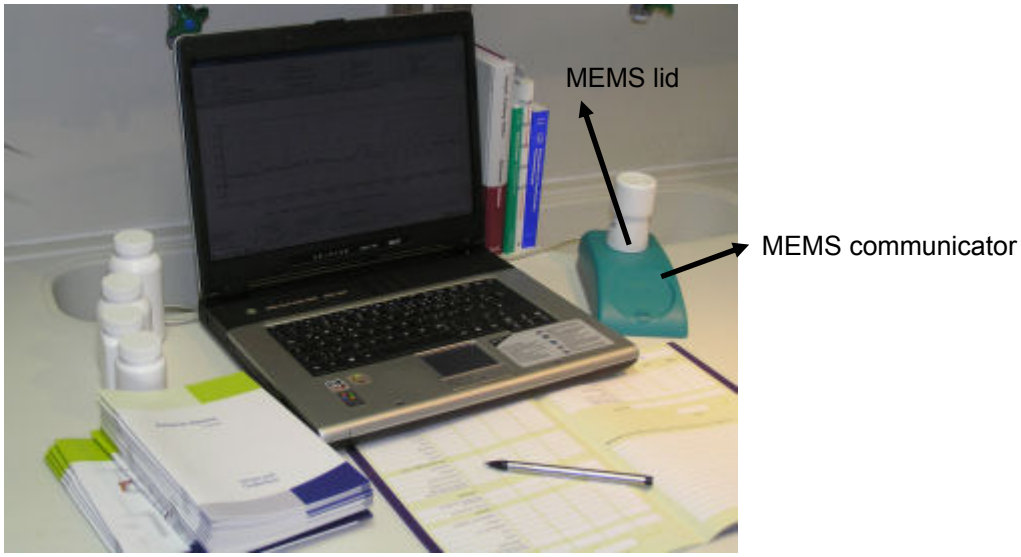


Fig. 7 Medication Event Monitoring System (MEMS®)

The microprocessor recorded every opening (date, hour, minute) of the medication container. All data could be downloaded to a personal computer by a hardware component (MEMS® communicator) and a software (PowerView®). Tab. 5 summarises details of the employed MEMS® technology.

Tab. 5 Details of the employed MEMS® technology

Module	Version
MEMS®	MEMS® 6 Track Cap 38 mm – special batch: shorter battery life (20 months)
Containers	60 mL and 100 mL HDPE vials
Hardware	MEMS® 6 Communicator
Software	MEMS® 6 WakeUp 2.1.0 (activation of MEMS®)
Software	PowerView® Version 3.4.1 (display of MEMS® data)

MEMS®: Medication Event Monitoring System, HDPE: high density polyethylen

The software PowerView® was able to display patients' medication taking profiles (chronology plot in Fig. 8). We monitored the medication taking behaviour of this model patient for 30 days. The drug was supposed to be taken once a day. On eight out of 30 days (27%) no dose was taken. The chronology plot was part of the compliance report which we used in MGMM (see 0). Refills of MEMS® vials were performed and documented in patients' regular community pharmacies (Appendix D). A priori, we removed refill events as well as self-reported non-usage periods (e.g. due to hospital stays) from the dataset. All MEMS® data, which were downloaded to PowerView®, were converted and transferred to Microsoft® Excel or SPSS® 15.0 for Windows for further data analysis.

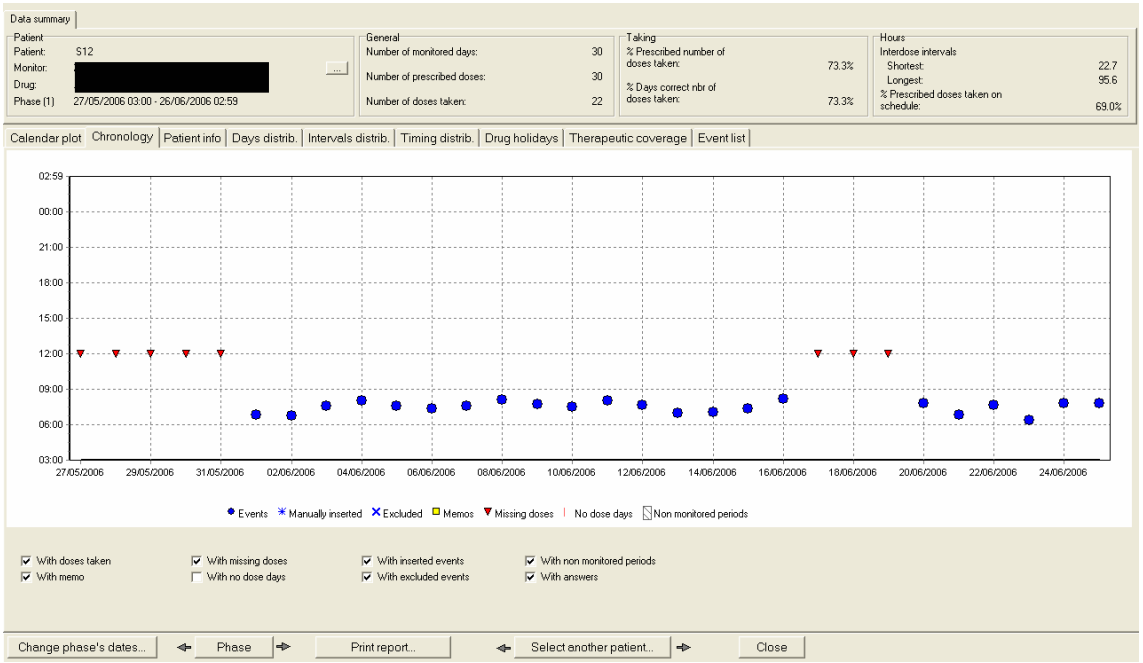


Fig. 8 Chronology plot in PowerView®: time versus date of (omitted) MEMS® opening; blue dots represent MEMS® openings; red triangles represent omitted MEMS® openings

Daily Compliance

Daily compliance in the main phase served as primary outcome measure, defined as percentage of days with correctly administered doses of medication. It was calculated for individual months as well as the total main phase comprising six months.

$$DC, \% = \left(\frac{\text{Days with correct intake}}{\text{observed days}} \right) \times 100 \qquad \text{Eq. 1}$$

DC: daily compliance

In addition, the relative intervention effect was calculated [58]:

$$\text{RIE}, \% = \left(\frac{\tilde{x}_{IE} - \tilde{x}_{IB}}{\tilde{x}_{IB}} \right) \times 100 - \left[\left(\frac{\tilde{x}_{CE} - \tilde{x}_{CB}}{\tilde{x}_{CB}} \right) \times 100 \right] \quad \text{Eq. 2}$$

RIE: relative intervention effect

$\tilde{x}_{IE}$: median DC in the intervention group at the end of the study (i.e. during the sixth month)

$\tilde{x}_{IB}$: median DC in the intervention group at the beginning of the study (i.e. during the baseline period)

$\tilde{x}_{CE}$: median DC in the control group at the end of the study (i.e. during the sixth month)

$\tilde{x}_{CB}$: median DC in the control group at the beginning of the study (i.e. during the baseline period)

Compliant and non-compliant patients

Patients were dichotomised into compliant (daily compliance $\geq$ 80%) or non-compliant (daily compliance < 80%) for every month [32]. Additionally, an odds ratio (OR) was calculated with its 95% confidence interval ($CI_{95\%}$) for the probability of observing a non-compliant month in the intervention versus the control group [59].

$$\text{OR} = \frac{\frac{M_{nc}^{IG}}{M_{c}^{IG}}}{\frac{M_{nc}^{CG}}{M_{c}^{CG}}} \quad \text{Eq. 3}$$

M_{nc}^{IG} : number of non-compliant months in the intervention group

M_{c}^{IG} : number of compliant months in the intervention group

M_{nc}^{CG} : number of non-compliant months in the control group

M_{c}^{CG} : number of compliant months in the control group

Standard errors for the calculation of confidence intervals were calculated according to the following equation:

$$\text{SE}(\log_e \text{OR}) = \sqrt{\frac{1}{M_{nc}^{IG}} + \frac{1}{M_{c}^{IG}} + \frac{1}{M_{nc}^{CG}} + \frac{1}{M_{c}^{CG}}} \quad \text{Eq. 4}$$

A $CI_{95\%}$ for the $\log_e$ OR was obtained as 1.96 standard errors on either side of the estimate [59]. Subsequently, we antilogged these limits to give a confidence interval for the OR itself [59].

Dosing intervals

Dosing intervals were assessed separately for once daily and twice daily regimens.

Morning versus evening dose

Morning doses (MD) were defined as all MEMS® recordings from 3:00 am to 2:59 pm and evening doses (ED) as all MEMS® recordings from 3:00 pm to 2:59 am. The following equations were used. To assess whether it was more likely to omit an evening than a morning dose an OR with $CI_{95\%}$ was calculated for the probability of an omitted morning versus an omitted evening dose [59]:

$$OR = \frac{\frac{ED_{om}}{ED_{ad}}}{\frac{MD_{om}}{MD_{ad}}} \qquad \text{Eq. 5}$$

ED_{om}: number of omitted evening doses

ED_{ad}: number of administered evening doses

MD_{om}: number of omitted morning doses

MD_{ad}: number of administered morning doses

We also calculated standard errors for the determination of confidence intervals.

$$SE(\log_e OR) = \sqrt{\frac{1}{ED_{om}} + \frac{1}{ED_{ad}} + \frac{1}{MD_{om}} + \frac{1}{MD_{ad}}} \qquad \text{Eq. 6}$$

A $CI_{95\%}$ for the $\log_e$ OR was obtained as 1.96 standard errors on either side of the estimate [59]. Subsequently, we antilogged these limits to give a confidence interval for the OR itself [59].

Morisky questionnaire

We also determined compliance employing the four questions of the Morisky questionnaire at T_0 and T_7 (Appendix B) [60]. Patients with a Morisky score of four were classified as compliant whereas patients with a Morisky score smaller than four (i.e. patient answered “no” in at least one of the questions) were categorised as non-compliant. Patients with at least one monthly daily compliance smaller than 80% were

classified as non-compliant (MEMS® compliance). Sensitivity and specificity of the Morisky questionnaire were investigated by comparison with the data from the MEMS® recordings serving as reference [59]. Sensitivity was calculated by the following formula:

$$\text{sensitivity} = \frac{\text{number of patients, who were non-compliant according to Morisky and MEMS}}{\text{number of patients, who were non-compliant according to MEMS}} \quad \text{Eq. 7}$$

Furthermore, the specificity of the Morisky questionnaire was calculated:

$$\text{specificity} = \frac{\text{number of patients, who were compliant according to Morisky and MEMS}}{\text{number of patients, who were compliant according to MEMS}} \quad \text{Eq. 8}$$

Standard errors for sensitivity and specificity were determined by the following equation [59]:

$$SE = \sqrt{\frac{s(1-s)}{n}} \quad \text{Eq. 9}$$

s: sensitivity or specificity

n: number of non-compliers (sensitivity) or compliers (specificity) according to MEMS®

We obtained 95% confidence intervals as 1.96 standard errors on either side of the estimate.

In addition, we also estimated the positive predictive value, the probability that an individual who is non-compliant according to the Morisky questionnaire will be a “true” positive (i.e. a non-complier according to MEMS®), and the negative predictive value, the probability that an individual who is compliant according to the Morisky questionnaire will be a “true” complier according to MEMS®

2.2.2 Knowledge in pharmacotherapy

Knowledge in pharmacotherapy was recorded by interview using a structured form at T_0 and T_7 (Appendix B). We questioned the person responsible for pharmacotherapy (i.e. patient or caregiver) about the indication of every drug as well as taking behaviour in relation to a meal. Normally, this interview was performed at patients’ home. Medication packages were involved to facilitate recognition.

Within a diploma project at our department a questionnaire was developed to assess patients’ *knowledge in pharmacotherapy* (Appendix B) [61]. A pharmaceutical judgement was needed to assess *knowledge in pharmacotherapy* because

patients/caregivers often used lay terminology which was different from the wording in patient information leaflets. We distributed the questionnaire to three community pharmacists who filled it in individually (Fig. 9). It contained 264 statements of 22 patients (ID1-22) about indication of an individual drug and about administration in relation to a meal. Additionally, pharmacists assessed the need of counselling for 22 patients at both occasions (T_0 and T_7). To characterise interrater reliability intraclass correlation coefficients (ICC) were calculated by the following equation:

$$ICC = \frac{\sigma^2_{patients}}{\sigma^2_{patients} + \sigma^2_{observers} + \sigma^2_{error}} \quad \text{Eq. 10}$$

$\sigma^2_{patients}$: variance of patients

$\sigma^2_{patients}$: variance of observers

$\sigma^2_{patients}$: residual variance

ICC is mathematically equal to weighted kappa using quadratic weights [62]. Subsequently, we held two meetings to reach consensus about differing answers and to discuss problems of the questionnaire. During these meetings we kept the minutes.

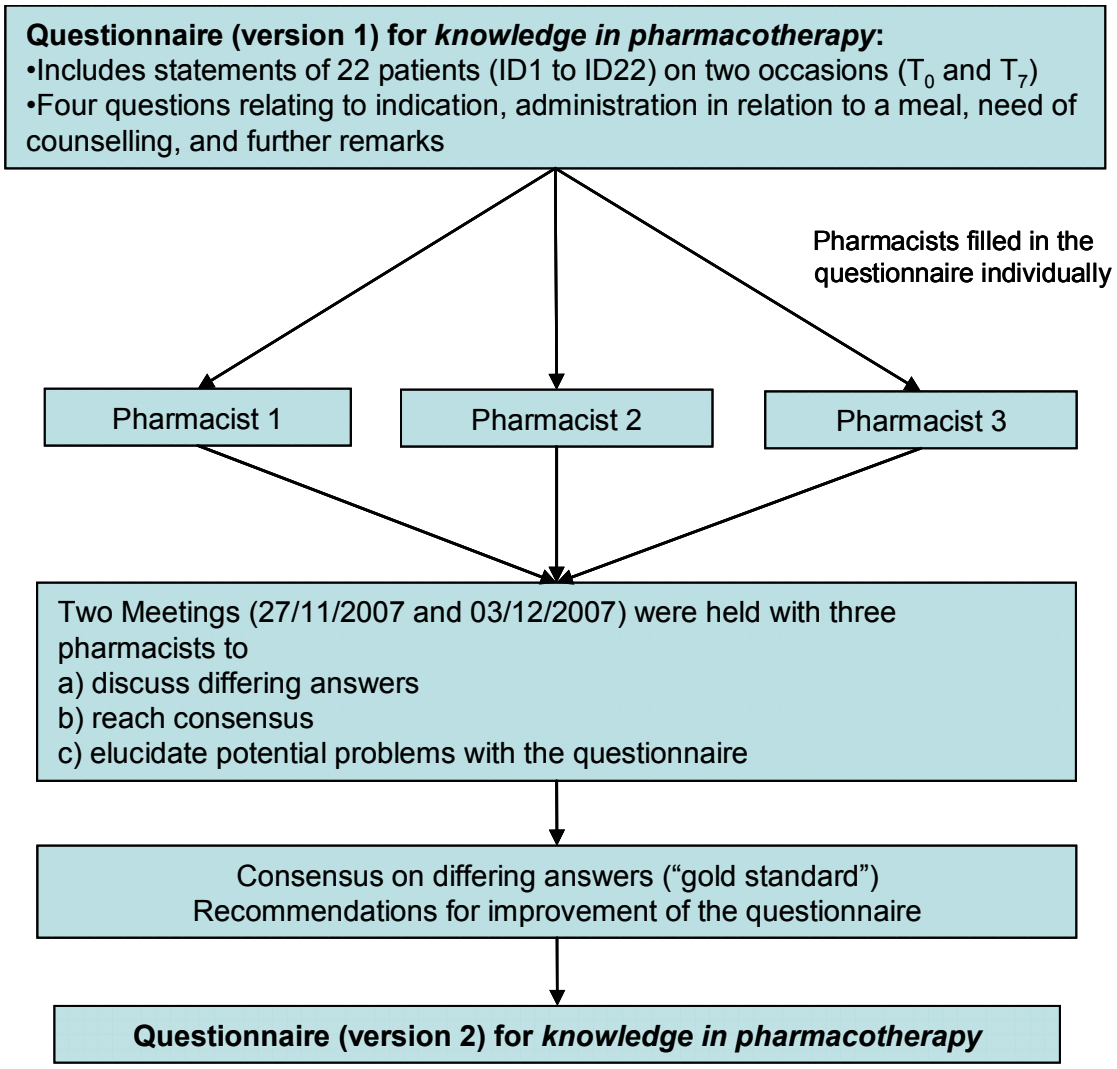


Fig. 9 Process of the assessment of *knowledge in pharmacotherapy*

A second version of the questionnaire for the assessment of knowledge in pharmacotherapy was developed (Appendix B) based on recommendations of the rating pharmacists and further theoretical input (Fig. 9) [63]. Interrater reliability of the second version was estimated by three pharmacists independently assessing 100 additional patients'/caregivers' statements (ID22-33).

2.2.3 Satisfaction with information about medicines

Satisfaction with information about medicines was determined by use of the Satisfaction with Information about Medicines Scale (SIMS) [64]. We wanted the person who was responsible for pharmacotherapy (i.e. patient or caregiver) to fill in the SIMS questionnaire. The SIMS was translated into German according to common questionnaire translation practices by Mahler et al. at the University of Heidelberg [65].

Unlike the original version of Horne et al. which deals with information received about medicines, the German version refers to information on medication provided by GP only. In order to accommodate the German version for our research purposes, “GP” was replaced by “pharmacist”. The SIMS consists of 17 items. Participants were asked to rate the amount of information they had received using a defined response scale, e.g. *about right* was given a score of 1 and *none received* a score of 0 (Tab. 6).

Tab. 6 Satisfaction with Information about Medicines Scale (SIMS): ratings and respective score

Rating of information received about medicines	**Score**
About right	1
None needed	1
Too much	0
Too little	0
None received	0

Results were analysed at three different levels:

- a detailed medicine information profile, obtained by examining the ratings of each individual item to identify patients’ particular needs of information
- a total satisfaction rating, obtained by summing the scores of each item. Scores ranged from 0 to 17 with high scores indicating a high degree of overall satisfaction with the amount of medication information received
- two subscale scores, identifying patients’ satisfaction with information about the *Action and usage of medication* (items 1-9), and the *Potential problems of medication* (items 10-17)

Unlike all other outcomes the SIMS scores of patients in the intervention group at T_7 (i.e. after the pharmaceutical care intervention) were compared to results of a cross-sectional study investigating satisfaction with information about medicines [66], which served as a historical control. This was due to the fact that the German translation of the SIMS questionnaire was not yet available for the most part of the study.

For the calculation of standard errors and confidence intervals see Eq. 9 and subsequent text.

2.2.4 Health-related quality of life

We determined caregivers' HRQOL using the Short Form 12 (SF-12). The SF-12 is based on the Short Form 36 (SF-36) which is a widely-used 36-item generic health status questionnaire. In response to the need to have a shorter instrument that could be completed more rapidly, the developers of SF-36 produced the SF-12 [67]. The SF-12 is a weighted regression-based summative instrument where different weights are applied for scoring mental and physical health from the same items [68]. The same eight domains as the SF-36 are covered and categorical response scales are used (Tab. 7). Physical Component Summary (PCS) and Mental Component Summary (MCS) scales had been produced in a German population using norm-based methods [68]: Scores of PCS and MCS are transformed to have a mean value of 50, standard deviation of 10, where scores above or below 50 are above or below average physical or mental well-being, respectively [67]. The score ranges from 0 to 100.

Tab. 7 Domains and summary scales of the SF-12 scale

Domain	Number of items	Items involved	Summary Scale
Role limitation – physical	2	2, 3	Physical Component Summary scale
Physical functioning	2	4, 5	
Bodily pain	1	8	
General Health	1	1	
Energy/Vitality	1	10	Mental Component Summary scale
Social functioning	1	12	
Role limitation – emotional	2	6, 7	
Mental health	2	9, 11	

Moreover, it is not recommended by the developers of the SF-12 to report domain scales [68]. Summary scales were not calculated if one of the items had not been answered. Here, imputation of missing values – as can be performed for the SF-36 – is not advisable for the SF-12 [68].

From the SF-12 a preference-based single index measure of health, the "SF-6D (SF-12)", was estimated according to the algorithm of Brazier and Roberts [69]. The SF-6D (SF-12) uses seven items from the SF-12, namely items 2, 5, 6, 8, 10, 11,

and 12. It can be regarded as a continuous outcome scored on a 0.29-1.00 scale, with 1.00 indicating “full health” [70].

In addition, the standardised response mean (SRM) was calculated as the most widely used measure of the size of effects [71]. The SRM is the mean of the changes in quality of life scores recorded at assessments of the same subjects at two different times ($\bar{x}_{Time2} - \bar{x}_{Time1}$), divided by the standard deviation of those changes in scores ($SD_{Difference}$).

$$SRM = \frac{\bar{x}_{Time2} - \bar{x}_{Time1}}{SD_{Difference}} \qquad \text{Eq. 11}$$

The standard error (SE) of SRM was calculated according to the following equation [71]:

$$SE\,(SRM) = \sqrt{\frac{1}{n} + \frac{SRM^2}{2(n-1)}} \qquad \text{Eq. 12}$$

We obtained 95% confidence intervals as 1.96 standard errors on either side of the estimate.

2.2.5 Drug related problems

A drug related problem (DRP) is defined as an event or circumstance that actually or potentially interferes with desired health outcomes [72]. DRPs can lead to ineffective pharmacotherapy and may cause drug related morbidity and mortality [72]. For the categorisation of drug related problems we employed the problem-intervention-documentation classification system (PI-Doc®) [73]. It comprises a coding for problems, interventions and outcomes of interventions. This system is structured as a decision tree comprising main groups and subgroups. The main groups coding problems are “inappropriate drug choice”, “inappropriate drug use by the patient/compliance”, “inappropriate dosage”, “drug-drug interactions”, “adverse drug reaction”, and “other problems”. Moreover, the PI-Doc® system was validated by Mattenklotz [74]. Pharmacists in the intervention group used a documentation form for drug related problems (Appendix C) [53].

2.2.6 Further process outcomes

Further outcomes were the number of documented counselling sessions (visits), Bundesapothekerkammer (BAK, Federal Pharmacists' Chamber) guidance oriented consultations, and MGMM meetings. Additionally, it was analysed whether a medication review was implemented and documented for each patient.

2.2.7 Feasibility of pharmaceutical care

We investigated the feasibility of the pharmaceutical care model from the pharmacists' perspective. Here, qualitative methodology was employed. As a practical qualitative method the narrative report was used [75]. Questionnaires were sent to all involved pharmacists at the end of the pilot study, regardless of whether they managed to recruit patients (ten recruiters and eight non-recruiters). Hence, sampling was purposeful. If necessary the author of this thesis reminded the pharmacists twice by telephone (after two weeks and after four weeks). Non-recruiting pharmacists were only to state the difficulties in recruiting patients and reasons why patients chose not to participate (Appendix B). In addition, all recruiting pharmacists answered three questions that aimed to identify pharmacists' observations, struggles and successes (Appendix B). Furthermore, the author of this thesis analysed the qualitative results from Stengel's diploma thesis (focus group of caregivers as well as caregivers' statements during the completion of questionnaires) [66].

Analysis of the narrative reports was performed according to the framework method [76, 77]. The framework approach is a more deductive form of analysis that is increasingly used in health care research [77].

The five stages of data analysis using the framework approach comprise [76]:

- *familiarisation* – immersion in the raw data by reading transcripts and studying notes, to list key ideas and recurrent themes
- *identifying a thematic framework* – identifying all the key issues, concepts and themes by which the data can be examined and referenced. This is carried out by drawing on *a priori* issues and questions derived from the aims and objectives of the study as well as issues raised by the respondents themselves and views and experiences that recur in the data. The end product of this stage is a detailed index of the data, which labels the data into manageable chunks for subsequent retrieval and exploration.

- *indexing* – applying the thematic framework or index systematically to all the data in textual form by annotating the transcripts with numerical codes from the index, usually supported by short text descriptors to elaborate the index heading. Single passages of text can often encompass a large number of different themes each of which has to be recorded, usually in the margins of the transcript.
- *charting* – rearranging the data according to the appropriate part of the thematic framework to which they relate and forming charts. For example, there is likely to be a chart for each key subject area or theme with entries for several respondents. Unlike simple cut and paste methods that group verbatim text, the charts contain distilled summaries of views and experiences. Thus, the charting process involves a considerable amount of abstraction and synthesis.
- *mapping and interpretation* – using the charts to define concepts, map the range and nature of phenomena, create typologies and find associations between themes with a view to providing explanations for the findings. The process of mapping and interpretation is influenced by the original research objectives as well as by the themes that have emerged from the data themselves.

2.2.8 Working Hypotheses

The following hypotheses were investigated within the pilot study:

- Compliance measurement of antidementia drugs by different methods is feasible in the community pharmacy setting.
- Patients' compliance with pharmacotherapy is increased by pharmaceutical care.
- *Knowledge in pharmacotherapy* is increased by pharmaceutical care.
- Pharmaceutical care increases the HRQOL of caregivers.
- Pharmaceutical care can optimise pharmacotherapy, e.g. drug related problems can be detected and solved.
- The basis of a feasible pharmaceutical care concept for Alzheimer patients and their caregivers can be developed.
- Structures can be built up which allow the integration of pharmaceutical care into existing health services for Alzheimer patients and their caregivers.

2.2.9 Statistical analysis

For descriptive data analysis of our study, means or medians were calculated as measure of central tendency and range or 95% confidence interval for variability or precision, depending on the attributes of the respective variables.

Statistical data analysis within the study was performed by use of SPSS® for Windows, Version 15 (SPSS® Inc., USA) and Microsoft® Excel 2003 (Microsoft Corp., USA).

2.3 *In silico* study to characterise forgiveness of donepezil

We performed PK/PD *in silico* simulations to characterise the forgiveness of donepezil, using Microsoft® Excel 2003. Three approaches (A, B and C) were applied via trace-driven simulation [78] using different compliance patterns as input (function): Approach A used the compliance data from the pilot study (control group only) to evaluate therapeutic undersupply for individual patients taking donepezil. Approaches B and C served as sensitivity analysis to characterise the forgiveness of donepezil. For Approach B, discrete daily compliance values (0-100%) were simulated using a step size of 10%. These selected compliance patterns were created via the pseudo-random number generator in Excel for a period of 200 days. Eventually for approach C, scenarios of 1-7 dosage omissions at steady-state (14 days run-in phase, 7 days follow-up phase) were simulated.

The utilised PK and PD models are summarised in Tab. 8. For donepezil, linear PK was assumed [45]. Long-term treatment with (irregular) multiple dosing (up to 200 days with Δt = 1 min) was implemented by using the principle of superposition [79]. As main outcome parameter for all three simulation approaches the so called “time with therapeutic undersupply” (TTU) was defined as time (percentage or hour) with the PD biomarker below the minimum therapeutic inhibition, i.e. < 40% inhibition of peripheral cholinesterase. Additionally, for approach C forgiveness according to Urquhart was determined as the “drug’s post-dose duration of action minus the prescribed interval between doses” [33].

Tab. 8 Pharmacokinetic and pharmacodynamic models for donepezil with parameter values and reference to literature, utilised for the *in silico* simulation

Model type (name) & equation	Variables and parameters		Reference
Pharmacokinetic model (two compartment model)			
$C = D \cdot \left[\begin{array}{l} A \cdot e^{-\alpha \cdot (t - lag\,time)} + \\ B \cdot e^{-\beta \cdot (t - lag\,time)} - \\ (A + B) \cdot e^{-k_a \cdot (t - lag\,time)} \end{array} \right]$	for D = 5 mg A = 3.502 ng/mL B = 1.209 ng/mL α = 0.445 h^{-1} β = 0.014 h^{-1} k_a = 1.319 h^{-1} lag time = 0.96 h	for D = 10 mg A = 4.536 ng/mL B = 1.234 ng/nL α = 0.542 h^{-1} β = 0.015 h^{-1} k_a = 1.696 h^{-1} lag time = 0.68 h	[80]
Pharmacodynamic model (E_{max} model)			
$E = \frac{E_{max} \cdot C}{EC_{50} + C}$	E_{max} = 100.8% EC_{50} = 15.6 ng/mL		[81]

A, B = intercepts of the two exponential terms

α, β = macro (hybrid) rate constants

C = total plasma drug concentration

D = dose

E = effect, i.e. inhibition of peripheral cholinesterase, %

EC_{50} = drug concentration at half of maximum effect

E_{max} = maximum effect

k_a = absorption rate constant

t = time

3 Results

3.1 Pharmaceutical care pilot study: recruitment and follow-up

Recruitment into the control group was performed at the Gerontopsychiatric Clinic of Charité University Hospital. Thirty-nine patients/caregivers who fulfilled the inclusion criteria were invited to participate in our study. Overall, 31 (79%) patients/caregivers were enrolled into the study (Fig. 10 upper part). The main reason (six out of eight refusals) for nonparticipation in the control group was MEMS®-related inconveniences (e.g. incompatibility of MEMS® and use of weekly pill-boxes). Unfortunately, no data on nonparticipants was available in the intervention group. In all patients two study visits (T_0 and T_7) were performed and MEMS® data was recorded as well. Twenty-one patients of the intervention group were recruited in eight cooperating community pharmacies (Fig. 10 lower part). Sixteen patients completed the study leaving five patients lost to follow-up.

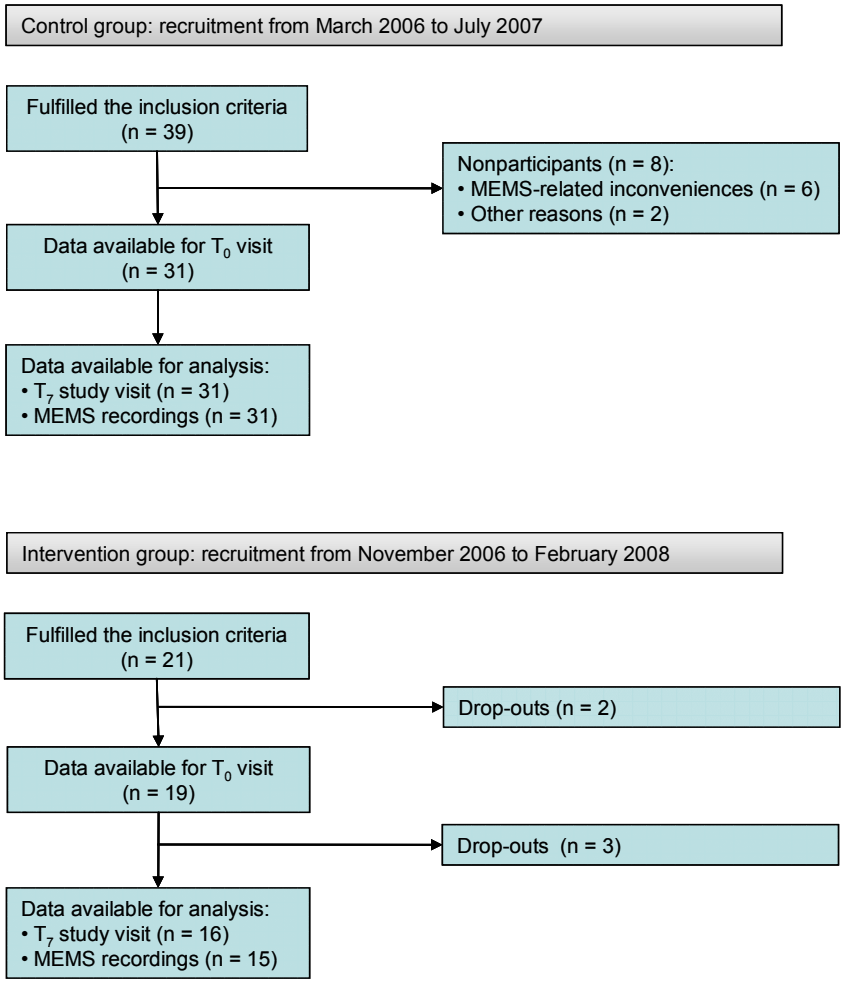


Fig. 10 Flow diagram displaying recruitment and follow-up of the study; control group: upper part, intervention group: lower part

3.2 Pharmaceutical care pilot study: patient and caregiver characteristics

In the control and intervention group 50% of all patients were between 71 and 82 years old. Both sexes were almost equally represented in intervention and control group. In both groups duration of antidementia pharmacotherapy at inclusion ranged from drug-naïve to 6.5 years with 2-12 concomitantly administered drugs. The majority of patients were on a once daily antidementia regimen with donepezil being the most prevailing drug. Moreover, in the control group more than two-thirds of all caregivers were solely responsible for patients' pharmacotherapy. Contrary to that, in the intervention group this situation was less prevalent (ca. 50%) [Tab. 9].

Tab. 9 Patient characteristics in control (n = 31) and intervention group (n = 19) at T_0

Characteristics	Control group	Intervention group
	n (%)	*n (%)*
Sex: women	17 (55)	10 (53)
Responsibility for pharmacotherapy		
Patient only	2 (6)	4 (21)
Patient supported by caregiver	6 (19)	5 (26)
Patient supported by professional care	-	1 (5)
Caregiver only	22 (71)	9 (47)
Professional care only	1 (3)	-
Antidementia drugs in MEMS® at inclusion[a]		
Donepezil	12 (35)	8 (53)
Galantamine	12 (39)	-
Memantine	6 (19)	3 (20)
Piracetam	-	1 (7)
Rivastigmine	1 (3)	3 (20)
Regimen of antidementia drug in MEMS®		
Once daily	24 (75)	11 (73)
Twice daily	7 (25)	4 (27)
	median (min-max)	*Median (min-max)*
Age in years	76 (47-96)	79 (59-84)
Duration of MEMS® monitoring in days[b, c]	180 (140-180)[b]	140 (20-180)[c]
Duration of antidementia pharmacotherapy at inclusion in months	18 (0-78)	2 (0-78)
Number of regularly administered drugs	6 (2-12)	7 (2-12)

MEMS®, medication event monitoring system;

[a] Intervention group: In four out of 19 patients (21%) a MEMS® vial was never filled: Two patients were supported by an ambulatory nurse or caregiver who refilled their daily pill-box. We did not want to interfere in this "running system". Two other patients were prescribed rivastigmine transdermal therapeutic systems which do not fit into a MEMS® container.

[b] Control group: Eight out of 31 patients (26%) have non-monitored periods (e.g. due to hospital stays) or incomplete follow-up.

[c] Intervention group: Six out of 16 patients (63%) have non-monitored periods (e.g. due to hospital stays) or incomplete follow-up.

In the intervention group more than two-thirds of all caregivers were female (Tab. 10). Contrary to that, there were less than 50% female caregivers in the control group.

Furthermore, in both groups at least 75% of all caregivers were spouses. In both groups caregivers had a similar age distribution with a median around 70.

Tab. 10 Characteristics of caregivers at baseline (n = 30 in control group, n = 16 in intervention group)

Characteristics	Control group	Intervention group
	n (%)	*n (%)*
sex: women	13 (42)	12 (71)
relationship to patient		
spouse	26 (87)	12 (75)
son or daughter	2 (7)	2 (13)
son or daughter in law	-	1 (6)
other relatives	-	1 (6)
others	2 (7)	-
	median (range)	
age in years	72 (52-86)	70 (35-87)

In ten percent of all cases in the control group (n = 3) the patient was questioned (*knowledge in pharmacotherapy*, see 3.3.3.2) and filled in questionnaires (Morisky and SIMS questionnaire, see 3.3.2 and 3.3.4). From these, two patients were solely responsible for pharmacotherapy whereas one patient was supported by a caregiver. In 32% of all cases in the intervention group (n = 6) the patient was questioned (*knowledge in pharmacotherapy*, see 3.3.3.2) and filled in questionnaires (Morisky and SIMS questionnaire, see 3.3.2 and 3.3.4). In four cases the patient was solely responsible for pharmacotherapy. Moreover, in two cases the patient was supported by professional care or a caregiver. In all other cases the caregiver was questioned or filled in questionnaires.

3.3 Pharmaceutical care pilot study: outcomes

3.3.1 Primary outcome: daily compliance

We downloaded compliance data from MEMS caps using software called PowerView®. Fig. 11 displays the calendar plot of patient #12 (control group) in PowerView® indicating the number of MEMS openings during every day of the monitored period.

