Adherence to polypharmacy from a pharmaceutical care perspective

Evaluation of an electronic medication dispenser and of tailored adherence interventions in primary care

INAUGURALDISSERTATION ZUR ERLANGUNG DER WÜRDE EINES DOKTORS DER PHILOSOPHIE

vorgelegt der Philosophisch-Naturwissenschaftlichen Fakultät der Universität Basel

von Samuel Sebastian Allemann aus Welschenrohr (SO)

Basel, 2017

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät auf Antrag von

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Basel, den 21. Februar 2017

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Acknowledgements

This thesis was completed under the supervision of Prof. Kurt E. Hersberger and Dr. Isabelle Arnet from the Pharmaceutical Care Research Group, Department of Pharmaceutical Sciences, at the University of Basel.

I would like to express my deepest gratitude to all of you who helped me to develop and improve this thesis during the past four years.

Most of all, I wholeheartedly thank Kurt Hersberger for accepting me into his wonderful group, for his continuous support and guidance, but also for the freedom he gave me to explore the many facets of Pharmacy. With your passion for research, education, and patient care at the counter, you are a continuous source of motivation for me and for our profession. Likewise, I would like to thank Isabelle Arnet for her committed support on a scientific and personal level through every stage of my thesis. You guided me through the convoluted and sometimes nebulous paths of my thesis and showed me the light at the end of many tunnels. Both of you demonstrate what "care" means in practice, every day and far from academic theory.

I would like to thank Prof. Bernard Vrijens for serving as co-referee. Your contributions to the field of adherence research were an inspiration for me throughout my thesis and meeting you and many colleagues at the ESPACOMP conferences was an annual highlight during the past 4 years.

Many thanks to Prof. Christoph Meier for representing the faculty in my dissertation committee. Your cordial advice and rich discussions during many occasions were an appreciated source of motivation.

Many thanks also to Dr. Markus Lampert, Andrea Studer, Dr. Seraina Mengiardi-Nemec, and Maya von Moos for their support during the postgraduate training in clinical pharmacy at the Kantonsspital Bruderholz. I enjoyed the weekly excursions to the top of the hill, changing my viewpoints and keeping the link between clinical research and practice.

I would like to give my heartfelt thanks to my colleagues of the Pharmaceutical Care Research Group—Vera Bernhardt, Esther Spinatsch, Sandra Unfer-Grauwiler, Seraina Mengiardi-Nemec, Philip Walter, Corinne Zöbeli, Verena Renggli, Susanna Papa, Chrisitine Spaar, and of course our special Kurt's Gang: Fabienne Böni, Markus Messerli, Carole Kaufmann, Karen Maes, Corina Metaxas, Dominik Stämpfli, Valerie Wentzky, Tamara Imfeld, Lea Brühwiler,

Claudia Gregoriano, and Helene Studer. With you I shared many unforgettable congresses, lunch breaks, team events, ski weekends, and countless other moments. Special thanks to Fabienne, Dominik, and Karen for offering me shelter after late-nights or before early-days. Sandra, Fabienne, and Dominik also provided valuable corrections and inputs for this thesis.

I would like to further thank all the great collaborators who contributed to this thesis. Many thanks to my master students Fabienne Suppiger, Marcello von Planta, Seraina Disler, and Duy Nguyen for their hard work and valuable contributions. Further, I would like to thank the Ambulatory Care Service of the Psychiatric University Hospital Basel: Kenneth Dürsteler, Hannes Strasser, Marc Vogel, Alexander Brandenberger, Anna-Katrin Ehrsam, René Giesel, Susanne Schoen, Regine Steinauer, and the rest of the team were incredibly welcoming and helpful during our common projects. Special thanks to Ken for sharing your ideas and many stimulating conversations during our "harmonious" lunch breaks. Many thanks also to the patients who participated in our research projects and shared their stories with me.

Many thanks to the "Notfallapotheke Basel": Reni Allemann, Susi Thürkauf, and the many pharmacists, technicians, and other staff of the team. I appreciate your trust in me and your patience for supporting our projects with your passion.

I would also thank the international collaborators of the Patient Adherence Review (PAR) team from the McMaster University in Canada: Prof. R Bryan Haynes, Dr. Robby Nieuwlaat, and Tamara Navarro. Many thanks to all the great researchers who enabled many inspiring moments during ESPACOMP, PCNE, and ESCP conferences. I would like to especially thank Pernille Dam from Pharmakon in Denmark for her friendship and for introducing me to the Danish Pharmacy world.

I would like to thank the members of the Pharmacoepidemiology Unit of Christoph Meier, the clinical pharmacy department of the University Hospital of Basel, and the other research groups of the Department of Pharmaceutical Sciences for their collegiality and friendship. Special thanks to Nadja Stohler for the stimulating conversations during our runs along the Rhein. You encouraged me to expand my professional relationships and showed me that we as young pharmacists can make a difference.

Last, but not least, I would like to express my deepest gratitude to my parents Anne and Thomas, to my sisters Sabine and Simone, to my beloved girlfriend Kathrin, and to my friends. Your unconditional support and encouragement were a blessing during the past four years and make my life so much more enjoyable.

Thank you.

List of abbreviations

ABC	Ascertaining Barriers to Compliance
ACTG	AIDS Clinical Trials Group
ADD	Automated Dose Dispensing
ADHD	Attention Deficit Hyperactivity Disorder
APPOSTEL	Adherence to Polypharmacy in Patients with Opioid Substitution Therapy using ELectronics
ATC	Anatomical Therapeutic Chemical
COI	Cost-of-illness
DOT	Directly Observed Therapy
GAF	Global Assessment of Functioning
GSI	Global Severity Index
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IADL	Instrumental Activities of Daily Living
IMB	Information-Motivation-Behavior
LOA	Leistungsorientierte Abgeltung
MCS	Mental Composite Score
MEMS	Medication Event Monitoring System
MeSH	Medical Subject Headings
MMA	Medication Management Aid
MTM	Medication Therapy Management
OAS	Outpatient Addiction Service
OAT	Opioid-assisted Treatment
PAR	Patient Adherence Review
PCNE	Pharmaceutical Care Network Europe
PCS	Physical Composite Score
PhC	Pharmaceutical Care
POEMS	POlymedication Electronic Monitoring System
PSDI	Positive Symptom Distress Index
QoL	Quality of Life
RCT	Randomized Controlled Trials
RNA	Ribonucleic Acid
SFr	Swiss Franc
SKOS	Swiss conference for social benefits
SOP	Standard Operation Procedure
SPSS	Statistical Package for the Social Sciences
TDF	Theoretical Domains Framework
t_{Var}	Time Variability
USB	University Hospital Basel
WHO	World Health Organization

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Summary

Background

Modern medicine offers a multitude of evidence-based treatments for many chronic diseases. As a result, the prescription of multiple medications to treat one or more conditions in the same patient has become increasingly common, especially in the elderly. Even when prescribed according to best evidence, this polypharmacy is associated with various risks, such as medication errors and non-adherence, leading to adverse drug reactions and drug-drug-interactions, outpatient visits, hospitalizations, and increased costs.

The most recent definition describes medication adherence as "the process by which patients take their medications as prescribed, composed of initiation, implementation and discontinuation". Each component (initiation, implementation, and discontinuation) describes different aspects of adherence and requires specific approaches for its management. Various direct and indirect methods measure adherence with differing validity, reliability, and potential bias. Electronic monitoring has been described as gold-standard especially during the implementation phase because of high resolution and low intrusiveness. Electronic monitoring of polypharmacy is possible by repackaging all suitable medications into unit-of-use portions and monitoring each dosing time.

Over the past decades, overall adherence to medication has been reported to average around 50% - 75% across various conditions and settings. Non-adherence may be the principal reason for gaps between efficacy and effectiveness of treatments. Due to negative outcomes of non-adherence, such as increased morbidity, mortality, and costs, the improvement of medication adherence has been a focus for the World Health Organization since 2003.

Medication adherence is not a stable personality trait but a complex behavior influenced by discrete factors. Various theoretical models aimed to explain non-adherence. Determinants of non-adherence are often grouped in five dimensions: patient-related, social/economic, health system/healthcare team, condition-related, and therapy-related factors. Polypharmacy may cause non-adherence because of pill burden alone, but dosing frequency and regimen complexity have also been described to negatively affect adherence. Recently, the Theoretical Domains Framework (TDF) was developed to simplify the investigation of behaviors such as adherence and to facilitate intervention design.

Interventions to improve adherence are diverse, often complex, and show inconsistent results. Research about interventions addressing barriers associated with polypharmacy is

scarce. Reducing pill burden or the frequency of medication intake may improve adherence; however, this approach is not always feasible. Medication management aids (MMA) are widely used tools to overcome challenges with complex regimens. MMAs are used to organize oral and solid medications by day and time, to act as visual reminders, and to provide visual adherence feedback. They can either be filled by the patients themselves, by a caregiver, or are supplied pre-packed by the pharmacy. Apart from the visual cue to take their medication, more advanced electronic MMAs (e-MMAs) may offer more explicit reminders, such as visual or audible alerts. Electronic monitoring can be used to provide customized feedback. Various e-MMAs for polypharmacy exist, but only few studies using these devices have been published.

Pharmacists as suppliers of medications with frequent patient contact are in a unique position to interview patients about barriers to treatment and to offer individual support to enhance their adherence. Throughout the past century, the role of community pharmacists has shifted from a product-centered role to a provider of patient-centered services. Key objective is to improve the patient's health by promoting a rational use of medications; a practice often referred to as “pharmaceutical care” (PhC). The management of polypharmacy and medication adherence represent important aspects of pharmaceutical care. With the emergence of other terms describing medicines-related patient care, substantial confusion remains about what PhC includes and how to differentiate it from other terms. In Switzerland, pharmacists provide various services related to polypharmacy and medication management reimbursed by health insurances, such as pharmacy-filled MMAs or a structured medication review.

Goal

The goal of this thesis was to investigate adherence to polypharmacy from a pharmaceutical care perspective. This goal was approached by a) re-defining pharmaceutical care; b) evaluating the prevalence of the prescription of split preparations for elderly patients; c) exploring the use of a remote e-MMA for prepackaged polypharmacy in primary care patients; and d) investigating the congruence between patient characteristics and adherence interventions in published trials.

Overview of the projects

Project A

Project A aimed to review existing definitions of PhC and to describe the process of developing a redefined definition. A literature search was conducted to identify existing definitions of PhC. To ease comparison between definitions, we developed a standardized syntax to paraphrase the definitions. The literature search identified 19 definitions that were paraphrased using the standardized syntax (provider, recipient, subject, outcome, activities). During a dedicated meeting, a moderated discussion about the definition of PhC was organized. Twenty-four experts defined PhC as "the pharmacist's contribution to the care of individuals in order to optimize medicines use and improve health outcomes."

Project B

Project B aimed to analyze the prescription patterns of split tablets in general and of quetiapine in particular. Orders from 29 community pharmacies for unit-of-use soft pouch blisters for 1,321 patients residing in 53 retirement homes in northwestern Switzerland were analyzed. Out of 4,784,999 tablets that were repacked in 2012 in unit-of-use pouch blisters, 8.5% were fragmented. The patients were on average 81.5 years old and obtained 1.7 fragments. A total of 43.7% of patients received two or more fragments. The fragments concerned 132 different active substances, and 50% of them were psycholeptics or psychoanaleptics. The most often split tablets were preparations with pipamperone (15.8%), levodopa/decarboxylase inhibitor (10.2%), and quetiapine (6.5%). Prescription of half quetiapine tablets appeared to be constricted to the region of Basel.

Project C

For **Project C**, we investigated an e-MMA for pharmacy-filled blister pouches, which has been developed in the Netherlands and is currently marketed by Philips®. **Project C1** aimed to collect opinions on MMAs in general and on the abovementioned e-MMA in particular. The study involved a 14-day trial with the e-MMA and a focus group to identify general attributes of MMAs, their applicability to the e-MMA, and possible target groups for the e-MMA. Six participants using long-term polypharmacy and willing to try new technologies completed the 14-day trial and participated in the focus group. Participants rated ten of 17 general attributes as clearly applicable to the e-MMA and five as unsuitable. Attributes pertained to three interrelated themes: product design, patient support, and living conditions. Envisaged target groups were patients with time-sensitive medication regimens, patients with

dementia, the visually impaired, and several patients living together to prevent accidental intake of the wrong medication.

A potential target group might be older opioid-dependent patients: They often suffer from chronic diseases and disability in addition to their opioid dependence. As a result, they often need to deal with polypharmacy and complex regimens. Together with a high prevalence of psychological problems and low social support, these patients are at high risk for medication non-adherence, especially during the implementation phase. E-MMAs might be feasible to simultaneously monitor and improve implementation of dosing regimens for these patients.

Thus, **Project C2** aimed to describe the demographics of patients on opioid-assisted treatment (OAT) from an Outpatient Addiction Service (OAS) in Basel, Switzerland. Additionally, we aimed to assess the numbers and nature of medications dispensed to patients of the OAS with a focus on opioid substitution treatments, methylphenidate, and treatments for other comorbidities. We performed a longitudinal observational study with historical data recorded between 2002 and 2013. During the study period, the number of patients increased from 112 to 154. Mean age rose from 37.1 to 45.0 years. Alongside, the number of active ingredients per patient increased from 2.71 to 3.55. The proportion of patients receiving 3 or more substances increased from 40% to almost 60%. Most substances were used in the therapeutic area of the nervous system, which includes all substitution medications and methylphenidate preparations. Methadone remained the predominant substance for OAT, but its use declined by 25%. Most of this proportion was replaced by sustained-release Morphine preparations. Methylphenidate prescriptions declined from 21.4% in 2002 to 16.9% in 2013. Short-acting preparations were fully replaced by long-acting formulations. These results confirmed the increasing age and use of polypharmacy for opioid-dependent patients of the OAS.

Based on these information, we implemented a novel remote electronic medication supply model with the e-MMA in collaboration with the OAS and the emergency pharmacy in Basel, Switzerland. In **Project C3**, we report the first long-term experiences with the novel supply model for two opioid-dependent patients with HIV. John (beginning dementia, 52 years, 6 tablets daily at 12 am) and Mary (frequent drug holidays, 48 years, 5-6 tablets daily at 8 pm) suffered from disease progression due to non-adherence. We electronically monitored adherence and clinical outcomes during 659 (John) and 953 (Mary) days between July 2013 and April 2016. Both patients retrieved over 90% of the pouches within 75 minutes of the scheduled time. Technical problems occurred in 4% (John) and 7.2% (Mary) of retrievals but

on-site support was seldom required. Viral loads fell below detection limits during the entire observation period.

Project C4 aimed to evaluate for the first time a quantitative and qualitative (mixed-method) single-case study design to investigate the use of the e-MMA in other patients on OAT with polypharmacy. Five patients from the OAS participated in a sequential multiple-baseline single subject study. Adherence was monitored with the e-MMA during a baseline phase. An intervention phase with built-in audible and visual reminders from the e-MMA started response-guided after at least 4 weeks of baseline measurement of adherence. After completion, participants entered a follow-up phase with or without the e-MMA. Participants (three females, 2 males) had a mean age of 48 years (34–68), took on average 7 medications during 3 dosing times per day (excluding OAT), and spent on average 70% (30%–100%) of their weekdays at home. Participants were followed for an average of 160 days (39–253, IQR = 87). Electronic monitoring covered 85.5% of the observation period (80.4%–93.5%, IQR = 5.3). Three participants completed the whole study. An intervention phase with intake reminders was implemented for two patients, the others did not use the built-in reminders. During the entire study period, overall taking adherence was 88%. Participants retrieved on average 61% of pouches within the dosing intervals (regular dispense), 26% more than 75 minutes before the agreed dosing times (pre-dispense), and 9.2% more than 75 minutes after the agreed dosing time (missed dispense). Errors during dispense occurred in 2.8% of retrievals. Taking adherence increased by more than 25% to almost 100% for both participants when audible and visual reminders were introduced during the intervention phase. The built-in reminders of the e-MMA reduced missed doses to zero, compared to 15% missed doses without the built-in reminders. The average time variability of retrieval (t_{Var}) was 88 ± 33 minutes and did not change with the built-in reminders. Clinical and humanistic outcomes did not change during the study period for all participants. Participants generally accepted the e-MMA, especially for the security of having enough medication at home, the possibility to pre-dispense pocket-doses, and the assurance of regular intakes.

Finally, in **Project C5**, we aimed to perform a cost-of-illness (COI) evaluation of patients receiving OAT and polypharmacy, and to compare the novel electronic medication supply model to usual care (base case). We estimated COI from a societal perspective for eligible patients of the OAS during one year. Total yearly COI per patient was 109‘611 Swiss Francs (SFr), with direct costs accounting for 30% of the total costs. With the novel supply model, total yearly costs per patient increased by SFr 2’509 for repackaging of medication, leasing of the e-MMA, and time spent for travel, refill, and support (+ 2.2% compared to base case).

Sensitivity analysis showed that the results were robust and overall costs did not substantially change with various estimations.

Project D

Despite much research, interventions aimed at improving medication adherence report disappointing and inconsistent results. A potential explanation might be that approaches seldom match interventions and patient determinants of non-adherence in clinical trials.

Consequently, we aimed to assess congruence between patient characteristics and adherence interventions in **Project D**. Common categories shared by patient determinants of non-adherence and interventions have never been proposed. In **Project D1**, we aimed at retrieving potential interventions and patient determinants from published literature on medication adherence, match them like locks and keys, and categorize them according to the TDF. We extracted 103 interventions and 42 determinants that we divided in 26 modifiable and 16 unmodifiable determinants. All interventions and modifiable determinants were matched within 11 categories (knowledge; skills; social/professional role and identity; beliefs about capabilities; beliefs about consequences; intentions; memory, attention and decision processes; environmental context and resources; social influences; emotion; and behavioral regulation).

In **Project D2**, we applied the results from Project D1 to a Cochrane database with 190 randomized controlled trials (RCTs) on adherence-enhancing interventions. We developed a congruence score consisting of 6 features related to inclusion criteria, patient characteristics at baseline, and intervention design. We correlated overall congruence score and individual features with intervention effects regarding adherence and clinical outcomes. The inclusion of non-adherent patients was the single feature significantly associated with effective adherence interventions ($p = 0.003$). Moreover, effective adherence interventions were significantly associated with improved clinical outcomes ($p < 0.0001$). However, neither the overall congruence score, nor any other individual feature (i.e. “determinants of non-adherence as inclusion criteria”, “tailoring of interventions to the inclusion criteria”, “reasons for non-adherence assessed at baseline”, “adjustment of intervention to individual patient needs”, and “theory based interventions”) were significantly associated with intervention effects.

Conclusions

In conclusion, the thesis showed:

- It was possible to paraphrase definitions of PhC using a standardized syntax focusing on the provider, recipient, subject, outcomes, and activities of PhC practice. During a one-day workshop, experts in PhC research agreed on a definition, intended to be applicable for the present time, representative for various work settings, and valid for countries in- and outside of Europe.
- Tablet splitting is a pharmaceutical care issue with potential consequences on adherence, which plays a major role in dosage adjustments for geriatric patients. Although limited to certain regions, fragments of certain tablets are prescribed against the recommendations from the manufacturer. Pharmaceutical companies should be encouraged to introduce new strengths to an existing range of products, in view of an optimization of care. If splitting tablets is necessary, patient counseling is recommended and pharmacies should deliver the appropriate tools or offer repackaging into MMAs for patients.
- The appearance of MMAs, but also its functionality and the whole medication supply process play an important role with regards to the design and targeting of MMAs. In a focus group discussion, the evaluated e-MMA with pre-packaged polypharmacy met the majority of the requirements set to an MMA. Patients' living conditions like mobility remain the key determinants for their acceptance of the e-MMA. Especially patients with time-sensitive medication regimens, patients with dementia, the visually impaired, and several patients living together might benefit from the e-MMA.
- With our database analysis, we confirmed the globally observed shift towards an older population with OAT in a Swiss setting. An increase in the number of substances and medications might lead to an increased risk for drug-drug interactions, adverse events, and non-adherence. Traditional OAT with liquid Methadone is increasingly being replaced by solid formulations such as Buprenorphine and sustained-release Morphine. Other disorders further complicate the safe and effective therapy of these complex patients. Taken together, the developments of the past 10 years call for new care models for older patients with OAT. The increasing age and the complexity of their medication might warrant a closer collaboration of health care professionals. Alternative supply models to assist patients with their medication management and to support medication adherence are needed in particular for older patients with OAT and polypharmacy.

- Continuous medication supply and persistence with treatment over more than 1.7 years, timing adherence of more than 90%, and suppressed HIV viral load are first results from two case reports supporting the feasibility of a novel supply model with an e-MMA for opioid-dependent patients with polypharmacy.
- The use of a mixed-method single-subject design showed promising results for the evaluation of an e-MMA for polypharmacy. Our pilot study showed that the e-MMA may ensure correct implementation of dosing regimens for opioid-substituted patients with polypharmacy when certain prerequisites are considered. Various drawbacks limit the applicability of the device to monitor adherence. A careful assessment of patient's barriers to medication adherence and a structured medication review should be the first steps when considering the use of the e-MMA for a patient. Overall, the flexibility of single-subject research designs offers considerable advantages for the evaluation of adherence interventions.
- Cost-of-illness for older patients with OAT and polypharmacy is high, especially when considering indirect costs, such as productivity loss due to disability. According to our cost comparison model, the novel electronic medication supply model increases overall costs marginally, but might offset the costs of more expensive alternatives such as nursing homes.
- In published trials on medication adherence, the congruence between interventions and determinants can be assessed with matching interventions to determinants. To be successful, interventions in medication adherence should target current modifiable patient determinants and be tailored to the unmodifiable patient determinants.
- A 6-item score to assess congruence between patient characteristics and adherence interventions was not significantly associated with intervention effects in 190 RCTs included in a Cochrane review. The presence of only six studies that included non-adherent patients and the inter-dependency of this item with the remaining five precluded a conclusive assessment of congruence between patient characteristics and adherence interventions. The selection of non-adherent patients, measuring adherence-related patient characteristics at baseline, and matching interventions to the study population should be the first steps in the design of future adherence studies capable of demonstrating effectiveness of their intervention.

Outlook

This thesis offers recommendations from a pharmaceutical care perspective about the e-MMA on the one hand and about adherence to polypharmacy in general on the other hand.

Future research about the e-MMA should aim at:

- quantitatively evaluating the validity of our findings in larger populations of patients with high perceived necessity of treatment, self-reported non-adherence, unforgiving treatments, low social support, and high psychologic distress. However, other alternatives should be considered for on-demand treatments and problematic substance use.
- developing and implementing robust care models for older patients with polypharmacy and opioid-assisted therapy.
- evaluating the effectiveness of the e-MMA in terms of clinical, humanistic and economic outcomes.
- evaluating the long-term benefits and cost-effectiveness of the novel supply model.

Future research to improve adherence to polypharmacy should aim at:

- providing guidelines for the appropriate design and analyses of single-subject trials in adherence research, including recommendations for statistical analysis.
- developing instruments to reliably assess modifiable and unmodifiable determinants of non-adherence and to select appropriate interventions in research and practice.

This thesis provides first experiences with the use of single-subject research in combination with electronic monitoring of adherence. With a fraction of the costs of a large RCT, our results demonstrate the advantages and limitations, as well as potential target groups for the e-MMA. Our matched categories for determinants of non-adherence and interventions might provide guidance for the choice of interventions to be assessed during the course of such single-subject trials. Ultimately, solid single-case trials that are conducted as part of everyday pharmaceutical care might fill the gap between efficacy and effectiveness for medication treatments.

General Introduction

Polypharmacy

The term "Polypharmacy", first appeared in western literature in the 19th century. A medical lexicon from 1846 defined Polypharmacy (from Greek *Poly* – "much" and *Pharmakon* – "medicine") as *"a prescription, consisting of a number of medicines; hence the name "Polyphar'macus" given to one who is in the habit of prescribing a number of medicines, and who's prescriptions are loaded with ingredients. The term is taken in bad part"*[1]. Polypharmacy—compounding together multiple ingredients—was regarded at the time as unscientific, compared to "modern" Homeopathy that in its pure form only used one ingredient[2].

Fast forward 150 years: Despite ongoing efforts, supporters of homeopathy have yet to provide scientific evidence for its efficacy and polypharmacy is still of great concern. Various definitions of polypharmacy exist today: Besides indicating the use of multiple medications, polypharmacy has been defined as the prescription of medications that do not match diagnosis, contain duplications or interactions, are prescribed for an excessive duration, or are inappropriate in other ways[3]. However, these definitions add confusion instead of clarification, for it has been recognized that the use of multiple medications can be appropriate when correctly prescribed for multiple comorbidities[4]. To avoid ambiguity, the term polypharmacy should only indicate the use of multiple medications by an individual and not include a valuation of its appropriateness. There is no consensus about the cut-off for the number of medications that define polypharmacy. Again, to avoid ambiguity, any number of medications greater than one could define polypharmacy, getting back to the original definition from 1846. For the purpose of this thesis, polypharmacy is defined as the concurrent use of two or more medications.

Modern medicine has developed evidence-based treatments for many chronic diseases. As a result, the prescription of multiple medications to treat one or more conditions in the same patient has become increasingly common, especially in the elderly[5-8]. In Scotland, the proportion of adults receiving more than 5 medications doubled to over 20% between 1995 and 2010[5]. Other studies indicate that more than 50% of elderly patients use more than 5 prescription medications in the United States or Europe[9,10]. In Switzerland, the proportion with prescriptions for 5 or more medications is 17% for community-dwelling adults and over 40% for those aged 65 years and older[11]. Among 6 European countries, Switzerland had the

highest proportion (21%) of patients with 10 or more medications admitted to a University Hospital[12]. With the demographic shift towards older age and the concurrent increase in morbidity, the prevalence of polypharmacy will most likely increase in the future.

Polypharmacy is associated with various benefits and risks. When prescribed appropriately, multiple medications may extend life expectancy and improve quality of life[4]. In contrast, the inappropriate use of multiple medications may increase the risk for adverse drug reactions and drug-drug-interactions, outpatient visits, hospitalizations, and costs[4,13,14]. However, appropriate polypharmacy is not without risks: Even when prescribed according to best evidence, the use of multiple medications has been associated with risks, such as medication errors and non-adherence[15,16]. Indeed, the number of medications appeared to be the most important predictor of harm[17].

This thesis focuses on the risks of appropriate polypharmacy and its association with medication adherence.

Medication adherence

"Patient compliance [sic adherence] has become the best documented, but least understood, health behavior." – Becker & Maiman, 1975[18]

The prescription of medication is not equal to its correct use: Patients may administer prescribed medications incorrectly, inconsistently, or not at all. According to the World Health Organization (WHO), adherence is "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a health care provider"[19]. The keyword here is "agreed", which differentiates the term "adherence" from "compliance", another term used to describe the same behavior[20]. While adherence and compliance focus on the patient's behavior, "concordance" emphasizes the relationship between patient and healthcare professional (Box 1)[21].

Box 1: Terminology of Compliance, Adherence, and Concordance[21]

Compliance:	The extent to which a patient's behavior matches the prescriber's advice.
Adherence:	The extent to which the patient's behavior corresponds with agreed recommendations from a health care provider.
Concordance:	The extent to which the prescription represents a shared decision, in which the beliefs and preferences of the patient have been taken into consideration.

More recently, the Ascertaining Barriers to Compliance (ABC) project team defined medication adherence as "the process by which patients take their medications as prescribed, composed of initiation, implementation and discontinuation" (Box 2 and Figure 1)[22].

Box 2: Adherence Taxonomy[22]

Initiation:	Intake of the first dose of a prescribed medication.
Discontinuation:	Stopping of taking the prescribed medication, for whatever reason(s).
Implementation:	the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose.
Persistence:	length of time between initiation and the last dose, which immediately precedes discontinuation.

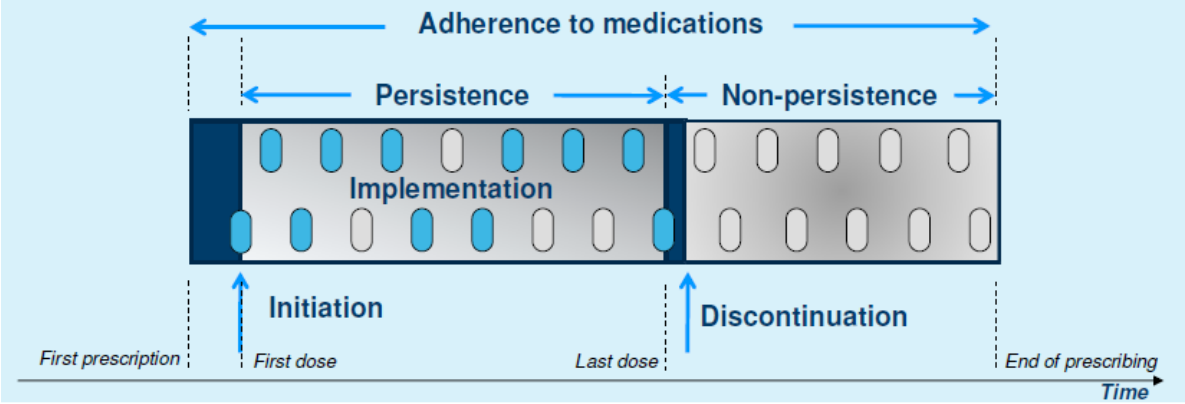

Figure 1: Illustration of the process of adherence to medication, reprinted with permission of the author

Each component (initiation, implementation, and discontinuation) describes different aspects of adherence and requires specific approaches for its management. Adherence management is the "process of monitoring and supporting patients' adherence to medications by health care systems, providers, patients, and their social networks"[22].

This thesis focuses on the management of medication adherence during the implementation phase.

Adherence measurement

Measuring adherence is challenging: It must be feasible for the patient, valid, reliable and objective, continuous, not intrusive or invasive, easy to collect and analyze the data, capture multiple medications, affordable, sustainable, and generalizable[23]. Various methods for measuring adherence exist: direct methods reliably measure administration of medication (e.g., directly observed therapy [DOT], ingestible adherence monitors[24], and therapeutic drug

monitoring). Indirect methods measure adherence by proxy (e.g., pill count, pharmacy claims data[25], self-report[26], and electronic monitoring of medication containers[27]).

Each method offers advantages and disadvantages[23,28-31]. Electronic monitoring has been described as gold-standard especially during the implementation phase because of high resolution and low intrusiveness[32-34]. Devices registering the time and date of use, such as opening bottles or activation of inhalers, have been introduced in the 1980s[35]. As a result, it became possible to analyze medication use patterns in detail. The predominant device to monitor adherence with oral, solid formulations is the Medication Event Monitoring System (MEMS®; WestRock Switzerland SA, Sion, Switzerland) that has been used in 865 studies until December 2016[36]. Measures reported from electronic monitoring include taking adherence (proportion of prescribed number of medications administered each day), timing adherence (proportion of medications administered within a prescribed period), and timing variability (mean difference to the median intake time). Drawbacks of electronic monitoring include the possibility of false-positives and false-negatives by misuse of the device, a potential bias by reinforcing medication intake (Hawthorne effect), a device-specific limitation to certain dosage forms, and high costs[31]. Specific disadvantages of MEMS are the limitation to the monitoring of a single drug and the uncertainty about the number of removed medications per opening. Hence, the monitoring of polypharmacy is not feasible with these devices. Electronic monitoring of polypharmacy is possible by repackaging all suitable medications into unit-of-use portions and monitoring each dosing time. The "POlymedication Electronic Monitoring System" (POEMS; Confrérie Clinique S.A., Lausanne, Switzerland), for example, uses printed electronics affixed to a multi-compartment blister pack to measure adherence with polypharmacy[37].

Overall adherence to medication is often reported to average around 50% in developed countries[19]. A newer comprehensive review and meta-analysis of 569 studies from 50 years found average adherence to be around 75% across various conditions and settings[38]. Its distribution in a population is j-shaped: a large proportion of people shows perfect adherence (initiation, implementation, and persistence), a substantial proportion does not adhere at all (non-initiation and early discontinuation), and the rest exhibits partial adherence (inconsistent implementation)[39]. The "healthy adherer" effect describes the phenomenon that optimal adherence is associated with overall healthy behavior and vice versa[40]. Non-adherence leads to drug-specific issues regarding efficacy, safety, and drug resistance[41] and may be the principal reason for gaps between efficacy and effectiveness of treatments[42]. Due to the negative outcomes of non-adherence (e.g., increased morbidity, mortality, and costs),

the improvement of medication adherence has been a focus for the World Health Organization since 2003[19]. Non-adherence is a problem in hospital settings as well as in primary care. In hospitals, medication histories at admission may be incomplete due to non-adherence. Additionally, the (enforced) correct implementation of dosing regimens may lead to adverse events in previously non-adherent patients. In primary care, unsatisfactory treatment response due to non-adherence might lead to an escalation of therapy and inappropriate polypharmacy—which, in turn, increases the risk of non-adherence. Arguably, improving adherence might offer cost-effective improvements of clinical outcomes and quality of life[43].

Determinants of non-adherence

Medication adherence is not a stable personality trait but a complex behavior influenced by various factors. Different factors come into play in the 3 different stages of adherence. Starting (initiating) a treatment poses the first barrier, a continuous engagement with treatment poses additional barriers for implementation and may lead to discontinuation and non-persistence. Non-adherence might be either intentional or unintentional[44]. Unintentional non-adherence can further be divided into erratic and unwitting non-adherence[19] and has been shown to be predictive for intentional non-adherence[45]. This thesis mainly focuses on unintentional non-adherence.

Various theoretical models to explain non-adherence have been proposed. The complexity of the characteristics of adherence was already known by the end of the 1970s[18]. Despite much research in the 1980s and 1990s, few new insights arose. Research in the 1990s emphasized the influence of patient beliefs about health in general and about illness/medication in particular[46]. Qualitative research on patients' perspectives started with the new millennium and identified new issues like the quality of the doctor-patient relationship and patient health beliefs[47]. Grossly, five theoretical approaches could be identified that all consider non-adherence from a different perspective[48]:

- The oldest approach is the *biomedical model* that focuses on dispositional characteristics of the patient, such as demographic or personality traits.
- *Operant behavior and social learning theories* shifted the focus to the behaviors needed for adherence.

- In the *communication model*, the patient seeks expert advice and treatment from the healthcare professional. Adherence results from persuasion through effective communication.
- The *rational decision-health belief and reasoned action model* generated the patient's perception of risk and motivation for action.
- Finally, the *self-regulative systems theory* sees the patients as an active problem solver.

Multitudes of determinants reportedly contribute to non-adherence. A systematic review of reviews identified 771 factors that have either positive, negative, or neutral effects on adherence[49]. Determinants are often grouped in five dimensions: patient-related, social/economic, health system/healthcare team, condition-related, and therapy-related factors[19]. The impact of each determinant on adherence depends on individual patients and cannot be generalized. Particularly community-dwelling elderly patients with polypharmacy are vulnerable for non-adherence[50]. Polypharmacy may cause non-adherence because of pill burden alone, but dosing frequency and regimen complexity have also been described to negatively affect adherence[51-54]. Moreover, cognitive impairment and a lack of prospective memory may hinder the successful implementation of medication regimens[55,56].

Adherence interventions

Interventions to improve adherence are diverse, often complex, and show inconsistent results[57]. A systematic review of reviews analyzed interventions with regard to theoretical models and found no clear correlation between the effectiveness of interventions that were theory-based and those without an explicit theoretical background[58].

Adherence interventions can be broadly divided into technical, behavioral, educational, and multi-faceted approaches[58]. Technical interventions usually aim to reduce regimen complexity and include the use of fixed-dose combinations or unit-of-use packaging. Behavioral interventions often include reminders, feedback, support, or rewards. Educational interventions usually provide individual or group education during face-to-face sessions, via audio-visual or written materials, by telephone, mailings, or home visits. Finally, multi-faceted approaches use combinations of the various concepts and have been demonstrated effectiveness in long-term studies[59].

Recently, the Theoretical Domains Framework (TDF) was developed to simplify the investigation of behaviors such as adherence and to facilitate intervention design[60]. The

evidence for isolated intervention components is weak, but a multitude of interventions seem to improve adherence. Empowering the patient to actively participate in the choice of therapy, take responsibility for self-care, and receive social support have been reported to show the strongest effects for therapeutic success[61]. In a systematic review of adherence intervention studies using electronic monitoring to assess adherence, only interventions containing feedback on electronic monitoring and/or a cognitive-educational component were effective[62]. Research about interventions addressing barriers associated with polypharmacy is scarce. Reducing pill burden or the frequency of medication intake may improve adherence, however, this approach is not always feasible[63]. A Cochrane-Review assessed the use of "reminder-packaging"-systems, interventions that intend to remind patients to take their medication by packaging solid, oral medications into unit-of-use doses[64]. They found in 12 studies a mean improvement of adherence of 10% for patients using reminder-packaging systems compared to usual care. The use of electronic reminders, such as short message service (sms) or audiovisual reminder devices, was effective in improving short-term adherence (less than 6 months), but long-term effects remain unclear[65].

Medication management aids

The management of medications can be challenging, especially for patients with polypharmacy. Medication management aids (MMA) are commonly suggested and widely used tools to overcome challenges with complex regimens and problems with prospective memory. MMAs are used to organize oral, solid medications by day and time, act as visual reminders, and provide visual adherence feedback. As such, they intend to decrease medication errors and increase patients' independence[66]. However, some qualitative evidence suggests that MMAs may be seen as paternalistic and may not help with memory problems[67]. MMAs exist in various forms. They can either be filled by the patients themselves, by a caregiver, or are supplied pre-packed by the pharmacy[68]. Between 62% and 75% of older adults report at least part-time use of MMAs[69,70].

Most users fill them by themselves, but some studies suggest that their use may not be adequate to ensure optimal adherence[67,69,71]. Pharmacy-filled MMAs can either be the same devices used by patients (multicompartment adherence aids, "pillboxes"), or a special reminder packaging that needs additional equipment to prepare (multidrug punch card or blister pouches)[68]. While multidrug punch cards can be filled manually, the blister pouches are filled by machines and are increasingly provided by specialized blister centres[72]. In

Switzerland, this so-called automated dose dispensing (ADD) is mainly used for patients in nursing homes or other care facilities, while provision to primary healthcare patients is more common in the Nordic countries and the Netherlands[72]. Pharmacy-filled MMAs and ADD services are expected to increase safety, reduce medication costs, and save nurses working time[72]. MMAs offer various advantages but also suffer from drawbacks (Table 1). Despite the reported improvement of adherence in patients using these systems, knowledge about medications and cognitive function are reduced in patients receiving pharmacy-filled MMAs[73]. MMAs provide visual feedback whether a dose has already been taken or not and might deflect issues with cognitive impairment to a certain degree.

Electronic medication management aids

Apart from the visual cue to take their medication, more advanced electronic MMAs may offer more explicit reminders, such as visual or audible alerts. Reminders have been shown to improve adherence independently of MMAs[64,74]. Electronic monitoring can be used to provide customized feedback. The most advanced devices combine repackaging, reminders, and adherence feedback to patients and health care providers in real-time, and restrict access to medications according to schedule. Various electronic MMAs (e-MMAs) for polypharmacy exist, but only few studies using these devices have been published. A review of electronic adherence monitoring devices incorporated into the packaging of medication included 37 studies with 4326 patients[75]. The reviewers identified 5 common characteristics of e-MMA: recording and storing of dosing events, audiovisual reminders, digital displays, real-time monitoring, and feedback on adherence. They found effects ranging from a 2.9% decrease to a 34% increase in mean adherence for the studied e-MMAs and concluded that devices integrated into the care delivery system are most frequently associated with positive effects on adherence. Recently, a systematic reviews of electronic multi-compartment aids identified 6 studies of overall poor methodological quality[76]. A Canadian group performed a randomized controlled trial in 2013 with DoPill® (Figure 2), a device that generates a signal when the membrane covering one of its 28 cavities is removed[77]. The authors reported taking adherence (pills taken divided by pills given) and concluded that the device offered reliable and objective monitoring of adherence to pharmacotherapy for Schizophrenia and may help patients to manage their medication regimens. A cluster-randomized trial from 2015 used an electronic “medication monitor box” for treatment of tuberculosis in China[78]. They reported the mean of the percentage of patient-months on treatment where at least 20% of doses were missed and found significant lower missed doses in patients receiving reminders from the e-

MMA compared to no reminders or text-message based reminders. A Swedish study from 2016 assessed the use of Med-o-Wheel® (Figure 3) in patients after renal transplantation[79]. They aggregated the electronic monitoring data across the study period for the entire intervention group and reported a combined taking adherence of 97.8%. However, adherence in the control group was not assessed and graft rejection rates did not significantly differ between the two groups. Of 40 patients randomized to the intervention, three withdrew due to a "feeling of being monitored" and one because the experience of extreme stress due to the e-MMA. Medido® (Figure 4), an e-MMA for pharmacy-filled blister pouches, has been developed in the Netherlands and is currently marketed by Philips®. No studies investigating the device have been published at the beginning of this PhD project.

Table 1: Advantages (+) and disadvantages (-) of Medication management aids. Adapted from Böni 2015[80]

Multicompartment adherence aid	+	Independent filling by the patient
	+	Reusability
	+	Medication self-monitoring possible
	+	Visual intake reminder
	−	Lack of hygiene
	−	Restricted number of dosing times
	−	Risk of deteriorated stability and compatibility of deblistered medication
	−	Risk of inaccurate filling by the patient
Multidrug punch card	+	Hygiene
	+	Medication self-monitoring possible
	+	Visual intake reminder
	+	Electronic monitoring possible
	+	Not open to manipulation
	−	Not reusable / waste
	−	Restricted number of dosing times per day
	−	Risk of deteriorated stability and compatibility of deblistered medication
	−	Risk of handling difficulties by the patients
	−	Risk of fewer contact to health care professionals
	−	Risk of fading knowledge about packaged medication
Blister pouch	+	Hygiene
	+	Unrestricted dosing times per day
	+	Separable unit-doses
	+	Electronic monitoring possible
	+	Can be integrated in an automated dosing system
	+	Not open to manipulation
	−	Not reusable / waste
	−	Risk of deteriorated stability and compatibility of deblistered medication
	−	Risk of fewer contact to health care professionals
	−	Risk of fading knowledge about packaged medication
	−	No visual intake reminder
e-MMAs	+	Audiovisual reminders
	+	(Real-time) electronic monitoring
	+	Adherence feedback
	+	Dose restriction
	+	Notification to patient/caregiver in case of missed doses
	−	Require electricity and connectivity for data exchange
	−	Risk of being intrusive
	−	Large size
	−	Create dependence

- Display with date, time, and personalized messages
- Individually programmable audiovisual alarms for each of 28 cavities
- Detection of cavity opening with a dynamic membrane
- External power supply
- Rechargeable batteries (type AA)
- Integrated radio communication module (X-Bee)
- Height × width × length: 37.5 mm × 232.4 mm × 251 mm.
- Weight: 781 g

Figure 2: Do-Pill® (Groupe DOmedic Inc, Canada)

- Display with time
- Individually programmable dispensing of 1-4 doses per day
- Alarm to designated caregiver in case of missed dose
- Lockable
- Dosage cassettes with 14 and 28 compartments
- 2x AA alkaline batteries, battery life about one year
- Integrated communication module (GPRS, IRDA)
- Diameter × max. length × height: 120 mm × 132 mm × 60 mm.
- Weight: 296 g

Figure 3: Med-o-wheel® smart (Addoz Oy, Finland)

- Display with date, time, and personalized messages
- Dispensing of blister pouches for up to 4 weeks
- Individually programmable dispensing for unlimited doses
- Fully motorized dispensing and opening of the pouches
- Alarm to designated caregiver in case of missed dose
- Lockable
- External power supply and rechargeable back-up battery
- Integrated communication module (GPRS)
- Height × width × length: 140 mm × 140 mm × 225 mm.
- Weight: 1,486 g

Figure 4: Medido® (Innospense BV, The Netherlands)

The role of the community pharmacy

Health-care professionals—namely pharmacists, physicians, and nurses—are frequently involved in the provision of adherence interventions. A multinational cross-sectional survey showed that only half of the participants regularly ask patients with chronic conditions about adherence, and pharmacists were significantly less likely to intervene than other professionals[81]. However, pharmacists as suppliers of medications with frequent patient contact are in a unique position to interview patients about barriers to treatment and to offer individual support for enhancing adherence.

Community pharmacies are healthcare facilities with low entry barriers that provide various services related—but not limited—to medications. Throughout the past century, the role of community pharmacists has shifted from a product-centered role to a provider of patient-centered services[82,83]. In 2011, the International Pharmaceutical Federation (FIP) published in collaboration with the World Health Organization (WHO) a declaration of "Good Pharmacy Practice", which defined four major roles for the pharmacist beyond the traditional responsibilities in medication logistics (Box 3)[84].

Box 3: Roles of the pharmacist defined by the WHO/FIP Declaration 2011

Role 1:	Prepare, obtain, store, secure, distribute, administer, dispense and dispose of medical products.
Role 2:	Provide effective medication therapy management.
Role 3:	Maintain and improve professional performance.
Role 4:	Contribute to improve effectiveness of the health-care system and public health.

These roles actively involve pharmacists in the medication management process. Key objective is to improve the patient's health by promoting a rational use of medications. This practice can also be described with the term “pharmaceutical care” (PhC). The definition most often referred to was published by Hepler and Strand in 1990: “Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes which improve a patient's quality of life.” Other terms describing medicines-related patient care have evolved, such as medicines management[85], disease management[86], and medication therapy management (MTM)[87]. As a result, substantial confusion remains about what PhC includes and how to differentiate it from other terms. The management of polypharmacy and medication adherence represent important aspects of PhC and good pharmacy practice. The Pharmaceutical Care Network Europe (PCNE) aims to develop pharmacy along the lines of

pharmaceutical care through stimulation of research and implementation projects in the involved European countries[88]. In Switzerland, pharmacists provide various services related to polypharmacy and medication management reimbursed by health insurances. For patients with three or more medications, pharmacy-filled MMAs are currently reimbursed with 21.60 Swiss Francs (SFr) per week. Concurrent use of four or more medications during at least 3 months qualifies for a structured medication review (reimbursed with 48.60 SFr twice a year). This "Polymedication Check" for example identified adherence-related issues in 26.7 % of 450 outpatients included in a recent study[89].

Rationale and Approach

The goal of this thesis was to investigate adherence to polypharmacy and the tailoring of adherence interventions from a pharmaceutical care perspective. The thesis approaches this goal in four parts:

Project A

As medication adherence is a process influenced by large inter-individual variability, it needs to be tackled with individual patients in mind. Individual care around pharmaceuticals has been termed "pharmaceutical care" (PhC), but substantial confusion remains about its contents and differentiations from similar terms. **Project A** sets the scene with a re-definition of pharmaceutical care based on existing literature and a consensus of experts in the field.

Project B

Adherence to polypharmacy poses a multi-dimensional challenge to global health care systems. Similar to the increasing complexity of our therapies for chronic health conditions, no simple solution exists for the management of polypharmacy and adherence. **Project B** evaluates the prevalence of the prescription of split preparations for elderly patients, as an example for a common practice that increases regimen complexity and may have a negative impact on adherence.

Project C

Recent advances in the field provide opportunities to assist patients with polypharmacy and simultaneously monitor and improve adherence with electronic medication management aids (e-MMA). However, potential target groups of these e-MMAs and their use by patients

have not been investigated yet. **Project C** explores the use of a remote electronic medication management aid for prepackaged polypharmacy in primary care patients.

Project D

Despite much research, interventions aimed at improving medication adherence report disappointing and inconsistent results. A potential explanation might be that approaches seldom matched interventions and patient determinants of non-adherence in clinical trials. **Project D** examines the congruence between patient characteristics and adherence interventions in published trials.

Project synopsis

Project A Pharmaceutical Care redefined

A1 **Pharmaceutical Care – the PCNE definition 2013**
Publication in *Int J Clin Pharm*. 2014; 36: 544-55[90]

- to review existing definitions in literature in order to better understand their development
- to describe the process of achieving a redefined definition, during a one-day consensus meeting of experts.

Project B Split medications in pharmacy-filled blister pouches

B1 **Issues around the prescription of half tablets in Northern Switzerland: The irrational Case of Quetiapine**
Publication in *Biomed Res Int*. 2015[91]

- to analyze the general prescription patterns of split tablets in Switzerland.
- to evaluate the consequences of split tablets for community pharmacies, patients, and patient care organizations and discussing some recommendations for daily practice.

Project C A remote electronic medication management aid for prepackaged polypharmacy in primary care patients

C1 **Patient views on an electronic dispensing device for prepackaged polypharmacy: a qualitative assessment in an ambulatory setting**
Publication in *Integr Pharm Res Pract*. 2015: 167.[92]

- to collect and evaluate attributes of medication management aids important to patients
- to evaluate the use of a specific electronic MMA with polypharmacy pre-packaged in pouches in relation to these attributes
- to identify the target group that could benefit most from the electronic MMA.

C2 **Medication Profiles of Substituted Patients with Opioid Dependence Syndrome: A longitudinal observational study**
Project report from a Master's thesis[93]

- to describe the demographics of the study population
- to assess the numbers and nature of medications dispensed to included patients with a focus on opioid substitution treatments, methylphenidate, and treatments for other comorbidities

C3 **Novel remote electronic medication supply model for opioid dependent outpatients with polypharmacy - first long-term experiences in Switzerland from two case reports**
Manuscript submitted for publication [94]

- to report in detail of the first long-term experiences with a novel electronic medication supply model

C4 **Adherence to Polypharmacy in Patients with Opioid Substitution Therapy using ELectronics (APPOSTEL): A mixed-methods single-subject study**

Project report[95]

to assess a mixed-method single-subject study design with regards to:

- participant's adherence with an e-MMA
- the effect of intake reminders on adherence patterns
- the effect of the e-MMA on clinical and humanistic outcomes
- participants' acceptance of and satisfaction with the e-MMA

C5 **Economic Aspects of Medication Supply for Older Patients with Opioid-Substitution Therapy and Polypharmacy**
Manuscript prepared for publication[96]

- to perform a cost-of-illness evaluation of patients receiving opioid-substitution therapy and polypharmacy (base case)
- to establish a cost-comparison model for the novel supply model compared to the base case

Project D Congruence between patient characteristics and adherence interventions

D1 **Matching adherence interventions to patient determinants using the Theoretical Domains Framework**
Publication in *Front Pharmacol*. 2016; 7[97]

- to extract from literature salient a) interventions intended to improve adherence and b) related patient determinants of non-adherence
- to categorize the retrieved a) interventions and b) determinants
- to match a) and b)

D2 **Can congruence between patient characteristics and interventions explain effectiveness in medication adherence studies? An in-depth analysis of a Cochrane review**
Manuscript submitted for publication[98]

- to extract and code features regarding inclusion criteria, patient characteristics at baseline, and intervention design, according to our juxtaposition list
- to calculate a congruence score between potential modifiable determinants and the intervention based on these features
- to correlate the congruence score with the reported study effect on adherence and clinical outcomes

A – Pharmaceutical care redefined

Project A1

Pharmaceutical care – the PCNE definition 2013

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Int J Clin Pharm. 2014 Jun;36(3):544-55. doi: 10.1007/s11096-014-9933-x.
Epub 2014 Apr 20.

Abstract

Background: Twenty-three years after Hepler and Strand published their well-known definition of pharmaceutical care (PhC), confusion remains about what the term includes and how to differentiate it from other terms. The board of the Pharmaceutical Care Network Europe felt the need to redefine PhC and to answer the question: "What is Pharmaceutical Care in 2013". Objective: The aims of this paper were to review existing definitions of PhC and to describe the process of developing a redefined definition.

Methods: A literature search was conducted in the MEDLINE database (1964 - January 2013). Keywords included "pharmaceutical care", "medication (therapy) management", "medicine management", and "pharmacist care" in the title or abstract together with the term "defin*". To ease comparison between definitions, we developed a standardized syntax to paraphrase the definitions. During a dedicated meeting, a moderated discussion about the definition of PhC was organized.

Results: The initial literature search produced 186 hits, with 8 unique PhC definitions. Hand searching identified a further 11 unique definitions. These 19 definitions were paraphrased using the standardized syntax (provider, recipient, subject, outcome, activities). Fourteen members of PCNE and 10 additional experts attended the moderated discussion. Working groups of increasing size developed intermediate definitions, which had similarities and differences to those retrieved in the literature search. At the end of the session, participants reached a consensus on a "PCNE definition of Pharmaceutical Care" reading: "Pharmaceutical Care is the pharmacist's contribution to the care of individuals in order to optimize medicines use and improve health outcomes."

Conclusions: It was possible to paraphrase definitions of PhC using a standardized syntax focusing on the provider, recipient, subject, outcomes, and activities included in PhC practice. During a one-day workshop, experts in PhC research agreed on a definition, intended to be applicable for the present time, representative for various work settings, and valid for countries inside and outside of Europe.

Impact of findings on practice

- The aim of PCNE is to help to develop pharmacy along the lines of pharmaceutical care (PhC) in the involved European countries.
- We hope to harmonies the use of a single definition amongst European researchers and, ultimately, practitioners.
- This new PCNE definition of PhC directly derives from previous definitions and is intended to unite the current understanding of PhC with respect to the evolution of this practice philosophy during the last 35 years.

Introduction

The term "pharmaceutical care" (PhC) is frequently used as a keyword in health care literature, as an activity in patient care, or as a module within a teaching curriculum. In most cases, people refer to the definition given by Hepler and Strand in 1990[99]: "Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes which improve a patient's quality of life." A more patient-centered approach was endorsed by Linda Strand et al., who stated in 1997 that PhC is not only a theory but also a philosophy of practice[100].

Since then, new terms and concepts of medicines-related patient care have evolved, such as medicines management[85], disease management[86], and medication therapy management (MTM)[87]. Twenty-three years after the definition was published by Hepler and Strand, substantial confusion still remains about what PhC includes and how to differentiate it from such other terms. According to McGivney et al.[101], for example, MTM integrates both the philosophy and practice of PhC and elements of Disease Management. Some authors and authorities see PhC as a responsibility shared by all health professionals, while others restrict it to the pharmacy profession (see Table 1). These difficulties with definitions were also recently addressed in a joint editorial from the International Journal of Clinical Pharmacy and the journal Pharmacy Practice[102]. The board of the Pharmaceutical Care Network Europe (PCNE), a European network of researchers in the field of pharmaceutical care, therefore, felt the need to redefine PhC and to answer the question: "What is Pharmaceutical Care in 2013"[102].

The aims of this paper are (a) to review existing definitions in literature in order to better understand their development and (b) to describe the process of achieving a redefined definition, during a one-day consensus meeting of experts.

Methods

Literature search

A literature search was conducted in the MEDLINE database from 1964 to January 2013. The search was restricted to publications in English, German, or French. Keywords included "pharmaceutical care", "medication (therapy) management", "medicine management", and "pharmacist care" in the title or abstract together with the term "defin*" to identify existing definitions of PhC. The exact string is shown in Box 4. Each source was scanned for explicit definitions of PhC and cross-references. Co-authors of this paper provided additional sources for definitions not identified previously, usually from the grey literature.

Box 4: String used for literature search

((pharmaceutical care[Title/Abstract]) or (medication management[Title/Abstract]) or (medication therapy management[Title/Abstract]) or (medicine management[Title/Abstract]) or (pharmacist care[Title/Abstract])) AND (defin*[Title/Abstract])

The retrieved definitions were grouped by the year of publication and publisher. To ease comparison between definitions, we paraphrased the definitions using a standardized syntax developed by the authors, as shown in Figure 5. For this standardized transcription, we considered both the definition itself and the additional published information. Similar terms with the same meaning were subsumed under one term (e.g., "drug therapy" was considered equivalent to "pharmacotherapy"). For this paraphrase, we only considered activities explicitly described in the publication, such as the examples given in Figure 5.

Workshop for definition development

The workshop was organized on February 5, 2013 in Berlin. The board of PCNE had announced this workshop to all members. In addition, 44 experts in the field of pharmaceutical care were invited personally. A total of 24 individuals (all pharmacists, 14 members of PCNE) attended this one-day meeting, representing 11 different European countries, plus the USA and Australia. The meeting was facilitated by all authors, including a certified moderator, who led the workshop and the discussion, and was audio-recorded, with consent. Two weeks in advance, workshop participants were given the standardized syntax from Figure 5, together with a draft of Table 2 with PhC definitions and standardized paraphrases, to ensure that all started from a minimum position of knowledge.

In order to achieve a consensus of all invited experts, we chose a method in accordance with the "Consensus-Oriented Decision-Making model" developed by Tim Hartnett[103]. This method assured active participation of every individual and created a commonly shared understanding at the same time. It had been used successfully by the moderator in other contexts several times. The procedure was divided into two steps. First, the participant suggested a range of ideas about what PhC meant for them, in order to create a clear definition. Then, the participants analyzed this shared understanding in order to support the redefined definition and to represent the opinion of as many participants as possible. In the first step, small working groups of three participants from different countries had to agree on a definition that covered similarities between their ideas about PhC. In order to reach agreement, participants were asked to switch to a meta-level ("chunk up") and find the virtual meaning behind their definitions. "Chunking" means to reorganize or break down experiences into bigger or smaller pieces. "Chunking up" involves moving to a larger, more general or abstract level of information. A greater vision of ideas made it possible to reach consensus. Each group documented their results on flip charts and presented them to the other groups. Three consecutive rounds of two working groups merging and undertaking the same process led to the formation of a single large working group. At this point, we aimed to reach a first broad but consolidated definition.

In the next step, questions regarding provider, recipient, subject, and outcome of PhC helped to substantiate the broad definition. The aim was to fine-tune the definition ("chunk down"). "Chunking down" means moving to a more specific and concrete level of information. To ensure the consideration and discussion of all arguments for and against issues and to make decisions that accounted for all perspectives, it was necessary to continue working with all participants in one group in a plenary session. Step by step, all conflicting details were discussed and finally led to a precise definition of PhC. The audio-recorded statements were summarized and topics addressed were identified.

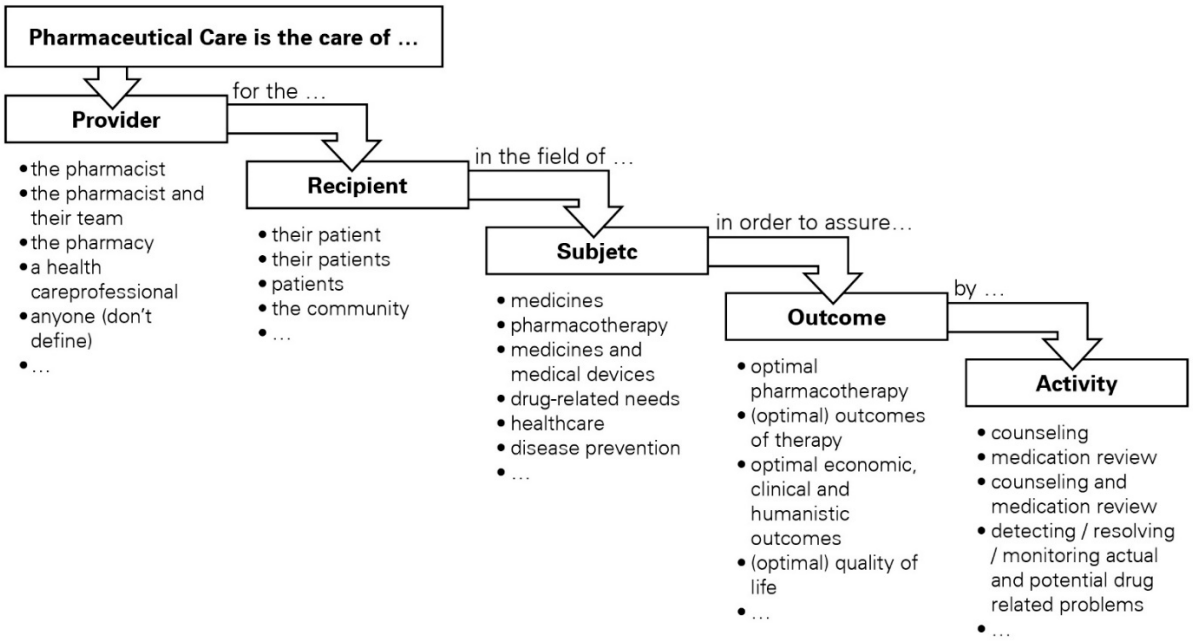

Figure 5: Standardized syntax for pharmaceutical care definitions, with examples to illustrate each domain (provider, recipient, subject, outcome, and activity)

Results

Literature search

The initial MEDLINE search produced 186 hits. After review of the search results based on the title, 37 publications were excluded. The abstracts of the remaining 149 publications were reviewed and 95 full-text publications were examined. From these, eight original definitions of PhC were identified. Most papers cited the definition developed by Hepler and Strand in 1990[99]. Additional sources from references cited in the bibliographies and from co-authors' inputs generated a total of 19 unique PhC definitions. Table 2 shows the definitions, with their authors and year of publication, and the relevant standardized paraphrase.

From the paraphrased versions of the definitions, it is apparent that the provider of PhC remained unspecified in the majority of definitions (9/19, 47%). Five of the first 8 definitions published before 1997 did not attribute a profession to the role of the provider while, in contrast, only 4 of the 10 definitions after 1997 did not define a provider. In 1997, Linda Strand introduced the generic term "practitioner", which was used in 4 definitions (21%) after 1997. However, 5 definitions regarded "the pharmacist" (26%) or "the pharmacist and his team" (5%) as the provider of PhC.

Fifteen (79%) definitions focused on the individual patient, and 3 (16%) defined the collective of patients as the recipients of PhC. The recipient remained unclear in one (5%)

definition. Nine (47%) definitions named "pharmacotherapy" as the subject, while 8 (42%) stated "drug-related needs" and one (5%) named "drug-use". In one (5%) of the definitions, no subject was mentioned.

"Optimal outcomes of therapy" and "optimal quality of life" account for half of the mentioned outcomes in 5 (26%) of the definitions each. Interestingly, the term "optimal quality of life" only appeared during the years 1990 to 1996. "Optimal pharmacotherapy" was defined as the outcome in 2 (11%) of the existing definitions. In 7 of the 19 definitions, other outcomes (2/19, 11%) or no outcomes (5/19, 26%) of PhC were specified.

Most definitions did not include specific activities to be performed in the PhC process (14/19, 75%). "Detecting, preventing, and resolving drug-related problems", "doing counselling, medication review, and evaluation of outcomes", "continuously monitoring its clinical and psychosocial effects", "monitoring their pharmacotherapy", and "establishing and administering a pharmaceutical care plan" were mentioned in one definition each (5%).

Workshop for definition development

Morning session: "Chunk up"

The aim of the morning session was to find an intermediate definition for PhC as a basis for discussion. The intermediate definitions were then harmonized in the afternoon plenary session. The results of the process are displayed in Figure 6. Six groups (1 – 6) of three participants each formulated an initial definition of PhC. These definitions were already quite specific but differed in most aspects (provider, recipient, subject, outcome, activities) between the groups. After the merging of pairs of groups into larger groups of six participants, four refined definitions were generated:

Groups **1/2** described PhC as "patient/health care which is delivered through pharmacy practice". The service is provided by pharmacy practitioners, not only to patients but to consumers as well. Pharmaceutical expertise is needed and PhC can be provided by the pharmacist or somebody else with that expertise.

For the participants of **Group 3/4** it was important that PhC was a practice philosophy. The provider does not have to be a pharmacist but a "competent practitioner that takes responsibility". The recipient of PhC is the individual patient. The listing of all PhC activities such as "detecting, resolving and monitoring actual and potential drug related problems" was replaced by "to resolve drug related needs". In this intermediate definition, the aim of PhC was "to assure optimal outcomes".

Table 2: Pharmaceutical care definitions sorted by year

Year	Author/Context	Definition	Standardized Paraphrase
1975	Mikeal, R. L.; Brown, T. R.; Lazarus, H. L.; Vinson, M. C. **Place published** USA **Publisher** School of Pharmacy **Type of Work** Interviews in short-term hospitals	The care that a given patient requires and receives which assures safe and rational drug usage[104].	Pharmaceutical Care is the care from **anyone** for **their patient** in order to **assure safe and rational drug usage.**
1980	Brodie, D. C.; Parish, P. A.; Poston, J. W. **Place published** Wales/USA **Publisher** School of Pharmacy **Type of Work** Statement	Pharmaceutical care includes the determination of the drug needs for a given individual and the provision not only of the drugs required but also of the necessary services (before, during or after treatment) to assure optimally safe and effective therapy. It includes a feedback mechanism as a means of facilitating continuity of care by those who provide it[105].	Pharmaceutical Care is the care from **anyone** for **their patient** in the field of **drug-related needs** in order to **assure optimally safe and effective pharmacotherapy**.
1987	Hepler, C. D. **Place published** USA **Publisher** N/A **Type of Work** NA/A	A covenantal relationship between a patient and a pharmacist in which the pharmacist performs drug-use-control functions (with appropriate knowledge and skill) governed by awareness of and commitment to the patients' interest[106].	Pharmaceutical Care is the care from **the pharmacist** for **their patient** in the field of **drug use** in order to **serve the interests of the patient**.
1990	Hepler, C. D.; Strand, L. M. **Place published** USA **Publisher** N/A **Type of Work** NA/A	Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes which improve a patient's Quality of Life[99].	Pharmaceutical Care is the care from **anyone** for **a patient** in the field of **pharmacotherapy** in order to **assure (optimal) quality of life.**
1992	Strand, Linda M. **Place published** Michigan, USA **Publisher** Upjohn **Type of Work** Commentary	Pharmaceutical Care is that component of pharmacy practice which entails the direct interaction of the pharmacist with the patient for the purpose of caring for that patient's drug-related needs[107].	Pharmaceutical Care is the care from **the pharmacist** for **their patient** in the field of **drug-related needs.**

Year	Author/Context	Definition	Standardized Paraphrase
1993	American Society of Hospital Pharmacists **Place published** USA **Publisher** American Society of Hospital Pharmacists **Type of Work** Political Statement	Pharmaceutical care is the direct, responsible provision of medication-related care for the purpose of the achieving definite outcomes that improve a patient's quality of life[108]].	Pharmaceutical Care is the care from **anyone** for **their patient** in the field of **pharmacotherapy** in order to **assure (optimal) quality of life.**
1993	Van Mil, J. W. F. **Place published** The Netherlands **Publisher** N/A **Type of Work** N/A	Pharmaceutical patient care (Farmaceutische Patiëntenzorg, FPZ) is the structured, intensive care of the pharmacist for an optimal pharmacotherapy in which the patient and his condition are the primary concern. The aim is to obtain optimal Health Related Quality of Life[109].	Pharmaceutical Care is the care from **the pharmacist** for **their patients** in the field of **pharmacotherapy** in order to **assure (optimal) quality of life**.
1996	Hepler, C. D. **Place published** Florida, USA **Publisher** Department of Pharmacy Health Care Administration **Type of Work** NA/A	The purpose of pharmaceutical care (in all practice settings) is to provide drug therapy intended to achieve definite outcomes that will improve a patient's quality of life[110].	Pharmaceutical Care is the care from **anyone** for **their patients** in the field of **pharmacotherapy** in order to **assure (optimal) quality of life**.
1997	Strand, L. M. **Place published** USA **Publisher** N/A **Type of Work** Remington Lecture	A practice for which the practitioner takes responsibility for a patient's drug therapy needs and is held accountable for this commitment[100].	Pharmaceutical Care is the care from a **practitioner** for **a patient** in the field of **drug related needs**.
1998	Munroe, WP; Dalmady-Israel, C. **Place published** N/A **Publisher** N/A **Type of Work** NA/A	Pharmaceutical care as a service which systematically and continuously monitors the clinical and psychosocial effects of drug therapy on a patient[111].	Pharmaceutical Care is the care from **anyone** for **a patient** in the field of **pharmacotherapy** by **continuously monitoring its clinical and psychosocial effects**.

Year	Author/Context	Definition	Standardized Paraphrase
1998	FIP Statement **Place published** The Hague, The Netherlands **Type of Work** Statement	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[112].	Pharmaceutical Care is the care from **anyone** for **a patient** in the field of **pharmacotherapy** in order to **assure (optimal) quality of life.**
1998	Cipolle, R. J.; Strand, L.; Morley, P. **Place published** New York **Publisher** MacGraw Hill **Type of Work** Book	Pharmaceutical care is a patient-centered practice in which the practitioner assumes responsibility for a patient's drug-related needs and is held accountable for this commitment. In the course of this practice, responsible drug therapy is provided for the purpose of achieving positive patient outcomes[113].	Pharmaceutical Care is the care from a **practitioner** for **a patient** in the field of **drug-related needs** in order to **assure (optimal) outcomes of therapy**.
1999	Granada Consensus **Place published** Granada, Esp **Type of Work** Consensus Paper	The detection, prevention and resolution of drug-related problems[114].	Pharmaceutical Care is the care from **anyone** in the field of **drug-related needs** by **detecting, preventing and resolving drug related problems**.
2004	van Mil, J. W.; Schulz, M.; Tromp, T. F. **Place published** Europe **Type of Work** Review **Type of Work** NA/A	Pharmaceutical care is a practice philosophy for pharmacy. It is the way of pharmacists to coach the individual patients with their medication. The concept deals with the way a patient should receive and use medication and should receive education on the use of medicines. The concept also deals with responsibilities, medication surveillance, counseling and the evaluation of all the outcomes of care[115].	Pharmaceutical Care is the care from **the pharmacist** for **their patient** in the field of **pharmacotherapy** in order **to assure (optimal) outcomes of therapy** by **doing counseling, medication review and evaluation of outcomes.**
2004	Berenguer, B.; La Casa, C.; de la Matta, M. J.; Martin-Calero, M. J. **Place published** Sevilla, Esp **Publisher** University Department of Pharmacology **Type of Work** Review	The pharmacists' compromise to obtain the maximum benefit from the pharmacological treatments of the patients, being therefore responsible of monitoring their pharmacotherapy[116].	Pharmaceutical Care is the care from **the pharmacist** for **patients** in the field of **pharmacotherapy** in order to **assure (optimal) outcomes of therapy** by **monitoring their pharmacotherapy.**

Year	Author/Context	Definition	Standardized Paraphrase
2005	Franklin, B. D.; van Mil, J. W. **Type of Work** Editorial **Publisher** N/A **Type of Work** NA/A	The person-focused care relating to medication, which is provided by a pharmacist and the pharmacy team with the aim of improving the outcomes of therapy[117].	Pharmaceutical Care is the care from **the pharmacist and their team** for **their patient** in the field of **pharmacotherapy** in order to **assure (optimal) outcomes of therapy**.
2011	Sanchez, A. M. **Place published** Madrid, Spain **Type of Work** Commentary **Type of Work** NA/A	Pharmaceutical care addresses the patient's drug-related needs comprehensively through a scheduled outline of tasks, in which the practitioner makes sure that the drug therapy is appropriately indicated, effective, safe, and convenient[118].	Pharmaceutical Care is the care from a **practitioner** for **their patient** in the field of **drug-related needs** in order to **assure optimal pharmacotherapy**.
2012	Blackburn, D. F.; Yakiwchuk, E. M.; Jorgenson, D. J.; Mansell, K. D. **Place published** Canada **Publisher** College of Pharmacy and Nutrition **Type of Work** Commentary	A patient-centered practice in which the practitioner would be accountable for the drug-related needs of specific individuals as well as groups of patients within a defined practice setting who are at high risk for drug- or disease-induced morbidity[119].	Pharmaceutical Care is the care from a **practitioner** for **patients** in the field of **drug-related needs**.
2012	Carollo, A.; Rieutord, A.; Launay-Vacher, V. **Place published** Europe **Publisher** ESCP **Type of Work** Guideline	The pharmaceutical contribution to patient care in identifying pharmaceutical care issues (medications-related issues) and establishing and administering a pharmaceutical care plan[120].	Pharmaceutical Care is the care from **anyone** for **patients** in the field of **drug-related needs** in order **assure (optimal) outcomes of therapy** by **establishing and administering a pharmaceutical care plan**.

Group 5/6 had a strong emphasis on the "outcome" of PhC in their definition, which was to "optimize the use of medicines and therapy". The activities were specified as "the provision of care, care programs and services". For this group it was important that the recipient was not only the individual patient but also society more broadly.

The definition of **group 7/8** described PhC as the "contribution of the pharmacist in the care for individuals"; hence, the recipient was not only the patient but also every individual. This group was the only group that named the pharmacotherapy as the subject of PhC. They saw the aim of PhC as "to assure the responsible use of medicine". The "responsible use of medicine" is based on the WHO-definition[121] meaning the effectiveness, including quality of life, efficiency and safety of medicines. The activities are not explicitly mentioned, as they are tools used to perform PhC.

In the next step, before reaching consensus on the final harmonized definition, pairs of groups were merged again. The two groups, each of twelve participants, then agreed on one intermediate definition each. The first group debated whether to disregard the concept that PhC was defined by "taking responsibility by providing care", with some participants arguing that it was not possible for the competent practitioner to take responsibility alone for the patient. The joined group defined the activities of PhC as "detecting, resolving and monitoring actual and potential drug-related problems".

In the other group, there was a debate on the phrasing of the outcome of PhC. A participant stated that it is not possible "to assure the responsible use of medicine" but rather "enhance both the responsible use of medicine and to improve health outcomes". In addition, the group agreed on a more general definition and to remove the subject "pharmacotherapy".

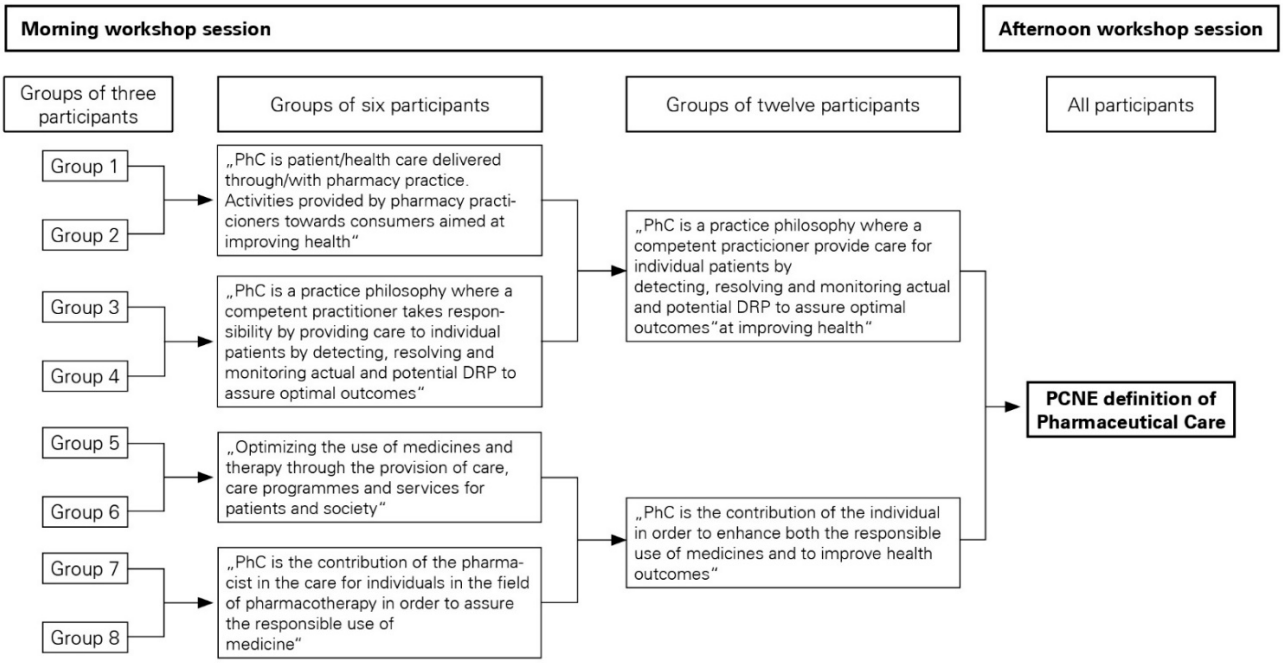

Figure 6: Process of definition development

Afternoon session: "Chunk down"

In the afternoon, all participants discussed the two intermediate definitions and their components together, in a plenary session. All aspects of the definitions retrieved in the literature search (provider, recipient, subject, outcome, and activities) emerged during the discussion, and new topics concerning the context of the definition arose as well.

The **scope** of the definition was discussed several times. The moderators proposed limiting the scope of use of the definition to research and professionals working within PCNE. Some participants argued that PCNE should set standards not only for its members, but also for other professionals, practitioners, and policy makers. However, all members agreed that if researchers used the definition consistently, it would be likely that other professionals, practitioners, and policy makers would adopt the meaning of our definition. Participants also pointed out that it was important to have a short and simple definition to avoid confusion and to promote dissemination.

The **concept of PhC** and its relation to other terms such as "Pharmacist Care", "Pharmacy Practice", and "Medication Management" was extensively discussed at an early stage of the chunk down session. Some participants argued, and it was acknowledged by others, that PhC did not need to be redefined at all, but that its relation to other terms needed clarification. All participants agreed that the PCNE definition should depict the evolution of PhC and clarify already existing definitions.

A frequently emerging topic was the **political relevance** of a redefined definition of PhC. Some participants claimed that PCNE should be responsible for communicating the value of PhC to policy makers. According to this, the definition should be used to distinguish the functions of pharmacists and to differentiate types of services and activities in a pharmacy (e.g., compounding, counselling, and provision of PhC). One participant mentioned that in the USA, the term MTM had replaced PhC because "medication therapy management" was thought to mean the same as "pharmaceutical care" to US policy makers. Differences between countries and languages were mentioned as problematic at a policy level. One participant, for example, stated that there is no exact translation of the English word "care" into Danish. These culture and language challenges have been known for some time, but were never properly addressed[122].

The **provider of PhC** was an area of conflict between participants. Every member of the group agreed that the provision of PhC was not limited to the pharmacy premises, but was independent of the place. Some argued that it should be the pharmacist exclusively, whereas others opted for the use of "healthcare professional" or "competent professional". However, most participants agreed that it was important to define specifically the role of the pharmacist, without excluding any other professional. Since PhC is a term mostly used by pharmacists, the profession should therefore be named in the definition. As one member highlighted, this was already implied in most previous definitions without explicitly stating it. Furthermore, it was felt that the definition should "energies pharmacists to deliver PhC". All participants but one agreed with using the term "contribution of the pharmacist". Thus, other healthcare professionals and the recipient of PhC are not excluded. Some people stated that medication-related care could be provided by other healthcare professionals, but this would then not be called PhC. The question was raised whether it should be "the pharmacist and the team", rather than the pharmacist alone. Participants agreed that PhC should be the *responsibility* of the pharmacist because they were the responsible person for pharmaceutical treatment by law. One participant argued that the education level of other pharmacy staff (technicians, assistants) differed between countries, while the pharmacist's education is similar worldwide. Thus, for example, pharmacy technicians were not able to deliver the same level of care in all countries and should not be part of the definition.

The **recipient of PhC** was less of a controversy. Participants agreed not to use the term "patient", but were initially undecided whether to use "individual", "society", or both "individual and society". In the end, everyone agreed to the use of "individuals", because PhC

could be delivered to a group of people simultaneously but should be a service tailored to each recipient individually.

The **subject of PhC** was discussed thoroughly. It was clear for all participants that PhC should be dealing with the care around medicines. On the other hand, some participants also wanted to address services that did not include medicines, because individuals often did not only have drug therapy problems when approaching a pharmacist. There was concern about losing such activities currently seen as PhC (e.g., lifestyle-related) and therefore that this would discourage others from using the definition. Other participants felt that almost all existing definitions dealt only with medicine-related needs or medicine use and that other services that are also provided in the pharmacy were not unrecognized. However, non-pharmacological treatment could be the subject of PhC when medicines were involved or were being evaluated in the course of the practice. Another subject of debate was the term "enhance the responsible use of medicines" previously used by the World Health Organization (WHO)[121]. However, participants felt that this connection to the WHO term would not be self-evident and that, by itself, "responsible use" was rather more system-oriented than patient-centered. Some participants argued for the substitution of "responsible" with "appropriate" or "rational" without agreeing on one or the other. In the end, the whole term was replaced with "optimize medicines use". Participants agreed that this expression is more patient-centered, conveyed the same meaning as the WHO term, and included interventions not directly related to medicines.

The **outcomes of PhC** were briefly discussed towards the end of the session. Participants agreed to include the term "improve health outcomes", referring to the scope of the definition, which aimed at researchers who relied on evidence-based protocols and measurable outcomes. One attendee pointed out that it was not possible for a pharmacist to improve health outcomes, but only to help individuals "to do it themselves". A term suggested by one participant was "quality of life" (QoL), but others rejected this, arguing that medicine use and health outcomes could be improved without measurably improving QoL.

All participants clearly agreed not to mention **specific activities** as part of PhC into the definition. The main concerns were that there were different activities and services provided in different countries, and because PhC should not be understood as the provision of standalone services, but rather as an integrated process linked to an individual assessment. Some participants also pointed out that not all PhC-related services were clearly defined, which would only add confusion to the definition. The final definition is phrased in Box 5.

Box 5: The PCNE definition of pharmaceutical care 2013:

«Pharmaceutical Care is the pharmacist's contribution to the care of individuals in order to optimize medicines use and improve health outcomes.»

To facilitate **dissemination,** participants agreed to have a position paper[123] created. To clarify choices made, important issues that were discussed at the meeting should be mentioned. They emphasized that acceptance of the agreed definition needs comments and explanation of the context. They also agreed on publication of both the position paper and a scientific article, and they asked the main moderators and initiators of the workshop to assume authorship. Finally, participants discussed and set up some rules on the procedure of publication.

Discussion

This paper proposes a redefined definition for pharmaceutical care. The definition has been created by experts, who felt the need to do so. In the result section, the discussion has been outlined on how the experts have reached the current definition. There is no need to reiterate the discussion here. In this section, we will discuss the process of the literature search and the workshop for the definition development.

Applying a systematic approach to identify unique definitions of PhC proved difficult because of the broad variety of possible terms. We decided to use a semi-structured approach with a focus on cross-references from publications identified with the MEDLINE search and inputs from co-authors. The initial MEDLINE search produced almost 200 hits, from which we identified 8 original definitions. The careful examination of the reference lists of the identified publications and inputs from co-authors yielded additional 11 sources for definitions, more than the database search itself. The inclusion of these definitions may have caused a selection bias, because new definitions were likely to be influenced by the definitions found in their reference list. This indicates some deficiency of our MEDLINE search. On the one hand, the search strategy itself was deliberately restrictive. On the other hand, some definitions originated from conferences or other grey literature and their sources are not covered by MEDLINE. Since it was not possible to predict the appearance of a definition on the sole basis of keywords in the title or abstract, many articles had to be scanned in full-text. As a result, a broad literature search that would have covered more sources was not feasible. Independent definitions not identified through our literature search, or the search performed by other authors, were thus missed in this work. As a consequence, we cannot assure the

completeness of our list. However, we can safely assume that the definitions with the highest impact on research and practice were considered. Remarkably, "pharmaceutical care" is not a Medical Subject Headings (MeSH) term, while "nursing care", or "dental care" are. MeSH terms significantly improve searching and it would be desirable to add "pharmaceutical care" to the MeSH vocabulary.

The use of a standardized syntax to paraphrase the definitions allowed for comparison between the different formulations. In some cases, we had to decide about the equivalence of terms (e.g., "drug therapy" and "pharmacotherapy"). To some extent, these decisions were subject to interpretation and could be discussed in a dedicated article. Additionally, it is clear that some information and intention of the original definition were lost during the process of paraphrasing. We understand that the individual wording and syntax of a definition contribute to its meaning. It was not our intention to replace existing definitions with a standardized version. We believe that our standardized syntax was suitable as a working tool for the experts participating in the workshop, to facilitate ease of comparison, to understand the evolution of the definitions over a period of years, and to create a new definition for future use.

The PCNE definition of PhC directly derives from those previous definitions and is intended to unite the current understanding of PhC with respect to the evolution of this practice philosophy during the last 35 years. Differences between previous definitions and the PCNE definition and further explanations about the wording and scope are discussed thoroughly in the position paper[123].

Participants were invited based on their affiliation to PCNE and as a consequence, the result is only representative for this subgroup of researchers and professionals. PCNE is an organization with 36 individual and 23 institutional members from 21 European countries. Additionally, it has observers from countries in other parts of the world. During the meeting, people were present from a large number of countries, as outlined in the acknowledgements. Although PCNE is not representative of the whole pharmaceutical care community, it is the only association that purposely unites researchers and health care professionals that deal with pharmaceutical care almost every day. Furthermore, active participants in the workshop included representatives from the European Association of Hospital Pharmacists (EAHP), the European Society of Clinical Pharmacy (ESCP), and international experts from overseas. This selection of participants from different countries and from a broad variety of work settings ensures the generalizability of the PCNE definition within and outside of Europe and for

different fields of work. In our opinion, this gives the group legitimacy to create a valid definition of PhC.

The chosen method of consensus by using the Hartnett model made sure that various ideas could be combined and concentrated to a shared understanding that focused on the crucial key points of PhC. The benefit of small working groups growing larger during the process was that participation of each individual was guaranteed and no opinion leader was able to take control of the discussion. This way, the result should be representative for the whole group. In his book "Consensus Oriented Decision Making"[103], Tim Hartnett emphasizes the importance of the following unifying principles for the consensus development process:

- inclusive and participatory (all group members included and encouraged to participate)
- agreement seeking (generating as much agreement as possible)
- process oriented (the way in which the decision is made is as important as the resulting decision, all participants are respected and their contributions are welcome)
- collaborative (all group members shape a decision that meets all the concerns as much as possible – participants don't compete and there are no winners and losers)
- relationship building (the resulting shared ownership of decisions and increased group cohesion can promote the implementation of decisions)
- whole group thinking (personal preferences are less important than a broader understanding of how to work together to help the group succeed)

The selected method met these characteristics and cleared the way for a group consensus. The effects of previous agreements and the dominance of opinion leaders were minimized by the changing of group composition and the obligation to find collaborative solutions. Limitations included that there was only limited time in the workshop, which impeded reflection on the inputs and forced participants to make quicker decisions than they might have wished. Due to the intensive program, the concentration of participants may have decreased towards the end. Reaching a consensus might have been driven by the wish to conclude, rather than having reached a shared agreement, although all participants have stated they were happy with the redefined definition at the end of the meeting.

Conclusion

Many definitions of PhC exist that differ greatly from each other. For comparison, it is possible to paraphrase each definition with a standardized syntax focusing on the provider, recipient, subject, outcomes, and activities included in the PhC practice. During a one-day workshop, experts in PhC research agreed on a definition that should be representative for

various work settings and should be valid for countries inside and outside of Europe, and adopted to the current time.

Acknowledgements

The authors would like to acknowledge the contributions of participants of this invitational conference: Cecilia Bernsten* (Sweden), Lawrence Brown (USA), Olivier Bugnon* (Switzerland), Tim Chen (Australia), Maria Cordina* (Malta), Tobias Dreischulte* (Germany), Fernando Fernandez-Llimos (Portugal), Veerle Foulon (Belgium), Richard Price (Belgium), Martin Henman* (Ireland), Hanne Herborg* (Denmark), Charlotte Kloft (Germany), Juliane Kresser (Germany), Tajda Miharija-Gala (Slovenia), Sirpa Peura* (Finland), Allison Roberts (Australia), Charlotte Rossing* (Denmark), Marion Schaefer* (Germany), Martin Schulz* (Germany), Dick Tromp* (The Netherlands), Tommy Westerlund* (Sweden). Furthermore, we are grateful to Mary Tully* for editing the final draft. *PCNE members

Conflicts of interest

The authors report no conflicts of interest.

Appendix

A.1.1 Synopsis for workshop participants

B – Split medications in pharmacy-filled blister pouches

Project B1

Issues around the prescription of half tablets in Northern Switzerland: The irrational Case of Quetiapine

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Biomed Res Int. 2015;2015:602021. doi: 10.1155/2015/602021. Epub 2015 Oct 11.

Abstract

Background: Prescription of fragmented tablets is useful for individualization of dose but includes several drawbacks. Although without score lines, the antipsychotic drug quetiapine was in 2011 the most often prescribed 1/2 tablet in discharge prescriptions at the University Hospital in Basel (USB, 671 beds). We aimed at analyzing the prescription patterns of split tablets in general and of quetiapine in particular in Switzerland.

Methods: All orders of community pharmacies for unit-of-use soft pouch blisters placed at Medifilm AG, the leader company in Switzerland for repackaging into pouch blisters, were analyzed.

Results: Out of 4,784,999 tablets that were repacked in 2012 in unit-of-use pouch blisters, 8.5% were fragmented, mostly in half (87.6%), and were predominantly psycholeptics (pipamperone 15.8%). Prescription of half quetiapine appears to be a Basel specificity (highest rates of fragments and half quetiapine).

Conclusions: Prescription of fragmented tablet is frequent. It represents a safety issue for the patient, and a pharmaceutical care issue for the pharmacist. In ambulatory care, the patient's cognitive and physical capacities must be clarified, suitability of the splitting of the tablet must be checked, appropriate aids must be offered, like a pill-splitting device in order to improve accuracy, and safe use of the drug must be ensured.

Introduction

Previous studies showed that fragmenting concerns every fourth tablet in ambulatory setting[124,125], predominantly because of dose adjustment, swallowing difficulties or costs[126-128]. However, some drawbacks exist, such as breaking difficulties, breaking in unequal parts, and loss of mass[128]. Further, changing the dosage form may degrade the active substance at the fractured surface, and thus alter its absorption characteristics. The site of action may not be reached, which may be clinically relevant, especially for substances with narrow therapeutic index[129]. The keeping of the halves may be difficult because of problems of stability and of identification. Further, controlled release forms are unsuitable for splitting, since their destruction can lead to dose-dumping and dose-dependent side effects by altering the liberation kinetics of the substance. Finally, substances with irritating or toxic properties, especially the CMR-substances (carcinogen, mutagen or toxic for reproduction) should be split only with protective measures (e.g., gloves, masks)[130].

The European regulatory authorities evaluated splitting tablets into segments[131]. This apparently simple operation bears a potential for dosage error that increases if the tablets are not scored. In view of the many exceptions where splitting is not allowed (enteric coated tablets, layered tablets, many modified-release dosage forms) the authorities concluded that manufacturers should provide information on the issues surrounding cutting tablets into smaller segments. In the US, the FDA, the American Medical Association, and other medical organizations consider tablet splitting as a risky practice and advise against it unless it's specified in the drug's labeling[132]. The analysis of electronic medication regimens from 54 wards of a large University hospital in Germany showed that 12.5% of all drugs were prescribed in split form[133]. Splitting was inappropriate for 2.7% of all drugs, mainly because of the absence of a score line. A retrospective study performed at the University Hospital Basel in Switzerland showed similar results[134]. Of the 36,751 electronic prescriptions delivered 2011 at discharge, 3,724 (10.1%) contained the mention "½" and concerned 4,888 single tablets. Of those ½ tablets, 16.4% were wrongly prescribed, predominantly due to inexistent score lines. Quetiapine (Seroquel®, Sequase® 25mg), a tablet with no score line, was the drug most often wrongly prescribed as half tablet.

Quetiapine is an atypical or second-generation antipsychotic agent similar in structure to clozapine, and exhibits strong antagonism of $5HT_2$ receptors and weak antagonism of D_2 receptors[135]. It is approved for the treatment of schizophrenia and bipolar disorders[136], and is widely used, mainly because it does not induce agranulocytosis[137] and thus, does not require blood monitoring. Its substantial advantage is further a favorable profile of acute

extrapyramidal side effects that occur in very rare cases[138]. Off-label use is common—i.e. unlabeled or unapproved use—in conditions such as agitation, anxiety, dementia, obsessive-compulsive disorders, psychosis[139], and delirium[140,141]. Because of many inconclusive study results, evidence is limited. A meta-analysis of seven randomized controlled studies with 3,257 participants evaluated the effects of quetiapine for anxiety disorders at doses ranging between 25-400 mg/day[142]. Monotherapy with quetiapine was better than placebo in reducing symptoms of generalized anxiety disorder, and was equivalent to antidepressants in improving depressive symptoms. In all studies, more subjects in the quetiapine group left the trials early due to adverse events (gained weight, sedation). The additional use of quetiapine at doses between 25-600 mg/d was established in a further meta-analysis only in the treatment of generalized anxiety disorder[139]. The small clinical studies mostly started doses at 25 mg/day[143-145]. We were able to find low-dose quetiapine at 12.5 mg only in one Italian study for the initiation of treatment in 41 patients with dementia and concomitant psychotic disorders[146] and in one Spanish study with 7 Parkinson's patients, where low-dose quetiapine was effective on psychotic symptoms, sleep disturbances and stress of the caregivers[147].

Building up on the local observation of 2012, we aimed at analyzing the general prescription patterns of split tablets in Switzerland. Thus, the questions of interest are *"What is the prevalence of split tablets in Switzerland? Is the wrong prescription of half quetiapine tablets restricted to a local habit in Basel?"* Further, we aimed at evaluating the consequences of split tablets for community pharmacies, patients and patient care organizations and discussing some recommendations for daily practice.

Material and Methods

We obtained all orders placed by Swiss community pharmacies at Medifilm AG, the leader company in Switzerland in the repackaging of medication into unit-of-use soft pouch blisters, located in the industrial area of Oensingen (canton Solothurn)[148]. Community pharmacists can order rolls of single pouches containing various medications to be taken at one time, mainly for long-term institutionalized patients. Segments of tablets can be ordered without restriction. Orders are submitted to quality assurance checks. When split tablets are required and corresponding lower dosage strength is available as single tablet on the market, an exchange takes place. If no lower dosage strength is available, and the formulation of the tablet is conventional (i.e. no enteric coat, no modified-release), the tablet is fragmented with an automatic pill-splitter. According to the Summary of Product Characteristics[136], quetiapine tablet is a round, 6mm in diameter, film-coated tablet without score line. Since its formulation

is without functional coating, the splitting of the lowest strength of quetiapine tablet (Seroquel® 25mg original brand, and Sequase® 25mg generic brand approved since 09.2011) is performed.

Presence of a score line and suitability for splitting of tablets were obtained from the Swiss Summary of Products Characteristics[136]. Archive files were retrieved from the open drug database ch.oddb.org.

Statistics

We used the SPSS statistical package version 21.0 (SPSS Inc., Chicago, IL, USA) for data description and the R system for computation and graphics[149]. Additional graphics were created with Power Map Preview for Excel 2013 (Microsoft Excel [computer software], Microsoft, 2013, Redmond, Washington, USA)

Results

Between January 1st and December 31th 2012, a total of 4,784,999 tablets were packed in unit-of-use soft pouch blisters by Medifilm. Of these, a total of 406,956 (8.5%) were fragments of tablets that had been ordered by 29 community pharmacies for 1,321 patients residing in 53 retirement homes in northern Switzerland. The homes have used in 2012 between 14 and 48,300 fragmented tablets (Table 3). The patients were in average 81.5 ± 14.7 years old (median 86; range 7-105) and obtained in average 1.7 fragments (median 1; range 1-8). A total of 577 (43.7%) patients received two or more fragments of tablets (Table 4). The majority of the fragments were halves (356,339; 87.6%) and quarters (45,375; 11.1%), and marginally thirds, two-thirds and three-quarters (5,242; 1.3%; Figure 7).

Table 3: Fragments and half quetiapine tablets by home (N=53) as frequency and as proportion of the total number of fragments (N=406,956). The cantons are given by their official abbreviations (BE: Berne, BS: Basel Stadt, AG: Aargau, SO: Solothurn, BL: Basel Land, LU: Lucerne, ZH: Zurich, SG: St. Gall, GR: Grisons).

ID	№ of fragments (%)	№ of half quetiapine (%)	Cantons								
			BE	BS	AG	SO	BL	LU	ZH	SG	GR
1	48300 (11.9)	409 (0.1)	x								
2	28255 (6.9)	1142 (0.3)	x								
3	22835 (5.6)	2445 (0.6)	x								
4	22415 (5.5)	578 (0.1)		x							
5	21996 (5.4)	988 (0.2)			x						
6	21178 (5.2)	3699 (0.9)		x							
7	20853 (5.1)	2478 (0.6)		x							
8	20840 (5.1)	458 (0.1)				x					
9	19557 (4.8)	3862 (0.9)					x				
10	18992 (4.7)	1597 (0.4)			x						
11	16065 (3.9)	778 (0.2)						x			
12	15756 (3.9)	1774 (0.4)			x						
13	14568 (3.6)		x								
14	14517 (3.6)	862 (0.2)					x				
15	13368 (3.3)	21 (0.01)	x								
16	11539 (2.8)	854 (0.2)							x		
17	10083 (2.5)	2133 (0.5)		x							
18	9861 (2.4)	582 (0.1)		x							
19	5963 (1.5)							x			
20	5868 (1.4)					x					
21	4990 (1.2)		x								
22	4968 (1.2)				x						
23	4466 (1.1)						x				
24	3518 (0.9)	775 (0.2)		x							
25	3124 (0.8)						x				
26	2526 (0.6)	523 (0.1)							x		
27	2480 (0.6)					x					
28	2435 (0.6)					x					
29	2334 (0.6)									x	
30	1456 (0.4)					x					
31	1427 (0.4)						x				
32	1078 (0.3)			x							
33	1004 (0.2)		x								
34	980 (0.2)	28 (0.01)		x							
35	905 (0.2)					x					
36	890 (0.2)					x					
37	836 (0.2)	126 (0.03)							x		
38	771 (0.2)					x					
39	751 (0.2)	223 (0.1)			x						

ID	Nº of fragments (%)	Nº of half quetiapine (%)	Cantons								
			BE	BS	AG	SO	BL	LU	ZH	SG	GR
40	719 (0.2)							x			
41	514 (0.1)							x			
42	414 (0.1)					x					
43	291 (0.1)					x					
44	276 (0.1)							x			
45	267 (0.1)				x						
46	224 (0.1)				x						
47	159 (<0.1)				x						
48	133 (<0.1)					x					
49	125 (<0.1)								x		
50	39 (<0.1)		x								
51	19 (<0.1)										x
52	14 (<0.1)			x							
53	14 (<0.1)		x								
Total	**406,956 (100%)**	**26,356 (6.5%)**	**8**	**9**	**8**	**11**	**5**	**5**	**3**	**1**	**1**

Table 4: Numbers of split medication by patient (N=1,321 patients)

Nº of fragments	Nº of patients (%)	Cumulative Nº of patients (%)
1	744 (56.3)	744 (56.3)
2	350 (26,5)	1,094 (82.8)
3	139 (10,5)	1,233 (93.3)
4	65 (4,9)	1,298 (98.2)
5	15 (1,1)	1,313 (99.3)
6	5 (0,4)	1,318 (99.7)
7	2 (0,2)	1,320 (99.9)
8	1 (0,1)	1,321 (100)

The fragments concerned 132 different active substances, and 50% of them were psycholeptics or psychoanaleptics (Figure 7). The most often split tablets were preparations with pipamperone (15.8%), levodopa/decarboxylase inhibitor (10.2%), and quetiapine (6.5%; Table 5). The ten most often fragmented tablets accounted for 57% of all split tablets (Table 5).

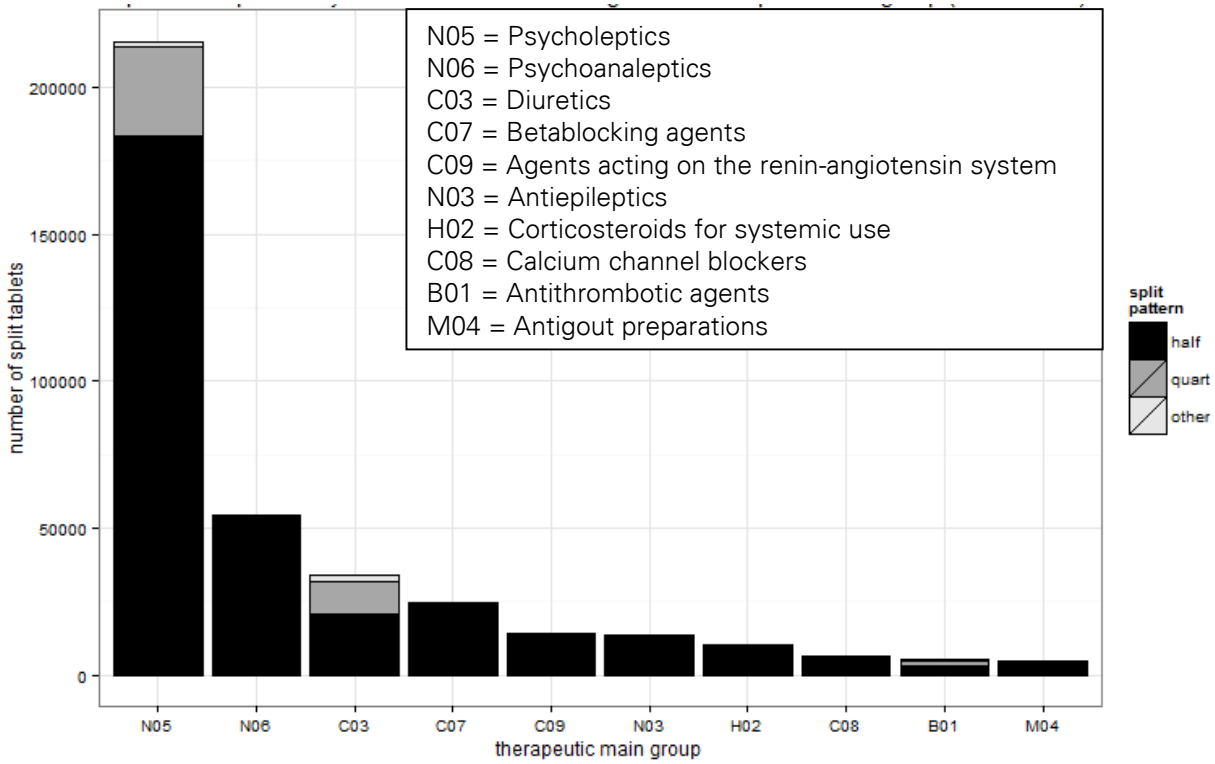

Figure 7: Distribution of the ten most often split tablets sorted by ATC therapeutic main group (N = 406'956).

Table 5: Ten most frequently split medication given by active substances (SPC: Summary of Product Characteristics).

	Proportion of split tablets [%]				
Active substance (original brand name)	**Total (cumulative)**	**quarter ¼**	**half ½**	**three-quarter ¾**	**Splitting is explicitly mentioned in the SPC (yes / no)**
Pipamperone (Dipiperon®)	15.8	6.2	9.3	0.3	y
Levodopa / Decarboxylase inhibitor (Madopar®)	10.2 (26.0)	-	10.1	0.1	y
Quetiapine (Seroquel®, Sequase®)	6.5 (32.5)	0.3	6.2	-	n
Lorazepam (Temesta®)	5.1 (37.6)	0.4	4.7	-	y
Mirtazapine (Remeron®, generics)	4.3 (41.9)	-	4.3	-	y
Torasemide (Torem®, generics)	3.9 (45.8)	2.2	1.2	0.5	y
Zolpidem (Stilnox®, generics)	3.2 (49.0)	-	3.2	-	y
Metoprolol (Beloc ZOK®, generics)	2.7 (51.7)	-	2.7	-	y
Citaloprame (Seropram®, generics)	2.7 (54.4)	-	2.7	-	y
Risperidone (Risperdal®)	2.6 (57.0)	-	2.6	-	n

The highest proportion of fragmented tablets was ordered for homes located in northern Switzerland, i.e. Basel (89,980; 22.1%), Berne (61,707; 15.2%) and Baden (38,503; 9.5%; Figure 8, heat map). The most split quetiapine tablets was ordered in Basel (10,273; 39%; Figure 8, bars) compared to the rest of Switzerland (i.e. French and Italian speaking parts).

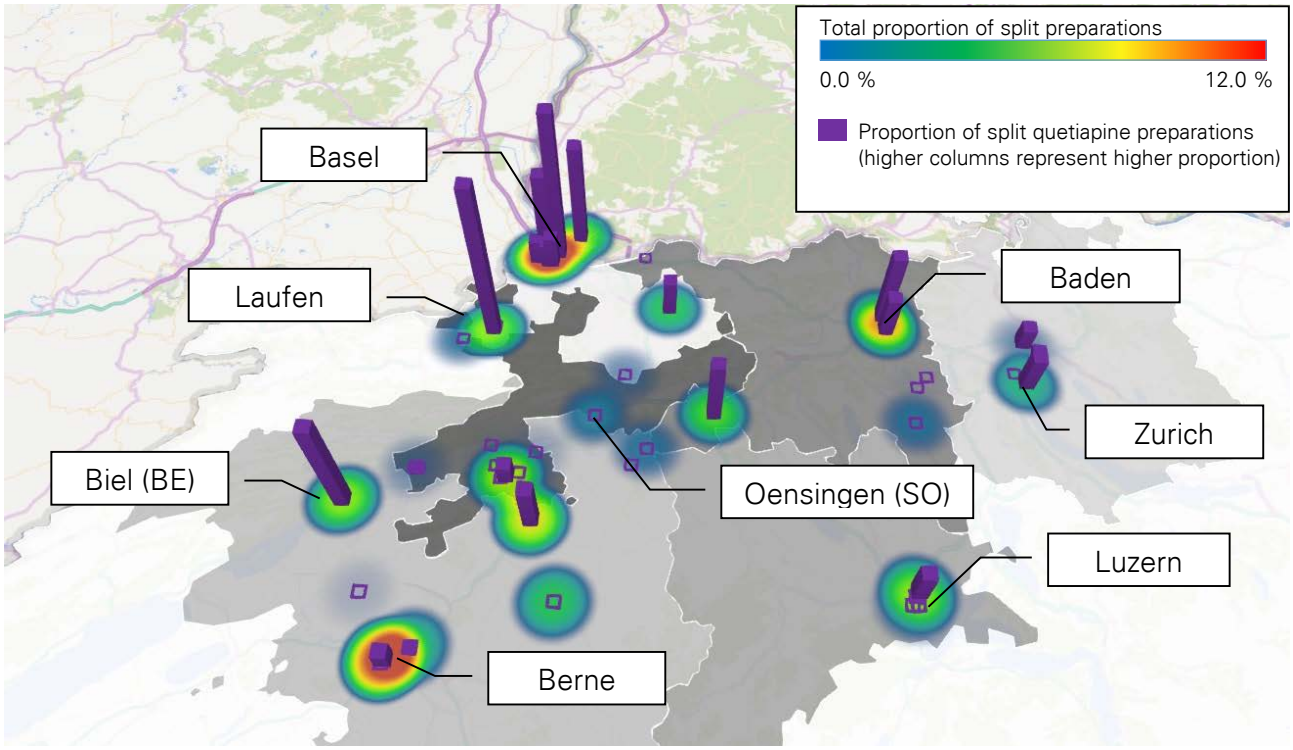

Figure 8: Geographical distribution of split tablets in general (heat map; the warmer the color (i.e. red), the higher the frequency, independently of the surface) and of half quetiapine tablets (purple bars; the higher the column, the higher the proportion) for each of the 51 retirement homes (N = 406,956). Grey areas indicate cantonal borders. The two distant homes located in the cantons SG and GR (<0.1% split tablets; no quetiapine) are not depicted.

Discussion

Fragments of tablets represented 8.5% of all tablets ordered 2012 by 53 community pharmacies in northern Switzerland for institutionalized patients. This value is probably below the effective prescription rates of fragmented tablets since splitting at the company Medifilm is reserved for cases where no lower dosage strength is available on the market. Consequently, the actual value of dispensed fragmented tablets in ambulatory setting might be higher, given that the exchange for a commercially available lower strength is not automated in community pharmacists during routine practice. A recent study in Swedish community pharmacies showed that 52.5% of the patients with a prescription for split tablets preferred whole tablets of the appropriate strength rather than to split tablets[150].

Nevertheless, prescribing fragments of tablets appears to be a very common practice in the ambulatory setting.

Out of the 10 most often ordered split tablets, two (quetiapine and risperidone) had doubtful legitimacy to be fragmented since the decision cannot be backed up with the product information. Although splitting a tablet that is not intended to be fragmented doesn't seem to be a prescribing error[151-153], it may reduce drug effectiveness and induce toxicity, and thus represents a safety issue.

Wrong prescription of ½ tablets usually does not cause significant patient harm, since for many drugs, especially those with a wide therapeutic range and a long half-life, dose fluctuations are unlikely to be clinically significant. The above applies for quetiapine, even more since its formulation is without functional coating or modified release.

In any case, some pitfalls exist when fragmenting tablets that are not intended to. First, patients may be easily confused about the correct dose. An effective instruction of the patients by the health professional is a prerequisite to minimize intake errors, especially when patients received information at the time of hospital discharge that diverges from the finally dispensed medication, e.g., obtaining half tablets during hospitalization, leading to an initial prescription of a half tablet that is modified to one tablet of a lower dose. In the worst case, patients may split the wrong medication, and take too few or too much medication. Second, patients might have poor visual acuity or dexterity that render fragmenting very uncertain. They need at least the right tools and should be given a pill-splitting device to improve accuracy. Third, patients may store the remaining fragments or crumbles inadequately, which may affect medication stability, or use a container with no labelling, which renders a later identification of the fragments almost impossible. Fourth, patients may split several medications, which seems to be a frequent situation with 43.7% of our patients obtaining two fragments or more. Because the identification of the fragments is limited, the presence of multiple fragments represents probably the riskiest situation, with a wrong intake resulting invariably from one handling error.

Given the potential risks, it is striking that half of the splitting concerned psychoactive substances in this elderly population. However, the appropriateness of splitting tablets may result from clinical observation. Because most manufacturer-based research excludes frail elderly, and as such the appropriate dose for such patients, the prescription of split tablets may be the result of over-sedation observed with whole tablets.

All above mentioned processes may represent safety issues, be time-consuming for patients, their relatives or caregivers in charge of the medication managements, and ultimately generate costs that may clear the savings initially advocated for splitting tablets[154]. Finally, since hand-written prescriptions are still common, misreading by the pharmacist of one-half (1/2) as one to two (1-2) tablets can only be ruled out if prescribers would order strength and dose of the medication in milligrams[155].

The USB is a 671-bed teaching hospital in northwestern Switzerland and serves as a major referral center for the 1 million region. At the USB, quetiapine is administered off-label for the prevention of delirium in the postoperative setting, starting at doses of 5mg/day with 5mg capsules exclusively produced at the hospital pharmacy. Quetiapine is also used off-label for the therapy of delirium according to an internal scheme[156] where multiple doses of 12.5mg up to 50mg/24h (<80 years) or 5mg up to 25mg/24h (>80 years) are administered on the first day, with doubling of the dose on the second day. According to this scheme, therapy should be reduced or stopped after 5 days. On the wards at the USB, a dose of 12.5mg quetiapine is administered as ½ tablet of 25mg strength according to a recommendation note of the Division of acute geriatrics. Quetiapine is the favorite drug for hospitalized elderly who are slightly disorientated and mildly agitated, e.g., who stand up and are at risks of falling. Further, quetiapine has a short half-life, an antihistaminic action, and a lower incidence of QTc prolongation compared with haloperidol, the standard delirium therapy.

From a clinical point of view, trials on pharmacological prevention of delirium did not show conclusive results[157]. No controlled maintenance treatment trials have been conducted with quetiapine, unlike for all other atypical antipsychotics which have demonstrated a positive effect on relapse prevention[138]. In studies that investigated effects on negative symptoms (emotional and social withdrawal, poverty of speech, lack of drive and motivation, disinterest) and used haloperidol as the comparator drug, quetiapine did not show any advantage[138]. Independently of the (non-)existing evidence, the internal scheme used at the USB recommends reducing or stopping treatment with quetiapine after 5 days, which information seems to get lost during hospitalization. Neglecting to annotate the duration of use, i.e. the “stop” date of a treatment, represents a prescription error which may be costly[158]. Further, preventive pharmacological therapy in geriatric patients can expose them to the unnecessary risk of adverse effects. Furthermore, all antipsychotics inclusive quetiapine are listed in the Beers Criteria as potentially inappropriate for use in elderly patients (quetiapine is an exception for patients with Parkinson’s disease)[159]. Thus, continued antipsychotic therapy in geriatric patients should be re-evaluated at each care transition, and stopped in

absence of clear indication. Particularly noteworthy is the fact that low-dose quetiapine does not seem to be administered for its antipsychotic effects but rather for its sedative effects in the elderly hospitalized patients, in an empiric manner and in absence of clear evidence for a proven alternative.

Finally, it seems that the irrational case of ½ quetiapine 25mg remains confined to Basel and its clinics and didn't spread out. However, the level is surprising high when one considers that 5 years had passed since the official introduction of the recommendation in the division of acute geriatrics.

The observation that community pharmacies ordering unit-of-use soft pouch blisters were massively located in northern Switzerland (with one marginal exception in the Grisons) may reflect a cultural difference between German speaking regions in the northern, and French and Italian speaking regions in the southern, and is not a limitation.

Conclusions

Tablet splitting has a major role in dosage adjustment and should be limited to specific clinical situation, i.e. titration of dose, pediatric and geriatric patients, and according to the recommendation of the product manufacturer. Physicians who prescribe to split a tablet that is not intended to be fragmented and pharmacists who dispense the drug accordingly should be aware that this renders the medication unlicensed. Since resolving the uncertainty about the prescription by the pharmacists or the nurses results in much unnecessary work, splitting tablet is not suited as a method of general cost reduction. Taking into account all problems linked to the handling of a half tablet (patients' dexterity and eyesight, conservation and confusion of the halves, wastage, therapeutic compliance), prescribing ½ tablet represents a safety issue. Thus, prescribers should make effort to use commercially available whole tablets. If splitting tablets is still necessary, patient counseling is recommended and pharmacies should deliver the appropriate tools or pharmacists split the tablets for the patient and repackage them.

Quetiapine 25mg remains the third most often prescribed half tablet in northern Switzerland in general and the first specifically in Basel. As off-label prescribing is claimed to be not evidence-based, to undermine the regulatory system, to be costly, to put the patient at risk and to impact negatively on pharmaceutical innovation[160], this situation is more than frightening. It is usually in the company's interests to extend the indications of its products. However, in this particular case, the pharmaceutical industry seems to limit its investment

probably because generic formulations are available. Pharmaceutical companies should be encouraged to introduce new strengths to an existing range of products, in view of an optimization of seamless care between the different health care professionals.

Acknowledgments

The authors wish to thank Markus Meier (Medifilm AG) for disclosing the database, Martin Recknagel for extracting the data files, and ywesee for providing the archived Swiss Summaries of Product Characteristics.

Disclosures

The authors declare that there is no conflict of interests regarding the publication of this paper. They are responsible for the content and writing of the paper. The Pharmaceutical Care Research Group, University of Basel, funded this study.

Appendix

C – A remote electronic medication management aid for prepackaged polypharmacy in primary care patients

Project C1

Patient views on an electronic dispensing device for prepackaged polypharmacy: a qualitative assessment in an ambulatory setting

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Integr Pharm Res Pract. 2015; 4. pp. 167-174. doi: 10.2147/IPRP.S90923.
Epub 2015 Nov 06.

Abstract

Objective: To collect opinions on medication management aids (MMAs) in general and on an electronic MMA (e-MMA) dispensing prepackaged polypharmacy in sealed pouches.

Study setting: The setting involved community-dwelling older adults in Basel, Switzerland, in 2013.

Study design: The study involved 1) a 14-day trial with the e-MMA and 2) a focus group to identify general attributes of MMAs, their applicability to the e-MMA, and possible target groups for the e-MMA.

Data collection methods: Six participants using long-term polypharmacy and willing to try new technologies completed the 14-day trial and participated in the focus group. Inductive content analysis was performed to extract data.

Principal findings: Participants rated ten of 17 general attributes as clearly applicable to the e-MMA and five as unsuitable. Attributes pertained to three interrelating themes: product design, patient support, and living conditions. Envisaged target groups were patients with time-sensitive medication regimens, patients with dementia, the visually impaired, and several patients living together to prevent accidental intake of the wrong medication.

Conclusion: The evaluated e-MMA for prepackaged polypharmacy met the majority of the requirements set for an MMA. Patients' living conditions, such as mobility, remain the key determinants for acceptance of an e-MMA.

Introduction

Health-care professionals not only have to provide patients with the correct diagnosis and appropriate therapy. They must also enable patients to "take their medication as prescribed", a seemingly simple behavior which is known as *medication adherence*[22].
A review of 50 years of adherence research estimates a mean adherence rate of 75.2 %, ranging from 65.5 % for sleep disorders to 88.3 % for HIV[38]. Non-adherence, or the failure to take medication as prescribed, strongly relates to negative outcomes[161]. The development of effective interventions to improve adherence is a quest many researchers and practitioners have been pursuing for decades. Due to its inherent complexity, there is no one-size-fits-all solution to combat non-adherence[57]. A simple method is the use of a device that holds a predefined number of medication organized by day and time according to a patient's individual therapy plan. Such medication management aids (MMA) exist in various shapes and they are widely used for presumably non-adherent patients, especially older adults[64].

Annotation of relevant literature

Between 62% and 75% of older adults report at least part-time use of MMAs[69,70]. MMAs can be managed by the patient or are pre-filled at a pharmacy or by another caregiver[68]. Despite their widespread use, the authors of a review of the effects of MMA concluded that the design and targeting of these devices need further research[64]. MMAs generally target therapy-related factors, condition-related factors, and social factors of non-adherence, aiming to improve unintentional non-adherence during the implementation phase[22]. Given the fact that all doses need to be prepared in advance for each intake time, patients are able to see whether they have already taken their medication or not. Hence, MMAs classify as "feedback and monitoring" interventions according to the "Behavior Change Technique" (BCT) Taxonomy[162]. Until now, the measurement of adherence with MMAs was restricted to indirect or subjective measures like pill counts, timeliness of refills or patients' self-report[37]. Electronic measurement is considered a "gold standard" but with polypharmacy this method is in its early stages[37]. Recently, electronic MMAs emerged, reminding patients with acoustic or visual alerts to take their medication, dispensing the right medication at the right time, and tracking each event. These developments allow for the objective measurement of adherence. We could identify only very few studies about electronic MMAs, either focusing on measuring adherence only[27,163] or on the technical specifications[164-166]. In a study assessing the satisfaction of 96 older adults with an electronic medication dispensing device in home care, participants accepted the device as "very easy to use, very reliable and helpful in the

management of their medications"[167]. Although a high rejection rate was reported, the study report did not address participants' motivation to use or reject the device in the first place. The final report on a project with electronic MMAs aiming at improving self-management among non-adherent patients concluded that "anyone who has difficulty remembering to take their medication" may benefit from such an intervention[168]. Of 380 participants of this project, more than 30% were in the early stages of dementia and approximately 20% had physical disabilities, such as dexterity issues or visual impairment. Around 10% left the study because they did not like the dispenser and around 7.5% because they were non-adherent. Around half of all patients approached to participate declined for various reasons, e.g., they did not like the look or the sound of the dispenser, they felt the dispenser was taking control of their medication management, or they did not want to take the device out to social events.

Thus, we hypothesize that programs using e-MMAs often missed to target the optimal users. The goal of this study was to gather information regarding the use of an electronic MMA by community-dwelling older adults using chronic polypharmacy. The aims were:

1. to collect and evaluate attributes of medication management aids important to patients;
2. to evaluate the use of a specific electronic MMA with polypharmacy pre-packaged in pouches in relation to these attributes;
3. to identify the target group that could benefit most from the electronic MMA.

Materials and methods

Participant selection

The investigators (IA and KH) recruited a convenience sample of community-dwelling older adults with self-disclosed long-term use of polypharmacy and willingness to try innovative technologies from a community pharmacy in Basel (Switzerland).

Medication Management Aid (MMA)

An Automatic Tablet Dispensing and Packaging System (ATDPS; Desk Type JV-30DE, HD-Medi, Germany) was used to repack all solid oral prescription medications for each participant into unit-of-dose pouches. Each pouch was imprinted with the patient's name, date of birth, date and time for intake, as well as number, name, color, and shape of the medication contained (Figure 9). Every participant received a roll with pouches for 14 days loaded into a dispenser installed at their homes. The dispenser (Medido®, Innospense BV,

Netherlands) was a remote controlled, electronic MMA reminding the patients with acoustic alerts to take their medication (Figure 10). Pushing the OK-button stops the alarm and delivers the pouches with pre-packaged medication. Date and time of delivery are simultaneously recorded with GPRS-technology. Delivery of doses ahead of schedule is possible by pushing the OK-button for 5 seconds. This important feature named pocket-doses enables patients to go out of the house during intake times. Time of dispense was individually set accordingly to participants' preferences. SA demonstrated the use of the dispenser during the installation and provided written instructions with telephone numbers to call an investigator for assistance in case of technical problems.

Figure 9: Unit-of-dose pouches with pre-packaged oral solid medication

Figure 10: Remote-controlled, electronic dispenser for the unit-of-dose pouches Medido® used in this study as specific e-MMA with power cord in lower right corner (height x width x length: 140 mm x 140 mm x 225 mm, weight: 1486 g)

Data collection

Participants were asked to write down any dispensing of pocket-doses, malfunctions, or noteworthy events during the 14 days of use. Upon returning of the dispenser, they were interviewed based on a short interview guide with the following questions to collect spontaneous reactions:

1. How was the operation of [the device]?
2. How did you integrate [the device] into your daily life
3. What additional benefits can [the device] provide for daily medication intake?
4. What monthly fee would you be willing to pay for [the device]?

Additionally, we invited all participants to attend a focus group. Focus groups provide concentrated interactions in a short time frame and allow the generation of data based on the synergy of the members in a group[169]. For this exploratory study, only one focus group was carried out using a semi-structured approach. Based on the answers from the short interviews and literature, a preliminary list with attributes was compiled by the investigators (Appendix A.2.3). A focus group script was developed and pilot tested with regards to comprehension and timeline with an 83-year-old female using chronic polypharmacy who was not enrolled in the study (Appendix A.2.2).

The focus group took place in a conference room of the University of Basel and lasted 2 hours. First, participants filled out a short form including demographics and data about their medication therapy. After a brief introduction, participants were guided through the following 4 steps:

1. write down attributes of MMAs in general judged as important (every participant individually);
2. clarify the meaning of the attributes (plenary discussion);
3. vote on the applicability of the attributes to the electronic dispenser, inclusive additional attributes from the preliminary list;
4. define target groups for the dispenser based on one's 14-day experience.

SA moderated the focus group, while IA took notes and compared the proposed attributes with the preliminary list. Participants used playing cards to vote on the attributes; one color (red hearts) for "yes I agree", another color (black clubs) for "no I disagree" and the joker to initiate a discussion. Whenever a joker was raised, participants discussed issues and repeated their voting afterwards, until no joker was displayed. The focus group was held in Swiss German and audio-taped. One researcher (SA) orthographically transcribed the recording in

German, preserving dialect expressions. Attributes and quotes mentioned in this article were translated into English by SA and IA.

Content analysis

Inductive content analysis was used as theoretical framework based on Krueger's approach[170] as outlined by Rabiee[169]. In brief, this method uses categories, which are derived directly from the data, as opposed to deductive content analysis that is based on earlier work[171]. Krueger's approach includes five interrelating stages: familiarization; identifying a thematic framework; indexing; charting; mapping and interpretation[169]. The data were coded by SA, reviewed by IA, and discussed by both for validation. Inconsistencies were resolved by consensus. Attributes were grouped in sets to form major themes. No attributes were excluded.

Qualitative data was entered into the software MAXQDA 11 (VERBI GmbH, Berlin, Germany) to support analyses. The study data are reported according to the COREQ guideline, a checklist with consolidated criteria for reporting qualitative research[172].

Results

Seven persons were contacted between February and May 2013. All accepted to participate and completed the full 14-day assessment period. One participant refrained from participating in the focus group due to conflicting dates and was excluded from analyses. Six participants (4 women, 2 men) aged 55 to 76 years (mean 65.3 years) attended the focus group (Table 6). All but 2 women were retired and all declared to spend in average 38% of their daytime activities (except weekends) at home. Three women lived alone (50%), the other participants shared a household with a partner. Participants were taking daily 2-5 (mean 3.3) solid oral medicines with a posology of 1-3 intake times and at least one intake in the morning. All 168 scheduled doses were delivered (100% reliability). All patients retrieved in total twenty-eight doses (17%) as pocket-doses for intake outside of the home.

During step 1, participants wrote down 13 individual attributes of MMAs judged as important. Two further attributes emerged from the discussion (step 2) and another 2 were proposed from the preliminary list, adding to a total of 17 attributes (Table 7).

Participants rated 10 attributes as clearly applicable to the e-dispenser (Table 7). Five attributes were rated as unsuitable, like the consumption of power and production of waste (ecological aspect), lack of mobility, insufficient information about the pre-packaged

medication, and perceived inflexibility of the intake times. Participants also expressed the desire to receive reminders of upcoming refill events and appointments with the physician. The votes on 2 attributes were equally distributed (good looking and place-saving). The themes that emerged during step 2 (discussion) were interrelated and concerned product design, patient support and living conditions.

Table 6: Description of the 6 patients completing 14 days of medication management with pre-packaged pouches and e-MMA, and individually set intake times.

Nr.	Sex*	Age (years)	Status*	Living condition*	Daytime activities at home	Nr. of daily oral, solid prescription medications	Intake time/s (hour: min)
P1	f	65	r	a	50%	3	07:00, 22:00
P2	m	67	r	p	50%	4	07:50, 19:00
P3	f	55	w	p	30%	3	07:00
P4	m	76	r	p	50%	5	07:30, 12:00, 18:30
P5	f	72	r	a	10%	3	09:20
P6	f	57	w	a	40%	2	06:10, 06:40, 18:20
mean		**65.3**			**38.3%**	**3.3**	

* f: female; m: male; r: retired; w: working; a: alone; p: with partner

Table 7: Attributes of MMAs judged important and participants' votes on applicability to electronic dispenser; unsuitable attributes are marked in grey. A raised joker entailed a discussion between the participants and a repeated voting, until no joker was displayed.

Attribute [times written]	**Applicable to e-dispenser**	
	Yes	**No**
is easy to use [4]	6	0
provides mental support [4]	6	0
assures timely intake [3]	6	0
assures regular intake [3]	6	0
assures correct dosing [2]	6	0
reduces regimen complexity [2]	6	0
functions autonomously [1]	6	0
is unobtrusive [1]	6	0
is reliable#	6	0
is hygienic*	6	0
looks good [1]	3	3
is space-saving [1]	3	3
permits flexible intake times#	2	4
provides medication information [1]	1	5
is mobile [1]	0	6
prompts for refill [2]	0	6
is ecological*	0	6

emerged from discussion (step 2)
* proposed from preliminary list

Product design

This theme relates to tangible attributes of the dispenser, which can be directly modified by changing its hard- or software (e.g., the size, ease of use, and reliability). Participants controversially discussed the size and appearance of the dispenser, which was compared to *"a monster"* and a *"toaster"* by P5. They found it difficult to find a place for the dispenser, wanting to hide it in *"a corner of the home"* ["eine Ecke in der Wohnung"] (P5). Conversely, P3 described the dispenser as *"more beautiful than expected"* ["schöner als erwartet"]. Participants agreed that the appearance was subject to individual likings, as was the location where it was placed. All participants found it easy to use the dispenser as instructed. P3 found the OK-button quite rough-running, but had no problems operating the device. P2 stated that the dispenser should allow narrower intervals than the 10-minute intervals to set reminders. P1, P2, and P6 mentioned the light emitted from the device as relatively bright, and the sound as quite loud. P5 stated that the design became less important when she started experiencing benefits from the dispenser: *"If I had to rely on it [the dispenser], I would have looked for some corner in the home, where it wouldn't be very dominant [laughs]. However, the look didn't play such a big role anymore. That has taken a back seat."* [„Ja wenn ich jetzt darauf angewiesen wäre (.) hätte ich irgend eine Ecke in der Wohnung gesucht, wo es nicht gerade dominant ist [lacht] (.) aber es hat ja das Aussehen hat dann keine so grosse Rolle mehr gespielt (.) Das ist in den Hintergrund getreten."] The pre-packaged medication in pouches was perceived as extremely reassuring and convenient. Simultaneous recording of the dispense time did not worry the participants.

Patient support

This theme relates to the impact of the dispenser on patients' ability to adhere to their therapy (e.g., the effectiveness of the dispenser in assuring the regular and timely intake of the correct dose). P1 mentioned that the dispenser acted as an alarm clock in the morning and that she took her medications on time, while she would otherwise just take them *"any time before going to bed"* ["irgendwann vor dem ins Bett gehen"]. Participants also discussed the complexity of medication regimens, stating that the dispenser seemingly reduced the burden of taking multiple medications: *"Because I only had one pouch, I only took one. It was like, less than before, when I have to take three drugs. Because it was like the three were on their own."* [„Weil ich nur eine Tüte hatte, habe ich nur eins genommen. es war wie, weniger als vorher, wenn ich 3 Medikamente nehmen muss. Weil es wie von alleine die drei gewesen ist."] (P4). However, participants voiced concerns about the handling of medication changes

when there were still pouches in the dispenser: *"I find it difficult, when I have to go to a doctor and I receive a new drug, it's not in the pouches. How does one do it, do I take it myself until the roll is finished, the additional drug? Or when something needs to go out, does one empty out all pouches into a pill box, so it's not wasted?"* [„Ich finde es noch schwierig, wenn ich jetzt zum Arzt muss und ein neues Medikament erhalte, ist das nicht in den Beuteln. Wie macht man das, nehme ich es dann einfach selber bis die Rolle fertig ist, das zusätzliche Medikament. Oder wenn etwas raus muss, leert man alle Beutel in ein Dosett, damit es keine Verschwendung ist?"] (P1). Similarly, participants had the feeling of losing knowledge about their medication: *"It is a danger; one simply takes what comes out and doesn't think about how they [the drugs] act and how it plays together."* [„Es ist schon die Gefahr, man nimmt einfach was da hinaus kommt und überlegt sich gar nicht, wie die wirken und wie es zusammenspielt."] (P1). Two participants felt relieved by the device and mentioned that they had not to think about taking their medication because the dispenser took care of everything: *"He [the dispenser] thinks for me and he beeps and then he spits it [the medication] out, everything ready, found it wonderful actually. Well, it is a luxury for me, you see, I don't need it but it is, er, would be a great luxury."* [„der denkt für mich und er piepst und dann spickt er es hinaus, alles parat, habe es wunderbar gefunden eigentlich (.) Also ist Luxus für mich oder brauche es nicht aber ist äh wär ist ein toller Luxus gewesen."] (P5).

Living conditions

This theme covers the attributes flexibility of intake times and patient mobility. Three participants felt under pressure and other-directed because they had to be at home at specific times. P4 described a feeling of resistance to *"take commands"* from the dispenser. P2 reacted by switching the device off when leaving the house: *"Well, for me it was stress, especially in the evening. When I knew I wasn't there I just switched it [the dispenser] off. And then I switched it on again in the morning and it started up and that was no problem."* [„Gut für mich war auch Stress, vor allem am Abend. Wenn ich gewusst habe dass ich nicht da bin habe ich ihn einfach abgestellt. Und dann habe ich ihn am Morgen halt wieder eingeschaltet dann hat es wieder aufgestartet und das ist kein Problem gewesen."] P6 acknowledged the usefulness for retrieving pocket-doses for planned absences, but not for unplanned belatedness.

The impressions and expectations at first sight changed for most participants over time, sometimes dramatically. P3 and P5 declared initial negative attitudes toward product design, which changed to a positive attitude after using the dispenser for two weeks. Conversely, P2, P4, and P6 with initially neutral or positive expectations developed strong negative feelings

over time, describing aggression and stress. P6 was expecting no problems but felt enslaved and had the feeling of *"not taking the medication out of free will"* ["es war nicht mein freier Wille"]. The participant with the most positive experiences after the 14-day use was also the only participant reporting prior difficulties with taking the medication (P5).

Target groups for the dispenser

All participants agreed that the dispenser could be beneficial to some patients. The envisaged target groups were patients with time-sensitive medication regimens (transplant patients, HIV-patients), patients with dementia, the visually impaired, or generally patients requiring assistance with their medication. P4 mentioned that the dispenser could help distinguish the medication of several patients living together and prevent accidental intake of someone else's medication. P4 mentioned the possibility of using the dispenser for feedback purposes to discuss irregularities in a patient's medication-taking behavior. Participants had contradictory opinions about the appropriate age to start using the dispenser. On one hand, they stated that the dispenser would be appropriate only when patients could not cope without external assistance. On the other hand, they favored an early inception when patients were still capable of adopting to new technologies. Participants agreed that the device would be appropriate only for patients spending most of their time at home, or when only taking medication in the morning. All participants emphasized the importance of individually assessing patients' motivation and need of such a device.