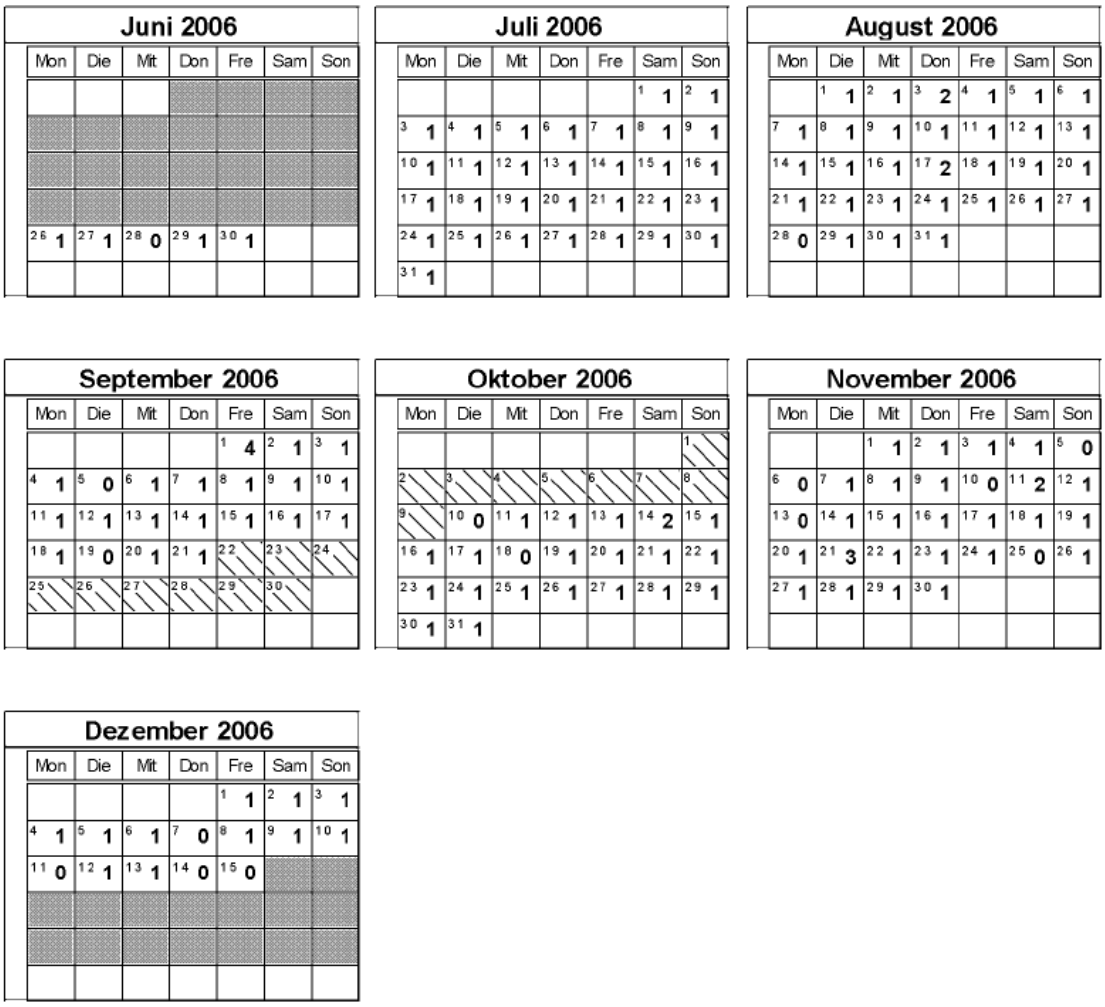


Fig. 11 Calendar plot of patient #12; days in white shading = monitored days; days in grey and striped shading = non monitored periods

During the main phase median daily compliance in the control group was 94% (range 48-99%) (Fig. 12). In the same period median daily compliance in the intervention group was 96% (range 73-99%). In comparison to the baseline phase, median daily compliance of the control group decreased by three percent points in the sixth month (Fig. 13). Contrary to that, in the intervention group median daily compliance increased

by seven percent points when comparing baseline to sixth month. In the control group there were by far more outliers and extreme values than in the intervention group (Fig. 13). The relative intervention effect in our study was 11%.

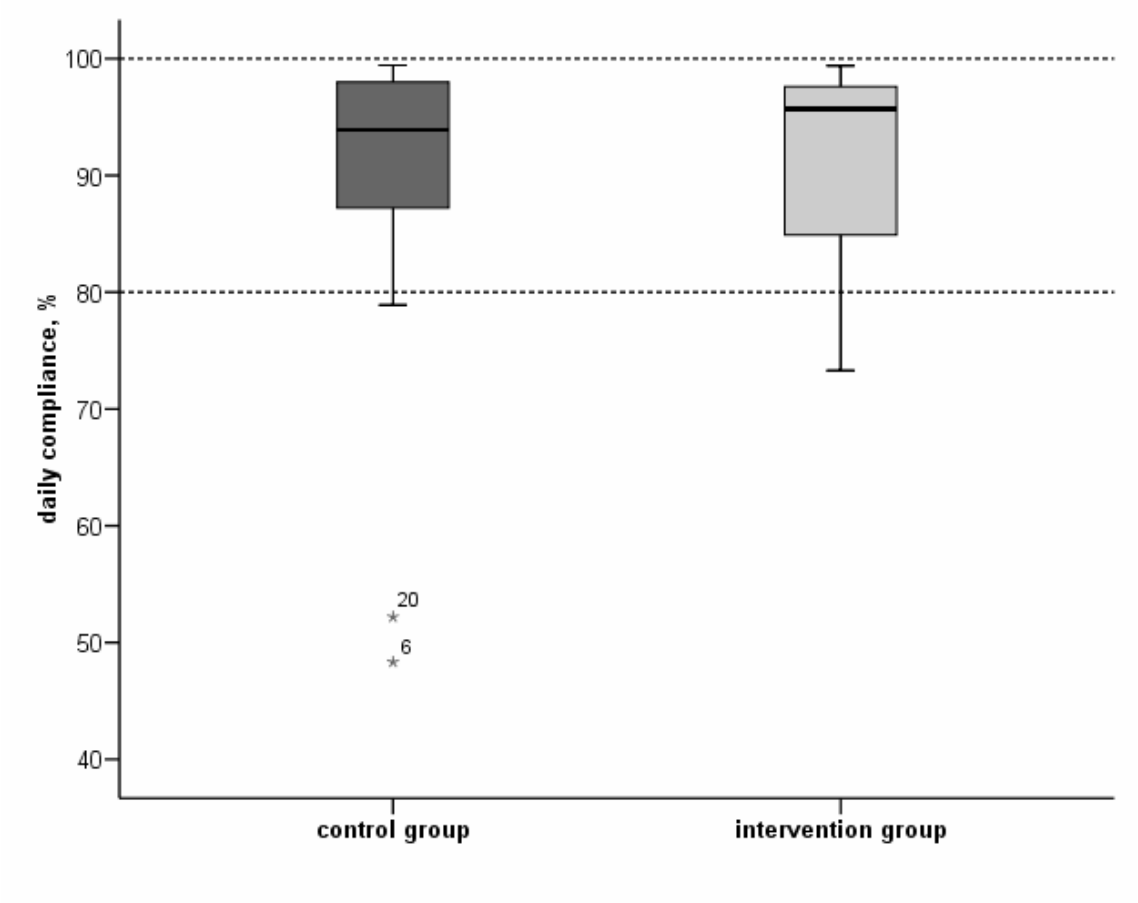


Fig. 12 Daily compliance during main phase in control group (n = 31) and intervention group (n = 15); index numbers of extreme values (> 3 times box height from the box: stars) represent individual patient ID.

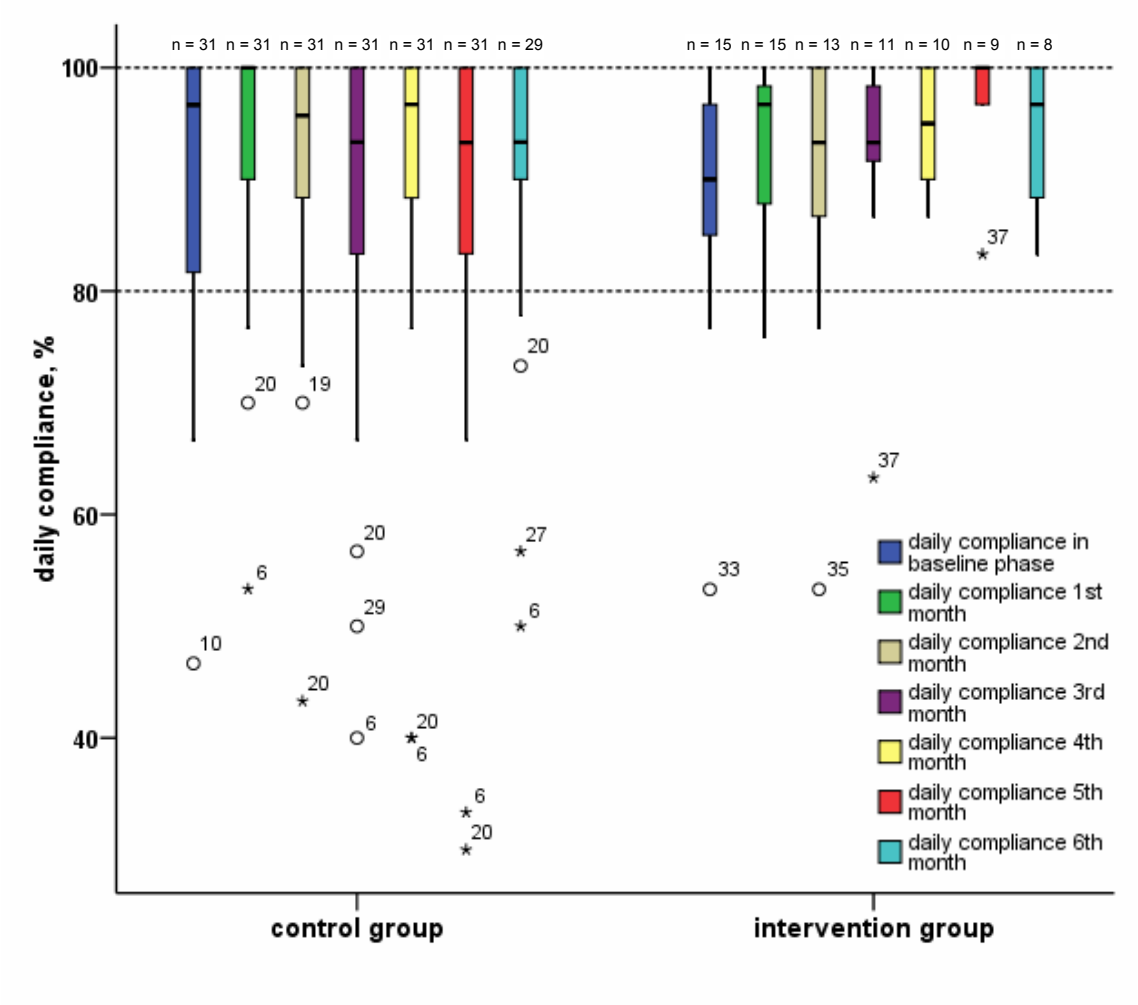


Fig. 13 Daily compliance during individual months of the study in control and intervention group; index numbers of outliers (1.5-3 times box height from the box: circles) and extreme values (> 3 times box height from the box: stars) represent individual patient ID.

By comparing daily compliance at the end of study (6th month) to baseline there was by far more variability in the control group than in the intervention group (Fig. 14).

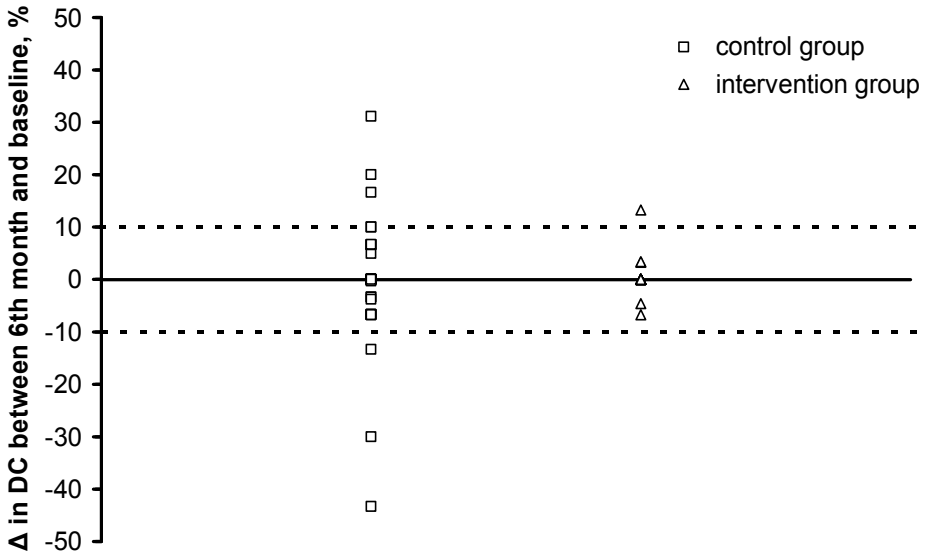


Fig. 14 Intraindividual difference in daily compliance (percent points) between 6th month and baseline in control group (n = 29) and intervention group (n = 8); dashed line at "+10" and "-10" indicate cut-offs for major changes in compliance; Δ: difference; DC: daily compliance

After dichotomisation of compliance (daily compliance ≥ 80% or < 80%), intraindividual compliance patterns by month revealed that ten patients (32%) in the control group were at least one month non-compliant (Fig. 15). Among these, two patients were non-compliant throughout the main phase. Four patients (27%) in the intervention group were at least one month non-compliant (Fig. 16). Indicated by OR of 0.5 ($CI_{95\%}$ = [0.35; 0.71]) it was half as likely to observe a non-compliant month in the intervention versus the control group. In the intervention group nearly half of all patients stopped using their MEMS® prior to the end of study whereas in the control group less than 10% terminated prematurely the use of MEMS®.

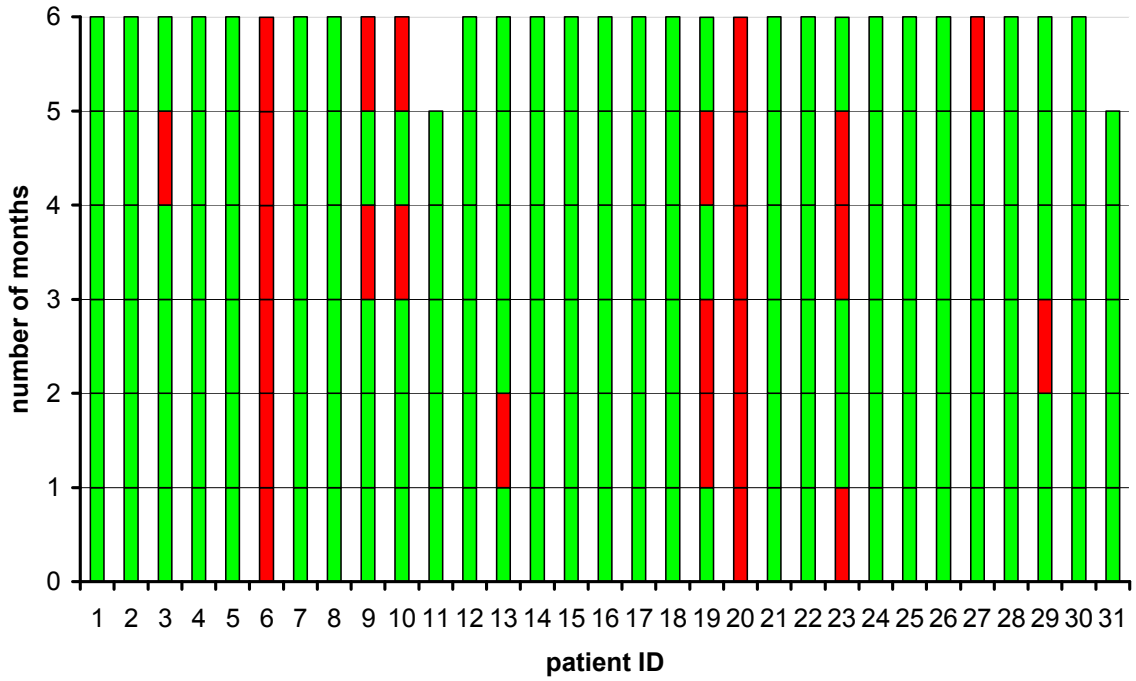


Fig. 15 Intraindividual daily compliance in the control group during main phase: compliant months (daily compliance ≥ 80%, green bars) and non-compliant months (daily compliance < 80%, red bars); patients #11 and #31 stopped using their MEMS® one month prior to the end of study.

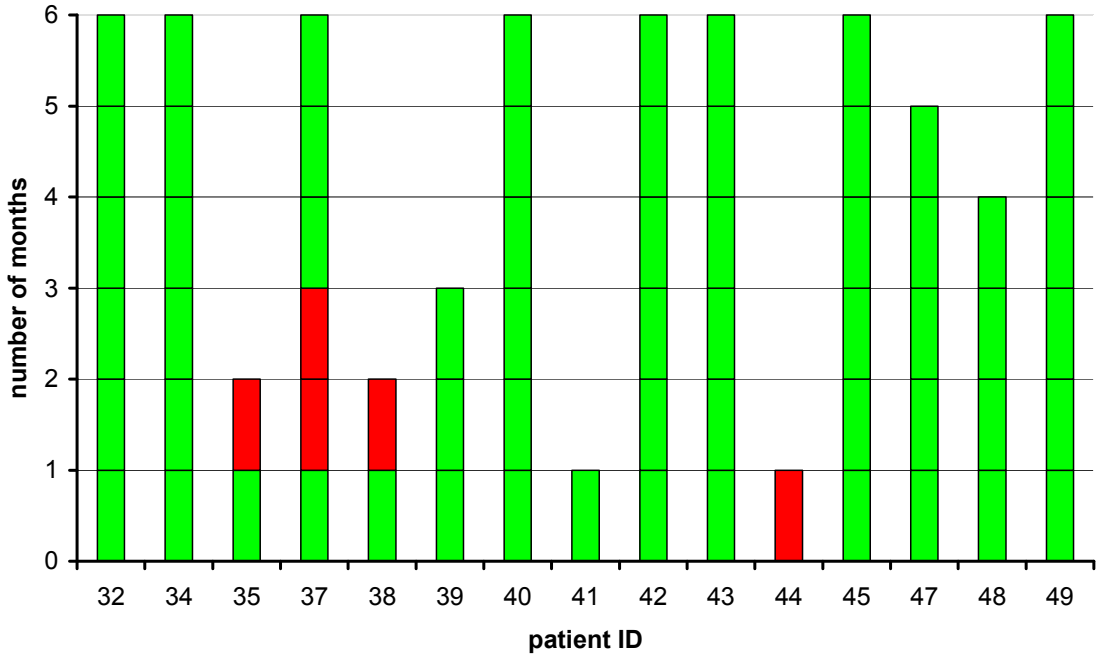


Fig. 16 Intraindividual daily compliance in the intervention group during main phase: compliant months (daily compliance ≥ 80%, green bars) and non-compliant months (daily compliance < 80%, red bars); patients #35, #38, #39, #41, #44, #47, #48 stopped using their MEMS® prior to the end of study.

3.3.2 Secondary compliance outcomes

Dosing intervals

For once daily regimens in the control group median dosing interval was 24.0 h (range: 0.27-388.05 h, n = 3897, Fig. 17). In the intervention group respective median dosing interval was 24.0 h (range: 0.50-335.35, n = 1446, Fig. 18). Moreover, for twice daily regimens (i.e. memantine and rivastigmine) median dosing interval was 12.05 h (n = 2578, range: 0.27-97.40 h, Fig. 19). In the intervention group corresponding median dosing interval was 12.0 h (n = 585, range: 0.72-47.12, Fig. 20). The main peak of the once daily regimen lay between 23 h and 25 h representing 68.9% and 65.4% of all dosing intervals in the control and intervention group, respectively. For the twice daily regimen the main peak was located between 11 h and 13 h constituting 35.4% and 76.1% of all dosing intervals in control and intervention group, respectively. Additional “peaks” were situated at 0-2 h, approximately 48 h and approximately 72 h for the once daily regimen and at 0-3 h, 23-25 h, approximately 36 h and approximately 48 h for the twice daily regimen.

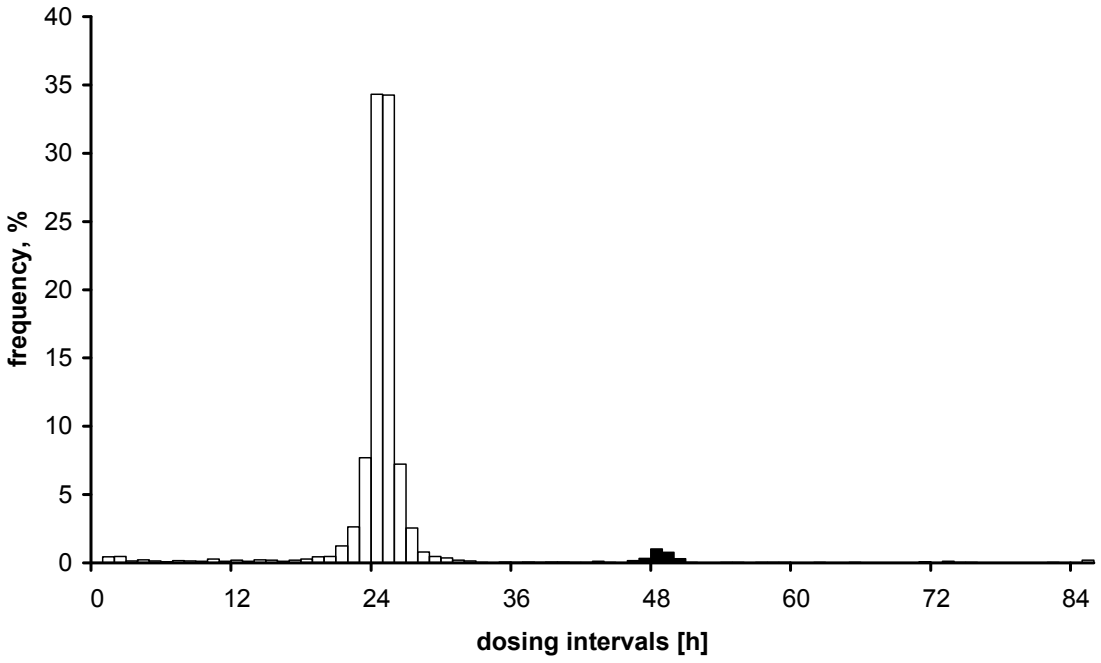


Fig. 17 Histograms displaying dosing intervals of once daily regimens in the control group (n = 3897), suggesting (at least) two different distributions (hollow bars and black bars); class width = 1 h.

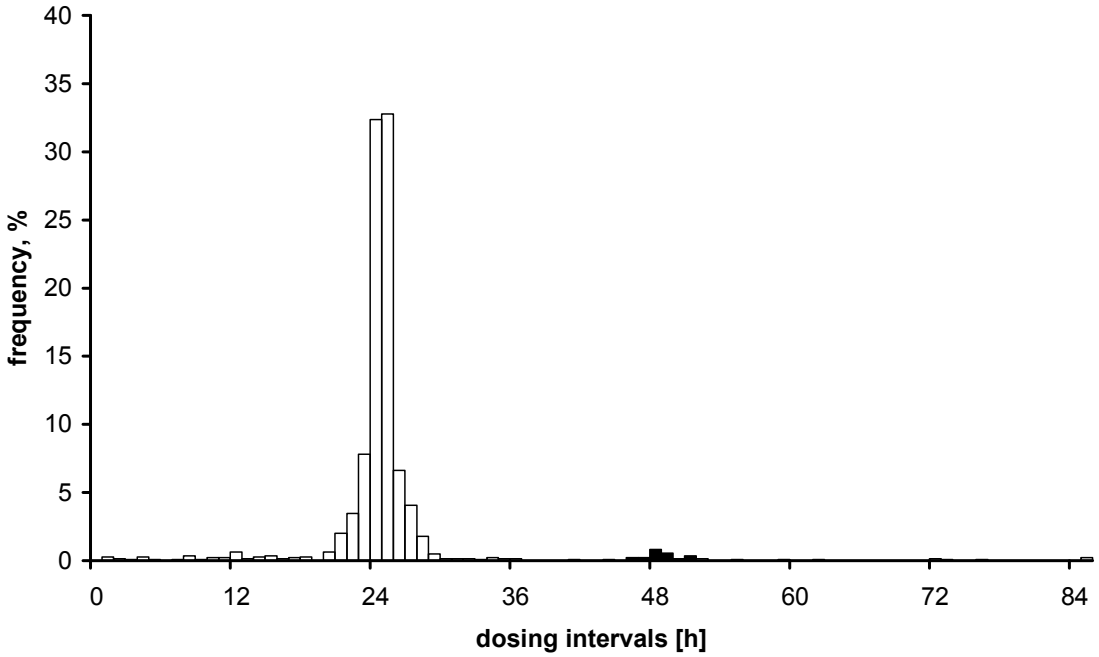


Fig. 18 Histograms displaying dosing intervals of once daily regimens in the intervention group (n = 1446), suggesting (at least) two different distributions (hollow bars and black bars); class width = 1 h.

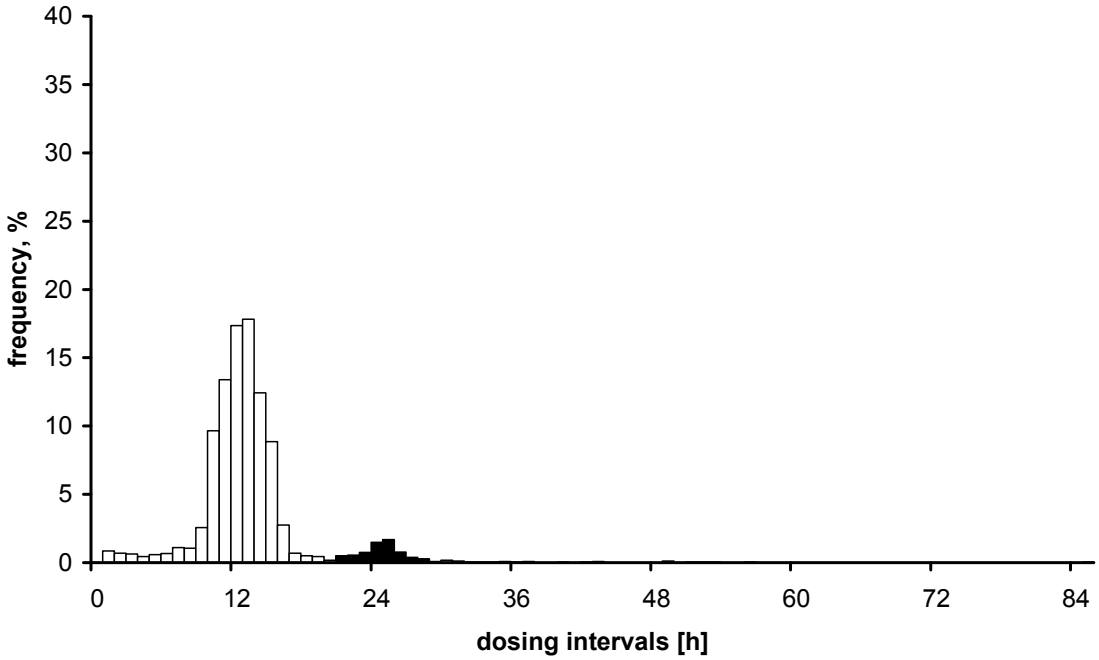


Fig. 19 Histograms displaying dosing intervals of twice daily regimens in the control group (n = 2578), suggesting (at least) two different distributions (hollow bars and black bars); class width = 1 h.

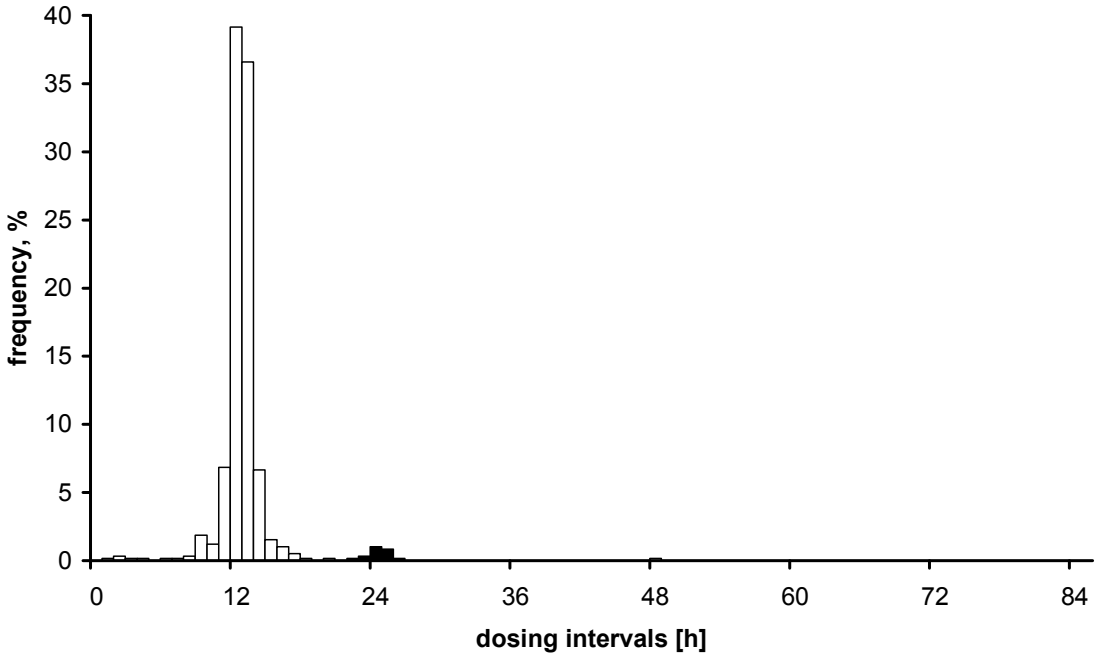


Fig. 20 Histograms displaying dosing intervals of twice daily regimens in the intervention group (n = 585), suggesting (at least) two different distributions (hollow bars and black bars); class width = 1 h.

Morning versus evening dose

Furthermore, evening doses were 1.6-fold more likely to be omitted than morning doses in all patients (OR = 1.62, $CI_{95\%}$ = 1.13-2.32).

Morisky questionnaire

The mean Morisky score in the control group remained unchanged at 3.7 from T_0 to T_7 whereas in the intervention group it increased from 3.2 to 3.6 (4 points meaning fully compliant, 0 points utterly non-compliant) [Tab. 11]. In the control group four patients scored higher (meaning increased compliance) on the second occasion and five scored lower. In contrast to this, four patients of the intervention group scored higher and only one patient scored lower.

Tab. 11 Means and standard deviations of Morisky scores in control and intervention group at the two evaluated occasions (T_0 and T_7)

	Control group	Intervention group
	$\bar{x}$ *(SD)*	$\bar{x}$ *(SD)*
Morisky score		
T_0	3.7 (0.7)	3.2 (1.2)
T_7	3.7 (0.8)	3.6 (0.6)

4 points meaning fully compliant, 0 points utterly non-compliant

The Morisky questionnaire yielded a sensitivity of 36% ($CI_{95\%}$ = 11%-61%) for detecting poor compliance (Tab. 12). Moreover, specificity of this questionnaire was 81% ($CI_{95\%}$ = 67%-95%). Furthermore, the positive predictive value (i.e. for non-compliance) was 0.45. The negative predictive value (i.e. for compliant behaviour) was 0.74.

Tab. 12 Cross-table with compliers/non-compliers detected by Morisky questionnaire with MEMS® compliance serving as reference

		MEMS® compliance (reference)		**Σ**
		non-compliant[3]	compliant[4]	
Morisky compliance ("test")	non-compliant[1]	5	6	11
	compliant[2]	9	25	34
	Σ	14	31	45

[1] Morisky score ≤ 3; [2] Morisky score = 4; [3] at least one month in main phase with MEMS® compliance < 80%; [4] no month with MEMS® daily compliance < 80%; MEMS®: Medication Event Monitoring System

3.3.3 Knowledge in pharmacotherapy

3.3.3.1 Development of the questionnaire

A questionnaire had to be developed for the assessment of *knowledge in pharmacotherapy*. Interrater reliability of the questionnaire (version 1) expressed by ICC was 0.88 ($CI_{95\%}$ = 0.85-0.90, n = 264) for knowledge of indication, 0.69 ($CI_{95\%}$ = 0.62-0.76, n = 264) for administration in relation to a meal, and 0.60 ($CI_{95\%}$ = 0.36-0.77, n = 42] for need of counselling. Eighteen percent of all answers were assigned to the two middle categories in question 1 assessing patients' knowledge of indication. Interestingly, this was only 2% in question 2 concerning patients' knowledge about possible drug-food interactions.

During the second meeting we elucidated pharmacists' problems with the questionnaire (Tab. 13). Based on pharmacists' experiences an optimised questionnaire (version 2) was created (Appendix B). A key change was the employment of a rules-based structure in question 2 (Tab. 14). Answers were dichotomised into correct or incorrect by means of the rules. As a source of information the summary of product characteristics was chosen. Consequently, a pharmaceutical judgement being provided by raters was no longer required.

Tab. 13 Survey over raters' comments on the questionnaire (version 1) and changes implemented for optimised questionnaire (version 2)

Question	Raters' comments and recommendations	Changes implemented in version 2 of questionnaire
1[a]	The categories "stimme teilweise zu" (partially agree) and "stimme teilweise nicht zu" (partially disagree) are difficult to distinguish. Recommendation: to summarise both categories or to alter the wording to "stimme mehr zu" (agree more) and "stimme weniger zu" (agree less).	Introduction of a four step end-anchored scale without descriptors in the middle positions assigning three to zero points according to knowledge (3 points = 100% knowledge to 0 points = 0% knowledge)
1		Alphabetical order of drugs to facilitate comparison between statements
2[b]	Raters suggested to include administration times into the questionnaire (morning, noon, evening, at night). They also advised to further annotate the question because it is sometimes not absolutely clear whether it refers to food effect and/or taking time: They only fully agreed if patients administered donepezil 0.5 h to 1 h before or between main meals (donepezil should be taken at night, but its absorption is not influenced by food [82]).	Employment of a rules based structure dichotomising answers into correct or incorrect
2	Raters recommended to employ the term "fehlende Angaben" (missing data) instead of "keine Angabe" (not declared) in question 2.	Exclusion of missing data from the questionnaire
2	The word "unterschiedlich" (differently) in this context is difficult to interpret.	Change wording to „mal nüchtern, mal zum Essen" (sometimes on an empty stomach, sometimes with food)
2	The wording „(0.5 h-1.0 h) vor oder zwischen den Hauptmahlzeiten" (0.5 h to 1 h before or between main meals) should be renamed in „auf nüchternen Magen (0.5-1.0 h vor dem Essen oder mindestens 2 h nach dem Essen)" (on an empty stomach [0.5 h to 1.0 h before or between meals]).	Implemented accordingly
3[c]	Raters recommended the deletion of the category "sehr niedrig" (very low).	Deletion of question 3 (impossible to assess since drugs are not longer grouped according to individual patient)
4[d]		Deletion of question 4 (impossible to assess since drugs are not longer grouped according to individual patient)
		Further structural changes (e.g. cover page, directions, last page) [63]

[a] knowledge of indication, [b] knowledge of administration in relation to a meal, [c] need of counselling, [4] free text field for further remarks

Tab. 14 Rules based structure for the determination of patients' knowledge in drug-food interactions

Advice on administration (drug-food interaction) in summary of product characteristics	Correct patients' answers
On an empty stomach or before a meal	On an empty stomach (0.5 h to 1.0 h before or between meals)
With or directly after a meal	With or directly after a meal
Independent of a meal	All answers are correct
No information in summary of product characteristics	All answers are correct

Interrater reliability of the questionnaire (version 2) expressed by ICC was 0.83 ($CI_{95\%}$ = 0.76-0.88, n = 100) for knowledge of indication (Appendix B) which is slightly lower than in version 1.

3.3.3.2 Determination of *knowledge in pharmacotherapy*

In the control group mean knowledge of indication (calculated per drug) slightly decreased from 78% (T_0) to 77% (T_7). In contrast, this outcome increased from 73% (T_0) to 78% (T_7) in the intervention group. Whereas in the control group almost no changes were observed between T_0 and T_7 with approximately 15% wrong answers (0% knowledge) given (Fig. 21), this fraction of drugs decreased by approximately 3% points in the intervention group (Fig. 22). Very apparent was the 5% points increase of drugs where patients could name the correct indication in the intervention group (100% knowledge).