When asked for the monthly fee participants would be willing to pay, the answers ranged from 0 to 25 Swiss francs (SFr) per month (0 to 28 USD). P6 noted that 25 SFr would be appropriate when the dispenser could show a clear beneficial effect. In contrary, P2 participant stated that the dispenser should be free of charge when someone is in need for it. However, if someone is able to cope without the dispenser but wishes to use it, a monthly fee of 10-20 SFr seems appropriate according to this participant. The same participant pointed out that one might treat the device carelessly when provided at no charge.

Discussion

The concept of electronic medication management aid (e-MMA) or "smart pillbox" is not new and an increasing number of devices combine the functionality of an MMA with electronic monitoring[173]. E-MMAs with pre-packaged pouches mostly target patients living at home who receive support from home care services for their medication therapy. Instead of the daily

visit(s) to prepare the doses and supervise correct intake, the caregiver only has to refill the dispenser in predefined intervals while maintaining supervision of correct dosing.

Our results show that the assessed e-MMA meets most of the general requirements set for an MMA in the areas of patient support and implications on patient habits. The participants reported no technical problems with the e-MMA, probably due to careful oral and written instruction before use and their interest in electronic technologies. The major limitation voiced by our participants concerned the restricted mobility inherent to a bulky device that needs continuous power supply. This aspect may restrict the applicability of the e-MMA to patients with limited mobility. Similarly, a report by the University of Birmingham reviewing electronic dispensers also stated that "people who regularly leave the home may also find it less practical"[174]. Retrieving pouches before intake times (pocket-dose) to overcome this limitation was not often put into practice by our mobile participants. Anticipating an absence that will collide with an intake time requires cognitive abilities known as prospective memory[56]. A lack of prospective memory is associated with non-adherence[56]. Therefore, the patients who could benefit from an e-MMA may be those who are unlikely to anticipate an absence during a later intake time. Alternately, the mobile patients who could most benefit from the dispenser may be those with only one intake time in the morning, since they do not need to be at home at specific times in the afternoons or evenings. Obtrusiveness was not an issue, however, the participants only judged the physical dimension of the term (i.e. technology is not perceived as undesirable and physically prominent[175], giving the German word "unauffällig"). The psychological dimension of the term (i.e. the tendency to intrude, especially upon privacy)[175] was not mentioned as drawback of the e-MMA, even though all participants were aware of the electronic real-time monitoring. Two participants declared a certain reluctance to "follow" a machine, which however refers more to their relationship to the aspect of dependence and its symbol of loss of function and abilities[175] than to an objection to the e-MMA. Thus, according to the model of obtrusiveness in telehealth[176], our e-MMA possesses an adequate size (physical dimension), is user friendly (usability dimension), does not invade personal sphere (privacy dimension) and has optimal performance (function dimension).

The design of an MMA is important as acknowledged by other authors[64]. Our results suggest that design might be an initial barrier but is likely to fade after the patient experiences concrete benefits from the device. Thus, health-care professionals should more point out the potential benefits of the device on the regulated intake and less the external appearance. The fact that the voting for the two attributes "looks good" and "is space-saving" were distributed

equally demonstrates the mixed feelings of the participants. However, since appearance and size are subject to personal liking, those attributes should not be emphasized by the health professional. Further, participants of our study accustomed to the e-MMA in only 14 days and were likely to change their preconceived opinions about the device during this short period. Therefore, it may be appropriate to propose an evaluation period of 2-4 weeks to reluctant patients and to offer the device at no costs for this accommodation time.

Patients' characteristics represent only one of the five dimensions of non-adherence (beside condition, therapy, socio-economic situation, health care system[19]. An adherence intervention like an e-MMA can have a significant influence on clinical outcomes, as long as it targets patients with the need for and the motivation to use an e-MMA. Thus, each case needs individual assessment and e.g., intentionally non-adherent patients should be ruled out, as stated in the Birmingham report[174].

We could not find any publication concerning the appropriate age to propose an e-MMA to a patient taking chronic medication. Our study participants recognized that the main condition for adopting and integrating an e-MMA into daily routine remains that it fits patient's habits. This favors an early inception of the device since mental flexibility may decrease with advancing age. As a consequence, cognitive dysfunction or dementia may be incompatible with an electronic medication management aid, although some authors suggest that those patients represent the target group for the provision of an e-MMA to combat non-adherence[177]. In the "Automated Pill Dispenser Project", more than 70% of participants were 75 years of age and older, and almost half of these were older than 85 years[168]. The same study also advised against the use of such aids in patients with moderate to severe dementia. Further studies should investigate these contradictory suggestions.

We acknowledge some limitations to the study. Our sample was not representative for the general population. This may limit the external validity and generalizability of our findings, since other participants could have judged different attributes important. This could be overcome by conduction additional focus groups in different populations. Literature suggests conducting at least three to four focus groups to reach theoretical data saturation[169]. We chose to conduct only one focus group since the topic of electronic medication devices is not new and a preliminary list of attributes could be generated from the literature. As a consequence, we considered the literature as the reflection of several experts' opinions and our focus group as the last opinions-gathering group.

Our study shows some strengths. Consensus on the most attributes of the e-MMA was obtained unanimously. Because participants voted by raising their card simultaneously and individually without seeing the others' choices, this consensus cannot mirror the desire to vote in accordance with the group.

Our results have theoretical and practical implications, such as the need to improve the design and targeting of MMAs. Not only should the appearance of the MMA, but also its functionality and the whole medication supply process be considered during the design process. Further prospective, randomized and controlled intervention trials should aim at quantitatively evaluating the validity of our findings in larger populations of patients with time-sensitive medication regimens, patients with dementia, the visually impaired, and several patients living together.

Acknowledgements

We would like to thank the staff of the pharmacy "Apotheke Hersberger am Spalebärg" for their support with recruitment and the staff of the "Notfall Apotheke Basel" for housing our equipment to produce the unit-of-dose pouches. This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of conflicting interests

The Authors declare that there is no conflict of interest.

Project C2

Medication profiles of substituted patients with opioid dependence syndrome: A longitudinal observational study

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Project report based on the Master's thesis by Fabienne Suppiger, supervised by Prof. Kurt E. Hersberger[a], Dr. Kenneth Dürsteler[b], and Samuel Allemann[a]

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Abstract

Background: Opioid-assisted treatment (OAT) is the preferred treatment for opioid-dependent patients. OAT is provided in controlled settings to approximately 19'400 of the 22'000-27'000 opioid-dependent patients in Switzerland. Thanks to the success of OAT, life expectancy for opioid-dependent patients improved greatly. Recently, sustained-release Morphine has gained interest for OAT. Similarly, Methylphenidate, approved for the treatment in attention deficit hyperactivity disorder, has been considered for substitution of Cocaine dependency. The prevalence of the use of these substances and other medications in an ageing population remains unclear.

Objectives: An outpatient addiction service (OAS) provides OAT and other medications to opioid-dependent patients in Basel (Switzerland) and records all dispensing events in an electronic database. This study is a first-time retrospective analysis of the patient collective, the drug prescriptions and dispensing practice at the OAS in Basel.

Methods: We performed a longitudinal observational study with historical data recorded between 2002 and 2013 at the OAS in Basel. We analyzed demographic properties, general information about medications, information about opioid substitution treatment, and Information about treatment with methylphenidate. We applied Mann-Whitney U-Test for comparisons of two independent groups, Wilcoxon signed-rank test for paired groups, and linear regression to estimate trends.

Results: Between 2002 and 2013, the number of patients increased from 112 to 154. Mean age rose from 37.1 to 45.0 years. Alongside, the number of active ingredients per patient increased from 2.71 to 3.55 per year. Most substances were used in the therapeutic area of the nervous system, which includes all substitution medications and methylphenidate preparations. Methadone remained the predominant substance for OAT, but its use declined by 25%. Most of this proportion was replaced by sustained-release Morphine preparations. Methylphenidate prescriptions declined from 21.4% in 2002 to 16.9% in 2013. Short-acting preparations were fully replaced by long-acting formulations.

Conclusion: Treatment facilities providing OAT must accommodate their setting for older patients with polypharmacy. A more diverse selection of different treatments increases the complexity of pharmacotherapy and requires close collaboration of different healthcare providers.

Introduction

Between 0.1% and 0.7% of the population in Western Europe are affected by a problematic opioid use[178]. While the number of new opioid-dependent patients in Switzerland declined sharply in the past two decades, the prevalence of opioid-dependence remained stable[179]. This can be explained by the medicalization of the problem, its recognition as a chronic condition, and the success of opioid-assisted treatment (OAT). In 2010, an estimated 22'000 to 27'000 people in Switzerland were opioid-dependent and roughly 19'400 received OAT. Over 90% were treated with Methadone, around 8% with Diacetylmorphine (Heroine), 5% with Buprenorphine, and 1% with other opioids, such as sustained-release Morphine[180]. Due to its long half-life, methadone is considered the gold standard for OAT. However, its side effects and serious interactions with other medications pose limitations for its use. Recently, sustained-release morphine preparations have gained interest for use in OAT[181]. Long-term OAT has been shown to reduce various risks associated with illicit drug use, including infectious diseases, overdoses, premature deaths, disability, crime, prostitution, and social isolation[182]. As a result, life expectancy for patients increased considerably, leading to an increasing age of opioid-dependent patients receiving OAT[183-185]. In Basel, Switzerland, the proportion of patients with OAT aged 50 years and older increased tenfold between 1996 and 2003, while that of patients younger than 30 years plunged from 52% to 12%[186]. Due to their history of drug abuse and its associated lifestyle, patients often appear prematurely aged and suffer from chronic diseases and disability, such as Arthritis, Hypertension, chronic lung disease, stomach ulcers, coronary disease, liver cirrhosis, or diabetes mellitus[187]. Additionally, the prevalence of chronic infections, such as Hepatitis B and C or human immunodeficiency virus (HIV) are significantly higher compared to the general population[183,184,188]. Consequently, many older patients with OAT often need additional long-term medications, resulting in polypharmacy and complex regimens. Together with a high prevalence of psychological problems and low social support, these patients are at high risk for medication non-adherence.

Opioid-dependent patients often use other addictive substances, such as Alcohol, Nicotine, Cocaine, Amphetamines, or Benzodiazepines. In a representative sample of 578 persons with opioid use disorders, around 70% met criteria for dependence on an additional substance, and 20% were Cocaine-dependent[189]. Abuse of Cocaine is associated with negative health effects and can trigger affective disorders and psychoses. Similar to OAT, there have been attempts to replace Cocaine with medications to avoid adverse effects. Although the stimulant Methylphenidate appears promising to be substituted for Cocaine, several randomized

controlled trials have not been able to show a reduction in Cocaine use or craving[190]. In Switzerland, Methylphenidate is approved for the treatment of attention deficit hyperactivity disorder (ADHD) and for Narcolepsy. The global prevalence of adult ADHD has been estimated at 3.4%[191,192], but up to 30% of cocaine-dependent patients and 25% of patients receiving OAT fulfil diagnostic criteria for adult ADHD. Especially in context with concomitant substance abuse, the prescription of Methylphenidate for adult ADHD should require a careful diagnosis and only long-acting formulations should be used[193]. Despites its potential risk of abuse, the benefits of treatment with Methylphenidate for adult ADHD outweighs the potential risks[194].

Rationale

The shift to an older age of patients with OAT poses multiple challenges for appropriate therapy. Apart from other risk factors, such as a high prevalence of psychological problems and low social support, increasing age and polypharmacy could be additional barriers to medication adherence for patients with opioid substitution therapy. Due to its interaction potential and possible side-effects, Methadone may not be ideal for OAT in older patients with polypharmacy. Other options are available, but there is a lack of information about the prevalence of their use. ADHD might be an additional risk factor associated with both substance use disorders and non-adherence[195]. Due to a high risk of abuse, the short-acting Methylphenidate formulations do not offer benefits in the treatment of these patients and only the use of long-acting formulations is recommended. It is unclear how these recommendations are being followed. One of the largest provider of OAT in Basel, Switzerland, electronically registers all dispensed medicines in a database since 2002. The analysis of this data might offer a better understanding of the current medication profiles of this population with the potential to inform future work to improve medication supply and treatment in this setting.

Aims

Our goal was to establish a thorough understanding of the medication profiles of opioid dependent users in an outpatient addiction service (OAS) in Basel, Switzerland. We aimed to:

- describe the demographics of the study population
- assess the numbers and nature of medications dispensed to patients of the OAS with a focus on opioid substitution treatments, methylphenidate, and treatments for other comorbidities

Methods

Study design and setting

We performed a longitudinal observational study with historical data. The setting was the Outpatient Addiction Service (OAS) of the Psychiatric University Hospital in Basel, Switzerland. The OAS offers treatment to patients with substance use disorders, mental and somatic disorders, and social impairments and problems. Patients are treated by a multidisciplinary team consisting of professionals from the fields of medicine, nursing, social work and psychology. Up to 100 patients per day visit the public dispensing point of the OAS to obtain their medication. Patients take their (substitution) medication on site under supervision at least once per week and receive additional doses and medications for take-home.

Participants

We included all datasets of patients registered in the substitution program that received medications from the OAS between 2002 and 2013 and had a prescription for at least one medication on the reference day for each year.

Data sources and variables

Data were sourced from the electronic claims database of the OAS. We extracted the following variables for the years between 2002 and 2013 from the Access®-based database (Microsoft, Redmond, Washington - USA):

- Unique case number
- Date of birth
- Sex
- Name of the medication
- Database specific number for the medication
- Dosage
- Galenic form
- Unity

The reference day for this extraction was June 30th of each year or the following Monday if this date fell on a weekend. The data were then imported to Excel® (Microsoft, Redmond, Washington - USA) for further processing.

Procedures

The database showed several deficiencies that needed correction before analysis: the substance number used internally did not uniquely define a substance, the substance name

was arbitrary chosen, and preparations and active ingredient were only partially specified. It also contained typing errors, the pharmaceutical form was not consistent, and the unit for liquid and solid dosage forms was used inconsistently. We added the following variables:

- Active ingredients
- Anatomical therapeutic chemical (ATC) Codes
- Pharma-Codes (Swiss identifier for product entities)

The variable "unit" was split into "dose" and "dose intensity" in order to distinguish the prescribed dose for solid and liquid dosage, respectively. For comparability, all substitution drug doses were converted to methadone-equivalent doses.

We excluded the following items from analysis:

- Dressing materials (e.g., Elastomull®)
- Vaccinations (e.g., Twinrix®, Engerix®)
- Preparations without active ingredients (e.g., Sodium chloride NaCl).

Duplicate cases, which referred to the same drug with a different drug name were unified. For summary statistics, we aggregated the data by case and year.

We validated the processed data by comparing two random samples of each year with the raw data in the Excel files and corrected our procedures until we reached 100% conformity between comparisons.

Plausibility of doses was assessed by comparison with data from a second reference day adjacent to the extraction date. In case of discrepancies, the daily dose was corrected according to Table 8. Additional doses (e.g., reserve doses) were not included in the calculation of the daily dose for a single patient.

Variables

We analyzed demographic properties (age, sex), general information about medication (number of dispensed substances [active ingredients] and number of medications [unique galenic forms] per patient), total number of unique substances dispensed by the OAS and their therapeutic area, information about opioid substitution treatment (substance, galenic form, and dose used for OAT), and Information about treatment with methylphenidate (prevalence, galenic form and dose).

Statistical methods

Statistical analyses were performed using SPSS® (Statistical Package for the Social Sciences, IBM, Armonk, New York - USA).

We calculated means and medians, minimum, maximum, and standard deviations for descriptive variables. We applied Mann-Whitney U-Test for comparisons of two independent groups, Wilcoxon signed-rank test for paired groups, and linear regression to estimate trends. A p-value < 0.05 was considered significant.

Table 8: Correction criteria and performed measures.

Event	Action
Dose only on reference day available	Manual control of data by checking prescriptions in database
Dose only on comparison day available	Case excluded
Dose on one of the two days is twice as high = reserve dose	Lower dose (without reserve dose) is taken
Dose on one of the two days is 50% higher = replacement dose	Lower dose (without replacement dose) is taken
Dose is an integer multiple of the other day = holiday supply	Dose is divided by appropriate number of days
Dose at one of the two dates is ± 20 mg = titration	Dose of reference day is taken
Dose on both days amount to 20 mg or 200 mg	Manual control of data by checking prescriptions in database
Dose at one of the two days is 0.00 mg = no collection of medication; alcohol-blowing test (>1.5‰)	Manual control of data by checking prescriptions in database
Doses of the two days were by a not apparent factor apart = advanced collection or partial disposal of medication	Lower dose (without pre-collection/partial dose) is taken

Funding and Approvals

The study was funded by the University of Basel and has been approved by the Ethics Committee of northwestern Switzerland [EKNZ- 2014-012].

Results

Participants

In 2002, the OAS treated 112 individual patients, increasing to 154 patients in 2013. The trend implies a linear increase of 4.4 patients per year ($R^2 = 0.84$, Figure 11). Throughout the study period, approximately one third of the patients were female.

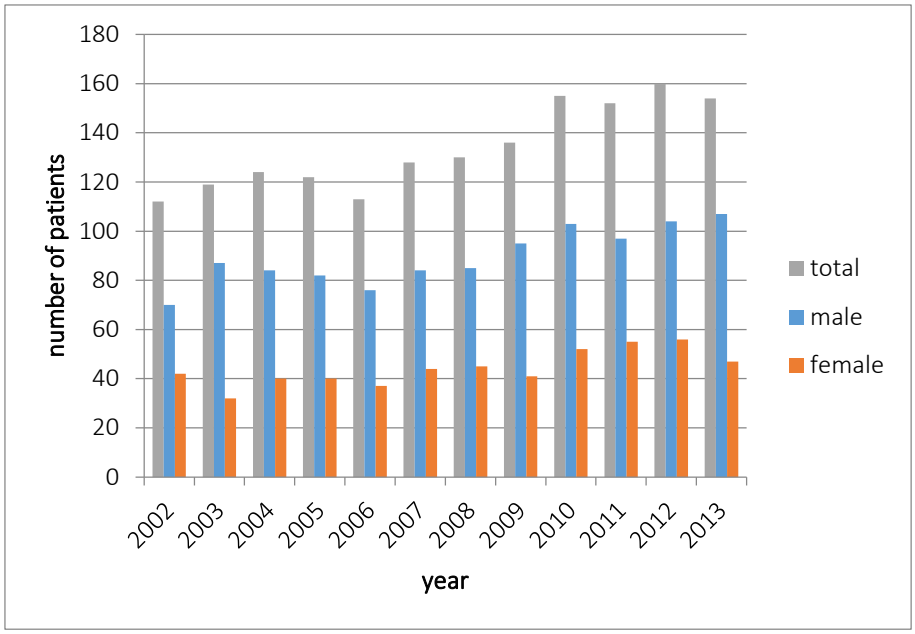

Figure 11: Gender and total number of the patient population from 2002 to 2013.

The mean age in 2002 was 37.1 years, increasing linearly to 45.0 years in 2013 ($R^2 = 0.985$, Figure 12). Female patients were younger than males in 2002 (35.8 vs. 37.8 years), but older in 2013 (46.5 vs. 44.4 years). For all reported years the age difference was not significant (U-Test, $p > 0.05$).

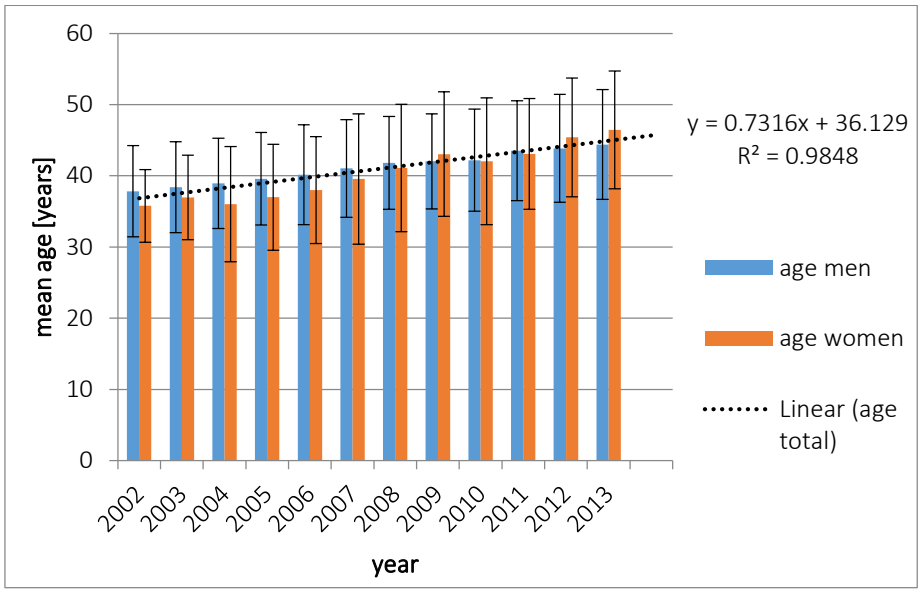

Figure 12: Mean age of the patient population from 2002 to 2013.

Medication profiles

The mean number of substances (active ingredients) dispensed per patient increased from 2.71 (range 1 – 10) in 2002 to 3.55 (range 1 – 13) in 2013 (Figure 13). On average, women had insignificantly more substances than men. Age was not significantly associated with the number of substances (U-Test, $p > 0.05$). In 2002 and 2013, 39% and 58.4% of the patients received 3 or more substances, respectively.

The mean number of medicines was slightly higher than the mean number of substances and increased from 2.89 (1 – 11) in 2002 to 3.86 in 2013 (1 – 15, Figure 13).

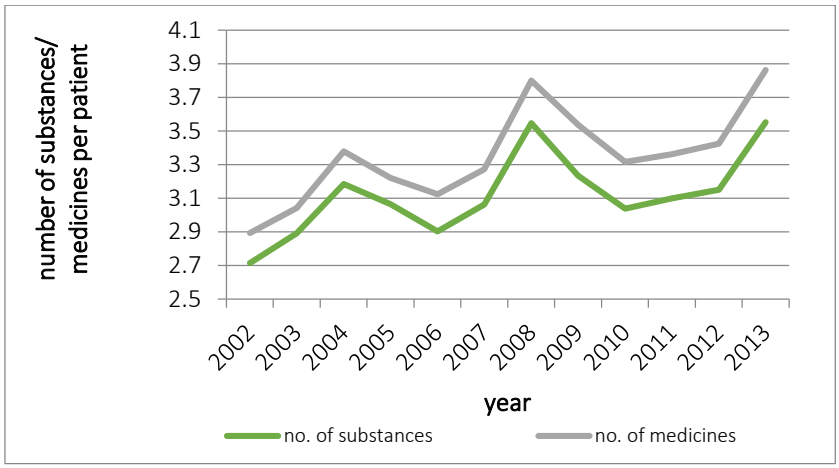

Figure 13: Mean number of substances and medicines per patient from 2002 to 2013.

The OAS dispensed 57 different substances in 2002 and 76 in 2013 (Figure 14). Most substances were used in the therapy of the nervous system, including all substitution medication and methylphenidate preparations. An increase of substances was observed for treatments of the nervous system, the cardiovascular system, blood and hematopoietic system, muscular & skeletal system, and alimentary system & metabolism. In contrast, the use of substances for the urogenital tract, dermatology, and anti-infectives declined.

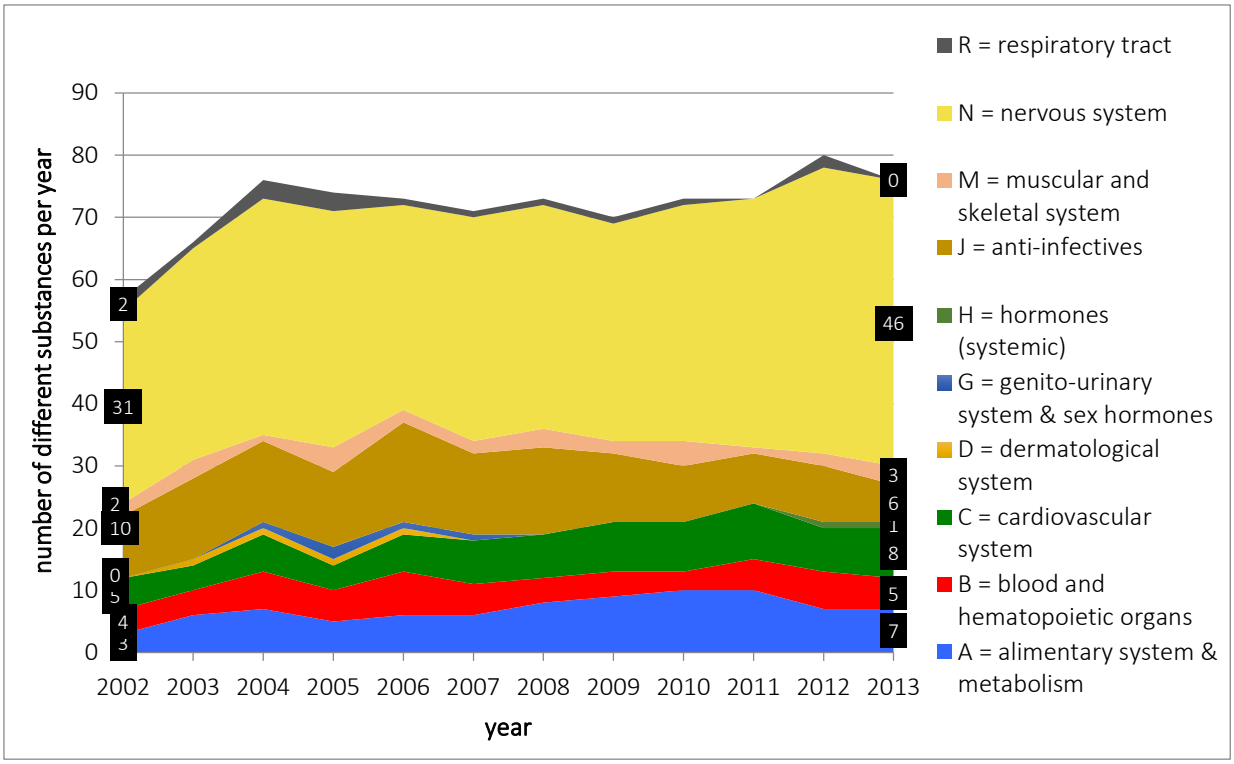

Figure 14: Total substances per year and therapeutic area from 2002 to 2013. Characters in legend correspond to the first digit of the ATC Code.

Despite the increased diversity of dispensed substances, the ratio between dispensing of somatic (ATC-Code starting with A, B, C, D, G, H, J, M or R) and psychiatric substances (ATC-Code starting with N) was constantly around 1 to 5 (Figure 15).

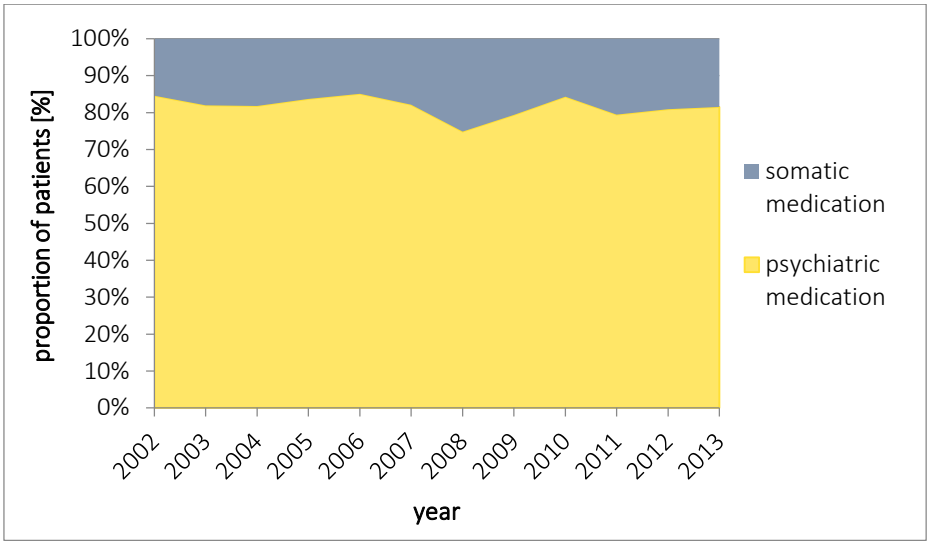

Figure 15: Relationship between psychiatric and somatic medication from 2002 to 2013.

The most frequently dispensed substances for the nervous system included methadone, methylphenidate, diazepam (benzodiazepine), zolpidem (hypnotic), clotiapine (neuroleptic) and mirtazapine (antidepressant). The most frequently dispensed substances for the somatic

system included esomeprazole and pantoprazole (proton pump inhibitors), vitamin B complex, thiamine (vitamin B1), and tenofovir (antiviral drug).

Opioid-substitution treatment

Methadone was the predominant treatment for OAT. However, the use of methadone among other substitution treatments decreased by more than 25% from 97.32% in 2002 to 70.78% in 2013. It was mostly replaced by long-acting morphine (12.3% MST Continus® and 11.7% Sevre-Long®). The use of Buprenorphine (Subutex®, Temgesic®) remained at constant percentages below 10%. Pethidine was only used by one woman from 2003 to 2013 and 0 to 7 patients per year did not receive any OAT (Figure 16). Up to 6.5% of patients received a combination of two medications. The most common combinations were methadone with MST Continus® or Sevre-Long®.

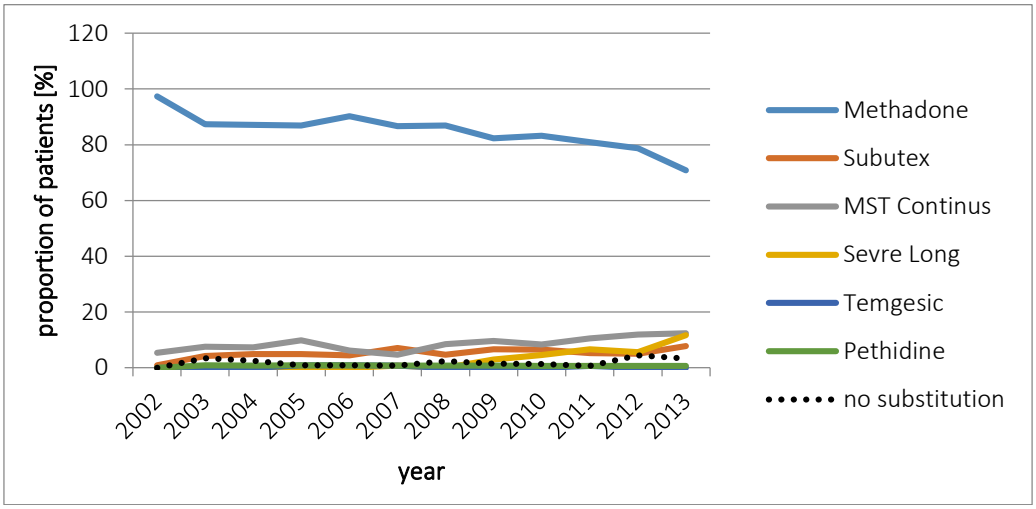

Figure 16: Substitution medication of the patient population from 2002 to 2013

Methadone was available in three different galenic forms: liquid, solid, and semisolid. While most patients used methadone in its liquid form, its use decreased from 65.18% in 2002 to 40.26% in 2013. The use of the solid form, i.e. tablets, remained constant between 32% and 42%. The use of the semisolid form (i.e. suppositories) was negligible. Three to six patients per year (1.95% - 4.46%) used a combination of the solid and the liquid form (Figure 17).

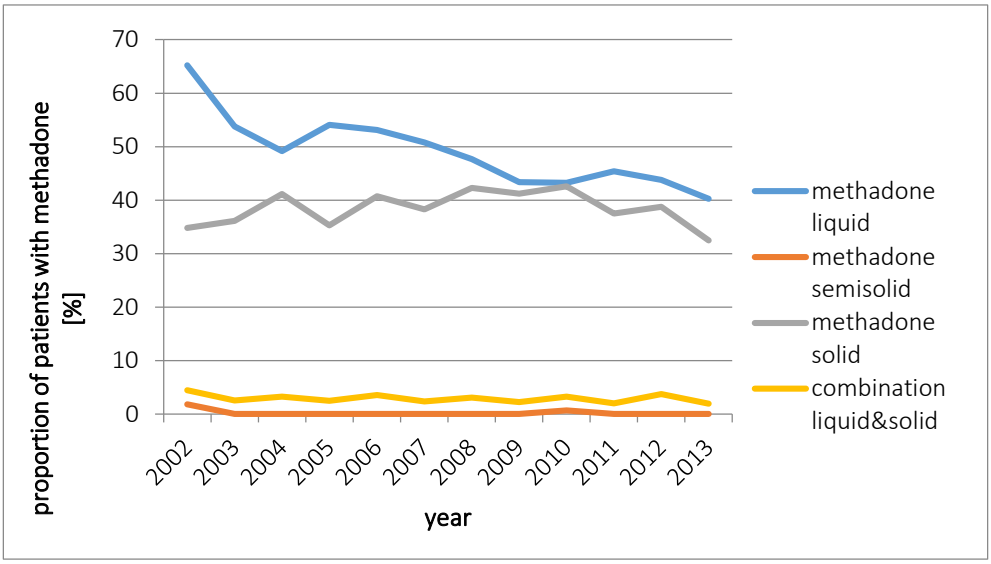

Figure 17: The use of the galenic form of methadone from 2002 to 2013.

The mean dose of OAT (methadone-equivalents) remained relatively constant at 114 mg (SD = 64.2 mg, range = 8.75 – 337.1 mg, Figure 18). Until 2011, men used an insignificantly higher mean dose than women.

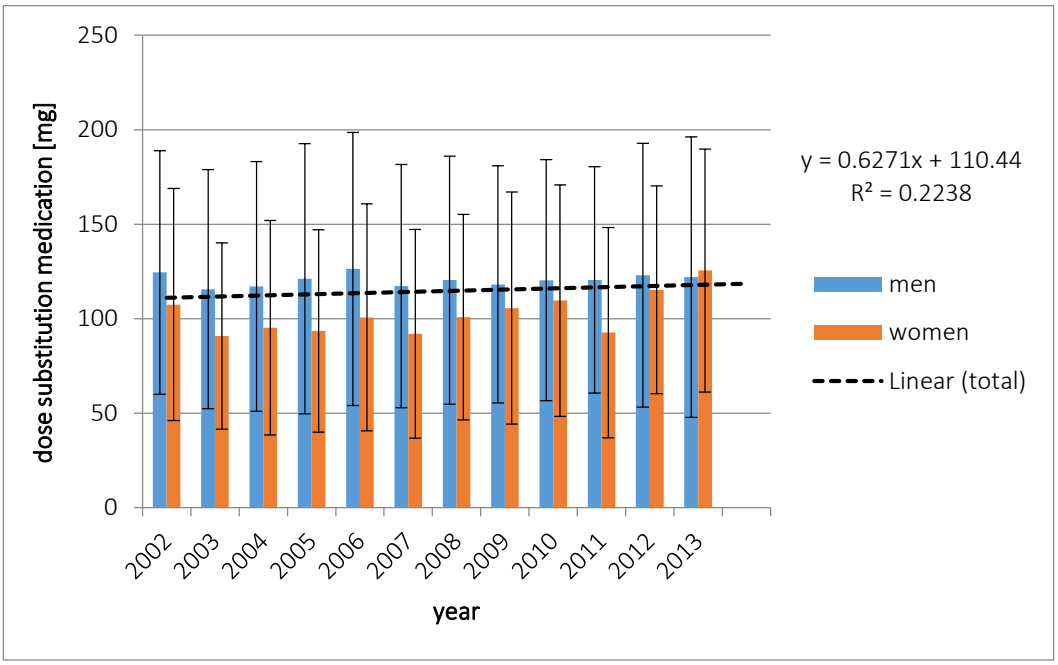

Figure 18: Mean dose of the substitution medication from 2002 to 2013.

Methylphenidate

The proportion of patients with a prescription for Methylphenidate decreased from 21.4% in 2002 to 16.2% in 2013. More importantly, the predominant use of short-acting preparations in 2002 was fully replaced by long-acting preparations by 2011 (Figure 19). After 2008, short-acting preparations were only used in combination with long-acting preparations. The mean dose varied around 50 mg per day but never exceeded 60 mg (Figure 20).

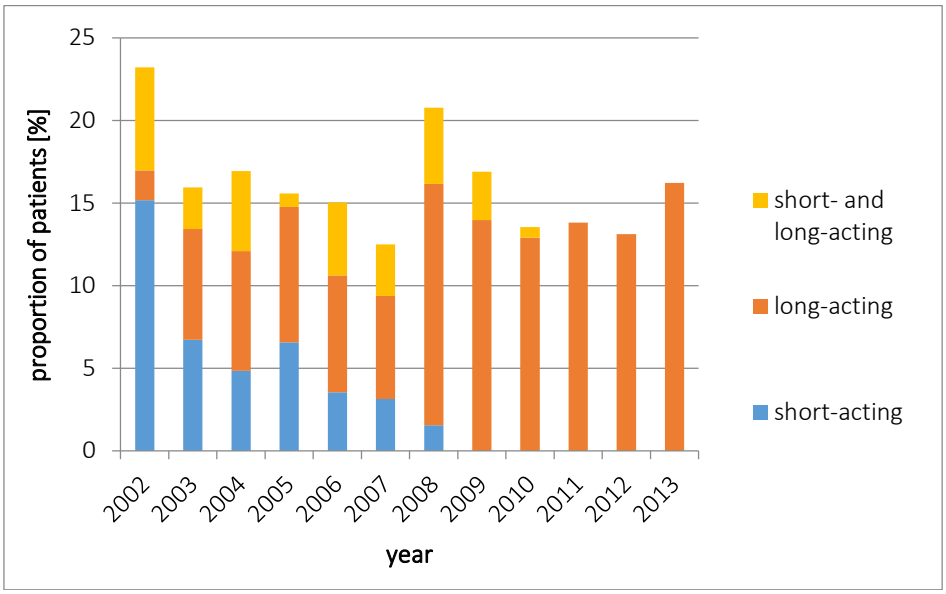

Figure 19: Duration of action of methylphenidate preparations from 2002 to 2013.

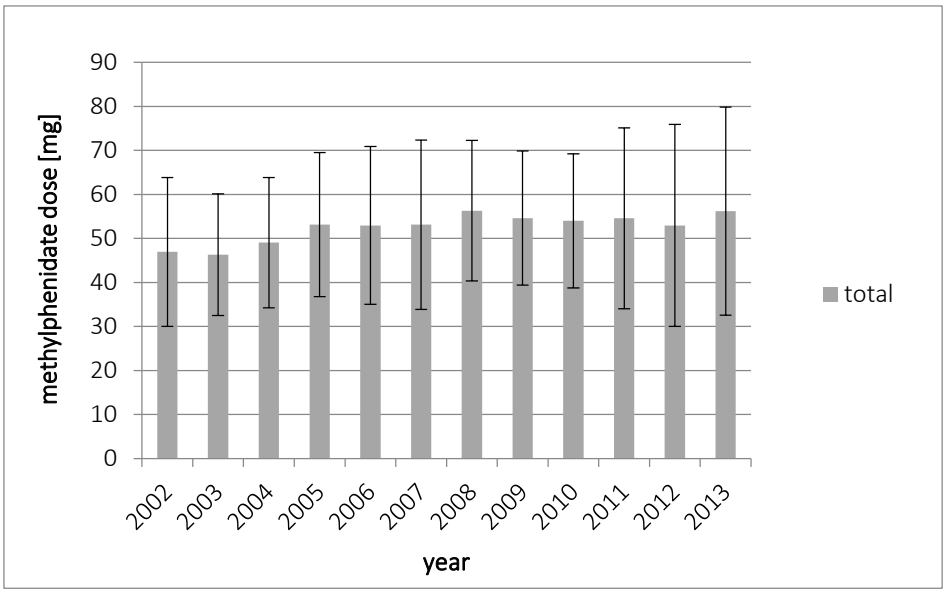

Figure 20: Mean dose of methylphenidate preparations from 2002 to 2013.

Discussion

Our retrospective, longitudinal analysis of the claims database of an OAS in Basel, Switzerland, offered important insights about the development of the patient population between 2002 and 2013.

First, we observed an increase in the number of patients, their age, and the number of medications. The phenomenon of an aging population with OAT has received global attention[186,196]. The stable prevalence in Switzerland coincides with the decline in Heroin use in Switzerland and improved retention rates of OAT[179,184]. Surprisingly, the increase in the number of substances was not associated with age. Although polypharmacy is often linked to age, this correlation may be an indirect one. Polypharmacy has been directly correlated with comorbidities and chronic pain[197]. Patients receiving OAT often have multiple comorbidities from an early age. Furthermore, young drug addicts today differ from past generations: While in the past many otherwise healthy persons slithered into opioid dependence, most patients entering treatment today have been psychiatrically ill before their substance abuse. Additionally, the awareness for comorbidities in patients receiving OAT may have increased and psychological and somatic investigations for patients entering treatment might surpass those in the past. The older patients remaining in treatment may be the healthiest proportion, surviving their sicker peers (Neyman bias). The observation that the assortment of substances used increased, but the proportion of somatic treatments remained stable also supports these assumptions. Nevertheless, many patients with substance-related disorders are prematurely aged as a result of the risks associated with substance abuse and suffer from chronic diseases and psychosocial problems[187,188]. Notably, antiviral drugs were among most frequently dispensed medications for somatic treatments.

Second, Methadone remained the predominant substance for OAT, but its use declined by 25% during the observation period. This decline mainly affected the liquid formulation and has been compensated by an increase of sustained-release Morphine and Buprenorphine. This observation might be explained by the higher risk for drug-drug interactions and side effects observed with Methadone compared to Morphine or Buprenorphine. Additionally, sustained-release Morphine preparations have been approved for OAT in Switzerland as recently as in 2013. Hence, their use is expected to increase even more in the future. However, the cost of these formulations are a lot higher compared to the liquid Methadone solution. Moreover, the use of solid formulations has been discouraged in the past due to the higher risk of diversion of tablets and capsules, especially when they are dispensed in their original blister packaging.

Third, the use of Methylphenidate decreased during the observation period. Although the prevalence remained substantially higher than that of adult ADHD in the general population, the use by 16% of the study population is lower than the prevalence for adult ADHD suggested for opioid-dependent patients. Evidently, short-acting formulations have been consequently replaced by long-acting formulations, a development facilitated by the approval of long-acting formulations for ADHD. This change was mainly driven by the high potential for abuse of short-acting formulations. The same trend has been observed in a nationwide study from Iceland among adult ADHD patients[198]. However, long-acting formulations do not abolish the risk of abuse entirely.

Strengths and Limitations

Our study has some strengths. We used a data set of high quality that has been consistently and uniformly in use since 2002. It contains data from a clearly defined population and the long retention in care ensures a good representation of longitudinal data.

We report some limitations. First, we only used one reference day for each year. It was not possible to aggregate the data of every day to ensure complete coverage of the population. Therefore, some cases might be missing from the sample. However, we compared the data from each reference day to a second date for plausibility and did not find many discrepancies. Second, a discontinuation of therapy or an exit from the program is unapparent in the data. Additionally, the same patient may receive a different case number when re-entering OAT after dropping out. Third, we only covered medications dispensed by the OAS. The OAS is a psychiatric clinic and does not routinely investigate or prescribe treatment for somatic diseases. Hence, our results most likely underestimate the number of medications prescribed to patients, especially with regards to somatic diagnoses. Fourth, we did not have indications for treatments, for example for Methylphenidate. This information might be important to explain changes in prescription patterns. Finally, our results show a large variability, indication a high diversity and potential heterogeneity of the study population. Apart from analysis of averages, it might be worthwhile to look at the extremes and evaluate single cases.

Interpretation

Although we showed a trend towards an aging population with OAT that has been linked to an increase in chronic conditions, we did not see a general increase in somatic medications for these patients. We observed a peak in the number of substances and medications in 2008 that coincided with a higher proportion of somatic medications. It might be possible that one

of the resident physicians put more attention towards somatic conditions compared to other years. Indeed, patients might visit other physicians and obtain additional medications from other sources. While this is likely the case for some patients, others may remain under-treated. The care for the ageing population with OAT has been reported to be insufficient [187,196]. A study from Germany indicated that the supply system for those patients needs adaption[199]. Moreover, Switzerland and other European countries face potential shortages of OAT providers[200-202]. The consolidation of the treatment for older patients with OAT would most likely increase the safety and effectiveness of therapies. Additionally, the declining mobility of these patients warrants changes to the supply of medication. Daily or even weekly visits to a dispensing center might not be feasible for some patients. However, legislations restrict dispensing of OAT to short intervals. Yet, studies show that takeaway doses for extended periods improves treatment outcomes and retention in care for steady patients[203,204]. Moreover, many nursing homes are not prepared to care for older patients with OAT[205].

Generalizability

Our study considered only patients from one treatment center. Our results indicate a large variability of the sample in terms of age, number, and type of medications. Compared to a nationwide study reporting a mean age of 39.1 years in 2012, our sample was considerably older[202]. Because the OAS is specialized to treat opioid-dependent patients with mental disorders, these may potentially show a higher complexity compared to other opioid-dependent patients. Nevertheless, our results are relevant to other settings, as the increasing age and associated complexity is observed globally. The high standards and evidence-based practices inherent to a university hospital may be reflected in an early adoption of new treatment options, such as sustained-release Morphine or Methylphenidate for Cocaine addiction. Thus, the prevalence of these treatments might differ in other settings. Yet, novel approaches might rapidly disseminate in a small country like Switzerland, as OAT is generally provided by specialists who engage in continuous education.

Conclusion

With our database analysis, we confirmed the globally observed shift towards an older population with OAT. Furthermore, we were able to show an increase in the number of substances and medications, leading to an increased risk of drug-drug interactions, adverse events, and non-adherence. Additionally, we observed a shift from the traditional OAT with

liquid Methadone to solid formulations, such as Buprenorphine and sustained-release Morphine. Other disorders, such as ADHD, further complicate the safe and effective therapy of the complex patients. Taken together, the developments of the past 10 years call for new care models for older patients with OAT. The increasing age and complexity of their medication might warrant a closer collaboration of health care professionals. Alternative supply models to assist patients with their medication management and support medication adherence are needed for older patients with OAT and polypharmacy.

Acknowledgements

Many thanks to Fabienne Suppiger for her hard work during initial collection and analysis of the data. Many thanks also to Dr. Kenneth Dürsteler and Dr. med. Hannes Strasser for providing valuable support and input throughout the project, Thomas Müller for extracting the data, and the staff of the OAC for providing insight into their everyday work.

Project C3

Novel remote electronic medication supply model for opioid-dependent outpatients with polypharmacy - first long-term experiences in Switzerland from two case reports

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Manuscript submitted for publication (Jan 2017)

Summary

We report the first long-term experiences with a novel remote electronic medication supply model for two opioid-dependent patients with HIV. John (beginning dementia, 52 years, 6 tablets daily at 12 am) and Mary (frequent drug holidays, 48 years, 5-6 tablets daily at 8 pm) suffered from disease progression due to non-adherence. We electronically monitored adherence and clinical outcomes during 659 (John) and 953 (Mary) days between July 2013 and April 2016. Both patients retrieved over 90% of the pouches within 75 minutes of the scheduled time. Technical problems occurred in 4% (John) and 7.2% (Mary) of retrievals but support was seldom required. Viral loads fell below detection limits during the entire observation period. Continuous medication supply and persistence with treatment of over 1.7 years, timing adherence of more than 90%, and suppressed HIV viral load are first results supporting the feasibility of the novel supply model for patients on opioid-assisted treatment and polypharmacy.

Background

Along with the ageing of the general population, the number of older users of illicit substances (or older drug users) is also growing in Europe[206] and in Switzerland[186]. Besides age-related comorbidities, which occur earlier than in the general population, they may be affected by chronic viral infections that can take decades to cause significant illness or death. Treatment of these conditions are expensive and require high adherence levels to be effective[207]. Medication adherence is "the process by which patients take their medications as prescribed, composed of initiation, implementation and discontinuation"[208]. Substance use itself has been reported to negatively affect adherence[209-214], and substance use disorders often coincide with multiple risk factors for medication non-adherence, such as psychiatric comorbidities[215], low socioeconomic status[38], lack of social support[38], unemployment[211], and unstable housing[216]. Non-adherence to medication has negative effects on health outcomes, and costs[19].

Opioid-assisted treatment (OAT) is the recommended treatment for opioid dependence[217]. It is efficacious, cost-effective and well tolerated[218]. In Switzerland, OAT is offered by a wide range of providers, such as general practitioners, specialized clinics, and addiction centres[180]. In the city of Basel, from the second treatment month onwards, individual take-home doses for up to 6 days per week are possible[219]. Because of the high frequency of mandatory visits and the distances between patients and providers, the provision of OAT is a daily challenge for patients and providers alike[202]. The outpatient addiction service (OAS) of the Psychiatric Hospital of the University of Basel, Switzerland, provides OAT and other medications for 220 patients, approximately 100 of which visit the service daily.

Because existing nursing homes or home care services are often not suited or willing to accommodate patients with substance use disorders, outpatient treatment and surveillance are provided as long as possible. The deteriorating health of older drug users, the risks associated with non-adherence, and reduced mobility are putting considerable strain on existing resources. Thanks to regular appointments, caregivers may ensure initiation and persistence with treatments, but may not be able to assure correct implementation of the dosing regimen. Many patients take their medications irregularly due to a lack of structure in their daily routine. As a result, treatment success may be compromised, resulting in health risks not only for patients, but also for society. The cost of providing care to the ageing older drug users is expected to increase and innovative solutions to optimize medication management compatible with OAT are needed. In this context, we developed a novel medication supply model with interdisciplinary collaboration between the OAS, an HIV clinic,

and the Emergency Pharmacy of Basel, in order to guarantee adherence by using an electronic medication management aid (e-MMA) for pre-packed polypharmacy located at patients' homes. A qualitative analysis of the e-MMA suggests that patients with time-sensitive medication regimens or patients with dementia could benefit the most[92]. We present first results of two cases followed over more than 2 years and draw lessons from the experiences.

Case Presentation

We present two cases of outpatients living in social housing in Basel who obtained medication including OAT from the OAS Basel. After some years, conventional care and adherence to medication were questioned, especially after missed appointments and flares of HIV viral load. Both patients accepted the novel supply model and the electronic monitoring of the entire medication. Both patients consented to the publication of their cases.

John was 50 years old when he entered the study on July 2, 2013. He had been diagnosed with HIV at the age of 25 as a result of intravenous drug use. A liver biopsy in 2014 showed cirrhosis and severe activity due to chronic HCV infection and alcohol abuse (1 liter of beer per day; Metavir score F4, A3). He lost his girlfriend to suicide and lived with a friend who also suffered from substance-related disorders. He was unemployed and spent most of his days at home. After diagnosis of a long-QT syndrome in early 2013, he was switched from methadone to 1'200 mg (6 tablets) of long-acting morphine daily. Remaining treatment consisted of 5 tablets once daily: Ritonavir 100 mg, darunavir 2x 400 mg, tenofovir/emtricitabine 245 mg/200 mg, and pantoprazole 40 mg. Viral load reached 1000 copies per milliliter (copies/ml) during 2012 and early 2013. His viral load fell below detection limits after he was obliged to visit the OAS daily (instead of once weekly) to assure regular intake of his medication. However, he continued to miss appointments and the situation remained unsatisfactory for him and his caregivers. Evaluation in the local memory clinic revealed a diagnosis of moderate Alzheimer's disease and a moderate depressive episode.

Mary was 46 years old when she entered the study on 18 August, 2013. She had been diagnosed with HIV at the age of 19. She suffered from hypertensive cardiopathy, chronic lymphedema in both legs, and suspected chronic obstructive pulmonary disease (COPD). She had a history of hepatitis C and was a heavy smoker. Her OAT consisted of methadone (170 mg) and she received sustained-release methylphenidate (90 mg) for Attention Deficit Hyperactive Disorder (ADHD). She lived with a friend. Both were not working and rarely left

home. In 2012, she started to take her HIV medication only sporadically and stopped altogether in early 2013. As a result, her viral load increased sharply to over 250'000 copies/ml. A low CD4 count (< 200 x 10^9 cells) necessitated the introduction of a prophylaxis against Pneumocystis carinii in summer 2013. Her caregivers convinced her to resume therapy with the same treatment as before and her viral load started to decrease. She understood the need for treatment but lacked the motivation to adhere despite intensive psychological support. At the time, additionally to OAT and methylphenidate, she was taking: Lopinavir/ ritonavir 200 mg/50 mg 4 tablets once daily, darunavir/ emtricitabine 245 mg/200 mg 1 tablet once daily, and sulfamethoxazole/ trimethoprim 800 mg/160 mg 1 tablet every Monday, Wednesday, and Friday. Her hypertension was not an issue at the time and an approach of watchful waiting was considered appropriate with the intention not to jeopardize adherence to HIV medication.

Novel supply model and assessments

Core element of the novel supply model is keeping the opioid-assisted treatment in the institution according to the existing law requirement, and delocalizing the remaining co-medication to the patient's home with an e-MMA (Medido®, Innospense BV, Netherlands; Figure 21). The remaining solid oral prescription medications were repackaged into unit-of-dose pouches with an Automatic Tablet Dispensing and Packaging System (ATDPS; Desk Type JV-30DE, HD-Medi, Germany). Each pouch is imprinted with the patient's name, date of birth, date and time for intake, as well as number, name, color, and shape of the medication contained (Figure 22). Rolls of pouches for 1-3 weeks are placed in the e-MMA, which reminded the patients with audiovisual alerts to take their medication. A web-based application allows to set the time of dispense individually according to participants' preferences. Pushing the OK-button stops the alarm and delivers the pouches with pre-packaged medication. A sensor in the dispenser registers a barcode printed on the top of each pouch and cuts the pouches accordingly. Date and time of delivery are simultaneously recorded with GPRS-technology. Delivery of doses ahead of schedule (so-called pocket-doses) is feasible by pushing the OK-button for 5 seconds. This feature enables patient mobility, i.e. to be outside of home during scheduled intake times.

Figure 21: Remote-controlled, electronic medication management aid, Medido®, used in this study to dispense the unit-of-dose pouches. Notes: Height × width × length: 140 mm × 140 mm × 225 mm. Weight: 1,486 g. The inset shows the power cord.

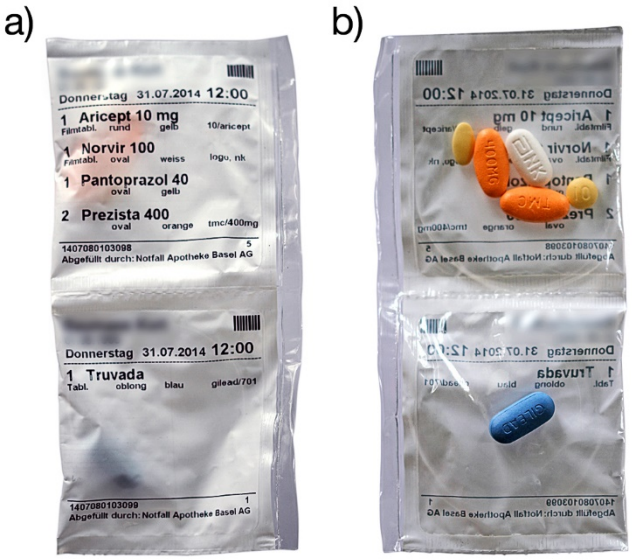

Figure 22: Unit-of-dose pouches with prepacked oral solid medication from front (A) and back (B). Note: Patient's name and date of birth were concealed for privacy reasons.

The e-MMA was installed at the patients' homes by the responsible caregiver of the OAS and a pharmacist from PCRG (Figure 23). Patients were instructed in detail about its proper use. They were also given a written manual including a telephone hotline number in case of problems with the dispenser. The hotline was operated by a pharmacist of the research group (SA or IA) during weekdays and by the Emergency Pharmacy during weekends and public holidays. Every 3 weeks, medications were repackaged according to the current treatment plan and the e-MMA was refilled during a pre-scheduled visit at the patient's home. If a patient failed to retrieve a dose from the dispenser within 75 minutes after the predefined time of intake, or in case of malfunctioning, the dispenser automatically sent an alert SMS to the hotline number. The pharmacist then contacted the patient by phone, inquired the

situation, acted accordingly (either by remote action or by visiting the patient at home) and made sure that medication intake had been warranted. Primary outcomes were taking adherence assessed by electronic monitoring and HIV status (viral load, CD4 count) assessed during routine visits in the HIV clinic. Electronic adherence data was analyzed and graphed with the statistical software R[149]. For taking adherence, we calculated frequencies of pre-dispense (doses dispensed before the scheduled time), regular dispense (doses dispensed during the 75-minute scheduled interval), late dispense (doses dispensed more than 75 minutes after the first alarm), forgotten doses (dispensed remotely after pharmacist intervention) and erroneous dispense (errors during dispense due to technical problems).

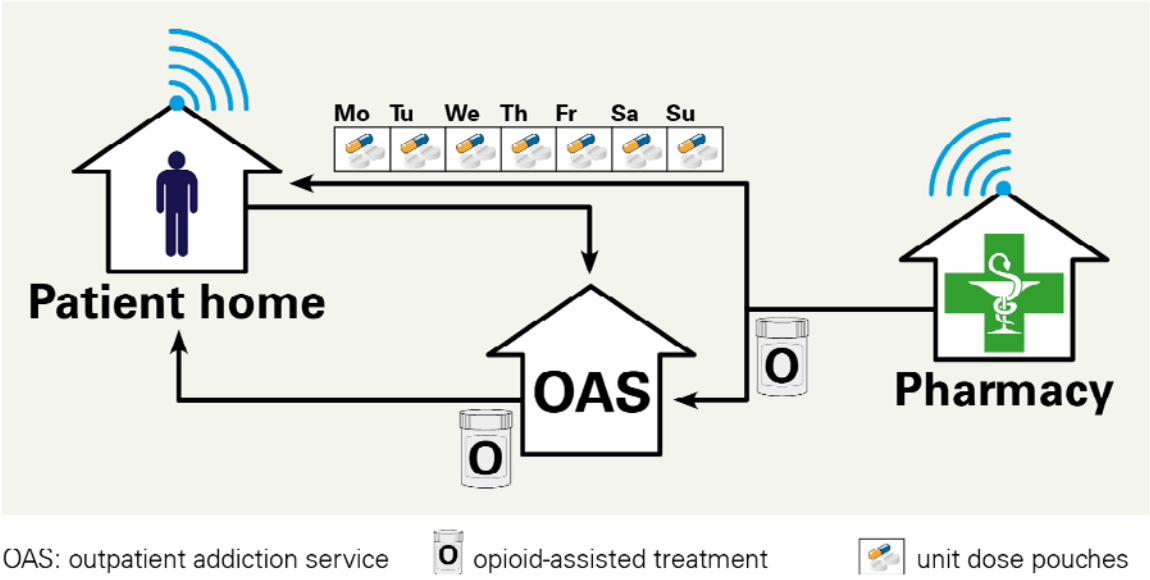

Figure 23: Novel medication supply model where the community pharmacy provides unit-of-use pouches (medication roll Mo-Su) with all solid oral medications directly to patient home, except opioids for OAT and methylphenidate (S). The pouches are loaded into a lockable, remote-controlled dispenser that can be programmed according to a patient's medication schedule. The dispenser records dates and times of medication retrievals and wirelessly transmits them to a server (blue waves). Patients obtain the opioid agonist therapy (S) from the outpatient addiction service (OAS) in regular intervals, at least once weekly, according to local law requirements.

Follow-up and outcomes

The e-MMAs were installed in the kitchen (John) and in the living room (Mary). Dispense times were scheduled in line with consistent habits of daily life, i.e. 12 pm for John (first meal of the day) and 8 pm for Mary (watching TV). John was followed for 659 days. At the time of drafting of this article, Mary is still using the e-MMA. We present data from 953 days. Adherence was electronically monitored during 655 days (99.2%, John) and 911 days (95.6%, Mary; Table 9). Missing days (John: 0.8%, Mary: 4.4%) were due to technical problems with the dispenser.

Table 9: Description of the electronic adherence monitoring for John and Mary. Regular dispense: doses dispensed during the 75-minute scheduled interval; Pre-dispense: doses dispensed before the scheduled time); late dispense (doses dispensed more than 75 minutes after the first alarm); forgotten: doses dispensed remotely after pharmacist intervention; Erroneous dispense: technical errors during dispense

	John	**Mary**
Days of follow-up	659	953
Number of rolls replacement during refill visits	31	46
Days with electronic monitoring	655 (99.2%)	911 (95.6%)
regular dispense	615 (94.0%)	843 (92.2%)
pre-dispense	1 (0.2%)	5 (0.5%)
late dispense	8 (1.2%)	0
forgotten	4 (0.6%)	0
dispensed with errors	26 (4.0%)	66 (7.2%)
resolved remotely	25	60
resolved at patient's home	1	6

Pill burden of John was reduced by one tablet through substitution of darunavir 2x 400 mg with 1x 800 mg. For dementia, a therapy with the acetylcholine-esterase inhibitor donezepil was initiated in October 2013 and subsequently increased to the maximal dose of 10 mg. John was satisfied with the treatment and reported no adverse events. Still, he expressed concerns regarding the persistent cognitive problems – disorientation and forgetfulness. He retrieved 8 doses (1.2%) more than 75 minutes after the scheduled time and forgot to retrieve 4 doses (0.6%, Table 9 and Figure 24). This deviation was due to an appointment or a visit at the OAS, preventing him from being back home in time for the scheduled intake. His flat mate would sometimes retrieve the pouches and leave them on the counter for him (frequency not known). Errors during dispense of the pouches typically coincided with the end of a medication roll and did not require any intervention. Dementia remained stable (assessment in spring 2014) and the pattern of retrieved pouches from the dispenser did not change. With the exception of a blip in November 2013, his viral load remained suppressed below 20 copies/ml and CD4 cells continued to rise (Figure 25). In April 2015, his flat mate suddenly died and the patient decided together with the care staff of the OAS that he would not continue to live independently. He moved to a supervised care home that adopted his medical care and medication supply with the dispenser was therefore terminated.

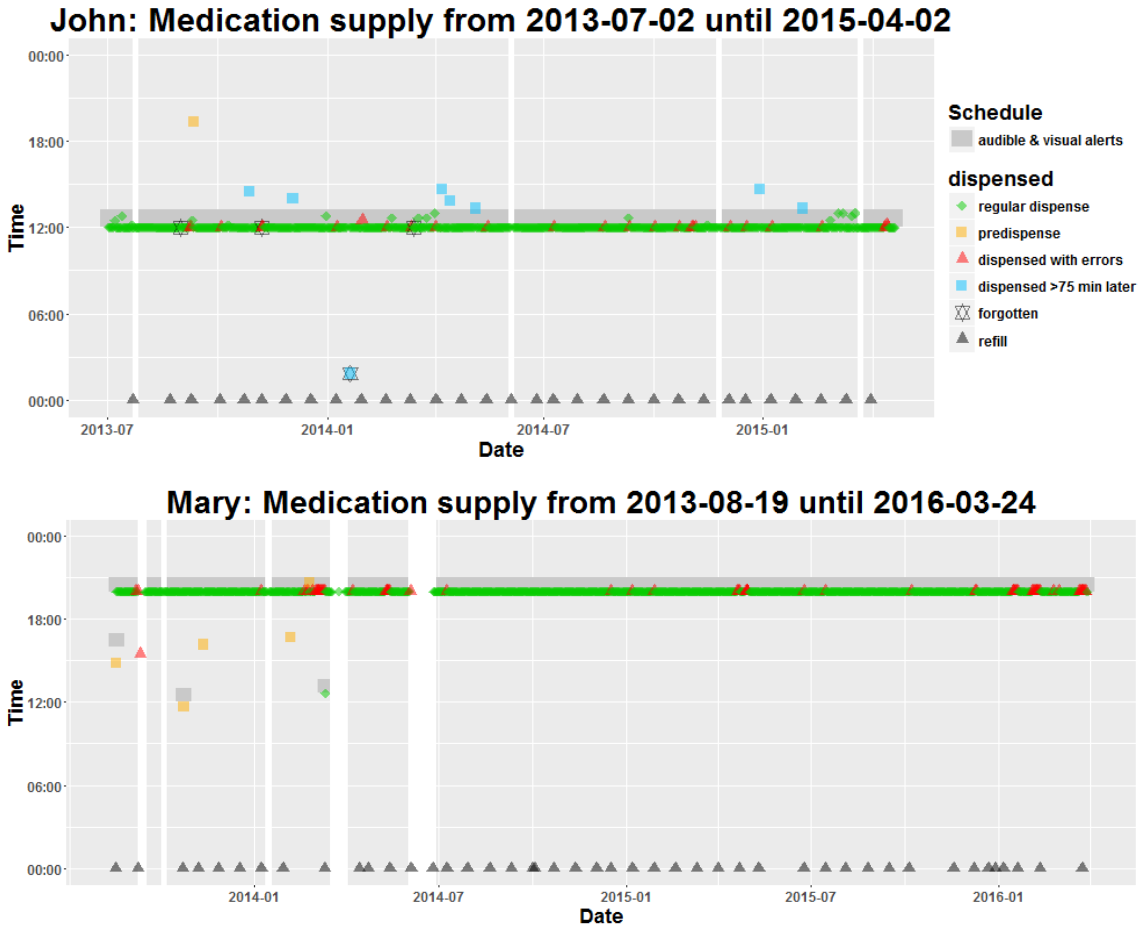

Figure 24: Time of medication dispense for John (659 days) and Mary (953 days) recorded with electronic monitoring. White areas are days with missing electronic monitoring (John: 0.8%, Mary: 4.4% of all days)

During the first months, Mary experienced several technical problems. Pouches sometimes got stuck in the dispenser, or the dispenser would cut the pouches in the wrong area, which required a visit to the patient for reconfiguration of the dispenser. Despite these issues, the patient was grateful for the intervention and reported regular intake of the medication. In early 2014, viral load fell below detection limits and CD4 counts started to rise (Figure 25). After one year, the dispenser was replaced and technical difficulties that required attention of the pharmacist ceased almost completely (Figure 24). In instances where technical problems still caused the device to improperly cut pouches, the patient would help herself using scissors. Although she was requested to immediately call the hotline in case of technical issues, Mary would only mention them during the three-weekly refill visits.

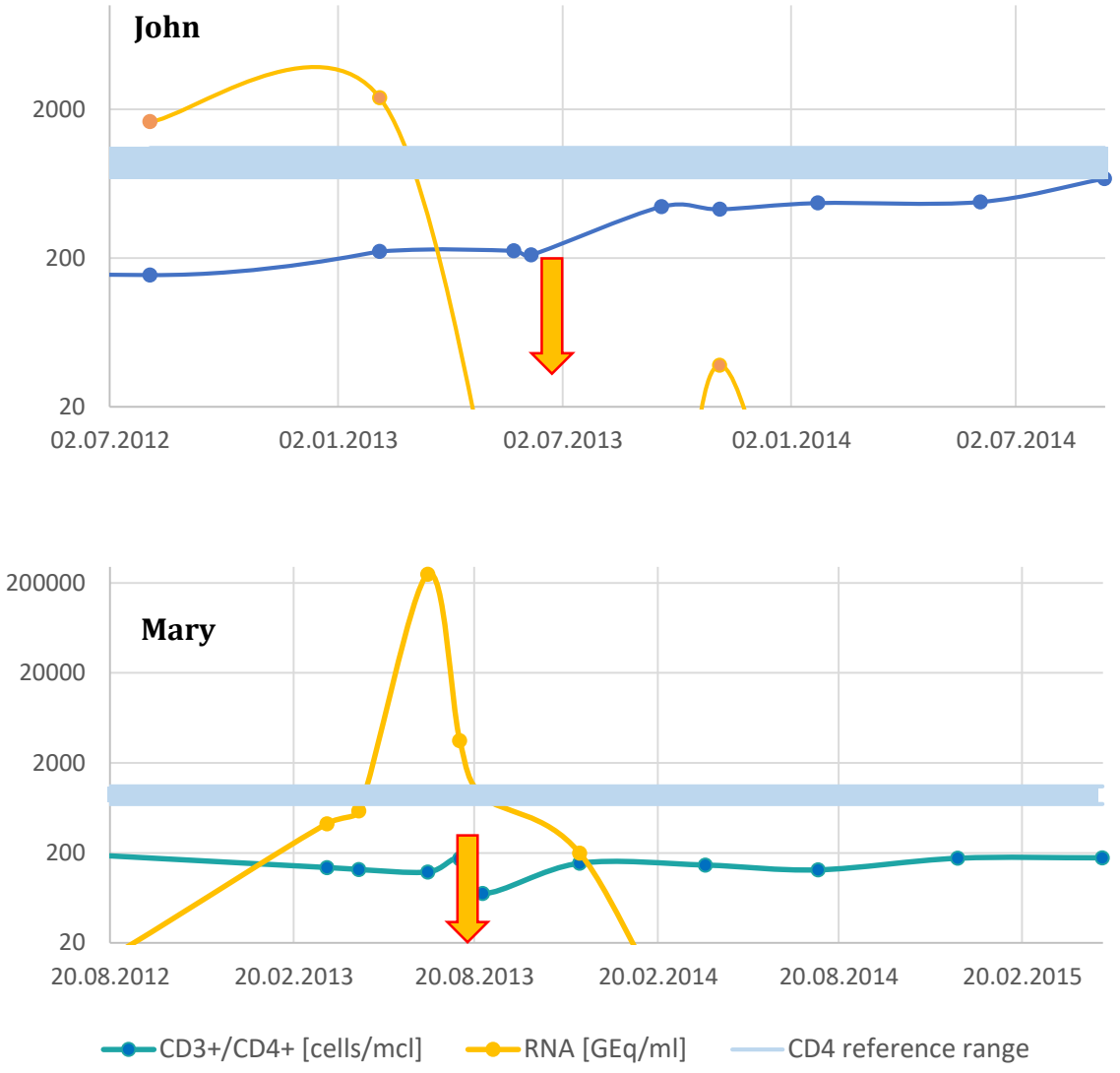

Figure 25: HIV viral load and CD4 cell count of John and Mary. Start of electronic monitoring is marked with an arrow.

In December 2015, Mary mentioned that when she was busy in the flat and the alarm would ring, she would sometimes press the OK-button to retrieve the pouches, but would walk away and go back to her business. Sometimes, she would then forget to take the medications later and save the pouches in a drawer. Between May and December 2015, she reportedly skipped 21 days of medication (10% over 8 months). Because viral load was constantly suppressed and CD4 counts recovered, prophylaxis of Pneumocystis carinii was discontinued in September 2015. In spring 2016, home visits for dispenser refill were discontinued. The medication rolls were delivered to the OAS where Mary would pick them up during her regular visits and load them into the dispenser at home. At the time of drafting of this article (November 2016), appointments are kept and the laboratory results are satisfactory.

Discussion

A novel medication supply model with electronic adherence monitoring of polypharmacy showed sustained treatment implementation and suppressed viral loads in two opioid-dependent HIV patients over 1.7 and 2.5 years, respectively. The drop of viral loads started when patients resumed therapy after intervention of their caregivers. It has been demonstrated that adherence interventions for long-term treatments need regular follow-ups to remain effective[220]. However, the intensive care to assure adherence for John was not sustainable on the long term, and correct implementation of the treatment regimen was not guaranteed for Mary. Our novel supply model offered a sustainable solution to assure adequate implementation and persistence with treatment. In line with our findings, larger trials of such devices suggest an improvement of adherence and clinical outcomes for patients with kidney transplants[79] and schizophrenia[77]. These trials, however, were usually of shorter duration and did not focus on implementation of dosing regimens. Additionally, repackaging of medications in unit-of-use pouches might prevent disturbance in case of changes in treatment, such as the up-titration of anti-dementia therapy, or initiating of preventive and irregular treatment, e.g., the prophylaxis of Pneumocystis carinii. Adapting the content of the pouches is possible without modifying the intake habits. This insures that changes in treatment do not coincide with variable intake times and thus might prevent non-adherence.

Electronic monitoring makes changes in dosing patterns instantly apparent and allows for a timely intervention. Feedback from electronic monitoring has been shown to effectively improve adherence[62]. The only prerequisite is a system entirely reliable and without deficiencies to avoid interference with measurements. We experienced technical problems that compromised monitoring and increased workload for the care staff. These were unpredictable, not reproducible, and complicated the care process. As a consequence, caregivers received unsuspected alerts that could not be ignored. Nevertheless, patients declared satisfaction with the novel supply model, probably because the technical problems did not jeopardize medication intake.

Our study has several strengths. First, we included patients from a population with a high probability of non-adherence and a high prevalence of time-sensitive medication regimens, such as highly active anti-retroviral therapy (HAART) for HIV. Thus, the success of our intervention in these complex patients demonstrates the potential of our supply model. Second, we measured adherence to polypharmacy. Typically, devices for electronic monitoring are designed for single preparations. The monitoring of polypharmacy thus

requires multiple devices and may complicate the management of medications. With our e-MMA, all medications were dispensed in unit-of-use pouches, which enhanced the likelihood of concurrent intake.

We acknowledge some limitations. First, measuring adherence with the e-MMA might overestimate adherence because medication retrieval does not equal ingestion. Literature suggests that electronic monitoring might underestimate adherence[221], although the contrary has also been argued[222]. The latter seems more plausible in our cases. Mary, for example, retrieved all of her pouches on time but set them aside and forgot to take at least 10% of them during an 8-month period. The greater the distance (time and place) between electronic monitoring and actual ingestion of the medication, the higher the risk of false-positive results. With the electronic dispenser, the signal is generated when patients press the button to stop the alarm and to retrieve the pouches. During the few seconds of dispensing and cutting the pouch, the patient may walk away and forget the intake later on. Furthermore, patients or other persons living in the same household might press the button to stop the alarm without the intention of taking their medication. Consequently, intentional non-adherence must be ruled out before using this kind of an e-MMA. Other systems, such as electronic punch cards (POEMS[37]), measure the emptying of a cavity directly before ingestion and are thus less likely to overestimate actual intake of tablets and distort the measurement of adherence.

Second, although John and Mary experienced a benefit from the dispenser, case reports cannot generate results to claim effectiveness of an intervention. Additionally, the generalizability of our results is limited. We evaluated the e-MMA in two patients that matched the envisaged target groups suggested in a qualitative study of the dispenser. Living conditions like mobility could pose a barrier to acceptance of the stationary dispenser[92]. This might be less of an issue in opioid-dependent patients who often have no employment. Recent data from a Swiss survey indicate unemployment rates of 50% among patients with OAT[202]. However, patients not matching the envisaged target groups may also benefit from the novel supply model and further studies should evaluate this.

Finally, we did not evaluate the financial implications of the novel supply model. Costs for repackaging of medications are reimbursed in Switzerland for patients with polypharmacy (i.e. more than 3 medications during 4 months). Costs of the e-MMA and additional costs for service and support are currently not reimbursed by health insurances. However, savings from improved adherence might offset the additional costs, as shown in previous studies where better adherence resulted in significant cost savings[223,224].

Conclusion

Continuous medication supply and persistence with treatment over more than 1.7 years, timing adherence of more than 90%, and suppressed HIV viral load are first results supporting the feasibility of the novel supply model. Further trials should aim at evaluating the effectiveness of the supply model in terms of clinical, humanistic and economic outcomes and in patients that do not necessarily match the envisaged target groups.

Acknowledgements

We would like to thank the staff of the OAS for their support with recruitment and communication with the patients, especially Alexander Brandeberger and Anna-Katrin Ehrsam. In addition, we would like to thank the staff from the emergency Pharmacy for housing our equipment, handling the medication logistics, and operating the telephone hotline. This study was supported by an unrestricted grand from Mundipharma AG, Switzerland.

Project C4

Adherence to Polypharmacy in Patients with Opioid Substitution Therapy using ELectronics (APPOSTEL): A mixed-methods single-subject study

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End Project Report
ClinicalTrials.gov Identifier: NCT02701660

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Abstract

Background: Older opioid-dependent patients often suffer from chronic diseases and disability in addition to their opioid dependence. As a result, they often need to deal with polypharmacy and complex regimens. Together with a high prevalence of psychological problems and low social support, these patients are at high risk for medication non-adherence, especially during the implementation phase. Electronic medication management aids (e-MMA) might be appropriate to simultaneously monitor and improve implementation of dosing regimens for these patients.

Objectives: We aimed to evaluate for the first time a quantitative and qualitative (mixed-method) single-subject study design to investigate the use of an e-MMA in patients on opioid-assisted treatment (OAT) with polypharmacy.

Methods: Five patients from an outpatient addiction service (OAS) in northern Switzerland participated in a sequential multiple-baseline single subject study. We used an e-MMA with prepackaged unit-of-use pouches to monitor adherence during a baseline phase. An intervention phase with built-in audible and visual reminders from the e-MMA started response-guided after a minimum of 4 weeks. After completion, participants entered a follow-up phase with or without e-MMA. Primary outcome was taking adherence, defined as the proportion of correctly retrieved pouches in relation to prescribed doses. Secondary outcomes were proportion of pouches retrieved within 75 minutes before or after agreed dosing times (timing adherence), pre-dispenses, missed dispenses, errors during dispenses, time variability of dispenses, clinical outcomes when available from routine assessments, humanistic outcomes, and satisfaction with the e-MMA. We used visual analysis to assess adherence measures. Data were aggregated in weekly windows and linear regression was used to estimate trends. Other quantitative outcomes were compared between pre- and post-intervention phases. Qualitative outcomes were analyzed descriptively.

Results: Between November 2014 and August 2015, 3 women and 2 men with a mean age of 48 years, taking in addition to OAT a median of 7 medications during 3 dosing times per day were included in the study. The median observation period was 160 days with electronic monitoring. Three participants completed the whole study, one deceased after 14 weeks during the intervention phase (death unrelated to the study) and one withdrew during the baseline phase because he entered stationary treatment. An intervention phase with intake reminder was implemented for two participants. During the entire study period, the median taking adherence was 88%. Participants retrieved a median of 61% pouches within the

dosing intervals (regular dispense), 26% more than 75 minutes before the agreed dosing times (pre-dispense), and 9.2% more than 75 minutes after the agreed dosing time (missed dispense). Errors during dispense occurred in 2.8% of retrievals. The average time variability of retrieval (t_{Var}) was 88 ± 33 minutes. For both patients completing the intervention phase, taking adherence increased by more than 25% to almost 100% and no missed doses were observed when audible and visual reminders were introduced. Timing adherence initially improved dramatically, but trended towards baseline-levels during the intervention period. Conversely, pre-dispenses and time variability were stable during the baseline phase and showed increasing trends during the intervention phase. Clinical outcomes were available for 3 participants. Physical and Mental Quality of life were below average for all participants and varied considerably between measurements. Generally, clinical and humanistic outcomes remained unchanged during the study period for all participants. Participants accepted the e-MMA, especially for the security of having enough medication at home, the possibility to pre-dispense pocket-doses, and the assurance of regular intakes. No adverse events linked to the e-MMA were observed.

Conclusions: Participants in our single-subject study showed high taking adherence and sufficient timing adherence when using the e-MMA. The e-MMA may ensure correct implementation of dosing regimens for opioid-substituted patients with polypharmacy when certain prerequisites are considered. Various drawbacks limit the applicability of the device to monitor adherence. A careful assessment of patient's barriers to medication adherence and a structured medication review should be the first steps when considering the use of the e-MMA for a patient with OAT. Overall, the flexibility of single-subject research designs offers considerable advantages for the evaluation of adherence interventions.

Introduction

Older opioid-dependent patients are a manifold vulnerable group. Due to their history of drug abuse and its associated lifestyle, patients often appear prematurely aged and suffer from chronic diseases and disability, such as arthritis, hypertension, chronic lung disease, stomach ulcers, coronary heart disease, liver cirrhosis, or diabetes mellitus[187]. Additionally, the prevalence of chronic infections, such as Hepatitis B and C or human immunodeficiency virus (HIV), are significantly higher compared to the general population[183,184,188]. Consequently, many older patients with OAT often need additional long-term medications, resulting in polypharmacy and complex regimens. Together with a high prevalence of psychological problems and low social support, these patients are at high risk for medication non-adherence.

Medication adherence is "the process by which patients take their medications as prescribed, composed of initiation, implementation and discontinuation"[22]. Persistence describes the time period between the first dose (initiation) and after the last dose (discontinuation). However, being persistent does not mean that patients' actual dosing corresponds to the prescribed regimen (implementation). Correct implementation is important for patients with opioid dependence syndrome, not only to assure optimal treatment of psychiatric or somatic illnesses, but also to minimize dependence and withdrawal symptoms. Adherence management is the "process of monitoring and supporting patients' adherence to medications by health care systems, providers, patients, and their social networks"[22]. Thus, management of adherence always requires the monitoring of said behavior and an adequate intervention to improve adherence if needed.

Measurement of adherence is challenging: it has to be feasible for patients, valid, reliable and objective, continuous, not invasive, easy to administer and analyze, cover multiple medications, affordable, sustainable, and generalizable[23]. Currently, no existing method satisfies all these criteria. In contrast to most other methods, such as direct measurement of drug concentrations in the blood or urine, pill count, pharmacy refill data, self-report, electronic monitoring meets almost all the requirements.

A multitude of interventions to improve adherence have been studied. Generally, the evidence for the plethora of adherence interventions across conditions remains week, due to the large heterogeneity and methodological problems[220,225,226]. The strongest effects are reached when patients actively participate in the choice of therapy, take on responsibility for self-care, and receive social support[227]. A Cochrane-review assessed the use of interventions

that intend to remind patients to take their medication by packaging solid, oral medications into unit-of-use doses ("reminder-packaging")[64]. They found a mean improvement of adherence of 10% in patients using reminder-packaging systems. The use of electronic reminders, such as short message service (sms) or audiovisual reminder devices, was effective in improving short-term adherence (less than 6 months), but long-term effects remain unclear[65]. In a systematic review of adherence intervention studies using electronic monitoring to assess adherence, only interventions containing feedback of electronic monitoring and/or a cognitive-educational component were effective[62]. In summary, interventions enabling patients to actively participate and take responsibility for self-care, using reminder-packaging, electronic reminders, and adherence feedback, may be feasible to improve adherence. Electronic medication management aids (e-MMA) fulfil these criteria and might additionally be feasible for the electronic monitoring of medication adherence.

Little is known about the adherence of opioid dependent patients to their medication. Few cohort studies from Switzerland and France assessed self-reported adherence of HIV-infected drug users during the past 4 and 1 weeks, respectively[228,229]. Patients with stable opioid substitution therapy report significantly higher adherence (70.9% declare full adherence) than patients without substitution (54.8%)[228]. Some argue that the frequent contacts with a dispensing institution required for OAT have a positive influence on therapy adherence[230]. In contrast, other studies have shown that contingent take-home doses of substitution medication improve therapy attendance[203,204,231]. In another study, full adherence was guaranteed by using buprenorphine for opioid substitution as subcutaneous implant[232]. After 24 weeks, the fraction of urine samples negative for opioids were 25% compared to 13% in the control group and participants had higher study completion rates, lower clinician-rated and patient-rated withdrawal, lower patient-rated craving, and better clinician-rated and patient-rated global improvements. These studies all address adherence to substitution therapy. However, evidence for interventions to improve adherence to additional medications not intended for substitution therapy remains scarce. Due to the complexity of their situations, (older) patients with substance-related disorders are regularly excluded from studies investigating medication adherence[220]. The abovementioned e-MMAs might be appropriate to simultaneously monitor and improve implementation of dosing regimens for these patients. Two case reports of opioid-substituted HIV patients using an e-MMA showed consistent high adherence, suppressed viral load, and sustained persistence over more than 2 years[94]. In a study assessing an e-MMA in home care, participants accepted the device as "very easy to use, very reliable and helpful in the management of their medications"[167]. The

final report on another project with e-MMAs aiming at improving self-management among non-adherent patients concluded that "anyone who has difficulty remembering to take their medication" may benefit from such an intervention[168].

In contrast to cohort studies and RCTs, case studies, single-subject research designs, and N-1 RCTs are applied to individual patients rather than groups of patients. They have been described to be particularly useful to implement in clinical practice and to assess behavioral interventions[233]. It is important to note that case studies are not identical to case reports. While the former follows a predefined research methodology, the latter describes clinical practice and does not involve research methodology[233]. Single-subject research designs are (quasi-)experiments where individual subjects serve as their own control. Carefully selected variables are systematically observed, measured, graphed, and analyzed over time. During baseline and intervention phases, the variables are repeatedly measured. The literature recommends at least 5 repeated measures before introducing the treatment (intervention phase). Usually, the graphed data are analyzed visually regarding their level, trend, and variability between the baseline and intervention phases. This approach offers the advantage that it is readily understood by clinicians, patients, and researchers.

Goal and aims

Our goal was the first-time evaluation of a quantitative and qualitative (mixed-method) single-case study design to investigate the use of an e-MMA in opioid-substituted patients with polypharmacy. Our aims were to develop and evaluate the study design with regards to:

- participant's adherence with an e-MMA
- the effect of intake reminders on adherence patterns
- the effect of the e-MMA on clinical and humanistic outcomes
- participants' acceptance of and satisfaction with the e-MMA

Methods

Design

We applied a sequential multiple-baseline single subject design. Participants completed a baseline phase where the e-MMA was only used to measure adherence (phase A), followed by an intervention phase with intake reminders (phase B), and a follow-up phase with or without the e-MMA (up to 6 months). The intervention phase started response-guided after a minimum of 4 weeks when patients were accustomed to the e-MMA. To maximize external

validity, we used systematic inter-subject replication across multiple participants. Participants and researchers were not blinded to study phase or assessments. The study is reported according to the SCRIBE criteria for the reporting of single-case studies of behavioral interventions[234].

Setting

The study was conducted in a mid-sized city (> 165'000 inhabitants) in northwestern Switzerland between November 2014 and August 2016. We recruited patients from the outpatient addiction service (OAS) of the Psychiatric University Hospital Basel, Switzerland. The setting and population have been described elsewhere[93]. Briefly, the OAS offers treatment to patients with substance use disorders, mental and somatic disorders, and social impairments and problems. Up to 100 patients per day visit the public dispensing point of the clinic to obtain their medication. Patients take their (substitution) medication on site under supervision at least once per week and receive additional doses and medications for take-home. During the study, all medications except substitution medication were provided by the emergency pharmacy of Basel (Notfallapotheke Basel). The community pharmacy is located next to the University hospital and is open between 5 pm and 8 am during weekdays, and 24 hours during weekends and public holidays.

Participants

Participants were recruited by the care staff of the OAS during routine visits. Patients were considered for inclusion according to inclusion criteria (Table 10) when their caregiver deemed them suitable.

Table 10: Inclusion and exclusion criteria

Inclusion criteria
▸ written informed consent given ▸ reading and writing skills in German ▸ stable housing situation in the canton of Basel-City and adjacent municipalities ▸ accessibility by phone ▸ minimum duration in opioid substitution treatment for 2 months ▸ polypharmacy (> 3 solid oral medications) ▸ routine monitoring of clinical parameters less than 1 week before inclusion or agreed within 1 week from inclusion ▸ insured with Swiss health insurance
Exclusion criteria
▸ opioid substitution treatment with Diacetylmorphine ▸ more than 2 drugs that cannot be packaged in pouches (e.g., liquids)

Approvals

This study was approved by the Ethics Committee of northwestern Switzerland (EKNZ 2014-071). A written informed consent form was handed to participants, discussed, and signed before beginning the initial baseline assessment. The study protocol has been registered on ClinicalTrials.gov (ID NCT02701660).

Materials and procedures

An Automatic Tablet Dispensing and Packaging System (ATDPS; Desk Type JV-30DE, HD-Medi, Germany) located at the Emergency Pharmacy in Basel was initially used to repack all solid oral prescription medications except substitution treatment for each participant into unit-of-dose pouches. Each pouch was imprinted with the patient's name, date of birth, date and time for intake, as well as number, name, color, and shape of the medication contained (Figure 26). If the treatment included medications that were taken on demand, the full daily dose was repackaged into a single pouch. Starting from March 2015, the pouches were repackaged by a large blister center in northwestern Switzerland (Medifilm AG, Oensingen) and delivered to the Emergency Pharmacy.

The dispenser (Medido®, Innospense BV, Netherlands) was a remote controlled e-MMA reminding the patients with audible and visual alerts to take their medication (Figure 27). Pushing the OK-button stops the alarm and delivers the pouches with pre-packaged medication. A sensor in the dispenser registers a barcode printed on the top of each pouch and cuts the pouches accordingly. Delivery of doses up to 24 hours ahead of schedule is possible by pushing the OK-button for 5 seconds. This important feature allows pocket-doses that enable patients to go out of the house during intake times. Date and time of delivery are simultaneously recorded with GPRS-technology and stored in a secure server. We used these data to assess adherence.

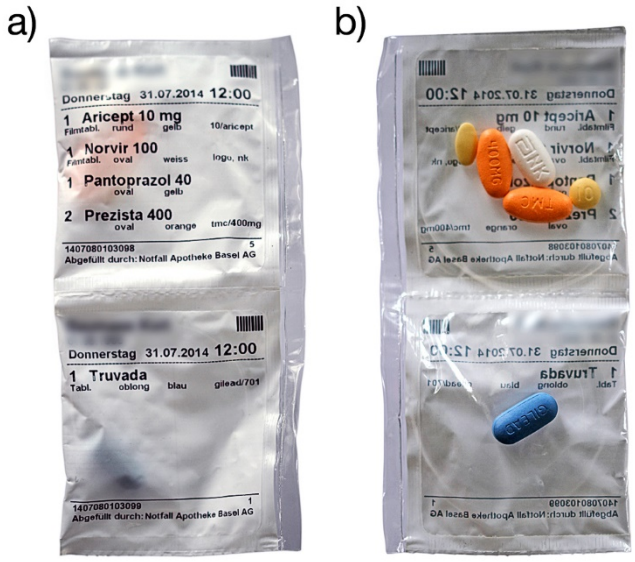

Figure 26: Unit-of-dose pouches with prepacked oral solid medication from front (A) and back (B). Note: Patient's name and date of birth were concealed for privacy reasons.

Figure 27: Remote-controlled, electronic dispenser, Medido®, used in this study as specific electronic medication management aid for the unit-of-dose pouches. Notes: Height × width × length: 140 mm × 140 mm × 225 mm. Weight: 1,486 g. The inset shows the power cord.

Intervention

The supply of medication through the e-MMA required a novel supply model that was organized in collaboration with the OAS, the Pharmaceutical Care Research Group (PCRG) of the University of Basel, and the Emergency Pharmacy of Basel, Switzerland (Figure 28).

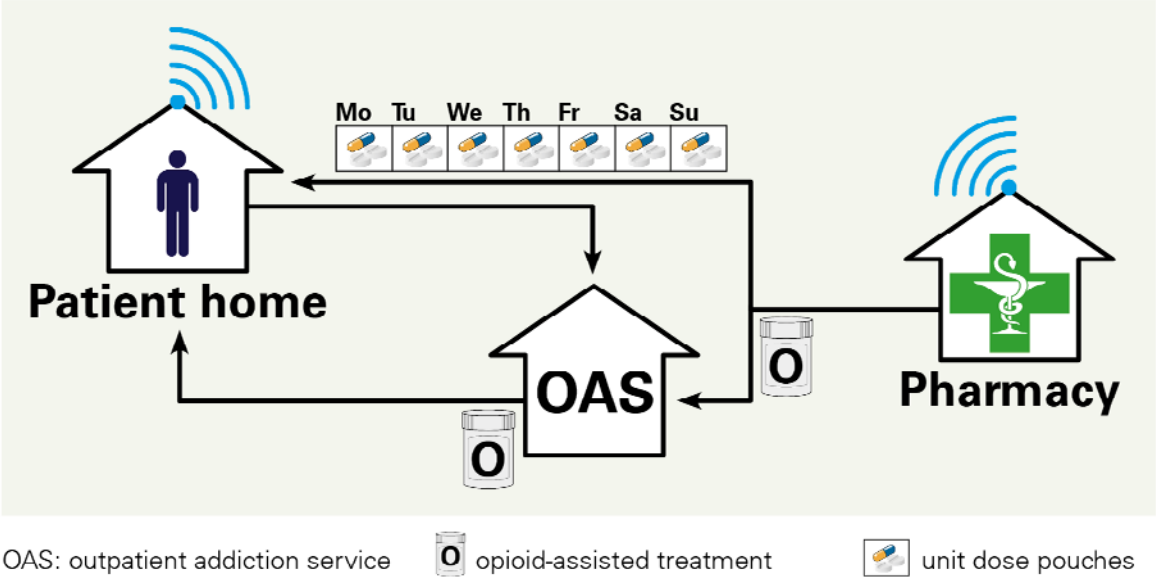

Figure 28: In this medication supply model, the pharmacy provides unit-of-use pouches of all solid oral prescription medications except substitution treatment directly to patients' homes. The pouches are loaded into a lockable, remote-controlled dispenser that can be programmed according to a patient's medication schedule. The dispenser records dates and times of medication retrievals and wirelessly transmits them to a server. Patients collected their opioid substitution therapy from the OAS in regular intervals, at least once weekly, according to local law requirements.

The dispenser was installed at the participants' homes and patients were instructed about its proper use. They were given a written manual including a telephone hotline number in case of problems or difficulties with the e-MMA. The hotline was operated by a pharmacist of the PCRG during weekdays and by the emergency pharmacy during weekends and public holidays. Every 3 weeks, medications were repackaged according to the current treatment plan and the e-MMAs were refilled during a pre-scheduled visit at the patients' homes (Figure 29).

Dosing times were discussed, set according to participants' preferences, and adjusted during the study period if needed. Participants were allowed to retrieve doses not more than 24 hours prior than the agreed dosing time. During baseline phases, the alarm was inaudible and set to at least 2 hours after the agreed dosing times. Participants were instructed to retrieve the pouches at the agreed dosing time autonomously and immediately before intake by pushing the OK-button. For the intervention phase, the alarm was switched on for the agreed dosing times and patients were instructed to retrieve the pouches when the alarm sounded and immediately ingest their medication. In case of malfunctioning, or if a patient missed to retrieve a dose from the dispenser within 75 minutes during the intervention phase, the dispenser would automatically send an alert to the responsible pharmacist. The pharmacist would then contact the patient and make sure that medication intake was warranted. Patients continued to collect their substitution medication from the OAS once

weekly according to legal requirements. To assure procedural fidelity, standard operation procedures (SOPs) were developed and used for all steps.

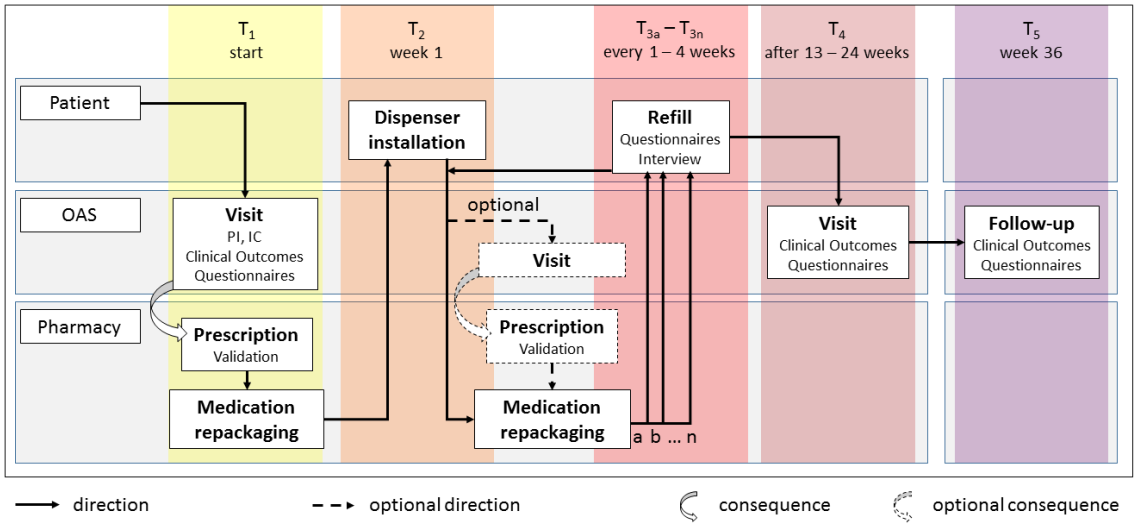

Figure 29: Course of the study. OAS: Outpatient Addiction Service, PCRG: Pharmaceutical Care Research Group

Measures

Our primary outcome measure was taking adherence during the implementation phase, defined as the proportion of correctly retrieved pouches in relation to prescribed doses between dispenser installation (T_2) and end of intervention (T_4, Figure 29). Since the e-MMA guaranteed dispensing of every dose, we defined correct dispensing when a dose was retrieved before or within the predefined time interval for dispensing. The time interval was set to a grace period of 75 minutes after the agreed dosing time. If a patient retrieved a dose after the grace period, it was considered as missed. In case of multiple intake times per day, each dose was counted separately.

Our secondary outcome measures were:

Dosing patterns (between T_2 and T_4)	continuous assessment with e-MMA ▸ frequencies of pre-dispense (doses retrieved > 75 minutes before the agreed dosing time) ▸ regular dispense (doses retrieved within 75 minutes before or after the agreed dosing time; timing adherence) ▸ missed dispense (doses retrieved more than 75 minutes after the agreed dosing time) ▸ erroneous dispense (errors during dispense due to technical problems)
Time-variability of medication retrieval (t_{Var}[235]; between T_2, and T_4)	▸ continuous assessment with e-MMA
Self-reported adherence (T_1, T_4, T_5)	▸ translated and adapted versions of the ACTG Adherence questionnaire[236]
Quality of Life (QoL; T_1, T_3, T_4, T_5)	▸ Physical and Mental Composite Scores (PCS, MCS) of the SF-12 self-report questionnaire[237]
Psychological distress (T_1, T_4, T_5)	▸ SCL-90R self-report questionnaire[238]
Instrumental Activities of Daily Living (IADL; T_1, T_4, T_5)	▸ IADL Scale of Lawton-Brody[239]
Satisfaction (T_3, T_4)	▸ self-report questionnaire at T_4 ▸ interviews during T_3 with the following questions about the e-MMA: o What did you experience since the last refill? o When did the e-MMA bother you? o When have you been glad about the e-MMA?
Individual clinical outcomes (e.g., blood pressure, blood sugar, HIV count; between T_1 and T_5)	▸ only for participants completing the study when available from routine assessments

Analyses

As recommended for single-subject research, we used visual analysis for electronic adherence measures. Visual inspection of the graphed data allows to draw conclusions about the intervention effects[240]. For this first exploratory study, we found this to be the most appropriate method to assess reliability and consistency of intervention effects. In case of multiple intake times per day, we aggregated the dosing patterns and averaged the time-variability of medication retrieval (t_{Var}) for all scheduled intake times[235]. Raw adherence patterns (dosing times and types) were plotted for all participants. We plotted weekly

adherence patterns for the two participants with distinct baseline and intervention phases. For this purpose, frequencies of pre-dispense, regular dispense, and late dispense, along with t_{Var} were aggregated in weekly intervals and graphed. Windows with less than 4 days (e.g., at the end of baseline and intervention phases) were not included for analyses because of insufficient comparability. Trend lines for baseline and intervention phases were calculated using linear regression. We used the statistical Software R for processing of the raw dispenser data, for calculations, and for graphing[149].

Other quantitative outcomes (Quality of Life [QoL], Psychological distress, IADL, clinical outcomes) were compared individually between pre- and post-intervention phases. Questionnaires regarding patient satisfaction and adherence were analyzed descriptively. Patient interviews were audio-taped, verbatim transcribed, and analyzed with MaxQDA (VERBI GmbH, Berlin, Germany). A combination of inductive and deductive content analyses was applied based on earlier research with the same e-MMA[92]. Participants' statements about satisfaction with the dispenser were coded into the themes "patient support", "product design", and "living conditions"[92].

Results

Participants

Between November 2014 and August 2015, five patients accepted to participate in the study. Participants (three female, two male), had a mean age of 48 years (34 – 68), took a median of 7 medications during 3 dosing times per day (excluding OAT), and spent on average 70% (30%–100%) of their weekdays at home (Table 11). Participants received a median of 10 (5–15) refill visits with an interquartile range (IQR) of 6 during a median observation period of 160 days (39–253, IQR = 87). A median 85.5% of days were electronically monitored (80.4%–93.5%, IQR = 5.3, Table 12). All participants experienced periods without retrieval of the pouches from the e-MMA. Reasons for interruptions were holidays, hospitalizations, or technical difficulties with the e-MMA. During interruptions, participants used the pouches without the dispenser or received medications in the hospital or from other sources (e.g., OAS).

Table 11: Baseline characteristics of participants

Participant	**Carmen**	**Brunhilde**	**Albert**	**Denise**	**Erdin**
Age [years]	36	68	57	45	34
Sex [Male/Female]	F	F	M	F	M
Level of education	basic apprentice-ship	vocational school	University	basic apprentice-ship	vocational school
Living conditions	social housing, alone	community-dwelling with grand-daughter	therapeutic Living Community	social housing, alone	living with family
Working status	not working	not working	not working	not working	not working
Time spent at home during workdays	50%	100%	30%	70%	100%
Quality of Life (SF-12)					
PCS	41.79	34.06	27.41	39.34	33.91
MCS	35.55	38.02	40.99	29.1	28.33
Psychological Distress (SCL 90R)					
GSI	1.7	0.85	1.18	2.8	1.31
PST	78	43	50	78	63
PSDI	1.99	1.67	2.12	2.89	1.86
IADL	7	5	5	7	3
Expectation of e-MMA on:					
medication intake	more regular intake	more regular intake	take medication earlier and inde-pendently	more regular intake	more control over intake
everyday life	more structure	no impact	more indepen-dent	not much, less messy with medication management	no impact
Number of medication monitored (excluding OAT)	8	12	5	7	6
Therapy	morphine (sustained-release)*, diazepam, methyl-phenidate (sustained-release)*, pregabalin, quetiapine, trimipramine, calcium, multivitamin, vitamin A, zinc	morphine (sustained-release), metamizole, zolpidem, mirtazapine, sertralin, aspirin, atorvastatin, nebivolol, torasemide, calcium, folic acid, iron, L-thyroxine	morphine (sustained-release)*, diazepam, methyl-phenidate (sustained release), aspirin, panto-prazole, ramipril	methadone* diazepam, abacavir, darunavir, etravirine, raltegravir, ritonavir, L-thyroxine	methadone*, diazepam, clonazepam, quetiapine, escitalo-pram, iron, pantoprazole
Scheduled dosing times per day	4	4	2	2	3
Clinical outcomes monitored	Vitamins A, B1, B6, B12, D, E, Zinc	none	GAF	viral load, CD4 cells	none

GAF: Global Assessment of Functioning, **GSI:** Global Severity Index, **IADL:** Instrumental Activities of Daily Living, **MCS:** Mental Composite Score, **PCS:** Physical Composite Score, **PSDI:** Positive Symptom Distress Index, **PST:** Positive Symptom Total, *** Substance not monitored**

Table 12: Sequence completed for all participants. An intervention phase with the built-in intake reminder was implemented for Brunhilde and Carmen. All other participants did not use the intake reminders of the dispenser.

ID*	No. of refill visits		Observation period (days)	Days with e-monitoring (%)
Carmen	**Total:**	**13**	**12.5.15 – 11.11.15 (184)**	**172 (93.5)**
	Baseline:	5	12.5.15 – 16.7.15 (66)	54 (81.8)
	Intervention:	8	17.7.15 – 11.11.15 (118)	118 (100.0)
Brunhilde	**Total:**	**7**	**22.1.15 – 28.4.15 (97)**	**83 (80.4)**
	Baseline:	4	22.1.15 – 24.2.15 (36)	33 (91.7)
	Intervention:	3	25.2.15 – 28.4.15 (61)	45 (73.8)
Albert		**15**	**27.11.14 – 6.8.15 (253)**	**216 (85.5)**
Denise		**10**	**14.8.15 – 20.1.16 (160)**	**135 (84.4)**
Erdin		**5**	**15.8.15 – 22.9.15 (39)**	**35 (89.7)**

* not actual patient names

At inclusion, according to the ACTG questionnaire, all patients were very sure or absolutely sure that they would take all their medications as prescribed. All participants but Denise were very sure or absolutely sure that their medication had a positive effect on their health. They received no or little support from family and friends (Brunhilde, Carmen, Albert, and Denise), or a lot (Erdin). Their satisfaction with the support from family and friends was high (Carmen, Brundhilde, and Albert) or low (Denise and Erdin). Brunhilde and Erdin reported frequent missed intakes during the past 4 weeks, Carmen reported occasional missed intakes, and Albert and Denise reported no missed intakes.

Three participants completed the whole study (Carmen, Albert, and Denise). Brunhilde deceased after 14 weeks during week 8 of the intervention phase (death unrelated to the study) and Erdin withdrew after 6 weeks during the baseline phase because he entered stationary treatment. An intervention phase with intake reminder was implemented for Brunhilde and Carmen. All other participants did not use the intake reminders of the dispenser. Albert pre-dispensed all doses at the earliest moment possible, Denise wanted to use her own mobile phone as an alarm because she did not like the sound of the dispenser, and Erdin withdrew during the baseline phase.

Adherence patterns and effect of intake reminders

During the entire study period, the median taking adherence was 88%. Participants retrieved a median 61% of pouches within the dosing intervals (regular dispense), 26% more than 75 minutes before the agreed dosing times (pre-dispense), and 9.2% more than 75 minutes after the agreed dosing time (missed dispense). Errors during dispense occurred in 2.8% of retrievals. The average time variability of retrieval (t_{Var}) was 88 ± 33 minutes. The individual proportions varied widely between participants (Table 13).

Table 13: Primary and secondary adherence outcomes between T_2 and T_4.

ID		Taking A. (%)	Timing A. (%)	Pre-disp. (%)	Missed (%)	Errors (%)	t_{Var} [min]
C.	**Total:**	**544 (87.3)**	**381 (61.2)**	**163 (26.2)**	**64 (10.3)**	**15 (2.4)**	**100**
	Baseline:	142 (67.3)	100 (47.4)	42 (19.9)	64 (30.3)	5 (2.4)	88
	Intervention:	402 (97.3)	281 (68.2)	121 (29.4)	0 (0.0)	10 (2.4)	106
B.	**Total:**	**219 (88.0)**	**178 (71.5)**	**41 (16.5)**	**23 (9.2)**	**7 (2.8)**	**83**
	Baseline:	92 (79.3)	80 (69.0)	12 (10.3)	21 (18.1)	3 (2.6)	108
	Intervention:	127 (95.2)	98 (73.7)	29 (21.8)	2 (1.5)	4 (3.0)	57
A.		**456 (97.9)**	**3 (0.6)**	**453 (97.2)**	**0 (0.0)**	**10 (2.1)**	**65**
D.		**152 (74.1)**	**128 (62.4)**	**24 (11.7)**	**31 (15.1)**	**22 (10.7)**	**53**
E.		**88 (93.6)**	**2 (2.1)**	**86 (91.5)**	**1 (1.1)**	**5 (5.3)**	**137**

Carmen often missed to retrieve her medications during the baseline phase, especially in the evenings (Figure 30). Simultaneously, she had a high proportion of pre-dispenses, especially for the morning doses. During the baseline phase, Carmen was hospitalized for 12 days during which she did not use the dispenser. She entered the intervention phase after 9 weeks and as a result, missed dispenses decreased from 30% (baseline) to zero (intervention phase, Table 13). Her dispensing pattern was relatively stable during the baseline phase (Figure 31). After entering the intervention phase, regular dispenses initially increased by more than 40% but showed a decreasing trend towards the end of the intervention phase. Contrary, pre-dispenses showed an upward trend during the intervention phase. T_{Var} varied between 43 min and 138 min but was overall stable during the baseline phase. During the intervention phase, t_{Var} varied greatly between 3 min and 225 min with an increasing trend towards the end of the intervention phase (Figure 31).

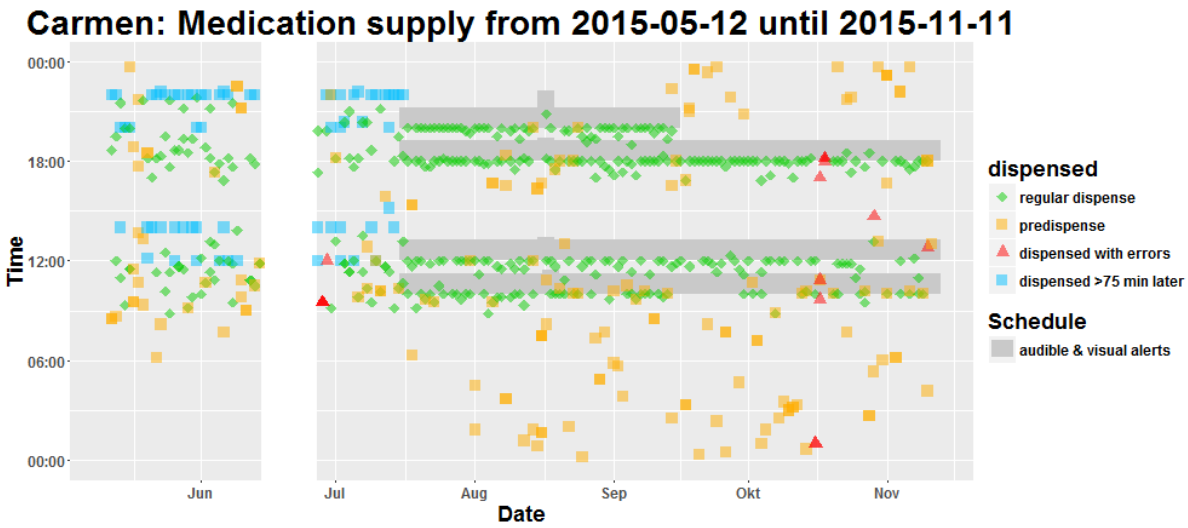

Figure 30: Time of medication retrieval for Carmen recorded with electronic monitoring. White areas are days with missing electronic monitoring.

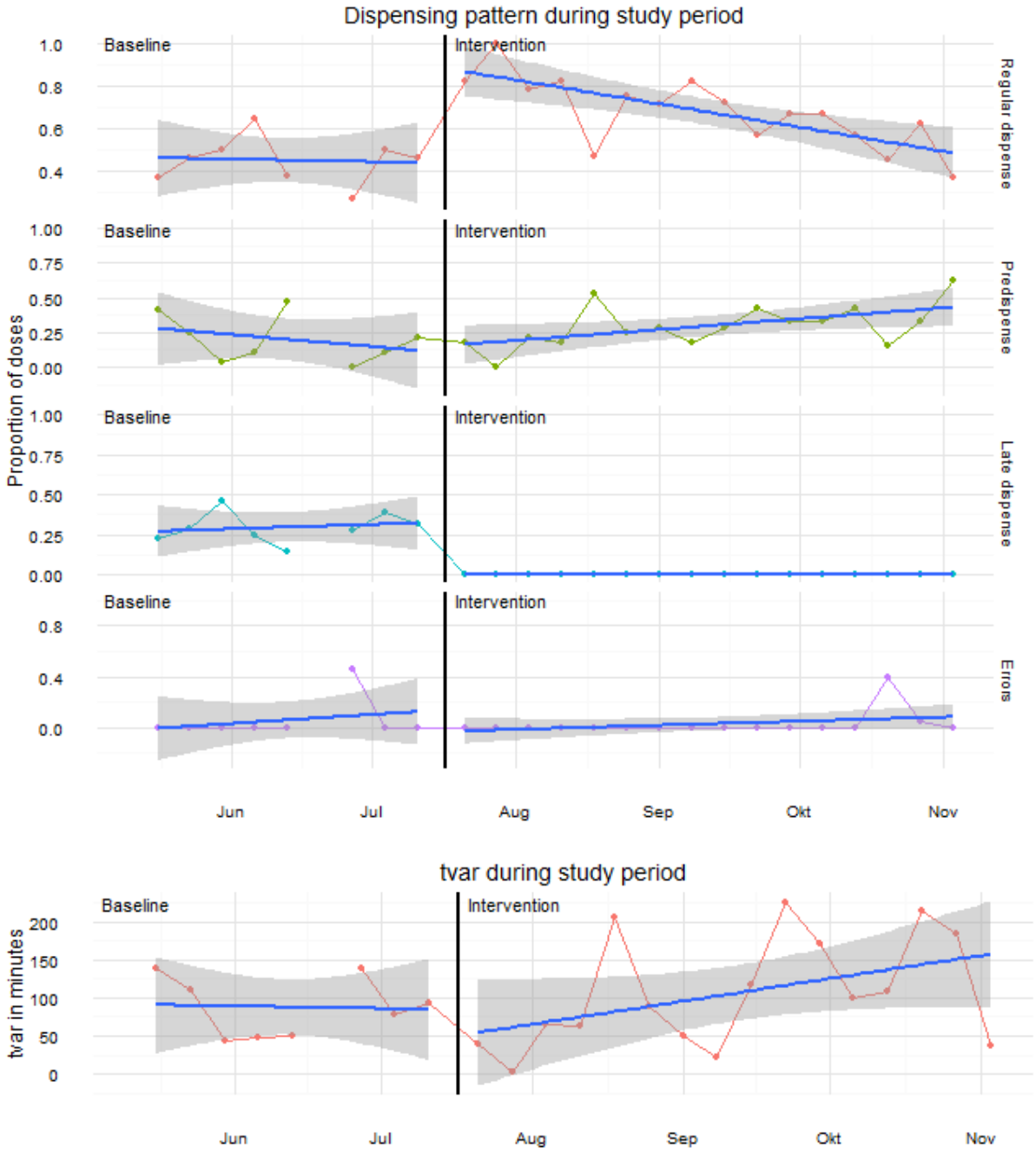

Figure 31: Dispensing patterns and t_{Var} for Carmen during baseline and intervention phase. Blue lines depict linear trends, with grey areas indicating the 95%-confidence interval.

Brundhilde missed almost 20% of doses during the baseline phase, especially in the evenings (Figure 32). She entered the intervention phase with intake reminders after 5 weeks and as a result, missed dispenses decreased to 1.5% during the intervention phase (Table 13). Similarly, time variability halved from 108 to 57 minutes. She was hospitalized 2 weeks after start of the intervention phase and entered psychiatric rehabilitation shortly after her hospital stay. During this period, she was not able to use the dispenser. After her return home, she continued to show high taking adherence (Figure 33).

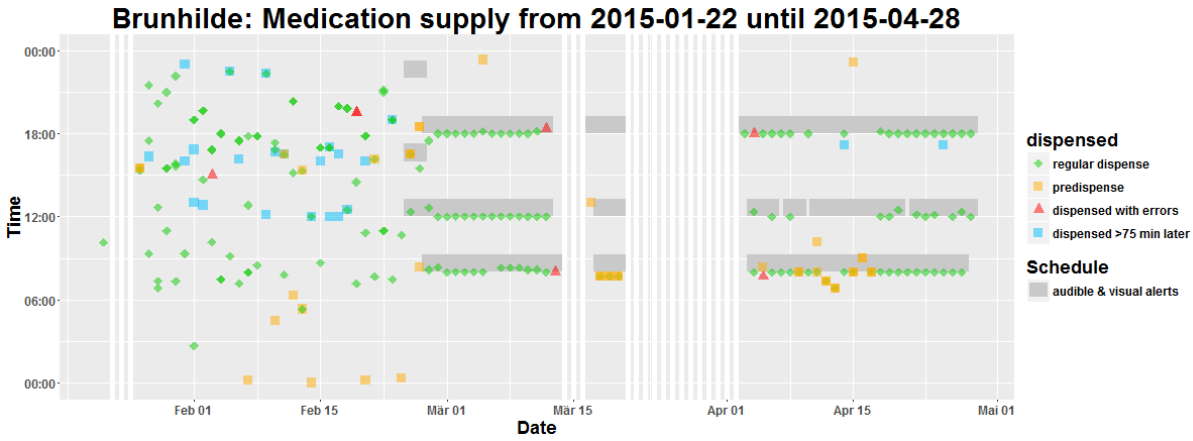

Figure 32: Time of medication retrieval for Brunhilde recorded with electronic monitoring. White areas are days with missing electronic monitoring.

While her dispensing pattern was relatively stable during the baseline phase, frequencies of regular dispenses and pre-dispenses varied greatly during the intervention phase (Figure 33). However, this can partly be explained by the participant's instability in March 2015 when she sometimes retrieved pocket-doses before entering the hospital or psychiatric rehabilitation. While conforming to the schedule during the first weeks of the intervention phase, she started to pre-dispense her evening painkillers in the morning. Since she did not want the dispenser to sound an alarm too early in the morning, her morning dose of painkillers was scheduled for retrieval in the evening.

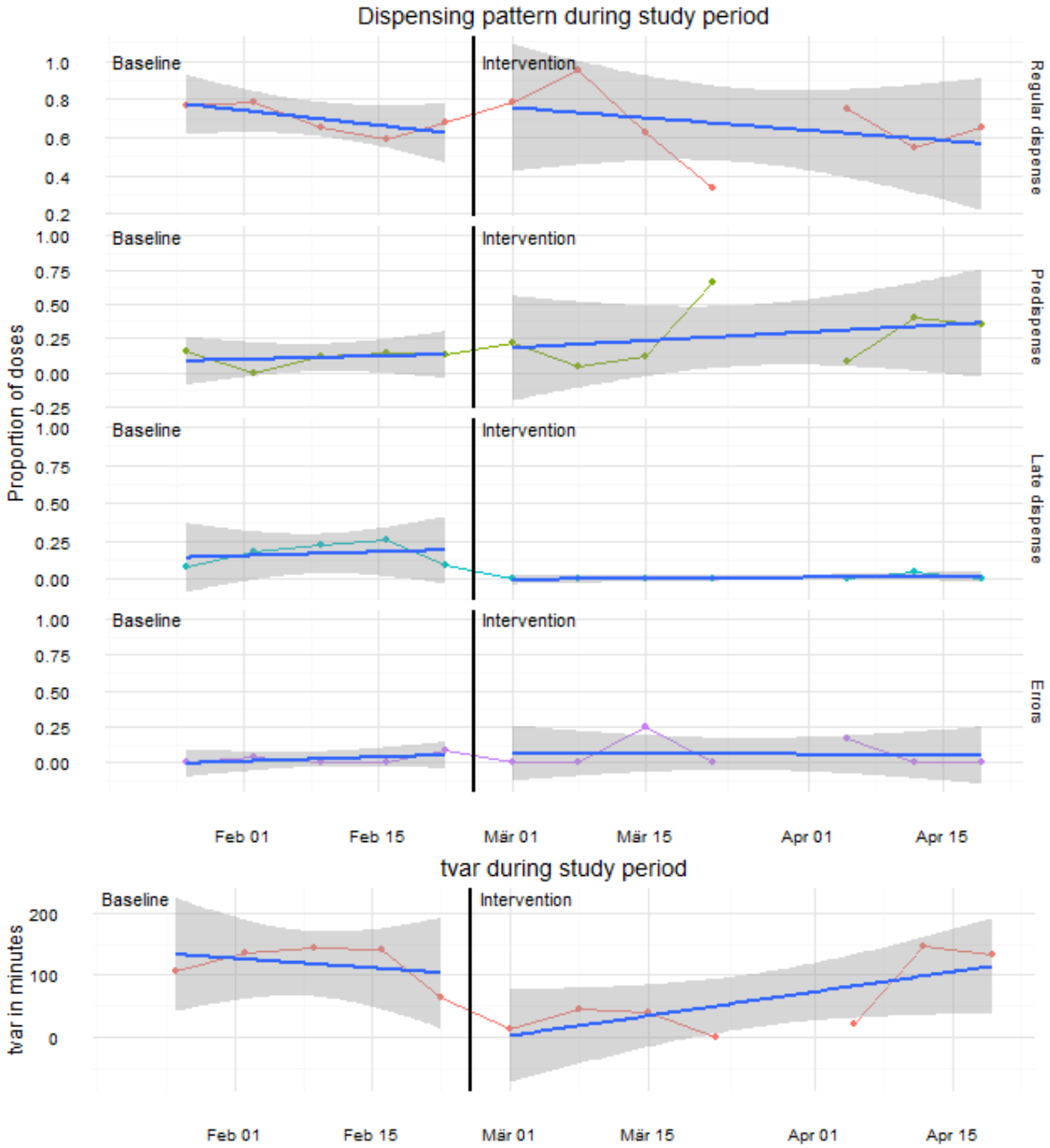

Figure 33: Dispensing patterns and t_{Var} for Brunhilde during baseline and intervention phase. Blue lines depict linear trends, with grey areas indicating the 95%-confidence interval.

Albert pre-dispensed almost all pouches at the earliest moment possible, 24 hours prior to schedule (97.9%, Figure 34 and Table 13). He did not use the e-MMA as an intake reminder, but he needed support to organize his medication management, mainly to prevent him from overusing methylphenidate. Days without monitoring occurred often due to frequent short holidays, especially after he left the therapeutic living community in April 2015 and moved into his own flat. Additionally, he reported that the e-MMA was stolen twice, although the truthfulness of his claims were never confirmed. His dispensing pattern did not change considerably during the study period. T_{Var} varied between 1.64 and 206 minutes (mean 65 min) and showed a downward trend during the study period (Figure 42 in Appendix A.3.9).

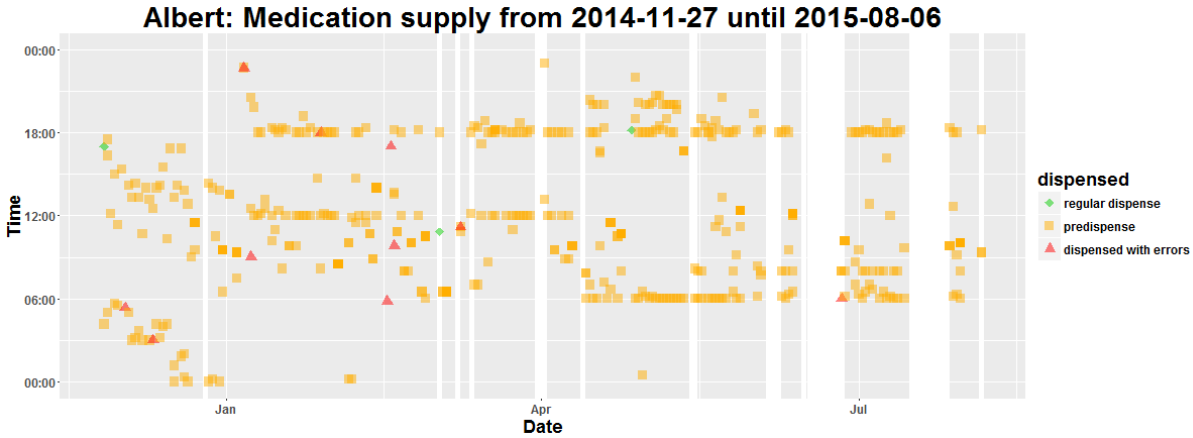

Figure 34: Time of medication retrieval for Albert recorded with electronic monitoring. White areas are days with missing electronic monitoring.

Denise showed a high timing adherence (62.4%, Table 13). Similar to Albert, she did not use the e-MMA as an intake reminder but relied on her own mobile phone for alarms. After a few weeks, she did not longer want her thyroid hormones to be included in the pouches because she preferred to take them from the original pill bottle. As a result, she no longer had two monitored intake times. Possibly due to the size of her tablets, she experienced frequent errors during bag dispense, which led to two unmonitored intervals (Figure 35).

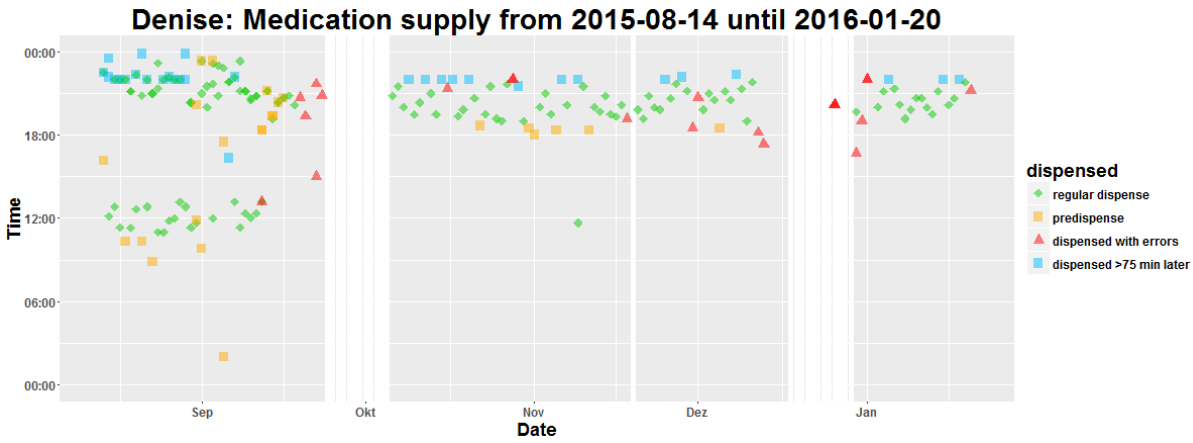

Figure 35: Time of medication retrieval for Denise recorded with electronic monitoring. White areas are days with missing electronic monitoring.

With 53 minutes, her overall t_{Var} was the lowest of all participants, possibly explained by the additional reminders from her mobile phone. Her dispensing pattern varied during the study period but no clear trends were observed (Figure 43 in Appendix A.3.9).

Erdin pre-dispensed most of his pouches (91.5%, Table 13 and Figure 44/Figure 45 in Appendix A.3.9). Similar to Albert, he did not use the e-MMA as an intake reminder, but to prevent him from overconsuming, in his case Benzodiazepines. In contrast to Albert, who complied with the restrictions imposed by the e-MMA, he tried to bypass the dose restriction and retrieve the pouches manually using tweezers or tongs. When he realized that the e-MMA would not prevent him from overconsumption, he withdrew from the study and entered stationary treatment.

Effect of the e-MMA on clinical and humanistic outcomes

Clinical outcomes were available for Carmen, Albert, and Denise (Table 14). Generally, clinical and humanistic outcomes remained stable during the study period for all participants with available outcome measures. Albert's Global Assessment of Functioning (GAF) Score indicated serious impairment in judgement and delusional influence on behavior and did not considerably change between phases. Vitamin levels of Carmen decreased between T_1 and T_4 but rose to normal levels at T_5. HIV RNA remained suppressed for Denise throughout the study period.

Table 14: Available clinical outcomes for Albert, Carmen, and Denise during pre- and post-intervention phases (T1 and T4) and follow-up (T5)

ID	Clinical outcome	Unit	Reference	Pre (T_1)	Post (T_4)	Follow-up (T_5)
Albert	GAF	-		29	30	30
Carmen	Vitamin A	µmol/l	1.05 – 2.45	0.67	0.86	1.16
	Vitamin B1	nmol/l	67 – 200	94	90	128
	Vitamin B6	nmol/l	35 – 110	206	75	117
	Vitamin B12	pmol/l	179 – 660	369	261	-
	Vitamin D	nmol/l	75 – 220	77	77	61
	Vitamin E	µmol/l	11.0 – 50.0	34.3	25.1	-
	Zinc	µmol/l	9.2 – 18.4	-	9.2	10.4
Denise	HIV viral load	Copies/ml	<20	<20	<20	<20
	CD4 count	Cells/µl	700 – 1100	667	546	737

Physical and Mental Quality of life were below average for all participants and varied considerably between measurements. Typically, physical quality of life (PCS) remained stable during the intervention period, but was lower at follow-up (T_5). Mental quality of life (MCS) increased between T_1 and T_4, and decreased during follow up (Table 15). All patients considerably suffered from psychological distress. For Albert and Denise, the Global Severity Index (GSI) and Positive Symptom Distress Index (PSDI) decreased while using the e-MMA. In contrast, GSI and PSDI increased for Carmen (Table 15).

Instrumental Activities of Daily Living (IADL) varied between 3 and 8 points across participants, with 8 being the maximal possible score. Carmen and Denise were independent except for medication responsibility. Albert scored 5 points at inclusion, indicating a medium level of dependence with deficiencies in the areas cooking, medication, and finances. His score improved during the study period (for cooking and finances) and reached independence in all areas at follow-up T_5 when he did not use the dispenser anymore.

No adverse events linked to the e-MMA were observed.

Table 15: Humanistic outcomes for participants A, C, and D during pre- and post-intervention phases (T_1 and T_4) and follow-up (T_5)

	Quality of life (SF-12)		Psychological Distress (SCL 90R)			
	PCS	MCS	GSI	PST	PSDI	IADL
Carmen						
Pre (T_1)	41.79	35.55	1.72	78.00	1.99	7
Post (T_4)	44.2	39.98	1.81	71.00	2.30	7
Follow-up (T_5)	32.31	36.48	2.30	81.00	2.56	7
Albert						
Pre (T_1)	27.41	40.99	1.18	50.00	2.12	5
Post (T_4)	26.17	55.64	0.97	49.00	1.78	7
Follow-up (T_5)	20.15	41.92	1.46	43.00	3.05	8
Denise						
Pre (T_1)	39.34	29.1	2.50	78.00	2.88	7
Post (T_4)	39.03	40.13	1.77	66.00	2.41	7
Follow-up (T_5)	32	39.89	1.57	64.00	2.20	8

Participants' acceptance of the e-MMA

Participants generally accepted the e-MMA and welcomed the pharmacist for refills and follow-ups in their homes. However, they expressed different opinions about the e-MMA during interviews and in the satisfaction questionnaire at the end of the study period (Table 16). All patients mentioned that the e-MMA gave them the security that they had enough medication at home and they appreciated the possibility to pre-dispense pocket-doses.

Table 16: Participants' positive and negative statements about the e-MMA

	Experiences with the e-MMA regarding…		
Participant	… Patient Support	… Product Design	… Living Conditions
Carmen	**Positive:** assured regular intake, medications were well organized, encouraged her to get up, gave her security that she had enough medication **Negative:** could still forget medication intake	**Negative:** Alarm woke her up	**Positive:** independence, possibility of pre-dispensing pocket-doses **Negative:** inconvenience when busy with other things
Brunhilde	**Positive:** assured regular intake, gave her security that she had enough medication **Negative:** something new forced upon her	**Positive:** worked reliably (after initial technical problems) **Negative:** Alarm woke her up	**Positive:** possibility of pre-dispensing pocket doses **Negative:** Inconvenient to reach when in pain
Albert	**Positive:** presence of e-MMA acted as a reminder to take medication, helped to organize his weekly dose, gave him security that he had enough medication, relieved him from carrying a lot of medication around	**Positive:** worked reliably, was hygienic, and he would be able to break it in case of emergency to get to his medication	**Positive:** independence, did not have to rely on other people for his medication, possibility of pre-dispensing pocket-doses **Negative:** inflexibility in case of special requests, not mobile, dependent on the dispenser
Denise	**Positive:** pre-packed medication, easy to use, assures regular intake, especially when feeling tired, gave her security that she had enough medication **Negative:** loss of control over medication	**Positive:** hygienic **Negative:** produces unnecessary waste, unpleasant sound, gets in the way, tablets fall out of the pouch, technical issues, alarm woke her up	**Positive:** less messy (no medication packages or pill boxes lying around), possibility of pre-dispensing pocket doses
Erdin	**Positive:** controlled dispense, gave him security that he had enough medication	**Negative:** technical problems, does not prevent him from accessing medication	**Positive:** possibility of pre-dispensing pocket doses

Participants finishing the study (Albert, Carmen, and Denise) reported overall satisfaction with the e-MMA. None of the participants felt uncomfortable during home visits or reported constraints in social life or contacts with caregivers from the OAS. Carmen and Albert rated support with their medication as satisfactorily, knew who to contact in case of issues, felt that issues were resolved promptly, and wanted to continue to use the e-MMA. Only Denise experienced persisting technical problems that were not adequately addressed. Only Albert

reported troubles with visits to the OAS for medication dispense and he wished to also receive OAT from the e-MMA.

Carmen reported problems with motivation to take certain medications for malnutrition and expected the e-MMA to support regular intake. She was satisfied with the novel supply model because her medications were pre-packaged according to a regular schedule and she remained independent. She reported high satisfaction with the regular intake reminders and mentioned that the dispenser helped her to "pick herself up" and structure her day sometimes. On the other hand, the alarms were sometimes inconvenient, especially when she was busy doing other things. As a result, she would sometimes pre-dispense morning doses in the previous evening (especially during the weekends) or only push the button to stop the alarm without taking her medication. She continued to use the e-MMA after study completion and was still using it at press time of this report (Jan. 2017).

Albert was initially unsatisfied with the situation in his therapeutic living community where medications were handed out by caregivers. He felt patronized and described the e-MMA as a relief that allowed him to be more independent, both with his medication and his daily life. He mentioned the better hygiene of the dispenser and that its presence reminded him to take the medications that he would normally take irregularly (e.g., medications for heart condition). The e-MMA worked reliably and gave him a predictable security. Ultimately, he was able to move out of the therapeutic living community and to live independently. Later, he acknowledged that he was addicted to Methylphenidate and that the e-MMA helped him to organize his weekly dose. Although it would not prevent him from overconsumption if he wanted to use more (e.g., from other sources), the e-MMA guaranteed that he would not run out of medication when he could not control himself. Drawbacks for him were the inflexibility of the system, especially for short-term holidays. On the one hand, he would have preferred a solution without the dispenser, e.g., weekly take-home doses. On the other hand, he did not like to carry large quantities of medication from the OAS and appreciated that with the new supply model he had his medications at home. He continued to use the e-MMA after study completion but discontinued when he was able to get weekly take-home doses.