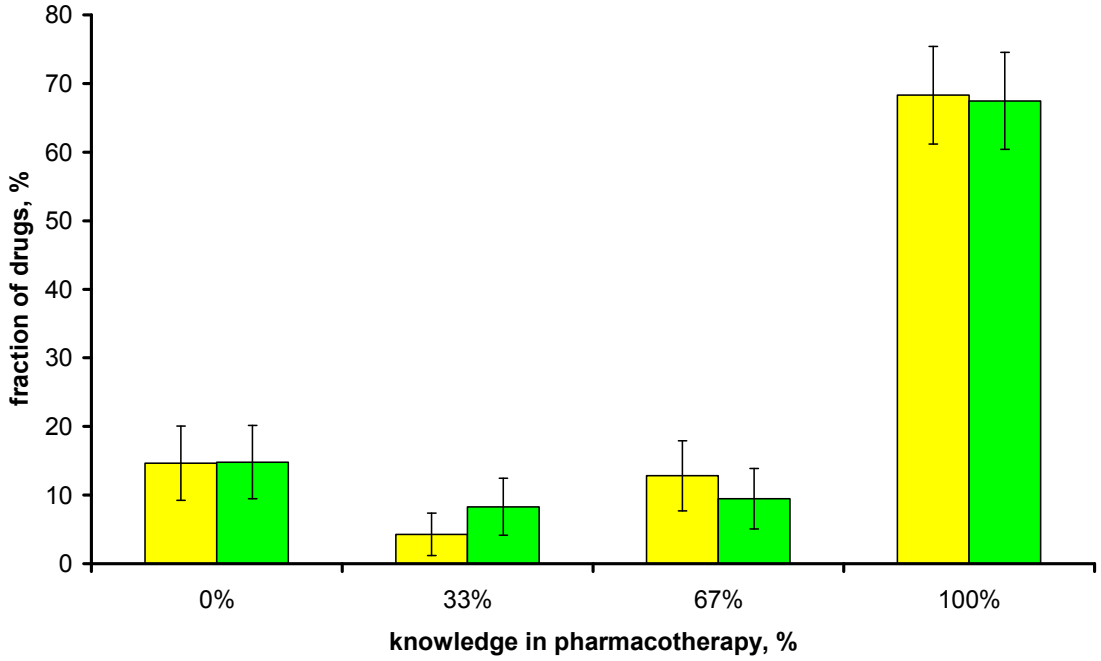


Fig. 21 Knowledge of indication in the control group; yellow bars represent T_0 (n = 164), green bars represent T_7 (n = 169); error bars stand for 95% confidence intervals.

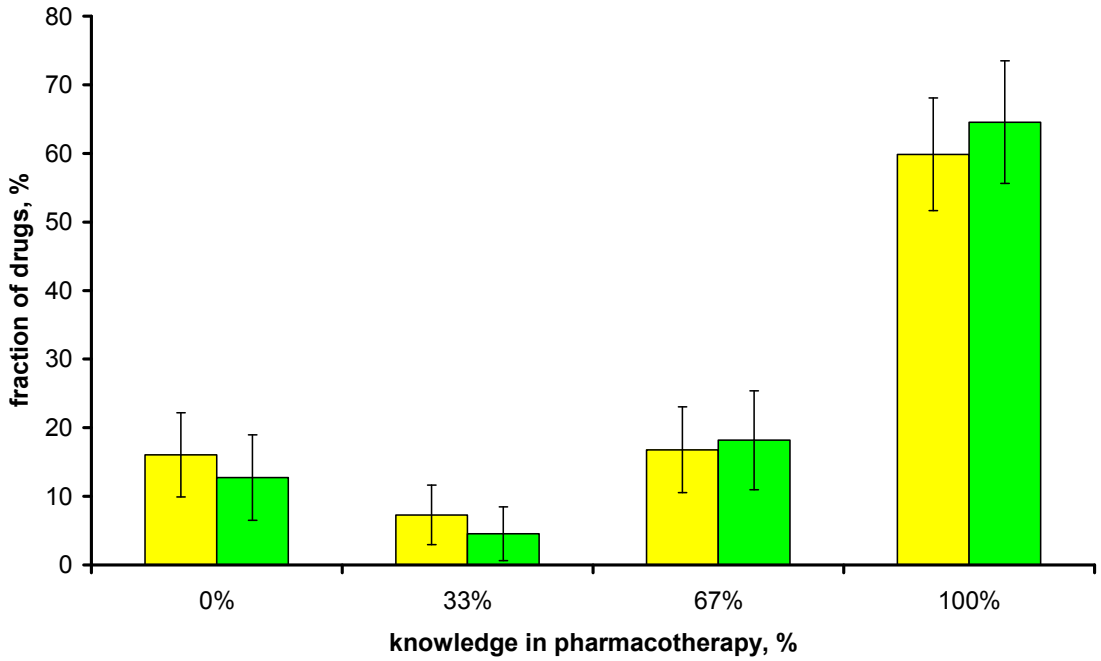


Fig. 22 Knowledge of indication in the intervention group; yellow bars represent T_0 (n = 137), green bars represent T_7 (n = 110); error bars stand for 95% confidence intervals.

Eighty-five drugs were classified of which 13 (15%) should be taken on an empty stomach, 21 (25%) with food, 41 (48%) independent of a meal, and 10 (12%) with no information in the summary of product characteristics.

At T_0 approximately 13% of all evaluated drugs (n = 157) were administered inappropriately in relation to a meal in the control group (Tab. 15). At T_7 this fraction decreased by one percent. Surprisingly, inappropriate administration increased in the intervention group from 9.9% to 15.2%.

Tab. 15 Taking behaviour in relation to a meal in control and intervention group at T_0 and T_7

Group		T_0	T_7
		Number of drugs (%)	Number of drugs (%)
Control group	inappropriate TBRM	20 (12.7)	19 (11.8)
	total	157 (100)	161 (100)
Intervention group	inappropriate TBRM	13 (9.9)	15 (15.2)
	total	131 (100)	99 (100)

TBRM = taking behaviour in relation to a meal

3.3.4 Satisfaction with information about medicines

All the results from the cross-sectional study have already been reported in Stengel's diploma thesis [66]. At this point, we only summarise key results.

Unlike intervention and control cohort there were fewer women in the cross-sectional study (35% versus more than 50%) [Tab. 16]. 52% of all caregivers were solely responsible for pharmacotherapy, which was similar to the intervention group. Moreover, the majority of caregivers were spouses (80%), followed by children (14%) and other relatives (6%). Furthermore, nearly half of all caregivers had a secondary modern school qualification.

Tab. 16 Characteristics of caregivers and patients in cross-sectional study (n = 71)

Characteristics	Cross-sectional study
	n (%)
Sex of caregivers: women	25 (35)
School-leaving qualification of caregivers	
Secondary modern school qualification	33 (47)
Secondary school certificate	6 (9)
Polytechnic school certificate	19 (27)
Advanced technical school certificate	5 (7)
higher education entrance qualification	6 (9)
Other	2 (3)
Responsibility for pharmacotherapy	
Caregiver only	37 (52)
Patient supported by caregiver	22 (31)
Patient supported by caregiver and professional care	8 (12)
Patient supported by professional care	4 (6)
Number of patients' regularly administered drugs[1]	
1	4 (6)
2	8 (11)
3	16 (23)
4	18 (26)
5 and more	24 (34)
Regular customer in one community pharmacy[1]	
always	54 (77)
Often, but also other community pharmacies	14 (20)
Varying community pharmacies	2 (3)
	median (range)
Age of caregivers	69 (39-85)

[1] this item was missing in one patient

We questioned caregivers about their sources of medicines information for the Alzheimer patient. As expected, more than 90% of all caregivers considered the physician as a source (Fig. 23). Surprisingly, only about one third of all caregivers viewed the pharmacist as a source for this type of information. Moreover, three percent of all caregivers stated they had not received any information.

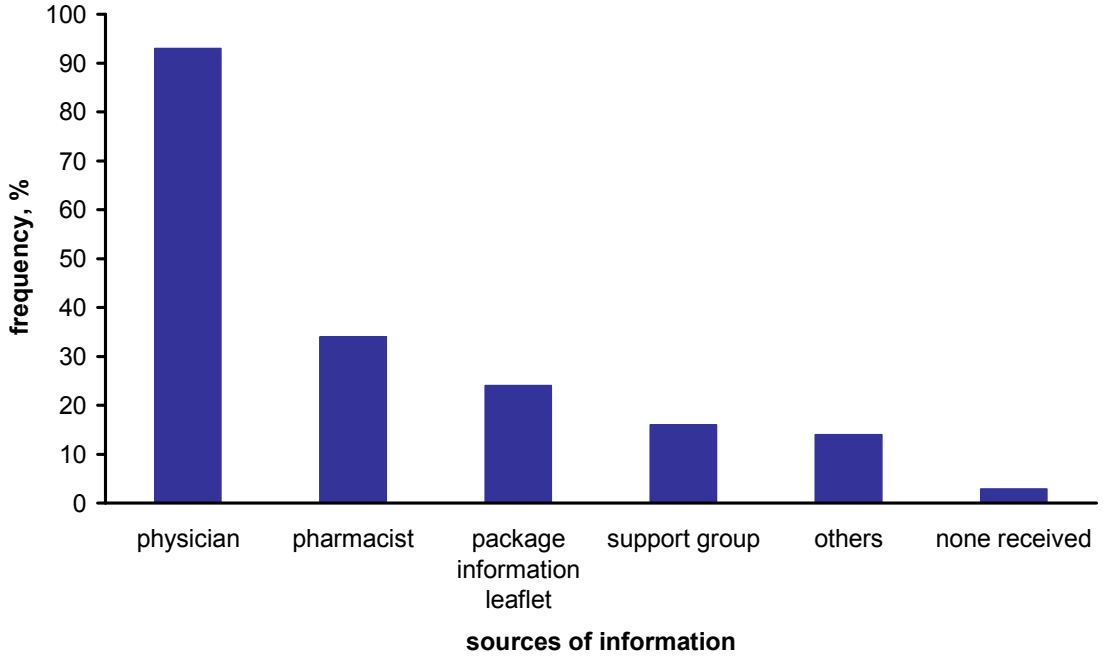


Fig. 23 Caregivers' sources of medicines information for Alzheimer patient; they could give multiple answers (n = 70).

Fifty percent of all caregivers in the cross-sectional study had a SIMS score ranging from 2 to 15 (mean = 8.3, $CI_{95\%}$ = 6.7-9.9) whereas patients/caregivers in the intervention group were much more satisfied with 50% having a SIMS between 13 and 17 (mean = 15, $CI_{95\%}$ = 13.7-16.3) [Fig. 24].

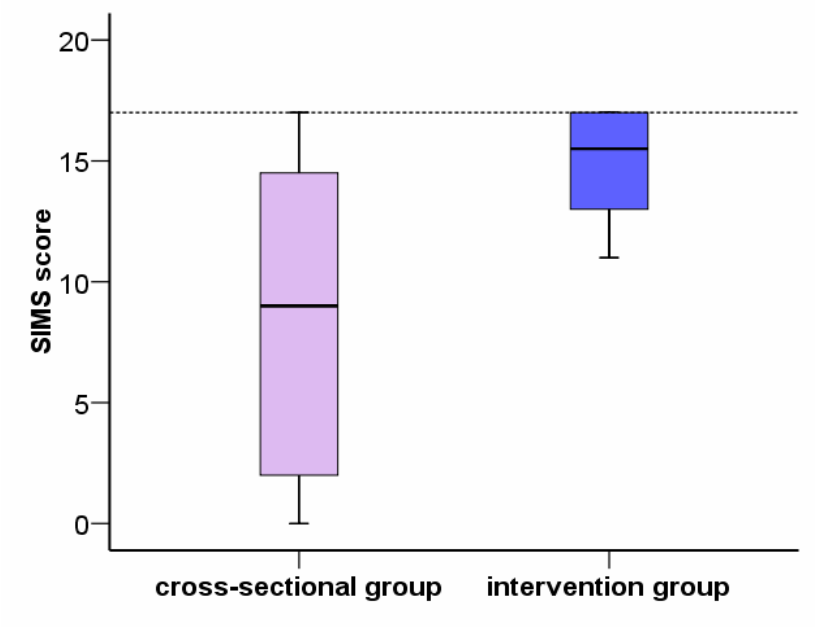


Fig. 24 Distribution of the SIMS score in cross-sectional group (n = 64) and intervention group (n = 12); dotted line indicates the maximum attainable score of 17.

Mean subscale 1 in the cross-sectional study and intervention group were 5.1 (57% of total subscale) and 8.5 (94%), respectively. Moreover, mean subscale 2 in the cross-sectional study and intervention group were 3.3 (41% of total subscale) and 6.6 (83%), respectively.

Fig. 25 provides a profile of patient satisfaction with the 17 medicines information topics in the cross-sectional study. About two-thirds of all patients were satisfied with information about name, indication, supply, and use of medication. Contrary to that, less than 40% are satisfied with information related to side-effects (items 10, 11, 12).

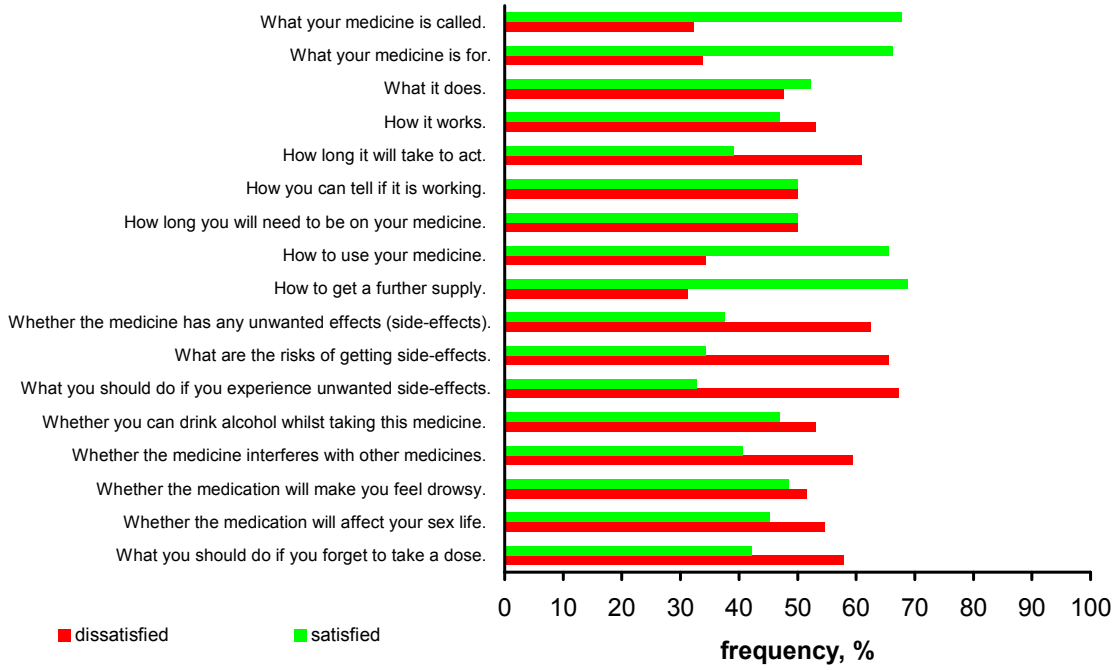


Fig. 25 Satisfaction and dissatisfaction with information about medicines in the cross-sectional study (n = 64)

In the intervention group there were always more than two-thirds of all patients/caregivers satisfied with information on all topics of the SIMS score (Fig. 26). Patients/caregivers were least satisfied with information about the risks of side-effects. By contrast, they were fully satisfied with instructions how to use the medicine.

“Dissatisfied” nearly exclusively means having received too little or no information. Very seldom patients/caregivers ticked “too much information” (less than one percent per item on average).

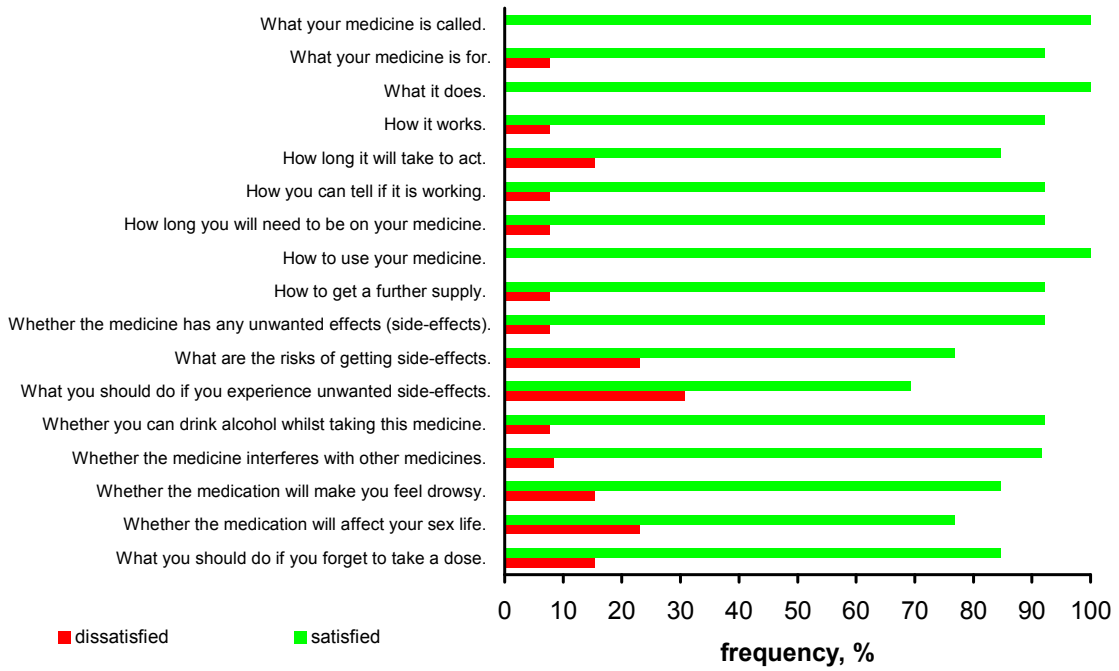


Fig. 26 Satisfaction and dissatisfaction with information about medicines in the intervention group (n = 12)

In all 17 items of the SIMS questionnaire by far more patients in the intervention group showed satisfaction than patients in the cross-sectional study (Fig. 27). Remarkably, the “best” item in the cross-sectional study (i.e. having the highest frequency of satisfaction) nearly coincided with the “worst” item in the intervention group (i.e. with the lowest frequency of satisfaction).

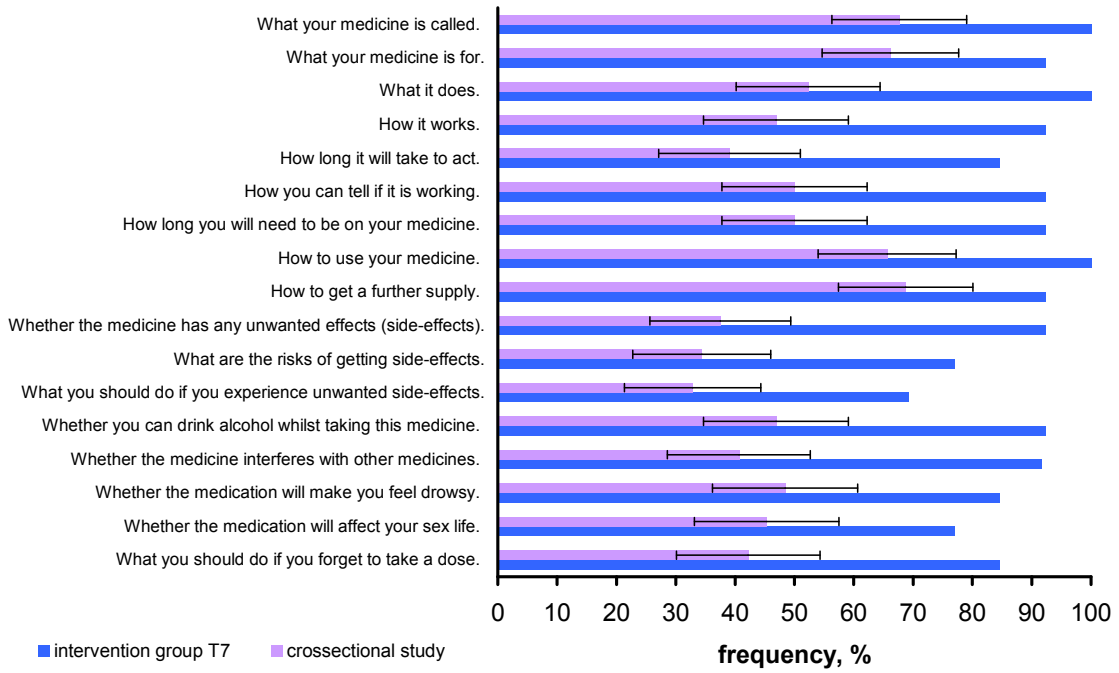


Fig. 27 Satisfaction with information about medicines: intervention group (n = 12) versus cross-sectional study (n = 64); error bars represent 95% confidence intervals (we did not calculate confidence intervals for the intervention group due to small sample size).

The SIMS total satisfaction rating displayed a pronounced floor as well as ceiling effect (in the intervention group there was only a ceiling effect with 25% of patients/caregivers assigning full points) [Fig. 28]. Fourteen percent of all patients/caregivers were completely dissatisfied with the information they had received from their pharmacist. Furthermore, twenty-one percent of all patients/caregivers were entirely satisfied. In summary, more than one-third of all patients/caregivers were either fully satisfied or fully dissatisfied.

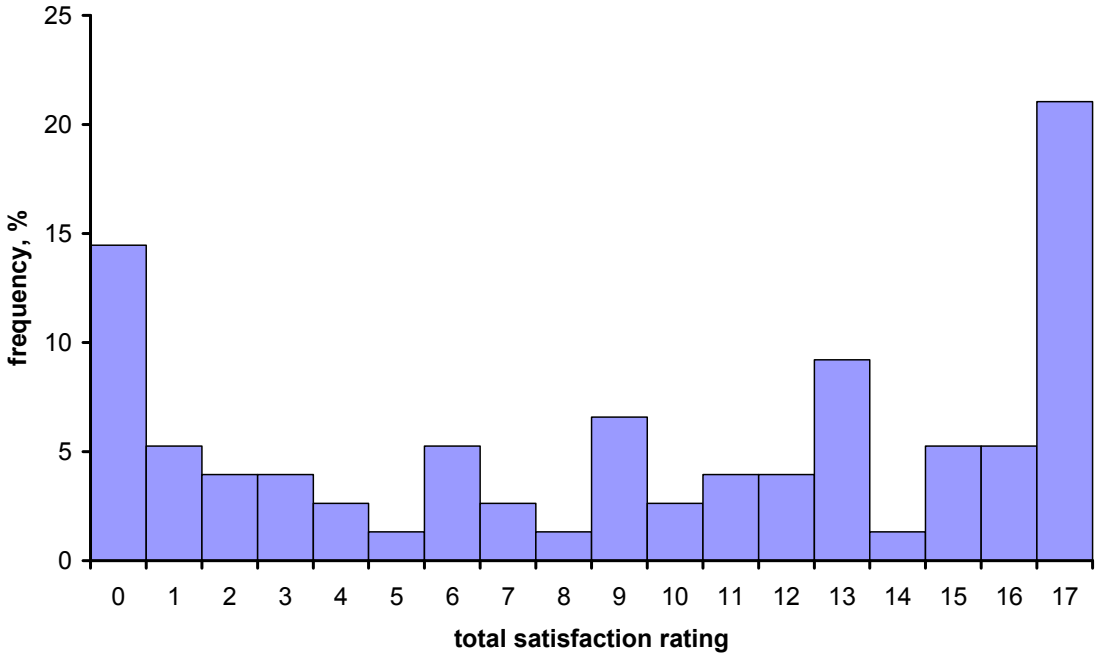


Fig. 28 Distribution of SIMS total satisfaction rating in cross-sectional study as well as intervention group (n = 76)

3.3.5 Health-related quality of life

Caregivers' health-related quality of life was determined by the SF-12 and the SF-6D (SF-12). More than 20% of all caregivers could not be included into the analysis because a missing item in the questionnaire at T_0 or T_7 did not allow the calculation of the summary scores (Tab. 17). In total, HRQOL data of 73% (57%) of caregivers in the control group (intervention group) could be included into analysis.

Tab. 17 Missing data in SF-12 dataset

Reason for missing data	Number of patients
	n
Missing item in T_0 and/or T_7 questionnaire[a]	10
Caregiver not present during interview(s)	2
Patient did not want caregiver to fill in the form	1
Drop-out (missing data in T_7)	2

[a] Already one missing item in a SF-12 questionnaire does not allow the calculation of summary scores [68].

Physical and mental summary scales (PCS, MCS) of the SF-12 remained stable in both groups with the exception of the PCS in the intervention group. Here, a slight

decrease could be seen (small effect size) [Tab. 18]. Confidence intervals of effect sizes were particularly wide in the intervention group due to the small sample size ranging e.g. from small positive to highly negative effects on the PCS.

Tab. 18 Physical and mental summary scale of the SF-12: central tendency, dispersion and effect size

	Control group (n = 22)		Intervention group (n = 9)	
	$\bar{x}$ *(SD)*	SRM [$CI_{95\%}$]	$\bar{x}$ *(SD)*	SRM [$CI_{95\%}$]
Physical summary scale				
T_0	42.9 (10.4)		46.2 (8.3)	
T_7	42.8 (10.8)		44.2 (8.7)	
Effect size		-0.01[a] [-0.43; 0.40]		-0.34[a] [-1.01; 0.33]
Mental summary scale				
T_0	46.7 (10.3)		50.3 (8.6)	
T_7	45.6 (9.1)		50.6 (8.4)	
Effect size		-0.10[a] [-0.52; 0.32]		0.03[a] [-0.62; 0.68]

[a]Effect sizes of 0.2-0.5 are being regarded as small, 0.5-0.8 are moderate, those 0.8 and above are large [71]. CI: confidence interval; SD: standard deviation; SRM: standardised response mean; T_0: baseline score; T_7: score at seven months from baseline

In the control group the SF-6D (SF-12) deteriorated with an effect size of greater than 0.2 meaning a small effect (Tab. 19). In contrast to that, the SF-6D (SF-12) stayed stable in the intervention group (effect size < 0.2). Again wide confidence intervals of effect sizes due to small sample size comprise, e.g. small positive effects as well as moderate negative effects in the control group.

Tab. 19 The SF-6D (SF-12): central tendency, dispersion and effect size

	Control group (n = 25)		Intervention group (n = 10)	
	$\bar{x}$ *(SD)*	SRM [$CI_{95\%}$]	$\bar{x}$ *(SD)*	SRM [$CI_{95\%}$]
T_0	0.730 (0.145)		0.790 (0.130)	
T_7	0.703 (0.122)		0.776 (0.154)	
Effect size		-0.217 [-0.640; 0.206]		-0.106 [-0.762; 0.549]

[a]Effect sizes of 0.2-0.5 are being regarded as small, 0.5-0.8 are moderate, those 0.8 and above are large [71]. CI: confidence interval; SD: standard deviation; SRM: standardised response mean; T_0: baseline score; T_7: score at seven months from baseline.

3.3.6 Drug related problems

Forty eight drug related problems were documented by community pharmacists in 18 patients (2.7 drug related problems per patient on average). The most predominant drug related problem was inappropriate drug choice (almost every third), followed by inappropriate drug use by the patient and inappropriate dosage (both approximately one one-fifth) [Tab. 20].

Tab. 20 Drug related problems as documented by community pharmacists in the intervention group (n = 48)

PI-Doc® code	Problems	n	Percentage
A	**Inappropriate drug choice**	**14**	**29%**
A3	Contraindications by other disease not considered	1	2%
A5	Unintended use of two drugs of the same therapeutic class	1	2%
A8	Unsuitable preparation	1	2%
A13	Suspected prescribing error due to sound-alike drug	1	2%
A15	Drug is ineffective	1	2%
A16	Patient does not receive a drug although an indication exists	2	4%
A17	Drug is inappropriate for age group	4	8%
A18	Prescription of a drug although no indication is present	3	6%
C	**Inappropriate drug use by the patient/compliance**	**10**	**21%**
C2	Handling problems	3	6%
C7	Unsuitable time of application	7	15%
D	**Inappropriate dosage**	**10**	**21%**
D3	Overdosage	2	4%
D4	Underdosage	7	15%
D5	Unsuitable dosage intervals	1	2%
W	**Drug-drug interaction**	**4**	**8%**
W1	Reference to an interaction by literature	4	8%
U	**Adverse drug reaction**	**6**	**13%**
U2	Symptoms of an adverse drug reaction	6	13%
S	**Other problems**	**4**	**8%**
SK2	Information supplied by other health care professionals misinterpreted	1	2%
SK4	Erroneous patient related documentation in pharmacy	1	2%
ST6	No longer prescribed drugs in medicine chest	1	2%
ST7	Problems with device for therapy self control	1	2%

Most prevalent were general interventions such as contacting the physician (Tab. 21). Interventions due to inappropriate drug use by the patient and due to inappropriate dosage came in second and third place, respectively. Median time to handle a drug related problem was 10 min (n = 24, Min = 3 min, Max = 60 min). 54% of all drug related problems were solved, 29% were partly solved, and 15% could not be solved. Furthermore, in almost half of all drug related problems (22 out of 48 DRPs) pharmacists contacted a physician.

Tab. 21 Interventions to solve drug related problems (n = 48)

PI-Doc® code	Problems	n	Percentage
IO	**General interventions**	**18**	**38%**
Iallg1	Interviewing and counselling of the patient	7	15%
Iallg2	Contacting the physician	8	17%
Iallg3	Refer a patient to a physician	3	6%
IA	**Intervention inappropriate drug choice**	**7**	**15%**
IA1	Selecting or recommending an appropriate drug for the indication	4	8%
IA4	Recommendation to stop a drug	3	6%
IC	**Intervention: inappropriate drug use by the patient/compliance**	**9**	**19%**
IC1	Advice for correct application	1	2%
IC2	Demonstration of the correct application, practicing with the patient	1	2%
IC7	Advice with regard to optimal time of application	7	15%
ID	**Intervention: inappropriate dosage**	**8**	**17%**
ID3	Clarification with regard to an overdosage	6	11%
ID4	Clarification with regard to an underdosage	2	4%
IW	**Intervention: drug interactions**	**2**	**4%**
IW4	Information about possible interactions and countermeasures	1	2%
IW5	Monitoring of possible symptoms caused by drug interactions	1	2%
IU	**Intervention: adverse drug reaction (ADR)**	**1**	**2%**
IU5	Administration of drug to treat ADR of another drug	1	2%
IS	**Intervention: other problems**	**3**	**6%**
ISK2	Detailed explanation of the situation, eliminate misunderstanding	1	2%
ISK4	Communication of problem among pharmacy staff	1	2%
IST6	Demonstration of the device for therapy self control, practicing with the patient	1	2%

3.3.7 Further process outcomes

With the exception of three patients/caregivers there was always one pharmacist responsible for the provision of pharmaceutical care in the intervention group (Tab. 22). The median number of counselling sessions was four (projected: five). In almost three quarters of all patients a medication review was implemented and documented. Surprisingly, BAK guidance oriented counselling was relatively rarely documented. Thirty-seven percent of all patients received one or more guidance oriented consultations. Furthermore, only 50% of all patients were provided at least one MGMM consultation.

Tab. 22 Survey over further process outcomes

Patient ID	Pharmacists or technicians involved in PC	Counselling sessions	Medication reviews	BAK guidance oriented counselling	MGMM
	n	n	n	n	n
32	1	2	1	1	1
33	1	4	1	1	md
34	1	4	0	0	2
35	2[a]	5	1	0	0
36	2[a]	4	1	0	0
37	1	4	1	3	1
38	1	5	1	1	md
39	1	2	1	0	0
40	1	4	1	2	md
41	1	3	1	1	1
42	1	2	1	0	0
43	1	5	1	0	1
44	3[b]	3	0	0	0
45	1	4	1	2	3
46	1	0	0	0	0
47	1	2	1	0	1
48	1	5	0	0	0
49	1	2	1	0	1
50	1	1	0	0	0

[a] Patients 35 and 36 were recruited and initially cared for by a study pharmacist. Due to maternity leave pharmaceutical care was continued by the research pharmacist (OS).

[b] Patient 44 was recruited by a study pharmacist. Due to maternity leave pharmaceutical care was continued by two pharmacy technicians.

MEMS®: medication event monitoring system; MGMM: measurement-guided medication management; md: missing data; PC: pharmaceutical care

3.3.8 Feasibility of pharmaceutical care intervention

From 18 pharmacists (recruiters and non-recruiters) who received the questionnaire 14 replied (78%). Two recruiters and two non-recruiters did not reply. Moreover, the minutes of a focus group with three caregivers were analysed. Comments during the completion of the satisfaction questionnaire in the cross-sectional study were recorded for 22 caregivers [66]. Emerging topics were grouped into four major themes, such as image of community pharmacy, interaction with physicians, interaction with patients and caregivers, and community pharmacy setting.

The cross-sectional study was conducted in several cities (e.g. Leipzig = L and Augsburg = A) [66]. Caregivers were coded accordingly. Pharmacists' statements from the narrative reports were coded with a "P".

Interaction with patients and caregivers

The presence of mutual trust between pharmacist and patient/caregiver was helpful for the initiation of pharmaceutical care. If this was not present patient and caregiver often denied study participation.

"The patient doesn't want to participate because he fears data abuse and disclosure of personal problems as well as he doesn't know what pharmaceutical care is." [P5]

A central barrier was that patients had no prior experience and knowledge of the changing role of community pharmacy towards pharmaceutical care.

Within pharmaceutical care pharmacists appreciated the change from a customer focused to a therapeutic relationship. One pharmacist [P12] valued as a success *"the personal opening up of two patients and their caregivers"*. The therapeutic relationship also extended beyond the study:

"All patients I cared for ask for me if they are uncertain or if they need independent information." [P18]

Additionally, it was very important for caregivers to have somebody to talk to *"release psychological stress"* [P1].

Pharmacists succeeded in informing patients about medication intake and drug interactions. Barriers were seen in the higher priority of physicians in counselling. Arguments for pharmaceutical care were lacking if the patient felt well-informed by the respective physician. Here, the accountability of the pharmacist remained unclear.

Moreover, patients feared pharmaceutical care could use up too much time (frequent visits to pharmacy, completing forms).

Interaction with physicians

Contacts between pharmacists and physicians were nearly exclusively by telephone. At inclusion the study pharmacists had to get in touch with the respective physician to confirm patients' ability to consent. This step turned out to be a major barrier during the course of the study.

"The biggest problem was the cooperation with the physicians, especially the signature at inclusion." [P18]

Physicians' often displayed scepticism about pharmaceutical care (i.e. increased pharmacists' involvement in pharmacotherapy). Many GPs and specialists were not willing to discuss or implement therapy changes with the pharmacist. Even GPs and specialists did not always communicate and cooperate to optimise pharmacotherapy. One patient [patient 42] with renal failure and hypertension was not prescribed an ACE inhibitor. The pharmacist [P5] contacted the nephrologist who supported the use of an ACE inhibitor in this patient. But he did not want to interfere with the pharmacotherapy prescribed by the GP. Only if GP had asked for an evaluation of pharmacotherapy, he would have given a recommendation to start an ACE inhibitor.

"Even after having talked to the nephrologist, I reach nothing concerning the prescription of an ACE-inhibitor – communication between the two doctors is not realisable." [P5]

But there are also examples where pharmacists and physicians cooperated successfully.

"The patient [patient 49] has been treated on Aricept 5 mg for quite a while. His wife is unsatisfied, since he more and more degrades and participates less in daily activities. Having talked to me, the psychiatrist increased the dose to 10 mg … According to his wife he blossoms out. He is much more alert." [P5]

In the future pharmaceutical care should seek more involvement of physicians or at least they should be more informed about additional pharmacists' activities. One pharmacist also recommended multidisciplinary quality circles with pharmacists and physicians [P12].

Community pharmacy setting (institution and personal)

Lack of time was the most prevalent barrier to pharmaceutical care in the community pharmacy setting.

"Documentation and literature research always took place at home in my free time since in everyday working life there's no time to do that." [P18]

In particular, one pharmacist [P12] annotated that she had no time in her daily routine to prepare herself for the phone calls to physicians.

Furthermore, pharmacists referred to the lack of reimbursement for pharmaceutical care. Without payment pharmaceutical care presents a loss-making business. Moreover, study pharmacists suffered from lack of support from colleagues and pharmacy owners. Additionally they criticised the set-up of the community pharmacy as being inappropriate for pharmaceutical care (e.g. lack of discretion).