Denise was initially skeptical and felt like a "guinea pig" for participating in the study. However, she expected the e-MMA to disburden her from preparing her medication in advance and assure regular intake. Additionally, she expected less medication boxes lying around. She was satisfied with the pre-packaged pouches but only for her HIV medications. She preferred to take the other medications (e.g., thyroid hormones) from the original container because she felt that repackaging produced unnecessary plastic waste. She

remained ambivalent during the whole study period: on the one hand, she described a loss of control with the dispenser because she felt that medication management was one of the only things where she could still be in control. On the other hand, she repeatedly stressed that the pre-packed medications in the e-MMA were helpful because they were well organized and ready to take. Ultimately, she did not want to continue using the dispenser after study completion.

Discussion

Interpretation

The assessment of adherence with an e-MMA showed high taking adherence but low timing adherence for 5 participants in our single-subject study. Additionally, the time variability (t_{Var}) was high with an average of 1.5 hours. Participants with low self-reported adherence at baseline (i.e. Carmen and Brunhilde) were the only participants using the audible and visual reminders of the e-MMA. Remarkably, taking adherence increased by more than 25% to almost 100% for both participants when reminders were introduced during the intervention phase. These results are consistent with current evidence for the effectiveness of electronic reminders on adherence[65]. The built-in reminders of the e-MMA reduced missed doses to zero, compared to 15% missed doses with external reminders used by Denise. To stop the built-in reminder, patients have to retrieve their medication from the e-MMA. In contrast, external reminders, such as mobile phone alarms, can be switched off without having to approach the e-MMA. Of course, retrieval of pouches does not imply ingestion of medication. However, other studies have suggested that proximity of reminders to an action such as medication intake increases the completion of said action[241].

The high time variability can be explained by the number of intake times and the high rate of pre-dispensed doses. A higher number of intake times may increase time variability when multiple doses are retrieved at the same time, for example when pre-dispensing pocket doses. Several other reasons might explain the high rate of pre-dispenses in this study: First, we instructed participants to autonomously dispense medications to measure baseline adherence, bypassing the e-MMA's reminder function. As a result, patients might have formed a habit of pre-dispensing their pouches, even when audible and visual reminders were activated. The number of pre-dispenses dropped after the start of reminders for Carmen and Brunhilde, but increased again for both patients during the intervention phase. Two previous case reports with the e-MMA showed over 90% timing adherence with almost no pre-

dispenses when audible and visual alerts were present from the beginning[94]. Second, we included medication in the pouches that did not necessarily need to be taken at fixed intervals, but were dosed on demand (e.g., diazepam). Although we repackaged the full daily dose of these medications in one pouch, this might have encouraged participants to pre-dispense pouches containing their on-demand medications and thus increase time variability. Finally, substance abuse might have been an issue for some medications repackaged into pouches (e.g., methylphenidate, benzodiazepines), encouraging patients to pre-dispense their daily doses.

Arguably, the importance of timely dosing depends on the respective therapy. Due to differences in pharmacologic properties, it is more important for some medications to be taken at exact times than for others. The probability of therapeutic success under imperfect adherence compared to perfect adherence has previously been described as "forgiveness" of medications [242]. A typical example for unforgiving medications are treatments for infectious diseases, such as HIV. In our study, Denise was treated for HIV infection and thus, the low time variability of less than one hour appears critical to ensure effective treatment. In contrast, Carmen's therapy consisted of supplements for malnutrition and psychoactive substances, which are considered more forgiving. Although her time variability was substantially larger than Denise's, her adherence patterns may be appropriate for her specific therapy. Thus, the specificities of a patient's treatment (e.g., forgiveness, presence of on-demand medications) should always be considered when assessing adherence to polypharmacy.

Although not a focus of this study, we included clinical outcomes when routinely assessed and available during the study period. Overall, we observed marginal improvements or stagnancy, indicating that our intervention did not negatively affect treatments. Obviously, the e-MMA might offer the largest benefits to patients with low adherence and unmet clinical outcomes. However, consideration of humanistic outcomes might be more appropriate in multi-morbid patients with polypharmacy. Physical and Mental quality of life (QoL) were low in our study, and participants showed high levels of psychological distress. QoL is affected by a range of concepts, such as physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment[243]. QoL is reportedly lower than average in patients with substance-use disorders, and improvements in QoL should be a priority for these patients[244]. Our results indicate trends towards the improvement of mental QoL, which might be explained by the additional attention participants received during the study. Additionally, IADL indicated a high independence of

participants that could be sustained or increased with the e-MMA. Participants also reported independence and security of medication availability as biggest advantages of the e-MMA. Most importantly, the e-MMA did not interfere with the care they received from the OAS.

Strengths and limitations

Our study has several strengths. First, the use of single-case methodology allows for flexibility in the implementation of the intervention[245]. Second, adherence is a complex behavior that needs to be approached on an individual level. As such, single-case research designs might be more appropriate for the first-time assessment of interventions to improve adherence on the patient level compared to group-based randomized controlled trials. Third, a mixed-methods approach combining quantitative and qualitative methodology offers a more complete picture and allows to put the quantitative observations into context.

We acknowledge some limitations. First, we present a first-time analysis of adherence data from a novel e-MMA in a single-subject study. The design of the e-MMA with the sequential dispensing of doses might limit the interpretability of the chosen measures. The sequential design of the medication pouches required dispensing of every dose before the next dosing time. In case of multiple dosing times that sometimes were only two hours apart, we needed sufficient time to intervene in case of a missed dose. While disadvantageous for the unconfounded measurement of adherence, this design ensures the timely implementation of complex regimens in practice. Especially in case of multiple intake times per day, other methods for monitoring adherence to polypharmacy might be more appropriate. For example, the "POlymedication Electronic Monitoring System" (POEMS; Confrérie Clinique S.A., Lausanne, Switzerland) uses printed electronics affixed to a multi-compartment blister pack to measure adherence with polypharmacy and monitors each dose independently[37]. Second, the results obtained from questionnaires might be confounded due to a social-desirability bias[246]. This might contribute to the relatively high self-reported adherence and the high satisfaction with the e-MMA, because the intervention was delivered by the same person that handed out the questionnaires. However, SF-12 and SCL-90R questionnaires were not directly linked to the intervention and we did not observe any answer tendencies. Social desirability bias could be accounted for with the use of social desirability scales[247]. Third, we did not use randomization. In single-subject research designs, the order of baseline and intervention phase or starting points for each phase can be randomized[248]. With our small pilot study, we did not reach sufficient power for meaningful randomization. Further studies with more patients might benefit from a randomized design to increase internal

validity. Forth, we did not use statistical analyses for the interpretation of our results. Statistical analyses can sometimes assist in interpreting the results of single-subject studies, but cannot be used to generalize the results for other patients. Currently, no standards for statistical analysis of single-subject research exist[240]. The development of statistical methods to assess adherence in single-subject research might offer advantages for future research. Finally, our study was not designed to show improvements in clinical, humanistic, or economic outcomes. Ultimately, the goal of adherence interventions should be to improve clinical and humanistic outcomes and increase cost-effectiveness of treatments[249].

Applicability

Our results suggest that the evaluated e-MMA ensures high taking adherence in opioid-substituted patients with polypharmacy. Furthermore, the audible and visual alerts might improve taking and timing adherence, but do not reduce time variability. Clinical and humanistic outcomes did not show conclusive changes during the study period. Future research should aim at evaluating the effect of the e-MMA on clinical and humanistic outcomes for selected patients. Our results suggest that the use of the e-MMA might be applicable for patients with:

- High perceived necessity of treatment
- Self-reported non-adherence
- Unforgiving treatments
- Low social support
- Psychologic distress

However, other alternatives should be considered for:

- On-demand treatments
- Problematic substance use

These findings add to the results of two case reports of opioid-substituted patients with HIV using the e-MMA for 1.7 and 2.5 years, respectively[94]. In both cases, patients demonstrated continuous persistence with treatment, timing adherence of more than 90%, and suppressed HIV viral load with the e-MMA.

Although single-case studies cannot provide evidence on the population level, successful replication of single-subject studies may provide a strong indication of generalizability[250]. It has been suggested that at least five methodologically strong research reports from at least

three different research teams at three different settings with a total of at least 20 cases may provide sufficient evidence for clinical recommendations[251].

Conclusions

The use of a mixed-method single-subject design showed promising results for the evaluation of an e-MMA for polypharmacy. Our pilot study showed that the e-MMA may ensure correct implementation of dosing regimens for opioid-substituted patients with polypharmacy when certain prerequisites are considered. Various drawbacks limit the applicability of the device to monitor adherence. A careful assessment of patient's barriers to medication adherence and a structured medication review should be the first steps when considering the use of the e-MMA for a patient. Overall, the flexibility of single-subject research designs offers considerable advantages for the evaluation of adherence interventions.

Acknowledgments

We would like to thank the staff of the OAS for their support with recruitment and communication with the patients, especially Dr. med. Manuel Sutter, René Giesel, Anna-Katrin Ehrsam, Susanne Schoen, and Regine Steinauer. Many thanks to the Department of Infectious Diseases of the University Hospital of Basel for providing access to clinical patient data. In addition, we would like to thank the staff from the emergency Pharmacy for housing our equipment, handling the medication logistics, and operating the telephone hotline.

Funding

This study received funding from Munipharma AG, Switzerland and the Psychiatric University Clinics of Basel, Switzerland. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Appendix

Project C5

Economic aspects of medication supply for older patients with opioid substitution therapy and polypharmacy

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Manuscript prepared for submission

Abstract

Background and Objectives: The number of older patients with opioid-assisted therapy (OAT) and polypharmacy is rising globally. Alternative supply models to assist these patients with their medication management and support medication adherence are needed. Higher adherence has been associated with reduced overall healthcare costs and reduced hospitalization risk. However, evidence about cost-effectiveness of adherence-enhancing interventions is sparse. Electronic medication management systems might offer a benefit to older drug users receiving polypharmacy. We aimed to a) perform a cost-of-illness (COI) evaluation of patients receiving OAT and polypharmacy and to b) compare a novel electronic medication supply model to usual care.

Methods: We estimated COI from a societal perspective for eligible patients of an outpatient addiction service (OAS) during one year. Direct medical costs for each patient were obtained from health insurance records for the year 2014. Direct non-medical and indirect costs were estimated based on a survey of patients' caregivers. For the cost-comparison model, we calculated the mean costs for the novel supply model, estimated changes in direct medical costs based on available literature, and compared costs to usual care. A sensitivity analysis was performed based on the variability of cost items for the novel supply model.

Results: We included 29 patients (mean age of 47 ± 6.3 years, 6 ± 2 medications, 48.3% female) and health insurance records were available for 21 patients. None of the patients pursued a paid employment and 86% received disability benefits. Total yearly cost per patient was 109'611 Swiss Francs (SFr), with direct costs accounting for 30% of the total costs. With the novel supply model, total yearly costs per patient increased by SFr 2'509 for repackaging of medication, leasing of the dispenser, and time spent for travel, refill, and support (+ 2.2% compared to base case). Sensitivity analysis showed that the results were robust and overall costs did not substantially change with various estimations.

Conclusion: Cost-of-illness for older patients with OAT and polypharmacy is high, especially when considering indirect costs, such as productivity loss due to disability. A novel electronic medication supply model increases overall costs marginally, but might offset the costs of more expensive alternatives, such as nursing homes. Further studies should evaluate the long-term benefits and cost-effectiveness of the novel supply model.

Introduction

Healthcare costs are rising worldwide. A major driver of this development is the demographic shift to an older multi-morbid population. Globally, mental and substance use disorders were the leading cause of years lived with disability in 2010[252]. Up to 50% of opioid-dependent patients suffer from one or more psychiatric comorbidities[253]. Illicit drug users have higher rates of emergency medical visits and hospitalization than other high risk groups[254,255]. In 2002, hospitalization costs of opioid-dependent patients in the United States (US) were US$ 13'393 in a two-year period, 2.5 times higher than those of average patients[256]. Alongside the trend in the general population, the age of patients with opioid-assisted therapy (OAT) is also increasing[183-185]. The concomitant increase in multi-morbidity leads to an even higher potential for negative health outcomes for patients with OAT. Older drug users are likely to suffer from the accumulated physical and mental health effects of polysubstance use, overdoses and infections[257]. On the one hand, drug use causes premature ageing of the body[258,259]. On the other hand, effective therapies extend lives. Consequently, older drug users become prone to conditions that normally occur with greater frequency among much older people, such as alcohol- and tobacco-related illnesses, including diabetes, hypertension, osteoporosis, arthritis, cardiovascular conditions, and chronic lung disease. In addition, older drug users may also be affected by progressive conditions that may take decades to cause significant illness or death: A study estimated that in 2010, 2.1% of opioid users were HIV-positive and 43% had chronic hepatitis C virus (HCV) infection[260]. Pharmacotherapy has become standard in the therapy of most chronic conditions. Consequently, many older and thus multi-morbid patients with OAT also take multiple chronic medications. In a sample of 154 opioid-substituted patients from an outpatient addiction service (OAS) in Basel, Switzerland, 58.4% used 3 or more active ingredients in 2013[93]. Although many studies have shown clinical and economic benefits of pharmacotherapy when used consequently, adherence to medication is generally only around 75% and even lower with psychiatric illnesses[38]. Opioid-dependent patients are at high risk for non-adherence due to high prevalence of psychological problems, substance abuse, unemployment, low socioeconomic status, and low social support[38,211,215,216,261,262].

Low medication adherence has been associated with increased morbidity, mortality, and costs. The world health organization estimated the annual cost of medication non-adherence at US$ 300 billion world-wide[19]. Higher adherence has been associated with reduced overall healthcare costs and reduced hospitalization risk for diabetes, hypertension, hypercholesterolemia, and chronic heart failure[223]. Unfortunately, little evidence exists about

cost-effectiveness of adherence-enhancing interventions[43,263,264]. Recently, electronic medication management aids (MMAs) emerged, reminding patients with acoustic or visual alerts to take their medication, dispensing the right medication at the right time, and tracking each event. A review of telemedicine and telecare for older patients found mostly positive results, especially for behavioral outcomes such as adherence[265]. Furthermore, the "Safe at home" project evaluated assistive technology to improve the independence of older patients and reported net savings of over £ 1.5 million during 21 months for 233 service users compared with 173 non-users[266].

Rationale

Opioid-dependent patients pose a high burden on health-care expenditures, and the increasing age and complexity of this population will likely lead to additional costs. Alternative supply models to assist patients with their medication management and support medication adherence are needed for older patients with OAT and polypharmacy. Electronic medication dispensers might offer a benefit to older drug users receiving polypharmacy. First, a remote support assures independence of the patients. Second, real-time monitoring assures high medication adherence without the need of too many visits to a dispensing point. A novel remote electronic medication supply model was feasible to maintain medication supply and assure correct implementation of dosing regimens of more than 90% for such patients. The sustained persistence and consistent implementation accomplished with this model may reduce healthcare costs and the savings might compensate for the additional costs of the novel model.

Aims

Our goal was to analyze the cost aspects of the medication supply for opioid-substituted patients. We aimed to:

- Perform a cost-of-illness evaluation of patients receiving OAT and polypharmacy (base case)
- establish a cost-comparison model for the novel supply model compared to standard medication supply (base case)

Methods

Study design and setting

First, we performed a COI study for patients with OAT and polypharmacy from a societal perspective (base case). We considered tangible costs using a prevalence-based approach and estimated direct and indirect costs during one year. Second, we generated a cost-comparison model for the novel supply model versus the base case. The setting was the outpatient addiction service (OAS) of the Psychiatric University Hospital in Basel, Switzerland. The OAS offers treatment to patients with substance use disorders, mental and somatic disorders, and social impairments and problems. Patients are treated by a multidisciplinary team consisting of professionals from the fields of medicine, nursing, social work and psychology. Up to 100 patients per day visit the public dispensing point of the OAS to obtain their medication in the traditional way. Patients take their (substitution) medication on site under supervision at least once per week and receive additional doses and medications for take-home. Medications are either prepared in advance or immediately before dispensing. In some cases, the OAS prepares and delivers medications including OAT for patients living in supervised settings (Figure 36). With the novel supply model, patients receive OAT at the OAS once per week, while all other medications are supplied approximately three-weekly in unit-dose pouches with an automated electronic dispenser located at the patient's home. The dispenser is an electronic medication management system described elsewhere in detail[94]. Briefly, it dispenses pre-packed medication according to a schedule and remotely monitors medication retrievals.

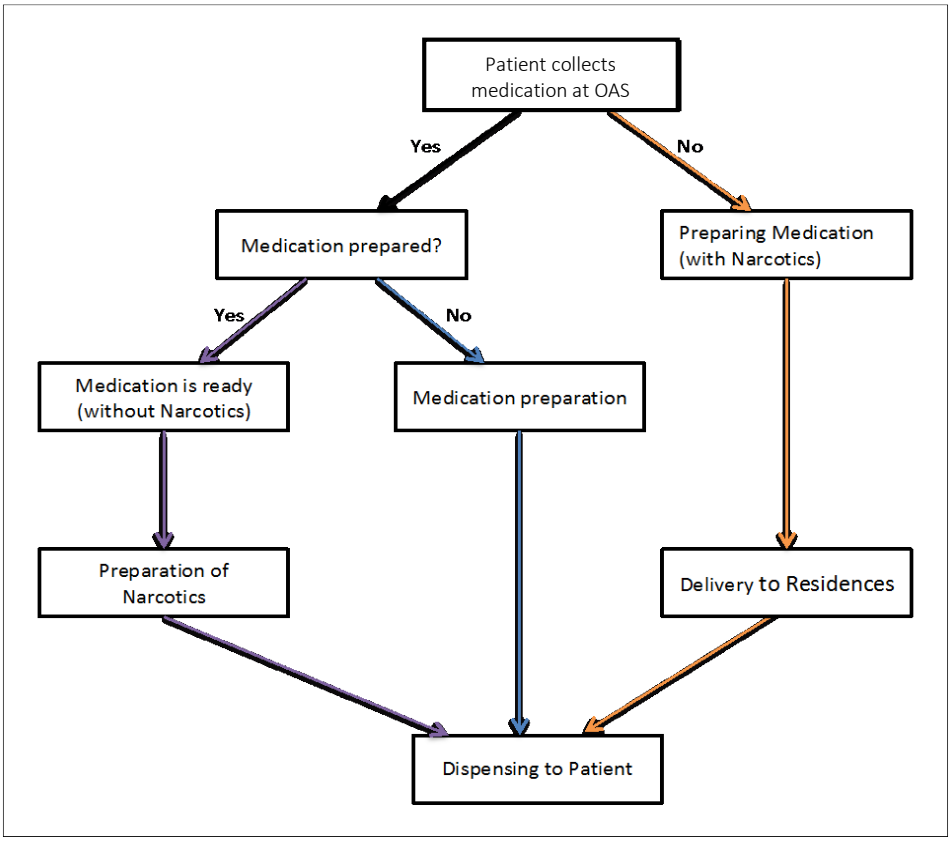

Figure 36: The three possibilities of the medication process at the OAS

Target population

Patients were included in a two-step process. First, all patients of the OAS were screened in a pseudonymized database for the number of medications. Patients receiving more than 3 medications per day were identified and included based on the following criteria:

- reading and writing literacy in German
- stable housing situation in canton Basel-Stadt and adjoining municipality
- polymedication (treatment with more than 3 drugs per day)
- insured with a Swiss health insurance
- provided signed written consent

Measures

Direct medical costs (Swiss Francs, SFr) were obtained for each patient from health insurance records for the year 2014. We differentiated between hospital costs, psychiatric treatments (including OAT and other medications dispensed in the OAS), other medical services, pharmacy costs, laboratory tests, and home care. Costs for repackaging of medication for the novel supply model were derived from the collective remuneration agreement between the

Swiss pharmacist association and health insurers (tariff "Wochendosiersystem", LOA IV). For direct non-medical costs of the traditional medication supply, we measured the time (minutes) necessary for dispensing medications in the OAS. Time spent between patients advancing to the counter and their departure was measured with a stopwatch during one day for each counter. Dispensing of prepared medication or interruptions, such as alcohol breath tests, were noted for each measurement. Medication preparation time for patients receiving pre-prepared medications was measured during four different days. Direct non-medical costs for the novel supply model were estimated by measuring time spent for travel and refills (two patients), as well as support (four patients) between November 2013 and April 2015. Time-units were converted to monetary costs using hourly wages of health-care professionals with no management function according to the Swiss federal statistical office for 2012[267]. Costs of the dispenser were based on an annual fee paid to the supplier (Innospense BV, The Netherlands).

A questionnaire that was distributed to caregivers captured information about individual patients in order to calculate direct non-medical costs and indirect costs. We questioned the caregivers and not patients to avoid social desirability bias. We contacted patients in case of missing information. Layout, comprehensibility, and completeness of the questionnaire were assessed in a pilot with 4 PhD students of the Pharmaceutical Care Research Group, 2 Master students, and 2 caregivers from the OAS. The final questionnaire included 5 questions and took 5 minutes to answer. Questions 1-4 covered direct non-medical costs (frequency of visits to the OAS per week, preparation of medications in advance, travel time from patient's home to OAS and means of travel, and support with medication management at home) and question 5 covered indirect costs (profession, employment, working ability, social benefits). Together with the questionnaire, caregivers were asked to provide medication lists and diagnoses for each patient to verify the inclusion criteria.

Indirect costs included productivity losses (human capital method) and disability/social benefits in Swiss Francs. Gross monthly wages were obtained from the Swiss federal statistical office for 2012[267,268]. Information about disability benefits and extraordinary benefits were obtained from an information sheet of the service point of the old age, disabled and survivors' social security system in collaboration with the Federal office for social insurance[269]. Information about social benefits was obtained from the Swiss conference for social benefits (SKOS)[270].

Analysis

Data were analyzed with SPSS® Version 22 (Statistical Package for the Social Sciences, IBM, Armonk, New York - USA). We calculated means and medians, minimum, maximum, and standard deviations for descriptive variables. We applied Mann-Whitney U-Test and chi-square tests for comparisons of two independent groups and Spearman tests for correlations. A p-value < 0.05 was considered significant.

For the cost-comparison model, we calculated the mean costs for the novel supply model and performed a sensitivity analysis by adding and subtracting one standard deviation from individual cost items (i.e., travel, refill, and support). We assumed that costs for some elements of direct medical costs (i.e., hospital costs, other medical treatments, and laboratory tests) would decrease, while costs for pharmacy-dispensed medications would increase. We excluded psychiatric treatments from this assumption, because these included OAT, which would not change with the novel supply model. A study assessing the association between medication adherence and healthcare costs estimated a gross reduction of medical costs by 20% and an increase of medication costs by 45% for perfect adherence versus various levels of non-adherence[223]. We therefore calculated our cost-comparison model with these estimations and assumed that indirect costs remained unchanged with the novel supply model.

Funding and approvals

The study was funded by the University of Basel and has been approved by the Ethics Committee of northwestern Switzerland [EKNZ: 2014-071].

Results

Participants

The screening identified 78 patients (32% female) receiving more than 3 medications. They had a mean age of 45 ± 7.6 years and received on average 5 ± 2 medications (min = 3, max = 13) from the OAS. Of 40 patients contacted for inclusion, 29 agreed to participate and 11 did not fulfil the inclusion criteria.

Direct and indirect cost of illness

We received 21 cost accountings from health insurances that we included for analysis. The questionnaire was answered for 29 patients (mean age of 47 ± 6.3 years, 6 ± 2 medications,

48.3% female). Most patients (80%) visited the OAS once per week and 83% collected their medications without previous preparation (Table 17). None of the patients received any kind of support with their medications at home. Approximately one third of the patients (31%) did not have a professional qualification and none of the patients pursued a paid employment. A large majority (90%) was incapable of working and thus 86% received disability benefits.

For the traditional medication supply, we measured 35 dispensing events at both counters. The average time spent per patient without pre-prepared medication was 4 minutes and did not differ between counters ($p > 0.5$). Pre-preparation of medications measured in 14 instances took 10.3 minutes per patient per one-week supply.

Cost of illness

The base-case COI was 109'564 SFr per year per patient (n=21, Table 18). The biggest share of the total costs were related to the indirect costs (70%). Direct non-medical costs (homecare and traditional medication supply at the OAS accounted for 1.3% of total costs. Most of the patients (n=9) had a COI between 100'000 SFr and 115'000 SFr, while 5 patients had costs under 80'000 SFr. The highest COI was 194'655.60 SFr (Figure 37). Costs were not significantly associated with age, sex, number of medications, frequency of visits to the OAS per week, preparation of medications in advance, travel time from patient's home to OAS and means of travel, or support with medication management at home ($p > 0.05$).

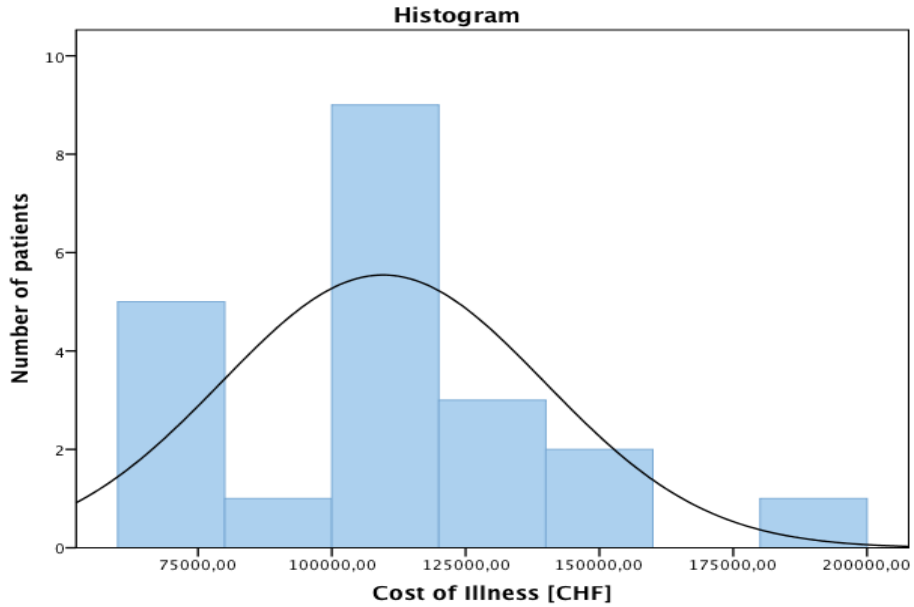

Figure 37: Histogram of base-case COI (n = 21)

Table 17: Results for the questionnaire (N = 29)

Questions	Answers	Frequency (n=29)
1) Number of OAS visits per week	1	23 (80%)
	2	5 (17%)
	3 or more	1 (3%)
2) Medication supply	Without preparation	24 (83%)
	With preparation and supply at OAS	5 (17%)
3a) Time for travel to OAS	0-15 min.	1 (3%)
	15-30 min.	19 (66%)
	30-45 min.	5 (17%)
	60 min. or more	4 (14%)
3b) Way of travel	Walking	5 (17%)
	Bike	4 (14%)
	Public transport	21 (72%)
	Taxi	3 (10%)
	Private car	2 (7%)
4a) Support at home for medication management	Yes	-
	No	29 (100%)
	No answer	-
5a) Professional education	None	9 (31%)
	Postal services	2 (7%)
	Health care sector	5 (17%)
	Construction sector	4 (14%)
	Manufacturing (rubber and plastic products)	1 (3%)
	Manufacturing (food)	1 (3%)
	Manufacturing (chemicals)	1 (3%)
	Manufacturing (others)	1 (3%)
	Other services	1 (3%)
	No answer	4 (14%)
5b) Paid employment	Yes	-
	No	29 (100%)
	No answer	-
5d) If no, capable of working?	Yes	1(3%)
	No	26 (90%)
	Unsure	2 (7%)
5e) Recipient of…	Disability benefits	25 (86%)
	Social benefits	4 (14%)

Table 18: Base case of COI for patients with OAT and polypharmacy

Cost Items			Average Cost [SFr]	%
Direct costs	Medical costs	Hospital	11'459.05	10.5
		Psychiatric treatments	17'654.25	16.1
		Other medical services	1'142.40	1.0
		Pharmacy	890.36	0.8
		Lab tests	303.05	0.3
	Non-medical costs	Homecare	1'355.30	1.2
		OAS visits	163.90	0.1
	Total		**32'968.31**	30.1
Indirect costs		Productivity loss	57'273.70	52.3
		Disability/social benefit	19'368.85	17.7
	Total		**76'642.60**	69.9
Total costs			**109'610.91**	100.0

Cost comparison model

For the novel supply model, the mean time spent per refill event were approximately 43.5 minutes per patient on travel and loading of the dispenser (n = 48). Support was provided to four patients in a total of 82 instances and took on average 6 minutes per patient per instance. Notably, one patient was responsible for 64.6% of all support cases. The majority of issues could be resolved remotely (76.8 %). With an hourly wage of SFr 34.50, the novel supply model was approximately 12 times more expensive than dispensing of medication at the OAS counter (Table 19: Direct non-medical costs for medication supply).

Table 19: Direct non-medical costs for medication supply

Task	Average time ± SD [min]	Costs [SFr]
Traditional supply model		
Dispensing at counter (n=35)	4 ± 2.3	2.06
Preparation in advance (n=14)	10.3 ± 5.3	5.92
Novel supply model		
Travel (n=48)	33.5 ± 13.1	19.26
Refill (n=48)	10 ± 5.7	5.75
Support (n=82)	6 ± 7	3.45

SD: Standard deviation, SFr: Swiss Francs

With the novel medication supply, total costs per year increased by SFr 2'508 (repackaging of medication, leasing of the dispenser, refill every 3 weeks, OAS visit once weekly, and 14 support cases) to SFr 112'119. This accounted for 2.2% and 7.1% of the total costs and direct costs of the base case, respectively. With the novel supply model and an estimated reduction of direct medical costs by 20% (except psychiatric treatments and pharmacy costs) and an increase of pharmacy costs by 45%, the costs per year increased by SFr 328.52 (+ 0.3% compared to base case, Table 20). Sensitivity analysis showed that costs did not substantially change with various estimations (Models B and C).

Table 20: Cost-comparison model between the base case and the novel supply model. We estimated a reduction of medical costs except pharmacy costs by 20% and an increase of pharmacy costs by 45% (Model A) and performed a sensitivity analysis (Models B and C) by adding and subtracting one standard deviation from individual cost items (i.e., travel, refill, and support).

	Base case	Model A	Model B	Model C
Direct costs				
Direct medical costs				[SFr] (%)
Hospital	11'459.05 (10.5)	9'167.24 (8.3)	9'167.24 (8.3)	9'167.24 (8.3)
Lab tests	303.05 (0.3)	242.44 (0.2)	242.44 (0.2)	242.44 (0.2)
Other medical services	1'142.4 (1.0)	913.92 (0.8)	913.92 (0.8)	913.92 (0.8)
Psychiatric treatments	17'654.25 (16.1)	17'654.25 (16.1)	17'654.25 (16.0)	17'654.25 (16.1)
Pharmacy	890.36 (0.8)	1'291.022 (1.2)	1'291.022 (1.2)	1'291.022 (1.2)
Medication repackaging		1'123.20 (1.0)	1'123.20 (1.0)	1'123.20 (1.0)
Direct non-medical costs				
Homecare	1'355.3 (1.2)	1'355.30 (1.2)	1'355.30 (1.2)	1'355.30 (1.2)
OAS visits	163.9 (0.1)	107.62 (0.1)	107.62 (0.1)	107.62 (0.1)
Dispenser leasing		960.00 (0.9)	960.00 (0.9)	960.00 (0.9)
Dispenser service		433.54 (0.4)	620.91.17 (0.6)	246.17 (0.2)
Dispenser support		48.30 (<0.1)	104.65 (0.1)	-
Total direct costs	**32'968.31 (30.1)**	**33'296.83 (30.3)**	**33'540.55 (30.4)**	**33'061.16 (30.1)**
Total indirect costs	**76'642.55 (69.9)**	**76'642.55 (69.7)**	**76'642.55 (69.6)**	**76'642.55 (69.1)**
Total costs	**109'610.86 (100.0)**	**109'939.38 (100.0)**	**110'183.10 (100.0)**	**109'703.71 (100.0)**
Difference to base case		**328.52 (+ 0.3)**	**572.24 (+ 0.5)**	**92.85 (+ 0.1)**

Discussion

Interpretation

To our knowledge, this is the first study of the COI for patients with OAT and polypharmacy. We found a high total costs, with over SFr 109'000 per patient per year. Direct medical costs amounted to almost 30% of all costs, half of which accrued for psychiatric treatment and a third during hospital admissions. OAT likely represents a significant portion of the psychiatric treatment costs, as it was provided by the psychiatric clinic. Also, the OAS dispenses additional medications to some patients which were included in the psychiatric treatments as well. As a result, pharmacy costs were comparably low, accounting for only 0.8% of the total costs. Hospital costs were more than twice as high as those reported for opioid users in the US in 2002[256]. Apart from an overall increase of costs between 2002 and 2014 and differences in healthcare systems between the US and Switzerland, the additional costs could be associated with the increased age of the opioid-substituted population. Between 2002 and 2013, the mean age of patients with OAT in the OAS increased from 37 to 45 years[93]. Although we were not able to show a correlation between age and costs in our

sample, health care costs generally increase with greater age[271]. Homecare costs only amounted to roughly 1% of total costs. Apparently, patients with OAT are independent, as previously shown in a single-subject study with 5 patients[95]. None of the patients received support with their medications at home. The question remains, whether some of the patients would benefit from added support. Most patients visit the OAS only once a week, which is the minimum legal requirement in Switzerland. This might be explained by the seniority of the patients who are generally in treatment for many years and do not require more frequent supervision of medication intake. Still, 20% of our sample required two or more visits per week. The need to attend all appointments and the supervised consumption poses a barrier to OAT for most patients[202]. On one hand, data from the US indicates that extended take-home periods may improve outcomes and retention in care[203,204]. A novel medication supply model with an electronic dispenser might assist to extend take-home periods for up to 4 weeks. On the other hand, frequent contacts are important to OAT providers[202]. Medications were most often dispensed without preparation in advance, which resulted in very little costs generated by medication dispensing in the OAS. However, the increasing polypharmacy and complexity of treatments could add more stress to caregivers with the potential of dispensing errors[272]. Indirect costs due to productivity loss and disability benefits amounted to almost 70% of total costs. In our sample, the unemployment rate was 100%, although two-thirds had secondary education. As a result, travel costs for patients to visit the OAS were irrelevant for our cost analysis.

We estimated the annual costs for the novel supply model at roughly SFr 2'500 for repackaging of medication, leasing of the dispenser, refill every 3 weeks, technical support, and OAS visits once weekly. This accounted for 2.3% of total costs, with repackaging into unit-dose pouches and leasing for the dispenser being the main cost items. The remuneration for the weekly repackaging of polypharmacy in Switzerland is paid for by health insurances when patients receive three or more medications (OAT not included). Compared to the fragmented dispensing provided by the OAS, unit-dose pouches offer various benefits: Patients receive medications for every intake time in a sealed pouch labelled with the date and time of intake. The repackaging process is subject to strict quality controls and the identity of the contents is guaranteed. This reduces the potential for erroneous dispensing almost to zero. Our estimated price for dispenser leasing is based on the prices set by the distributor. At the time of our study, this dispenser was not routinely available in Switzerland. Hence, the actual market price for the device might differ from our estimation should it become available in Switzerland. Additional service costs have to be considered. We

assumed that the dispenser would be refilled by caregivers at patients' homes every three weeks. The travel time to patients for refill events accounted for the highest share of service costs. With the novel supply model, an average duration of 30 minutes for travel equated to the mean time required for the majority of patients to visit the OAS. Higher patient numbers would reduce time spent per patient and reduce costs of the novel supply model. Embedding the service into existing home care services might be a valuable option. Another possibility for stable and reliable patients would be to collect the refill medications at the OAS during a routine visit and refill the dispenser themselves.

Our cost-comparison model showed that the novel medication model might be almost cost-neutral. We assumed no change of psychiatric treatments and indirect costs with the novel supply model. However, these are the major cost items for these patients and a success of the novel supply model may result in a reduction of these costs. For example, increased independence might enable patients to pursue paid employment. Furthermore, other alternatives to the traditional supply model, such as assisted living or nursing homes, would be much more expensive.

Limitations

We acknowledge some limitations. First, we studied only a small population from a local setting. Our sample size was too limited to show significant correlations between costs and patient characteristics such as number of medications or age. Although the comparison with a more representative sample of Swiss opioid-substituted patients showed a similar age and gender distribution as our sample, we cannot guarantee the applicability of our results to other settings. For example, the abovementioned survey showed an unemployment rate of roughly 50% in 2012[202], compared to 100% unemployment in our sample. Consequently, COI for the whole population of opioid-substituted patients in Switzerland will be lower than what we report for multi-morbid patients with polypharmacy. Second, we did not consider costs of premature deaths. On one hand, the primary purpose of the novel supply model is not to reduce mortality, but to increase independence of patients with suboptimal medication adherence. Thus, costs of premature deaths were not of immediate interest to our study. On the other hand, patients with stable OAT suffer from a multitude of different diseases. As a result, we were not able to generalize costs of premature deaths. Third, we did not calculate the total burden of disease at a population level and we only considered a time horizon of one year. Although the cumulative costs of patients with OAT and polypharmacy might be of interest, our aim was to gauge the financial consequences of a novel medication supply model

on an individual level. Finally, we were not able to use actual effectiveness data of the novel supply model. No studies exist that provide data about effects on adherence or costs for this intervention. We estimated costs based on a few select cases where the novel supply model was tested with patients from the target population. Our assumptions regarding effects on costs were based on data from the US that stem from different settings and a different healthcare system. However, our sensitivity analysis showed that costs with the novel supply changed marginally with a range of possible estimations.

Conclusion

COI for older patients with OAT and polypharmacy is high, especially when considering indirect costs, such as productivity loss due to disability. A novel electronic medication supply model increases overall costs marginally, but might offset the costs of more expensive alternatives, such as nursing homes. Further studies should evaluate the long-term benefits and cost-effectiveness of the novel supply model.

Acknowledgements

We would like to thank the staff of the OAS for their support with recruitment, assessment of participants, and communication with health insurances.

Appendix

A.4.1 Patient information and informed consent form
A.4.2 Questionnaire about cost of illness for caregivers

D – Congruence between patient characteristics and adherence interventions

Project D1

Matching adherence interventions to patient determinants using the Theoretical Domains Framework

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Front Pharmacol. 2016 Nov 14;7:429. doi: 10.3389/fphar.2016.00429. Epub 2016 Nov 14.

Abstract

Background and Objectives: Despite much research, interventions to improve medication adherence report disappointing and inconsistent results. Tailored approaches that match interventions and patient determinants of non-adherence were seldom used in clinical trials. The presence of a multitude of theoretical frameworks and models to categorize interventions and patient determinants complicated the development of common categories shared by interventions and determinants. We retrieved potential interventions and patient determinants from published literature on medication adherence, matched them like locks and keys, and categorized them according to the Theoretical Domains Framework (TDF).
Methods: We identified the most relevant literature reviews on interventions and determinants in a pragmatic literature search, extracted all interventions and determinants, grouped similar concepts to umbrella terms and assigned them to TDF categories. All steps were finalized in consensus discussion between the authors.
Results: Sixteen articles (5 with determinants, 11 with interventions) were included for analysis. We extracted 103 interventions and 42 determinants that we divided in 26 modifiable and 16 unmodifiable determinants. All interventions and modifiable determinants were matched within 11 categories (Knowledge; Skills; Social/professional role and identity; Beliefs about capabilities; Beliefs about consequences; Intentions; Memory, Attention and decision processes; Environmental context and resources; Social influences; Emotion; and Behavioral regulation).
Conclusion: In published trials on medication adherence, the congruence between interventions and determinants can be assessed with matching interventions to determinants. To be successful, interventions in medication adherence should target current modifiable determinants and be tailored to the unmodifiable determinants. Modifiable and unmodifiable determinants need to be assessed at inclusion of intervention studies to identify the patients most in need of an adherence intervention. Our matched categories may be useful to develop interventions in trials that investigate the effectiveness of adherence interventions.

Introduction

After 4 decades of research on adherence to medication, the progress is disappointing and adherence remains a fragmented construct. Medication adherence is briefly defined as the behavioral response to an agreed medical recommendation[19] and is measured either dichotomously (either one is adherent, or one is not) or continuously. Recently, medication adherence has been defined to consist of three different components: initiation, implementation, and discontinuation[208]. Non-adherence is not simply the reverse of adherence. Two patients can be equally non-adherent with respect to measuring adherence, for example take only 60 % of their pills. At the same time, the reasons for these patients to be non-adherent may vary widely.

The complexity of the characteristics of adherence was already known by the end of the 1970s[18]. Despite much research in the 1980s and 1990s, few new insights arose. Research in the 1990s emphasized the influence of patient beliefs about health in general and about illness/medication in particular[46]. Qualitative research on patients' perspectives started with the new millennium and identified new issues like the quality of the doctor-patient relationship and patient health beliefs[47]. Grossly, five theoretical approaches could be identified that all view non-adherence from a different perspective[48]. The oldest approach is the biomedical model that focuses on dispositional characteristics of the patient, such as demographic or personality traits. Operant behavior and social learning theories shifted the focus to the behaviors needed for adherence. In the communication model, the patient seeks expert advice and treatment from the healthcare professional; adherence results from persuasion through effective communication. The rational decision-health belief and reasoned action model generated the patient's perception of risk and motivation for action. Finally, the self-regulative systems theory sees the patients as an active problem solver. Extent and factors of non-adherence have been extensively investigated, and a plethora of strategies to improve adherence was developed, mostly without consistent success[57].

A systematic review of reviews analyzed interventions with regard to theoretical models and found no clear correlation between the effectiveness of interventions that were theory-based and those without an explicit theoretical background[58].

The most recent approach, the Theoretical Domains Framework (TDF), was developed to integrate the various behavior change theories. It aimed to simplify the investigation of behaviors such as adherence and to facilitate intervention design[60].

Success in a complex process like adherence can only be achieved with the integration of many ingredients, and a single obstruction causes failure. This concept is sometimes referred to as the "Anna Karenina principle", referring to the first sentence in Tolstoy's novel Anna Karenina: “Happy families are all alike. Every unhappy family is unhappy in its own way.” In this regard, it takes one deficient factor to cause non-adherence. Therefore, the purpose of any intervention strategy should be to compensate for each reason causing non-adherence. As acknowledged by others[273-275], it seems thus obvious that a tailored approach is required, i.e. an approach that adapts the intervention to individual needs, i.e. that adapts the keys (interventions) to the locks (patient determinants).

Various attempts to categorize interventions ended up with coarse sections like educational, behavioral, social, and mixed forms[276] or simple groupings[59]. In the field of behavior change research, a recent international consensus developed a framework (the Behavior Change Technique Taxonomy) with 93 behavior change techniques clustered in 16 groups[162]. Although not specific for medication adherence, the new taxonomy has been used to classify interventions in the field of adherence research[277]. As behavior change is only one aspect of medication adherence, this unilateral framework appears limited to categorize the sum of all adherence interventions. A broader view on adherence was captured by a Cochrane Review on interventions to improve safe and effective medicines use[278]. Interventions were grouped in 8 categories: Providing information or education; Facilitating communication and/or decision making; Acquiring skills and competencies; Supporting behavior change; Support; Minimizing risks or harms; Improving quality, and Consumer system participation.

Patient determinants of non-adherence were often categorized according to the five dimensions of non-adherence proposed by WHO[19] or variations of these concepts[279]: Social- and economic-related factors; Health system/health care team-related factors; Therapy-related factors; Condition-related factors, and Patient-related factors.

Matching possible targets for medication adherence to the types of interventions will yield more insight in effective strategies able to overcome the different barriers for medication adherence. To our knowledge, common categories shared by interventions and patient determinants of non-adherence have never been proposed. As a result, interventions for improving adherence and patient determinants were seldom matched in clinical trials. As an example, from 109 studies aimed at improving patient adherence, only 13% reported the assessment of patient determinants at baseline [225]. Even though some studies reported tailoring of interventions to patient characteristics, the specific procedure remains often unclear and thus, the results are almost impossible to replicate[225].

In this article, we retrieved potential interventions and patient determinants from published literature on medication adherence and aimed at matching them like locks and keys.

Goals/Aims

- To extract from literature salient a) interventions intended to improve adherence and b) related patient determinants of non-adherence
- To categorize the retrieved a) interventions and b) determinants
- To match a) and b)

Methodology

Search strategy

Several recent systematic literature reviews exist on interventions and patient determinants of non-adherence. It seemed superfluous to repeat this process and thus, we abstained from a systematic literature search with broad major/MeSH terms, such as "patient compliance". Rather and in order to identify literature with the highest relevance to our aims, we pursued a pragmatic search strategy to identify existing reviews with the terms "intervention" and "determinant" or "factor" which are widely used in conjunction with medication adherence. We combined these specific terms with the established terms "adherence" or "compliance".

We searched Medline via Pubmed on March 10, 2015 (without time limits) with the following terms and a limit set to reviews:

a) intervention*[title] AND (improv*[title] OR enhanc*[title]) AND medication[title] AND (adherence[title] OR compliance[title])
b) (determinant*[title] OR factor*[title]) AND medication[title] AND (adherence[title] OR compliance[title])

Titles and abstracts of the search results were screened for relevance by two investigators (SA, IA). To assure a generic view on medication adherence (not restricted to specific diseases, medications or settings), we excluded full-text articles when they investigated:

- single conditions
- single medication groups
- specific providers
- specific target groups
- single intervention
- economic evaluations
- specific adherence measurement methods

Data extraction and processing

All extractions were performed in MAXQDA 11 (VERBI GmbH, Berlin, Germany). All steps were performed separately for interventions and determinants.

In the first step, IA and SA reviewed full-texts from the included articles. Both investigators independently extracted items of a) interventions and b) determinants for non-adherence and scanned the reference list for additional articles. Investigators were not blinded with regard to authors or journal. The lists were reviewed by both investigators in a consensus discussion and umbrella terms were introduced for items with similar connotations.

In the second step, IA and SA independently matched each intervention to individual determinants. Items that did not match were listed separately.

In the third step, IA and SA assigned the matched interventions and determinants to the 14 domains of the Theoretical Domains Framework (TDF). We chose the TDF because it offers the most recent framework, combines various theoretical models, and has a strong empirical base. We determined consistency among raters performing an interrater reliability analysis using the Kappa statistic.

Disagreements were resolved by discussion until consensus was reached (first and second steps) or by an adjudicator (third step).

Results

Literature Search

A total of 65 articles were obtained (Figure 38). Two articles were updated versions of previous Cochrane analyses[280,281]. Screening of the reference lists yielded two additional articles that were included in the review[47,278]. Five articles were excluded after screening of titles and abstracts because they were not relevant to our aims. After full-text screening, 44 articles were excluded because they investigated (a) single conditions (18; schizophrenia, psychiatric disorder, transplantation, diabetes, hypertension, Parkinson, inflammatory bowel, rosacea); (b) single medication groups (14; antidepressant, cardiovascular, heart failure, antipsychotic, osteoporosis, hypoglycemic and lipid lowering agents); (c) specific providers (4; pharmacist, physician, nurse); (d) specific target groups (1; children); (e) single intervention (4; HIT, technology-mediated, cultural responsive, electronic reminders); (f) economic evaluations (2); (g) adherence measurement methods (1; electronically compiled drug dosing history).

The final set included 16 articles (11 with interventions, 5 with determinants, Table 21).

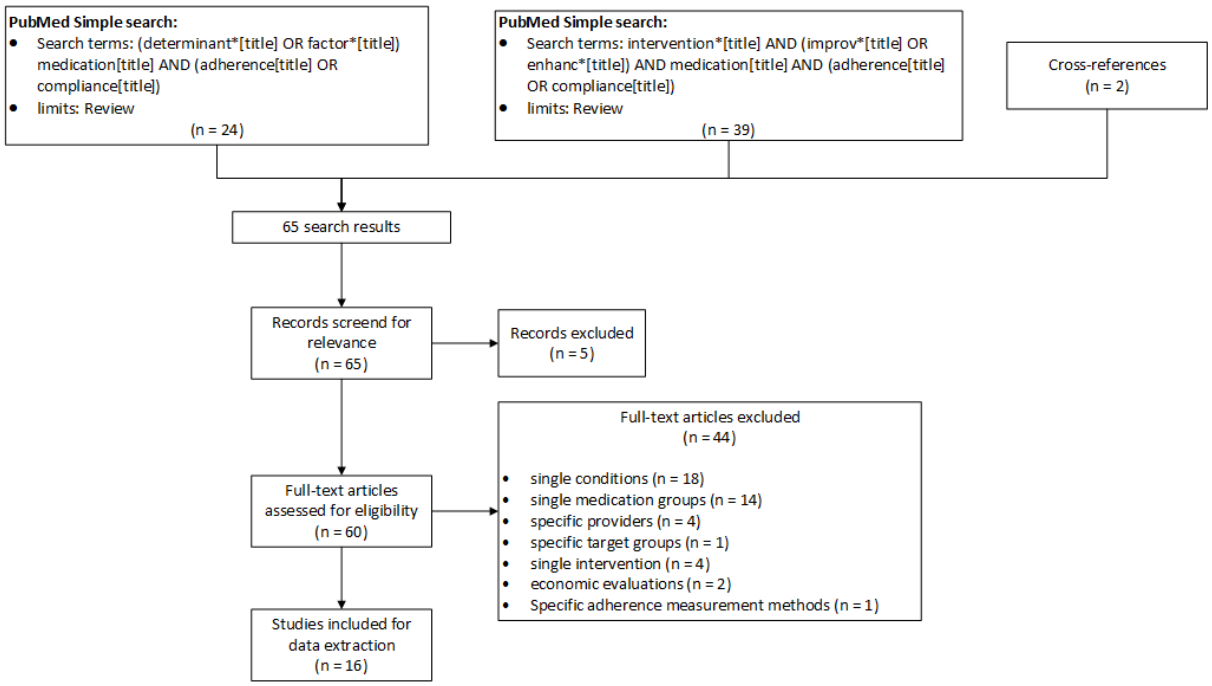

Figure 38: PRISMA flow diagram (22) for study selection process

We extracted 103 different interventions, including variations of the same concept, such as different forms of reminders. We extracted 42 determinants that we divided into 26 modifiable and 16 unmodifiable determinants. We defined modifiable determinants as factors that may be changed by interventions (such as knowledge or behaviors) and unmodifiable determinants as those that are unchangeable (such as age). Some unmodifiable determinants may appear modifiable at first sight, such as level of education or employment situation. However, those determinants are not targeted by the adherence interventions, albeit they may influence the choice of an appropriate intervention. Thus, unmodifiable determinants (Box 6) were not included in the matching procedure.

Box 6: Unmodifiable determinants of non-adherence

- *Age* [51,279,282,283]
- *Gender* [283]
- *Level of education* [51,283] (literacy)
- *Employment situation* [283]
- *Financial situation* [279,283] (socioeconomic status, lack of insurance, income, material resources)
- *Insurance type/coverage* [284]
- *Ethnicity and culture* [279,282-284] (language difficulties, race, immigration status)
- *Housing situation/living situation* [279,283,284] (lack of fixed address, living alone, marital status)
- *Cognitive impairment* [51,279,283]
- *Illness chronicity* [284]
- *Illness severity* [279,282-284] (absence, reduction, disappearance or fluctuation of symptoms)
- *Polymorbidity* [284]
- *Change of therapy* [282,283]
- *History of non-adherence* [283]
- *Past treatment response* [284]
- *Duration of treatment* [279,282]

Table 21: Overview of included literature

Title [original language]	Authors	Year	Type of study	Country	Conditions	Medications
Determinants						
Thinking differently the patient medication compliance: From an injunctive posture to a working alliance between the patient and the healthcare provider - Concepts and determinants [French][279]	Baudrant-Bogaa M, Lehmann A, Alleneta A	2012	General Review	France	ns	ns
The impact of medication regimen factors on adherence to chronic treatment: a review of literature[51]	Ingersoll KS, Cohen J	2008	Review	USA	chronic illness (asthma, diabetes, HIV disease, and hypertension/ cardiovascular disease, mental disorders, pain, and other diseases), contraception	ns
Medication non adherence – predictive factors and diagnostic [German][282]	Schäfer-Keller P, Garzoni D, Dickenmann M, De Geest S	2010	General Review	Switzerland	ns	ns
Medication Adherence: Factors influencing compliance with prescribed medication plans[283]	Vlasnik JJ, Aliotta SL, DeLor B	2005	General Review	USA	ns	ns
A systematic literature review of psychosocial and behavioral factors associated with initial medication adherence: a report of the ISPOR medication adherence & persistence special interest group[284]	Zeber JE, Manias E, Williams AF, Hutchins D, Udezi WA, Roberts CS, Peterson AM	2013	Systematic Review	USA	Acute and chronic conditions (hypertension, diabetes, cardiovascular disease, depression or anxiety, Asthma, osteoporosis, epilepsy, cancer, multiple sclerosis, other diseases)	ns

Title [original language]	Authors	Year	Type of study	Country	Conditions	Medications
Interventions						
A review of interventions used to improve adherence to medication in older people[285]	Banning M	2009	Review	United Kingdom	ns	ns
Interventions for enhancing medication adherence[59]	Haynes RB, Yao X, Degani A, Kripalani S, Garg A, McDonald HP	2005	Systematic Review	Canada	medical disorders (including psychiatric), but not addiction	self-administered
Interventions for enhancing medication adherence[280]	Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X	2008	Systematic Review	Canada	medical disorders (including psychiatric), but not addiction	self-administered
Interventions to enhance medication adherence in chronic medical conditions[276]	Kripalani S, Yao X, Haynes RB	2007	Systematic Review	Canada	chronic medical conditions	self-administered
Interventions to enhance patient adherence to medication prescriptions interventions to enhance patient adherence to medication prescriptions[286]	McDonald HP, Garg AX, Haynes RB	2002	Scientific Review	Canada	Medical or psychiatric disorders (hypertension, schizophrenia or acute psychosis, asthma, chronic obstructive pulmonary disease, depression, HIV, diabetes, rheumatoid arthritis, epilepsy, hyperlipidemia and cardiovascular disease, acute infections)	self-administered
Interventions for enhancing medication adherence[220]	Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, Agoritsas T, Mistry N,	2014	Systematic Review	Canada	medical disorders (including psychiatric), but not addiction	self-administered

Title [original language]	Authors	Year	Type of study	Country	Conditions	Medications
	Iorio A, Jack S, Sivaramalingam B, Iserman E, Mustafa RA, Jedraszewski D, Cotoi C, Haynes RB					
Interventions to improve safe and effective medicines use by consumers: an overview of systematic reviews[278]	Ryan R, Santesso N, Lowe D, Hill S, Grimshaw J, Prictor M, Kaufman C, Cowie G, Taylor M	2014	Overview of reviews	Australia	acute and chronic diseases	ns
Medication non-adherence among older adults: a review of strategies and interventions for improvement[287]	Schlenk EA, Dunbar-Jacob J, Engberg S.	2004	General Review	USA	ns	ns
Interventions to improve medication compliance in older patients living in the community[288]	van Eijken M, Tsang S, Wensing M, de Smet PA, Grol RP.	2003	Systematic Review	The Netherlands	ns	ns
Patient adherence to treatment: three decades of research. A comprehensive review[47]	Vermeire E, Hearnshaw H, Van Royen P, Denekens J.	2001	Comprehensive Review	Belgium	ns	ns
Interventions to improve medication adherence in people with multiple chronic conditions: a systematic review[289]	Williams A, Manias E, Walker R.	2008	Systematic Review	Australia	3 or more chronic conditions	ns

ns: not specified

Matching procedure

From the original 14 domains of the TDF, eleven suffice to categorize our 103 interventions and 26 modifiable determinants (Table 22). No intervention or determinant could be assigned to the 3 original domains "Optimism"," Reinforcement" and "Goals". Because heterogeneous interventions and determinants were included in the domain "Environmental context and resources", we created the subdomains "Regimen", "Adverse events", "Integration and coordination of care", and "Financial aspects" (Table 23).

The interrater reliability was substantial with a Cohen's Kappa of 0.7 (95% CI 0.5 – 0.9, $p < 0.001$).

Table 22: Final eleven categories of the TDF with corresponding definitions sufficient to categorize interventions and patient determinants

Category	Interventions and determinants focusing on …
1. Knowledge	… the awareness of the existence of something
2. Skills	… the ability or proficiency acquired through practice
3. Social/professional role and identity	… behaviors and displayed personal qualities of an individual in a social or work setting
4. Beliefs about capabilities	… the acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use
5. Beliefs about consequences	… The acceptance of the truth, reality, or validity about outcomes of a behavior in a given situation
6. Intentions	… the conscious decision to perform a behavior or a resolve to act in a certain way
7. Memory, attention and decision processes	… the ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives
8. Environmental context and resources	… any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behavior
9. Social influences	… those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviors
10. Emotion	… the complex reaction pattern, involving experiential, behavioral, and physiological elements, by which the individual attempts to deal with a personally significant matter or event
11. Behavioral regulation	… anything aimed at managing or changing objectively observed or measured actions

Table 23: Matched adherence interventions and patient determinants according to eleven TDF categories. Items were extracted from literature (103 interventions and 25 determinants). Examples and synonyms from the literature are given in brackets.

Interventions	Determinants (examples)
KNOWLEDGE	

• educate patients[276,278]
  o provide information, e.g.
  • provide copy of medical record[288]
  • provide medication charts/fact sheets[59,278,280,287]
  o provide instruction, e.g.
  • visual, verbal, written materials[59,278,280,288]
  • self-help workbook[286]
• programmed learning[59,280,286]	

• adequate labelling[47]
• icon-labelled medication containers[285]
• harm-reduction training[278]
• counsel, give advice about treatment
  o Benefits[59,276,280]
  o Importance[59,280]
  o Goal[59,280]
  o Mode of action[59,276,280]
  o Causes of low effect[59,280]
  o Correct use (of medication/device)[47,59,276,278,280]
  o Medication adherence[59,276,280]
• discuss knowledge about treatment[278]
	• *knowledge about therapy and devices*[279,283] (know-how)

• counsel, give advice about
  o Target disease[280]
  o Symptoms[59,276,280,286]
  o Health[59,280]
• discuss knowledge about health[278]
	• *knowledge about illness*[279,283] (insight into the disease, understanding of the need for treatment)

SKILLS	
• swallowing training[276] • easy-to-use packaging[47] • physiotherapy[59] • self-administration training[278]	• *physical difficulties*[279,283] (swallowing difficulties, difficulties in handling small tablets or opening drug containers, visual impairment)
• self-management skills[276,278] • problem-solving training[286] • inpatient self-medication programs[287]	• *health literacy*
• communication skills training[47,278]	• *communication skills*[279,282,283]

Interventions	Determinants (examples)
SOCIAL/PROFESSIONAL ROLE AND IDENTITY	

• contract[276]
• improve relationship[47,276,278]
  o consumer involvement
  ▪ encouraging doctor-patient co-operation
  ▪ patient-centeredness
  ▪ taking into account of spiritual and psychological dimensions which may be of primary importance to patients
  ▪ accurate recognition of the patient's problem by the health care provider
	• *relationship patient – health care professional*[279,282-284] (therapeutic alliance)

BELIEFS ABOUT CAPABILITIES	
• patient empowerment[59,276,280]	• *beliefs about self*[279,283] (perceived importance of self-care)
BELIEFS ABOUT CONSEQUENCES	
• cognitive restructuring[59,280] • cognitive behavioral therapy[276,278,280]	

• discuss
  o beliefs[278]
  o barriers[278]
  o ambivalence to treatment[59,280]
  o adherence[280]
	• *beliefs about treatment*[279,283,284] (faith in medication, concerns about taking drugs, fear of addiction, preferences, perceived harms versus benefits)

• discuss
  o beliefs[278]
  o barriers[278]
  o stigma[59,280]
	• *beliefs about health*[279,283,284] (anger, denial of the illness or its significance, apathy, confidence)

	• *beliefs about health care system*[283,284] (trust in health care system)
INTENTIONS	

• counselling about lifestyle[276]
  o diet[59,280,287]
  o exercise[59,280]
  o smoking[59,280]
	• *lifestyle*[279,283,284] (stress, substance abuse, smoking, alcohol use)

• rewards[59,220,276,278,280,286]
  o material
  o monetary
• motivational interviewing[278]
• action plans[278]
	• *Motivation*[51,279,282,283] (readiness to change)

Interventions	Determinants (examples)
MEMORY, ATTENTION AND DECISION PROCESSES	

• reminders
  o postcard[278]
  o mailings[286]
  o prescription refill[59,280,286]
  o telephone-linked computer system[59,220,276,278,280,286,288]
  o appointment[59,278,280,286]
  o phone call[220,278,286,288]
  o mobile text messages[220]
  o alarms[278]
• organizers[47,278]
• unit-of-use dispensing [59,280]
• automated dispenser [288]
• directly observed therapy[59,276,278,280]
• patient diary[220,276]
• reminder pill packaging[59,276,278,280]
• disposing of excessive medication[59,276,280]
• feedback on medication use[47,59,276,280]
	• *forgetfulness*[51,282,283]

ENVIRONMENTAL CONTEXT AND RESOURCES	
Regimen	
• tailor treatment to daily habits[47,59,280,287] • simplified dosing regimens[47,59,276,278]	• *intrusiveness*[51] (inconvenience, attention to routine)
• reducing the frequency of dosing[47,59,276,278,280] • combination pills[220]	• *pill burden*[51,279,283] (units per dose, doses per day)
• changing the medication formulation[59,278,280]	• *specificity of regimen*[51,279,283,284] (time-dependence, storage and food restrictions, formulation, time needed for treatment)
Adverse events	

• counselling
  o Safety[59,280]
  o Adverse events[276,280]
• delayed antibiotic prescriptions[278]
	• *adverse events*[51,282-284] (treatment-associated adverse reactions)

Interventions	Determinants (examples)
Integration and coordination of care	

• collaborative care[47,285]
• reduced frequency of visits[280]
• liaising with general practitioner[59,280]
• pharmaceutical care services[59,278,280]
  o medicine reconciliation[278,285] (recognition of medication discrepancies)
  o medicines review[278]
  o review illness history[59,280]
  o care plan[278]
  o multisystemic therapy[280]
• clarify responsibility for administration of therapy[283]
	• *number of providers*[51,283,284]

• increase the convenience of care[59,280]
  o short waiting time[47]
  o short intervals between appointment[47]
• provision of therapy at worksite[59,280]
• home visits[276,278]
	• *access to care*[279,283,284] (difficulties in getting prescriptions filled, lack of transportation)

• discharge planning[285] • (Post-discharge) Follow-up[59,278,280,287] • periodic reinforcement[289] • mass mailings[278]	• *continuity of care*[279]
• remote internet-based treatment support[220]	• *availability of health care professionals*[279,282] (overworked personnel, organization of care, quality of care network)
	• *prescribing errors*[284]
Financial aspects	
• financial incentives[59,278,280] • co-payments[47,278,286]	• *cost of treatment*[282-284] (inability to afford medication, cost of care, out-of-pocket medication expenses)
SOCIAL INFLUENCES	

• (culturally modified) family intervention[59,276,278,280,286]
• social support
  o lay health mentoring[59,280]
  o (couple-focused) group programs[59,276,278,280]
	• *social/family support*[279,283,284] (disrupted family structure)

EMOTION	
• psychological therapy[59,220,278,280,285,289] • crisis intervention[59,280]	• *psychological problems*[51,279,282,283] (depression, apathy, psychosis)
BEHAVIORAL REGULATION	

• point-of-care testing[276]
• self-monitoring
  o treatment[59,278,280]
  o symptoms[286]
	• *monitoring of treatment*[283]

Discussion

Based on a literature review, we were able to match 103 adherence interventions and 26 patient determinants within 11 common categories. The fact that interventions were more diverse than patient determinants is not surprising, as there is usually more than one way to target a single determinant. In a previous review on patient determinants, the authors grouped similar contents together and ended up with 40 heterogeneous umbrella terms[49]. What appears nearly identical to our 42 patient determinants is slightly different, since no overlap existed with our determinants for 6 of the 40 umbrella terms ("Social stigma of disease"; "Prescription coverage"; "Prescription by a specialist"; "Certain diagnoses/indications"; "Drug type", and "Well organized treatment"). A subset of patient determinants must be considered unmodifiable, such as age, gender, or culture. In our view, this distinction is essential for the choice of adherence interventions. In order to be effective, we postulate that interventions have on one hand to *target* current *modifiable* patient determinants and on the other hand to be *tailored* to the *unmodifiable* patient determinants. This lack of distinction among the patient determinants in previous literature may explain partly why no meta-analysis could demonstrate an overall benefit of interventions aimed at enhancing adherence[290]. Further research is needed to investigate if adherence is improved when the intervention is matched to the patient determinants for non-adherence according to our matching list.

The importance of tailoring interventions to patient characteristics has been acknowledged previously[273-275]. To our knowledge, no published framework aimed to match interventions and patient determinants of non-adherence. Specific toolboxes for tailored interventions cover a restricted number of interventions or patient determinants[291,292]. Their intended use is the application in daily practice where a workable toolbox trumps a comprehensive framework. The 5 WHO dimensions that could be used to classify both interventions and patient determinants are too coarse to provide meaningful guidance[19]. The Theoretical Domains Framework (TDF) has been the most recent and complete effort to develop theory-informed behavior change interventions[293] or assess the underlying theoretical constructs of interventions[294]. Because it was not specifically developed for interventions and patient determinants of non-adherence, some adaption was warranted. While we were able to assign all interventions and patient determinants to one of the domains, we did not use 3 of the original 14 domains: "Optimism", "Reinforcement" and "Goals". Optimism (i.e. the confidence that things will happen for the best or that desired goals will be attained) may theoretically differ from beliefs, but we chose not to differentiate between the two concepts for practical

reasons. By definition, reinforcement (i.e. increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus) can only apply to interventions. Hence, we were not able to use this domain for shared interventions and determinants. Instead, we assigned interventions belonging to the Reinforcement domain to "Intentions". Goals (i.e. mental representations of outcomes or end states that an individual wants to achieve) also overlaps with Intentions and we chose not to differ between the two concepts.

Some of the extracted interventions did not target patient determinants. They represent much more unspecific interventions, such as general education to improve knowledge. In contrast, one extracted determinant (Prescribing errors) could not be matched to a specific intervention. Although it is obvious that studies to reduce prescribing errors were performed, they may not have been aimed at enhancing adherence to treatment.

Our matching list allows for the assessment of congruency between interventions and patient determinants in published trials. Under the prerequisite that a causal relationship exists between our interventions and corresponding patient determinants, our list may help to assess the quality of published studies and their results[220]. Furthermore, our matching list may be useful to develop interventions and to plan trials to assess the effectiveness of interventions with respect to modifiable and unmodifiable patient determinants.

We acknowledge some limitations. First, we applied a very specific search strategy to identify the most relevant literature. A systematic approach with broader search terms and additional databases might have yielded more articles, however, may not have yielded additional items of interventions or patient determinants. The 85% overlapping between our determinants and those retrieved from a systematic review of reviews[49] reinforces this assumption. Second, we did not consider the effectiveness of the interventions, the frequency of the patient determinants, nor the impact size of the patient determinants on adherence. Consequently, matching interventions to patient determinants based on our results does not guarantee for a successful adherence intervention. Other concepts may be important to consider: determinants may be different for each component of medication adherence: initiation, implementation, and discontinuation[49,208]. The current literature lacks the information about which determinant is associated to each of the three phases. Third, our final matching list was not externally validated. However and in line with others, the existence of approximatively 40 different determinants seems plausible.

Our study has some strengths. First, we based our selection on published models and theories, and previously proposed categories. Consequently, our matching list represents a robust framework in line with underlying theories. Second, reliability was given from 2 independent investigators for extraction and categorization reaching substantial agreement. Third, the exclusion of reviews with focus on specific diseases, populations or other criteria guarantees a broad applicability of the matching list.

Conclusion

Matched interventions and patient determinants in common categories are needed to assess the congruency between interventions and patient determinants in published trials on medication adherence. Our matching list may be useful to develop interventions in trials that investigate the effectiveness of adherence interventions. Application of this list will show its practicability and may initiate its refinement and further development into a practical tool. To be successful, interventions in medication adherence should target current modifiable patient determinants and be tailored to the unmodifiable patient determinants. Modifiable and unmodifiable determinants need to be assessed at inclusion of intervention studies to identify the patients most in need of an adherence intervention.

Acknowledgements

We would like to thank Dr. Liset van Dijk for her critical review and valuable inputs to the manuscript and Corina Metaxas, MSc for serving as adjudicator to resolve disagreements between investigators. The authors declare no financial or commercial conflict of interest. All authors contributed to the design of the study. SA and IA performed the analysis and drafted the manuscript. RN, BvdB, and KH critically revised the work prior to submission. All authors approved the manuscript in its final version for submission and agreed to be accountable for the work presented.

Project D2

Can congruence between patient characteristics and interventions explain effectiveness in medication adherence studies? An in-depth analysis of a Cochrane review

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Manuscript submitted for publication (Jan 2017)

Abstract

Background: Due to the negative outcomes of medication non-adherence, interventions to improve adherence have been the focus of countless studies. In their latest update of a Cochrane review reporting inconsistent effects of adherence interventions, the authors offered access to their database for sub-analysis. We aimed to use this database to assess congruence between adherence-related patient characteristics and interventions and its association with intervention effects.

Methods: We developed a congruence score consisting of 6 features related to inclusion criteria, patient characteristics at baseline, and intervention design. Two independent raters extracted and scored items from the 190 studies available in the Cochrane database. We correlated overall congruence score and individual features with intervention effects regarding adherence and clinical outcomes using Kruskal Wallis rank sum test and Fisher's exact test.

Findings: Interrater-reliability for newly extracted data was almost perfect with a Cohen's Kappa of 0.92 (95% CI 0.89 – 0.94, $p < 0.001$). The inclusion of non-adherent patients was the single feature significantly associated with effective adherence interventions ($p = 0.003$). Moreover, effective adherence interventions were significantly associated with improved clinical outcomes ($p < 0.0001$). However, neither the overall congruence score, nor any other individual feature (i.e. "determinants of non-adherence as inclusion criteria", "tailoring of interventions to the inclusion criteria", "reasons for non-adherence assessed at baseline", "adjustment of intervention to individual patient needs", and "theory based interventions") were significantly associated with intervention effects.

Interpretation: The presence of only six studies that included non-adherent patients and the inter-dependency of this feature with the remaining five might preclude a conclusive assessment of congruence between patient characteristics and adherence interventions. In order to obtain clinical benefits from effective adherence interventions, we encourage researchers to select non-adherent patients, measure adherence-related patient characteristics at baseline, and match interventions to the study population.

Funding: This study was funded by the University of Basel, Switzerland.

Introduction

Medication adherence describes the behavior by which patients take their medications as prescribed, and is divided in the phases of initiation, implementation, and discontinuation[295]. Medication adherence was reported to average around 75% across various conditions and settings[38]. Due to the negative outcomes of non-adherence, such as increased morbidity, mortality, and costs, the improvement of medication adherence has been a focus for the World Health Organization since 2003[19]. Medication adherence is determined by a multitude of factors[18,49,51,279,282-284]. Various models had been proposed to explain non-adherence[48]. The most recent is the Theoretical Domains Framework (TDF), which integrated multiple behavior theories and provides a method to assess professional and other health-related behaviors.

The Cochrane collaboration published a review of interventions to enhance adherence and subsequent updates[57,59,220]. According to the latest update, interventions intended to enhance medication adherence show uncertain results and evidence of their effects remains low. A high risk of bias and heterogeneity in the measurement of adherence outcomes (e.g., pill counts, self-report, pharmacy claims data, or electronic monitoring) represent the main reasons[16]. Other issues have been suggested that might impair study results, such as including patients regardless of their current adherence[225,273] or not assessing determinants of non-adherence at baseline. From 109 randomized controlled trials (RCTs), only 13% performed this assessment[225]. Further and unsurprisingly, interventions are often unsatisfactorily described and thus not reproducible. This limitation has been recognized and a checklist has been proposed to better report interventions in future studies[296]. Finally, most interventions do not ensue from theoretical models[58] although interventions aimed at changing behavior have been shown to be more effective if based on theoretical models[297]. Only 39% of the 109-abovementioned studies used theory-based interventions[225]. Although some interventions without theoretical background were found to be effective, such as technical interventions (e.g., the use of pillboxes), theoretical considerations are important to identify essential components of the interventions[296]. Using the TDF, a systematic approach to develop interventions based on theory and potential determinants has been proposed.[293]

Determinants of non-adherence cover patient characteristics and could also relate to other factors, such as the provider and health system[19]. In a precedent work based on a pragmatic literature review, we proposed to classify determinants of non-adherence as either modifiable (i.e. factors that may be changed by interventions, such as knowledge or behaviors) or unmodifiable (i.e. factors that are unchangeable, such as age)[97]. We juxtaposed

modifiable determinants of non-adherence with interventions aimed at improving medication adherence. In brief, we matched 26 modifiable determinants to 103 interventions within 11 common categories derived from the TDF (Knowledge; Skills; Social/professional role and identity; Beliefs about capabilities; Beliefs about consequences; Intentions; Memory, Attention and decision processes; Environmental context and resources; Social influences; Emotion; Behavioral regulation). An additional 16 determinants were regarded as unmodifiable. This approach may be useful to assess the congruence between patient characteristics and interventions in studies aimed to improve adherence.

Why is it important to do this analysis?

In their latest update, the authors of the abovementioned Cochrane review[220] offered access to their database to facilitate sub-analyses of their data. We hypothesize that the congruence between adherence-related patient characteristics and interventions can partly explain the variability of effectiveness in medication adherence studies. To our knowledge, the congruence between interventions designed to enhance medication adherence and patient characteristics reported in clinical studies has not been investigated yet. Multiple features regarding inclusion criteria, baseline adherence assessment and intervention design may serve to determine the level of congruence between interventions and patient characteristics.

First, assessing the level of non-adherence at inclusion is important to select only non-adherent participants. Otherwise, the effects of the intervention will be diluted and the power of the trial to detect a significant effect will be diminished through the presence of adherent patients. Second, non-adherence is affected by a multitude of patient characteristics. When inclusion criteria are based on determinants of non-adherence, the chance of selecting non-adherent patients should increase. Thus, selecting patients based on modifiable determinants of non-adherence, together with matching the intervention to these determinants, should ensure that patients who are most likely to benefit from an intervention are included (for example selecting patients with poor knowledge about their treatment for an educational intervention). Third, assessing the reasons for non-adherence at baseline allows for adjustment of the intervention to patients' individual needs. This may increase the efficacy of the intervention. Finally, interventions designed according to theoretical models might be more effective.

Objectives

We aimed to analyze the contents of the Cochrane database[220] with these objectives:

- To extract and code features regarding inclusion criteria, patient characteristics at baseline, and intervention design, according to our juxtaposition list
- To calculate a congruence score between potential modifiable determinants and the intervention based on these features
- To correlate the congruence score with the reported study effect on adherence and clinical outcomes

Methods

Study design and sample

Data from 190 RCTs were included from an updated Cochrane review on interventions that intended to improve patient adherence to self-administered medications[220]. For overall methods of this review we refer to the main publication[220]. In brief, eligibility criteria for the Cochrane review were RCTs with unconfounded tests of adherence interventions, studies that reported at least one adherence measure (e.g., pill count) and one clinical outcome (e.g., blood pressure) with at least 80% follow-up, and included patients who had received prescription medication for a medical disorder, including psychiatric diseases, but not for addiction.

Data extraction

Cochrane data were supplied in excel format. We retrieved the following items:

- Study ID
- Inclusion/Exclusion (eligibility) criteria
- Intervention and comparator details
- Details of outcome measurement for adherence and clinical outcomes
- Answers (Yes, No, Uncertain) and details to the following questions: “Was the intervention explicitly theory based?”; “Were the reasons for not adhering to the medication(s) assessed in the recruited subjects at baseline?”; “Was there a statistically significant effect on adherence and clinical outcomes?”

From the retrieved items, we:

- extracted all findings addressing the level of patient adherence as an inclusion criterion
- extracted all findings addressing determinants of non-adherence as inclusion criteria and attributed them to the corresponding determinants from our juxtaposition list[97] and thereafter to the corresponding TDF domain (Appendix A.5.1)
- attributed interventions from studies with extracted determinants directly to TDF domains because their complexity rendered attribution to interventions from the juxtaposition list inapplicable
- extracted all findings on adjustment of the intervention to individual patients' needs

Two researchers (IA, SA) independently extracted and coded the relevant information. Both researchers discussed inconsistencies and an adjudicator resolved disagreements.

Data analysis

The following 6 features related to inclusion criteria, patient characteristics at baseline, and intervention design were selected (Table 24):

- Is the level of adherence an inclusion criterion?
- Are determinants of non-adherence in the inclusion criteria?
- Does the intervention match determinants in the inclusion criteria (tailoring to the study population)?
- Are individual reasons for non-adherence assessed at baseline?
- Is the intervention adjusted to individual patient needs (tailoring to the individual)?
- Is the intervention design based on theoretical models?

We scored each feature on an ordinal rating scale as "No", "Uncertain", or "Yes" corresponding to dummy variables from 0 to 2 used for statistical analysis. For each study, we computed a congruence score by summarizing the scores for each feature. A maximum score of 12 indicates congruence with all features.

Statistical analysis

The interrater-reliability for newly extracted data on determinants and intervention congruence was determined using Kappa statistics.

We computed frequencies for each feature and medians, range, and interquartile range for the congruence score. We used a binary variable ("Yes" or "No") to describe whether studies were able to show a significant effect (i.e., significant difference between intervention and control groups) regarding adherence and clinical outcomes. We tested associations between ordinal variables (congruence score, individual features) and categorical variables (effects on adherence, clinical outcomes) using a Kruskal Wallis rank sum test. We tested associations

between categorical variables using Fisher's exact test. We considered p-values < 0.05 as significant and did not adjust for multiplicity of data challenges. Statistical analyses were performed in R version 3.2.2[149].

Table 24: Features to assess congruence between interventions and patient characteristics

Feature	Score 0 (no)	Score 1 (uncertain)	Score 2 (yes)
Is the level of adherence an inclusion criterion?	Level of adherence is not reported as inclusion criterion	Eligibility criteria indicate inclusion of non-adherent patients, and no objective adherence measurement is mentioned	Only non-adherent patients based on objective adherence measurement are included
Are determinants of non-adherence in the inclusion criteria?	Inclusion criteria report no modifiable determinant of non-adherence	Inclusion criteria are insufficiently reported	Inclusion criteria contain modifiable determinant(s) of non-adherence
Does the intervention match determinants in the inclusion criteria (tailoring to the study population)?	Intervention does not match the category of the determinant	It is uncertain whether the intervention matches the determinant	Intervention does match the category of the determinant
Are individual reasons for non-adherence assessed at baseline?	Reasons for non-adherence are not assessed at baseline	Reasons for non-adherence are assessed at baseline, but only for the intervention group	Reasons for non-adherence are assessed at baseline for intervention and control groups
Is the intervention adjusted to individual patient needs (tailoring to the individual)?	Intervention is not adjusted to patients individual needs	It is uncertain whether intervention is individualized	Intervention is adjusted to patient individual needs
Is the intervention design based on theoretical models?	Intervention is not theory-based	It is uncertain whether intervention is theory-based	Intervention is based on theory detailed in study

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Interrater-reliability for newly extracted data was almost perfect with a Cohen's Kappa of 0.92 (95% CI 0.89 – 0.94, p < 0.001).

Congruence Score and effectiveness

The 190 studies reported in total 212 different interventions. The median overall congruence score was 3 (Range 0 – 11) with an interquartile range (IQR) of 3. Interventions with a significant effect on adherence had slightly higher median congruence score compared to interventions with no effect on adherence (3.5 [IQR = 3] vs. 3 [IQR = 2]; p = 0.28; Figure 39). Recruitment of non-adherent patients was the only individual feature significantly associated with effective interventions regarding adherence (p = 0.003, Table 25). Clinical outcomes were not significantly associated with the overall congruence score (p = 0.2, data not shown). "Adjustment of intervention to individual patient needs" showed the highest association with effective interventions regarding clinical outcomes (p = 0.07, Table 25). The fusion of the categories "uncertain" and "no" did not affect the associations with neither the overall score nor individual features (data not shown).

Interventions with a significant effect on adherence were more likely to report significant clinical outcomes (OR = 6, $CI_{95\%}$ = 3.1 - 12, p < 0.00001). This highly significant association remained significant (p = 0.0001) for a subsample of 29 studies with the highest quality (i.e., lowest bias according to the original review[220]).

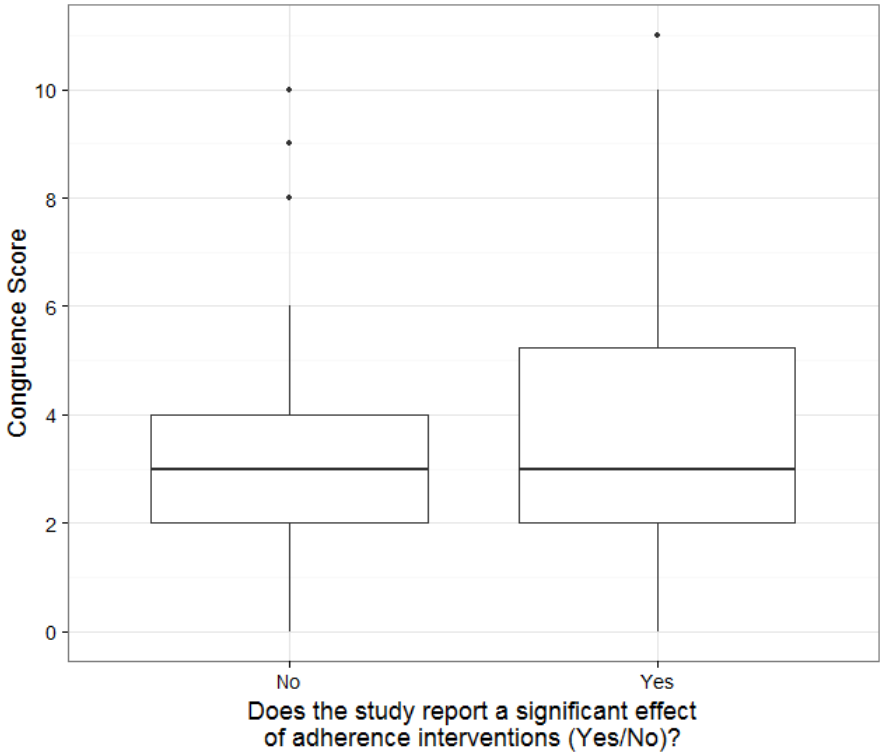

Figure 39: Boxplot of Congruence Scores for interventions with (N = 112) and without (N = 100) significant effect of the adherence intervention

Table 25: Association between congruence features and intervention effect for 212 interventions from 190 studies.

	Association (p-value) with intervention effect on:	
Feature	**Adherence**	**Clinical Outcomes**
Level of adherence as inclusion criterion	0.003*	0.3
Determinants of non-adherence as inclusion criteria	0.6	0.6
Matching intervention and determinants in the inclusion criteria	0.6	0.7
Individual reasons for non-adherence assessed at baseline	0.3	0.8
Adjustment of intervention to individual patient needs	0.7	0.07
Intervention design based on theoretical models	0.12	0.4

Level of adherence as inclusion criterion

Of the 190 studies, 6 (3%) included participants based on their level of adherence: either with less than 80% adherence measured by electronic monitoring[298], medication possession ratio[299], pill count[300], or structured questionnaire[301] (four studies), or with a cut-off of 75% and 50% adherence[302,303], measured electronically and by prescription refill, respectively (two studies). The majority of the studies (180; 95%) did not report the level of adherence as eligibility criterion. Two studies remained uncertain[304,305] and another two did not report any eligibility criteria[306,307].

Determinants of non-adherence as inclusion criteria

Eligibility criteria contained determinants of non-adherence according to our juxtaposition list[97], either as inclusion criteria (n = 66, 35%), exclusion criteria (n = 33, 17%), or both (n = 61, 32%).

Ninety-nine studies (52%) contained 11 modifiable determinants in the eligibility criteria. A total of 13 unmodifiable determinants were present in 130 studies (68%, Figure 40).

Of the 190 studies, 46 (24%) included patients with modifiable determinants of non-adherence. The six modifiable determinants were: "Psychological problems" (e.g., depression or schizophrenia; n = 25), "Pill burden" (e.g., multiple medications; n = 10), "Lifestyle" (e.g., drug or alcohol abuse, smoking; n = 7), "Adverse events", "Continuity of care", and "Specificity of regimen" (Figure 40). The modifiable determinants most frequently excluded were "Psychological problems" (n = 39), "Lifestyle" (n = 19), and "Physical difficulties" (e.g., visual or hearing impairment; n = 14).

Unmodifiable determinants most prevalent in the inclusion criteria were "Change of therapy" (e.g., new treatment or treatment adjustment; n = 30), "Age" (e.g., children or elderly; n = 29), "Duration of treatment" (e.g., long-term treatments; n = 17), and "Illness severity" (e.g., uncontrolled conditions; n = 17). Patients with unmodifiable determinants of non-adherence were excluded because of "Cognitive impairment" (n = 45), "Polymorbidity" (n = 8), "Age" (n = 5), and "Level of education" (e.g., literacy, n = 5).

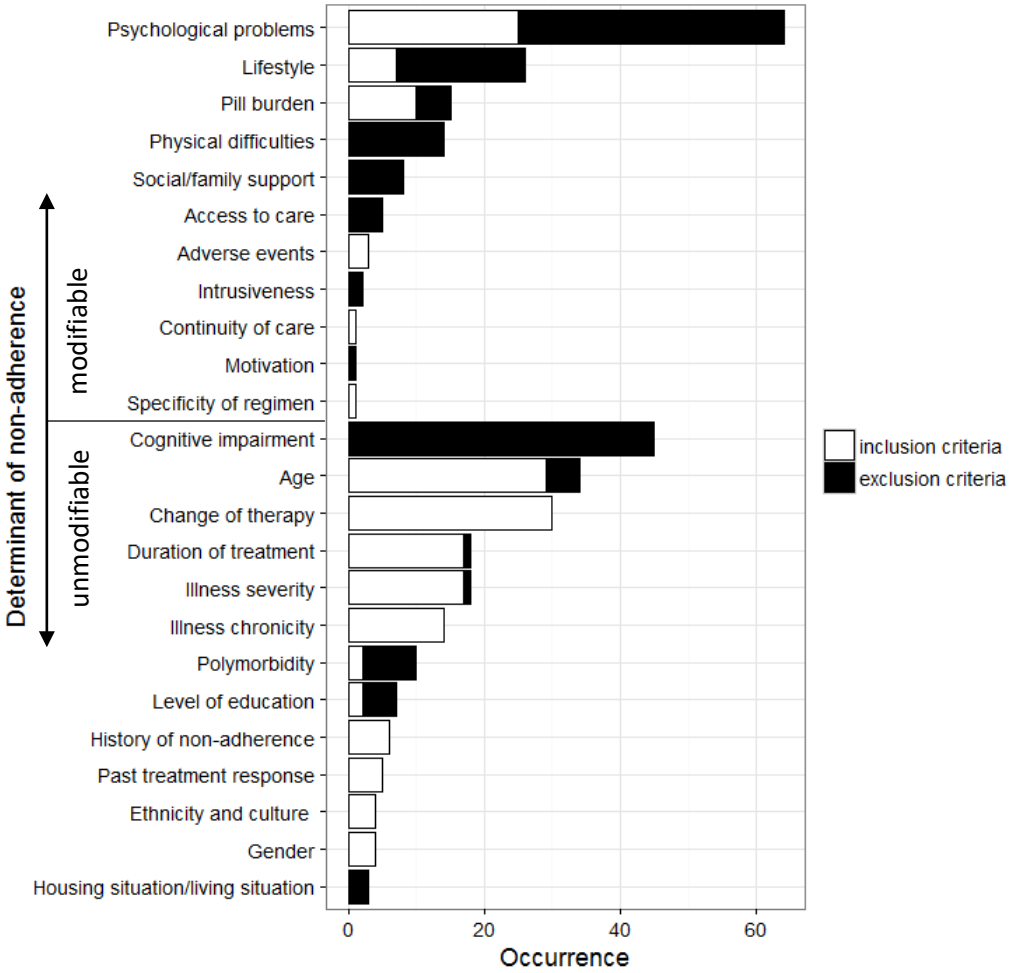

Figure 40: Cumulative number of studies (n = 160) with modifiable and unmodifiable determinants of non-adherence in the eligibility criteria according to our juxtaposition list[97]

Matching between interventions and determinants in the inclusion criteria

A total of 47 determinants were present in the 46 studies that reported a modifiable determinant of non-adherence in the inclusion criteria. The determinants contributed to only 3 of the 11 TDF categories in our juxtaposition list (Figure 41). According to our juxtaposition list, 30 (64%) were addressed by the intervention (e.g., during an intervention for patients with psychological problems as determinant of non-adherence, life events before and after the diagnosis of schizophrenia were assessed and methods to avoid or resolve these circumstances were discussed[308]). In a further 16 interventions (34%), the determinants did not match the inclusion criteria. One case was uncertain whether the intervention addressed the determinant (family therapy for patients with schizophrenia without further information about the intervention components[309]). The majority of determinants and interventions were in the TDF category "Emotion" (Psychological problems, n = 25, 53%). The most diverse category was "Environmental context and resources" with the determinants "Pill burden"

(n = 10, 21%), “Adverse events” (n = 3, 6%), “Continuity of care” (n = 1, 2%) and “Specificity of regimen” (n = 1, 2%).

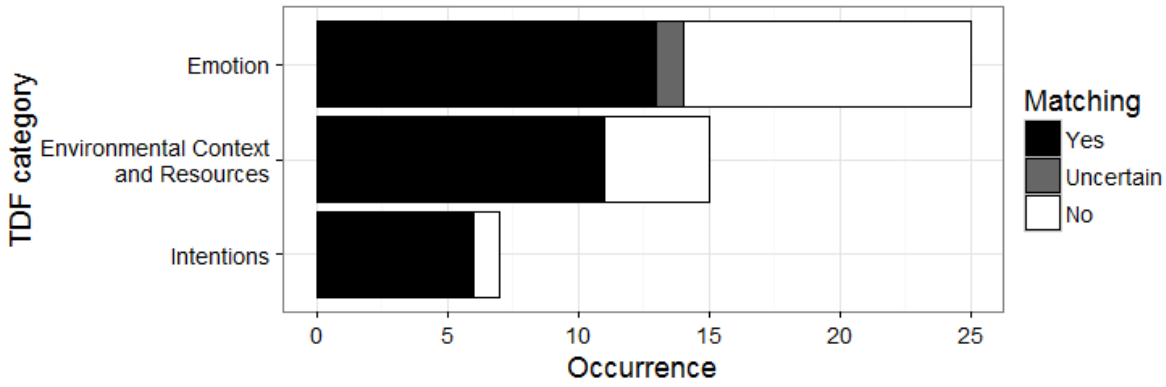

Figure 41: Matching of interventions to determinants of non-adherence in TDF categories according to our juxtaposition list. Of the 11 TDF categories in our juxtaposition list, only 3 were used for matching.

Reasons for non-adherence assessed at baseline

Of the 190 studies, 18 (15%) assessed the individual participants’ reasons for non-adherence at baseline, 115 (60%) did not, and it was uncertain for 47 (25%). Extraction of the determinants of non-adherence assessed at baseline was impossible for most studies due to approximate phrasings. In some studies, there was only a mention that the reasons were assessed without further details; in others, only a selection of the reasons was indicated.

Adjustment of intervention to individual patient needs

Of all reported interventions (n = 212; some studies used multiple interventions), 143 (68%) were adjusted to the individual needs of the patient, 46 (23%) were not personalized, and 23 (11%) remained uncertain. Personalization was most often achieved by individualization of education, counselling, or treatment plans based on patient needs.

Theoretical models

The majority of the studies did not report whether the intervention was theory-based (n = 118, 63%). A third of the studies (n = 66, 34%) explicitly based their intervention on theory and 6 (3%) remained uncertain. We identified 33 different underlying theories or models, and some studies reported more than one theory or model on which the intervention was founded. The most prevalent theories were the self-efficacy theory (n = 8) and the social cognitive theory (n = 7). The social learning theory, the health belief model and the

information-motivation-behavior skills (IMB) models were used 5 times each (Appendix A.5.2).

Discussion

Because the effects of interventions intended to enhance adherence to medication are largely uncertain[220], we hypothesized that the analysis of congruence between patient characteristics and interventions would help resolve some of the uncertainty. Among 190 analyzed RCTs, the "inclusion of non-adherent patients" was the sole single feature significantly associated with effective interventions regarding adherence. For example, a study assessing a reduction in blood pressure found significant differences between intervention and control groups only for initially non-adherent patients[310]. Another study from 1978 found a reduction in blood pressure only in patients declaring difficulties remembering to take their medication and concluded that these patients may benefit the most from an intervention.[36] The inclusion of non-adherent patients is likely to increase the difference in adherence measured between control and intervention groups. Alternatively, the inclusion of adherent patients is likely to mask any actual effective interventions because adherence can only be improved to a certain extent ('ceiling effect')[311]. Indeed, baseline adherence was often high when reported[312]. Our results thus confirm the assertion of other authors that emphasizes the importance of including non-adherent patients in adherence studies[225,226].

All other individual features (i.e. "determinants of non-adherence as inclusion criteria", "tailoring of interventions to the inclusion criteria", "reasons for non-adherence assessed at baseline", "adjustment of intervention to individual patient needs", and "theory based interventions") were not associated with effective interventions. At first sight surprising, this result may be explained by the large impact of the inclusion of adherent patients instead of non-adherent patients. Indeed, any association with these features might be masked if patients are already well adherent. Ultimately, adherence interventions should aim at improving clinical outcomes. We showed that interventions with a significant effect on adherence also significantly improved clinical outcomes. However, clinical outcomes were neither associated with the overall congruence score, nor with individual features. This might partly be explained by intervention components influencing clinical outcomes, but not adherence, such as placebo effects resulting from ameliorated patient-physician relationships.

Our results are not surprising. Despite the frequent occurrence of patient characteristics in the inclusion criteria, only few were relevant for adherence interventions. For example, only

3% of the studies screened adherence level before recruitment, and 24% included patients with modifiable determinants of non-adherence (such as pill burden). In addition, the majority of modifiable determinants fit into the TDF domain "emotion" and only half of the interventions matched the modifiable determinants of the patients. In line with our study, another review showed that interventions mostly targeted determinants in different TDF domains, such as "memory, attention and decision processes", "knowledge", "environmental context and resources", "social influences" and "beliefs about consequences".[294] This lack of congruence between patient characteristics and interventions might diminish the overall effect. Finally, although two-thirds of the interventions were adjusted to individual patient needs, most of the interventions did not target non-adherent behavior. In other words, they were not tailored to specific determinants of non-adherence, and thus, were unlikely to show a significant effect.

Our juxtaposition list was helpful to assess and code patient characteristics and interventions. It is noteworthy that the most frequent modifiable determinants were "psychological problems" (such as depression or schizophrenia), "pill burden" or "lifestyle" (such as alcohol or illicit drug use), probably because these determinants are well defined and easy to measure in comparison with other modifiable determinants, such as "motivation" or "access to care", and thus better suited as inclusion criteria[313]. The high frequency of "psychological problems" as eligibility criteria deserves some comments. This attraction may be explained by the many studies reporting non-adherence amongst patients with these conditions. Interventions can target treatment (best to measure with modifiable determinants) or be operationalized through motivational interviewing, which is recognized as method of first choice when behavioral change is the outcome[314,315].

Unfortunately, we were not able to use our juxtaposition list to classify individual determinants of non-adherence assessed at baseline, due to the poor reporting of study procedures. Unlike with clearly stated inclusion criteria, the description of baseline assessment generally remained unspecific concerning the determinants of non-adherence (e.g., reasons were assessed but not described in the manuscript[263,316-318]).

Strengths and limitations

Our study has several strengths. To our knowledge, this is the first systematic assessment of congruence between patient characteristics and adherence interventions. We used an explicit juxtaposition list to assess congruence. With this approach, we reached near-perfect interrater-reliability between the two researchers extracting the data.

We acknowledge some limitations. First, we selected six features to assess congruence between patient characteristics and interventions based on theoretical considerations from the literature.[58,225,226,273,293,296,297] However, other features might exist and might contribute to congruence. Second, the coding of the single features was a long cognitive process and was often linked to assumptions of the descriptions found in the studies, especially for the "determinants of non-adherence at inclusion" (e.g., "analgesia prescription that included instructions for administration every 4 hours" described a very specific regimen and thus the determinant "specificity of regimen" was assigned to this inclusion criterion [41]) or "tailoring of the intervention to those determinants" (e.g., the intervention "formulating a daily medication schedule" was matched to the determinant "pill burden" because a reduction in the frequency of dosing might allow a reduction of the number of pills to take[319]). Because these features were not reported very precisely in the retrieved studies, our coding may be afflicted with some uncertainty. However, the very high inter-rater reliability ($\kappa = 0.92$) between the extractors minimizes this bias. On the other hand, a bias is less likely towards the more obvious coding of the features "including non-adherent patients" and "intervention based on theoretical models" - which showed the strongest association with adherence outcomes - because they were clearly described in the majority of studies. Third, effectiveness of interventions depends on further quality-related features, such as risk of bias, which we did not control for. Likewise, interventions might be more effective based on other factors, such as underlying disease, setting, type of medication, etc. We did not control for the many heterogeneities in the studies, which could contribute to the weak associations identified. Fourth, we did not differentiate between the interventions, although different types of interventions might be more effective than others to tackle the same determinant. Various studies have analyzed these associations and have found that some interventions are indeed more effective than others[58,320]. Fifth, we did not adjust for multiple statistical testing. However, the significant associations were strong ($p < 0.01$) compared to all other associations and would have remained significant with adjustment, e.g., using a stricter p-value. Finally, a dichotomous classification of intervention effects into significant and non-significant may be too coarse to reveal a significant association. Other measures, such as the effect size, might offer a better resolution[321], but large methodological differences between studies hindered the meaningful calculation and comparison of effect sizes between studies.

Conclusion

We tested the hypothesis that effective adherence interventions may be explained by congruence between patient characteristics and interventions. For this purpose, we developed a score consisting of 6 features and applied it to 190 RCTs.

We showed for the first time that including non-adherent patients was significantly associated with effective adherence interventions. We also showed that effective adherence interventions were significantly associated with improved clinical outcomes, a relationship that remained significant in a subset of the highest quality studies. However, we were not able to demonstrate an overall positive effect of congruence between patient characteristics and adherence interventions. This might be explained by the presence of only six studies that included non-adherent patients and by the inter-dependency of the remaining five features with the first (i.e., the inclusion of non-adherent patients). In order to obtain clinical benefits from effective adherence interventions, we encourage adherence researchers to select non-adherent patients, measure individual determinants at baseline in a systematic manner, and select and tailor interventions based on the (most important) modifiable determinants in the study population, also in a systematic manner.

Declaration of interests

There is no conflict of interest of any of the authors. This study was funded by the University of Basel, Switzerland. Data was supplied by the McMaster University Patient Adherence Review Team, ON, Canada.

Contribution of Authors

SA: Involvement in all stages of study design, secondary data extraction, analysis, and writing of the manuscript
RN: Involvement in primary Cochrane review, study design, and reviewing of the manuscript
TN: Involvement in primary Cochrane review, study design, and reviewing of the manuscript
RBH: Involvement in primary Cochrane review, study design, and reviewing of the manuscript
KH: Involvement in study design and reviewing of the manuscript
IA: Oversight and involvement in all stages of study design, secondary data extraction, analysis, and writing of the manuscript

Appendix

General discussion and conclusions

The goal of this thesis was the investigation of adherence to polypharmacy and the tailoring of adherence interventions from a pharmaceutical care perspective. Although adherence has been studied for decades, it has been described as the least understood health behaviour[18]. Many disciplines are involved in medication adherence research, such as medical and pharmaceutical sciences, behavioral and social sciences, but also biostatistics and economics. Neither discipline can be ignored when attempting to provide a scientific contribution relevant to patients. Consequently, this thesis covers a broad range of topics and employed a multitude of methodologies, from semi-structured qualitative patient interviews to large-scale quantitative data analysis. Several projects contributed to this thesis.

Project A aimed to harmonize the use of single pharmaceutical care (PhC) definition amongst European researchers and practitioners. Since the widely-cited definition by Hepler and Strand from 1990[99], new terms and concepts of medicines-related patient care, such as "medicines management", "disease management"[86], and "medication therapy management" (MTM)[87], have added confusion to the meaning of PhC and its differentiation from other terms. We identified existing definitions of PhC in a literature review and paraphrased them in a generic format regarding provider, recipient, subject, and outcome of PhC. During a one-day workshop of the Pharmaceutical Care Network Europe (PCNE), 24 experts from 11 countries defined PhC based on the literature review and in accordance with the consensus-oriented decision-making model[103]. As a result, the new definition of PhC directly derives from previous definitions and is intended to unite the current understanding of PhC with respect to the evolution of this practice philosophy during the last 35 years. It is important to note that "pharmaceutical care" is not equal to the "care around pharmaceuticals", a misunderstanding especially common among representatives of the pharmaceutical industry. Since its publication, the new definition has been cited 29 times as of December 2016. In addition to the publication, describing the results of the literature review and the process of the definition development, PCNE published a position paper discussing the wording and scope of the new definition[123]. Three aspects of the PCNE definition deserve special attention: The explicit mentioning of the pharmacist as the responsible provider of PhC, the focus on the care of individuals, and the optimization of medicines use as main subject. Although many professionals are involved in the provision of pharmacotherapy, it is clearly the center of attention for pharmacists. Consequently, pharmacists have also been identified as ideal providers for interventions to improve safe and effective medicines use[278]. Defining PhC as

the "contribution" of the Pharmacist implies collaboration between healthcare providers and does not exclude other providers. The focus on individuals is crucial for the improvement of adherence interventions. Adherence is a multi-dimensional behavior affected by many different determinants that are unique to every patient. PhC describes a process that includes a follow-up to determine the impact of the service, distinguishing PhC from simple counselling. The optimization of medicines use as the main subject of PhC is highly relevant to adherence management and has been endorsed as one of four key roles of pharmacists by the International Pharmaceutical Federation (FIP)[84].

Project B aimed to evaluate the prevalence of the prescription of split preparations for elderly patients, a common practice that increases regimen complexity and may have a negative impact on adherence[51]. Previous studies showed that every fourth tablet is split in ambulatory settings[322,323] predominantly because of dose adjustment, swallowing difficulties, or costs[324,325]. We performed a first-time analysis of data from a blister center providing repackaging services for community pharmacies. Our study showed that fragments of tablets represented 8.5% of all tablets ordered in 2012 by 53 community pharmacies in northern Switzerland for institutionalized patients. Thus, institutionalized patients with pharmacy-filled medication management aids (MMAs) receive less fragmented medications than primary-care patients without medication management provided by their pharmacy. Our results most likely represent the cases in which fragmenting is necessary for dose adjustments, because fragmenting at the blister center is reserved for cases where no lower dosage strength is available on the market. Almost half of all patients in our study received 2 or more fragments. Although necessary in clinical practice, splitting tablets poses a potential safety issue and should not be performed with the intent to reduce costs[326]. A recent study in Swedish community pharmacies showed that 52.5% of the patients with a prescription for split tablets preferred whole tablets of the appropriate strength rather than split tablets[327]. Pharmacy-filled MMAs might reduce the proportion of fragments, increasing safety of and adherence to polypharmacy.

Although the majority of older adults report at least part-time use of MMAs[69,70], the authors of a review of the effects of MMA concluded that the design and targeting of these devices need further research[64]. Studies with e-MMA often only report aggregated data[77-79]. With **Project C**, we aimed to explore the use of a remote electronic medication management aid (e-MMA) for prepackaged polypharmacy in ambulatory patients. The e-MMA has been developed and used in the Netherlands for community-dwelling elderly patients requiring assistance with their

medication management. However, no data on e-MMAs from Switzerland exists and the device has never been used in patients with opioid-assisted treatment (OAT).

In **Project C1**, we provided a group of participants with the e-MMA for two weeks and assessed their experience in a Focus Group. Participants rated 10 of 17 general attributes as applicable to the e-MMA and five as unsuitable. Attributes pertained to 3 interrelated themes: Product design, patient support and living conditions. Our results show that the assessed e-MMA meets most of the general requirements set for an MMA in the areas of patient support and implications on patient habits. Envisaged target groups were patients with time-sensitive medication regimens, patients with dementia, the visually impaired, and several patients living together to prevent accidental intake of the wrong medication. The major limitation voiced by our participants concerned the restricted mobility inherent to a bulky device that needs continuous power supply. This aspect may restrict the applicability of the e-MMA to patients with limited mobility, an aspect also mentioned for a similar e-MMA evaluated elsewhere[174]. A recent qualitative study with pharmacists, physicians, nurses, social workers, and patients about their views on electronic multi-compartment medication devices showed similar results regarding the applicability of such devices[328].

Our analysis of medication profiles of patients receiving OAT from an outpatient addiction service in Basel, Switzerland *(***Project C2***)* showed an increase in the number of substances and medications over 10 years, leading to an increased risk of drug-drug interactions, adverse events, and non-adherence. Additionally, we observed a shift from the traditional OAT with liquid Methadone to solid formulations, such as Buprenorphine and sustained-release Morphine. Disorders such as ADHD further complicate the safe and effective therapy of these complex patients. The deteriorating health of older drug users, the risks associated with non-adherence, and reduced mobility are putting considerable strain on existing resources. Because existing nursing homes or home care services are not suited to accommodate patients with substance use disorders, ambulatory treatment and surveillance are provided as long as possible. As a result, the cost of providing care to the ageing drug users is supposed to increase and innovative solutions to optimize medication management compatible with OAT are needed.

Little is known about the adherence of opioid dependent patients to their medication. Few cohort studies from Switzerland and France assessed self-reported adherence of HIV-infected drug users during the past 4 and 1 weeks, respectively[228,229]. Patients with stable opioid substitution therapy report significantly higher adherence than patients without substitution[228]. In **Project C3**, we evaluated a novel medication supply model using the e-

MMA and showed sustained treatment implementation and suppressed viral loads in two opioid dependent HIV patients over 1.7 and 2.5 years, respectively. Our novel supply model offered a sustainable solution to assure adequate implementation and persistence with treatment. Additionally, repackaging of medications in unit-of-use pouches might prevent disturbance in case of changes in treatment, such as the up-titration of anti-dementia therapy, or initiating of preventive and irregular treatment, such as prophylaxis of Pneumocystis carinii. However, we experienced technical problems that compromised monitoring and increased workload for the care staff. These were unpredictable, not reproducible, and complicated the care process. Nevertheless, patients declared satisfaction with the novel supply model, probably because the technical problems did not jeopardize medication intake. The success of our intervention in these complex patients demonstrates the potential of our supply model.

In a subsequent single-subject study (**Project C4**), we aimed to assess the use and effects of the e-MMA with a mixed-methods approach. Our results suggest that the evaluated e-MMA ensures high taking adherence in opioid-substituted patients with polypharmacy. Furthermore, the audible and visual alerts might improve taking and timing adherence, but do not reduce time variability. Arguably, the importance of timely dosing depends on the respective therapy. Due to differences in pharmacologic properties, it is more important for some medications to be taken at exact times than for others. The probability of therapeutic success under imperfect adherence compared to perfect adherence has previously been described as "forgiveness" of medications [242]. Thus, the specificities of a patient's treatment (e.g., forgiveness or presence of on-demand medications) should always be considered when assessing adherence to polypharmacy. Obviously, the e-MMA might offer the largest benefits to patients with low adherence and unmet clinical outcomes. However, consideration of humanistic outcomes might be more appropriate in multi-morbid patients with polypharmacy. Quality of life (QoL) is reportedly lower than average in patients with substance-use disorders, and improvements in QoL should be a priority for these patients[244]. Our results indicate trends towards the improvement of mental QoL, which might be explained by the additional attention participants received during the study. Participants reported independence and security of medication availability as biggest advantages of the e-MMA. Importantly, the e-MMA did not interfere with the care they received from the OAS.

Our results suggest that the use of the e-MMA might be applicable for patients with:

- High perceived necessity of treatment
- Self-reported non-adherence
- Unforgiving treatments
- Low social support
- Psychologic distress

However, other alternatives should be considered for:

- On-demand treatments
- Problematic substance use

In addition to improvements in clinical and humanistic outcomes, higher adherence has been associated with reduced overall healthcare costs[224]. With **Project C5**, we aimed to perform a cost-of-illness evaluation of patients receiving OAT and polypharmacy and to establish a cost-comparison model for the novel supply model compared to standard medication supply. We found high total costs, with over SFr 109'000 per patient per year. Direct medical costs amounted to almost 30% of all costs, half of which accrued for psychiatric treatment and a third during hospital admissions. Surprisingly, costs were neither associated with age, sex, or number of medications. We estimated the annual costs for the novel supply model at roughly SFr 2'500 for repackaging of medication, leasing of the dispenser, refill every 3 weeks, technical support, and OAS visits once weekly. This accounted for 2.3% of total costs, with repackaging into unit-dose pouches and leasing for the dispenser being the main cost items. The remuneration for the weekly repackaging of polypharmacy in Switzerland is paid for by health insurances when patients receive three or more medications (OAT not included). The increasing polypharmacy and complexity of treatments could add more stress to caregivers when dispensing medications together with OAT at the OAS, which could lead to dispensing errors[272]. Compared to the fragmented dispensing provided by the OAS, unit-dose pouches offer various benefits: Patients receive medications for every intake time in a sealed pouch labelled with the date and time of intake. The repackaging process is subject to strict quality controls and the identity of the contents is guaranteed. This reduces the potential for erroneous dispensing almost to zero. Our cost-comparison model showed that the novel medication model might be almost cost-neutral but might provide clinical benefits as demonstrated Project C3. Other alternatives to the traditional supply model, such as assisted living or nursing homes would be much more expensive and further reduce patients' independence.

In summary, **Project C** demonstrated that the e-MMA might offer a suitable solution to supply polypharmacy to older patients with OAT. Although ingestion of medication is not guaranteed when pouches are dispensed, the e-MMA improves implementation of regimens by assuring the availability of the right medications at the right times. A white paper recently published by Philips claims that the average taking adherence with this e-MMA was 93% in a sample of 1379 patients monitored for 6.7 months on average[329]. Patients in this sample took an average of 3 doses per day, and adherence remained stable when having more than 2 daily dosing times. A multicenter randomized controlled trial assessed the feasibility and efficacy of the e-MMA in Parkinson's disease[330]. The study included 78 patients aged over 40 years, with a minimum of 4 daily dosing times, and experiencing on-off fluctuations. The results suggest no significant overall improvement after 3 and 6 months in any of the outcomes (Linear Disability Scale, quality of life [QoL], experienced health status, QoL of caregivers). However, exploratory sub-analysis suggested that older patients with more severe symptoms might benefit from the intervention. Adherence was not reported in this study, impeding the interpretation of the results. However, the evidence from this thesis and the white paper from Philips suggest that patients using the e-MMA demonstrate sustained persistence and sufficient implementation of dosing regimens. Thus, a failure to show clinical improvements could be explained in three ways: First, study duration may be too short to show a significant difference. Second, adherence of participating patients could be already high at inclusion or improved during the study in both groups equally. Third, despite being non-adherent at inclusion, participants may not benefit from the intervention. The first reason would be relevant to all clinical trials, the second and the third apply to all adherence intervention studies.

According to the latest update of a Cochrane review, interventions intended to enhance medication adherence show uncertain results and evidence of their effects remains low[220]. The review included RCTs with unconfounded tests of adherence interventions, studies that reported at least one adherence measure (e.g., pill count) and one clinical outcome (e.g., blood pressure) with at least 80% follow-up, and included patients who had received prescription medication for a medical disorder, including psychiatric diseases, but not for addiction. It has been argued that including patients regardless of their current adherence might impair effectiveness of adherence interventions[225,273]. Furthermore, the selection of appropriate patients and tailoring of adherence interventions has been suggested to improve effectiveness of interventions[273].

Thus, **Project D** aimed to assess the congruence between patient characteristics and adherence interventions in published trials and investigate its association with intervention effects. A plethora of determinants of non-adherence and interventions to improve adherence have been reported in countless studies. Although several attempts have been made to suggest interventions based on various determinants, shared categories to include determinants and intervention did not exist.

In **Project D1**, we extracted salient determinants and interventions and categorized them in shared categories derived from the Theoretical Domains Framework (TDF). We identified 103 different interventions and 42 determinants that we divided in 26 modifiable and 16 unmodifiable determinants. In our view, this distinction between modifiable and unmodifiable determinants is essential for the choice of adherence interventions. In order to be effective, we postulate that interventions have to target current modifiable patient determinants and be tailored to the unmodifiable patient determinants. We were able to match all interventions and the 26 modifiable determinants in 11 shared categories, not using 3 of the original TDF categories. Because it was not specifically developed for interventions and patient determinants of non-adherence, some adaption of the TDF to specifically address adherence might prove useful in future projects.

In **Project D2**, we analyzed data of the abovementioned Cochrane review with regards to congruence between characteristics of the included patients and the adherence intervention. We showed for the first time that the inclusion of non-adherent patients is significantly associated with effective adherence interventions. Moreover, effective adherence interventions were significantly associated with improved clinical outcomes. Due to an insufficient number of studies including non-adherent patients, we were not able to draw conclusions about the effect of congruence between patient characteristics and adherence interventions.

Limitations

Limitations of the individual projects were discussed thoroughly for each study. The overall limitations of this thesis were:

- the pharmacists-centered view on adherence. As discussed previously, different healthcare providers and disciplines contribute to adherence research and management. Most researchers involved in the design and supervision of this thesis

were pharmacists, and therefore the results might be biased towards a favorable view of the pharmacist.

- the involvement of one researcher in the design, collection of data, analysis, and interpretation. This might lead to a bias in favor of the research hypotheses (observer bias)[331].
- the change in behavior of people when they are monitored more closely (Hawthorne effect)[332]. Research about adherence is often affected by the Hawthorne effect, which might have affected our results in Project C. However, monitoring of adherence was part of the intervention and would persist outside of research projects.
- the evaluation of the electronic dispenser in Project C in a local setting. The OAS is specialized to treat opioid-dependent patients with mental disorders and these patients may potentially show a higher complexity compared to other opioid-dependent patients. Nevertheless, our results are relevant to other settings, as the increasing age and associated complexity is observed globally.
- the small sample sizes, which limit the validity of our results. Different research designs have been ranked in a hierarchical manner, mainly to provide guidance to appraise the evidence in systematic reviews. Various versions of a so-called "evidence pyramid" ranked study designs from weak to strong. The hierarchy represents the internal validity (risk of bias) of study types. Consequently, case reports and case series rank lowest, followed by case control and cohort studies, randomized clinical trials (RCTs), and systematic reviews and meta-analyses on top. Recently, a new pyramid has been proposed, advocating for less strict separation of study designs and viewing systematic reviews as "lenses" through which evidence is assessed[333]. In the field of adherence research, the applicability of results in practice plays an important role. Consequently, some versions of the pyramid have been adapted to incorporate applicability. As a result, N-1 trials as a form of single-subject research have been placed above RCTs, because their results apply directly to patients[334].

Conclusions

The following conclusions derive from this thesis:

- It was possible to paraphrase definitions of PhC using a standardized syntax focusing on the provider, recipient, subject, outcomes, and activities of PhC practice. During a one-day workshop, experts in PhC research agreed on a definition, intended to be

applicable for the present time, representative for various work settings, and valid for countries in- and outside of Europe.

- Tablet splitting is a pharmaceutical care issue with potential consequences on adherence, playing a major role in dosage adjustments for geriatric patients. Although limited to certain regions, fragments of certain tablets are prescribed against the recommendations from the manufacturer. Pharmaceutical companies should be encouraged to introduce new strengths to an existing range of products, in view of an optimization of seamless care between the different health care professionals. If splitting tablets is necessary, patient counseling is recommended and pharmacies should deliver the appropriate tools or offer repackaging into MMAs for patients.
- The appearance of MMAs, but also its functionality and the whole medication supply process play an important role with regards to the design and targeting of MMAs. In a focus group discussion, the evaluated e-MMA with pre-packaged polypharmacy met the majority of the requirements set to an MMA. Patients' living conditions like mobility remain the key determinants for their acceptance of the e-MMA. Especially patients with time-sensitive medication regimens, patients with dementia, the visually impaired, and several patients living together might benefit from the e-MMA.
- With our database analysis, we confirmed the globally observed shift towards an older population with OAT in a Swiss setting. An increase in the number of substances and medications might lead to an increased risk of drug-drug interactions, adverse events, and non-adherence. Traditional OAT with liquid Methadone is increasingly being replaced by solid formulations, such as Buprenorphine and sustained-release Morphine. Other disorders further complicate the safe and effective therapy of the complex patients. Taken together, the developments of the past 10 years call for new care models for older patients with OAT. The increasing age and complexity of their medication might warrant a closer collaboration of health care professionals. Alternative supply models to assist patients with their medication management and tosupport medication adherence are needed for older patients with OAT and polypharmacy.
- Continuous medication supply and persistence with treatment over more than 1.7 years, timing adherence of more than 90%, and suppressed HIV viral load are first results supporting the feasibility of a novel supply model with an e-MMA for polypharmacy.
- Medication supply with the e-MMA may ensure correct implementation of dosing regimens for opioid-substituted patients with polypharmacy when certain

prerequisites are considered. Various drawbacks limit the applicability of the e-MMA to monitor adherence to polypharmacy. A careful assessment of patient's barriers to medication adherence and a structured medication review should be the first steps to provide meaningful information from electronic monitoring. The flexibility of single-subject research designs offers considerable advantages for the evaluation of adherence interventions.

- Cost-of-illness for older patients with OAT and polypharmacy is high, especially when considering indirect costs, such as productivity loss due to disability. According to our cost comparison model, the novel electronic medication supply model increases overall costs marginally, but might offset the costs of more expensive alternatives, such as nursing homes.
- In published trials on medication adherence, the congruence between interventions and determinants can be assessed with matching interventions to determinants. To be successful, medication adherence interventions should target current modifiable patient determinants and be tailored to the unmodifiable patient determinants.
- A 6-item score to assess congruence between patient characteristics and adherence interventions was not significantly associated with intervention effects in 190 RCTs included in a Cochrane review. The presence of only six studies that included non-adherent patients and the inter-dependency of this item with the remaining five precluded a conclusive assessment of congruence between patient characteristics and adherence interventions. The selection of non-adherent patients, measuring adherence-related patient characteristics at baseline, and matching interventions to the study population should be the first steps to design future adherence studies capable of demonstrating effectiveness of their intervention.

Outlook

Adherence is a complex behavior with individual determinants and no one-size-fits-all solution. As stated in the definition that has been developed as part of this thesis, pharmaceutical care focuses on individuals. This fits well with the idea of adherence interventions that target modifiable determinants and are tailored to unmodifiable determinants of non-adherence. In line with the global shift of the pharmacist's role towards the provision of patient-centered services, this thesis encourages pharmacists to assume responsibility for the provision of adherence support for patients with polypharmacy in primary care, including older drug users with OAT. In line with our research, others have

recognized the need for alternative supply models for OAT. As an example, a research group from the US has registered a trial to evaluate the feasibility, acceptability, and usability of a novel platform that integrates text messaging reminders, secure e-MMAs, and daily remote brief motivational recovery support visits with supervised self-administration of buprenorphine via videoconferencing[335]. Future research about the e-MMA should aim at:

- quantitatively evaluating the validity of our findings in larger populations of patients with high perceived necessity of treatment, self-reported non-adherence, unforgiving treatments, low social support, and high psychologic distress. However, other alternatives should be considered for: on-demand treatments and problematic substance use.
- developing and implementing robust care models for older patients with polypharmacy and opioid-assisted therapy.
- evaluating the effectiveness of the e-MMA in terms of clinical, humanistic and economic outcomes.
- evaluating the long-term benefits and cost-effectiveness of the novel supply model.

Although currently not marketed for patients with OAT, the e-MMA evaluated in this thesis is expected to launch in the USA and other parts of Europe in the near future[336]. Other companies, including the pharmaceutical industry, start to consider adherence in the development of their products more often. Similar to standards for research in traditional drug development, the scientific evaluation of adherence interventions requires clear guidelines and best practice. A cornerstone has been laid with the ABC taxonomy of adherence in 2012[208]. Frameworks for planning and critiquing medication adherence research have been published for prospective study designs[337] and retrospective database research[338]. ESPACOMP, the European Society of Patient Adherence, Compliance, and Persistence, has recently developed the ESPACOMP Medication Adherence Reporting Guidelines (EMERGE) for the reporting of adherence research[339]. These efforts are needed, because adherence research during the past decades has struggled to provide consistent and convincing results for adherence interventions using classical randomized controlled trials (RCTs). This thesis showed that congruence between patients included for RCTs and interventions used in these studies was consistently low. Apart from the large heterogeneity and low methodological quality often cited as the reason for the inconsistent results, the choice of study design may play an important role as well. Population-based trials are indispensable to demonstrate safety and efficacy of treatments that should become available to the public. They may also be appropriate for public-health studies, for which the societal

perspective is of greater interest than effects on individuals. For a behavior such as adherence, with interventions that must be tailored to individual modifiable and unmodifiable determinants, study designs other than those focusing on mean group effects (i.e. RCTs) might be more appropriate. By definition, adherence interventions are designed to improve effectiveness, not efficacy of treatments. In the age of precision medicine and personalized healthcare, in which affordable devices that collect healthcare data of individuals become ubiquitous, research designs that account for individual variability should become standard to assess effectiveness as soon as safety and efficacy have been demonstrated for any intervention[340]. Especially in the field of polypharmacy, where no two patients receive the same treatments for the same diseases, single-subject research designs might be the solution to demonstrate effectiveness of adherence-enhancing interventions at the patient level.

Future research to improve adherence to polypharmacy should aim at:

- exploring the potential of the novel approach to use single-subject designs in adherence research.
- providing guidelines for the appropriate design and analyses of single-subject trials in adherence research, including recommendations for statistical analysis.
- developing instruments to reliably assess modifiable and unmodifiable determinants of non-adherence and to select appropriate interventions in research and practice.

This thesis provides first experiences with the use of single-subject research in combination with electronic monitoring of adherence. With a fraction of the costs of a large RCT, our results demonstrate the advantages and limitations, as well as potential target groups for the e-MMA. Our matched categories for determinants of non-adherence and interventions might provide guidance for the choice of interventions to be assessed during the course of such single-subject trials. Ultimately, solid single-case trials that are conducted as part of everyday pharmaceutical care might fill the gap between efficacy and effectiveness for medication treatments.

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Appendix

A.1. Project A1

A.1.1. Synopsis for workshop participants

PHARMACEUTICAL CARE NETWORK EUROPE

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Invitational conference PCNE 5th February 2013 in Berlin:

Redefining Pharmaceutical Care

Dear colleague,

On **Tuesday 5th February 2013** we will meet in Berlin, discuss different definitions of Pharmaceutical Care and hopefully end up with a (new) definition which we will call "The PCNE definition of Pharmaceutical Care".

Enclosed you receive a discussion paper which may help to clarify the current dilemmas around the concept and its definition and support a fruitful discussion.

This **synopsis** was compiled by Samuel Allemann, a novice PhD student from the University of Basel who got input from Foppe van Mil and Kurt Hersberger. Samuel performed an open literature research and established a synopsis for our discussion.

Please consider this document as a first draft and open to discussion.

23-01-2013

Prof. Dr. K.Hersberger
(PCNE Chairman, Basle, Switzerland)

Pharmaceutical Care Definitions: A Synopsis

Working paper

As a base for discussion around the definition of PC, an open literature search was performed using PubMed and Google Scholar. Cross-references provided additional sources for definitions not identified previously. Each source was scanned for explicit definitions of PC and references to existing definitions. With these techniques, 18 unique definitions of PC were identified. Additionally, background information such as the publisher of the definition or context of the publication (setting, type of work) were extracted where applicable (see Table 1).

The definitions were arranged according to year of publication and aspects of the definition. A list of possible attributes (the provider, recipient, subject, outcome and activity) was generated. With those attributes, the author's definitions were transcribed into generic definitions, each using a consistent syntax (see Figure 1).

Samuel Allemann, PhD Student, Department of Pharmaceutical Sciences, University of Basel 23-01-13

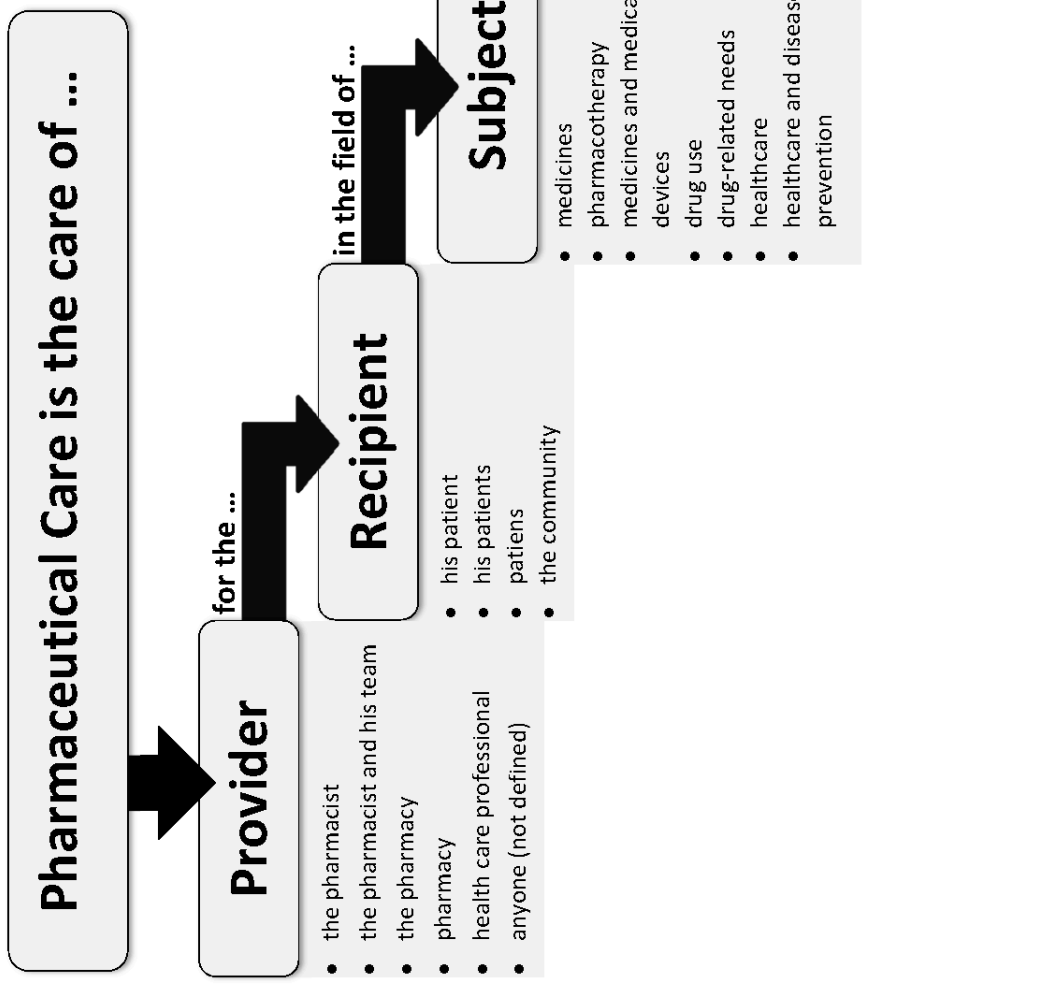


Figure 1: Possible attributes for the provider, recipient, subject, outcome and activity to specify the term Pharmaceutical Care

Samuel Allemann, PhD Student, Department of Pharmaceutical Sciences, University of Basel 23-01-13

Table 1: Pharmaceutical Care definitions and generic descriptions

Year	Author/Context	Definition	Generic Description
1975	Mikeal, R. L.;Brown, T. R.;Lazarus, H. L.;Vinson, M. C. **Place published** **Publisher** **Type of Work**	The care that a given patient requires and receives which assures safe and rational drug usage.	Pharmaceutical Care is the care of **anyone** for **his patient** in order to **assure optimal drug use**.
1980	Brodie, D. C.;Parish, P. A.;Poston, J. W. **Place published** **Publisher** **Type of Work**	Pharmaceutical care includes the determination of the drug needs for a given individual and the provision not only of the drugs required but also of the necessary services (before, during or after treatment) to assure optimally safe and effective therapy. It includes a feedback mechanism as a means of facilitating continuity of care by those who provide it.	Pharmaceutical Care is the care of **anyone** for **his patient** in the field of **pharmacotherapy and drug use** in order to **assure optimal pharmacotherapy**.
1987	Hepler, C. D. **Place published** **Publisher** **Type of Work**	A covenantal relationship between a patient and a pharmacist in which the pharmacist performs drug-use-control funtions (with appropriate knowledge and skill) governed by awareness of and commitment to the patients' interest.	Pharmaceutical Care is the care of **the pharmacist** in the field of **drug use** in order to **serve the interests of the patient**.
1990	Hepler, C. D.;Strand, L. M. **Place published** **Publisher** **Type of Work**	Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes which improve a patient's Quality of Life.	Pharmaceutical Care is the care of **anyone** for **his patient** in the field of **pharmacotherapy** in order to **assure (optimal) quality of life**.
1992	Strand, Linda M. **Place published** Michigan, USA **Publisher** Upjohn **Type of Work**	Pharmaceutical Care is that component of pharmacy practice which entails the direct interaction of the pharmacist with the patient for the purpose of caring for that patient's drug-related needs.	Pharmaceutical Care is the care of **the pharmacist** for **his patient** in the field of **drug-related needs.**

1993	American;Pharmacists, Society of Hospital **Place published** USA **Publisher** American Society of Hospital Pharmacists **Type of Work** Political Statement	Pharmaceutical care is the direct, responsible provision of medication-related care for the purpose of the achieving definite outcomes that improve a patient's quality of life.	Pharmaceutical Care is the care of **anyone** for **his patient** in the field of **pharmacotherapy** in order to **assure (optimal) quality of life**.
1993	Netherlands **Place published** **Publisher** **Type of Work**	Pharmqaceutical patient care (Farmaceutische Patiëntenzorg, FPZ) is the structured, intensive care of the pharmacist for an optimal pharmacotherapy in which the patient and his condition are the primary concern. The aim is to obtain optimal Health Related Quality of Life.	Pharmaceutical Care is the care of **the pharmacist** for **his patient** in the field of **pharmacotherapy** in order to **assure (optimal) quality of life**.
1996	Hepler, C. D. **Place published** Florida, USA **Publisher** Department of Pharmacy Health Care Administration **Type of Work**	The purpose of pharmaceutical care (in all practice settings) is to provide drug therapy intended to achieve definite outcomes that will improve a patient's quality of life.	Pharmaceutical Care is the care of **anyone** for **his patient** in the field of **pharmacotherapy** in order to **assure (optimal) quality of life**.
1997	Strand, L. M. **Place published** **Publisher** **Type of Work**	A practice for which the practitioner takes responsibility for a patient's drug therapy needs and is held accountable for this commitment.	Pharmaceutical Care is the care of **health care professional** for **his patient** in the field of **drug related needs**.
1998	Munroe, WP; Dalmady-Israel, C. **Place published** **Publisher** **Type of Work**	Pharmaceutical care as a service which systematically and continuously monitors the clinical and psychosocial effects of drug therapy on a patient.	Pharmaceutical Care is the care of **anyone** for **his patient** in the field of **pharmacotherapy**.
1999	Grandada Consensus **Place published** **Publisher** **Type of Work**	The detection, prevention and resolution of drug-related problems.	Pharmaceutical Care is the care of **anyone** in the field of **pharmacotherapy** by **detecting and resolving actual and potential drug related problems**.