Image of community pharmacy (institution and personal)

Generally the role of community pharmacy for Alzheimer patients/caregivers varied considerably. Provision of drug information does not seem to be of major importance for many patients/caregivers:

"I am very positive about my pharmacist. They deliver items; there I get all my health magazines." [caregiver 2 in focus group]

GPs and neurologists are primarily seen as source of information concerning drugs with the pharmacist lacking behind. Also a shop-keeper image is prevalent.

"I primarily regard the pharmacy as a shop. Perhaps for further queries, but apart from this the doctor is responsible. I don't see the pharmacist as the person who is responsible for profound information to the patient. That is the doctor. The pharmacist should not turn into a pseudo-doctor in diagnostics, indication and prescription of medicines." [L-03]

By contrast, other patients long for more involvement of their pharmacist.

"Counselling in my pharmacy is a good thing, especially since my doctor does not always do everything. In general, there should be more counselling in the pharmacy." [L-04]

Moreover, barriers to counselling expressed by caregivers were the pharmacy being too crowded and changing persons in charge, which impedes the establishment of a therapeutic relationship.

"It's really difficult in a big community pharmacy when there are a lot of personnel. You don't always get the same contact person. …" [A-02]

The setting of the individual community pharmacy had an impact on pharmacists' interaction with patients/caregivers and physicians. Additionally, it also influenced the general image of community pharmacy (Fig. 29). The image of community pharmacy and its interactions with physicians impacted one another.

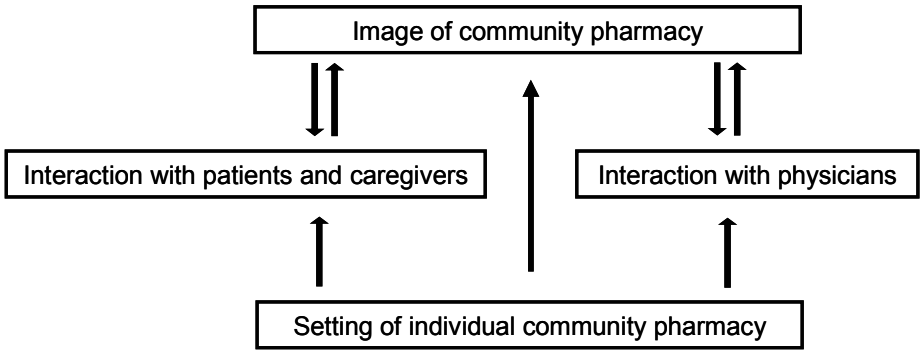


Fig. 29 Mapping of the main themes influencing feasibility of pharmaceutical care

3.4 Forgiveness of donepezil

We simulated three different approaches to characterise the forgiveness of donepezil: individual compliance patterns, discrete compliance patterns (10%-100%), and dosage omissions.

To determine their possible therapeutic undersupply individual compliance patterns of twelve patients of the control group comprising 1873 MEMS® recordings with either 5 mg (n = 3) or 10 mg (n = 9) donepezil were simulated (approach A). In the 5 mg donepezil dosing group, two patients (#13 and #23) out of three were undersupplied during certain longer time periods. Patient #23 exhibited non-compliant behaviour particularly from dose 95 to 114 (Fig. 30a) resulting in pronounced therapeutic undersupply (Fig. 30b). Moreover, for both patients it was found that one occasionally omitted dose (dosing interval ≈ 48 h) did not cause therapeutic undersupply. However, a series of one dose omission triggered the appearance of undersupplied periods. Very interestingly, daily compliance in the main phase for patient #13 and #23 was 87.2% and 80.0%, respectively, i.e. they were regarded as compliant according to the commonly employed 80% cut-off criterion. None of the patients taking 10 mg donepezil displayed any undersupplied periods.

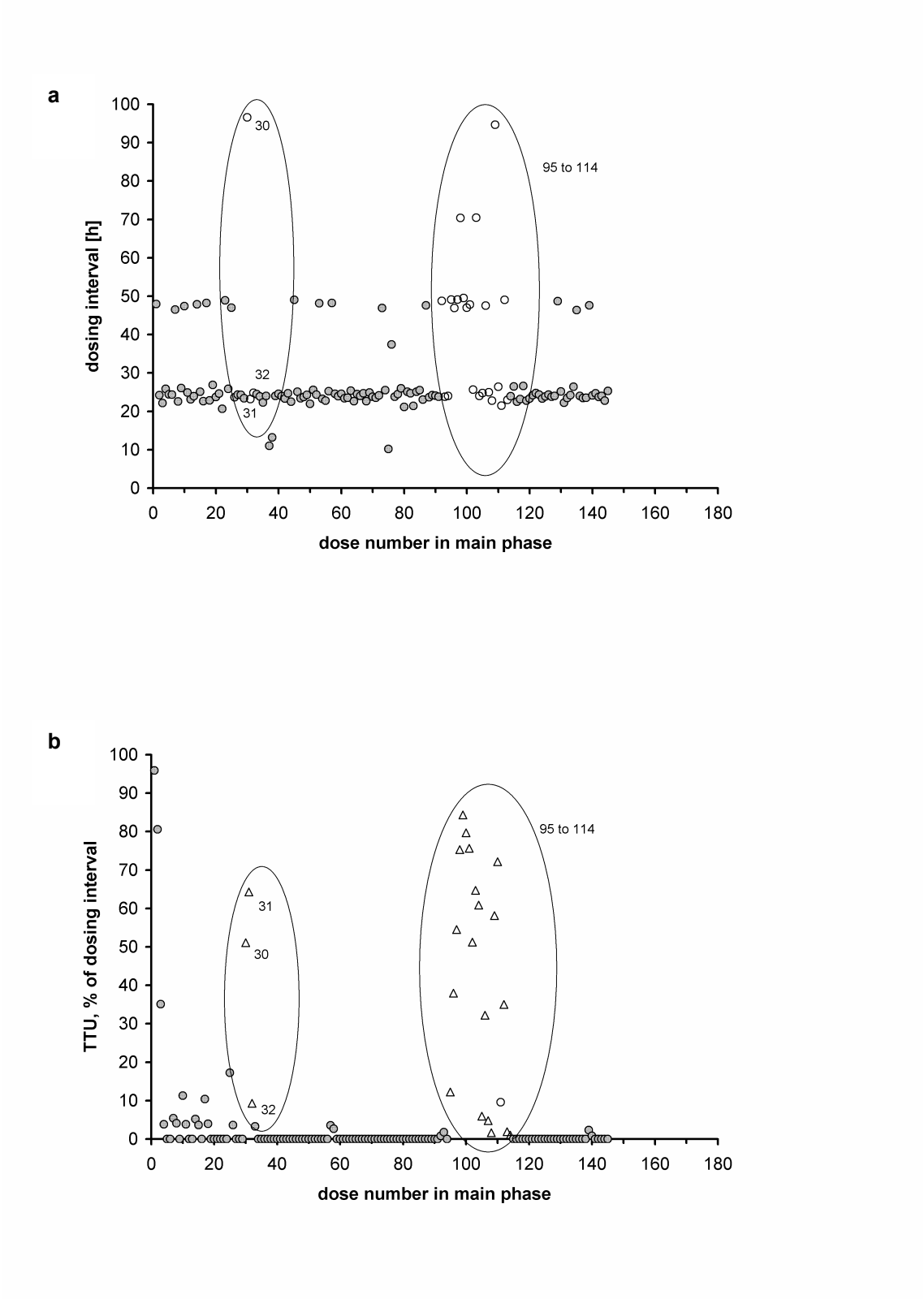


Fig. 30 Results from simulation approach A: dosing intervals (a) and time with therapeutic undersupply (TTU, b) of patient #23 taking 5 mg donepezil versus dose number; open triangles represent relevant periods of therapeutic undersupply; figures represent individual dose number.

Simulations of discrete compliance values are displayed in Fig. 31 (approach B). For 5 mg donepezil negligible therapeutic undersupply was observed with daily compliance exceeding 90% leading to 2.9% TTU of total time. Moreover, for 10 mg donepezil negligible therapeutic undersupply was observed with daily compliance greater than 80% leading to 0.3% TTU of total time. For 5 mg donepezil 80% compliance already led to a TTU of 11%, further increasing to a TTU of 29% at 70% compliance.

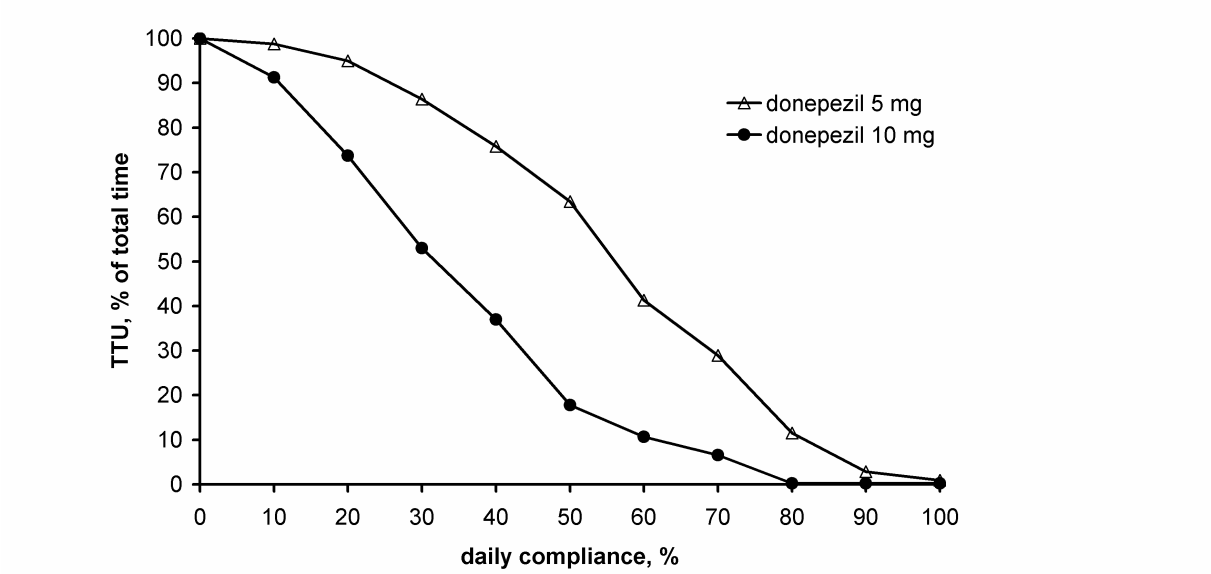


Fig. 31 Simulation approach B: time with therapeutic undersupply (TTU) in percentage of total time versus discrete daily compliance values.

Approach C characterised the influence of 1-7 dosage omissions at steady-state on the inhibition of cholinesterase (Fig. 32 to Fig. 34). In the case of 5 mg donepezil two or more dosage omissions caused therapeutic undersupply (Fig. 32 and Fig. 34). For 10 mg three or more dosage omissions at steady state led to therapeutic undersupply (Fig. 33 and Fig. 34). Forgiveness according to Urquhart was calculated as 68.4 h for 10 mg and 28.3 h for 5 mg donepezil, respectively (i.e. the PD effect lasted for almost 3 d and more than 1 d beyond the dosing interval, respectively).

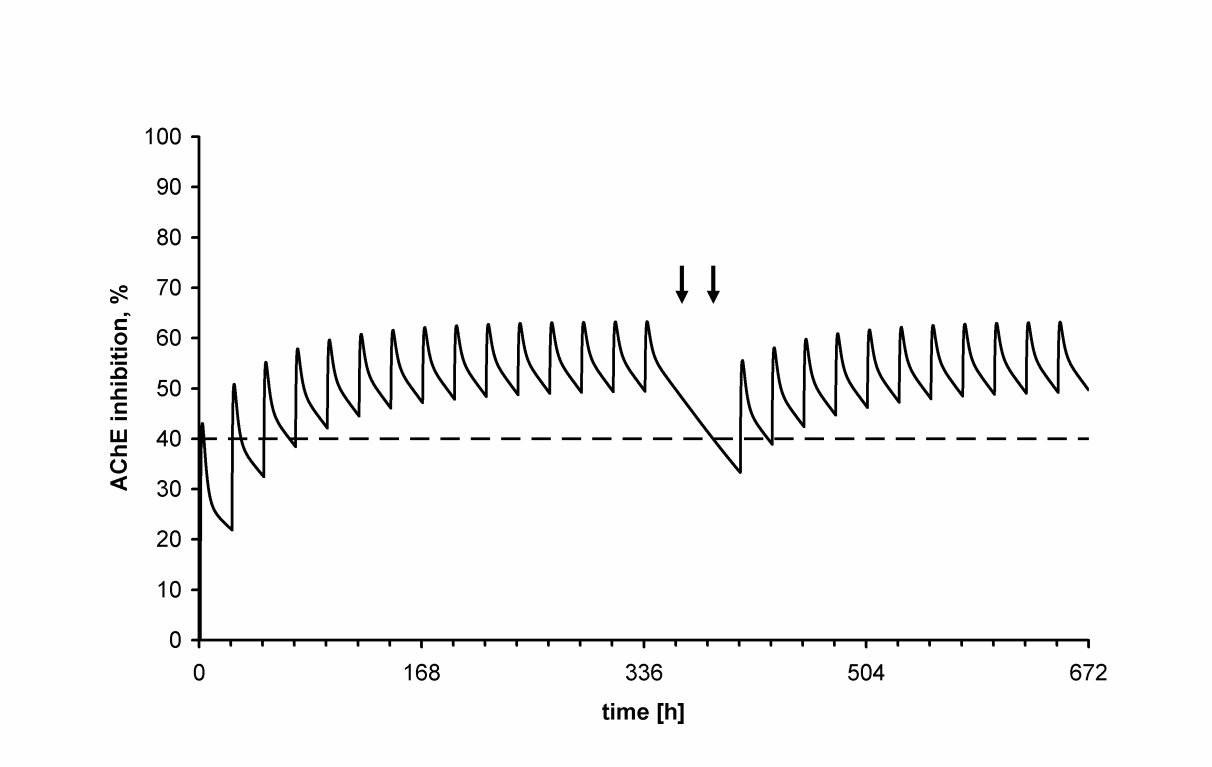


Fig. 32 Results from simulation approach C: effect-time courses of two dosage omissions (arrows) for 5 mg donepezil, 40% peripheral acetylcholinesterase (AChE) inhibition represents the minimum therapeutic inhibition (dashed line).

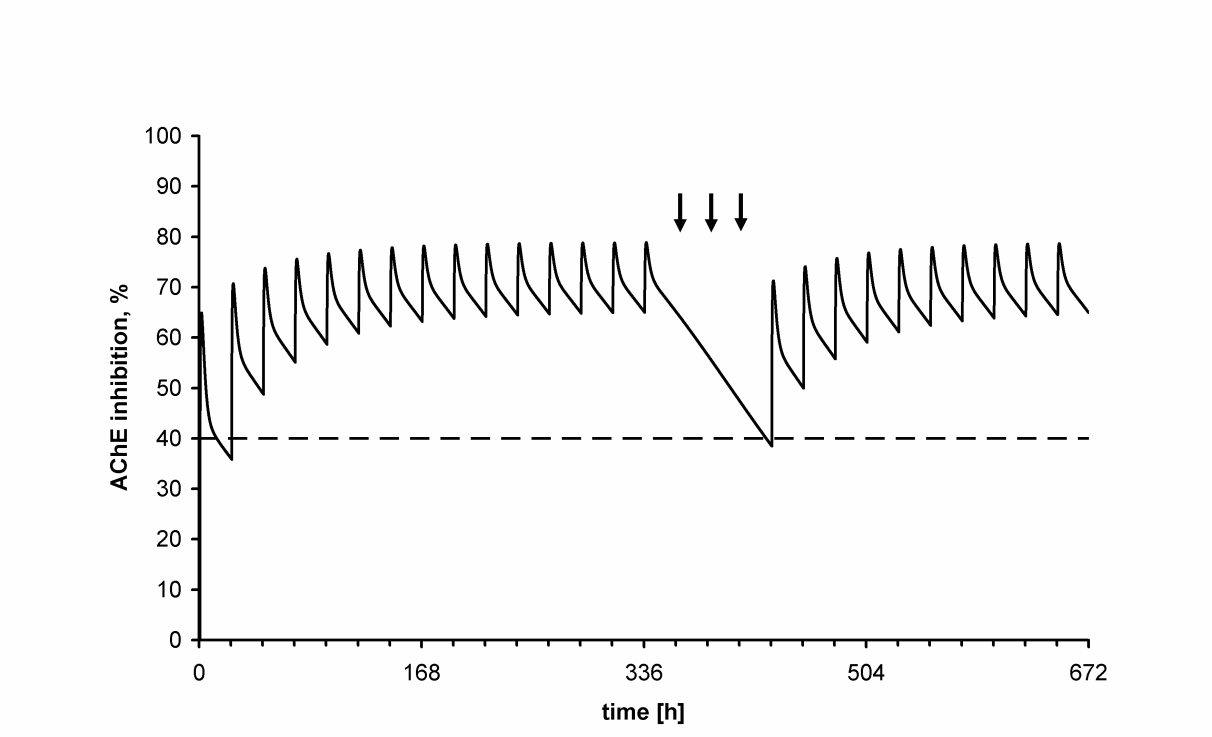


Fig. 33 Results from simulation approach C: effect-time courses of three dosage omissions (arrows) for 10 mg donepezil, 40% peripheral acetylcholinesterase (AChE) inhibition represents the minimum therapeutic inhibition (dashed line).

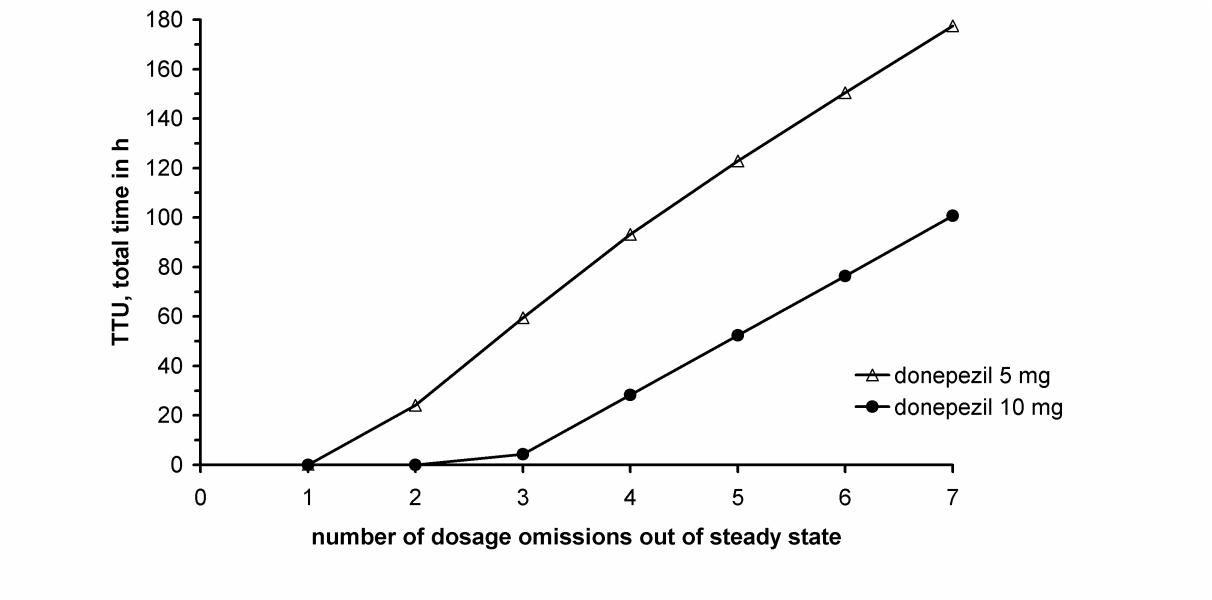


Fig. 34 Results from simulation approach C: total time with therapeutic undersupply (TTU) in hours versus number of dosage omissions.

4 Discussion and Perspectives

The research implemented for this dissertation project follows the framework of the Medical Research Council (MRC) for the development and evaluation of randomised controlled trials for complex interventions [83]. Complex interventions are built up a number of components, which may act both independently and interdependently. The active “ingredient” seems to be difficult to name. Our pharmaceutical care intervention consisted of e.g. interpersonal, organisational, oral and written counselling, monitoring, and medication review elements fulfilling the requirements of a complex intervention. Comparable to the development of a drug the MRC framework comprises five phases: preclinical development (theory), phase I (modelling), phase II (exploratory trial), phase III (definite randomised controlled trial), and phase IV (long-term implementation). Within this dissertation project preclinical development (e.g. analysis of literature, definition of intervention, study design, setup of infrastructure), phase I (*in silico* study to characterise forgiveness, cross-sectional study [66]) and phase II (pilot study) could be realised. Since no prior research was conducted in this field we performed no sample size calculation for the pilot study. In addition, we performed descriptive statistics in agreement with our clinical epidemiologists. Findings from our pilot study can be used for sample size calculation and hypothesis testing in a definite randomised controlled trial.

4.1 Compliance

Median daily compliance was very high in intervention and control group, both exceeding 90% during every month of the observation period. By comparing the baseline phase to the final month of the study, median daily compliance in the intervention group increased by 7% points, whereas it decreased by 3% points in the control group. Moreover, it was half as likely to observe a non-compliant month in the intervention compared to the control group. The Morisky questionnaire yielded a sensitivity of 36% for detecting poor compliance and a specificity of 81%.

Electronic monitoring of medication events – based on electronic detection of opening a container – presents an indirect method of estimating when and how much drug has been taken. Errors in compliance estimation will occur if a patient opens the container without taking the drug or takes another number of tablets than the one prescribed. Apparently irrational openings could also be detected in the investigated population,

but the number was low (1.2% of all recorded openings). In contrast, Arnet and Haefeli recognised so called “curiosity events” in nearly 20% of patients’ electronic monitoring systems which were due to showing the device to relatives or friends or uncertainty whether they had closed the electronic monitoring device [84]. In another study, 23% of all patients sometimes opened the electronic monitoring device but did not take the medication [36]. 38% of their patients sometimes took more than one dose of medication (e.g. for later pocket dosing) [36].

Denhaerynck et al. recently developed a validation framework with each electronic monitoring device accompanied by a form for the documentation of deviations from “normal” usage and a structured interview at the end of the study [85]: Uncensored data showed a 3.4% higher non-compliance than the censored data, which could be considered as an overestimation of non-compliance [85]. Nevertheless, another study revealed that uncorrected electronic monitoring data could successfully project measured plasma concentrations of drugs [86]. In our study, pharmacy refills and self-reported non-usage periods (e.g. due to hospital stays) were excluded from further analysis which might have relevantly improved the quality of the data.

A strong argument against using a MEMS® device in our study was the use of a multi-compartment pill-box [36, 87, 88]. Urquhart pointed out that patients should not be discouraged from the use of multi-compartment pill-boxes [33]. Unfortunately, electronic multi-compartment monitors are not (yet) available. Initially electronic monitoring might present a compliance enhancing intervention if patients and caregivers were not ‘blinded’ but informed about the monitoring device. Klein et al. did not inform patients about the functionality of the MEMS monitors to avoid any compliance enhancing effect of electronic monitoring [89]. A downside of this approach is that patients might not return MEMS containers to the study centre. Denhaerynck et al. investigated the compliance enhancing effect in transplant patients by omitting the first month of electronic monitoring from their analysis: The exclusion of the first 35 days of a 3-month measurement period did only result in a 0.4% decrease in daily compliance. They concluded that the compliance enhancing effect of electronic monitoring only had minor clinical significance [85]. Patients in our study even had an increase in median daily compliance by 3% points from baseline phase to first month in the control group. Consequently, our findings do not support an initial compliance enhancing effect of electronic monitoring and the first four weeks of MEMS use (i.e. our baseline phase) might present a realistic picture of medication taking behaviour.

Despite certain disadvantages, such as incompatibility with the use of multi-compartment pill-boxes, electronic monitoring presents the most reliable method for the

determination of compliance [34]. Four studies determined persistence (i.e. the duration of time from initiation to discontinuation of therapy [25]) for donepezil and rivastigmine in treatment naïve patients using pharmacy-refill data [90-93]: Nearly one third of all patients stopped donepezil or rivastigmine therapy within 60 days of starting therapy [91]. There were no marked differences in persistence between both drugs [91, 93]. In general, especially during the dosage up-titration period, adverse drug reactions (mainly gastrointestinal) occur that usually cease later in the course [82]. In the study conducted by Roe and co-workers 14% of all patients who continued donepezil therapy for at least six months showed gaps in supply for at least six weeks [92]. In our study, ca. 30% of all patients in the control group were considered non-compliant (80% cut-off criterion) in at least one month demonstrating how much more sensitive electronic monitoring has to be regarded compared to pharmacy refill data. During the course of the study, median compliance slightly decreased by 3% points in the control group, whereas it increased by 7% points in the intervention group. A longer study should assess whether the differences between intervention and control group will be more substantial over a longer period.

Dose timing errors of twice daily drugs occurred more frequently than in the control group. Here, patients administered only one third of all doses within an eleven to thirteen hours interval compared to more than 75% in the intervention group. In the field of antibiotics one investigation demonstrated that only 10% of amoxicillin capsules in a tid regimen were taken within the predefined interval (8 $\pm$ 1 h) [94]. This may lead to decreased effectiveness and facilitate the development of resistance. The clinical relevance is questionable but should be elucidated in further pharmacokinetic-pharmacodynamic simulations. A pharmacokinetic-pharmacodynamic simulation study by Lansky et al. demonstrated that errors in timing of ciprofloxacin doses with a standard deviation less than 2 h had a minor effect on antibiotic efficacy [95]. Results from our forgiveness study demonstrated that the clinical relevance of dose timing errors of donezepil might be negligible (3.4).

In general, evening doses in our study were 1.6-fold more likely to be omitted than morning doses, which corresponds to findings of a large MEMS® database study [96]. Investigators analysed compliance of nearly 5000 patients taking antihypertensive medication [96]. Medication taking is probably easier to be integrated into morning than evening activities. Here, especially qualitative research is needed to further characterise this observation.

Interventions that could effectively improve medication compliance were almost always complex [28]. Our pharmaceutical care program was a multifaceted intervention

comprising educational (guidance-oriented counselling), behavioural (MGMM and medication chart) and provider-focused strategies (systematic medication review and solving DRPs). Three studies investigating the effect of MGMM on compliance with hyperlipidaemia, mental, and diabetes patients could attain relative intervention effects of 5%, 10%, and 33%, respectively [97-99]. Our relative intervention effect is comparable to those achieved by Cramer et al. in patients with serious mental disease [97]. The intervention effects in Rosen's et al. diabetes study seem to be outstanding [98]. This could be at least partly explained by the selected study design. The study commenced with a 4-week baseline period. Subsequently, only patients who had less than 80% baseline compliance were randomly assigned to intervention or control group. This procedure decreases the "ceiling effect" which makes it difficult to observe any compliance-enhancing effect in a population with already high baseline compliance. Originally it was projected to implement this selection criterion accordingly. Nevertheless, we stopped this plan due to very low recruitment rates.

George et al. reviewed interventions targeted at improving medication taking in elderly patients prescribed multiple medications [58]. Pharmaceutical care was the key theoretical framework and achieved positive relative intervention effects on compliance between 3% and 43%. Compliance was determined by self-report or pill-count. None of the studies in this review employed electronic monitoring providing the most accurate and valuable data for assessing dosage regimen compliance [32, 33]. A potential confounding in Lee's et al. intervention, which achieved a relative effect of 43%, could be the increased frequency of pill counts in the intervention group [100]. Control patients were subjected to pill-counts (from medication bottles) only at the end of study whereas intervention patients underwent bimonthly counts using their 30-day blister packs (meaning twelve pill-counts). Patients in the intervention group were also asked to use adhesive tape to return any unused medication into their blister pack to be counted. This raises the possibility that dose dumping could have been more prevalent in the intervention group than in the control group.

To our knowledge, two German studies investigated the effect of pharmaceutical care on compliance using MEMS [89, 101]. Both employed a two-armed prospective, controlled study design with Klein et al. also randomly allocating patients into pharmaceutical care and standard care group. Patients who received pharmaceutical care in both studies showed statistically significantly better compliance than patients who received standard care only. Unlike our study pharmaceutical care was solely provided by the investigator limiting its external validity.

In our intervention group patients were on average in a milder disease stadium. We did not determine a psychometric score, but we concluded this from the average prior treatment duration which was shorter in the intervention than in the control group (two months versus eighteen months). Additionally, a higher fraction of patients in the intervention group was solely responsible for pharmacotherapy (21% versus 6% in the control group). A consequence could have been a lower compliance as well as reduced efficacy of the compliance enhancing intervention [102]. We performed a sensitivity analysis excluding all patients who were solely responsible for pharmacotherapy (n = 6). Median baseline compliance in both groups did not change at all. Surprisingly, the relative intervention effect decreased from 10% to 7% suggesting that patients who were solely responsible were still able to manage their pharmacotherapy and probably even responsive to a compliance enhancing intervention.

Compliance determined by electronic monitoring as well as the Morisky score improved in the intervention group. A sensitivity analysis revealed that intervention effects on the Morisky score were maintained, even if the three drop-outs in the intervention group were deleted from analysis. George et al. showed that the Morisky score proved a useful screening technique with a sensitivity of 74% and specificity of 72% for < 80% and $\geq$ 80% compliance to antidepressants, respectively [103]. This contrasts with our findings where particularly the sensitivity was not very high (36%). The specificity in our study was similar to the findings of George et al. (81%). Conclusively, use of the Morisky questionnaire is not recommended for further studies in this patient group. Maybe alternative self-report measures such as the Medication Adherence Rating Scale should be validated against MEMS® [104].

4.2 Knowledge in pharmacotherapy

In this study, we developed a questionnaire for the determination of patients' *knowledge in pharmacotherapy*. Interrater reliability of the final questionnaire expressed by ICC was 0.83 ($CI_{95\%}$ = 0.76-0.88, n = 100). Mean knowledge of indication slightly decreased from 78% to 77% in the control group. In contrast, this outcome increased from 73% to 78% in the intervention group. Surprisingly, pharmaceutical care could not improve patients' taking behaviour in relation to a meal. Here, approximately 10% to 15% of all drugs were administered inappropriately in both groups.

Whether parametric statistics can be applied in the analysis of ordinal data remains a controversy [63]: Same scientists favour the application of parametric statistics, others are completely against it [105]. The four step scale in the questionnaire (version 1)

presents a categorised latent variable which can only standardised by maximising inter-experimenter agreement [105]. This questionnaire displayed interrater reliability exceeding 0.8 meaning a very good agreement [106]. For the optimised questionnaire (version 2) we only labelled the endpoints, thus fulfilling the requirements of an interval scale.

We deleted the item relating to need of advice in the optimised questionnaire due to low interrater reliability (ICC ~ 0.4). It was apparent that not only individual knowledge of pharmacotherapy contributed to pharmacists' judgement but also other facts, e.g. number of medicines or drugs which are in very need of explanation. Also having all statements concerning a single drug nearby (i.e. removal of patient relatedness) facilitated the completion of the questionnaire. Consequently, the pharmacist did not have to browse through the questionnaire any more when comparing statements and judgments to the same drug.

At first glance patient knowledge in pharmacotherapy seems to be of minor importance. But informed patients are more likely to comply with drug treatment [107, 108], may be less anxious, more confident, and better able to be responsible for their own medication and treatment plan [109]. In one study knowledge of the prescribed medication was even associated with reduced visits of the emergency department [110]. Interestingly, the majority of drug related problems after discharge from hospital seem to be due to lack of knowledge about the aim or function of a drug [111].

Within the pharmaceutical care intervention, especially counselling according to BAK guidance aimed at improving *knowledge in pharmacotherapy* [29]. But pharmacists more often concentrated on the medication review and documentation of drug related problems. Only 37% of all patients in the intervention group received one or more guidance oriented consultations. Therefore, pharmacists could only increase the average knowledge of indication by 5% points. Other studies on cognitive services involving pharmacists displayed mixed results. In their randomised controlled trial, Lowe et al. achieved a ten-fold increase in knowledge of purpose in the intervention group compared to the control group [112]. In contrast to that, other studies could not relevantly show an effect of a pharmaceutical care intervention on knowledge of indication [113, 114]. Hanlon et al. explained this by the already high level of attention in their control patients due to nurse counselling [114].

To our knowledge, Alzheimer patients'/caregivers' *knowledge in pharmacotherapy* has not been examined yet. Modig et al. investigated the *knowledge in pharmacotherapy* of patients above 65 years and multiple illnesses. Seventy-one percent knew the indication of at least 75% of their medicines [115]. This corresponds to our findings in

the control group where patients assigned the correct indication (100% knowledge) to ca. 70% of all drugs. In another study, which investigated *knowledge in pharmacotherapy* of a group of patients aged 75 years in a cross-sectional study, 60% of all patients could name the right purpose of at least 75% of their medication [107]. This is in line with baseline results in our intervention group. Moreover, both studies dichotomised knowledge whereas we employed a four point scale. We preferred this approach since it allows a more graduated pharmaceutical judgement of patients' statements. Furthermore, above mentioned studies did not investigate the reliability of their judgements. In our study community pharmacists assessed the appropriateness of responses in a reproducible way.

The summary of product characteristics (SPC) was used to evaluate the taking behaviour in relation to a meal. Ten percent of these did not contain any information concerning drug-food interactions. This is in line with findings of a Spanish working group who reported only 73% of investigated SPCs contained information on drug-food interactions [116]. Consequently, regulatory bodies should claim the integration of information about recommended taking behaviour in relation to a meal in every SPC.

The pharmaceutical care intervention could not improve the taking behaviour in relation to a meal. Individualised reminder charts were supposed to improve patients' administration behaviour [52]. It is doubtful whether pharmacists regularly generated them. Maybe we should have facilitated the generation of these charts in the Alzheimer quality circle. Practicing medication reviews in the quality circle definitely contributed to its success.

4.3 Satisfaction with information about medicines

In the cross-sectional study only about one third of all caregivers viewed the pharmacist as a source of drug information. The average SIMS score was 8.3 (49% of total score). Moreover, less than 40% of all caregivers were satisfied with information about side-effects. Patients in the intervention group were by far more satisfied than patients in the cross-sectional study with an average SIMS score of 15 (88% of total score). In both groups patients were more satisfied with information about action and usage than potential problems of medication.

Unlike other outcomes such as HRQOL or knowledge, we determined satisfaction with information about medicines at the end of the intervention phase only. This was due to the fact that the German version of the SIMS questionnaire was available for us not

until the beginning of the intervention phase. Consequently, the chosen research methodology can be denoted as a post-test-only non–equivalent groups design [46]. With this research design it was not possible to determine whether any difference in outcome for the two groups is due to the treatment, or to other differences between the groups [46].

Very apparent was the high percentage of caregiving men in the cross-sectional study (65%) in contrast to the intervention group (29%). Bonnet and colleagues investigated radiotherapy patients' needs of information [117]. In this study women were more interested in practical information and men more interested in technical aspects. Furthermore, women were more satisfied with information than men. Perhaps these findings cannot be generalised, but they may indicate that the presence of non-equivalent groups causes difficulties in interpretation.

The SIMS displayed a pronounced ceiling and floor effect with ca. 35% of all questionnaires giving full or zero points. This is due to the structure of the questionnaire which contains items with the same answering scheme only. In this type of questionnaire there is a tendency to tick the same answer throughout the questionnaire which projects the general impression to all single items [118].

The primary source of drug information for Alzheimer caregivers was the physician. The pharmacist presented the second most important source of information but with only approximately one third of all patients mentioning him/her as a source of information. In contrast to that, the pharmacist plays an even much smaller role in information on cancer treatment. Patients more frequently utilise the media as sources of information (60% consult books, 39% television, 33% internet and magazines) [119]. Unlike Alzheimer disease cancer is not primarily a disease of the old age and consequently cancer patients are often younger. Whereas in the cancer study 37% of all patients were older than 60 years, more than 80% of all caregivers in the cross-sectional study were 60 years and older [66, 119]. Younger patients and caregivers are probably more open-minded and skilful to the use of media, in particular the internet. It is alarming that approximately three percent of all caregivers had not yet received any information from any source. Here, it is especially a task for the pharmacist to actively address patients'/caregivers' information needs. Pharmaceutical care actively addresses information needs and was associated with a considerably higher satisfaction with information about medicines. Having scheduled appointments with the pharmacist instead of solely contacts at the counter means more time to address caregivers'/patients' information needs.

In general, patients/caregivers were more satisfied with information on action and usage than on potential problems. Probably pharmacists regarded information on action and usage as essential for the successful administration of medication. Further time would be consumed by information on drug-drug interaction, adverse drug events and other potential drug related problems. Daily business routine in a community pharmacy could be a barrier to provide necessary drug information, suggested e.g. by the BAK counselling guidance [29, 120]. Group counselling could be an efficient strategy to address information needs of particular patient groups [121].

So far, the SIMS questionnaire was employed in studies investigating satisfaction of HIV, bipolar, chronic care, and rheumatoid patients with information about medicines [65, 121-123]. In line with our findings, three studies showed a higher satisfaction in subscale 1 (action and usage) than in subscale 2 (potential problems) [65, 122, 123]. An exception was the study by Homer et al. where no differences between subscales were observed [121]. Probably health-care professionals only reluctantly talk to patients about potential problems such as adverse drug reactions because they fear patients' motivation to take the medication would deteriorate. Six studies showed that telling patients about adverse drug effects did not affect their compliance, but these studies also suffered from small sample sizes [28]. Here, more research has to be conducted to elucidate health-care professionals' and patients' attitudes to further investigate the influence of "negative" information on compliance. Most satisfied were HIV patients [123], rheumatoid patients [121], and Alzheimer patients/caregivers in our intervention group. They were offered counselling after initiation of therapy (HIV and rheumatoid arthritis) or a complex pharmaceutical care intervention (Alzheimer). Perceived satisfaction was lower in bipolar patients and Alzheimer caregivers in the cross-sectional study. Alzheimer caregivers were particularly dissatisfied with information about adverse drug reactions. Moreover, bipolar patients should be offered more information about drowsiness and concomitant consumption of alcohol with medicines.

The items of the SIMS questionnaire were evaluated in ca. 30% of all cases with "no information needed". The reason could be that first the physician had already provided sufficient information or second the patient/caregiver did not consider the respective aspect as necessary or relevant. Our qualitative research suggests that the first aspect should not be underestimated (4.6). Nevertheless, physicians often fail to communicate to patients important facts about their medicines, such as how long to take the medication or potential adverse drug effects [124].

4.4 Health-related quality of life

Physical and mental summary scales of the SF-12 remained stable in both groups with the exception of the physical summary scale in the intervention group. Here, a slight decrease could be seen (small effect size). In the control group the SF-6D (SF-12) deteriorated with an effect size of greater than 0.2 implying a small effect. In contrast to that, the SF-6D (SF-12) remained stable in the intervention group (effect size < 0.2).

Missing items in ten SF-12 questionnaires (22%) relevantly reduced the sample size of caregivers. This is in line with German studies on pharmaceutical care where the fraction of SF-12 questionnaires containing missing items was between 29.7% and 39% [125]. The percentage of questionnaires with missing items was probably slightly lower since a research pharmacist was present during the completion in contrast to a mailed questionnaire. To calculate mental and physical summary scales of the SF-12 all items have to be present [68]. For the estimation of the utility measure SF-6D (SF-12) seven items of the SF-12 are only required [69]. Consequently, we could calculate the SF-6D (SF-12) for four additional patients.

Family members caring for individuals with dementia at home often describe the experience as “enduring stress and frustration” and the term caregiver burden is most frequently used to characterise this phenomenon [126]. Caregiving is associated with reduced HRQOL for both mental and physical functioning [127]. Patients in the intervention group of our study had a higher quality of life at baseline than patients in the control group in both scales of the SF-12. This could be due to the fact that patients in the control group were on average already in a more advanced stadium of Alzheimer dementia, i.e. patients required more care and attention from their caregivers. We did not apply a particular psychometric test (e.g. MMSE), but certain facts alluded to that. The median of treatment duration was one and a half year in the control group in contrast to two months only in the intervention group. Furthermore, six percent and twenty-one percent of Alzheimer’s patients were solely responsible for their pharmacotherapy in control group and intervention group, respectively. Progression of Alzheimer’s disease has been associated with lower health-related quality of life for caregivers [127]. This corresponded to findings in our study, where HRQOL expressed by SF-12 and SF-6D (SF-12) was higher in caregivers of the intervention group at both occasions.

Pickard and Hung concluded in their review that less than half of all identified studies, which investigated the impact of clinical pharmacy services on health-related quality of life, report significant changes in HRQOL [128]. This could be due to insufficient power

and follow-up periods. Nevertheless, certain pharmacy services, such as asthma management, appear to relevantly improve HRQOL [128]. Two German studies investigating cognitive pharmacy services (i.e. advanced services that go beyond simple dispensing of drugs) for asthma and migraine patients could demonstrate a statistically significant impact on the mental sum scale of the SF-36 [23, 129]. Based on the mean difference between changes in intervention and control group and a standard deviation in the German norm population individual effect sizes for the asthma study and the migraine study were 0.16 and 0.17, respectively. Although statistical significance could be demonstrated, effects of the intervention on health-related quality of life as measured by SF-36 are minor (effect size smaller than 0.2) [71]. Nevertheless, Schulz et al. observed more relevant changes in the summary scale of the disease-specific Living with Asthma Questionnaire. Here, a small effect size of 0.45 was achieved (standard deviation taken from [22]). Generic questionnaires such as the SF-36 may not be as responsive as disease specific questionnaires, but they allow comparisons between interventions and conditions [130]. Consequently, future studies should incorporate instruments, such as the Zarit Burden Interview (German version), to further evaluate effects of pharmaceutical care on Alzheimer's caregivers' burden or health-related quality of life [126, 131].

Positive effects of our intervention on HRQOL seem to be minor with an effect size of 0.13 and 0.11 for SF-12 (mental summary scale) and SF-6D (SF-12), respectively. Authors of a meta-analytic study concluded that multicomponent interventions most significantly reduced caregiver burden in contrast to discrete interventions, such as support groups, education, psychoeducation, counselling, and respite care [132]. Especially, collaborative care including e.g. nurses, GPs, psychiatrists and care managers could relevantly improve caregivers' depression as measured by the Patient Health Questionnaire-9 (effect size 0.3) [133].

4.5 Process outcomes

Pharmacists documented approximately three drug related problems per patient on average. Median time to handle a drug related problem was 10 min. More than half of these could be solved. The most predominant drug related problem was inappropriate drug choice. Moreover, the median number of counselling sessions was four.

Probably due to its complexity the intervention was not implemented to full extend. Pharmacists concentrated on the contents of the quality circle sessions, which were medication review and documentation of DRP. Especially, MEMS® and BAK guidance counselling were not performed as projected. This could be due to time constraints (see 4.6). Additionally, the paper format of the BAK guidance sheet obstructed the use in counselling at the counter because sheets were not at hand or probably a colleague served the patient/caregiver without knowing about the study procedures. Further studies evaluating guidance oriented counselling should employ computerised formats, which are incorporated into the computer system of the pharmacy [134]. The implementation of MEMS® consultations was discouraged in several ways. First, the patient population heavily relied on weekly pill-boxes, thus often giving up use of MEMS®. Second, pharmacists could not download MEMS® data when they wanted to. They had to contact a research pharmacist who performed the download at patients' homes and provided the pharmacists with a compliance report. Only the pharmacist in Nottuln had a MEMS® communicator and access to the online platform ViewCompliance® to independently generate a compliance report [135]. But providing all pharmacists with access to the platform would be associated with higher costs.

We used PI-Doc® for the classification of drug related problems [73]. Mattenklotz recently validated the German versions of the PCNE (Pharmaceutical Care Network Europe) classification and PI-Doc® [74]. She concluded that both systems have good and comparable comprehensibility, completeness, unambiguousness, internal consistency, and practicability. Nevertheless, ease of coding was better in PI-Doc® with 40% less time needed on average. But unlike the PCNE classification system PI-Doc® is not based on a clear definition, both for the DRP in general and for each DRP subcategory [136]. In PI-Doc® categories cover a wide range from technical (e.g. prescription illegible) to clinical issues (e.g. adverse drug reaction). Some researchers distinguish clinical DRPs from technical problems [137, 138].

In Germany the ABDA - Bundesvereinigung Deutscher Apothekerverbände (Federal Union of German Associations of Pharmacists) conducted a general population based study on the prevalence of DRP [72]. Participating pharmacists were advised to document all drug related problems within a selected week. The ABDA reported that 7.7% of all DRPs were due to drug-drug interactions, which is very consistent with our findings (8%). However, in our setting the most frequent DRP was inappropriate drug choice (29%) which by far exceeds respective fraction in the ABDA study (ca. 8%). Comparison to the ABDA study was generally hampered by the fact that they did not report percentages of the PI-Doc® main categories. In our study pharmacists

conducted a systematic medication review, whereas pharmacists in the ABDA study provided counselling according to the Ordinance on the Operations of Pharmacies [47]. Our approach was more appropriate for the identification of inappropriate drug choice, especially since tools such as the Beers criteria were employed [54]. Furthermore, inappropriate dosage played a major role (~ 1/5 of all DRPs). This is in line with findings from Leemans et al. and Krähenbühl et al. [137, 138]. Most antidementia drugs do not start with the maintenance dose, they have to be uptitrated which complicates pharmacotherapy [139]. In many instances pharmacists could solve DRPs due to underdosage.

Median time to solve a drug related problem in our study was 10 min which is more than in the ABDA study (5 min) [72]. Furthermore, pharmacists in the ABDA study could solve a higher fraction of DRPs (81.7% versus 54% in our study). A reason for these observations could be the high fraction of technical problems (ca. 50%) such as illegible prescription or supply problems in the ABDA study. These technical problems might be easier to solve and take less time than clinical drug related problems. Moreover, physician contact rates were comparable (61% in the ABDA study versus 46% in our study).

Analysis of DRPs in particular patient groups could be used to design standardised checklists containing frequently occurring DRPs which support the provision of pharmaceutical care. Also new media like the internet should be further utilised to detect patients' drug related problems: In a first investigation Schröder et al. characterised Parkinson outpatients' drug related problems using online forums [140].

DRPs present the key process parameter documenting pharmacists' activity. Conclusively, it would be very valuable if pharmacists documented DRPs as part of their everyday activities, at best electronically in the pharmacy's computer system. Additionally, a monitoring centre could be set up to benchmark DRP data provided by pharmacies [137]. Individual pharmacies can be coached according to their own DRPs' documentation profile. A national electronic database already exists in Sweden since 2004 [141]. A recent economic evaluation of this database revealed that potential societal cost savings of pharmacy interventions extrapolated to Sweden at the national level were estimated at € 358 million [142].

4.6 Feasibility of pharmaceutical care

Concerning the feasibility of the pharmaceutical care intervention four major themes were identified such as image of community pharmacy, interaction with physicians, interaction with patients and caregivers and community pharmacy setting, which are also interacting with one another.

The amount of qualitative data in our study was very limited with only one caregiver focus group. In general, focus group studies can comprise anything from six to 50 focus groups [77]. Conclusively, we did not reach the point of data saturation where no more new topics emerged. In addition, we did not audiotape the focus group, which is generally recommended. Nevertheless, a minute taker was present who carefully took notes [66]. Due to limited resources we chose narrative reports as a very economic format in qualitative research to elucidate pharmacists' views. Audiotaped semi-structured or in-depth interviews would have resulted in a more complete picture of the situation. But transcribing and analysing audiotaped materials is a much longer process. Each hour of material can take six to seven hours of transcribing depending on the quality of the tape let alone coding and analysis [77]. Moreover, one single investigator (OS) performed the coding and the interpretation of qualitative data from narrative reports. Multiple coding involving at least two investigators could have increased the trustworthiness of the data and subsequent analysis [143]. Despite these limitations qualitative research within this dissertation project presents a promising approach to explain the context of quantitative findings.

A barrier for pharmaceutical care in our study was that patients/caregivers did not know about this new service and the changing role of community pharmacy. A public campaign could foster patient demand in pharmaceutical care [144]. Moreover, patients' relationships with their doctors tend to be foremost in the management of medicines [145]. If the patient feels well-informed and well-medicated, it is difficult to demonstrate the additional benefit of pharmaceutical care. If tasks are to be redistributed between the professions, including the possibility of transferring activities from physicians to pharmacists, patients/caregivers have to be convinced of a health-care team instead of a physician-centred approach.

Pharmaceutical care brings about an enhanced way of collaboration between physician and pharmacist. In our study pharmacists reported that physicians were frequently unaware and sceptical about the concept of pharmaceutical care. Trustworthiness, understanding of roles, and intensity of interaction seem to be major determinants of successful collaborative care [146]. Particularly, trustworthiness cannot be established

within a short period of time. The physician evaluates the pharmacist's ability through the quality of the recommendations made by the pharmacist. Only if useful recommendations are given over time, the physician will trust in the pharmacist's expertise [146]. In our study communication between pharmacist and physician was almost exclusively by telephone. Lack of face-to-face interactions seems to present a key barrier for the establishment of mutual trust and successful collaboration [147]. Here, case conferences could provide a useful opportunity for pharmacists and physicians to share information and to discuss treatment options [148]. Also multidisciplinary quality circles comprising GPs and pharmacists, which are practiced in the Netherlands on a broad scale, could enhance collaboration [149, 150]. Furthermore, improvement of pharmacists' communication skills is needed for the successful implementation of their recommendations in practice. Here, theories such as psychological reactance should also be discussed and how to cope with it [151]. Reactance theory suggests that when recommended to take a particular action, a motivational state compels us to react in a way that confirms our freedom to choose [151]. Consequently, offering two alternative recommendations seems to be more promising because it provides a greater freedom to choose to the physician. Communication training within our study was unfortunately insufficient (in meeting 3 of quality circle only) and aspects such as reactance theory were not covered. In addition, roles and accountability among health care professionals should be defined in a clearer way. The Advisory Council on the Assessment of Developments in the Health Care System in Germany (Sachverständigenrat zur Begutachtung der Entwicklung im Gesundheitswesen) recommends the reorganisation of the division of labour in the health sector if it leads to a better match between the requirements of a constantly changing health care system and the aims, tasks and competencies of its players [152].

Lack of time and reimbursement were identified as key barriers for the provision of pharmaceutical care. This is in line with international findings, where pharmacists expressed similar concerns [153-157]. Probably time constraints of pharmacists could be solved by better time management including delegation of tasks [158]. Mark suggested that an efficient pharmacy organisation in combination to robotisation, and task specialisation can expand the care related work in community pharmacies [159]. Here, sound research of the German community pharmacy setting is desperately needed. In addition, refurnishing of counter areas should be discussed to increase privacy of consultations [160]. Community pharmacists are currently reimbursed for the distribution of drugs with very little incentive for the provision of pharmaceutical care. An exception present the family pharmacy program, which is reimbursed by the

statutory insurance company BARMER Ersatzkasse [21]. Pharmacists can charge € 8 plus value added tax for oral or written communication with a GP. In addition, pharmacists can charge € 22 plus value added tax for a single intervention which aims at improving blood glucose control in type 2 diabetic patients.

According to qualitative research by Hughes and McCann in the UK pharmacists have a shopkeeper image. Many GPs in their focus groups saw pharmacists as business people or specialist retailers, and believed this represented a conflict of interest in health care [161]. This image might also be present in Germany with an impact on interaction with patients as well as physicians.

4.7 Forgiveness of donepezil

PK/PD *in silico* simulations revealed that two out of three patients being prescribed donepezil 5 mg in the control group were therapeutically undersupplied during certain periods. For 10 mg donepezil forgiveness of donepezil was estimated as 80% daily compliance or two dosage omissions at steady-state. Moreover, for 5 mg donepezil forgiveness of donepezil was estimated as 90% daily compliance or one dosage omissions at steady-state.

Inhibition of peripheral cholinesterase served as a biomarker of pharmacological response in Alzheimer's disease. Jann et al. concluded in their review that daily doses of cholinesterase inhibitors needed to achieve a consistent peripheral cholinesterase inhibition of more than 40% corresponded to those causing improvement in cognition and functional activity scores [45]. Four doses of donepezil were investigated in randomised placebo-controlled studies. 1, 3, 5 and 10 mg donepezil once daily exhibited a mean red blood cell (RBC) inhibition of acetylcholinesterase (AChE) of 19.4%, 44.3%, 63.9% and 74.7% [81, 162]. From these, 5 and 10 mg demonstrated significant clinical improvement compared with placebo (ADAS-cog and CIBIC plus): There were positive associations between the AChE inhibition and change in ADAS-cog and CIBIC plus [81]. As the strength of association was not reported the predictive value of RBC AChE inhibition needs further evaluation [81, 163]. Nevertheless, it provides evidence of potential efficacy. Hence, 40% inhibition served as a reasonable cut-off below which only minor efficacy has to be expected.

In the present *in silico* study the use of PK models from literature was found to be suitable. Since population pharmacokinetic models are not available that provide variability parameters, PK variability could unfortunately not be implemented in the

simulations. Moreover, for approaches B and C, where the influence of daily compliance and dosage omission on therapeutic coverage/undersupply was investigated, a high magnitude of PK variability could complicate the outcome. Future *in silico* simulations for donepezil should account for population PK models that quantify variability, when available. Besides, the current simulation had to be limited to donepezil because for other antidementia drugs literature data on PK and PD was insufficient but is highly warranted.

From three patients being prescribed donepezil, who were at least one month non-compliant ('usual' daily compliance < 80%), two displayed periods of therapeutic undersupply. Especially the combination of a drug holiday (dosing interval exceeding 96 h) and several single dose omissions triggered therapeutic undersupply. These characteristics in electronic monitoring reports present an indicator of potential insufficient therapeutic coverage and have to be discussed with the patient/caregiver [57]. In the absence of electronic monitoring patients or caregivers should be questioned in an empathic, non-patriarchal style about their medication taking behaviour. An old, still widely-held idea going back to research in the cardiovascular field in the 1960ies, was that taking 80% of the prescribed doses generally qualifies as satisfactory compliance [164]. This view, however, has to be regarded as pharmacodynamically naïve since forgiveness of each drug product is determined by its individual dosage form, and very importantly by PK and PD characteristics [165]. Eighty percent compliance already results in more than 10% therapeutic undersupply for 5 mg donepezil daily, i.e. for 5 mg donepezil 90% compliance is suggested to serve as a cut-off in the future. For 10 mg donepezil daily 80% compliance was assessed to be still appropriate. Both donepezil dosages forgive a common compliance error: one occasionally omitted tablet. Compared to other therapeutic areas donepezil exhibited a high degree of forgiveness. If a single gestagen-only pill is taken more than three hours late, there will be a need of back-up contraception [166]. The forgiveness of once daily antihypertensives atenolol and betaxolol can be estimated as about 6 hours and more than 48 hours [167]. These results were generated by controlled (verum only group), blinded trials partially substituting verum against placebo, whereas we have implemented *in silico* simulations, in this way providing a lower level of evidence. Studies early in the era of antiretroviral therapy demonstrated the need for > 95% compliance in order to achieve and sustain viral suppression [37]. High rates of viral suppression could also be attained at more moderate compliance with newer antiretroviral regimens (e.g. lopinavir/ritonavir) [41]. Beyond this, sparse or no evidence is available on forgiveness of major therapeutic classes.

An assessment of the completeness of clinical pharmacology information in the drug labelling in a representative sample of package inserts had shown that only about 10% had “adequate” coverage of compliance issues and 76% had no information on the subject [168]. Detailed instructions on how to deal with dose omissions are provided for contraceptives but not for other important drugs [169]. Here, PK/PD simulations can play an important role in contributing to overcome these difficulties and can provide the necessary information for the rational development of compliance instructions for drug labelling. Consequently, forgiveness of all drugs needs to be investigated and labelling should include information on the consequences of major patterns of non-compliance.

4.8 Conclusion and Perspectives

For the first time a pharmaceutical care intervention for Alzheimer patients and their caregivers was evaluated. Based on our working hypothesis compliance measurement by different methods was feasible. Pharmaceutical care provided by community pharmacists could maintain compliance with antidementia drugs on a high level. Furthermore, caregivers and patients were highly satisfied with information about medicines. Additionally, knowledge about indication of pharmacotherapy increased. In contrast to that, knowledge about medication intake and caregivers’ HRQOL could not be improved. This could be due to e.g. insensitivity to change of a generic HRQOL instrument. The most important drug related problem was inappropriate drug choice. Moreover, qualitative research revealed facilitators and barriers which are responsible for success and failure of the pharmaceutical care intervention.

The cross-sectional study identified that only 30% of caregivers were satisfied with information on drug related problems from their pharmacist.

In addition, we characterised the forgiveness of donepezil allowing the identification of clinically relevant non-compliance in MEMS compliance reports.

Future research should pursue collaborative care approaches integrating pharmaceutical care for Alzheimer patients/caregivers into medical, nursing, and social care concepts. An example for an collaborative care approach for dementia patients/caregivers is the PREVENT program integrating e.g. primary care clinicians, geriatricians, social psychologists, and gerontopsychiatrists [133]. Nevertheless, projects in highly specialised populations such as ambulatory Alzheimer patients cannot sustainably change everyday practice in community pharmacy due to the low number of patients in every setting. Here, projects in a more general patient population

exploring a less complex intervention are desperately needed. In addition, computerised documentation systems could facilitate the uptake of pharmaceutical care. A model could be the nationwide electronic DRP database in Sweden [141]. Along with that, patients' image of community pharmacy needs to be chanced from a shop to a care focused environment to generate demand for pharmaceutical care.

5 References

1. Hampel H, Padberg F, Möller HJ. Alzheimer-Demenz. 1st ed. Stuttgart: Wissenschaftliche Verlagsgesellschaft mbH; 2003.
2. Maurer K, Volk S, Gerbaldo H. Auguste D and Alzheimer's disease. Lancet; 349: 1546-1549, 1997.
3. U.S. National Institutes on Health [homepage on the internet]. Bethesda: National Institute on Aging [updated 2009 Feb 05; cited 2009 Apr 03]. Available from http://www.nia.nih.gov/Alzheimers/Resources/HighRes.htm.
4. Munter LM, Voigt P, Harmeier A, Kaden D, Gottschalk KE, Weise C, et al. GxxxG motifs within the amyloid precursor protein transmembrane sequence are critical for the etiology of Abeta42. EMBO J; 26: 1702-1712, 2007.
5. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. Lancet; 368: 387-403, 2006.
6. diPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. Pharmacotherapy - A Pathophysicologic Approach. Sixth ed: McGraw-Hill Medical; 2005.
7. Wilkinson DG, Francis PT, Schwam E, Payne-Parrish J. Cholinesterase inhibitors used in the treatment of Alzheimer's disease: the relationship between pharmacological effects and clinical efficacy. Drugs Aging; 21: 453-478, 2004.
8. IQWiG. Cholinesterase inhibitors in Alzheimer's disease. Final report A05-19A. Cologne: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). February 2007.
9. Geldmacher DS. Treatment guidelines for Alzheimer's disease: redefining perceptions in primary care. Prim Care Companion J Clin Psychiatry; 9: 113-121, 2007.
10. Parsons CG, Stoffler A, Danysz W. Memantine: a NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system--too little activation is bad, too much is even worse. Neuropharmacology; 53: 699-723, 2007.
11. IQWiG. Ginkgo in Alzheimer's Disease. Executive summary of final report A05-19B. Cologne: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). September 2008.
12. Gill SS, Bronskill SE, Normand SL, Anderson GM, Sykora K, Lam K, et al. Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med; 146: 775-786, 2007.
13. Rochon PA, Normand SL, Gomes T, Gill SS, Anderson GM, Melo M, et al. Antipsychotic therapy and short-term serious events in older adults with dementia. Arch Intern Med; 168: 1090-1096, 2008.
14. Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C, Wang PS. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. CMAJ; 176: 627-632, 2007.
15. Feil DG, MacLean C, Sultzer D. Quality indicators for the care of dementia in vulnerable elders. J Am Geriatr Soc; 55 Suppl 2: 293-301, 2007.
16. Ancelin ML, Artero S, Portet F, Dupuy AM, Touchon J, Ritchie K. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. BMJ; 332: 455-459, 2006.

17. Lu CJ, Tune LE. Chronic exposure to anticholinergic medications adversely affects the course of Alzheimer disease. Am J Geriatr Psychiatry; 11: 458-461, 2003.

18. Brodaty H, Green A, Koschera A. Meta-analysis of psychosocial interventions for caregivers of people with dementia. J Am Geriatr Soc; 51: 657-664, 2003.

19. Graff MJ, Vernooij-Dassen MJ, Thijssen M, Dekker J, Hoefnagels WH, Rikkert MG. Community based occupational therapy for patients with dementia and their care givers: randomised controlled trial. BMJ; 333: 1196, 2006.

20. Dreischulte T, Schwalbe O, Simons S. Die richtige Medizin. Dtsch Apoth Ztg; 148: 56-61, 2008.

21. Eickhoff C, Schulz M. Pharmaceutical care in community pharmacies: practice and research in Germany. Ann Pharmacother; 40: 729-735, 2006.

22. Mangiapane S, Schulz M, Muhlig S, Ihle P, Schubert I, Waldmann HC. Community pharmacy-based pharmaceutical care for asthma patients. Ann Pharmacother; 39: 1817-1822, 2005.

23. Schulz M, Verheyen F, Muhlig S, Muller JM, Muhlbauer K, Knop-Schneickert E, et al. Pharmaceutical care services for asthma patients: a controlled intervention study. J Clin Pharmacol; 41: 668-676, 2001.

24. Sorge I, Müller U. Typ-2-Diabetes - Erster bundesweiter Betreuungsvertrag. Pharm Ztg; 154: 692-693, 2009.

25. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: terminology and definitions. Value Health; 11: 44-47, 2008.

26. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care; 42: 200-209, 2004.

27. Cramer JA, Rosenheck R. Compliance with medication regimens for mental and physical disorders. Psychiatr Serv; 49: 196-201, 1998.

28. Haynes R, Yao X, Degani A, Kripalani S, Garg A, McDonald H, et al. Interventions to enhance medication adherence. Cochrane Database Syst Rev; CD000011, 2005.

29. Bundesapothekerkammer. Leitlinie der Bundesapothekerkammer zur Qualitätssicherung. Information und Beratung des Patienten bei der Abgabe von Arzneimitteln - Erst- und Wiederholungsverordnung im Rahmen der Pharmazeutischen Betreuung. 2006.

30. Elliott RA, Barber N, Clifford S, Horne R, Hartley E. The cost effectiveness of a telephone-based pharmacy advisory service to improve adherence to newly prescribed medicines. Pharm World Sci; 30: 17-23, 2008.

31. Lenaghan E, Holland R, Brooks A. Home-based medication review in a high risk elderly population in primary care--the POLYMED randomised controlled trial. Age Ageing; 36: 292-297, 2007.

32. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med; 353: 487-497, 2005.

33. Urquhart J. The electronic medication event monitor. Lessons for pharmacotherapy. Clin Pharmacokinet; 32: 345-356, 1997.

34. Cramer JA. Microelectronic systems for monitoring and enhancing patient compliance with medication regimens. Drugs; 49: 321-327, 1995.

35. Spilker B. Methods of assessing and improving compliance in clinical trials. In: Cramer J, Spilker B, editors. Patient compliance in medical practice and clinical trials. 1st ed. New York: Raven Press; 1991. p. 37-56.

36. Bova CA, Fennie KP, Knafl GJ, Dieckhaus KD, Watrous E, Williams AB. Use of electronic monitoring devices to measure antiretroviral adherence: practical considerations. AIDS Behav; 9: 103-110, 2005.

37. Shuter J. Forgiveness of non-adherence to HIV-1 antiretroviral therapy. J Antimicrob Chemother; 61: 769-773, 2008.

38. Urquhart J. Pharmionics: research on what patients do with prescription drugs. Pharmacoepidemiol Drug Saf; 13: 587-590, 2004.

39. Urquhart J. Defining the margins for errors in patient compliance with prescribed drug regimens. Pharmacoepidemiol Drug Saf; 9: 565-568, 2000.

40. Choo PW, Rand CS, Inui TS, Lee ML, Ma CC, Platt R. A pharmacodynamic assessment of the impact of antihypertensive non-adherence on blood pressure control. Pharmacoepidemiol Drug Saf; 9: 557-563, 2000.

41. Shuter J, Sarlo JA, Kanmaz TJ, Rode RA, Zingman BS. HIV-infected patients receiving lopinavir/ritonavir-based antiretroviral therapy achieve high rates of virologic suppression despite adherence rates less than 95%. J Acquir Immune Defic Syndr; 45: 4-8, 2007.

42. Boissel JP, Nony P. Using pharmacokinetic-pharmacodynamic relationships to predict the effect of poor compliance. Clin Pharmacokinet; 41: 1-6, 2002.

43. Nony P, Boissel JP. Use of sensitivity functions to characterise and compare the forgiveness of drugs. Clin Pharmacokinet; 41: 371-380, 2002.

44. Williams PJ, Ette EI. Pharmacometrics: Impacting Drug Development and Pharmacotherapy. In: Ette EI, Williams PJ, editors. Pharmacometrics - The Science of Quantitative Pharmacology. 1st ed. Hoboken: Wiley; 2007. p. 1-19.

45. Jann MW, Shirley KL, Small GW. Clinical pharmacokinetics and pharmacodynamics of cholinesterase inhibitors. Clin Pharmacokinet; 41: 719-739, 2002.

46. Robson C. Real World Research. Second ed. Oxford: Blackwell Publishing; 2002.

47. Apothekenbetriebsordnung (Ordinance on the Operation of Pharmacies) in the version of the publication of 26th September, 1995 (Federal Law Gazette I, page 1195) last amended pursuant to the Amendment Act for the Federal Pharmacists Regulation and other legislation dated 20st July 2007 (Federal Law Gazette I, page 1574).

48. Beyer M, Gerlach FM, Flies U, Grol R, Krol Z, Munck A, et al. The development of quality circles/peer review groups as a method of quality improvement in Europe. Results of a survey in 26 European countries. Fam Pract; 20: 443-451, 2003.

49. Fountain KM, Farmer JN. State of confusion: sorting out a complex medication regimen for a 79-year-old woman. Consult Pharm; 22: 944-948, 2007.

50. Apotheken - Falsch beraten in Berlin. Test; 2008.

51. Cipolle RJ, Strand LM, Morley PC. Pharmaceutical Care Practice. 1st ed; 2004.

52. Raynor DK, Booth TG, Blenkinsopp A. Effects of computer generated reminder charts on patients' compliance with drug regimens. BMJ; 306: 1158-1161, 1993.

53. Schaefer M, Schulz M. Band 1 Grundlagen der Pharmazeutischen Betreuung. Eschborn: Govi-Verlag; 2000.

54. Schwalbe O, Freiberg I, Kloft C. Die Beers-Liste. Ein Instrument zur Optimierung der Arzneimitteltherapie geriatrischer Patienten. Med Monatsschr Pharm; 30: 244-248, 2007.

55. Carnahan RM, Lund BC, Perry PJ, Pollock BG, Culp KR. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. J Clin Pharmacol; 46: 1481-1486, 2006.

56. Augsburger Qualitätszirkel. Interaktionstabelle des Augsburger Qualitätszirkels [monograph on the internet]; 2006 [cited 2009 Apr 3]. Available from: http://www.abda.de/fileadmin/pdf/ZAPP/Beratungshilfen/IA-Tab-gesamt.Stand_28.03.06a.pdf.

57. Rosen MI, Ryan CE, Rigsby MO. Motivational Enhancement and MEMS Review to Improve Medication Adherence. Behav Med; 19: 183-190, 2002.

58. George J, Elliott RA, Stewart DC. A systematic review of interventions to improve medication taking in elderly patients prescribed multiple medications. Drugs Aging; 25: 307-324, 2008.

59. Bland M. An introduction to medical statistics. Third ed. Oxford: Oxford University Press; 2000.

60. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care; 24: 67-74, 1986.

61. Llopis Czemper O. Knowledge of Alzheimer Patients and their Caregivers in Pharmacotherapy [diploma thesis - draft version]. Halle: Martin-Luther-Universität Halle-Wittenberg; 2008.

62. Norman GR, Streiner DL. Biostatistics - The Bare Essentials. Third ed. Hamilton: B.C. Decker; 2008.

63. Porst R. Fragebogen - Ein Arbeitsbuch. 1st ed. Wiesbaden: VS Verlag für Sozialwissenschaften 2008.

64. Horne R, Hankins M, Jenkins R. The Satisfaction with Information about Medicines Scale (SIMS): a new measurement tool for audit and research. Qual Health Care; 10: 135-140, 2001.

65. Mahler C, Greulich S, Ludt S, Szecsenyi J. Information zur Medikation - wie bewerten Patienten das Medikamentengespräch? Der Einsatz des SIMS (Satisfaction with Information about Medicines Scale). Internationale Konferenz Pflege und Pflegewissenschaft; 2007; Nürnberg/Fürth; 2007. p. 30.

66. Stengel L. Zufriedenheit mit der Arzneimittelinformation durch Apotheker bei Angehörigen von Alzheimer-Patienten [diploma thesis]. Halle: Martin-Luther-Universität Halle-Wittenberg; 2009.

67. Fitzpatrick R, Bowling A, Gibbons E, Haywood K, Jenkinson C, Mackintosh A, et al. A structured review of patient-reported measures in relation to selected chronic conditions, perceptions of quality of care and carer impact. Oxford: National Centre for Health Outcomes Development (Oxford site) November 2006.

68. Bullinger M, Kirchberger I. Der SF-36 Fragebogen zum Gesundheitszustand. Testhandbuch. Göttingen: Hogrefe; 1998.

69. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. Med Care; 42: 851-859, 2004.

70. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ; 21: 271-292, 2002.

71. Fayers PM, Machin D. Quality of Life - The assessment, analysis and interpretation of patient-reported outcomes. 2nd ed. Chichester: Wiley; 2007.

72. Hammerlein A, Griese N, Schulz M. Survey of drug-related problems identified by community pharmacies. Ann Pharmacother; 41: 1825-1832, 2007.

73. Schaefer M. Discussing basic principles for a coding system of drug-related problems: the case of PI-Doc. Pharm World Sci; 24: 120-127, 2002.

74. Mattenklotz A. Vergleichende Validierung von zwei Klassifizierungssystemen für arzneimittelbezogene Probleme (PCNE und PiDoc) [master thesis]. Berlin: Charité University Hospital 2007.

75. Pottie K, Haydt S, Farrell B, Dolovich L, Sellors C, Hogg W. Narrative reports to monitor and evaluate the integration of pharmacists into family practice settings. Ann Fam Med; 6: 161-165, 2008.

76. Pope C, Ziebland S, Mays N. Qualitative research in health care. Analysing qualitative data. BMJ; 320: 114-116, 2000.

77. Pope C, Mays N. Qualitative research in health care. Oxford: Blackwell Publishing; 2006.

78. Law AM. Simulation, Modeling and Analysis. 4th ed. New York: McGraw-Hill; 2007.

79. Thron CD. Linearity and superposition in pharmacokinetics. Pharmacol Rev; 26: 3-31, 1974.

80. Mihara M, Ohnishi A, Tomono Y, Hasegawa J, Shimamura Y, Yamazaki K, et al. Pharmacokinetics of E2020, a new compound for Alzheimer's disease, in healthy male volunteers. Int J Clin Pharmacol Ther Toxicol; 31: 223-229, 1993.

81. Rogers SL, Doody RS, Mohs RC, Friedhoff LT. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group. Arch Intern Med; 158: 1021-1031, 1998.

82. Eisai. Aricept® -Fachinformation. Eisai GmbH Frankfurt/Main Deutschland. 2007.

83. Anonymous. Medical Research Council. MRC Health Services and Public Research Board. Framework for development and evaluation of RCTs for complex interventions to improve health. http://www.mrc.ac.uk/pdf-mrc_cpr.pdf; 2000.

84. Arnet I, Haefeli WE. Overconsumption detected by electronic drug monitoring requires subtle interpretation. Clin Pharmacol Ther; 67: 44-47, 2000.

85. Denhaerynck K, Schafer-Keller P, Young J, Steiger J, Bock A, De Geest S. Examining assumptions regarding valid electronic monitoring of medication therapy: development of a validation framework and its application on a European sample of kidney transplant patients. BMC Med Res Methodol; 8: 5, 2008.

86. Vrijens B, Tousset E, Rode R, Bertz R, Mayer S, Urquhart J. Successful projection of the time course of drug concentration in plasma during a 1-year period from electronically compiled dosing-time data used as input to individually parameterized pharmacokinetic models. J Clin Pharmacol; 45: 461-467, 2005.

87. Schoenthaler A, Ogedegbe G. Patients' perceptions of electronic monitoring devices affect medication adherence in hypertensive African Americans. Ann Pharmacother; 42: 647-652, 2008.