2004	Cipolle, R. J.;Strand, L.; Morley, P. **Place published** New York **Publisher** MacGraw Hill **Type of Work** Book	Pharmaceutical care is a patient-centered practice in which the practitioner assumes responsibility for a patient's drug-related needs and is held accountable for this commitment. In the course of this practice, responsible drug therapy is provided for the purpose of achieving positive patient outcomes.	Pharmaceutical Care is the care of **health care professional** for **his patient** in the field of **pharmacotherapy** in order to **assure (optimal) outcomes of therapy** .
2004	van Mil, J. W.;Schulz, M.;Tromp, T. F. **Place published** Europe **Publisher** **Type of Work** Review	Pharmaceutical care is a practice philosophy for pharmacy. It is the way of pharmacists to coach the individual patients with their medication. The concept deals with the way a patient should receive and use medication and should receive education on the use of medicines. The concept also deals with responsibilities, medication surveillance, counseling and the evaluation of all the outcomes of care.	Pharmaceutical Care is the care of **the pharmacist** for **his patient** in the field of **pharmacotherapy** by **doing counseling and medication review *in order to evaluate the outcomes of care***.
2004	Berenguer, B.;La Casa, C.;de la Matta, M. J.;Martin-Calero, M. J. **Place published** **Publisher** **Type of Work**	The pharmacists' compromise to obtain the maximum benefit from the pharmacological treatments of the patients, being therefore responsible of monitoring their pharmacotherapy.	Pharmaceutical Care is the care of **the pharmacist** for **patients** in the field of **pharmacotherapy** in order to **assure maximum benefits of treatment**.
2005	Franklin, B. D.;van Mil, J. W. **Place published** **Publisher** **Type of Work** Editorial	the person-focused care relating to medication, which is provided by a pharmacist and the pharmacy team with the aim of improving the outcomes of therapy.	Pharmaceutical Care is the care of **the pharmacist and his team** for **his patient** in the field of **pharmacotherapy** in order to **assure (optimal) outcomes of therapy** .
2011	Sanchez, A. M. **Place published** Madrid, Spain **Publisher** **Type of Work** Commentary	Pharmaceutical care addresses the patient's drug-related needs comprehensively through a scheduled outline of tasks, in which the practitioner makes sure that the drug therapy is appropriately indicated, effective, safe, and convenient.	Pharmaceutical Care is the care of **health care professional** for **his patient** in the field of **drug-related needs** in order to **assure optimal pharmacotherapy**.

2012	Blackburn, D. F.;Yakiwchuk, E. M.;Jorgenson, D. J.;Mansell, K. D. **Place published** Canada **Publisher** College of Pharmacy and Nutrition **Type of Work** Commentary	A patient-centered practice in which the practitioner would be accountable for the drug-related needs of specific individuals as well as groups of patients within a defined practice setting who are at high risk for drug- or disease-induced morbidity.	Pharmaceutical Care is the care of **health care professional** for **patients** in the field of **drug-related needs**.
2012	Carollo, A.;Rieutord, A.;Launay-Vacher, V. **Place published** Europe **Publisher** ESCP **Type of Work** Guideline	The pharmaceutical contribution to patient care in identifying pharmaceutical care issues (medications-related issues) and establishing and administering a pharmaceutical care plan.	Pharmaceutical Care is the care of **anyone** for **patients** in the field of **drug-related needs** in order **assure (optimal) outcomes of therapy** by **detecting and resolving and monitoring actual and potential drug related problems**

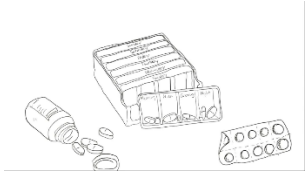
This document is seen as a first draft and open to discussion.

A.2. Project C1

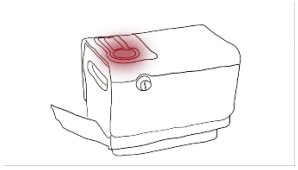
A.2.1. Video abstract

Accessible under https://youtu.be/J_4kUy0kgyc

Hello, my name is Samuel Allemann. I'm a PhD student of the Pharmaceutical Care Research Group from the University of Basel in Switzerland. Many people struggle with taking their medication as prescribed, especially when dealing with polypharmacy, meaning that they have to take multiple medications at the same time. The behavior of taking medication as prescribed is called medication adherence.



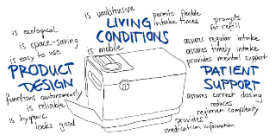
A simple method to improve adherence is the use of a pillbox that holds a predefined number of medication organized by day and time according to a patient's individual therapy plan. To judge if these interventions work, one has to measure adherence. This can be done simply by asking the patient, counting the remaining pills, looking at pharmacy claims data or use an electronic device that records date and time of medication removal.



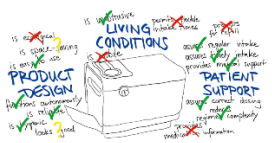
Recently, electronic pillboxes emerged, reminding patients with acoustic or visual alerts to take their medication, dispensing the right medication at the right time, and tracking each event. We wanted to know people's opinions on an electronic pillbox and for whom it may be suitable to use.

We gave the pillbox to 6 people and let them use it for 2 weeks.

Then all participants met for a focus group. First, we asked them what they thought were important attributes of a system assisting with their medication management.



Participants came up with 13 different attributes they thought were important. We added another 4 to a total of 17 attributes. We grouped the attributes into broader themes around product design, patient support and living conditions.



Second, we let them vote whether the electronic pillbox possessed these attributes or not. Participants rated 10 attributes as clearly applicable to the electronic pillbox. Five attributes were rated as unsuitable and the votes on 2 attributes were equally distributed.

Third, we wanted to know who they imagine could make use of such an electronic pillbox. Envisaged target groups were patients with time-sensitive medication regimens, patients with dementia, the visually impaired, and several patients living together to prevent accidental intake of the wrong medication.

Further prospective, randomized and controlled intervention trials should aim at quantitatively evaluating the validity of our findings in larger populations of these patients.

A.2.2. Focus group script

Date	05.06.2013	**Time**	14.00-16.00 Uhr	**Location**	
Objectives	• To gather information regarding the use of medido by patients • To gather and evaluate attributes of medication management systems important to patients • To evaluate the use of medido in connection with the attributes • To identify individuals which can benefit from medifilm/medido				
Methods	• Focus Group				
Responsibility	**IAr, SAI**				

Time	**Activity**	**Method**	**Outcome**	**Resp.**
14.00	Participants are welcomed and the aims of the focus group are outlined: *"Guten Tag. Danke, dass Sie sich die Zeit für uns nehmen.* *Mein Name ist Samuel Allemann, ich bin Doktorand an der Universität Basel und untersuche zusammen mit meiner Betreuerin, Frau Dr. Isabelle Arnet, den Medifilm und medido.* *Sie haben alle während zwei Wochen medifilm und medido zu Hause benützt. Medifilm und medido sind relativ neue Entwicklungen, deren Einsatz bei selbstständigen Personen, die zu Hause leben, kaum untersucht wurde. Aus Ihren Erfahrungen möchten wir ableiten, was Ihnen bei der Medikamenteneinnahme wichtig ist und für welche Personen medifilm und medido hilfreich bei der Organisation der Medikamenteneinnahme sein können."* *Outline agenda: Definitionen, Methodik, Ablauf*	Moderation	Establish setting for discussion, give background and aims.	SAI
14.20	Participants are asked to shortly introduce themselves and describe their previously/normally used medication managmenet system. *"Stellen Sie sich bitte der Reihe nach mit Ihrem Namen vor. Erzählen Sie bitte kurz, wie Sie Ihre Medikamenteneinnahme normalerweise organisieren, wenn Sie kein medido zu Hause haben: Wie oft nehmen Sie regelmässig Medikamente ein, wo bewahren Sie sie auf, wie erinnern Sie sich an die Einnahme."*	Participants speak in sequence	Bring participants closer together, opportunity to relate later comments to their previous/usual medication management system.	SAI
14.25	Participants are asked to individually identify important attributes of compliance aids and to write them on paper cards with a uniquely colored pen to identify every participant. *"Stellen Sie sich vor, Sie möchten ein Auto kaufen. Ein Auto dient vor allem dazu, jemanden von A nach B zu bringen. Trotzdem gibt es unzählige verschiedene Modelle mit verschiedenen Eigenschaften. Jedem sind andere Eigenschaften wichtig: Jemand möchte ein besonders schnelles Auto, einer anderen Person ist ein möglichst tiefer Benzinverbrauch wichtig, jemand Drittes bevorzugt ein Auto mit Einparkhilfe oder Tempomat.* *Denken Sie jetzt daran, wie Sie Ihre Medikamenteneinnahme organisieren. Bei der Organisation der Medikamenteneinnahme gibt es viele verschiedene Systeme. Jedes System dient vor allem dazu, Sie bei der Medikamenten-*	Participants write individually Moderation: • Flipchart with car and different attributes. • Flipchart with set of medication and question marks.	Collect individual opinions without being influenced by other participants or moderator. Participants create personal interest in discussion. Explain the task with an analogy to guide participants to the type of categories expected.	SAI SAI

	einnahme zu unterstützen. Alle haben aber verschiedene Eigenschaften. Notieren Sie jeder für sich Eigenschaften, die Ihnen ähnlich wie beim Autokauf wichtig sind, wenn Sie sich für das perfekte System zur Unterstützung bei der täglichen Medikamenteneinnahme entscheiden müssten. Denken Sie breit und versuchen Sie, so viele verschiedene Eigenschaften wie möglich zu finden. Schreiben Sie auf jede Karte nur einen Begriff."			
14.35	The cards are collected and arranged accordingly. See preliminary list at the end for possible attributes.	Backoffice: Organize Attributes to groups, write categories on Posters and add all attributes pertaining to the category below.		IAr
14.55	While the attributes are sorted, participants discuss the following question:	Open group discussion • Flipchart with medido	Asses user's experiences with medido not necessarily relating to attributes of the machine itself, but to the personal nature of the user and his or her attitude towards medido.	SAI
15.10	*"Sie haben medifilm und medido zwei Wochen lang benutzt. Denken Sie daran zurück, als sie die Maschine zum ersten Mal gesehen haben. Wie haben Sie medifilm und medido zu Beginn gefunden? Wie ist es heute?"* Coffee Break			
	"Wir haben nun über Ihre persönliche Haltung medifilm und medido gegenüber gesprochen. Vorhin haben Sie notiert, welche Eigenschaften Ihnen beim Medikamentenmanagement wichtig sind. Wir haben die Ergebnisse zusammengefasst und werden nun eine nach der andern durchgehen. Ich zeige Ihnen eine Eigenschaft und wir besprechen sie kurz, damit alle dasselbe darunter verstehen. Sie haben drei Jasskarten erhalten: Eine rote, eine schwarze und einen Joker. Überlegen Sie bei jeder Eigenschaft, ob diese für sie auf den medido zutrifft. Entscheiden Sie sich für ja, legen Sie die rote Karte verdeckt vor sich hin. Trifft die Eigenschaft für Sie nicht auf medido zu, legen Sie die schwarze Karte verdeckt vor sich hin. Können Sie sich nicht entscheiden, oder gibt es Gründe die sowohl dafür, als auch dagegen sprechen, legen Sie den Joker verdeckt vor sich hin. Wenn sich alle entschieden haben, drehen Sie die Karte für alle sichtbar um."	Open group discussion • Flipchart with cards: Black = agree, red = do not agree, Joker = undecided • Poster with categories and attributes	Consolidate attributes, so every participant understands and agrees on the meaning. Gather information on individual experiences with medido regarding different attributes Systematically collect every participant's opinion on every attribute while making sure that everyone considers each other's ideas.	SAI
15.30	For every attribute identified, we count the number of cards displayed by the participants. If all participants agree or disagree on the attribute, we move on to the next attribute. If they display both red and black cards, we discuss pros and cons. Whenever a Joker is displayed, we discuss the issues. After the discussion, there is another voting round where everyone has to decide on either the red or black card.			
15.50	*„Denken Sie an Personen aus Ihrem Bekanntenkreis oder aus der Familie, die auch regelmässig Medikamente einnehmen. Wem würden Sie medifilm und medido empfehlen und weshalb? Medifilm alleine?"*	Moderation • Flipchart with pictures of different people: Old, young, mobile, polypharmacy…	Profiling of medido	SAI
16.00	Wrap up, thank participants, outlook End			

A.2.3. Preliminary list of attributes

Categories and attributes

- Price
  - Must be affordable
  - Does not burden taxpayer
- Portability
  - Has to be portable
  - Unit-doses need to be detachable
  - Must not be too heavy
- Hygiene
  - Must be hygienic
  - Must be washable
- Handling
  - Must be easy to use
    - For persons with visual impairments
    - For persons with hearing impairments
    - For persons with dexterity issues
- Autonomy
  - Must be autonomous
  - Must be refilled by someone
  - Must leave me in control
  - Must not create a feeling of being controlled
  - Must accompany my medication taking
  - Must (not) remind me about my medication
- Reliability
  - Must always function
  - Must be fail-proof
  - Must function independent from continuous power-supply
- Unobtrusiveness
  - Must not be too big
  - Must look good
  - Must fit in a cupboard
  - Must be apparent
- Expenditure of time
  - Must not take up too much time
  - Must work quickly
  - Must not require additional effort
- Safety
  - Must contain right medicines
  - Intake times must be correct
  - Must show if medicines were taken or not
- Comprehensibility
  - Must be easy to understand
  - Must not be complicated
- Robustness
  - Must not break
  - Must be robust
- Ecology
  - Must not produce too much waste
  - Must not use too much power
  - Must be reusable

*Red = should be discussed

A.3. Project C4

A.3.1. Ethical approval EKNZ 2014-71

Beschlussmitteilung der Ethikkommission Nordwest- und Zentralschweiz

Die Ethikkommission Nordwest- und Zentralschweiz hat das nachstehende Forschungsprojekt anlässlich der Ausschuss-Sitzung vom 19. März 2014 (in der Zusammensetzung, wie sie auf Seite 2 wiedergegeben ist) eingehend begutachtet.

Titel des Forschungsprojektes Ref.Nr. **EKNZ: 2014-071**

Ferngesteuerte Medikamentenabgabe und elektronisches Adherence-Monitoring bei ambulanten Patienten mit Abhängigkeitssyndrom und Polymedikation

Prüfer/in

Name, Vorname, Titel:	Hersberger, Kurt E., Prof. Dr.
Funktion:	Leiter Pharmaceutical Care Research Group PCRG
Adresse:	Universität Basel, Klingelbergstrasse 50, 4056 Basel

Die Ethikkommission stützt ihre Beurteilung auf die Unterlagen, wie sie im Basisformular vom 30. Januar 2014 abschliessend aufgezählt sind.

☐ normales Verfahren **X** vereinfachtes Verfahren ☐ Nachbegutachtung

Die Ethikkommission kommt zu folgendem **Beschluss**:

X A positiv
☐ **B positiv mit Bemerkungen** (siehe Seite 2ff)
☐ **C mit Auflagen** (siehe Seite 2ff)
Nachbegutachtung durch Ethikkommission notwendig ☐
schriftliche Mitteilung an Ethikkommission ausreichend ☐
☐ **D negativ (mit Begründung und Erläuterung für die Neubeurteilung)** (siehe Seite 2ff)
☐ **E Nicht-Eintreten (mit Begründung)** (siehe Seite 2ff)

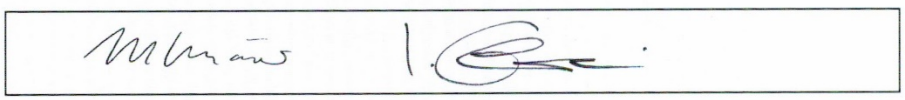
Der Beschluss gilt auch für die im "Antrag auf Begutachtung" gemeldeten weiteren Prüfer/innen im Zuständigkeitsbereich der Ethikkommission.

Pro Memoria: **Pflichten des/der verantwortlichen Prüfers/in**
- Geprüfte Produkte und Vergleichsprodukte (Arzneimittel und Medizinalprodukte) müssen - zur Sicherstellung der Qualität und der Sicherheit - fachgerecht hergestellt, evaluiert und eingesetzt werden.
- Meldepflicht bei:
  a) schwerwiegenden unerwünschten Ereignissen (serious adverse events) unverzüglich
  b) neuen Erkenntnissen, die während des Versuchs verfügbar werden und die Sicherheit der Versuchspersonen sowie die Weiterführung des Versuchs beeinflussen können
  c) Änderung des Protokolls (Versuchsplans)
  d) Ende oder Abbruch der Studie
- Zwischenbericht: einmal pro Jahr
- Meldungs- oder Bewilligungspflicht von Studien bei Swissmedic bzw. anderen Bundes- oder kantonalen Behörden - sofern erforderlich (bei sponsorisierten Studien ist dies die Pflicht des Sponsors)
- Schlussbericht

Für die Ethikkommission:

Ort, Datum: Basel, 16. Mai 2014 Name(n): Dr. M. Schärer
Fr. I. Oberli

Unterschrift(en):



Ref. Nr. EKNZ: 2014-071

Zusammensetzung der Ethikkommission

Die Ethikkommission tagte in der nachfolgend erwähnten Zusammensetzung und war damit beschlussfähig (Art. 32 der Verordnung über klinische Versuche mit Heilmitteln vom 17. 10. 2001)

					am Beschluss beteiligt	
	Name, Vorname	**Berufliche Stellung / Titel**	**m**	**f**	**ja**	**nein**
Vorsitz	Dr. M. Schärer	Vizepräsident der EKNZ	X	☐	X	☐
	Prof. T. Kühne	Ausschuss-Mitglied der EKNZ	X	☐	X	☐
	Prof. M. Kränzlin	Ausschuss-Mitglied der EKBB	X	☐	X	☐
	Dr. iur. J. Müller	Ausschuss-Mitglied der EKNZ	X	☐	X	☐

Empfehlungen

(erweiterbar)

Auflagen:

- **Die initialen Auflagen der EKNZ (siehe Schreiben vom 22. März 2014) wurden erfüllt.**

(erweiterbar)

Bemerkungen

- **Die EKNZ hat die nachfolgend erwähnten Dokumente zur oben genannten Studie zustimmend zur Kenntnis genommen:**
  - **Studienprotokoll - Version 2.0 vom 21. April 2014**
  - **TeilnehmerInneninformation und Einverständniserklärung - Version 2.0 vom 07. April 2014**
  - **Case Report Form - Version 2.0 vom 07. April 2014**
  - **Fragebogen ‚Patientenzufriedenheit'**
  - **GCP-Zertifikate Prof. Hersberger, Dres. M. Vogel, I. Arnet und K. Dürstler.**
- **Die EKNZ bestätigt, dass sie nach GCP-ICH-Richtlinien arbeitet.**

(erweiterbar)

A.3.2. Patient information and informed consent form

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Kurzfassung der Studieninformation	**Details Seite**
Ferngesteuerte Medikamentenabgabe und elektronisches Adherence-Monitoring bei ambulanten Patienten mit Abhängigkeitssyndrom und Polypharmazie – eine Machbarkeitsstudie	
Was wir Ihnen mitteilen wollen: Wir möchten Sie hiermit bitten, an unserem Forschungsprojekt teilzunehmen. Wir untersuchen Patienten mit Abhängigkeitssyndrom in einer opioidgestützten Substitutionstherapie, die täglich mehr als 3 Medikamente einnehmen. Sie befinden sich in einer opioidgestützten Substitutionstherapie und nehmen täglich mehr als 3 Medikamente ein. Deshalb lassen wir Ihnen diese Studieninformation zukommen. Ihr Arzt wird Sie beraten, welche weiteren Möglichkeiten zu Ihrer Behandlung bestehen.	
Was wir mit unserer Studie erreichen wollen: Wir möchten ein neues Versorgungsmodell mit einer ferngesteuerten Abgabe von Medikamenten bei Ihnen zu Hause untersuchen.	4
Was bedeutet die Teilnahme an der Studie für Sie: Sie werden wie gewohnt im ADS von Ihrem Arzt behandelt. Für die Dauer der Studie von 6 Monaten erhalten Sie einen elektronischen Dispenser. Der Dispenser enthält Ihre festen Medikamente. Die Verpackung der Substitutionsmedikamente ist in gewissen Fällen ebenfalls möglich. Alle 2-4 Wochen wird ein Studienmitarbeiter bei Ihnen zu Hause den Dispenser nachfüllen. Diese Besuche dauern in der Regel 10-30 Minuten und beinhalten ein kurzes Interview. 3 Monate nach Ende der Studie werden Sie zu einem Nachfolgetermin im ADS aufgeboten, wobei Sie dieselben Fragebogen wie zu Beginn ausfüllen müssen. Die Fragen betreffen Ihrer Lebensqualität, Therapietreue, Beikonsum, Alltagskompetenz und Zufriedenheit.	4-6
Welcher Nutzen und welches Risiko mit der Studie für Sie verbunden sind: Mit der Teilnahme an der Studie müssen Sie nicht mehr alle Medikamente im ADS beziehen, sondern erhalten alle festen Medikamente zu Hause aus einem elektronischen Dispenser. Als Studienteilnehmer gehören Sie zu den ersten Patienten in der Schweiz, die von dieser Möglichkeit profitieren können. Die Teilnahme an der Studie ist mit keinen zusätzlichen Risiken verbunden.	6
Welche Rechte Sie haben, wenn Sie an der Studie teilnehmen: Sie entscheiden frei, ob Sie an der Studie teilnehmen wollen oder nicht. Nicht-Teilnahme ändert nichts an Ihrer laufenden medizinischen Betreuung. Wenn Sie sich jetzt entscheiden teilzunehmen, können Sie jederzeit wieder aus der Studie aussteigen. Sie müssen Ihre Entscheidungen nicht begründen. Während der Studie erheben wir medizinische Daten über Sie. Wenn Sie später aussteigen, werden die erhobenen Daten bis zum Zeitpunkt Ihres Ausstiegs ausgewertet. Ihre Daten werden anonymisiert aufbewahrt.	5
Welche Pflichten mit der Teilnahme an der Studie für Sie verbunden sind: Wenn Sie teilnehmen, müssen Sie zu Ihrer Sicherheit bestimmte Regeln befolgen. Sie verpflichten sich dazu, den bei Ihnen zu Hause installierten Medikamenten-Dispenser sorgfältig gemäss Gebrauchsanweisung zu benützen. Während der Studiendauer von 6 Monaten können Sie die Schweiz nicht oder nur sehr beschränkt für kurze Zeit verlassen. Die Studienmitarbeiter müssen zum Nachfüllen des Dispensers Ihre Wohnung alle 2-4 Wochen für 10-30 Minuten betreten können.	6
Was mit Ihren Daten geschieht: Wir halten alle gesetzlichen Regeln des Datenschutzes ein. Wir verwenden Ihre Daten nur im Rahmen der Studie. Alle Beteiligten unterliegen der Schweigepflicht.	6-7

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Was Sie mit Ihrer Einwilligung bestätigen: Nebst dieser Kurzfassung finden Sie auf den nachfolgenden Seiten umfassende Zusatzinformationen. Diese sind integrierter Bestandteil der Information. Mit der Unterzeichnung der Einwilligungserklärung akzeptieren Sie das vollständige Dokument.	
An wen Sie sich wenden können: Sie können während den Bürozeiten auf alle Fragen betreffend der Studie Auskunft erhalten von Herrn Samuel Allemann, Studienmitglied, Tel. 061 267 15 19. Für alle Angelegenheiten, die Ihre medizinische Versorgung betrifft, bleibt Ihr Betreuer/Ihre Betreuerin vom ADS Ihre Ansprechsperson.	

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Prof. Kurt E. Hersberger

Ferngesteuerte Medikamentenabgabe und elektronisches Adherence-Monitoring bei ambulanten Patienten mit Abhängigkeitssyndrom und Polypharmazie – Eine Machbarbeitsstudie

Sehr geehrte Dame, sehr geehrter Herr

Wir sind Apotheker, die zusammen mit dem Ambulanten Dienst Sucht (ADS) der Universitären Psychiatrischen Kliniken (UPK) Basel diese Studie durchführen. Mein Name ist Samuel Allemann, ich bin verantwortlich für das Medikamenten-Abgabesystem. Sponsor dieser Studie ist das Departement Pharmazeutische Wissenschaften der Universität Basel.

1. Auswahl der Personen, die an der Studie teilnehmen können

Es können alle Personen teilnehmen, die beim Ambulanten Dienst Sucht (ADS) der Universitären Psychiatrischen Klinik (UPK) Basel in einer opioidgestützten Subtstitutionsbehandlung sind und täglich mehr als 3 Medikamente einnehmen müssen. Ausserdem müssen Sie älter als 18 Jahre alt sein.
Nicht teilnehmen hingegen dürfen Personen, die sich in einer heroingestützten Behandlung befinden. Auch nicht teilnehmen dürfen Personen, wenn sie keinen festen Wohnsitz im Kanton Basel-Stadt oder einer angrenzenden Gemeinde haben.

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2. Ziele der Studie

Wir wollen mit dieser Studie untersuchen, ob die ferngesteuerte, elektronische Abgabe von Medikamenten mit dem Dispenser Medido® ihre Versorgung verbessert. Der Dispenser hat die folgenden Eigenschaften:

- Elektronisch gesteuerte Abgabe von allen festen, oralen Medikamenten (Tabletten, Kapseln, Dragées, …) in dosisgenauen Verpackungseinheiten
- Kapazität für die Versorgung mit Medikamenten während 2-4 Wochen
- Überwachung der Gerätefunktion über Mobilfunk
- Elektronische Aufzeichnung der Medikamentenausgabe und
- Übermittlung der aufgezeichneten Daten an das Studienzentrum

3. Allgemeine Informationen zur Studie

- Zweck der Studie ist zu evaluieren, ob eine Versorgung aller Ihrer Medikamente mit einem elektronischen Dispenser bei Ihnen machbar ist und mit Vorteilen für das Erreichen Ihrer Therapieziele einhergeht. Der Dispenser medido® wird in den Niederlanden bei älteren Patienten zu Hause verwendet und von den holländischen Krankenkassen rückvergütet. In der Schweiz ist der Dispenser noch nicht verfügbar. Der Dispenser ist nach europäischen Normen zertifiziert und trägt das entsprechende CE-Zeichen
- Die Studie ist offen, d.h. alle Informationen sind von allen Beteiligten bekannt. Ihr Arzt hat vorgeschlagen, dass Sie Ihre Medikamente mit dem Dispenser erhalten.
- Die Studie dauert 6 Monate mit einem Folgetermin 3 Monate nach Studienende. Es werden insgesamt ca. 10 Personen an der Studie teilnehmen.
- Wir machen diese Studie so, wie es die Gesetze in der Schweiz vorschreiben. Ausserdem beachten wir alle international anerkannten Richtlinien. Die zuständige Kantonale Ethikkommission hat die Studie geprüft und bewilligt.
- Eine Beschreibung dieser Studie finden Sie auch auf der Internetseite des Bundesamtes für Gesundheit: www.kofam.ch; www.humanforschunginfo.ch.

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Prof. Kurt E. Hersberger

4. Ablauf für die Teilnehmenden

Die Studie dauert 6 Monate mit einer Nachkontrolle 3 Monate nach Ende der Studie. Die Visiten erfolgen im Rahmen der Routinetermine mit dem ADS oder beim Patienten zu Hause. Die studienspezifischen Untersuchungen umfassen Fragebogen zu Ihrer Lebensqualität, zu Beikonsum, Einnahmetreue der Medikamente und Zufriedenheit mit dem Dispenser. Einige dieser Fragebogen kennen Sie bereits vom ADS. Die Standarduntersuchungen für Ihre jeweiligen Erkrankungen werden im Fall einer Studienteilnahme ebenfalls ausgewertet, finden jedoch auch ohne Studienteilnahme statt. Zusätzlich werden Bezugsdaten des vergangenen Jahres aus den Unterlagen des ADS zu Vergleichszwecken ausgewertet.
Der Ablauf ist in der folgenden Tabelle zusammengefasst:

Zeitpunkt	Ort	Dauer	Was
Heute	ADS	Ca. 1 Stunde	• Unterzeichnung der Einverständniserklärung • Ausfüllen der Fragebogen ○ Lebensqualität ○ Psychische Symptome ○ Therapietreue (Adherence) ○ Beikonsum ○ Alltagskompetenz • Terminvereinbarung für die Installation des Dispensers
In ca. 1 Woche	Bei Ihnen zu Hause	Ca. 30 Minuten	• Installation des Dispensers • Kurzinterview
Alle 1-4 Wochen	Bei Ihnen zu Hause	Ca. 10-30 Minuten	• Nachfüllen des Dispensers • Ausfüllen der Fragebogen ○ Lebensqualität ○ Beikonsum • Kurzinterview ○ Zufriedenheit
In 24 Wochen	ADS	Ca. 1 Stunde	• Abschlussinterview ○ Zufriedenheit • Ausfüllen der Fragebogen ○ Lebensqualität ○ Psychische Symptome ○ Therapietreue (Adherence) ○ Beikonsum ○ Alltagskompetenz ○ Zufriedenheit
In 37 Wochen	ADS	Ca. 1 Stunde	• Ausfüllen der Fragebogen ○ Lebensqualität ○ Therapietreue (Adherence) ○ Beikonsum

5. Rechte der Teilnehmenden

Sie nehmen nur dann an dieser Studie teil, wenn *Sie* es wollen. Niemand darf Sie dazu in irgendeiner Weise drängen oder dazu überreden. Ihre laufende medizinische Behandlung geht genau gleich weiter, wenn Sie nicht mitmachen. Sie müssen nicht begründen, warum Sie nicht mitmachen wollen. Wenn Sie sich entscheiden mitzumachen, können sie diesen Entscheid jederzeit zurücknehmen. Sie müssen ebenfalls nicht begründen, wenn Sie aus der Studie aussteigen wollen.

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Prof. Kurt E. Hersberger

Sie dürfen jederzeit alle Fragen zur Studie stellen. Wenden Sie sich dazu bitte an die Person, die am Ende dieser Studieninformation genannt ist.

6. Pflichten der Teilnehmenden

Wenn Sie bei der Studie mitmachen, müssen Sie bestimmte Regeln beachten. Dies ist notwendig für Ihre Sicherheit und Gesundheit. Wir werden Sie dabei so gut wir können unterstützen. Als Studienteilnehmende/r sind Sie verpflichtet,

- den medizinischen Anweisungen Ihres Studienarztes zu folgen und sich an den Studienplan zu halten;
- Ihren Studienarzt über den Verlauf der Erkrankung zu informieren und neue Symptome, neue Beschwerden und Änderungen im Befinden zu melden;
- Ihren Studienarzt über die gleichzeitige Behandlung und Therapien bei einem anderen Arzt und über die Einnahme von Medikamenten zu informieren. Nennen Sie bitte alle Medikamente, auch solche, die Sie selbst gekauft haben, für die Sie kein Rezept brauchen, oder auch Kräutertees, pflanzliche Arzneien etc. Sie müssen uns auch Medikamente der Alternativmedizin nennen: Homöopathie, Spagyrik, etc.
- den bei Ihnen zu Hause installierten Dispenser sorgfältig gemäss Gebrauchsanweisung zu benützen.
- während der Studiendauer von 6 Monaten die Schweiz nicht oder nur sehr beschränkt für kurze Zeit verlassen. Falls Sie öfters unterwegs sind oder in den nächsten 6 Monaten vorhaben, Ihren Wohnort zu verlassen, wenden Sie sich bitte an die Person, die am Ende dieser Studieninformation genannt ist.
- dem Studienpersonal zum Nachfüllen des Dispensers alle 2-4 Wochen für 10-30 Minuten Zutritt zu Ihrer Wohnung zu gewähren.

7. Nutzen für die Teilnehmenden

Wenn Sie bei dieser Studie mitmachen, kann Ihnen das eventuell eine Verbesserung der regelmässigen Einnahme Ihrer Medikamente bringen, sowie weniger Bezugstermine im ADS. Ausserdem können die Resultate wichtig sein für andere, die ebenfalls in einer opioidgestützten Subtstitutionsbehandlung sind und täglich mehr als 3 Medikamente einnehmen.

8. Risiken und Belastungen für die Teilnehmenden

Da Sie für die Studie keine anderen als Ihre bereits verordneten Medikamente einnehmen müssen und keine studienspezifischen Eingriffe vorgenommen werden, sind Sie keinen zusätzlichen Risiken oder Belastungen ausgesetzt.
Wenn Sie bei dieser Studie mitmachen, so ist der Dispenser und alle studienspezifischen Leistungen während der Studiendauer für Sie kostenlos.

9. Andere Behandlungsmöglichkeiten

Sie müssen bei dieser Studie nicht mitmachen. Wenn Sie nicht mitmachen, können Sie weiterhin wie bisher Ihre Medikamente beim ADS beziehen.

10. Ergebnisse aus der Studie

Der Studienarzt wird Sie während der Studie über alle neuen Erkenntnisse informieren, die den Nutzen der Studie oder Ihre Sicherheit und somit Ihr Einwilligung zur Teilnahme an der Studie beeinflussen können. Sie werden die Information mündlich und schriftlich erhalten.

11. Vertraulichkeit der Daten

Wir werden für diese Studie Ihre persönlichen und medizinischen Daten erfassen. Diese Daten werden wir verschlüsseln, d.h. wir werden anstelle Ihres vollen Namens nur eine Kombination aus Nummern, Buchstaben und Geburtsjahr verwenden (z.B. AEw6504), um Sie zu kennzeichnen.

UNIVERSITÄT BASEL

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Prof. Kurt E. Hersberger

Einzig der Leiter der Studie weiss, wer sich hinter dieser Abkürzung verbirgt. Die Forschenden werden nur mit den so verschlüsselten Daten arbeiten.
Es kann sein, dass die Studie während des Ablaufs überprüft wird. Dies können die Behörden tun, die sie vorab kontrolliert und bewilligt haben. Auch diejenige Institution, die die Studie bezahlt, kann den Ablauf überprüfen lassen. Sie alle sorgen dafür, dass die Regeln eingehalten werden und Ihre Sicherheit nicht gefährdet wird. Dazu muss der Leiter der Studie eventuell Ihre persönlichen und medizinischen Daten für solche Kontrollen offenlegen. Ebenso kann es sein, dass im Fall eines Schadens ein Vertreter der Versicherung Ihre Daten ansehen muss. Das darf dann aber nur die Daten betreffen, die unbedingt gebraucht werden, um den Schadensfall zu erledigen.
Alle Personen, die mit der Studie in irgendeiner Weise zu tun haben, müssen absolute Vertraulichkeit wahren. Wir werden Ihren Namen nirgends, in keinem Bericht, keiner Publikation, nicht gedruckt und nicht im Internet, veröffentlichen.

Verantwortlich für die Einhaltung der nationalen und internationalen Richtlinien zum Datenschutz ist der Sponsor in der Schweiz resp. der Vertreter des ausländischen Sponsors in der Schweiz.

12. Weitere Verwendung von Material und Daten

Sie können jederzeit aus der Studie aussteigen, wenn Sie dies wünschen. Die medizinischen Daten, die wir bis dahin erhoben haben werden wir trotzdem auswerten, weil sonst die ganze Studie ihren Wert verlieren würde.
Danach werden wir Ihre Daten und Ihr Material anonymisieren, d.h. wir werden endgültig Ihren Namen darauf löschen. Niemand wird danach mehr erfahren können, dass die Daten und das Material von Ihnen stammten.

13. Entschädigung für Teilnehmende

Wenn Sie bei dieser Studie mitmachen, bekommen Sie dafür keine Entschädigung.

14. Deckung von Schäden

15. Finanzierung der Studie

Die Studie wird mehrheitlich von der Universität Basel bezahlt.

16. Kontaktperson(en)

Bei allen Unklarheiten, Befürchtungen oder Notfällen, die während der Studie oder danach auftreten, können Sie sich jederzeit an eine dieser Kontaktpersonen wenden.

Leiter der Studie: Dr. med. Marc Vogel
Vollständige Adresse: Universitäre Psychiatrische Kliniken Basel, Wilhelm Klein Strasse 27, CH-4025 Basel, Tel. +41 (0)61 325 51 12

Mitarbeiter: Dr. med. Hannes Strasser, Dr. Kenneth Dürsteler, Dr. Isabelle Arnet, Samuel Allemann

UNIVERSITÄT BASEL

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17. Glossar (Erklärungsbedürftige Begriffe)

- ADS: Ambulanten Dienst Sucht
- opioidgestützten Substitutionstherapie: opioidabhängigen Menschen erhalten ein Substitutionsmedikament in ausreichender Dosierung verschrieben
- UPK: Universitäre Psychiatrische Kliniken in Basel

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Prof. Kurt E. Hersberger

Schriftliche Einwilligungserklärung zur Teilnahme an einer Studie

- Bitte lesen Sie dieses Formular sorgfältig durch.
- Bitte fragen Sie, wenn Sie etwas nicht verstehen oder wissen möchten.

NUMMER DER STUDIE: (BEI DER ZUSTÄNDIGEN ETHIKKOMMISSION)	EKNZ 2014-071
TITEL DER STUDIE:	Ferngesteuerte Medikamentenabgabe und elektronisches Adherence-Monitoring bei ambulanten Patienten mit Abhängigkeitssyndrom und Polypharmazie
verantwortliche Institution (Sponsor)	Prof. Kurt E. Hersberger, Pharmaceutical Care Research Group, Universität Basel, Klingelbergstrasse 50, 4056 Basel
ORT DER DURCHFÜHRUNG:	Basel
Leiter / Leiterin der Studie	Dr. med. Marc Vogel
Teilnehmerin/Teilnehmer Name und Vorname in Druckbuchstaben: Geburtsdatum:	☐ weiblich ☐ männlich

- Ich wurde vom unterzeichnenden Arzt mündlich und schriftlich über den Zweck, den Ablauf der Studie mit dem Medikamentendispenser Medido®, über die zu erwartenden Wirkungen, über mögliche Vor- und Nachteile sowie über eventuelle Risiken informiert.
- Meine Fragen im Zusammenhang mit der Teilnahme an dieser Studie sind mir zufriedenstellend beantwortet worden. Ich kann die schriftliche Studieninformation vom 30.1.2014/Version 1 behalten und erhalte eine Kopie meiner schriftlichen Einwilligungserklärung. Ich akzeptiere den Inhalt der zur oben genannten Studie abgegebenen schriftlichen Studieninformation.
- Ich nehme an dieser Studie freiwillig teil. Ich kann jederzeit und ohne Angabe von Gründen meine Zustimmung zur Teilnahme widerrufen, ohne dass ich deswegen Nachteile bei der weiteren medizinischen Betreuung erleide.
- Ich hatte genügend Zeit, meine Entscheidung zu treffen.
- Ich weiss, dass mein Hausarzt über meine Teilnahme an der Studie informiert wird.
- Ich weiss, dass meine persönlichen Daten nur in verschlüsselter Form zu Forschungszwecken weitergegeben werden können. Ich bin einverstanden, dass die zuständigen Fachleute des Auftraggebers der Studie, der Behörden und der Kantonalen Ethikkommission zu Prüf- und Kontrollzwecken in meine Originaldaten Einsicht nehmen dürfen, jedoch unter strikter Einhaltung der Vertraulichkeit.
- Ich bin mir bewusst, dass die in der Teilnehmerinformation genannten Pflichten während der Studie einzuhalten sind. Im Interesse meiner Gesundheit kann mich der Leiter / die Leiterin jederzeit von der Studie ausschliessen.

Ort, Datum	Unterschrift Studienteilnehmerin/Studienteilnehmer

Bestätigung des Studienarztes: Hiermit bestätige ich, dass ich dieser Teilnehmerin/diesem Teilnehmer Wesen, Bedeutung und Tragweite der Studie erläutert habe. Ich versichere, alle im Zusammenhang mit dieser Studie stehenden Verpflichtungen gemäss dem geltenden Recht zu erfüllen. Sollte ich zu irgendeinem Zeitpunkt während der Durchführung der Studie von Aspekten erfahren, welche die Bereitschaft der Teilnehmerin/des Teilnehmers zur Teilnahme an der Studie beeinflussen könnten, werde ich sie/ihn umgehend darüber informieren.

Ort, Datum	Unterschrift der Studienärztin/des Studienarztes

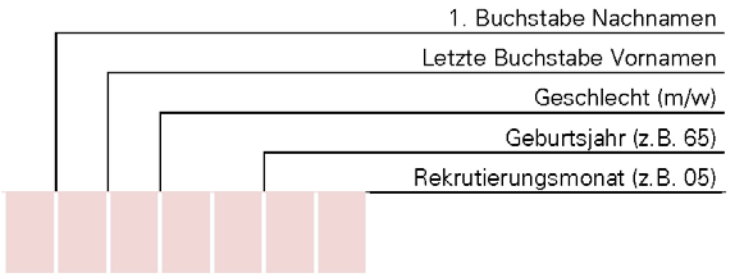
A.3.3. Case report form

Patientencode

Case Report Form

Ferngesteuerte Medikamentenabgabe und elektronisches Adherence-Monitoring bei ambulanten Patienten mit Abhängigkeitssyndrom und Polypharmazie – Eine Machbarkeitsstudie

Patientencode



Dispenser-Nr.:

Prüfer: _____ Visum: _____

Datum: _____ Unterschrift: _____

Case Report Form **Version 3.2**
02.03.2015

Patientencode

Nicht anonymisierte Kontaktdaten

Diese Seite ist nach der Erfassung getrennt vom CRF im Ethikdossier (Büro 476) aufzubewahren; eine Kopie wird in der Notfallapotheke hinterlegt.

Patient

Name*: _____ Vorname*: _____

Adresse*: _____ PLZ/Ort*: _____

Tel.#: _____ Mobile#: _____

Krankenkasse: _____ Kartennr.: _____

* Pflichtfelder.
# Falls keine eigene Kontaktnummer vorhanden ist, muss eine Kontaktperson angegeben werden, die im selben Haushalt lebt.

Kontaktperson

Name: _____ Vorname: _____

Tel.: _____ Mobile: _____

Zuständiger Betreuer im ADS

Name: _____ Vorname: _____

E-Mail: _____ Tel.: _____

Installation Dispenser

Der Installationszeitpunkt wird nach Absprache zwischen ADS, PCRG und Notfallapotheke festgelegt.

Datum: _____ Zeit: __ __ : __ __ Uhr

Bei der Dispenserinstallation hier und Seite 1 zu ergänzen:

Dispenser-Nr.: | | | | | | | | | | | | | | |

Regelung Ferienmitgabe

☐ Ferienmitgabe möglich Max. Anzahl Tage: _____ (länger nach Absprache mit ADS)
☐ Ferienmitgabe nur nach Absprache mit ADS möglich

Dispenser abgeschlossen? ☐ Ja ☐ Nein

Seite 3/20 Visum: _____

Case Report Form

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Medikationsplan (ohne Substitutionstherapie)

Blatt: ____

				Einnahmeschema			
Start	Stopp	Medikament / Wirkstoff / Gal. Form	Dosierung	__ : __ Uhr	__ : __ Uhr	__ : __ Uhr	__ : __ Uhr

Visum: _____

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Einschlusskriterien

	✓	x*
Der Patient ist mindestens 18 Jahre alt		
Der Patient hat die Einverständniserklärung unterschrieben		
Der Patient verfügt über Lese- und Schreibkompetenz in deutscher Sprache		
Der Patient hat einen festen Wohnsitz im Kanton Basel-Stadt oder einer angrenzenden Gemeinde		
Der Patient ist seit ≥2 Monaten in Substitutionsbehandlung beim ADS		
Der Patient nimmt täglich >3 feste, orale Medikamente ein		
Routinekontrolle der klinischen bzw. humanistischen Parameter vor weniger als 1 Woche erfolgt bzw. innerhalb 1 Woche ab Einschluss vereinbart		
Der Patient verfügt über eine gültige Krankenversicherung in der Schweiz		

*Falls ≥ 1 Einschlusskriterium **nicht zutrifft**, kann der Patient nicht an der Studie teilnehmen.

Ausschlusskriterien

	x	✓*
Der Patient ist in einer heroingestützten Behandlung		
>2 Medikamente, die nicht in Schlauchblister verpackt werden können (zB Flüssigkeiten)		

*Falls ≥ 1 Ausschlusskriterium **zutrifft**, kann der Patient nicht an der Studie teilnehmen.

T_1 – Einschluss

Datum: T T M M J J J J

Patienteninformation

Eine schriftliche Einverständniserklärung muss vom Patienten unterzeichnet werden bevor studienspezifische Massnahmen getroffen werden.

	✓	x
Hat der Patient aus freiem Wille eine schriftliche Einverständniserklärung unterschrieben?		
Ist die unterschriebene Einverständniserklärung in den Akten vorhanden?		

Visum: _____

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Demographie

Alter (Jahre) ☐☐ Geschlecht: weiblich ☐ männlich ☐

Beim ADS in Behandlung seit M M J J J J

Ausbildung

Welches ist die höchste Ausbildung, die Sie abgeschlossen haben?

- ☐ Obligatorische Schule
- ☐ Anlehre
- ☐ Berufslehre/-schule
- ☐ Maturitätsschule, DMS, HMS, FMS
- ☐ Höhere Fach- u. Berufsausbildung
- ☐ Universität, Fachhochschule

Wohn- /Arbeitssituation

1. Wohnen Sie … ☐ allein ☐ mit anderen
   → wie viele Personen leben mit Ihnen? ____
2. Haben Sie Kinder? ☐ Ja ☐ Nein
   → Falls Ja, wie viele leben mit Ihnen? ____
3. Gehen Sie einer bezahlten Tätigkeit ausserhalb von zu Hause nach?
   ☐ Ja ☐ Nein
4. Wie oft sind Sie an Werktagen (Mo bis Fr) tagsüber (7.00 bis 19.00 Uhr) zu Hause? Ein halber Tag entspricht 10%.

10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

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Anamnese Blatt ____

Code	Gebiet	Ja*	Nein
1	Herz-Kreislauf		
2	Atemwege		
3	Leber-Gallentrakt		
4	Gastrointestinaltrakt		
5	Urogenitaltrakt		
6	Endokrinologisch		
7	Hämatologisch		
8	Bewegungsapparat		

Code	Gebiet	Ja*	Nein
9	Neoplastisch		
10	Neurologisch		
11	Psychisch		
12	Immunologisch		
13	Dermatologisch		
14	Infektiologisch		
15	HNO-Trakt		
16	andere		

*Falls „Ja", Code für jede Erkrankung in die Tabelle unten eintragen und Details ergänzen. Bitte angeben, ob die Erkrankung behandelt wird.

			In Behandlung?	
Code		**Details** *inkl. Datum Erstmanifestation*	**Ja***	**Nein**
A				
B				
C				
D				
E				
F				
G				
H				

*Falls „Ja", Code mit fortlaufendem Buchstaben für jede Erkrankung in die Tabelle unten eintragen und Details ergänzen.

Code(s) mit Buchstaben	Behandelnder Arzt (Name, Adresse)	Hausarzt ▼

Visum: _____

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Klinische Parameter

Code(s) mit Buchstaben	Parameter	Messdatum*	Messwert

*Der letzte Messwert darf nicht mehr als 1 Woche vor T_1 erhoben worden sein.

	✓*	×
Haben Sie in den nächsten 3 Wochen einen Arzt-/Spitalbesuch geplant?		

* Falls zutreffend, bitte Details angeben:

Code mit Buchstaben	Details	Datum	Arzt/Spital

Substitutionsbehandlung

Medikament	Dosis/Tag	Bezüge/Woche

Visum: _____

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Patientencode

Fragebogen

	✓	x*
Der Fragebogen „Lebensqualität SCL-90R" ist in den Akten und ausgefüllt		

*Falls „Nein", wann wird der Fragebogen ausgefüllt? ☐ T_2 - Installation Dispenser

☐ anderes Datum: _____

	✓	x*
Der Fragebogen „Beikonsum" ist in den Akten und ausgefüllt		

*Falls „Nein", wann wird der Fragebogen ausgefüllt? ☐ T_2 - Installation Dispenser

☐ anderes Datum: _____

	✓	x*
Der Fragebogen „Adherence baseline" wurde ausgefüllt		

*Falls „Nein", wann wird der Fragebogen ausgefüllt? ☐ T_2 - Installation Dispenser

☐ anderes Datum: _____

	✓	x*
Der Fragebogen „Lebensqualität SF-12" wurde ausgefüllt		

*Falls „Nein", wann wird der Fragebogen ausgefüllt? ☐ T_2 - Installation Dispenser

☐ anderes Datum: _____

	✓	x*
Der Fragebogen „Alltagskompetenz" wurde ausgefüllt		

*Falls „Nein", wann wird der Fragebogen ausgefüllt? ☐ T_2 - Installation Dispenser

☐ anderes Datum: _____

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Datum: T T M M J J J J

T_2 – Dispenser Installation

Guten Tag, Herr/Frau «…», mein Name ist «…», ich bin «…» und komme heute mit Ihrem Betreuer/Ihrer Betreuerin «…» um den Medikamentendispenser zu installieren. Wie geht es Ihnen heute? .....

	×	✓*
Waren Sie in der letzten Woche ungeplant bei einem Arzt/in einem Spital?		
Haben Sie in den nächsten 3 Wochen einen Arzt-/Spitalbesuch geplant?		

* Falls zutreffend, bitte Details angeben:

Code der Anamnese (1-16)	Details	Datum	Arzt/Spital

	×	✓*
Haben sich Ihre Medikamente in der letzten Woche geändert?		

*Falls zutreffend, bitte Details angeben und Blatt „Medikationsplan" aktualisieren:

☐ Neuverordnung ☐ Stopp ☐ Dosisanpassung ☐ Substitution

Seite 12/20 Visum: _____

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Patientencode

Interviewleitfaden „Erwartung“

	✓	x*
Darf ich Ihnen ein paar Fragen zum Dispenser stellen?		
Ich würde Sie gerne auf Tonband aufnehmen, damit ich sicher nichts verpasse von dem, was Sie sagen. Ist das in Ordnung für Sie?		

* Falls abgelehnt, bitte begründen: _____

Wer hat Ihnen vorgeschlagen, den Dispenser auszuprobieren? « _____ »

Als «…» Ihnen vorgeschlagen hat, den Dispenser auszuprobieren, was ist Ihnen da durch den Kopf gegangen?

Was stellen Sie sich vor, wie wird sich der Dispenser auf Ihre Medikamenteneinnahme auswirken?

Was stellen Sie sich vor, wie wird sich der Dispenser auf Ihren Alltag auswirken?

	✓	x
Wurde das Kurzinterview gemäss Interviewleitfaden „Erwartung“ geführt?		

Instruktion Dispenser

	✓	x
Hat der Patient eine mündliche und schriftliche Instruktion zur Bedienung des Dispensers erhalten?		
Wissen Sie, wen Sie im Falle einer Funktionsstörung oder bei einer Frage zum Dispenser kontaktieren können?		

Refill-Termin

	✓	x*
Wurde bereits ein Refill-Termin vereinbart?		

*Falls nicht zutreffend, wann wird ein Termin vereinbart? Datum: T T M M J J J J

Wann findet der nächste Refill statt? Datum: T T M M J J J J

Visum: _____

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Datum: T T M M J J J J

☐ **T_3_ – Refill** ☐

Guten Tag, Herr/Frau «…», mein Name ist «…», ich komme heute um den Medikamentendispenser aufzufüllen. Wie geht es Ihnen heute? .....

	×	✓*
Waren Sie in der letzten Woche ungeplant bei einem Arzt/in einem Spital?		
Haben Sie in den nächsten 3 Wochen einen Arzt-/Spitalbesuch geplant?		

* Falls zutreffend, bitte Details angeben:

Code der Anamnese (1-16)	**Details**	**Datum**	**Arzt/Spital**

	×	✓*
Haben sich Ihre Medikamente in der letzten Woche geändert?		

* Falls zutreffend, bitte Details angeben und Blatt „Medikationsplan" aktualisieren:

☐ Neuverordnung ☐ Stopp ☐ Dosisanpassung ☐ Substitution

Visum: _____

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Patientencode

Erfahrung

Interviewleitfaden „Erfahrung"

	✓	x*
Darf ich Ihnen noch ein paar einfache Fragen zum Dispenser stellen?		
Ich würde Sie gerne auf Tonband aufnehmen, damit ich sicher nichts verpasse von dem, was Sie sagen. Ist das in Ordnung für Sie?		

* Falls abgelehnt, bitte begründen: _____

Sie dürfen frei und offen erzählen, was Sie denken. Es gibt kein richtig oder falsch.

Was haben Sie bisher mit dem Dispenser erlebt?

Wann hat Sie der Dispenser gestört?
- Was hat Sie in dieser Situation am Dispenser gestört?

Wann waren Sie über den Dispenser froh?
- Was fanden Sie in dieser Situation am Dispenser gut?

	✓	x
Wurde das Kurzinterview gemäss Interviewleitfaden „Erfahrung" geführt?		

Fragebogen

	✓	x
Der Fragebogen „Lebensqualität SF-12" wurde ausgefüllt		

	✓	x
Der Fragebogen „Beikonsum" wurde ausgefüllt		

Refill-Termin

	✓	x*
Wurde bereits ein Refill-Termin vereinbart?		

*Falls nicht zutreffend, wann wird ein Termin vereinbart? Datum: T T M M J J J J

Nächster Refill-Termin Datum: T T M M J J J J

Visum: _____

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Datum: T T M M J J J J

☐ T_4 – Schlussvisite

Wohn- /Arbeitssituation

1. Wohnen Sie … ☐ allein ☐ mit anderen
   ↳ wie viele Personen leben mit Ihnen? ____
2. Haben Sie Kinder? ☐ Ja ☐ Nein
   ↳ Falls Ja, wie viele leben mit Ihnen? ____
3. Gehen Sie einer bezahlten Tätigkeit ausserhalb von zu Hause nach?
   ☐ Ja ☐ Nein
4. Wie oft sind Sie an Werktagen (Mo bis Fr) tagsüber (7.00 bis 19.00 Uhr) zu Hause?
   Ein halber Tag entspricht 10%.

10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Dispenser-Rückgabe

	✓	x*
Wurde der Dispenser retourniert?		

*Falls nicht zutreffend, wann wird er retourniert? Datum: T T M M J J J J

	✓	x
Ist der Dispenser unbeschädigt?		
Ist das Netzteil vorhanden und unbeschädigt?		

Visum: _____

Case Report Form **Version 3.2**
02.03.2015

Patientencode

Klinische Parameter

Code der Anamnese (1-16)	Parameter	Messdatum*	Messwert

*Der letzte Messwert darf nicht mehr als 1 Woche vor oder nach T_5 erhoben werden.

Fragebogen

	✓	x*
Der Fragebogen „Adherence follow-up" wurde ausgefüllt		

*Falls „Nein", wann wird der Fragebogen ausgefüllt? ☐ anderes Datum: _____

	✓	x*
Der Fragebogen „Lebensqualität SF-12" wurde ausgefüllt		

*Falls „Nein", wann wird der Fragebogen ausgefüllt? ☐ anderes Datum: _____

	✓	x*
Der Fragebogen „Beikonsum" wurde ausgefüllt		

*Falls „Nein", wann wird der Fragebogen ausgefüllt? ☐ anderes Datum: _____

	✓	x*
Der Fragebogen „Alltagskompetenz" wurde ausgefüllt		

*Falls „Nein", wann wird der Fragebogen ausgefüllt? ☐ anderes Datum: _____

	✓	x*
Der Fragebogen „Zufriedenheit" wurde ausgefüllt		

*Falls „Nein", wann wird der Fragebogen ausgefüllt? ☐ anderes Datum: _____

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Interviewleitfaden „Erfahrung 2“

	✓	x*
Darf ich Ihnen noch ein paar einfache Fragen zum Dispenser stellen?		
Ich würde Sie gerne auf Tonband aufnehmen, damit ich sicher nichts verpasse von dem, was Sie sagen. Ist das in Ordnung für Sie?		

* Falls abgelehnt, bitte begründen: _____

Sie dürfen frei und offen erzählen, was Sie denken. Es gibt kein richtig oder falsch.

Wir haben zu Beginn der Studie darüber gesprochen, welche Erwartungen Sie an den Dispenser haben. Können Sie sich daran erinnern?

Sie hatten folgende Erwartungen, wie sich der Dispenser auf Ihre Medikamenten-einnahme auswirkt:

- .....
- .....
- .....
- .....

Wie haben sich diese Erwartungen für Sie erfüllt?

Sie hatten folgende Erwartungen, wie sich der Dispenser auf Ihren Alltag auswirkt:

- .....
- .....
- .....
- .....

Wie haben sich diese Erwartungen für Sie erfüllt?

	✓	x*
Wurde das Abschlussinterview gemäss Interviewleitfaden „Erfahrung 2“ geführt?		

Visum: _____

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Datum:

☐ T_5 – Follow Up

Wohn- /Arbeitssituation

1. Wohnen Sie … ☐ allein ☐ mit anderen
   ↳ wie viele Personen leben mit Ihnen? ____
2. Haben Sie Kinder? ☐ Ja ☐ Nein
   ↳ Falls Ja, wie viele leben mit Ihnen? ____
3. Gehen Sie einer bezahlten Tätigkeit ausserhalb von zu Hause nach?
   ☐ Ja ☐ Nein
4. Wie oft sind Sie an Werktagen (Mo bis Fr) tagsüber (7.00 bis 19.00 Uhr) zu Hause? Ein halber Tag entspricht 10%.

10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Klinische Parameter

Code der Anamnese (1-16)	Parameter	Messdatum*	Messwert

*Der letzte Messwert darf nicht mehr als 1 Woche vor oder nach T_5 erhoben werden.

Visum: _____

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Fragebogen

	✓	x*
Der Fragebogen „Adherence follow-up" wurde ausgefüllt		

*Falls „Nein", wann wird der Fragebogen ausgefüllt? ☐ anderes Datum: _____

	✓	x*
Der Fragebogen „Lebensqualität SF-12" wurde ausgefüllt		

*Falls „Nein", wann wird der Fragebogen ausgefüllt? ☐ anderes Datum: _____

	✓	x*
Der Fragebogen „Beikonsum" wurde ausgefüllt		

*Falls „Nein", wann wird der Fragebogen ausgefüllt? ☐ anderes Datum: _____

	✓	x*
Der Fragebogen „Alltagskompetenz" wurde ausgefüllt		

*Falls „Nein", wann wird der Fragebogen ausgefüllt? ☐ anderes Datum: _____

Visum: _____

A.3.4. ACTG baseline questionnaire (German version)

ACTG Adherence Baseline Questionnaire **v1.3**

Deutsche Übersetzung Samuel Allemann, PCRG Universität Basel

vom Interviewer auszufüllen

Datum: _____ Startzeit: _____ Patient Interviewer Beide

Patienten-ID: _____ Erfassung ☐ ☐ ☐

Ihre Antworten auf die folgenden Fragen werden dazu benützt, anderen Menschen mit komplizierten Therapien zu helfen. Bitte versuchen Sie, nach Möglichkeit alle Fragen zu beantworten. Wenn Sie eine Frage nicht beantworten möchten, streichen Sie sie bitte durch. Wenn Sie nicht wissen, wie Sie eine Frage beantworten sollen, fragen Sie eine Betreuungsperson. Vielen Dank für Ihre Mithilfe in dieser wichtigen Studie.

Anleitung: Bitte beantworten Sie die folgenden Fragen, indem Sie die zutreffende Zahl ankreuzen.

A. Wie sicher sind Sie, dass die folgenden Aussagen eintreffen werden?

Bitte kreuzen Sie für jede Aussage eine Antwort an.

	Überhaupt nicht sicher	Ziemlich sicher	Sehr sicher	Absolut sicher
1. Ich werde alle oder die meisten Medikamente gemäss Anweisung einnehmen können.	⓪	①	②	③
2. Die Medikamente werden sich positiv auf meine Gesundheit auswirken.	⓪	①	②	③
3. Falls ich die Medikamente nicht genau nach Vorschrift einnehme, wird sich meine Krankheit verschlimmern.	⓪	①	②	③

B. Die folgenden Aussagen betreffen Ihre soziale Unterstützung.

Bitte kreuzen Sie für jede Aussage eine Antwort an.

	Sehr unzufrieden	Ziemlich unzufrieden	Ziemlich zufrieden	Sehr zufrieden
1. Ich bin im Allgemeinen zufrieden mit der Unterstützung, die ich von meinen Freunden und Familienmitgliedern erhalte.	⓪	①	②	③

ACTG Adherence Baseline Questionnaire **v1.3**

Deutsche Übersetzung Samuel Allemann, PCRG Universität Basel

	Überhaupt nicht	Ein wenig	Ziemlich viel	Sehr viel	Keine Aussage möglich
2. Meine Freunde oder Familienmitglieder helfen mir, mich an meine Medikamenteneinnahme zu erinnern.	⓪	①	②	③	④

C. Es gibt verschiedene Gründe, weshalb Menschen ihre Medikamente möglicherweise nicht einnehmen. Hier ist eine Liste mit möglichen Gründen, weshalb Sie Ihre Medikamente in den letzten 4 Wochen eventuell nicht eingenommen haben.

☐ Ich habe in den letzten 4 Wochen KEINE Medikamente eingenommen → ankreuzen und weiter zu D.

Wie oft haben Sie in den letzten4 Wochen Ihre Medikamente NICHT eingenommen weil Sie:

Bitte kreuzen Sie für jede Aussage eine Antwort an.

	Nie	Selten	Manchmal	Oft
1. nicht zu Hause waren?	⓪	①	②	③
2. mit anderen Dingen beschäftigt waren?	⓪	①	②	③
3. es einfach vergessen haben?	⓪	①	②	③
4. zu viele Tabletten einzunehmen hatten?	⓪	①	②	③
5. Nebenwirkungen vermeiden wollten?	⓪	①	②	③
6. nicht wollten, dass andere Ihre Medikamenteneinnahme bemerken?	⓪	①	②	③
7. Ihre tägliche Routine geändert haben?	⓪	①	②	③
8. das Gefühl hatten, das Medikament sei giftig oder schädlich?	⓪	①	②	③
9. eingeschlafen sind/geschlafen haben zum Zeitpunkt der Einnahme?	⓪	①	②	③
10. sich unwohl oder krank fühlten?	⓪	①	②	③
11. sich niedergeschlagen/überfordert fühlten?	⓪	①	②	③
12. Probleme hatten, die Medikamente zu den vorgegebenen Zeiten einzunehmen (mit einer Mahlzeit, auf leerem Magen, etc.)?	⓪	①	②	③
13. keine Medikamente mehr hatten?	⓪	①	②	③
14. sich gut fühlten?	⓪	①	②	③

ACTG Adherence Baseline Questionnaire **v1.3**

Deutsche Übersetzung Samuel Allemann, PCRG Universität Basel

D. Wann haben Sie zum letzten Mal irgend eines Ihrer Medikamente nicht eingenommen? Bitte eine Antwort ankreuzen.

⑤ Innerhalb der **letzten Woche**

④ Vor **1–2 Wochen**

③ Vor **2–4 Wochen**

② Vor **1–3 Monaten**

① Vor **mehr als 3 Monaten**

⓪ Ich lasse **keine** Einnahme aus

⓪ Keine Antwort möglich

E. In der letzten Woche, wie oft kamen die folgenden Situationen vor:

Bitte kreuzen Sie für jede Aussage eine Antwort an.

	Nie/Selten	Manchmal	Oft	Meistens/ Immer
1. Ich hatte das Gefühl, die Schwermut nicht überwinden zu können, auch nicht mit Hilfe meiner Familie oder Freunde.	⓪	①	②	③
2. Ich hatte Mühe, mich auf das zu konzentrieren, was ich gerade tat.	⓪	①	②	③
3. Ich empfand alles was ich tat als anstrengend.	⓪	①	②	③
4. Ich hatte Probleme mit Schlafen.	⓪	①	②	③
5. Ich fühlte mich einsam.	⓪	①	②	③
6. Ich fühlte mich traurig.	⓪	①	②	③
7. Ich hatte das Gefühl, nicht richtig in Schwung zu kommen.	⓪	①	②	③

ACTG Adherence Baseline Questionnaire **v1.3**

Deutsche Übersetzung Samuel Allemann, PCRG Universität Basel

F. In den letzten 4 Wochen, wie oft haben Sie die folgenden Situationen erlebt:

Bitte kreuzen Sie für jede Aussage eine Antwort an.

	Nie	Fast nie	Manchmal	Oft	Sehr oft
1. Ich regte mich über etwas Unerwartetes auf.	⓪	①	②	③	④
2. Ich fühlte mich unfähig, die wichtigen Dinge in meinem Leben zu kontrollieren.	⓪	①	②	③	④
3. Ich fühlte mich nervös und gestresst.	⓪	①	②	③	④
4. Ich war zuversichtlich, meine persönlichen Probleme im Griff zu haben.	⓪	①	②	③	④
5. Ich hatte das Gefühl, die Dinge liefen so wie ich wollte.	⓪	①	②	③	④
6. Ich fühlte mich unfähig, alles Anstehende zu erledigen.	⓪	①	②	③	④
7. Ich fühlte mich fähig, mit Unannehmlichkeiten in meinem Leben umzugehen.	⓪	①	②	③	④
8. Ich hatte das Gefühl, alles im Griff zu haben.	⓪	①	②	③	④
9. Ich verspürte Ärger über Dinge, die ich nicht kontrollieren konnte.	⓪	①	②	③	④
10. Ich hatte das Gefühl, die Probleme wachsen mir über den Kopf.	⓪	①	②	③	④

G. Menschen haben verschiedene Gewohnheiten betreffend Gesundheit. Die folgenden Fragen betreffen Ihre Alkohol– und Drogenkonsum in der Vergangenheit und Gegenwart.

1. **In den letzten 4 Wochen, wie oft hatten Sie ein alkoholhaltiges Getränk – Bier, Wein, Schnaps, oder ein anderes Getränk mit Alkohol?** Bitte eine Antwort ankreuzen.

Täglich	Fast täglich	3–4 mal pro Woche	1–2 mal pro Woche	2–3 mal pro Monat	Einmal im Monat	Nie
⑥	⑤	④	③	②	①	⓪

Falls NIE: Weiter bei Frage Nr. **4**

ACTG Adherence Baseline Questionnaire **v1.3**

Deutsche Übersetzung Samuel Allemann, PCRG Universität Basel

2. **Denken Sie an die Tage in den letzten 4 Wochen, an denen Sie Alkohol getrunken haben. Im Allgemeinen, wie viele Einheiten tranken Sie insgesamt? Eine Einheit bedeutet eine 3.3 dl Büchse oder eine Stange Bier, 1 dl Wein, 4 cl Schnaps oder ein Mischgetränk mit 4 cl Schnaps.** Bitte eine Antwort ankreuzen.

1–2 pro Tag	3–4 pro Tag	5–6 pro Tag	7–8 pro Tag	9–11 pro Tag	≥ 12 pro Tag
⓪	①	②	③	④	⑤

3. **In den letzten 4 Wochen, wie oft hatten Sie 5 oder mehr alkoholische Getränke hintereinander, also innerhalb weniger Stunden (z.B. 2-4 Stunden)?** Bitte eine Antwort ankreuzen.