88. Wendel CS, Mohler MJ, Kroesen K, Ampel NM, Gifford AL, Coons SJ. Barriers to use of electronic adherence monitoring in an HIV clinic. Ann Pharmacother; 35: 1010-1015, 2001.

89. Klein A, Otto G, Kramer I. Impact of a pharmaceutical care program on liver transplant patients' compliance with immunosuppressive medication: a prospective, randomized, controlled trial using electronic monitoring. Transplantation; 87: 839-847, 2009.

90. Kogut SJ, El-Maouche D, Abughosh SM. Decreased persistence to cholinesterase inhibitor therapy with concomitant use of drugs that can impair cognition. Pharmacotherapy; 25: 1729-1735, 2005.

91. Mauskopf JA, Paramore C, Lee WC, Snyder EH. Drug persistency patterns for patients treated with rivastigmine or donepezil in usual care settings. J Manag Care Pharm; 11: 231-251, 2005.

92. Roe CM, Anderson MJ, Spivack B. How many patients complete an adequate trial of donepezil? Alzheimer Dis Assoc Disord; 16: 49-51, 2002.

93. Suh DC, Thomas SK, Valiyeva E, Arcona S, Vo L. Drug persistency of two cholinesterase inhibitors: rivastigmine versus donepezil in elderly patients with Alzheimer's disease. Drugs Aging; 22: 695-707, 2005.

94. Cals JW, Hopstaken RM, Le Doux PH, Driessen GA, Nelemans PJ, Dinant GJ. Dose timing and patient compliance with two antibiotic treatment regimens for lower respiratory tract infections in primary care. Int J Antimicrob Agents; 31: 531-536, 2008.

95. Lansky P, Sanda P, Weiss M. Modeling the influence of non-adherence on antibiotic efficacy: application to ciprofloxacin. Int J Clin Pharmacol Ther; 45: 438-447, 2007.

96. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ; 336: 1114-1117, 2008.

97. Cramer JA, Rosenheck R. Enhancing medication compliance for people with serious mental illness. J Nerv Ment Dis; 187: 53-55, 1999.

98. Rosen MI, Rigsby MO, Salahi JT, Ryan CE, Cramer JA. Electronic monitoring and counseling to improve medication adherence. Behav Res Ther; 42: 409-422, 2004.

99. Vrijens B, Belmans A, Matthys K, Klerk ED, Lesaffre E. Effect of intervention through a pharmaceutical care program on patient adherence with prescribed once-daily atorvastatin. Pharmacoepidemiol Drug Saf; 2005.

100. Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. JAMA; 296: 2563-2571, 2006.

101. Simons S. Pharmazeutische Betreuung onkologischer Patienten unter Therapie mit Capicetabin [dissertation]. Bonn: Rheinische Friedrich-Wilhelms-Universität Bonn; 2009.

102. Ownby RL. Medication adherence and cognition. Medical, personal and economic factors influence level of adherence in older adults. Geriatrics; 61: 30-35, 2006.

103. George CF, Peveler RC, Heiliger S, Thompson C. Compliance with tricyclic antidepressants: the value of four different methods of assessment. Br J Clin Pharmacol; 50: 166-171, 2000.

104. Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. Schizophr Res; 42: 241-247, 2000.

105. Kampen J, Swyngedouw M. The Ordinal Controversy Revisited. Quality & Quantity; 34: 87-102, 2000.

106. Grouven U, Bender R, Ziegler A, Lange S. Der Kappa-Koeffizient. Dtsch Med Wochenschr; 132(Suppl 1): e65-68, 2007.

107. Barat I, Andreasen F, Damsgaard EM. Drug therapy in the elderly: what doctors believe and patients actually do. Br J Clin Pharmacol; 51: 615-622, 2001.

108. Okuno J, Yanagi H, Tomura S, Oka M, Hara S, Hirano C, et al. Compliance and medication knowledge among elderly Japanese home-care recipients. Eur J Clin Pharmacol; 55: 145-149, 1999.

109. Kerzman H, Baron-Epel O, Toren O. What do discharged patients know about their medication? Patient Educ Couns; 56: 276-282, 2005.

110. Hope CJ, Wu J, Tu W, Young J, Murray MD. Association of medication adherence, knowledge, and skills with emergency department visits by adults 50 years or older with congestive heart failure. Am J Health Syst Pharm; 61: 2043-2049, 2004.

111. Paulino EI, Bouvy ML, Gastelurrutia MA, Guerreiro M, Buurma H. Drug related problems identified by European community pharmacists in patients discharged from hospital. Pharm World Sci; 26: 353-360, 2004.

112. Lowe CJ, Raynor DK, Purvis J, Farrin A, Hudson J. Effects of a medicine review and education programme for older people in general practice. Br J Clin Pharmacol; 50: 172-175, 2000.

113. Bernsten C, Bjorkman I, Caramona M, Crealey G, Frokjaer B, Grundberger E, et al. Improving the well-being of elderly patients via community pharmacy-based provision of pharmaceutical care: a multicentre study in seven European countries. Drugs Aging; 18: 63-77, 2001.

114. Hanlon JT, Weinberger M, Samsa GP, Schmader KE, Uttech KM, Lewis IK, et al. A randomized, controlled trial of a clinical pharmacist intervention to improve inappropriate prescribing in elderly outpatients with polypharmacy. Am J Med; 100: 428-437, 1996.

115. Modig S, Kristensson J, Kristensson Ekwall A, Rahm Hallberg I, Midlov P. Frail elderly patients in primary care-their medication knowledge and beliefs about prescribed medicines. Eur J Clin Pharmacol; 65: 151-155, 2008.

116. San Miguel MT, Martinez JA, Vargas E. Food-drug interactions in the summary of product characteristics of proprietary medicinal products. Eur J Clin Pharmacol; 61: 77-83, 2005.

117. Bonnet V, Couvreur C, Demachy P, Kimmel F, Milan H, Noel D, et al. Evaluating radiotherapy patients' need for information: a study using a patient information booklet. Cancer Radiother; 4: 294-307, 2000.

118. Bühner M. Einführung in die Test- und Fragebogenkonstruktion First ed. München: Pearson Studium; 2004.

119. Liekweg A, Eckhardt M, Taylor SC, Erdfelder E, Jaehde U. Psychometric assessment and application of a questionnaire measuring patient: satisfaction with information on cancer treatment. Pharm World Sci; 27: 96-103, 2005.

120. Svarstad BL, Bultman DC, Mount JK. Patient counseling provided in community pharmacies: effects of state regulation, pharmacist age, and busyness. J Am Pharm Assoc (2003); 44: 22-29, 2004.

121. Homer D, Nightingale P, Jobanputra P. Providing patients with information about disease-modifying anti-rheumatic drugs: Individually or in groups? A pilot randomized controlled trial comparing adherence and satisfaction. Musculoskeletal Care; Epub 2008 Sep 15.

122. Bowskill R, Clatworthy J, Parham R, Rank T, Horne R. Patients' perceptions of information received about medication prescribed for bipolar disorder: Implications for informed choice. J Affect Disord; 100: 253-257, 2007.

123. Gellaitry G, Cooper V, Davis C, Fisher M, Date HL, Horne R. Patients' perception of information about HAART: impact on treatment decisions. AIDS Care; 17: 367-376, 2005.

124. Tarn DM, Heritage J, Paterniti DA, Hays RD, Kravitz RL, Wenger NS. Physician communication when prescribing new medications. Arch Intern Med; 166: 1855-1862, 2006.

125. Keiner D. Methodischer Vergleich von verschiedenen Instrumenten zur Messung der Lebensqualität bei Osteoporose-Patienten [dissertation]. Berlin: Humboldt-Universität 2005.

126. Etters L, Goodall D, Harrison BE. Caregiver burden among dementia patient caregivers: a review of the literature. J Am Acad Nurse Pract; 20: 423-428, 2008.

127. Markowitz JS, Gutterman EM, Sadik K, Papadopoulos G. Health-related quality of life for caregivers of patients with Alzheimer disease. Alzheimer Dis Assoc Disord; 17: 209-214, 2003.

128. Pickard AS, Hung SY. An update on evidence of clinical pharmacy services' impact on health-related quality of life. Ann Pharmacother; 40: 1623-1634, 2006.

129. Hoffmann W, Herzog B, Muhlig S, Kayser H, Fabian R, Thomsen M, et al. Pharmaceutical care for migraine and headache patients: a community-based, randomized intervention. Ann Pharmacother; 42: 1804-1813, 2008.

130. Kheir NM, van Mil JW, Shaw JP, Sheridan JL. Health-related quality of life measurement in pharmaceutical care. Targeting an outcome that matters. Pharm World Sci; 26: 125-128, 2004.

131. Catalog of MAPI Institute [database on the internet]. Lyon: c2004 - [cited 2009 Apr 3]. Available from: http://www.mapi-institute.com/questionnaires-and-translation/ourcatalog/115-specific-questionnaires-caregivers.

132. Acton GJ, Kang J. Interventions to reduce the burden of caregiving for an adult with dementia: a meta-analysis. Res Nurs Health; 24: 349-360, 2001.

133. Callahan CM, Boustani MA, Unverzagt FW, Austrom MG, Damush TM, Perkins AJ, et al. Effectiveness of collaborative care for older adults with Alzheimer disease in primary care: a randomized controlled trial. JAMA; 295: 2148-2157, 2006.

134. Westerlund T, Andersson IL, Marklund B. The quality of self-care counselling by pharmacy practitioners, supported by IT-based clinical guidelines. Pharm World Sci; 29: 67-72, 2007.

135. AARDEX. http://www.aardex.ch/helpdesk/index.php?_m=knowledgebase&_a=view. Zug, Schweiz: Aardex Ltd.; 30.03.2007.

136. van Mil JW, Westerlund LO, Hersberger KE, Schaefer MA. Drug-related problem classification systems. Ann Pharmacother; 38: 859-867, 2004.

137. Krähenbühl JM, Kremer B, Guignard B, Bugnon O. Practical evaluation of the drug-related problem management process in Swiss community pharmacies. Pharm World Sci; 30: 777-786, 2008.

138. Leemans L, Veroeveren L, Bulens J, Hendrickx C, Keyenberg W, Niesten F, et al. Frequency and trends of interventions of prescriptions in Flemish community pharmacies. Pharm World Sci; 25: 65-69, 2003.

139. Benkert O, Hippius H. Kompendium der psychiatrischen Pharmakotherapie. Fifth ed. Heidelberg: Springer; 2005.

140. Schröder S, Zollner YF, Schaefer M. Drug related problems with Antiparkinsonian agents: consumer Internet reports versus published data. Pharmacoepidemiol Drug Saf; 16: 1161-1166, 2007.

141. Westerlund LT, Bjork HT. Pharmaceutical care in community pharmacies: practice and research in Sweden. Ann Pharmacother; 40: 1162-1169, 2006.

142. Westerlund T, Marklund B. Assessment of the clinical and economic outcomes of pharmacy interventions in drug-related problems. J Clin Pharm Ther; Epub 2008 Dec 22.

143. Barbour RS. Checklists for improving rigour in qualitative research: a case of the tail wagging the dog? BMJ; 322: 1115-1117, 2001.

144. Roberts AS, Benrimoj SI, Chen TF, Williams KA, Aslani P. Implementing cognitive services in community pharmacy: a review of facilitators used in practice change. International Journal of Pharmacy Practice; 14: 163-170, 2006.

145. Salter C, Holland R, Harvey I, Henwood K. "I haven't even phoned my doctor yet." The advice giving role of the pharmacist during consultations for medication review with patients aged 80 or more: qualitative discourse analysis. BMJ; 334: 1101, 2007.

146. Doucette WR, Nevins J, McDonough RP. Factors affecting collaborative care between pharmacists and physicians. Res Social Adm Pharm; 1: 565-578, 2005.

147. Chen TF, de Almeida Neto AC. Exploring elements of interprofessional collaboration between pharmacists and physicians in medication review. Pharm World Sci; 29: 574-576, 2007.

148. Bell JS, Aslani P, McLachlan AJ, Whitehead P, Chen TF. Mental health case conferences in primary care: content and treatment decision making. Res Social Adm Pharm; 3: 86-103, 2007.

149. Florentinus SR, van Hulten R, Kramer M, van Dijk L, Heerdink ER, Leufkens HG, et al. Which pharmacists contribute to high-level pharmacotherapy audit meetings with general practitioners? Ann Pharmacother; 40: 1640-1646, 2006.

150. van Mil JW. Pharmaceutical care in community pharmacy: practice and research in the Netherlands. Ann Pharmacother; 39: 1720-1725, 2005.

151. de Almeida Neto AC, Chen TF. When pharmacotherapeutic recommendations may lead to the reverse effect on physician decision-making. Pharm World Sci; 30: 3-8, 2008.

152. Sachverständigenrat zur Begutachtung der Entwicklung im Gesundheitswesen. Kooperation und Verantwortung - Voraussetzungen einer zielorientierten Gesundheitsversorgung. Gutachten 2007.

153. Dunlop JA, Shaw JP. Community pharmacists' perspectives on pharmaceutical care implementation in New Zealand. Pharm World Sci; 24: 224-230, 2002.

154. Uema SA, Vega EM, Armando PD, Fontana D. Barriers to pharmaceutical care in Argentina. Pharm World Sci; 30: 211-215, 2008.

155. van Mil JWF. Eurpean barriers to the implementation of pharmaceutical care. The International Journal of Pharmacy Practice; 9: 163-168, 2001.

156. Gastelurrutia MA, Fernandez-Llimos F, Benrimoj SI, Castrillon CC, Faus MJ. Barriers for the implementation of cognitive services in Spanish community pharmacies. Aten Primaria; 39: 465-470, 2007.

157. Latif A, Boardman H. Community pharmacists' attitudes towards medicines use reviews and factors affecting the numbers performed. Pharm World Sci; 30: 536-543, 2008.

158. Wang LN. How to make a success of MURs. Pharm J; 278: 315-318, 2007.

159. Mark MP. The general pharmacy work explored in The Netherlands. Pharm World Sci; 30: 353-359, 2008.

160. Mobach MP. Counter design influences the privacy of patients. Soc Sci Med; 68: 1000-1005, 2009.

161. Hughes CM, McCann S. Perceived interprofessional barriers between community pharmacists and general practitioners: a qualitative assessment. Br J Gen Pract; 53: 600-606, 2003.

162. Rogers SL, Friedhoff LT. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial. The Donepezil Study Group. Dementia; 7: 293-303, 1996.

163. Sramek JJ, Cutler NR. RBC cholinesterase inhibition: a useful surrogate marker for cholinesterase inhibitor activity in Alzheimer disease therapy? Alzheimer Dis Assoc Disord; 14: 216-227, 2000.

164. Urquhart J. How much compliance is enough? Pharm Res; 13: 10-11, 1996.

165. Urquhart J. Pharmacodynamics of variable patient compliance: implications for pharmaceutical value. Adv Drug Deliv Rev; 33: 207-219, 1998.

166. McCann MF, Potter LS. Progestin-only oral contraception: a comprehensive review. Contraception; 50: S1-195, 1994.

167. Johnson BF, Whelton A. A Study Design for Comparing the Effects of Missing Daily Doses of Antihypertensive Drugs. Am J Ther; 1: 260-267, 1994.

168. Spyker DA, Harvey ED, Harvey BE, Harvey AM, Rumack BH, Peck CC, et al. Assessment and reporting of clinical pharmacology information in drug labeling. Clin Pharmacol Ther; 67: 196-200, 2000.

169. Urquhart J. Role of patient compliance in clinical pharmacokinetics. A review of recent research. Clin Pharmacokinet; 27: 202-215, 1994.

Appendix

Appendix A Informed consent

Patient information leaflet
Letter to physician
Information sheet for physicians on pharmaceutical care
MEMS information sheet for physicians
Ability to consent form
Consent form
MEMS information sheet for patients and caregivers
SOP for the recruitment in the Gerontopsychiatric Clinic
SOP for the recruitment in a community pharmacy

Appendix B Questionnaires

Anamnesis form
Morisky questionnaire
Interview guide for *knowledge in pharmacotherapy*
Questionnaire for *knowledge in pharmacotherapy* (version 1)
Questionnaire for *knowledge in pharmacotherapy* (version 2)
Feasibility questionnaire

Appendix C Pharmaceutical care program

Medication history form
Review of system form
Medication plan
Medication review form
Counselling form according to an extended guidance of Bundesapothekerkammer (BAK)
Form for measurement guided medication management
Sample MEMS compliance report
Drug-related problem form

Appendix D MEMS documentation

Curriculum vitae

Publications

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Patientenaufklärung zur Studie „Pilot-Projekt zur Pharmazeutischen Betreuung von Alzheimer-Patienten und ihren Angehörigen in der ambulanten Therapie“ (Intensivbetreuungs-/Standardgruppe)

Sie bzw. Ihr Angehöriger werden aufgrund einer Alzheimer-Demenz regelmäßig in der gerontopsychiatrischen Hochschulambulanz der Charité oder von einem niedergelassenen Arzt behandelt.

Arzneimittel spielen bei der Therapie der Alzheimer-Demenz eine wichtige Rolle. Ihre volle Wirksamkeit können sie aber erst entfalten, wenn sie richtig und regelmäßig eingenommen werden. Gleichzeitig sollen Nebenwirkungen vermieden werden. Nimmt man gleichzeitig mehrere Arzneimittel ein, egal ob auf ärztliche Verordnung oder in der Apotheke ohne Rezept gekauft, können sich diese Arzneimittel gegenseitig in ihrer Wirkung beeinflussen.

Sie bzw. Ihr Angehöriger gehören zu den Patienten, die regelmäßig ein oder mehrere Medikamente einnehmen müssen. Wir möchten Sie bitten, an einer wissenschaftlichen Studie der Abteilung Klinische Pharmazie der Freien Universität Berlin in Zusammenarbeit mit der gerontopsychiatrischen Hochschulambulanz der Charité, niedergelassenen Ärzten und mehreren öffentlichen Apotheken in Berlin teilzunehmen.

Voraussetzung ist, dass Sie alle Ihre Arzneimittel in Ihrer Stamm-Apotheke holen und dem Apotheker während der nächsten 7 Monate alle angewendeten Arzneimittel lückenlos nennen.

Möchten Sie aus irgendeinem Grund nicht teilnehmen, haben wir dafür natürlich Verständnis.

1. Leitung der Studie

Die Studie „Pilot-Projekt zur Pharmazeutischen Betreuung von Alzheimer-Patienten und ihren Angehörigen in der ambulanten Therapie“ wird von Frau Professor Dr. Charlotte Kloft betreut. Frau Professor Dr. Charlotte Kloft leitet die Forschung/Abteilung für Klinische Pharmazie am Institut für Pharmazie an der Freien Universität Berlin. Dieses Pilot-Projekt wird durch die Förderinitiative Pharmazeutische Betreuung e.V. (c/o Referat Pharmazeutische Betreuung, Zentrum für Arzneimittelinformation und Pharmazeutische Praxis der ABDA, Deutsches Apothekerhaus, Jägerstraße 49/50, 10117 Berlin) unterstützt.

2. Zweck der Studie

Pharmazeutische Betreuung hat in den letzten Jahren weltweit an Bedeutung erlangt. Das Hauptziel der Pharmazeutischen Betreuung besteht darin, die Arzneimitteltherapie durch stärkere Einbeziehung des Apothekers und regelmäßige Information des Patienten zu verbessern. Durch intensive Beratung des Patienten zu seinen Arzneimitteln, Erkennen von Nebenwirkungen und Wechselwirkungen und Lösen von Problemen, die im Zusammenhang mit Arzneimitteln stehen, kann die Lebensqualität und auch die Zufriedenheit des Patienten verbessert werden. Bisher wurden keine Studien zur Bewertung der Pharmazeutischen Betreuung bei Alzheimer-Patienten und ihren Angehörigen durchgeführt. In dem geplanten Pilot-Projekt geht es um die Frage, inwieweit intensivierte Pharmazeutische Betreuung bei Morbus Alzheimer die Qualität der Arzneimitteltherapie der Patienten, das Wissen über die Arzneimitteltherapie und die Lebensqualität der Angehörigen verbessert. Um die Einnahmegewohnheiten bei der Arzneimitteltherapie erfassen und besser verstehen zu können, hat Ihr Apotheker das Arzneimittel gegen das nachlassende Gedächtnis in einem Arzneibehältnis gegeben, das mit einem speziellen Verschluss ausgestattet ist, der jedes Öffnen/Schließen des Arzneigefäßes registriert (elektronischer Arzneimittelverbrauchsmonitor). Der Verschluss enthält eine kleine Batterie und eine Elektronik, die ähnlich wie die in modernen Armbanduhren funktioniert.

Insgesamt sollen im Pilot-Projekt 28 Patienten in zwei Vergleichsgruppen aufgenommen werden, in Abhängigkeit davon, ob die Aufnahme in der Apotheke (Intensivbetreuungs-gruppe) oder beim Arzt (Standardbetreuungsgruppe) erfolgt.

3. Ablauf und Dauer der Teilnahme

Die Studiendauer beträgt maximal 7 Monate. Innerhalb dieser werden Sie intensiv von Ihrer Stamm-Apotheke betreut. Dazu erhält Ihre Apotheke einen Betreuungsplan, in dem die erforderlichen Informationen wie Medikamente und Erkrankungen aufgeführt sind. Um eine gezielte und individuelle pharmazeutische Betreuung durch Ihre Apotheke zu erfahren, ist ein Beratungsgespräch ca. alle 4 Wochen erforderlich. Hierbei werden auch

die Daten des elektronischen Arzneimittelverbrauchsmonitors in die Beratung einbezogen. Dieser wird nach einem Monat und danach in regelmäßigen Abständen bis zum Abschluss der Studie ausgelesen. Während der Beratung bespricht Ihr Apotheker mit Ihnen die Arzneimitteltherapie, evtl. Nebenwirkungen und Probleme, die im Zusammenhang mit den Arzneimitteln stehen. Vor und nach Beendigung der Studie erhalten Sie Fragebögen.
Im Rahmen der Studie besteht kein spezieller Versicherungsschutz für den Alzheimer-Patienten bzw. für den Angehörigen.

4. Mögliche Risiken

Bei Teilnahme an dieser Studie bestehen für Sie keinerlei Risiken.

5. Freiwilligkeit und Möglichkeit des Widerrufes

Die Teilnahme an der oben genannten Studie ist freiwillig. Sie können jederzeit und ohne Angabe von Gründen Ihre Einwilligung widerrufen bzw. zurückziehen, ohne dass das Vertrauensverhältnis zu Ihrem behandelnden Arzt und betreuenden Apotheker in irgendeiner Weise leidet oder dieses nachteilige Folgen für Ihre weitere Behandlung hat.
Sollten Sie bereit sein, an unserer Studie mitzuwirken, möchten wir Ihnen schon jetzt danken und stehen Ihnen für evtl. Fragen gerne und jederzeit zur Verfügung.

6. Möglicher Nutzen für die Allgemeinheit bzw. den Studienteilnehmer

Im Rahmen der Studie werden kostenfreie, intensive Beratungsgespräche mit Apothekern angeboten, welche dazu beitragen können, Probleme in der Arzneimitteltherapie (z.B. Wechselwirkungen zwischen verschiedenen Arzneimitteln) zu entdecken und zu lösen und so zum Wohlergehen jedes einzelnen Patienten beitragen. Die in diesem Pilot-Projekt gesammelten Erfahrungen werden maßgeblich dazu beitragen, vergleichbare Projekte in größerem Maßstab durchführen zu können und so in Zukunft eine ausgewogene und umfassende Versorgung von Alzheimer-Patienten und ihren Angehörigen entstehen zu lassen, in die das besondere Fachwissen des Apothekers als Arzneimittelexperte einfließt.

7. Datenschutz

Bei wissenschaftlichen Studien werden persönliche Daten und medizinische Befunde über Sie erhoben. Unter Beachtung der Schweigepflicht gehen wir jederzeit vertraulich mit Ihren Daten um. Die Weitergabe, Speicherung und Auswertung dieser studienbezogenen Daten erfolgt nach gesetzlichen Bestimmungen und setzt vor der Teilnahme an der Studie Ihre freiwillige Einwilligung voraus (siehe Patienteneinwilligung). Ihre persönlichen Daten werden in verschlüsselter Form gespeichert und weiterverarbeitet. Die Weitergabe der im Rahmen dieser Studie erhobenen Daten erfolgt verschlüsselt an die Stamm-Apotheke.

Nur ihre Stamm-Apotheke und die Abteilung Klinische Pharmazie der Freien Universität Berlin besitzen eine Verschlüsselungszuweisung und können Ihre verschlüsselten Daten mit Ihrer Person in Verbindung bringen. Die in Ihrer Stamm-Apotheke erfragten und verschlüsselt gespeicherten Daten werden der Abteilung Klinische Pharmazie der Freien Universität zur Auswertung zur Verfügung gestellt.

Sie können jederzeit Auskunft bei den für die Datenverarbeitung verantwortlichen Stellen über die Sie betreffenden Angaben verlangen. Ferner können Sie ggf. eine Berichtigung der Sie betreffenden Angaben verlangen. Sofern Sie sich entschließen sollten, die Studienteilnahme abzubrechen, werden die Sie betreffenden Angaben gelöscht. Ansonsten werden die Angaben für die Dauer von 10 Jahren nach dem Ende der Studie aufbewahrt, wie es der Gesetzgeber vorsieht.

Die Ergebnisse der Studie werden in anonymisierter Form veröffentlicht. Hierbei wird Ihre Identität nicht offenbart.

Sofern Sie weitere Fragen zur Studienteilnahme haben sollten, wenden Sie sich bitte an Herrn Apotheker und Diplom-Pharmazeut Oliver Schwalbe (Telefon: 030 838 50626).

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An die behandelnden Ärztinnen und
Ärzte der Patienten für das Pilot-Projekt

Pilot-Projekt zur Pharmazeutischen Betreuung von Alzheimer-Patienten und ihren Angehörigen in der ambulanten Therapie

Sehr geehrte Frau Doktor, sehr geehrter Herr Doktor,

die Abteilung Klinische Pharmazie der Freien Universität Berlin führt derzeit mit oben genannten Kooperationspartnern eine kontrollierte Studie zur Evaluierung der Dienstleistung Pharmazeutische Betreuung bei Morbus Alzheimer durch. Für diese Studie liegt ein positives Votum der Ethikkommission der Charité vor. Weitere Informationen zu diesem Projekt finden Sie im Anhang zu diesem Schreiben. Ein Einschlusskriterium der Studie ist die **Einwilligungsfähigkeit** des Patienten. Einwilligungsfähig ist nur, wer Art, Bedeutung und Tragweite (Risiken) der ärztlichen Maßnahme erfassen kann. Wir bitten, dies zu überprüfen und uns gegebenenfalls das beigelegte Formular unterschrieben zurückzufaxen. Bitte beachten Sie auch die **Kurzinformation zum elektronischen Arzneimittel-Verbrauchsmonitor**.
Vielen Dank!

Mit freundlichen Grüßen

Professor Dr. Charlotte Kloft

Dipl.-Pharm. Oliver Schwalbe

Kurzinformation zum Pilot-Projekt zur Pharmazeutischen Betreuung von Alzheimer-Patienten und ihren Angehörigen in der ambulanten Therapie
Kurzinformation zum elektronischen Arzneimittel-Verbrauchsmonitor
Formular Einwilligungsfähigkeit des Alzheimer-Patienten

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Kurzinformation zum „Pilot-Projekt zur Pharmazeutischen Betreuung von Alzheimer-Patienten und ihren Angehörigen in der ambulanten Therapie“ (Ärzte)

Pharmazeutische Betreuung wird definiert als „die konsequente Wahrnehmung der Mitverantwortung des Apothekers bei der Arzneimitteltherapie mit dem Ziel, bestimmte therapeutische Ergebnisse zu erreichen, die die gesundheitsbezogene Lebensqualität des Patienten verbessern“. In Deutschland sind bereits eine Reihe von wissenschaftlichen Projekten zur Pharmazeutischen Betreuung, vor allem bei chronischen Erkrankungen, durchgeführt worden (z.B. Diabetes mellitus und Asthma bronchiale). Verschiedene Studien zur intensivierten pharmazeutischen Betreuung konnten zeigen, dass sich mit dieser Dienstleistung relevante positive Effekte auf ökonomische, klinische und humanistische Outcomes erzielen lassen. Keines der bisher in Deutschland durchgeführten Projekte hat sich mit der Pharmazeutischen Betreuung von Alzheimer-Patienten und ihren Angehörigen befasst und folglich ist die Rolle des Apothekers in der Betreuung von Alzheimer-Patienten noch kaum erforscht. Er hat jedoch die Möglichkeit, durch vielfältige Anknüpfungspunkte, zusammen mit Betroffenen, Angehörigen, Pflegepersonal, Selbsthilfegruppen und Ärzten zur Optimierung der Arzneimitteltherapie bei Alzheimer-Patienten beizutragen.

Ziel des geplanten Pilot-Projektes ist, in einer ersten Untersuchung Grundlagen und Ansätze eines Pharmazeutischen Betreuungskonzeptes für Alzheimer-Patienten und ihre Angehörigen zu entwickeln. Im Rahmen der Studie soll dabei der Einfluss der intensivierten Pharmazeutischen Betreuung im Vergleich zu einer Standardbetreuung auf die Compliance des Patienten in der Antidementiva-therapie (primäre Zielgröße) und weitere Zielgrößen untersucht werden.

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Kurzinformation zum elektronischen Arzneimittelverbrauchsmonitor (MEMS®)

Zur Bestimmung der Compliance in der Antidementivatherapie soll ein elektronischer Arzneimittel-Verbrauchsmonitor (MEMS®) verwendet werden. Bei dieser Technologie handelt es sich um ein System zur Erfassung des Patienten-Einnahmeverhaltens für verordnete, per os zu applizierende Medikamente. Das System besteht aus zwei Teilen: einem standardisierten Behältnis mit Gewindeöffnung und einem Schraubverschluss für diesen Plastikbehälter. Ein in diesem Schraubverschluss enthaltener Mikroprozessor registriert elektronisch jede Öffnung und Schließung des Behälters (Datum und Uhrzeit).

Damit ein Entblistern und Umfüllen des Fertigarzneimittels in den Verbrauchsmonitor vorgenommen werden kann, ist es notwendig, dass ein **Rezept über ein Antidementivum** mit dem Hinweis **„zur Umfüllung in den Verbrauchsmonitor“** gekennzeichnet ist.

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Einwilligungsfähigkeit der Alzheimer-Patienten zur Studie „Pilot-Projekt zur Pharmazeutischen Betreuung von Alzheimer-Patienten und ihren Angehörigen in der ambulanten Therapie“

Der Patient/Die Patientin _____ besitzt die notwendige Einsichts- und Urteilsfähigkeit, um in die Teilnahme am „Pilot-Projekt zur Pharmazeutischen Betreuung von Alzheimer-Patienten und ihren Angehörigen in der ambulanten Therapie“ einwilligen zu können.

Berlin, den _____

_____
Unterschrift des Arztes

Angaben zum Arzt	Name: Anschrift: Telefon:

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Einwilligungserklärung zur Studie „Pilot-Projekt zur Pharmazeutischen Betreuung von Alzheimer-Patienten und ihren Angehörigen in der ambulanten Therapie“

Hiermit erkläre ich, _____ (Patient) bzw. _____ (Angehöriger/Pflegender), dass ich durch _____ mündlich und schriftlich über das Wesen, die Bedeutung und die Tragweite der wissenschaftlichen Untersuchung im Rahmen der o.g. Studie informiert wurde und ausreichend Gelegenheit hatte, meine Fragen hierzu in einem Gespräch mit Herrn Schwalbe zu klären.
Ich habe insbesondere die mir vorgelegte Patienteninformation vom _____ verstanden und eine Ausfertigung derselben und dieser Einwilligungserklärung erhalten.
Mir ist bekannt, dass ich meine Einwilligung jederzeit ohne Angabe von Gründen und ohne nachteilige Folgen für mich zurückziehen und eine Weiterverarbeitung meiner Daten jederzeit widersprechen und ihre Löschung bzw. Vernichtung verlangen kann.
Ich bin bereit, an der wissenschaftlichen Untersuchung im Rahmen der o.g. Studie teilzunehmen.

Einwilligungserklärung zur Datenverarbeitung
Bei wissenschaftlichen Studien werden persönliche Daten und medizinische Befunde erhoben. Die Weitergabe, Speicherung und Auswertung dieser studienbezogenen Daten erfolgen nach gesetzlichen Bestimmungen und setzen vor Teilnahme an der Studie folgende freiwillige Einwilligung voraus:
Ich erkläre mich damit einverstanden, dass im Rahmen dieser Studie erhobene Daten/Angaben über mich verschlüsselt und auf elektronischen Datenträgern aufgezeichnet, verarbeitet und die anonymisierten Studienergebnisse veröffentlicht werden.
Mit meinem Einverständnis zur Teilnahme erkläre ich gleichzeitig, dass ich mit der Weitergabe der im Rahmen dieser wissenschaftlichen Studie erhobenen Daten in verschlüsselter Form an meine Stamm-Apotheke _____ einverstanden bin.
Ich bin auch damit einverstanden, dass die in meiner Stamm-Apotheke erfragten und gespeicherten Daten in verschlüsselter Form der Abteilung Klinische Pharmazie der Freien Universität zur Auswertung zur Verfügung gestellt werden.
Nur die Stammapotheke und die Abteilung Klinische Pharmazie der Freien Universität Berlin besitzen eine Verschlüsselungszuweisung und können meine personenbezogenen Daten mit mir in Verbindung bringen.

Berlin, den _____ _____
Unterschrift des Patienten

Berlin, den _____ _____
Unterschrift des Angehörigen/Pflegenden

Berlin, den _____ _____
Unterschrift des aufklärenden Apothekers

Patienten-Informationen:

(wird vom Apotheker ausgefüllt)

Name: Vorname: Anschrift: Geb.: Alter: Telefon:	
Angehöriger	Name: Anschrift: Telefon:
Wer ist für Arzneimittel zuständig?	○ Patient ○ Angehöriger
Stammapotheke:	Name: Anschrift: Telefon: Ansprechpartner in Apotheke:
Behandelnder Hausarzt	Name: Anschrift: Telefon:
Behandelnder Facharzt (falls zutreffend)	Name: Anschrift: Telefon:
Krankenkasse	
=> Patient gehört zur	○ Intensivbetreuungsgruppe/Standardgruppe ○ Standardbetreuungsgruppe/Standardgruppe
Studien-Nr.	

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Das MEMS® (Medication Event Monitoring System) – Arzneimittelbehältnis
Hinweise zur Anwendung

1. Ihr Arzt _____ hat Ihnen das Arzneimittel _____ verordnet.
2. Entnehmen Sie Ihre Tabletten oder Kapseln bitte nur aus dem MEMS®-Arzneimittelbehältnis.
3. Öffnen Sie das Behältnis bitte nur, um tatsächlich Tabletten oder Kapseln zu entnehmen. Sollte das Behältnis versehentlich doch einmal außerplanmäßig geöffnet worden sein, notieren Sie bitte Datum und Uhrzeit und teilen Sie diese dem Studien-Apotheker beim nächsten Treffen mit.
4. Schließen Sie das Behältnis anschließend umgehend, indem Sie den Deckel wieder ganz zuschrauben.
5. Lassen Sie das Behältnis niemals länger geöffnet, als dies zur Entnahme der Tabletten oder Kapseln notwendig ist.
6. Lagern Sie das Behältnis an einem trockenen Ort und schützen Sie es vor Feuchtigkeit. Verwenden Sie bitte zur Reinigung kein Spülmittel oder Alkohol!
7. Bei Defekten am Behältnis oder Fragen zur Anwendung wenden Sie sich bitte umgehend an den die Studie betreuenden Apotheker Oliver Schwalbe (Telefonnummer siehe oben).

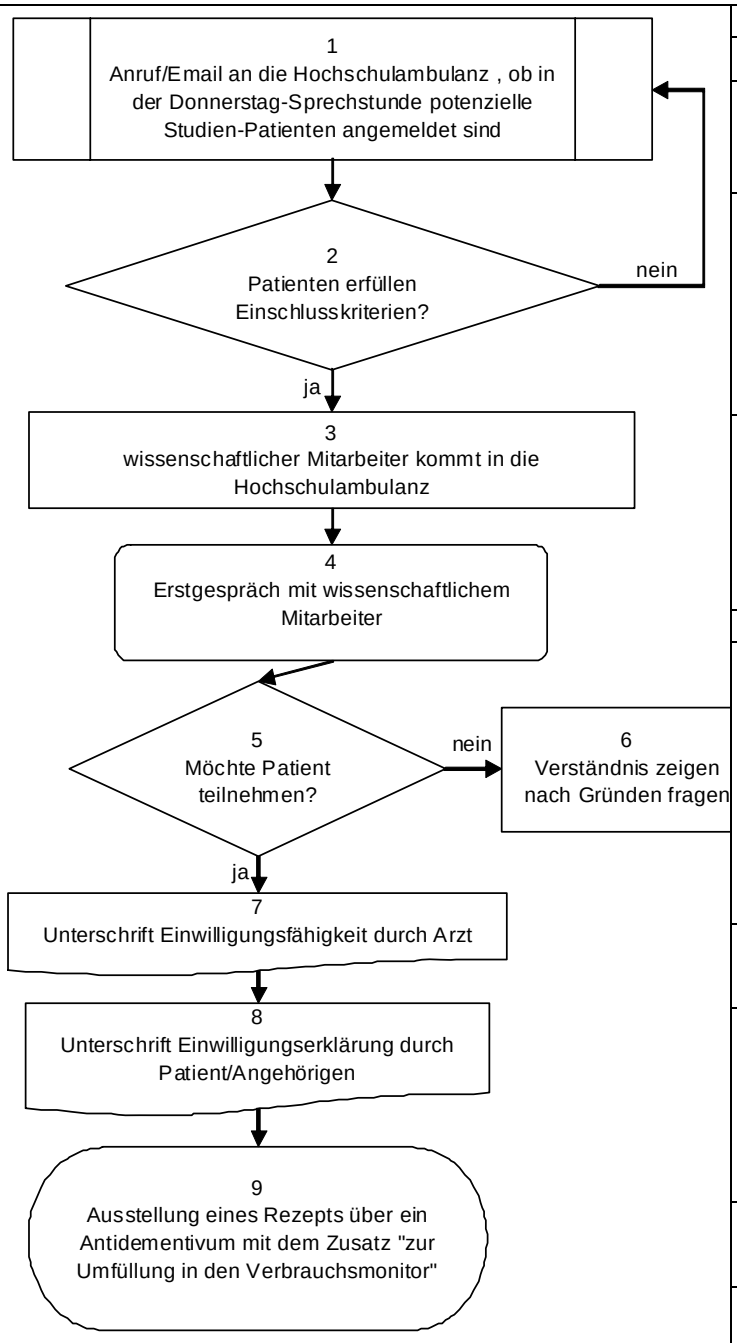
Bitte bringen Sie Ihr MEMS®-Arzneigefäß regelmäßig beim Einlösen des Rezeptes in die _____ mit.

Vielen Dank für Ihre Mitarbeit

Version: September 2005
erstellt von: Oliver Schwalbe

Abläufe für „Pilot-Projekt zur Pharmazeutischen Betreuung von Alzheimer-Patienten und ihren Angehörigen in der ambulanten Therapie“

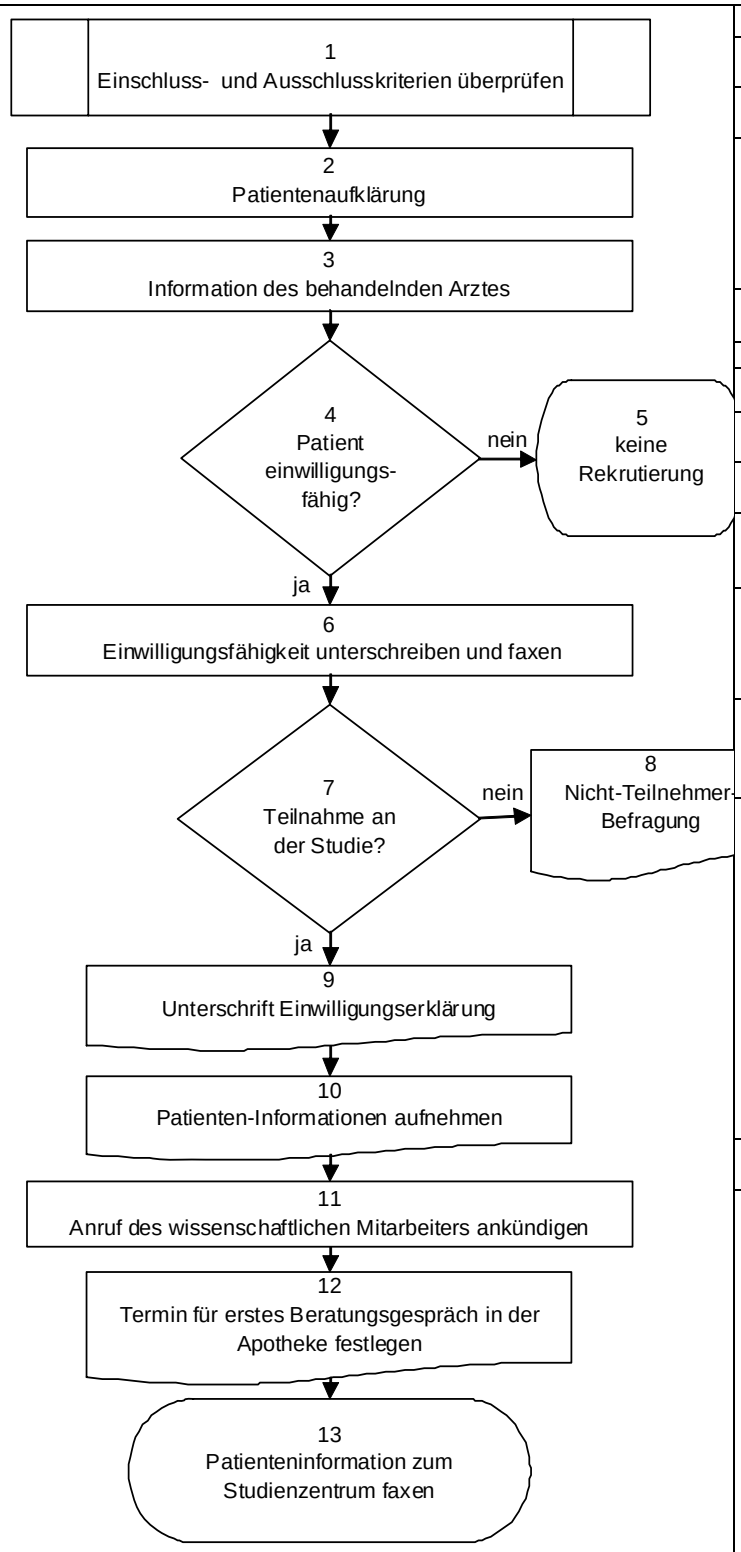
- Rekrutierung der Standardbetreuungsgruppe in der Hochschulambulanz der Charité



Nr.	VA	Hinweise
1	Wiss.	
2	Arzt	Siehe Ein- und Ausschlusskriterien im Studienordner und der Flyer zur Studie
3	Wiss.	Wiss. Mitarbeiter: Oliver Schwalbe **Tel.: 030 838 50626** **Mobil: 0172 8084303** **Fax: 030 838 50711** Email: oschwalb@zedat.fu-berlin.de
4	Wiss.	Siehe Prozess Erstgespräch mit wissenschaftlichem Mitarbeiter Findet in der Hochschul-ambulanz nach dem Arzttermin statt
5	Wiss.	
6	Wiss.	• Dokumentation der vom Patienten genannten Gründe im Dokument Einschlusskriterien (Angabe von Gründen freiwillig) • Interview für Nichtteilnehmer • Morisky-Score für Nicht-Teilnehmer
7	Arzt	Einwilligungsfähigkeit des Patienten, Formular im Studienordner
8	Wiss.	Kopie der Einwilligungserklärung dem Patienten mitgeben Formular im Studienordner wichtig: Übereinstimmung Datum mit 7.
9	Arzt	Behält wissenschaftlicher Mitarbeiter für die Erst-Belieferung des Patienten
		VA = Verantwortlicher **Wiss. = Wissenschaftlicher Mitarbeiter**

Abläufe für „Pilot-Projekt zur Pharmazeutischen Betreuung von Alzheimer-Patienten und ihren Angehörigen in der ambulanten Therapie“

- Rekrutierung der Intensivbetreuungsgruppe durch öffentliche Apotheken



Nr.	VA	Hinweise
1	Apo.	Im Gespräch mit Patienten und dem Angehörigen
2	Apo	Hilfsmittel: schriftliche Patientenaufklärung
3	Apo	• Arzt anrufen • Anschreiben, Kurzinformation (Studie, MEMS) und Einwilligungsfähigkeit an den Arzt faxen
4	Arzt	Arzt beurteilt, ob der Patient einwilligungsfähig ist
5		
6	Arzt	An die Apotheke
7	Pat./Ang.	
8	Pat./Apo	
9	Pat./Ang./ Apo	Dem Patienten/Angehörigen Einwilligungserklärung in Kopie mitgeben
10	Apo	• Name, Anschrift, usw. • Kundenkarte anlegen, wenn nicht bereits vorhanden
11	Apo	Herr Schwalbe macht einen Termin zur Erstbefüllung des MEMS und Erstbefragung des Patienten
12	Apo	• ca. 5 Wochen nach der Rekrutierung • Dokumentation im Zeitplan; • Patienten/Angehörigen bitten bei diesem Termin alle Arzneimittel – verschreibungspflichtig und nicht verschreibungspflichtig – mit in die Apotheke zu bringen
13	Apo	An Oliver Schwalbe, Fax: (030) 838 50 711
		Ang. = Angehöriger **Apo = Apotheker** **Pat. = Patient** **VA = Verantwortlicher** **Wiss. = Wissenschaftlicher Mitarbeiter**

Erstellt	**am: 13.11.2006**	**von: Oliver Schwalbe**	**Revision: 0**
Geprüft/Freigegeben	**am:**	**von:**	

Studien-Nr.: **Datum:**	**Erstanamnese**	Freie Universität Berlin Abteilung Klinische Pharmazie

Erstanamnese (Interview durch wissenschaftlichen Mitarbeiter)

Niereninsuffizienz	☐	1 = nein 2 = ja, keine Dialysepflicht 3 = ja, Dialysepflicht 4 = nicht bekannt
Leberinsuffizienz	☐	1 = nein 2 = ja 3 = nicht bekannt
Raucht der Patient?	☐	1 = nein 2 = ja
Wenn Raucher, wie viele Zigaretten pro Tag?	☐☐	

1. Sozialanamnese

Wohnen Patient und Angehöriger zusammen?	☐	1 = nein 2 = ja
Wie häufig besteht Kontakt zwischen Patient und Angehörigen?	☐	1 = täglich 2 = 3x wöchentlich 3 = 2x wöchentlich 4 = 1x wöchentlich 5 = < 1x wöchentlich
Wird professionelle Hilfe bei der Betreuung und Pflege des Alzheimer-Patienten in Anspruch genommen?	☐	1 = nein 2 = ja
Welche professionelle Hilfe wird in Anspruch genommen?	☐ ☐ ☐ _____	1 = ambulante medizinische Pflege 2 = ambulante Hauspflege 3 = Tagespflege 4 = Nachtpflege 5 = ambulante häusliche Betreuung 6 = Betreuungsgruppen 7 = private vergütete Unterstützung 8 = Kurzzeitpflege 9 = sonstige (bitte spezifizieren)
Wer ist für die Arzneimitteltherapie zuständig?	☐	1 = Patient allein 2 = Patient mit Unterstützung durch Angehörigen 3 = Patient mit Unterstützung durch professionelle Pflege/Betreuung 4 = Patient mit Unterstützung durch Angehörigen *und* professionelle Pflege/Betreuung 5 = nur Angehöriger 6 = nur professionelle Pflege/Betreuung
Welchen Schulabschluss haben Sie? (Patient)	☐	1 = kein Abschluss 2 = Volks-, Hauptschulabschluss 3 = mittlere Reife, Realschule oder ähnlicher Abschluss 4 = Polytechnische Oberschule mit 10. Klasse Abschluss (vor 1965: 8. Klasse Abschluss) 5 = Fachhochschulreife, fachgebundene Hochschulreife, Abschluss einer Fachoberschule 6 = Abitur, Allgemeine Hochschulreife, Erweiterte Oberschule

2. Antidementiva

Seit wann wird das Antidementivum (Antidementiva) verschrieben bzw. eingenommen? [Antidementiva: ATC-Code N06D]	☐☐/☐☐	1. Antidementivum (FAM-Name): seit Monat (xx)/Jahr(yy)
	☐☐/☐☐	2. Antidementivum (FAM-Name): seit Monat (xx)/Jahr(yy)

3. Frühere Medikation

Wurden vor dem aktuellen Antidementivum schon weitere Antidementiva eingesetzt?	☐	1 = nein 2 = ja
Wenn ja, welche Antidementiva wurden bereits eingesetzt?		

Studien-Nr.: **Datum:**	**Morisky-Score**	Freie Universität Berlin Abteilung Klinische Pharmazie

Fragen zur Einnahme von Arzneimitteln (Fragebogen für Patienten bzw. Verantwortlichen für Medikamente)

WICHTIG!
Bitte beachten Sie, dass hier Ihre ganz persönliche Meinung gefragt ist und es keine richtigen oder falschen Antworten gibt.
Bitte kreuzen Sie spontan, ohne darüber längere Zeit nachzudenken, immer das Antwortkästchen an, das Ihrer eigenen Meinung am ehesten entspricht.
Bevor Sie mit dem Ausfüllen der Fragebogens beginnen, lesen Sie sich bitte die jeweiligen Fragestellungen genau durch.

Wichtig für alle Angehörigen/Pflegenden von Alzheimer-Patienten: alle Fragen beziehen sich auf das Einnahmeverhalten des Patienten: z.B. Vergisst er/sie manchmal Ihre Medikamente einzunehmen?

Vergessen Sie manchmal Ihre Medikamente einzunehmen?	○	Ja
	○	Nein

Sind Sie manchmal sorglos beim Einnehmen Ihrer Medikamente?	○	Ja
	○	Nein

Wenn Sie sich besser fühlen, nehmen Sie dann manchmal keine Medikamente?	○	Ja
	○	Nein

Wenn Sie sich manchmal nach Einnahme Ihrer Medikamente schlechter fühlen, hören Sie dann damit auf?	○	Ja
	○	Nein

Studien-Nr.: **Datum:**	**Wissen zur Arzneimitteltherapie**	Freie Universität Berlin Abteilung Klinische Pharmazie

Wissen zur Arzneimitteltherapie (Interview durch wissenschaftlichen Mitarbeiter)

Wer ist für die richtige Anwendung von Medikamenten beim Patienten zuständig?	☐	1 = Patient alleine 2 = Patient mit Unterstützung des Angehörigen 3 = nur Angehöriger

Wer wird zu Indikation und Einnahme im Verhältnis zu einer Mahlzeit befragt?	☐	1 = Patient 2 = Angehöriger *wichtig: derselben Person auch den Fragebogen Morisky-Score vorlegen!*

1. Patienten bitten, bei der Befragung nicht in Packungsbeilage zu schauen *2. AM-Packung bei Befragung immer in die Hand nehmen* *3. Wenn der Patient dennoch in Packungsbeilage schaut, dann „weiß nicht" angeben* *4. Wenn der Patient keine Antwort weiß, dann „weiß nicht" angeben*		**Einnahme im Verhältnis zu einer Hauptmahlzeit**		
FAM (Wirkstoff)	**Wofür oder wogegen wird dieses Medikament eingesetzt?**[1]	**Wann nehmen Sie das Medikament ein?** **Nehmen Sie es zum Frühstück/Mittagessen/Abendessen ein?** **Wie lange davor?** **Wie lange danach?**		
		Auf nüchternen Magen (1/2 – 1h vor dem Essen oder mindestens 2 h nach dem Essen)	**Zu oder unmittelbar nach dem Essen**	**Mal nüchtern, mal zum Essen**
		☐	☐	☐
		☐	☐	☐
		☐	☐	☐

[1] Bitte immer genau den Wortlaut des Patienten bzw. Angehörigen aufschreiben!

1. Patienten bitten, bei der Befragung nicht in Packungsbeilage zu schauen *2. AM-Packung bei Befragung immer in Hand nehmen* *3. Wenn der Patient dennoch in Packungsbeilage schaut, dann „weiß nicht" angeben* *4. Wenn der Patient keine Antwort weiß, dann „weiß nicht" angeben*		**Einnahme im Verhältnis zu einer Hauptmahlzeit**		
FAM (Wirkstoff)	**Wofür oder wogegen wird dieses Medikament eingesetzt?**[1]	**Wann nehmen Sie das Medikament ein?** **Nehmen Sie es zum Frühstück/Mittagessen/Abendessen ein?** **Wie lange davor?** **Wie lange danach?**		
		Auf nüchternen Magen (1/2 – 1h vor dem Essen oder mindestens 2 h nach dem Essen)	**Zu oder unmittelbar nach einer Hauptmahl-zeit**	**Mal nüchtern, mal zum Essen**
		☐	☐	☐
		☐	☐	☐
		☐	☐	☐
		☐	☐	☐
		☐	☐	☐
		☐	☐	☐
		☐	☐	☐
		☐	☐	☐
		☐	☐	☐

Kommentare zur Befragung (z.B. Angehöriger hat sich bei Befragung nicht an Regeln gehalten und hat in die Packungsbeilagen angeguckt; Packungen sind nicht vorhanden)

[1] Bitte immer genau den Wortlaut des Patienten aufschreiben!

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„Pilot-Projekt zur Pharmazeutischen Betreuung von Alzheimer-Patienten und ihren Angehörigen in der ambulanten Therapie“

Fragebogen zum Wissen in der Arzneimitteltherapie (Version 1)

Inhalt

Kurzinformation zum Pilot-Projekt

Fragebogen

Datum:

Apothekerin:

Freie Universität Berlin

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Kurzinformation zum „Pilot-Projekt zur Pharmazeutischen Betreuung von Alzheimer-Patienten und ihren Angehörigen in der ambulanten Therapie“

‘Pharmazeutische Betreuung’ wird definiert als „die konsequente Wahrnehmung der Mitverantwortung des Apothekers bei der Arzneimitteltherapie mit dem Ziel, bestimmte therapeutische Ergebnisse zu erreichen, die die gesundheitsbezogene Lebensqualität des Patienten verbessern“. In Deutschland sind bereits eine Reihe von wissenschaftlichen Projekten zur Pharmazeutischen Betreuung, vor allem bei chronischen Erkrankungen, durchgeführt worden (z.B. Diabetes mellitus und Asthma bronchiale). Verschiedene Studien zur intensivierten pharmazeutischen Betreuung konnten zeigen, dass sich mit dieser Dienstleistung relevante positive Effekte auf ökonomische, klinische und humanistische Outcomes erzielt werden konnten. Keines der bisher in Deutschland durchgeführten Projekte hat sich mit der Pharmazeutischen Betreuung von Alzheimer-Patienten und ihren Angehörigen befasst und folglich ist die Rolle des Apothekers in der Betreuung von Alzheimer-Patienten noch kaum erforscht. Er hat jedoch die Möglichkeit, durch vielfältige Anknüpfungspunkte, zusammen mit Betroffenen, Angehörigen, Pflegepersonal, Selbsthilfegruppen und Ärzten zur Optimierung der Arzneimitteltherapie bei Alzheimer-Patienten beizutragen.

Ziel des geplanten Pilot-Projektes ist, in einer ersten Untersuchung Grundlagen und Ansätze eines Pharmazeutischen Betreuungskonzeptes für Alzheimer-Patienten und ihre Angehörigen zu entwickeln. Im Rahmen der Studie (Dauer: 7 Monate) soll dabei der Einfluss der intensivierten Pharmazeutischen Betreuung im Vergleich zu einer Standardbetreuung auf die Compliance des Patienten in der Antidementivatherapie (primäre Zielgröße) und weitere Zielgrößen untersucht werden.

Eine wichtige Zielgröße ist der Wissenstand des Patient bzw. des Angehörigen zur Arzneimitteltherapie. Für die Behandlung der kognitiven Symptomatik bei

Alzheimer-Demenz stehen mehrere Arzneistoffklassen zu Verfügung: Cholinesterase-Inhibitoren, der NMDA-Rezeptor-Antagonist Memantin und weitere Substanzen, die unter dem Begriff Nootropika zusammengefasst werden. Wir möchten aber nicht nur den Wissenstand zur Antidementivatherapie untersuchen, sondern zur gesamten Therapie der Patienten, um einen globalen Eindruck zum Wissenstand zu bekommen. Der Wissenstand wird zu zwei Zeitpunkte durchgeprüft; zu Beginn **(T1)** und am Ende der Studie (**T2**, sechs Monate später).
Vielen Dank, dass Sie uns bei der Auswertung unterstützen.

Studien-Nr.: **Datum:**	**Wissen zur Arzneimitteltherapie (Version 1)**	Freie Universität Berlin Abteilung Klinische Pharmazie

Aussage von Patienten über die eigene Therapie.

Hinweise zum Ausfüllen des Fragebogens:

- Verwenden Sie bitte nur Kugelschreiber (keinen Bleistift).
- Kreuzen Sie die Kästchen deutlich an: ☒. Bei versehentlicher Falschauswahl füllen Sie bitte das entsprechende Kästchen ganz aus ■ und kreuzen Ihre Auswahl erneut an ☒
- Kreuzen Sie immer nur **EINE** von den 5 Möglichkeiten an.
- Geben Sie bitte Freitextangaben in Druckbuchstaben an.

1. Inwieweit stimmen Sie der Aussage des Patienten zur Indikation des Fertigarzneimittels zu?

Fertigarzneimittel (Wirkstoff)	**Indikation nach Fachinformation**	**Indikation nach Aussage des Patienten**	**Bewertung des Apothekers**				
			Stimme voll zu	Stimme teil-weise zu	Stimme teil-weise nicht zu	Stimme gar nicht zu	Nicht beurteil-bar
Metoprolol 50 mg Tabletten	Hypertonie. Angina pectoris. Hyperkinetisches Herzsyndrom. Tachykarde Arrhythmien. Langzeitbehandlung nach Herzinfarkt. Migräneprophylaxe. Stabile chronische gering bis mäßig ausgeprägte Herzinsuffizienz bei eingeschränkter systolischer Ventrikelfunktion.	gegen hohen Blutdruck	☐	☐	☐	☐	☐
Aquaphor® 10 Tabletten (Xipamid)	Arterielle Hypertonie. Kardiale, renale und hepatogene Ödeme.	gegen hohen Blutdruck	☐	☐	☐	☐	☐
Captopril 50 Tabletten	Hypertonie. Herzinsuffizienz.	gegen hohen Blutdruck	☐	☐	☐	☐	☐
Aricept® 10 mg Filmtabletten (Donepezil)	Indiziert zur symptomatischen Behandlung der leichten bis mittelschweren Alzheimer-Demenz.	gegen Depression	☐	☐	☐	☐	☐

1. Inwieweit stimmen Sie der Aussage des Patienten zur Indikation des Fertigarzneimittels zu?

Fertigarzneimittel (Wirkstoff)	**Indikation nach Fachinformation**	**Indikation nach Aussage des Patienten**	**Bewertung des Apothekers**				
			Stimme voll zu	Stimme teil-weise zu	Stimme teil-weise nicht zu	Stimme gar nicht zu	Nicht beurteil-bar
Allopurinol 300 mg Tabletten	Alle Formen der Hyperurikämie	urologische Tablette	☐	☐	☐	☐	☐
Mirtazapin 15 mg Filmtabletten	Depressive Erkrankungen.	zum Einschlafen	☐	☐	☐	☐	☐
Cipramil 20 mg (Citalopram)	Behandlung depressiver Erkrankungen und Panikstörungen mit und ohne Agoraphobie.	gegen Depression	☐	☐	☐	☐	☐

2. Inwieweit stimmen Sie der Aussage des Patienten zur Einnahme des Fertigarzneimittels im Verhältnis zu einer Mahlzeit zu?

Fertigarzneimittel (Wirkstoff)	**Einnahmehinweis nach Fachinformation**	**Einnahme nach Aussage des Patienten**				**Bewertung des Apothekers**				
		(0.5 h-1.0 h) vor oder zwischen den Haupt-mahlzeiten	**Zu oder unmittelbar nach einer Hauptmahl-zeit**	**Unter-schiedlich**	**Keine Angabe**	Stimme voll zu	Stimme teil-weise zu	Stimme teil-weise nicht zu	Stimme gar nicht zu	Nicht beurteil-bar
Metoprolol 50 mg Tabletten	Es kann unabhängig von den Mahlzeiten eingenommen werden.	☐	☒	☐	☐	☐	☐	☐	☐	☐
Aquaphor® 10 Tabletten (Xipamid)	Die Tabletten am besten morgens nach dem Frühstück einzunehmen.	☒	☐	☐	☐	☐	☐	☐	☐	☐
Captopril 50 Tabletten	Kann vor, während und nach den Mahlzeiten eingenommen werden.	☐	☐	☐	☒	☐	☐	☐	☐	☐
Aricept® 10 mg Filmtabletten (Donepezil)	Sollte am Abend kurz vor dem Schlafen-gehen	☐	☐	☐	☒	☐	☐	☐	☐	☐

2. Inwieweit stimmen Sie der Aussage des Patienten zur Einnahme des Fertigarzneimittels im Verhältnis zu einer Mahlzeit zu?

Fertigarzneimittel (Wirkstoff)	**Einnahmehinweis nach Fachinformation**	**Einnahme nach Aussage des Patienten**				**Bewertung des Apothekers**				
		(0.5 h-1.0 h) vor oder zwischen den Haupt-mahlzeiten	**Zu oder unmittelbar nach einer Hauptmahl-zeit**	**Unter-schiedlich**	**Keine Angabe**	Stimme voll zu	Stimme teil-weise zu	Stimme teil-weise nicht zu	Stimme gar nicht zu	Nicht beurteil-bar
	eingenommen werden.									
Allopurinol 300 mg Tabletten	Die Tabletten werden nach einer Mahlzeit eingenommen.	☐	☐	☐	☒	☐	☐	☐	☐	☐
Mirtazapin 15 mg Filmtabletten	Als Einmaldosis am Abend vor dem Schlafengehen. Als zwei Einzeldosen, am Morgen und am Abend.	☐	☐	☐	☒	☐	☐	☐	☐	☐

3. Wie hoch schätzen Sie den Beratungsbedarf des Patienten ein?

Sehr hoch	Hoch	Mittel	Niedrig	Sehr niedrig
☐	☐	☐	☐	☐

4. Haben Sie weitere Anmerkungen zu diesem Patienten?

Wissen zur Arzneimitteltherapie

(Version 2)

CLINICAL PHARMACY

Hinweise zum Ausfüllen des Fragebogens

Anders als in der vorherigen Version ist dieser Fragebogen nicht nach Patient, sondern *nach Arzneistoff gegliedert.*	Acetylsalicylsäure . . . Vitamin B12
In bestimmten Fällen werden in der dritten Spalte (Indikation nach Roter Liste) aus Gründen der Übersichtlichkeit nur Auszüge wiedergegeben. Auslassungen sind mit „…“ gekennzeichnet.	Primäre Hyperlipoproteinämien … Sekundäre Hyperlipoproteinämie …
Die Aussagen der Patienten können Sie auf einer *vierstufigen Skala* bewerten. Die Antwortmöglichkeiten reichen von „stimme voll zu“ bis „stimme gar nicht zu“. Die beiden mittleren Antwortmöglichkeiten lassen eine Abstufung zu.	**Stimme voll zu** … **Stimme gar nicht zu** 3 2 1 0
Verwenden Sie bitte zum Ankreuzen nur Kugelschreiber (keinen Bleistift).	☒
Kreuzen Sie bitte immer nur EINE von den 5 Möglichkeiten an.	☐ ☐ ☐ ☒ ☐
Bei versehentlicher Falschauswahl füllen Sie bitte das entsprechende Kästchen ganz aus und markieren Sie Ihre neue Auswahl mit einem Kreuz.	■ ☒ ☐ ☐ ☐

Falls Sie Fragen oder Anmerkungen haben, erreichen Sie den zuständigen wissenschaftlichen Mitarbeiter Dipl.-Pharm. Oliver Schwalbe unter:

Telefon	(030) 838 50626 oder (0172) 808 43 03
Telefax	(030) 838 50711
Email	oschwalb@zedat.fu-berlin.de

Noch einmal herzlichen Dank für Ihre Mitarbeit und viel Spaß beim Ausfüllen des Fragebogens!

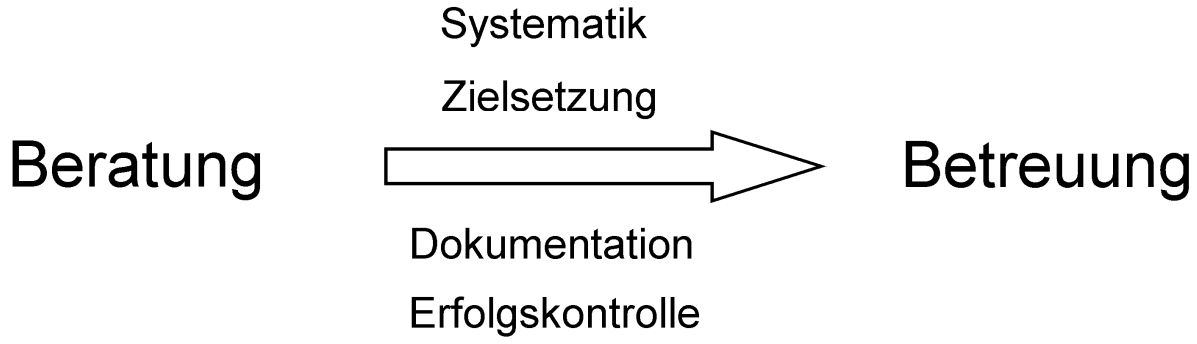
Inwieweit stimmen Sie der Aussage des Patienten zur Indikation des Arzneimittels zu?

N	Fertigarzneimittel (Wirkstoff)	Indikation nach Roter Liste	Indikation nach Aussage des Patienten	Stimme voll zu … Stimme gar nicht zu 3 2 1 0	Kann ich nicht beurteilen
13	ASS 100 (Acetylsalicylsäure)	Instabile Angina pectoris, akuter Myokardinfarkt, Reinfarktprophylaxe, nach arteriellen gefäßchirurg. od. interventionellen Eingriffen (z. B. nach ACVB, b. PTCA), Vorbeugung v. transitor. ischäm. Attacken (TIA) u. Hirninfarkten, nachdem Vorläuferstadien aufgetreten sind.	Blutverdünnung	☐ ☐ ☐ ☐	☐
23	ASS 100 mg 1A Pharma (Acetylsalicylsäure)	Siehe oben	ganz allgemein fürs Herz	☐ ☐ ☐ ☐	☐
45	Herz ASS ratiopharm 100 mg (Acetylsalicylsäure)	Siehe oben	Herz	☐ ☐ ☐ ☐	☐
73	Godamed 100 TAH (Acetylsalicylsäure)	Siehe oben	Verhütung Herzinfarkt	☐ ☐ ☐ ☐	☐
82	Godamed 100 TAH (Acetylsalicylsäure)	Siehe oben	Infarktvermeidung	☐ ☐ ☐ ☐	☐

Durchführbarkeit der Pharmazeutischen Betreuung von Alzheimer-Patienten und ihrer Angehörigen

Information und Beratung zu Arzneimitteln wird durch folgende Voraussetzungen erst zur Pharmazeutischen Betreuung: **Systematik, patientenbezogene Dokumentation, Zielsetzung und Erfolgskontrolle (Monitoring)**. Pharmazeutische Betreuung muss System haben, so z.B., wenn systematisch der Verbrauch an schnellwirksamen Betasympathomimetika von Asthma-Patienten aus der Patientendatei analysiert wird und anschließend dieser Sachverhalt mit dem Patienten abgeklärt wird. System liegt auch vor, wenn die Antidementiva-Dosierungen von Alzheimer-Patienten überprüft und bei zu niedriger Dosierung Rücksprache mit dem Arzt genommen wird. System bedeutet auch nachvollziehbare und qualitätsgesicherte Prozesse zu haben, welche Kostenträger auch leichter von einer angemessenen Honorierung überzeugen können.

Ein wichtiges Werkzeug zur Umsetzung der pharmazeutischen Betreuung ist die patientenbezogenen Dokumentation. Diese umfasst vor allem das Führen einer Patientendatei unter Einschluss der aktuellen Medikation mit Dosierungen, Grunderkrankungen, Arzneimittelunverträglichkeiten und arzneimittelbezogenen Problemen. Softwaremodule zur pharmazeutischen Betreuung sind bereits vorhanden. Die Dokumentation stellt eine Grundvoraussetzung dar, um im Rahmen der pharmazeutischen Betreuung effektiv die Qualität der Arzneimitteltherapie zu optimieren. Pharmazeutische Betreuung ist als Prozess zu sehen mit Zielstellung, Erfolgskontrolle (Monitoring) und gegebenenfalls Anpassung. Bei Erstverordnung eines Bluthochdruck-Arzneimittels werden dem Patienten das Ziel und weitere wichtige Aspekte der durchgeführten Arzneimitteltherapie erklärt, das Blutdruckmessgerät erläutert und nach zehn Tagen ein Feedback-Telefonat vereinbart, um nach der Verträglichkeit des Arzneimittels und der Blutdruckeinstellung zu fragen.



Im folgenden Teil möchten wir Ihre Erfahrungen im Pilot-Projekt sammeln. Bitte antworten Sie möglichst ausführlich und erwähnen Sie alle notwendigen Details des Patientenfalls/der Patientenfälle. Falls der Platz nicht ausreicht, bitte die Rückseite benutzen.

Schildern Sie bitte Ihre Erfahrungen bei der Patientenrekrutierung. Worin lagen Schwierigkeiten, Patienten/Angehörige für das Pilot-Projekt zu gewinnen? Warum wollten manche Patienten nicht am Pilot-Projekt teilnehmen?

Im folgenden Teil möchten wir Ihre Erfahrungen im Pilot-Projekt sammeln. Bitte antworten Sie möglichst ausführlich und erwähnen Sie alle notwendigen Details des Patientenfalls/der Patientenfälle. Falls der Platz nicht ausreicht, bitte die Rückseite benutzen.

Beschreiben Sie Erfahrungen, bei denen Sie das Gefühl hatten, mit Ihrer Pharmazeutischen Betreuungstätigkeit besonders erfolgreich gewesen zu sein.

Im folgenden Teil möchten wir Ihre Erfahrungen im Pilot-Projekt sammeln. Bitte antworten Sie möglichst ausführlich und erwähnen Sie alle notwendigen Details des Patientenfalls/der Patientenfälle. Falls der Platz nicht ausreicht, bitte die Rückseite benutzen.

Schildern Sie bitte Gegebenheiten, wo Sie Schwierigkeiten mit der Umsetzung der Pharmazeutischen Betreuung hatten? Wo sind Sie nicht weiter gekommen? Was waren die Ursachen dafür?

Im folgenden Teil möchten wir Ihre Erfahrungen im Pilot-Projekt sammeln. Bitte antworten Sie möglichst ausführlich und erwähnen Sie alle notwendigen Details des Patientenfalls/der Patientenfälle. Falls der Platz nicht ausreicht, bitte die Rückseite benutzen.

Platz für weitere Anmerkungen zum Pilot-Projekt

Pharmazeutische Anamnese		
	Alter	Geburtsdatum
	Gewicht	Größe
Demographie	Beruf	Geschlecht M/W
	Lebensumstände (z.B. Leben Patient und Angehöriger zusammen? Wer von beiden ist für die Arzneimitteltherapie zuständig?)	

Arzneimittel-Erfahrung	Wie steht der Patient generell zur Einnahme von Arzneimitteln?	Weitere Betreuung auf dem Gebiet nötig	
		Ja	Nein
	Was will/erwartet der Patient von seiner Arzneimitteltherapie?	Weitere Betreuung auf dem Gebiet nötig	
		Ja	Nein
	Welche Bedenken hat der Patient bei der Einnahme seiner Arzneimittel?	Weitere Betreuung auf dem Gebiet nötig	
		Ja	Nein
	Wie groß ist ihrer Meinung nach das Wissen des Patienten zu seinen Arzneimitteln?	Weitere Betreuung auf dem Gebiet nötig	
		Ja	Nein
	Gibt es kulturelle, religiöse oder ethische Gesichtspunkte, welche die Bereitschaft des Patienten zur Arzneimitteleinnahme beeinflussen?	Weitere Betreuung auf dem Gebiet nötig	
		Ja	Nein
	Beschreiben Sie die Einnahmegewohnheiten des Patienten.	Wichtig für weitere Betreuung	
		Ja	Nein

	Substanz	Verbrauch	Substanz	Verbrauch
Genussmittel und Drogen	Tabak □ Kein Tabakkonsum	□ 0-1 Packungen pro Tag □ > 1 Packung pro Tag □ ehemaliger Raucher □ versucht aufzuhören	Alkohol □ Kein Alkoholkonsum	□ > 2 Getränke pro Woche □ 2-6 Getränke pro Woche □ > 6 Getränke pro Woche □ Alkoholab-hängigkeit
	Koffein □ Kein Koffeinkonsum	□ < 2 Tassen pro Tag □ 2-6 Tassen pro Tag □ > 6 Tassen pro Tag □ Koffeinabhängigkeit	Weiterer Drogenkonsum	

Allergien und UAWs	Arzneimittelallergien (Wirkstoff, Zeitpunkt, Wirkung – Hautausschlag, Schock, Asthma, Übelkeit, Anämie)
	Arzneimittelunverträglichkeiten in der Vergangenheit

Aktuelle Medikation (verschreibungspflichtige und nicht-verschreibungspflichtige Arzneimittel, Vitamine, Nahrungsergänzungs- und Aufbaumittel)					
an	**ab**	**Arzneimittel (Wirkstoff)**	**Indikation**	**Dosierung**	**Bemerkungen**
03/06		Exelon® 6 mg Tabs (Rivastigmin)	Alzheimer-Demenz	1-0-1	Gutes Therapieansprechen bisher

Medikationshistorie (verschreibungspflichtige und nicht-verschreibungspflichtige Arzneimittel, Vitamine, Nahrungsergänzungs- und Aufbaumittel) der letzten 6 Monate					
an	**ab**	**Arzneimittel (Wirkstoff)**	**Indikation**	**Dosierung**	**Bemerkungen**
03/02	04/06	Exelon® 6 mg Tabs (Rivastigmin)	Alzheimer-Demenz	1-0-1	Gutes Therapieansprechen bisher

Grunderkrankungen (zur Unterstützung Review of Systems)

Unterschrift der/des durchführenden Apotheker/in: _____

Datum: _____

Erkrankungstabelle

Allgemeines	○	Appetitlosigkeit		**Urogenitaltrakt**	○	Regelbeschwerden
	○	Gewichts-veränderungen			○	Inkontinenz
	○	Schmerzen			○	Impotenz
	○	Schwindel			○	Verringerter Libido
Augen, Ohren, Nase, Hals	○	Sehstörung			○	Vermehrter Vaginal-Ausfluss oder Juckreiz
	○	Herabgesetztes Hörvermögen			○	Hitzewallungen
	○	Ohrgeräusche (Tinnitus)			○	Häufige Blasenentleerung
	○	Nasenbluten			○	Blutiger Urin
	○	Heuschnupfen			○	Niereninsuffizienz
	○	Glaukom		**Blut**	○	Viele Blutergüsse
	○	Blutigen Auswurf			○	Blutungen
Herz-Kreislauf-System	○	Schmerzen im Brustkorb			○	Anämie
	○	Fettstoffwechsel-störungen (Hyperlipidämie)		**Rumpf und Muskulatur**	○	Rückenschmerzen
	○	Bluthochdruck			○	Rheumatoide Arthritis, Osteoarthritis
	○	Herzinfarkt			○	Muskelschmerz
	○	Orthostatische Beschwerden		**Neurologie, Psychiatrie**	○	Kribbeln oder taubes Gefühl in den Extremitäten (Parästhesie)
Lunge	○	Asthma			○	Zittern (Tremor)
	○	Atemlosigkeit			○	Schwindel
	○	Keuchen, Pfeifende Atmung			○	Depression
Gastrointestinal-trakt	○	Sodbrennen			○	Selbstmordabsichten
	○	Oberbauchschmerzen			○	Angst, Nervosität
	○	Übelkeit			○	Konzentrationsstörung
	○	Erbrechen			○	Krämpfe
	○	Durchfall			○	Schlaganfall, transitorische ischämische Attacke
	○	Verstopfung			○	Gedächtnisstörungen
Haut	○	Ekzem/Psoriasis		**Infektionen**	○	HIV/AIDS
	○	Juckreiz (Pruritus)			○	Malaria
	○	Hautausschlag			○	Syphilis
Endokrines System	○	Diabetes			○	Gonorrhö
	○	Schilddrüsen-unterfunktion			○	Herpes
	○	Wechseljahres-beschwerden			○	Chlamydia
Leber	○	Cirrhose			○	Tuberculosis
	○	Hepatitis				
Ernährung/Flüssig-keit/Elektrolyte	○	Dehydratation				
	○	Ödeme				
	○	Kaliummangel				

Unterschrift der/des durchführenden Apotheker/in: _____

Erläuterungen zur Erkrankungstabelle

- Durch die Fragen der Erkrankungstabelle lassen sich Symptome des Patienten aufspüren, die mit der Einnahme von Arzneimitteln zusammenhängen können.
- Dem Patienten gegenüber verdeutlichen, dass die folgenden Fragen dazu dienen, nichts Wichtiges auszulassen und „das Bild“ zu vervollständigen
- Die folgenden Fragen dienen zur Unterstützung und können in dieser oder ähnlicher Form dem Patienten gestellt werden

Augen, Ohren, Nase, Hals

- Haben Sie irgendwelche Beschwerden mit Ihren Augen oder Ihrer Sehkraft?
- Tragen Sie eine Brille oder Kontaktlinsen?
- Haben Sie Beschwerden mit Ihren Kontaktlinsen?
- Sind Sie derzeit in Behandlung wegen Glaukom, Augeninfektionen, Ohrenschmerzen, Fieber oder Zahnschmerzen?
- Haben Sie derzeit Husten, Schnupfen, Halsschmerzen, Nasennebenhöhlenentzündung oder Heuschnupfen?

Kardiovaskuläres System

- Haben Sie jemals irgendwelche Herzbeschwerden gehabt: Herzrhythmusstörungen, Schmerzen im Brustkorb, Schwindelgefühl, Blutdruckprobleme?
- Wie war Ihr Blutdruck bei der letzten Messung?
- Wurde Ihr Cholesterol-Spiegel jemals gemessen? Wie hoch war er beim letzten Mal?

Lunge

- Haben Sie irgendwas mit der Lunge?
- Sind Sie kurzatmig oder haben Atemnot?

Gastrointestinales System

- Haben Sie Beschwerden mit Ihrem Magen, Sodbrennen, Gastritis oder Magengeschwüre?
- Haben Sie Bauchschmerzen, Probleme mit dem Darm, Übelkeit, Durchfall oder Erbrechen?

Haut

- Haben Sie irgendwelche Beschwerden mit Ihrer Haut?
- Haben Sie Juckreiz, Ausschlag, Akne, Ekzeme oder Bläschen auf der Haut?
- Benutzen Sie lokal wirkende Arzneimittel wie Salben oder Cremes?

Endokrines System

- Haben Sie irgendwelche Beschwerden mit der Schilddrüse?
- Wurde Ihr Blutzucker jemals überprüft?
- Wurde Ihnen jemals gesagt, dass Ihr Blutzucker zu hoch ist und dass Sie Diabetes haben

Urogenitaltrakt

- Haben Sie Probleme bei Wasserlassen?
- Irgendwelche Schmerzen dabei oder Verfärbungen des Urins?
- Haben Sie Pilzinfektionen, Regelbeschwerden oder Harnwegsinfektionen?
- Was machen Sie zur Osteoporoseprophylaxe?
- Wurde kürzlich ein Prostata-Test durchgeführt?

- Manche Leute, die dieses Arzneimittel einnehmen beobachten Veränderungen in Ihre Sexualität; haben Sie Veränderungen wahrgenommen?

Nieren
- Haben Sie Probleme mit Ihren Nieren?
- Wurde Ihnen jemals gesagt, dass Sie an einer Nierenerkrankung leiden?

Leber
- Haben Sie jemals Zeichen einer Gelbsucht an Siech bemerkt, wie Gelbfärbung von Augen und Haut?

Blut
- Bekommen Sie leicht „blaue Flecke“
- Wurde Ihnen jemals gesagt, dass Sie Anämie haben?
- Nehmen Sie Eisen-Tabletten ein?
- Nehmen Sie regelmäßig Folsäure ein?

Rumpf und Muskulatur
- Haben Sie irgendwelche Probleme mit Gelenken und ihrer Muskulatur?
- Haben Sie ausreichend Bewegung?
- Schmerzen, Schwellungen oder Druckschmerz?
- Leiden Sie unter Arthritis?
- Was für Arzneimittel nutzen Sie für leichte Schmerzen?

Neurolgie
- Irgendwelche Beschwerden mit Schwäche, Benommenheit, Kribbeln oder beim Laufen?
- Hatten Sie schon einmal Krampfanfälle?
- Gedächtnisprobleme?

Psychiatrie
- Irgendwelche Probleme mit Angstzuständen, Stimmung, Depression, Panikattacken oder Konzentration
- Was machen Sie zur Bewältigung des täglichen Stresses?

Informationen zu Ihren Arzneimitteln

Name:	Datum:

Hinweise zur Benutzung der Tabelle

- Diese Tabelle zeigt Ihnen, zu welchen Zeitpunkten Sie Ihre Arzneimittel am besten einnehmen oder anwenden
- Arzneimittel, bei denen eine nüchterne Einnahme erforderlich ist (1 h vor oder 2 h nach dem Essen), sind mit einem Stern (*) gekennzeichnet. Wichtige Hinweise werden in der Fußnote gegeben.
- Arzneimittel zur Einnahme bei Bedarf sind **nicht** in der Tabelle aufgeführt

Arzneimittel	Frühstück	Mittagessen	Abendessen	Schlafenszeit

Studien-Nr.: _____ Datum: _____	**Arzneimittel-Check** **Dosierungs-Check** **Kontraindikations-Check** **Interaktions-Check**	CLINICAL PHARMACY

Arzneimittel-Check

○	Prüfung auf abweichende Verordnungen (z.B. Namensverwechslungen)
○	Prüfung auf (Pseudo-) Doppelverordnungen (anhand des Medikationsprofils)
○	Prüfung auf Zugehörigkeit zur Beers-Liste
○	Prüfung auf Arzneimittel mit ausgeprägten anticholinergen Eigenschaften (Anticholinergic Drug Scale – Level 3)

Dosierungs-Check

○	Prüfung auf Unter-, Über- oder Fehldosierung (z.B. über ABDA-Datenbank)

Kontraindikations-Check

○	Prüfung auf Kontraindikationen (z.B. mittels der CAVE-Module)

Interaktions-Check

○	Prüfung auf Interaktionen (z.B. über automatisierten Interaktions-Check der ABDA-Datenbank)

Compliance-Check

○	Prüfung auf Non-Compliance (anhand des Medikationsprofils)

Studien-Nr.: _____ Datum: _____	**Information und Beratung im Rahmen der Pharmazeutischen Betreuung nach BAK-Leitlinie (modifiziert)**	CLINICAL PHARMACY

Angaben zum Arzneimittel

○	Erstverordnung (Erstgebrauch in der Selbstmedikation)	○	Wiederholungsverordnung (Wiederholungsgebrauch in der Selbstmedikation)
Handelsname®: _____		Darreichung: _____	
Wirkstoff(e): _____		Stärke: _____	

1. Inhaltliche Prüfung der Verordnung

	Erstverordnung		**Wiederholungsverordnung**
○	Prüfung der Indikation („Wofür nehmen Sie dieses Arzneimittel ein?“)	○	Prüfung auf Interaktionen (z.B. über automatisierten Interaktionscheck)
○	Prüfung auf Kontraindikation (z.B. mittels der CAVE-Module)	○	Prüfung auf (Pseudo-) Doppelverordnungen (anhand des Medikationsprofils)
○	Prüfung auf Interaktionen (z.B. über automatisierten Interaktionscheck)	○	Prüfung auf Über-, Unter- oder Fehldosierung (z.B. über ABDA-Datenbank)
○	Prüfung auf (Pseudo-) Doppelverordnungen (anhand des Medikationsprofils)	○	Prüfung auf Non-Compliance (anhand des Medikationsprofils)
○	Prüfung auf Über-, Unter- oder Fehldosierung (z.B. über ABDA-Datenbank und Medikationsprofil)		
○	Prüfung auf Zugehörigkeit zur Beers-Liste (siehe Anhang)		
○	Prüfung auf Arzneimittel mit ausgeprägten anticholinergen Eigenschaften (Anticholinergic Drug Scale – Level 3) (siehe Anhang)		

2. Informations- und Beratungsinhalte

	Erstverordnung		**Wiederholungsverordnung**
○	Orientierende Fragen (z.B. Einschätzung Krankheit aus eigener Sicht oder Wissensstand über die bisher durchgeführte Therapie)	○	Orientierende Fragen (z.B. Wirksamkeit und Verträglichkeit des Arzneimittels hinterfragen)
○	Basisinformationen zur Dosierung, Anwendung und Anwendungsdauer	○	nachfragen, ob weiterer Informationsbedarf zur Dosierung und Anwendung des Arzneimittels besteht.
○	Erläuterung von Wirkungen und Nutzen des Arzneimittels	○	Dem Informationsbedarf des Patienten entsprechend, Erläuterung von Wirkungen und Nutzen des Arzneimittels
○	Information über unerwünschte Arzneimittelwirkungen (*häufige* und *relevante*) und resultierende Handlungskonsequenzen	○	Dem Informationsbedarf des Patienten entsprechend, Information über unerwünschte Arzneimittelwirkungen (*häufige* und *relevante*) und resultierende Handlungskonsequenzen
○	Erklärung der korrekten Anwendung und Lagerung des Arzneimittels	○	Dem Informationsbedarf des Patienten entsprechend, Hinweis auf korrekte Anwendung und Lagerung des Arzneimittels
○	Individualisierte schriftliche Patienteninformation	○	Individualisierte schriftliche Patienteninformation
○	Unterstützende Maßnahmen (z.B. Aufkleber, weitere Informationsmaterialien, Zusatzempfehlungen)	○	Unterstützende Maßnahmen (z.B. Aufkleber, weitere Informationsmaterialien, Zusatzempfehlungen)
○	Follow-up-Telefonat		
		○	MEMS®-Compliance-Beratung
○	Aktualisierung des Dosierungsplans	○	Aktualisierung des Dosierungsplans

Unterschrift der/des durchführenden Apotheker/in: _____

Datum: _____

Studien-Nr.: _____ Datum: _____	**MEMS®-Compliance-Beratung**	CLINICAL PHARMACY

Besprechung der MEMS®-Daten mit dem Patienten/Angehörigen

Vor der Besprechung der MEMS®-Daten den Patienten/Angehörigen fragen, was er/sie erwartet, was die Daten des elektronischen Arzneimittelverbrauchsmonitor zeigen werden.

Hilfreiche Fragen in der Diskussion der MEMS®-Daten:

- Verbinden Sie die Einnahme von Arzneimitteln mit einer täglichen Tätigkeit? Weiterführende Frage: Wie haben Sie die Einnahme Ihrer Arzneimittel in den Ferien (oder an den Wochenenden oder an einem bestimmten Wochentag) organisiert?
- Sehen Sie bestimmte Muster, wann Sie Ihr Arzneimittel nicht eingenommen haben (z.B. am Wochenende, morgens, Sonntagmorgen)? Gibt etwas, was es zu diesen Zeiten schwierig macht, Ihre Arzneimittel einzunehmen?
- An diesem Morgen haben Sie Ihr Arzneimittel nicht eingenommen. Die folgenden Dosen haben Sie auch nicht eingenommen. Können Sie sich erinnern, was an diesem Tag passiert ist?

Strategien zur Optimierung der Compliance

- Verbinden der Einnahme von Arzneimitteln mit täglichen Vorgängen oder Tätigkeiten: z.B. Mahlzeit, Zähne-Putzen, spezifische Uhrzeit

Notizen:

AARDEX Ltd. **PowerView** **Compliance Bericht**

Patientennummer:	**S09**	Patienteninitialen:	
Patientenname:		Monitor-Nummer:	**203200**
Arzt:		Medikament:	**Ebixa**
Dosierung:	**Zweimal pro Tag**		

Resultate: **20/05/2006 03:00 bis 16/11/2006 02:59 (9)**		Anzahl beobachteter Tage:	**180**
Anzahl eingenommener Dosen:	**274**	Kürzester Intervall (Std):	**0.3**
Längster Intervall (Std):	**97.4**	% verschr. Anzahl Dosen eingenommen:	**76.1%**
% Tage mit korrekter Anzahl Dosen:	**48.3%**	% Dosen im richtigen Intervall:	**21.2%**
Therapeutische Deckung:	**90.4%**	Wirkungsdauer (in Stunden):	**24.0**
Anzahl verschriebene Dosis:	**360**		

Mai 2006

Mon	Die	Mit	Don	Fre	Sam	Son
					20 2	21 2
22 2	23 3	24 1	25 2	26 2	27 1	28 2
29 2	30 1	31 0				

Juni 2006

Mon	Die	Mit	Don	Fre	Sam	Son
			1 1	2 1	3 2	4 2
5 2	6 1	7 2	8 1	9 2	10 1	11 2
12 1	13 1	14 3	15 2	16 2	17 2	18 1
19 2	20 2	21 2	22 2	23 1	24 2	25 2
26 2	27 1	28 2	29 2	30 1		

Juli 2006

Mon	Die	Mit	Don	Fre	Sam	Son
					1 1	2 2
3 2	4 1	5 2	6 2	7 2	8 1	9 2
10 1	11 2	12 2	13 2	14 2	15 1	16 2
17 2	18 2	19 1	20 1	21 1	22 2	23 1
24 1	25 2	26 2	27 1	28 1	29 2	30 2
31 0						

August 2006

Mon	Die	Mit	Don	Fre	Sam	Son
	1 2	2 3	3 0	4 0	5 0	6 1
7 2	8 1	9 2	10 1	11 1	12 2	13 1
14 0	15 2	16 2	17 2	18 2	19 2	20 1
21 2	22 1	23 3	24 1	25 1	26 2	27 2
28 2	29 1	30 1	31 2			

September 2006

Mon	Die	Mit	Don	Fre	Sam	Son
				1 1	2 2	3 1
4 1	5 2	6 1	7 1	8 1	9 1	10 1
11 2	12 0	13 1	14 2	15 1	16 2	17 2
18 1	19 1	20 2	21 0	22 1	23 1	24 2
25 1	26 2	27 1	28 2	29 1	30 1	

Oktober 2006

Mon	Die	Mit	Don	Fre	Sam	Son
						1 2
2 3	3 1	4 0	5 2	6 0	7 1	8 0
9 2	10 2	11 6	12 2	13 4	14 1	15 1
16 1	17 2	18 4	19 2	20 1	21 2	22 2
23 2	24 2	25 2	26 2	27 1	28 2	29 2
30 2	31 1					

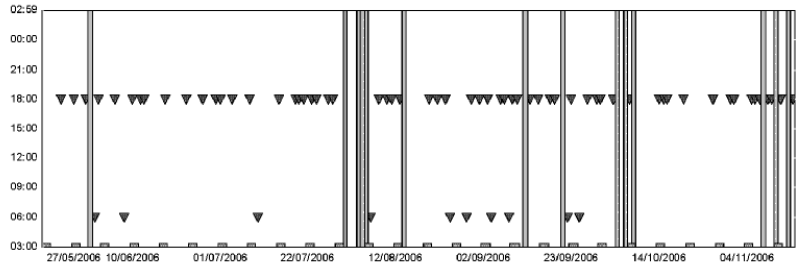
November 2006

Mon	Die	Mit	Don	Fre	Sam	Son
		1 1	2 2	3 2	4 2	5 1
6 1	7 1	8 0	9 1	10 1	11 0	12 1
13 2	14 0	15 1				

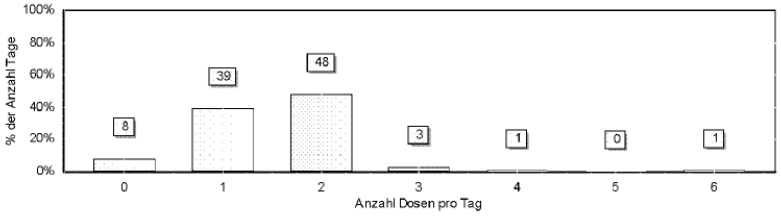
22/01/2009 1

Patient: S09 Monitor: 203200

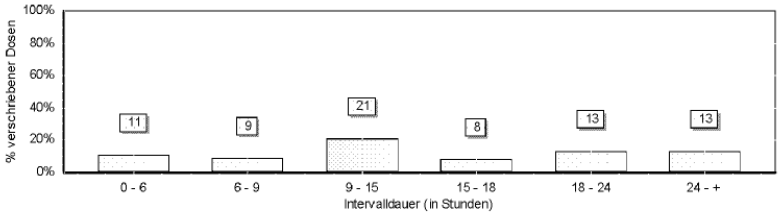
Vergessene Dosen



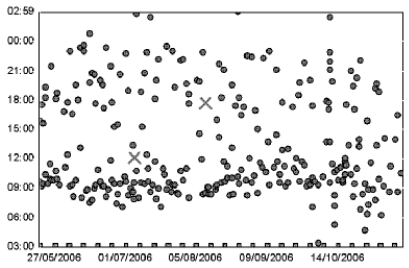
Verteilung der Tage



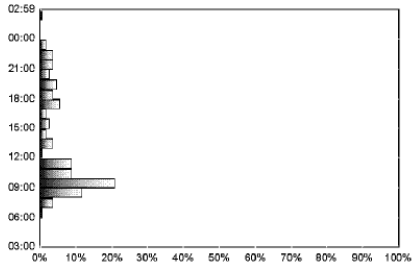
Verteilung der Intervalle



Chronologie



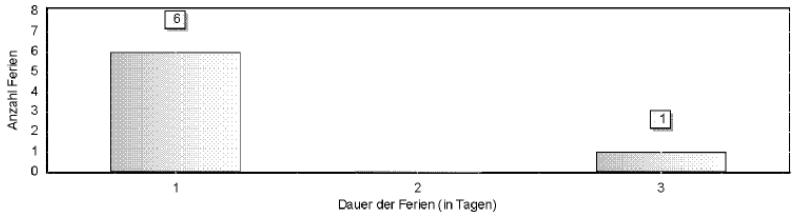
Verteilung der Einnahmezeiten



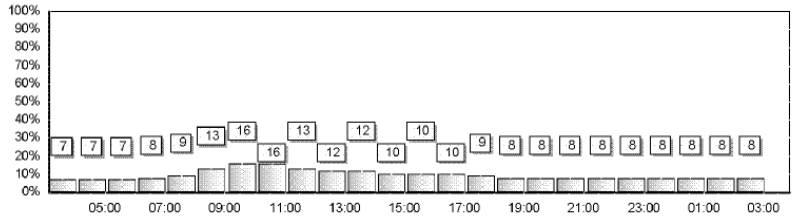
22/01/2009 2

Patient: S09 Monitor: 203200

Therapieferien



Verteilung der ungedeckten Stunden



22/01/2009 3

Studien-Nr.: _____ Datum: _____	**Arzneimittelbezogene Probleme**	CLINICAL PHARMACY

1. Arzneimittelangaben

○ Rp ○ OTC ○ Erst-VO ○ Wiederholungs-VO

Handelsname®: _____ Darreichung: _____

Wirkstoff(e): _____ Stärke: _____

ATC-Code: _____ (wird vom Studienzentrum ausgefüllt)

2. Angaben zum Problem

Problembeschreibung:

_____

_____

_____

_____

_____

Kontakt mit dem Arzt: ○ ja ○ nein

3. Angaben zur Intervention

Angaben zum Lösungsweg:

_____

_____

_____

_____

_____

○ Problem gelöst ○ Problem teilweise gelöst ○ Problem nicht gelöst

Zeitaufwand: _____ min

Codierung des ABP: _____ (wird vom Studienzentrum ausgefüllt)

Studien-Nr.: **Datum:**	**Daten zu elektronischem Arzneimittel-verbrauchsmonitor (MEMS)**	Freie Universität Berlin Abteilung Klinische Pharmazie

Dokumentationsbogen: auszufüllen von Apotheke

1. Angaben zum elektronischen Arzneimittelverbrauchsmonitor

Seriennummer des elektronischen Arzneimittelverbrauchsmonitors	☐☐☐☐☐☐	Nummer ist immer sechsstellig (wird vom Studienzentrum ausgefüllt)
Behältnisgröße	☐	1 = 60 mL 2 = 100 mL

2. Angaben zum Antidementivum

Name des in den elektronischen Arzneimittelverbrauchsmonitor abgefüllten Fertigarzneimittels _____		**Wichtig:** Stärke mit angeben!
Dosierung in mg	☐☐☐☐	**Wichtig** bei Einnahme von mehreren Dosiseinheiten pro Einzelgabe!
Einnahmeschema	☐ _____	1 = 1 x 1 2 = 2 x 1 3 = 3 x 1 4 = sonstige, bitte spezifizieren:

Dokumentation von Öffnungsvorgängen des elektronischen AM-Verbrauchsmonitors (MEMS) in der Apotheke, z.B. beim Befüllen

Studien-Nr.:	

Datum (z.B. 18.09.2005)	**Uhrzeit (z.B. 13:52)**	**Vorgang** 1 = Befüllung 2 = Sonstiges	**Chargenbezeichnung des umgefüllten Fertigarzneimittels**	**Masse des elektronischen AM-Verbrauchsmonitors <u>nach dem Befüllen</u> (inklusive Deckel) in g mit der Rezepturwaage (z.B. 163.49 g)**
☐☐. ☐☐. ☐☐☐☐	☐☐ : ☐☐	☐	______________________	☐☐☐ . ☐☐ g
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CURRICULUM VITAE

Oliver Schwalbe geboren am 20.02.1978

Berufliche Tätigkeit

Seit März 2009	Wissenschaftlicher Mitarbeiter an der Universität Bonn, Abteilung Klinische Pharmazie bei Professor Dr. Ulrich Jaehde: Kooperationsprojekt zusammen mit dem MVDA e.V. zur Qualitätssicherung patientenzentrierter Dienstleistungen
seit September 2006	Initiator und Moderator des Qualitätszirkels Alzheimer der Apothekerkammer Berlin
seit Januar 2005	Wissenschaftlicher Mitarbeiter an der Freien Universität Berlin und der Martin-Luther-Universität Halle-Wittenberg (Drittmittelstelle: gefördert durch Förderinitiative Pharmazeutische Betreuung e.V.), Promotion im Bereich Klinische Pharmazie unter der Leitung von Professor Dr. Charlotte Kloft zum Thema *Pharmazeutische Betreuung von ambulanten Alzheimer-Patienten und ihren Angehörigen*
2005	Lehre in Klinischer Pharmazie an der Freien Universität Berlin mit dem Schwerpunkt *Beratung in der Selbstmedikation*
August 2004 - Dezember 2004	Tätigkeit als Apotheker in der Bären-Apotheke, Berlin

Betreuung von Projekten

Betreuung von Wahlpflichtprojekten in Klinischer Pharmazie an der Freien Universität Berlin und der Martin-Luther-Universität Halle-Wittenberg zu folgenden Themen:

2008	*Bewertung der Arzneimittelfachwerbung von Lamisil® once mit Kriterien der Evidenz basierten Medizin*
2007	*Erarbeitung und Anwendung von Kriterien der Evidenz basierten Medizin zur Beantwortung pharmakotherapeutischer Fragestellungen*
2006	*Einsatz des Medication Appropriateness Index als Indikator für die Qualität in der Arzneimitteltherapie bei ambulanten Patienten*

Betreuung von Diplomanden in Klinischer Pharmazie an der Freien Universität Berlin und der Martin Luther-Universität Halle-Wittenberg zu folgenden Themen:

laufend	Olia Llopis Czemper *Pharmacotherapy Knowledge of Alzheimer Patients and their Caregivers*
2009	Linda Stengel *Zufriedenheit mit der Arzneimittelinformation durch Apotheker bei Angehörigen von Alzheimer-Patienten*
2008	Ines Freiberg *Compliance-Messung in der ambulanten Antidementiva-therapie unter Verwendung der MEMS-Technologie*
2008	Uta Tomaszewski *Einsatz der endogenen Referenzsubstanz Harnstoff in der Mikrodialysetechnik bei Intensivpatienten*

Ausbildung

Mai 2004	Verleihung des akademischen Grades Diplom-Pharmazeut
April 2004	Erteilung der Approbation als Apotheker
Juni 2003 - Mai 2004	Aufbaustudiengang Diplom-Pharmazie an der Rheinischen Friedrich Wilhelms-Universität Bonn Thema der Diplomarbeit: *Einsatz einer endogenen Referenzsubstanz (Harnstoff) in der Mikrodialyse zur Bestimmung der relativen Wieder-findung in humanen Proben* (unter der Leitung von Professor Dr. Ulrich Jaehde und Professor Dr. Charlotte Kloft)
Dezember 2002 - Mai 2003	1. Halbjahr des praktischen Jahres in der Auxilia-Apotheke, Berlin
Juli 2000 - August 2000	Hospital Work Experience for Pharmacy Undergraduates, Conquest Hospital, Hastings, Großbritannien
September 1999 - Juli 2000	Studium der Pharmazie an der University of Brighton, Großbritannien (Schwerpunkt Klinische Pharmazie und Pharmazeutische Betreuung)
März 1999	Famulatur in der Apotheke des Klinikums Krefeld
August 1998	Famulatur in der Skarabäus-Apotheke, Neukirchen
Oktober 1997 - Oktober 2002	Studium der Pharmazie an der Ernst-Moritz-Arndt-Universität Greifswald
Mai 1997	Abitur
1988 - 1997	Arndt-Gymnasium, Krefeld
1984 - 1988	Paul-Gerhard-Schule, Krefeld

Mitgliedschaften

European Society of Clinical Pharmacy (ESCP)

- Mitglied der Special Interest Groups Geriatrics and Medicine Information

Deutsche Pharmazeutische Gesellschaft (DPhG)

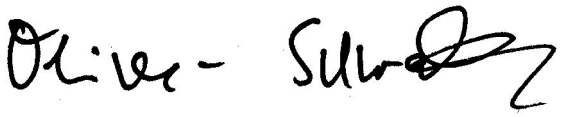
- Mitglied der Fachgruppe Klinische Pharmazie

International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

- Mitglied der Special Interest Group Medication Compliance and Persistence

Pharmaceutical Care Network Europe (PCNE)

Berlin, Juni 2009



Publications

Original papers

O. Schwalbe, C. Scheerans, I. Freiberg, A. Schmidt-Pokrzywniak, A. Stang, C. Kloft. Compliance of Alzheimer Patients and Forgiveness of Donepezil. In preparation

T. Dreischulte, O. Schwalbe, S. Simons. Die richtige Medizin. Dtsch. Apoth. Ztg., 148: 4908-4913 (2008).

O. Schwalbe, I. Freiberg, C. Kloft. Die Beers-Liste – Ein Instrument zur Optimierung der Arzneimitteltherapie geriatrischer Patienten. Med. Monatsschr. Pharm., 30: 244-248 (2007).

O. Schwalbe, S. Wunderlich, C. Kloft. Pharmakotherapie einer Patientin mit Alzheimer-Demenz. Med. Monatsschr. Pharm., 29: 222-224 (2006).

O. Schwalbe, C. Buerger, N. Plock, C. Joukhadar, C. Kloft. Urea as an endogenous surrogate in human microdialysis to determine relative recovery of drugs: analytics and applications. J. Pharm. Biomed. Anal., 41: 233-239 (2006).

Book chapter

K. Lennecke, S. Simons, O. Schwalbe. Compliance. In: Lehrbuch der Klinischen Pharmazie, Wissenschaftliche Verlagsgesellschaft, Stuttgart, accepted (2008).

Conference abstracts

O. Schwalbe, I Freiberg, C. Kloft. Adherence of Alzheimer Patients to Antidementia Drugs. Annual European Congress of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2007, Dublin, 20.-23.10.2007. Value Health, 10: A303 (2007). (poster)

O. Schwalbe, C. Kloft. Adherence to antidementia drugs determined by electronic monitoring. European Symposium on Patient Compliance and Persistence (ESPACOMP), Bonn. (poster)

O. Schwalbe, C. Kloft. Adherence to antidementia drugs determined by electronic monitoring. Jahrestagung der Deutschen Pharmazeutischen Gesellschaft (DPhG) 2006, Marburg, 04-07/10/2006. Tagungsband, 97 (2006). (poster)

O. Schwalbe, C. Kloft. Morbus Alzheimer: Design of a Pharmaceutical Care pilot study. Jahrestagung der Deutschen Pharmazeutischen Gesellschaft (DPhG) 2005, Mainz, 05-08/10/2005. Tagungsband, 95 (2005). (poster)

O. Schwalbe, C. Kloft. Pharmaceutical Care for Alzheimer's patients and their caregivers: A pilot study. Workshop der Deutschen Pharmazeutischen Gesellschaft (DPhG) – Fachgruppe Klinische Pharmazie 2005, Düsseldorf, 02-03/09/2005. (poster)

O. Schwalbe, C. Buerger, N. Plock, C. Scheerans, C. Kloft. Human Microdialysis: Urea as an Endogenous Reference Compound to Determine Relative Recovery of Drugs. World

Conference abstracts (continued)

Conference on Dosing of Antiinfectives 2004. Nuernberg, 06-11/09/2004. Tagungsband, A-122 (2004). (Poster)

O. Schwalbe, C. Bürger, N. Plock, C. Kloft. Harnstoff als endogene Referenzsubstanz zur Bestimmung der In-vivo-Wiederfindung in humanen Mikrodialysat-Proben. Deutsche Pharmazeutischen Gesellschaft (DPhG), Landesgruppe Berlin-Brandenburg – Der wissenschaftliche Nachwuchs stellt vor, Berlin, 05/07/2004. Tagungsband, P24 (2004). (Poster)

O. Schwalbe, C. Buerger, N. Plock, C. Kloft. Determination of in vivo recovery in human microdialysis samples: Urea as a reference compound. 4th International Symposium on Microdialysis, Wien, 18.-19.06.2004. Int. J. Clin. Pharmacol. Ther., 7: 398 (2004). (Poster)

O. Schwalbe, C. Buerger, N. Plock, C. Kloft. Urea as a reference compound to determine the in vivo recovery in human microdialysis samples. Jahrestagung der Deutschen Pharmazeutischen Gesellschaft (DPhG) 2003, Würzburg, 08-11/10/2003. Tagungsband 111 (2003). (Poster)

Presentations and Workshops

O. Schwalbe. Pharmazeutische Betreuung bei Alzheimer-Patienten. PHARMACON Davos, 08-13/02/2009. (workshop)

O. Schwalbe. Microelectronic monitoring of adherence behaviour - Practical aspects, analysis and interpretation. University of Nottingham, Nottingham, United Kingdom, 26/02/2008. (presentation)

O. Schwalbe. Die Beers-Liste – ein Instrument zur Optimierung der Arzneimitteltherapie geriatrischer Patienten. Klinische Pharmazie in der Praxis, Apothekerkammer Hamburg, Hamburg, 12/01/2008. (presentation)

O. Schwalbe, C. Kloft. Strategies for Optimising Compliance in Psychiatric Patients. Jahrestagung der Deutschen Pharmazeutischen Gesellschaft (DPhG) 2007, Erlangen, 10.-13.10.2007. Tagungsband, 160 (2007). (presentation)

Workshops zur Pharmazeutischen Betreuung innerhalb der Zertifikatsfortbildung Demenzerkrankungen der Apothekerkammer Baden-Württemberg, Stuttgart, November/December 2007 and November/December 2006. (workshop)

Referent im Rahmen der deutschlandweiten ABDA (Bundesvereinigung Deutscher Apothekerverbände)-Wochenendworkshops Patient & Pharmazeutische Betreuung zum Thema Der vergessene Patient – Senioren¬leiden Morbus Alzheimer, November 2006. (workshop)

Referent innerhalb des Praktikantenunterrichts nach Approbationsordnung für Apotheker (AAppO) zum Thema Pharmazeutische Betreuung, Möglichkeiten und Ziele in der Apotheke, Apothekerkammer Berlin, Berlin, November 2006. (presentation)

Wochenendworkshop Klinische Pharmazie Der vergessene Patient – Morbus Alzheimer, Fortbildungsveranstaltung der Bayerischen Apothekerkammer, Würzburg, July 2005. (workshop)

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- Professor Gabriele Wilz, Berlin Institute of Technology, Clinical and Health Psychology, Developmental Psychology (psychometric issues)
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Erklärung

Hiermit erkläre ich, dass ich mich mit der vorliegenden Dissertation erstmals um die Erlangung eines Doktorgrades bewerbe.

Ferner erkläre ich, dass ich die vorliegende Arbeit selbständig und ohne fremde Hilfe angefertigt, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die den verwendeten Werken wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Halle,