Täglich	Fast täglich	3–4 mal pro Woche	1–2 mal pro Woche	2–3 mal pro Monat	Einmal im Monat	Nie
⑥	⑤	④	③	②	①	⓪

4. Bitte kreuzen Sie für jede Frage „Ja“ oder „Nein“ an.

a. ② Nein ① Ja **Haben Sie jemals Marihuana konsumiert?**

Falls Sie diese Substanz konsumiert haben, haben Sie sie in den letzten 6 Monaten konsumiert?

① Ja ② Nein

b. ② Nein ① Ja **Haben Sie jemals Kokain (Pulver, Crack, Freebase) konsumiert?**

Falls Sie diese Substanz konsumiert haben, haben Sie sie in den letzten 6 Monaten konsumiert?

① Ja ② Nein

c. ② Nein ① Ja **Haben Sie jemals Heroin konsumiert?**

Falls Sie diese Substanz konsumiert haben, haben Sie sie in den letzten 6 Monaten konsumiert?

① Ja ② Nein

d. ② Nein ① Ja **Haben Sie jemals Amphetamine (Speed) konsumiert?**

Falls Sie diese Substanz konsumiert haben, haben Sie sie in den letzten 6 Monaten konsumiert?

① Ja ② Nein

5. **Sind Sie momentan in einer Substitutionstherapie?** ① Ja ② Nein

Falls Ja → Weiter bei Frage **H.**

Falls **Nein**, waren Sie jemals in einer Substitutionstherapie? ① Ja ② Nein

ACTG Adherence Baseline Questionnaire **v1.3**

Deutsche Übersetzung Samuel Allemann, PCRG Universität Basel

H. Die letzten Fragen betreffen Ihren Hintergrund.

1. **Welches ist die höchste Ausbildung, die Sie abgeschlossen haben?** Bitte eine Antwort ankreuzen.

   ⓪ Weniger als 7 Jahre Schule
   ① Obligatorische Schule
   ② Anlehre
   ③ Berufslehre/-schule
   ④ Maturitätsschule, DMS, HMS, FMS
   ⑤ Höhere Fach- u. Berufsausbildung
   ⑥ Universität, Fachhochschule

2. **Gehen Sie einer bezahlten Tätigkeit ausserhalb von zu Hause nach?** ① Ja ② Nein

3. **Haben Sie Kinder?** ① Ja ② Nein
   ↳ Fall **Ja**, wie viele leben mit Ihnen? ____

Vielen Dank für das vollständige Ausfüllen dieses Fragebogens.

vom Interviewer auszufüllen

Endzeit: _____ Visum: _____

A.3.5. ACTG follow-up questionnaire (German version)

ACTG Adherence Follow Up Questionnaire **v1.2**

Deutsche Übersetzung Samuel Allemann, PCRG Universität Basel

vom Interviewer auszufüllen

		Patient	Interviewer	Beide
Datum: _____				
Patienten-ID: _____	Erfassung	☐	☐	☐

DIESE SEITE MUSS VON PATIENT UND STUDIENPERSONAL ZUSAMMEN AUSGEFÜLLT WERDEN

A. Sie nehmen zurzeit die folgenden Medikamente in den aufgeführten Mengen und Häufigkeiten ein:

Medikamentenname/Stärke	Tabletten pro Dosis	Dosis/Dosen pro Tag

ACTG Adherence Follow Up Questionnaire **v1.2**

Deutsche Übersetzung Samuel Allemann, PCRG Universität Basel

Ihre Antworten auf die folgenden Fragen werden dazu benützt, anderen Menschen mit komplizierten Therapien zu helfen. Bitte versuchen Sie, nach Möglichkeit alle Fragen zu beantworten. Wenn Sie eine Frage nicht beantworten möchten, streichen Sie sie bitte durch. Wenn Sie nicht wissen, wie Sie eine Frage beantworten sollen, fragen Sie eine Betreuungsperson. Vielen Dank für Ihre Mithilfe in dieser wichtigen Studie.

Die nächsten Fragen betreffen die Medikamente, die Sie während der letzten 7 Tage eingenommen haben.

Die meisten Personen mit Ihrer Krankheit haben mehrere Medikamente, die sie zu verschiedenen Tageszeiten einnehmen müssen. Viele Menschen empfinden es als schwierig, sich immer an die Medikamente zu erinnern:

- Manche Menschen sind beschäftigt und vergessen, ihre Medikamente mitzunehmen.
- Manche Menschen empfinden es als schwierig, ihre Medikamente gemäss allen Anweisungen einzunehmen, z.B. “mit einer Mahlzeit” oder “auf leeren Magen”, “alle 8 Stunden”, “mit viel Flüssigkeit”.
- Manche Menschen beschliessen, die Einnahme auszulassen um Nebenwirkungen zu vermeiden oder sie wollen an diesem Tag einfach keine Medikamente einnehmen.

Wir möchten verstehen, wie Menschen mit Ihrer Krankheit tatsächlich mit ihren Medikamenten umgehen. Bitte teilen Sie uns mit, was Sie **tatsächlich** tun. Haben Sie keine Angst, uns zu sagen, dass Sie einige Ihrer Medikamente nicht einnehmen. Wir müssen wissen, was in Wirklichkeit geschieht; nicht was Sie denken, dass wir hören möchten.

ACTG Adherence Follow Up Questionnaire **v1.2**

Deutsche Übersetzung Samuel Allemann, PCRG Universität Basel

1. **Denken Sie an alle Tabletten, welche Sie während der letzten 7 Tage möglicherweise NICHT eingenommen haben.** Bitte füllen Sie die Tabelle mit einer Zahl pro Zelle und Medikament aus.

SOLLTEN SIE NICHT ALLE TABLETTEN EINER DOSIS EINGENOMMEN HABEN, ZÄHLEN SIE DIE GANZE DOSIS BITTE ALS "NICHT EINGENOMMEN".

Schritt 1 Name Ihrer Medikamente	**Wie viele Dosen haben Sie ausgelassen …**						
	Schritt 2 Gestern	**Schritt 3** Vorgestern (Vor 2 Tagen)	**Schritt 4** Vor 3 Tagen	**Schritt 5** Vor 4 Tagen	**Schritt 6** Vor 5 Tagen	**Schritt 7** Vor 6 Tagen	**Schritt 8** Vor 7 Tagen

ACTG Adherence Follow Up Questionnaire **v1.2**

Deutsche Übersetzung Samuel Allemann, PCRG Universität Basel

Die nächsten Fragen betreffen den Medikamentenplan auf der vorherigen Seite.

Sollten Sie nicht alle Tabletten einer Dosis eingenommen haben, zählen Sie die Dosis bitte als "nicht eingenommen".

B. Während der letzten 7 Tage, an wie vielen Tagen haben Sie alle Dosen ausgelassen?

- ☐ An keinem Tag
- ☐ An einem Tag
- ☐ An zwei Tagen
- ☐ An drei Tagen
- ☐ An vier Tagen
- ☐ An fünf Tagen
- ☐ An sechs Tagen
- ☐ An sieben Tagen
- ☐ Am Wochenende

C. Die meisten Medikamente müssen nach einem bestimmten Zeitplan eingenommen werden, z.B. "2 mal pro Tag" oder "3 mal am Tag" oder "alle 8 Stunden". Wie genau sind Sie in den letzten sieben Tagen Ihrem Zeitplan gefolgt?

Nie	Manchmal	Ungefähr die Hälfte der Zeit	Meistens	Immer
⓪	①	②	③	④

D. Hat eines oder mehrere Ihrer Medikamente spezielle Anweisungen, wie "mit Nahrung einnehmen" oder "auf leeren Magen" oder "mit viel Flüssigkeit einnehmen"?

① Ja ② Nein → ankreuzen und weiter zu Frage **E.**

↳ Falls **Ja**, wie oft haben Sie diese Anweisungen in den letzten sieben Tagen eingehalten?

Nie	Manchmal	Ungefähr die Hälfte der Zeit	Meistens	Immer
⓪	①	②	③	④

E. Manche Menschen merken, dass sie ihre Medikamente an Wochenend-Tagen vergessen. Haben Sie es am letzten Wochenende (Samstag oder Sonntag) verpasst, eines oder mehrere Ihrer Medikamente einzunehmen?

① Ja ② Nein

ACTG Adherence Follow Up Questionnaire **v1.2**

Deutsche Übersetzung Samuel Allemann, PCRG Universität Basel

F. Wann haben Sie zum letzten Mal eines Ihrer Medikamente nicht eingenommen? Bitte eine Antwort ankreuzen.

⑤ Innerhalb der **letzten Woche**

④ Vor **1–2 Wochen**

③ Vor **2–4 Wochen**

② Vor **1–3 Monaten**

① Vor **mehr als 3 Monaten**

⓪ Ich lasse **keine** Einnahme aus

⓪ Keine Antwort möglich

G. Es gibt verschiedene Gründe, weshalb Menschen ihre Medikamente manchmal nicht einnehmen. Hier ist eine Liste mit möglichen Gründen, weshalb Sie Ihre Medikamente in den letzten 4 Wochen eventuell nicht eingenommen haben.

Wie oft haben Sie in den letzten 4 Wochen Ihre Medikamente NICHT eingenommen weil Sie:

Bitte kreuzen Sie für jede Aussage eine Antwort an.

	Nie	Selten	Manchmal	Oft
1. Nicht zu Hause waren?	⓪	①	②	③
2. Mit anderen Dingen beschäftigt waren?	⓪	①	②	③
3. Es einfach vergessen haben?	⓪	①	②	③
4. Zu viele Tabletten einzunehmen hatten?	⓪	①	②	③
5. Nebenwirkungen vermeiden wollten?	⓪	①	②	③
6. Nicht wollten, dass andere Ihre Medikamenteneinnahme bemerken?	⓪	①	②	③
7. Ihre tägliche Routine geändert haben?	⓪	①	②	③
8. Das Gefühl hatten, das Medikament sei giftig oder schädlich?	⓪	①	②	③
9. Eingeschlafen sind/geschlafen haben zum Zeitpunkt der Einnahme?	⓪	①	②	③
10. Sich unwohl oder krank fühlten?	⓪	①	②	③
11. Sich niedergeschlagen/überfordert fühlten?	⓪	①	②	③
12. Probleme hatten, die Medikamente zu den vorgegebenen Zeiten einzunehmen (mit einer Mahlzeit, auf leerem Magen, etc.)?	⓪	①	②	③
13. Keine Medikamente mehr hatten?	⓪	①	②	③
14. Sich gut fühlten?	⓪	①	②	③

Vielen Dank für das vollständige Ausfüllen dieses Fragebogens.

A.3.6. Satisfaction questionnaire

vom Interviewer auszufüllen

Datum: _____ Startzeit: _____ Patient Interviewer Beide

Patienten-ID: _____ Erfassung ☐ ☐ ☐

Sie haben in den letzten Monaten an der Dispenserstudie teilgenommen. Herzlichen Dank! Uns interessiert, welche Erfahrungen Sie gemacht haben und wie Sie mit der Versorgung mit Ihren Medikamenten (d.h. wie Ihre Medikamente bis zu Ihnen kamen) und mit dem Dispenser (d.h. der metallische Behälter mit Ihrer Medikamentenrolle) zufrieden sind. Es gibt kein „richtig" oder „falsch", bitte kreuzen Sie an, ob die untenstehenden 27 Aussagen für Sie zutreffen. Es dauert ca. 6 Min.

Medikamentenversorgung	Stimme voll zu	Stimme eher zu	Stimme eher nicht zu	Stimme gar nicht zu	weiss nicht
Ich fühlte mich während den letzten 3 Monaten gut betreut, was meine Medikamente angeht.	☐	☐	☐	☐	☐
Wenn ich Fragen / Probleme hatte, wusste ich, an wen ich mich wenden konnte.	☐	☐	☐	☐	☐
Die Besuche bei mir zu Hause waren für mich unangenehm.	☐	☐	☐	☐	☐
Ich möchte den Dispenser auch in Zukunft benutzen.	☐	☐	☐	☐	☐
Die Versorgung zu Hause schränkte meine sozialen Kontakte ein.	☐	☐	☐	☐	☐
Ich möchte auch meine Substitutions-medikamente (z.B. Methadon) aus dem Dispenser erhalten.	☐	☐	☐	☐	☐
Die Versorgung zu Hause hat den Kontakt zu meinen Betreuern im ADS erschwert.	☐	☐	☐	☐	☐
Es bereitet mir Mühe, meine Medikamente im ADS abzuholen.	☐	☐	☐	☐	☐
Wenn Fragen / Probleme auftraten, wurden diese schnell gelöst.	☐	☐	☐	☐	☐

Patientenzufriedenheit **Version 2**
15.07.2015

Der Dispenser ...	Stimme voll zu	Stimme eher zu	Stimme eher nicht zu	Stimme gar nicht zu	weiss nicht
... ist einfach zu bedienen.	☐	☐	☐	☐	☐
... funktioniert jederzeit einwandfrei.	☐	☐	☐	☐	☐
... unterstützt mich bei der Einnahme meiner Medikamente.	☐	☐	☐	☐	☐
... gibt mir ein Gefühl von Sicherheit.	☐	☐	☐	☐	☐
... ist hygienisch.	☐	☐	☐	☐	☐
... stört, weil ich zu fixen Zeiten zu Hause sein muss.	☐	☐	☐	☐	☐
... beeinträchtigt mich in meinem Alltag.	☐	☐	☐	☐	☐
... lässt sich unauffällig platzieren.	☐	☐	☐	☐	☐
... gefällt mir optisch gut.	☐	☐	☐	☐	☐
... nimmt zu viel Platz ein.	☐	☐	☐	☐	☐
... liefert mir genügende Informationen zu meinen Medikamenten.	☐	☐	☐	☐	☐
... vereinfacht meine Therapie.	☐	☐	☐	☐	☐
... vereinfacht mein Leben.	☐	☐	☐	☐	☐
... hilft mir, meine Medikamente pünktlich einzunehmen.	☐	☐	☐	☐	☐
... hilft mir, meine Medikamente regelmässig einzunehmen.	☐	☐	☐	☐	☐
... hilft mir, meine Medikamente in der richtigen Dosis einzunehmen.	☐	☐	☐	☐	☐
... beruhigt mich, dass ich meine Medikamente richtig einnehme.	☐	☐	☐	☐	☐
... gibt mir das Gefühl, ständig überwacht zu sein.	☐	☐	☐	☐	☐

vom Interviewer auszufüllen

Endzeit: _____ Visum: _____

A.3.7. eMMA instruction

Medido® Spender
für Medikamentenblister

Erläuterung der Farben der Kontrollleuchten:

Grün
Im normalen Betrieb leuchtet das Lämpchen des Schalters grün. Das bedeutet, dass zwischen dem Spender und dem Gesundheitszentrum eine Verbindung besteht und der Wochenzeitplan von Ihnen eingehalten wurde.

Rot blinken + Alarmton:
Sie haben die Medikamente nicht zum geplanten Zeitpunkt eingenommen. Drücken Sie auf den Schalter **OK**, um den nächsten Medikamentenbeutel auszugeben.

Gelb und grün blinken:
Der Beutel wurde während des Hinweiszeitraums nicht ausgegeben. Wenn die Medikamente jetzt eingenommen werden sollen, drücken Sie für 2 Sekunden auf den Schalter OK.

Blau
Der Spender kommuniziert mit dem Gesundheitszentrum.

Rot
Es ist ein Fehler aufgetreten. Bitte kontaktieren Sie die Studienhotline: **077 442 85 23**

Medikamentendispenser-Studie EKNZ 2014-071, V1 / August 2014

DEPARTMENT
OF PHARMACEUTICAL SCIENCES

Pharmaceutical Care Research Group
Klingelbergstrasse 50
4056 Basel

Studienhotline bei technischen Problemen:
077 442 85 23

Phase A

Sie entnehmen die Medikamente selbstständig aus dem Dispenser. Innerhalb von 4 Stunden vor oder nach dem geplanten Zeitpunkt für die Einnahme können Sie die Medikamente ausgeben.
Dazu drücken Sie den Schalter **OK** für **vier Sekunden**. Das Licht des Schalters wird blau. Nach vier Sekunden ertönt ein Alarmsignal. Sobald Sie den Schalter loslassen, werden die Medikamente ausgegeben.
Die Beutel sind an der Ecke der Schweißnaht eingeschnitten. Entnehmen Sie die Medikamente erst dann, wenn Sie sie auch einnehmen werden. Wenn Sie dem Spender einen Medikamentenbeutel entnehmen, wird eine Mitteilung an das Gesundheits-zentrum gesendet.

Falls Sie zum geplanten Zeitpunkt der Einnahme nicht zu Hause sein werden, können Sie die Medikamente frühestens 8 Stunden vorher entnehmen. Falls Sie die Medikamente früher benötigen oder mehrere Tage verreisen, kontaktieren Sie bitte den ADS.

Vor dem Entfernen des Netzsteckers muss das Gerät an der linken Seite ausgeschaltet werden (oranger Schalter auf „0“)!

Medido® Spender
für Medikamentenblister

DEPARTMENT
OF PHARMACEUTICAL SCIENCES

Pharmaceutical Care Research Group
Klingelbergstrasse 50
4056 Basel

Studienhotline bei technischen Problemen:
077 442 85 23

Erläuterung der Farben der Kontrollleuchten:

Grün
Im normalen Betrieb leuchtet das Lämpchen des Schalters grün. Das bedeutet, dass zwischen dem Spender und dem Gesundheitszentrum eine Verbindung besteht und der Wochenzeitplan von Ihnen eingehalten wurde.

Rot blinken + Alarmton:
Es ist Zeit zur Einnahme der Medikamente. Drücken Sie auf den Schalter **OK**, um den nächsten Medikamentenbeutel auszugeben.

Gelb und grün blinken:
Der Beutel wurde während des Hinweiszeitraums nicht ausgegeben. Wenn die Medikamente jetzt eingenommen werden sollen, drücken Sie für 2 Sekunden auf den Schalter OK.

Blau
Der Spender kommuniziert mit dem Gesundheitszentrum.

Rot
Es ist ein Fehler aufgetreten. Bitte kontaktieren Sie die Studienhotline: **077 442 85 23**

Wenn der Einnahmezeitpunkt erreicht ist, gibt der Spender einen Alarmton aus, die Kontrolleuchten blinken rot und die Mitteilung **„MEDIKAMENTEN-ALARM“** wird angezeigt. Durch Drücken des Schalters **OK** wird das Medikament ausgegeben. Wenn Sie dem Spender einen Medikamentenbeutel entnehmen, wird eine Mitteilung an das Gesundheitszentrum gesendet.

Sie können dem Spender mehr als einen Medikamentenbeutel zugleich entnehmen, wenn Sie einige Zeit nicht zu Hause sind. Dazu drücken Sie den Schalter OK für vier Sekunden. Das Licht des Schalters wird blau. Nach vier Sekunden ertönt ein Alarmsignal und der Beutel wird ausgegeben. Die Beutel sind an der Ecke der Schweißnaht eingeschnitten. Diesen Vorgang wiederholen Sie, um weitere Beutel zu entnehmen. Wenn Sie dem Spender einen Medikamentenbeutel vorzeitig entnehmen, wird eine Mitteilung an das Gesundheitszentrum gesendet.

Vor dem Entfernen des Netzsteckers muss das Gerät an der linken Seite ausgeschaltet werden (oranger Schalter auf „0“)!

innospense

Medikamentendispenser-Studie EKNZ 2014-071, V1 / August 2014

A.3.8. Standard operation procedures

STANDARD OPERATING PROCEDURE
SOP No: EKNZ-2014-071.T1-1
SOP Titel: Patienteneinschluss

DEPARTMENT
OF PHARMACEUTICAL SCIENCES

SOP Nummer EKNZ-2014-071.T1-1
SOP Titel Patienteneinschluss

	NAME	TITEL	UNTERSCHRIFT	DATUM
Autor				
Review				
Freigabe				

Effektives Datum:	
Review Datum:	

Gelesen			
NAME	**TITEL**	**UNTERSCHRIFT**	**DATUM**

STANDARD OPERATING PROCEDURE
SOP No: EKNZ-2014-071.T1-1
SOP Titel: Patienteneinschluss

DEPARTMENT
OF PHARMACEUTICAL SCIENCES

Inhalt

STANDARD OPERATING PROCEDURE

SOP No: EKNZ-2014-071.T1-1

SOP Titel: Patienteneinschluss

DEPARTMENT
OF PHARMACEUTICAL SCIENCES

1. ZWECK

Rekrutierung/Einschluss der Patienten in die Studie, gemäß des Ethik-Antrags.

2. EINLEITUNG

In diesem SOP wird die Organisation vor der Studie beschrieben, welche vor allem den Einschlussprozess der Patienten beinhaltet.

3. ZIELE

Übersicht über Rekrutierung der Patienten im ADS, über den Aufbau der Ordner, Ausfüllen des CRF, Einschlussgespräch mit den Patienten, Sicherstellen dass alle Einschlusskriterien und keine Ausschlusskriterien erfüllt sind, Studieninformation, Einverständniserklärung und Infofax an alle Ärzte senden.

4. DEFINITIONEN

ADS	Ambulanter Dienst Sucht der Universitären Psychiatrischen Klinik (UPK) Basel
CRF	Case Report Form, ist ein Erhebungsbogen welcher die Untersuchungsdaten eines Patienten entsprechend dem Prüfplan einer Studie festhaltet
NA	Notfallapotheke Basel
Infofax	Informationsblatt welches an alle Ärzte der Patienten geschickt wird
PCRG	Pharmaceutical Care Research Group, Universität Basel

5. VERANTWORTLICHKEITEN

PCRG	Bestimmt wer in die Studie eingeschlossen wird, durchführen des Eintrittsgespräch, versenden des Infofax
ADS	Rekrutieren neue Patienten für die Studie

6. ARBEITSANWEISUNGEN

6.1 Patientenauswahl

Die Patienten werden von ihren behandelnden Ärzten des ADS im Rahmen von Routineuntersuchungen und –gesprächen rekrutiert. Die Patienteneignung wird individuell für jeden Fall von den betreuenden Fachpersonen beurteilt.

6.2 Aufbau der Ordner

Es gibt pro Patient zwei verschiedene Ordner indem die ganzen Dokumente abgelegt und aufbewahrt werden.

6.2.1 Feld-Ordner

Im Feld-Ordner werden nur Dokumente aufbewahrt, die anonymisiert bzw. mit dem Patientencode beschriftet sind. Er wird zu den Patientengesprächen mit genommen und enthält alle Dokumente die gebraucht werden, wie zB das CRF, Studieninformation und die Fragebögen. Der Ordner ist unterteilt in die Register „CRF“, „$T_{aktuell}$“, „$T_{nächster}$“ und

„$T_{vergangen}$“. Im „$T_{aktuell}$“ sind alle Dokumente abgelegt, die für das Eintrittsgespräch und der Dispenserinstallation gebraucht werden. Sobald diese ausgefüllt sind werden sie im „$T_{vergangen}$“ abgelegt und die Dokumente des „$T_{nächster}$“ ins „$T_{aktuell}$“ verlegt. Im Register „$T_{nächster}$“ kommen dann die Fragebögen die beim nächsten Treffen, hier dem Refill, gebraucht werden. Somit hat man eine gute Übersicht und alles beieinander. Wichtig ist dass S.3 im CRF, „ Nicht anonymisierte Kontaktdaten“, in den Notfallapotheke-Ordner abgelegt wird.

6.2.2 Notfallapotheke-Ordner

Dieser Ordner enthält alle Dokumente des Patienten die nicht anonymisiert sind und wird in der Notfallapotheke aufbewahrt. Er ist in die Register „Produktion“ und „weiteres“ aufgeteilt und enthält auch das Dokumentationsblatt welches eine Checkliste ist. Bei „Produktion“ sind die Produktionskontrollblätter v0.3 und v0.2 eingeordnet. Diese müssen immer nach einer Produktion ausgefüllt werden. Bei „Weiteres“ wird unter anderem S.3 vom CRF eingeordnet.

6.3 Case Report Form

Wie oben schon erwähnt, gibt es für jeden Patienten zwei verschiedene Ordner. Das CRF kommt in den Feld-Ordner ausser Seite 3, “nicht anonymisierte Kontaktdaten”.

Vor dem Einschlussgespräch kann das Deckblatt (S.1) ausgefüllt werden und teilweise auch schon S.3-7. Fehlende Infos müssen nach oder während dem Gespräch eingetragen werden. T1 des CRFs, also S.7-11 werden auch beim Eintrittsgespräch ausgefüllt.

6.3.1 Einschlusskriterien (S.5, CRF)

- Schriftliche Einwilligung unterschrieben
- Lese- und Schreibkompetenz in deutscher Sprache
- Stabile Wohnsituation in Basel und Umgebung
- Telefonische Erreichbarkeit gewährleistet
- Mindestdauer in Substiutionsbehandlung von 2 Monaten
- Polymedikation (>3 feste, orale Medikamente)
- Routinekontrolle der klinischen Parameter vor weniger als 1 Woche erfolgt bzw. Innerhalb 1 Woche ab Einschluss vereinbart
- Bei Schweizer Krankenversicherung versichert

6.3.2 Ausschlusskriterien (S.5, CRF)

- Heroingestützte Behandlung
- >2 Medikamente, die nicht in Schlauchblister verpackt werden können

6.4 Patienteninformation und Einverständniserklärung

6.4.1 Patienteninformation

Ist ein eigenes Dossier (Studieninformation) für den Patienten, mit den wichtigsten Informationen über die Studie. Dies wird dem Patienten beim ersten Treffen gegeben.

6.4.2 Einverständniserklärung

Die Einverständniserklärung ist auf der letzten Seite der Studieninformation und sollte vom Patienten wie auch vom Studienarzt unterschrieben werden. Die Einwilligungserklärung kommt dann in den NA-Ordner.

6.5 Fragebögen

Beim Eintrittsgespräch werden die Patienten gebeten 5 Fragebögen auszufüllen. Auf S.11 im CRF sind die Fragebögen aufgelistet und muss als Kontrolle ausgefüllt werden. Beim Fragebogen ACTG, Adherence Baseline Questionnaire, muss die Zeit gestoppt werden und kann desshalb nicht vom Patienten alleine ausgefüllt werden. Alle andern können beim Eintrittsgespräch dem Patienten mitgegeben und dann beim nächsten Termin, der Dispenserinstallation, wieder eingesammelt werden.

Am Ende des Gesprächs muss ein Termin vereinbart werden für die Dispenserinstallation. Das Datum wird auf S.3, wie auch auf S.12 im CRF notiert.

6.6 Infofax

Ist ein Informationsblatt über die Studie, welches an alle Ärzte des Patienten geschickt werden, ausser die des ADS. Beim Infofax muss immer der Name des Arztes und des Patienten angepasst werden.

7. VORLAGEN/FORMULARE

7.1 Vorlagen

- Infofax

7.2 Formulare

- CRF
- Dokumentationsblatt
- Studieninformation
- Einwilligungserklärung
- Fragebogen Lebensqualität SCL-90R
- Fragebogen Lebensqualität SF-12
- Fragebogen Beikonsum
- Fragebogen Adherence Baseline
- Fragebogen Alltagskompetenz

8. INTERNE UND EXTERNE REFERENZEN

8.1 Interne Referenzen

- SOP 2014-071.T1-2 Schlauchblisterproduktion

9. CHANGE HISTORY

SOP Nr.	Effektives Datum	Wesentliche Änderungen	Vorherige SOP Nr.
EKNZ-2014-071.T1-1		Erste Version	N/A

STANDARD OPERATING PROCEDURE
SOP No: EKNZ-2014-071.T1-2

SOP Titel: Schlauchblisterproduktion

DEPARTMENT
OF PHARMACEUTICAL SCIENCES

SOP Nummer EKNZ-2014-071.T1-2
SOP Titel Schlauchblisterproduktion

	NAME	TITEL	UNTERSCHRIFT	DATUM
Autor	Samuel	Allemann		
Review				
Freigabe				

Effektives Datum:	
Review Datum:	

Gelesen			
NAME	**TITEL**	**UNTERSCHRIFT**	**DATUM**

STANDARD OPERATING PROCEDURE

SOP No: EKNZ-2014-071.T1-2

DEPARTMENT
OF PHARMACEUTICAL SCIENCES

SOP Titel: Schlauchblisterproduktion

Inhalt

STANDARD OPERATING PROCEDURE

SOP No: EKNZ-2014-071.T1-2

DEPARTMENT OF PHARMACEUTICAL SCIENCES

SOP Titel: Schlauchblisterproduktion

1. ZWECK

Sicherstellen korrekter Produktion der ersten Medikamentenrolle und Übersicht über die Planung der Dispenser-Installation/Dispenser-Refills zur Vermeidung von Versorgungslücken.

2. EINLEITUNG

Mehrere Schritte bis Medikamente beim Patienten: Therapieplan, Medikamente und aktuelle Rezepte vorhanden, Produktionsfile erstellen, Medifilme produzieren, Produktion kontrollieren und dokumentieren.

3. ZIELE

Übersicht über Teilschritte Therapieplan, Medikamente vorhanden/bestellt, Produktionsfile erstellt, Produktion vorbereiten und durchführen, Kontrolle, Auslieferung

4. DEFINITIONEN

Medifilm	Firma, die Schlauchbeutel mit Medikamenten herstellt, wird synonym für die Bezeichnung "Schlauchbeutel" verwendet.
Apixxo	Software zum Verwalten der Therapiepläne und zum Erstellen der Produktionsfiles.
Produktionsfile	Textdatei, die aufgrund eines Therapieplans in Apixxo erstellt wird und anhand derer die Schlauchbeutel für einen bestimmten Zeitraum mit der HD-Medi produziert werden können.
HD Medi	Maschine zum Verpacken der Schlauchbeutel, steht im Container im Keller der Notfallapotheke (NA) Basel.
Produzent	Person, die die Schlauchblister produziert.
Bezugsperson	MitarbeiterIn des Ambulanten Dienst Sucht (ADS) der Universitären Psychiatrischen Kliniken (UPK) Basel, der/die als Bezugsperson für eine/n Patienten/-in gilt.
Adam	Dateiablagesystem
NA	Notfallapotheke Basel
ADS	Ambulanter Dienst Sucht der Universitären Psychiatrischen Kliniken (UPK) Basel

5. VERANTWORTLICHKEITEN

Produzent	Hauptverantwortung, besorgt aktuellen Therapieplan beim ADS und übernimmt allfällige Änderungen in Apixxo, bestellt Medikamente in der Notfallapotheke (NA), bestellt neue Rezepte im ADS, erstellt die Produktionsfiles und produziert Schlauchblister.
Bezugsperson	Verifiziert den aktuellen Therapieplan und gibt dem Produzenten eine Rückmeldung.

ApothekerIn NA	führt Medikamentenbestellungen aus, bestellt neue Rezepte
Arzt ADS	Stellt Rezepte aus, auch bei Änderungen des Therapieplans oder nach Ablauf eines Dauerrezepts aus.
Medifilm AG	Erstellt Produktionsfiles und legt sie auf Adam ab.

6. ARBEITSANWEISUNGEN

Bei der Erstproduktion:

6.1 Patient in Apixxo erstellen

Jeder Patient wird gemäss Produktionshandbuch, Teil XXX im Apixxo erfasst. Hier werden persönliche Informationen wie Adresse und Telefonnummern hinterlegt. Die Bezugsperson vom ADS wird als Empfänger erfasst.

6.2 Übernahme des Therapieplans

Nach der Rekrutierung und Einschluss in die Studie: Aktueller Therapieplan zusammen mit Bezugsperson im CRF eintragen. Der Therpieplan wird anschliessend im Apixxo gemäss Produktionshandbuch, Teil B, Abschnitt 5.XX erstellt und durch die Bezugsperson im ADS kontrolliert.

Beim Refill:

6.3 Prüfung des Therapieplans

Eine Woche vor jedem Refill überprüft der Produzent bei der Bezugsperson des ADS via E-Mail, ob sich der Therapieplan seit der letzten Produktion geändert hat. Bei der E-Mail Vorlage müssen jeweils Betreff, Refill-Datum und Verpackungsdatum angepasst werden. → *E-Mail Vorlage „Dispenser-Refill"*

Falls es Änderungen gibt, muss der Therapieplan im Apixxo gemäss Anleitung geändert werden. → *Anleitung Apixxo*

Falls sich die Einnahmmezeitpunkte ändern, muss de Dispenser neu programmiert werden. → *Anleitung Innospense Portal*

Bei Erstproduktion wie auch beim Refill:

6.4 Ausstellung von Rezepten

Produzent fordert von den zuständigen Ärzten im ADS Rezepte für die Medikamente an, auch bei jeder Neuverordnung oder nach Ablauf eines Dauerrezeptes. Dazu können die aktuellen Therapiepläne der Patienten gemäss → *Produktionshandbuch, Teil B, Abschnitt 5.3.2, Punkt 1* aus dem Apixxo heruntergeladen und dem zuständigen Arzt zur Unterschrift per E-Mail zugestellt werden.

→ *E-Mail Vorlage „Rezeptausstellung"*

Die unterschriebenen Cardex-Blätter gelten als Dauerrezept für 6 Monate.

6.5 Medikamentenbestellung

Nach Bestätigung des Therapieplans bestellt der Produzent die benötigten Medikamente 2 Tage vor der Schlauchblister-Produktion in der Notfallapotheke, damit sie rechtzeitig zur Verfügung stehen.

Die provisorische Medikamentenbestellung der letzten Produktion wird falls erforderlich durch die neu verordneten Präparate ergänzt.

→ *Formular „Medikamentenbestellung“*

Das komplette Formular wird per E-Mail oder Fax an die Notfallapotheke geschickt.

→ *E-Mail Vorlage „Medikamentenbestellung“*

6.6 Erstellung der Produktionsfiles

Der Produzent erstellt die Produktionsfiles gemäss → *Produktionshandbuch, Teil B, Abschnitt 6.1*. Die jeweilige Versorgungsdauer richtet sich nach den Medikationsmengen, Patientenpräferenzen und vorhandenen Ressourcen und beträgt in der Regel 3 Wochen.

Das Startdatum richtet sich nach dem Tag und der Uhrzeit des Dispenser-Refills. Findet der Refill vor der geplanten Einnahmezeit statt, ist das Startdatum der Refilltag. Findet der Refill nach der geplanten Einnahmezeit statt, ist das Startdatum der Tag nach dem Refill (Tag_{Refill} + 1).

Das Enddatum wird analog festgesetzt. Findet der Refill vor der geplanten Einnahmezeit statt, ist das Enddatum der Tag vor dem Refill (Tag_{Refill} - 1). Findet der Refill nach der geplanten Einnahmezeit statt, ist das Startdatum der Refilltag.

6.7 Produktion der Schlauchblister

6.7.1 Herunterladen der Produktionsfiles

Die Produktionsfiles werden von der Firma Medifilm AG erstellt und unter Adam → Medifilm abgelegt. Dort können sie heruntergeladen und im Ordner „OCR-Files“ gespeichert werden.

6.7.2 Auftrag generieren / ausführen

Die Schlauchblister werden anhand der Produktionsfiles gemäss → *Produktionshandbuch Teil D* und *Teil E* produziert. Jeder Patient verfügt über einen eigenen Medikamentenstock, der sich in einer Kiste im Container rechts oben unter der Decke befinden. Jede Kiste ist mit dem Patientencode beschriftet. Falls Kanister vorhanden sind, können die Medikamente mittels Kanister verpackt werden. Dazu wird die benötigte Menge an Tabletten für jeden Patienten separat aus dem jeweiligen Patientenvorrat in den Kanister gefüllt. Falls kein Kanister vorhanden ist, werden die betreffenden Medikamente mittels STS-Tray abgefüllt. Bevor die Produktion gestartet wird, sollte das Beutelformat kontrolliert werden. Ein weiterer wichtiger Punkt ist, dass während der Produktion die Schlauchbeutel stetig von der Maschine weg gezogen werden um keinen Stau zu verursachen.

6.7.3 Kontrolle / Dokumentation

Jeder Patientenordner enthält produktionsspezifische Formulare zur Dokumentation:

- → *Produktionskontrollblatt*: Hier wird für jede Produktion das Datum der Herstellung, Anzahl der produzierten Schlauchblistertage, Beutelnummern und die Schlauchbeutelkontrolle dokumentiert.

→ *Fehlerprotokoll*: Jeder Produktionsfehler wird anhand dieses Protokolls dokumentiert, gemäss → *Produktionshandbuch Teil E, Abschnitt 3*.

→ *Chargenkontrollblatt*: Der Ein- und Ausgang jeder Tablette wird hier mit Beutelnummer, Chargennummer und Verfalldatum protokolliert.

→ *Medikamentenbestellung*: Am Ende jeder Produktion wird anhand des voraussichtlichen Bedarfs der nächsten Produktion eine provisorische Medikamentenbestellung ausgefüllt. Diese wird eine Woche vor Refill nach Bestätigung des aktuellen Therapieplans ggf. angepasst.

6.8 Kontrolle der Schlauchblister

Jede Schlauchblisterrolle wird direkt nach der Produktion gemäss → *Produktionshandbuch, Teil E, Abschnitt 3* kontrolliert. Der Startbeutel und die Beutel einer Tagesmedikation werden mit dem iPad fotografiert. Jede Rolle wird nach dem Vier-Augenprinzip von einer zweiten Person kontrolliert.

6.9 Dispenser-Installation beim Patienten

Der Dispenser wird gemäss → *SOP 2014-071.T3 Dispenser-Installation* programmiert, beim Patienten installiert und mit der Medikamentenrolle befüllt.

6.10 Dispenser-Refill beim Patienten

Der Dispenser wird gemäss → *SOP 2014-071.T4 Dispenser-Refill* beim Patienten mit der neuen Medikamentenrolle gefüllt.

7. VORLAGEN/FORMULARE

7.1 *Vorlagen*

- E-Mail Vorlage „Dispenser-Refill“
- E-Mail Vorlage „Medikamentenbestellung“
- E-Mail Vorlage „Rezeptausstellung“

7.2 *Formulare*

- Produktionskontrollblatt
- Fehlerprotokoll
- Chargenkontrollblatt
- Medikamentenbestellung

8. INTERNE UND EXTERNE REFERENZEN

8.1 Interne Referenzen

- Produktionshandbuch
- Anleitung Innospense Portal
- SOP 2014-071.T2 Dispenser-Installation
- SOP 2014-071.T3 Dispenser-Refill

8.2 Externe Referenzen

- http://login.medifilm.ch

- https://portal.medido.com/
- http://adam.unibas.ch

9. CHANGE HISTORY

SOP Nr.	Effektives Datum	Wesentliche Änderungen	Vorherige SOP Nr.
EKNZ-2014-071.T1-2		Erste Version	N/A

STANDARD OPERATING PROCEDURE
SOP No: EKNZ-2014-071.T2
SOP Titel: Dispenser-Installation

DEPARTMENT
OF PHARMACEUTICAL SCIENCES

SOP Nummer EKNZ-2014-071.T2
SOP Titel Dispenser-Installation

	NAME	TITEL	UNTERSCHRIFT	DATUM
Autor				
Review				
Freigabe				

Effektives Datum:	
Review Datum:	

Gelesen			
NAME	**TITEL**	**UNTERSCHRIFT**	**DATUM**

STANDARD OPERATING PROCEDURE
SOP No: EKNZ-2014-071.T2
SOP Titel: Dispenser-Installation

DEPARTMENT
OF PHARMACEUTICAL SCIENCES

Inhalt

STANDARD OPERATING PROCEDURE

SOP No: EKNZ-2014-071.T2

SOP Titel: Dispenser-Installation

DEPARTMENT
OF PHARMACEUTICAL SCIENCES

1. ZWECK

Vorbereitung und Installation des Dispensers beim Patienten.

2. EINLEITUNG

Nach dem Einschluss des Patienten in die Studie und der ersten Schlauchblisterproduktion, steht die Dispenser-Installation zu Hause beim Patienten an.

3. ZIELE

Übersicht über Teilschritte: Programmierung, Installation und Erklärung des Dispensers.

4. DEFINITIONEN

CRF	Case Report Form, ist ein Erhebungsbogen welcher die Untersuchungsdaten eines Patienten entsprechend dem Prüfplan einer Studie festhaltet
Feld-Ordner	wird zu jedem Treffen mit den Patienten mitgenommen, da alle Fragebögen und das CRF welches gebraucht wird, dort abgelegt sind. Enthält nur anonymisierte Dokumente
Medido-Portal	Internetportal, auf welchem die Dispenser auf den Patienten programmiert und die Daten erfasst werden.
Medido® Spender	Infoblatt für den Patienten, welches den Dispenser erklärt
PCRG	Pharmaceutical Care Research Group, Universität Basel

5. VERANTWORTLICHKEITEN

PCRG Führt die Programmierung,Installation und Erklärung durch

6. ARBEITSANWEISUNGEN

6.1 Programmierung des Dispensers auf dem Medido-Portal

Jeder Dispenser wird auf den Patienten programmiert, sowie auch in welcher Zeitspanne die Medikamente ausgegeben werden sollen. Dies findet auf dem Medido-Portal statt.

-> Verweis auf Anleitung des Portals (gits nonid)

6.2 Dispenser-Installation

Beim Eintrittsgespräch wurde mit dem Patienten ein Termin festgelegt, an welchem die Installation statt finden soll. Dieses Datum ist auch im Feldordner, im CRF auf S. 12 notiert.

Zuerst wird mit dem Patienten ein Kurzinterview durchgeführt und S.12-13 im CRF ausgefüllt. Es handelt sich um Änderungen der Medikamente, ungeplante/zukünftige Spitalaufenthalte und die Erwartungen an den Dispenser.

Anschliessend wird dann der Dispenser installiert und mit Hilfe des → *Medido® Spender* Infoblatts erklärt. Ein optimaler Platz ist in der Nähe einer Steckdose und an einem Ort, an dem er die ganze Studie durch bleiben kann. Der Akku hält nur ca. 15 Min. und darf desshalb nicht länger ausgesteckt sein.

Bevor die Medikamentenverblisterung in den Dispenser kommt, darf der Patient nach der Erklärung mit einem Test-Blister üben.

Weiter sollten die Fragebögen vom Eintrittsgespräch, welche noch nicht ausgefüllt sind, spätestens jetzt ausgefüllt werden.

Am Ende des Gesprächs wird noch ein Termin für den Medikamenten-Refill vereinbart oder wann ein Termin festgelegt wird. Dies wird auch im CRF auf S.13 notiert. Der Refill der Medikamente ist beim ersten Mal nach einer Woche, ansonsten all 3-4 Wochen.

6.3 Medido® Spender

Ist ein Informationsblatt über den Dispenser, welches nochmals erklärt welche Farbe was bedeutet, die Studienhotline darauf steht und in welcher Phase der Studie man sich befindet plus kurze Beschreibung der Phase. Dieses Blatt darf der Patient behalten.

7. VORLAGEN/FORMULARE

7.1 Vorlagen

- Anleitung Medido Portal
- Medido® Spender

7.2 Formulare

- CRF

8. INTERNE UND EXTERNE REFERENZEN

8.1 Interne Referenzen

- SOP 2014-071.T3 Dispenser-Refill

8.2 Externe Referenzen

- https://portal.medido.com/

9. CHANGE HISTORY

SOP Nr.	Effektives Datum	Wesentliche Änderungen	Vorherige SOP Nr.
EKNZ-2014-071.T2		Erste Version	N/A

STANDARD OPERATING PROCEDURE
SOP No: EKNZ-2014-071.T3
SOP Titel: Dispenser-Refill

DEPARTMENT
OF PHARMACEUTICAL SCIENCES

SOP Nummer EKNZ-2014-071.T3
SOP Titel Dispenser-Refill

	NAME	TITEL	UNTERSCHRIFT	DATUM
Autor	Samuel	Allemann		
Review				
Freigabe				

Effektives Datum:	
Review Datum:	

Gelesen			
NAME	**TITEL**	**UNTERSCHRIFT**	**DATUM**

STANDARD OPERATING PROCEDURE

SOP No: EKNZ-2014-071.T3

SOP Titel: Dispenser-Refill

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STANDARD OPERATING PROCEDURE

SOP No: EKNZ-2014-071.T3

SOP Titel: Dispenser-Refill

DEPARTMENT
OF PHARMACEUTICAL SCIENCES

1. ZWECK

Nachfüllen des Dispensers.

2. EINLEITUNG

Nach der Installation des Dispensers findet über 6 Monate ein regelmässiger Refill des Dispensers beim Patienten zu Hause statt.

3. ZIELE

Übersicht über Teilschritte des Refills inklusive Kurzinterview und Fragebögen.

4. DEFINITIONEN

CRF	Case Report Form, ist ein Erhebungsbogen welcher die Untersuchungsdaten eines Patienten entsprechend dem Prüfplan einer Studie festhaltet

5. VERANTWORTLICHKEITEN

PCRG	Führt den Refill mit Interview und Fragebögen durch

6. ARBEITSANWEISUNGEN

6.1 Refill

Bei der Dispenser Installation wird auf S. 13 im CRF ein Termin für den Refill vereinbart und festgehalten. Dieses Datum steht auch nochmals im CRF auf S.14 bei T_3–Refill, die bei diesem Termin auch ausgefüllt werden muss.
Beim Refill wird der Dispenser mit neu produzierten Schlauchblistern aufgefüllt. Für wie lange, varriert je nach Patient und hängt davon ab wie viele Medikamente der Patient hat und wie viele dann im Dispenser platz haben. Normalerweise wird für 1-4 Wochen aufgefüllt.

6.2 Interview

Weiter wird bei diesem Termin ein Kurzinterview zur Erfahrung durchgeführt. Der Leitfaden hier zu ist im CRF S. 15 zu finden und muss ausgefüllt werden. Das Interview wird auf Tonband aufgenommen.

6.3 Fragebögen

Zwei Fragebögen zum Beikonsum und der Lebensqualität werden dem Patienten zum Ausfüllen gegeben. Auf S.15 im CRF sind die Fragebögen aufgelistet und müssen als Kontrolle ausgefüllt werden.

Der Fragebogen zum Beikonsum muss nur bei den ersten zwei Refills vom Patienten ausgefüllt werden.

Am Ende des Gesprächs muss ein neuer Refill-Termin oder nach der Zeitspanne T_3 ein Termin für die Schlussvisite, vereinbart werden. Das Datum, wird auf S.15 wie auch auf S. 14/16 im CRF notiert.

7. VORLAGEN/FORMULARE

7.1 Formulare

- CRF
- Fragebogen Lebensqualität SF-12
- Fragebogen Beikonsum

8. INTERNE UND EXTERNE REFERENZEN

8.1 Interne Referenzen

- SOP 2014-071.T4 Schlussvisite

9. CHANGE HISTORY

SOP Nr.	Effektives Datum	Wesentliche Änderungen	Vorherige SOP Nr.
EKNZ-2014-071.T3		Erste Version	N/A

A.3.9. Supplementary dispensing patterns

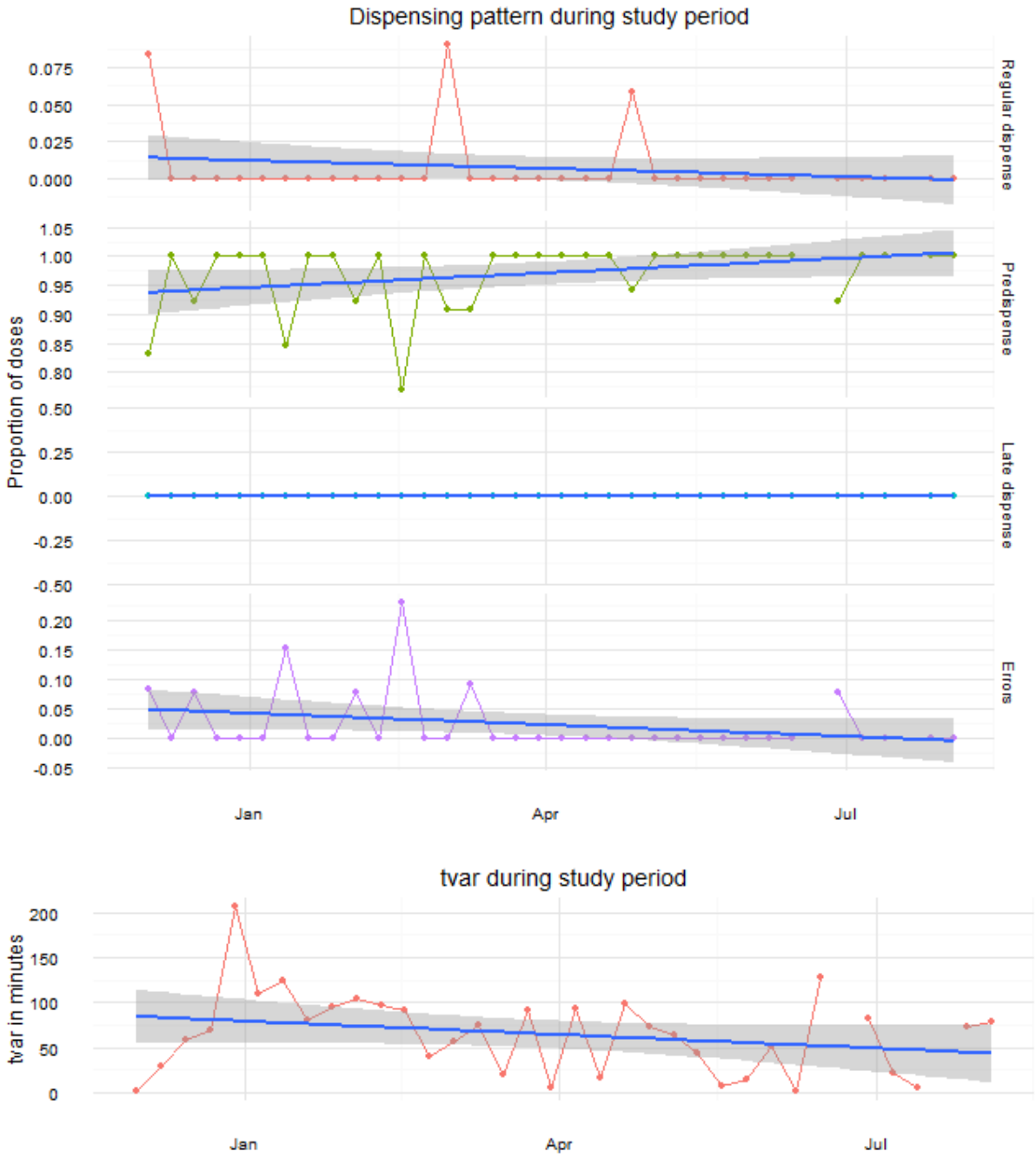

Figure 42: Dispensing patterns and t_{Var} for Albert. Blue lines depict linear trends, with grey areas indicating the 95%-confidence interval.

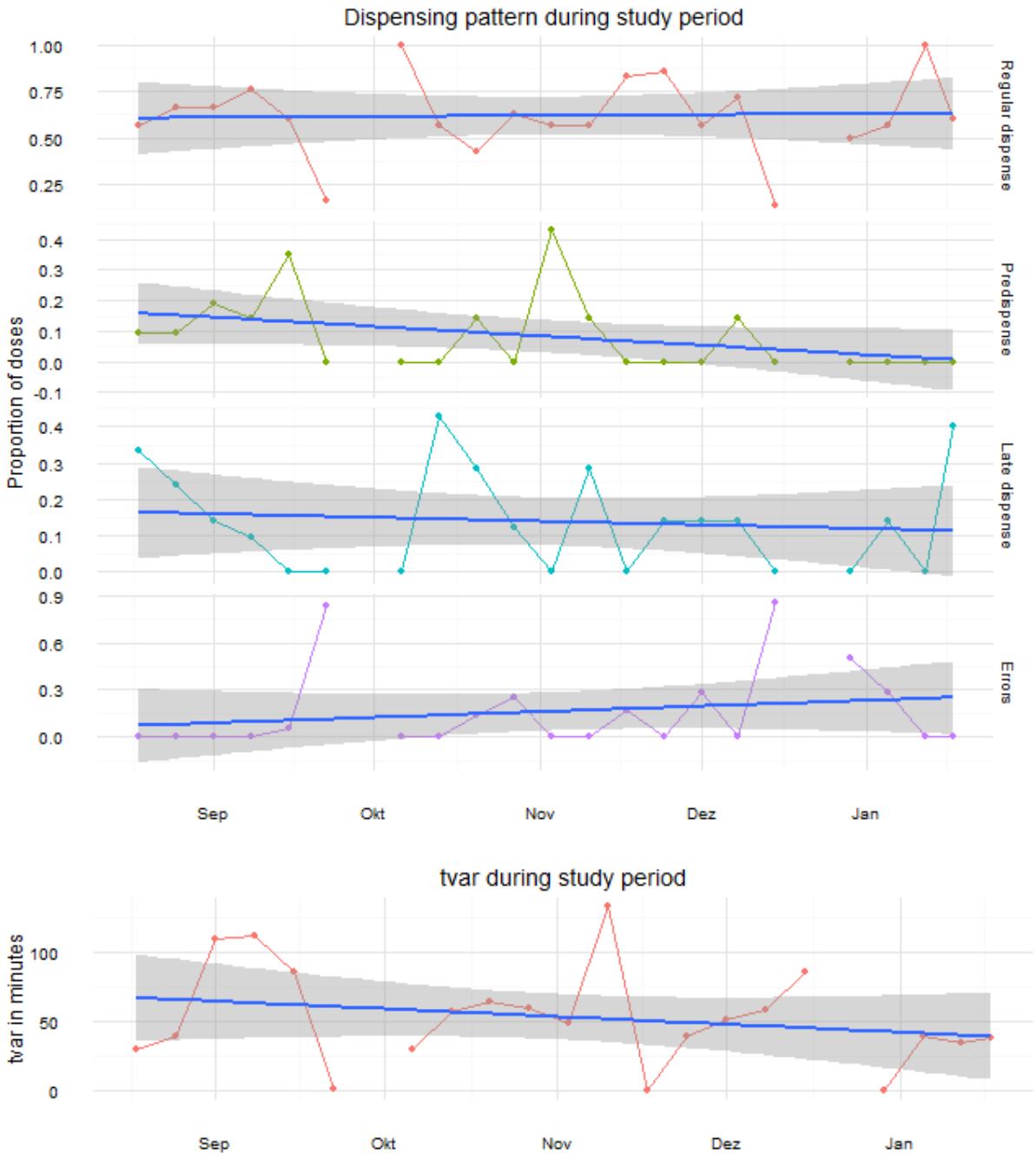

Figure 43: Dispensing patterns and t_{Var} for Denise. Blue lines depict linear trends, with grey areas indicating the 95%-confidence interval.

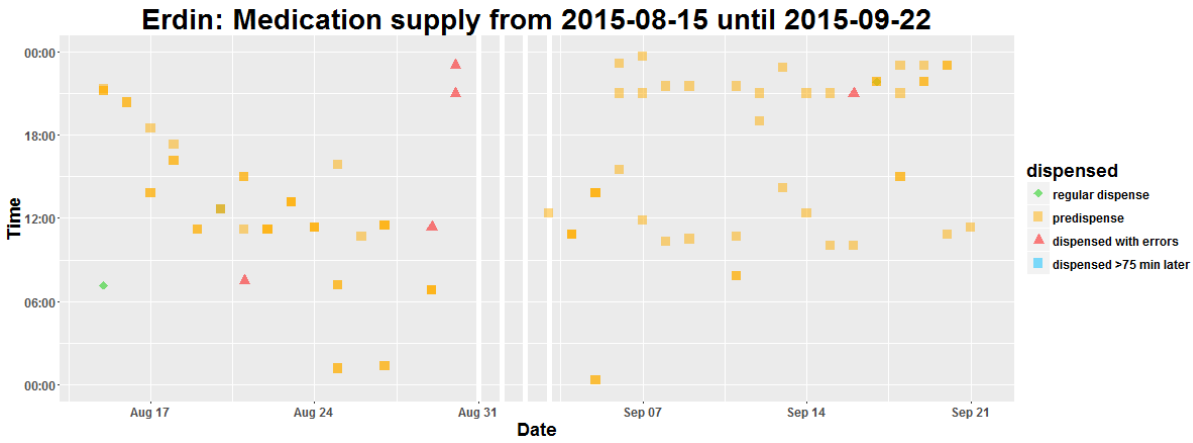

Figure 44: Time of medication retrieval recorded with electronic monitoring for Erdin. White areas are days with missing electronic monitoring.

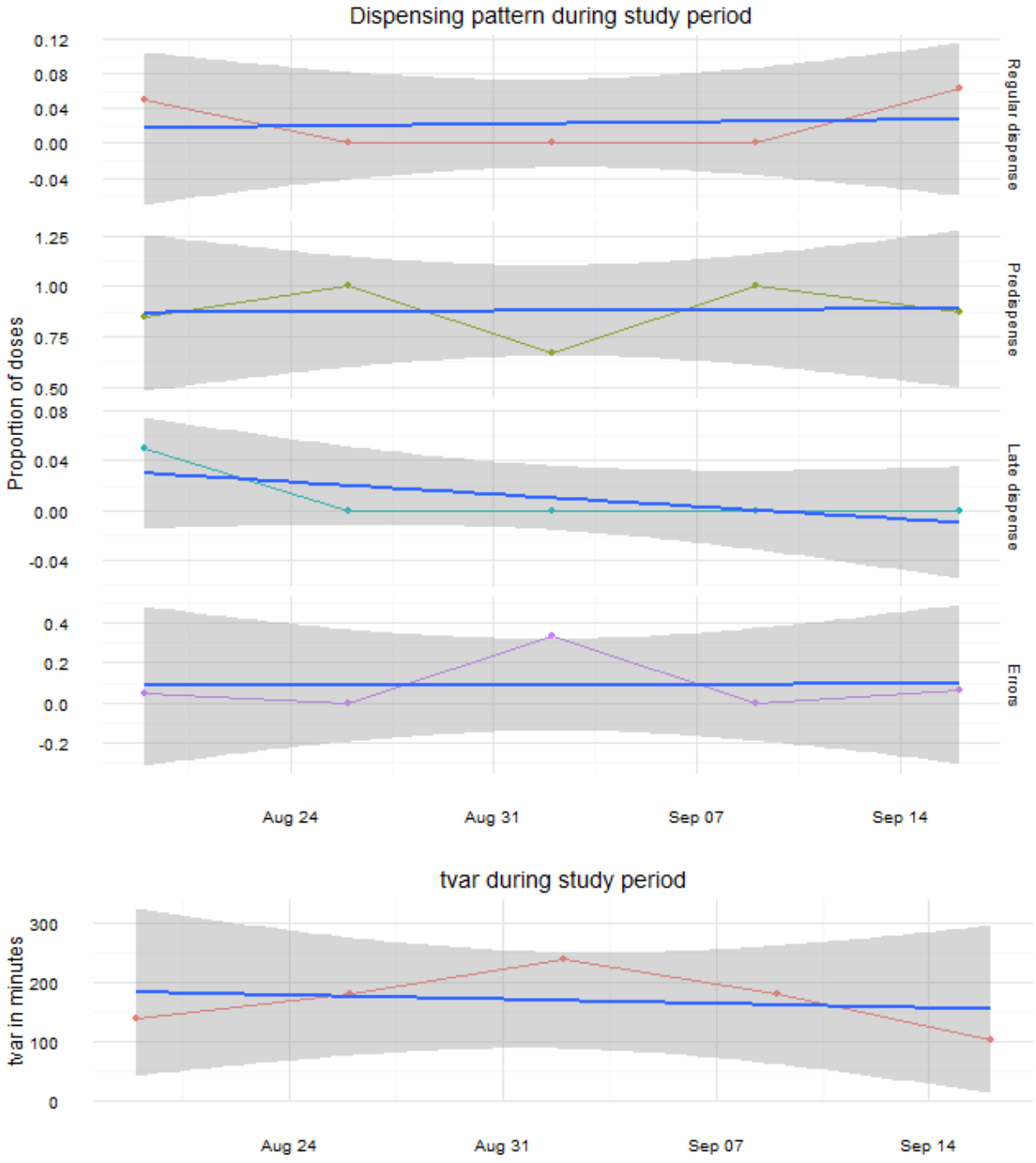

Figure 45: Dispensing patterns and t_{var} for Erdin. Blue lines depict linear trends, with grey areas indicating the 95%-confidence interval.

A.4. Project C5

A.4.1. Patient information and informed consent form

swissethics

Schweizerische Ethikkommissionen für die Forschung am Menschen
Commissions d'éthique suisses relative à la recherche sur l'être humain
Commissioni etiche svizzere per la ricerca sull'essere umano
Swiss Ethics Committees on research involving humans

Aufklärungsdokument über:

Die Weiterverwendung gesundheitsbezogener (nichtgenetischer) Personendaten für Forschungszwecke in unverschlüsselter Form (Art. 31 HFV)

Sehr geehrte Dame, sehr geehrter Herr

1. Wer wir sind:
Wir sind Apotheker, die zusammen mit dem Ambulanten Dienst Sucht (ADS) der Universitären Psychiatrischen Kliniken (UPK) Basel diese Studie durchführen. Mein Name ist Seraina Disler, ich studiere Pharmazie an der Universität Basel und schreibe momentan meine Masterarbeit über pharmakoökonomische Aspekte von elektronischen Medikamenten-Dispensern bei opioidsubstituierten Patienten. Sponsor dieser Studie ist das Departement Pharmazeutische Wissenschaften der Universität Basel.

2. Weshalb wir Sie anfragen:
Wir möchten Sie hiermit einladen, die medizinische Forschung zu unterstützen.
Ein Teil der Studie ist es, die Kosten der opioid-gestützten Therapie zu analysieren. Bei Ihrer medizinischen Behandlung fallen Kosten an, die über die Krankenkasse abgerechnet werden. Diese Daten können für die Forschung sehr wichtig sein. Deshalb möchten wir Sie bitten: erlauben Sie bitte Ihrer Krankenkasse, uns diese Daten zu Forschungszwecken weiterzugeben.

3. Ihre Rechte als Spender/in
Sie geben nur dann Ihre Daten für die Weiterverwendung zu Forschungszwecken frei, wenn Sie es wollen. Niemand darf Sie dazu in irgendeiner Weise drängen oder überreden wollen. Wenn Sie die Daten nicht freigeben wollen, müssen Sie nicht begründen, warum Sie sich dagegen entscheiden. Wenn Sie sich zur Freigabe entscheiden, können sie diesen Entscheid jederzeit zurücknehmen. Sie müssen nicht begründen, warum Sie Ihren Entscheid zurücknehmen wollen. Es wird sich nichts an ihrer laufenden Substitutionstherapie ändern und falls Sie Fragen zur Studie haben, dürfen sie diese jederzeit stellen.

4. Vertraulichkeit
Wir benötigen für diese Studie Ihre Krankenkassenabrechnung und behandeln Ihre Daten streng vertraulich. Nur diejenigen Personen, die am Projekt mitarbeiten und für Ihre Arbeit Ihre Daten unbedingt brauchen, dürfen damit arbeiten. Ansonsten bleiben ihre persönlichen Daten anonym und werden mit strikter Einhaltung der Vertraulichkeit behandelt.

5. Weitergabe der Daten
Falls eine entsprechende Anfrage vorliegt, werden wir Ihre Daten zu Forschungszwecken auch an Dritte in verschlüsselter Form weitergeben. Somit können Ihre Daten nicht zu Ihnen zurückverfolgt werden.

Einwilligungserklärung zur:

Weiterverwendung gesundheitsbezogener nichtgenetischer Daten zu Forschungszwecken in unverschlüsselter Form (Art. 31 HFV)

Name und Vorname der/s Patienten/in / der betroffenen Person:

Geburtsdatum:

Ich willige hiermit ein, dass die KRANKEVERSICHERUNG DES PATIENTEN für diese Studie einen detaillierten Auszug meiner Gesundheitskosten 2014 zur Verfügung stellt.

Ich bestätige, dass

- ich das zu dieser Einwilligungserklärung gehörende Aufklärungsdokument erhalten habe.
- ich darüber informiert wurde, dass meine Einwilligung freiwillig ist.
- ich weiss, dass ich diese Einwilligung jederzeit widerrufen kann, ohne Angabe von Gründen.
- ich weiss, wie meine Daten geschützt sind.
- ich darüber informiert wurde, dass meine Daten nach der Auswertung anonymisiert werden und nur diejenigen Personen welche an der Studie mitarbeiten, mit den Daten arbeiten dürfen.

Ort, Datum, rechtsgültige Unterschrift der Patientin / des Patienten bzw. der betroffenen Person oder ihrer / seiner berechtigten Vertretungsperson.

Ort, Datum, rechtsgültige Unterschrift der aufklärenden Person.

A.4.2. Questionnaire about cost of illness for caregivers

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DEPARTMENT
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Fragebogen über Krankheitskosten: für die Betreuer im ADS

In dieser Krankheitskosten-Analyse werden die Kosten der medikamentösen Versorgung im ADS identifiziert und analysiert. Dafür werden bestimmte Daten benötigt, welche durch diesen Fragebogen erhoben werden sollen. Da eine enge Betreuung zwischen Patient und Betreuer stattfindet, werden die Betreuer und nicht die Patienten direkt befragt.
In diesem Fragebogen sind unter dem Begriff „Patient", männliche wie auch weibliche Patienten/Patientinnen gemeint. Das Ausfüllen des Fragebogens dauert ungefähr 5 Minuten. Bitte retournieren Sie die ausgefüllten Fragebogen **bis am 24.4.15** im dafür vorgesehenen Umschlag.

Name des Betreuers: ..... **Name des Patienten: .....**

1) Wie oft kommt der Patient zur Medikamentenabgabe in den ADS?

...../ Woche ☐ Ich weiss nicht

---

2) Wie werden die Medikamente abgegeben?

☐ ohne Vorbereitung ☐ Vorbereitet und vor Ort abgegeben ☐ Vorbereitet und von externen Betreuern abgeholt ☐ Ich weiss nicht

---

3a) Wie lange dauert der Weg des Patienten von zu Hause bis zum ADS?

☐ 0-15 min. ☐ 15-30 min. ☐ 30-45 min. ☐ 60 min. oder länger ☐ Ich weiss nicht

3b) Wie kommen die Patienten ins ADS?

☐ zu Fuss ☐ Velo ☐ Öffentliche Verkehrsmittel ☐ Taxi ☐ Ich weiss nicht

---

4a) Erhält der Patient zu Hause Unterstützung mit seinen Medikamenten?

☐ Ja ☐ Nein ☐ Ich weiss nicht

4b) Falls ja, von wem?

☐ privat (Familie, Freunde, etc...) ☐ professionell (Spitex, betreutes Wohnen, etc..) ☐ Ich weiss nicht

4c) Wie viele Arbeitstage wird der Patient zu Hause betreut?

(10% = ein halber Arbeitstag/Woche) ..... ☐ Ich weiss nicht

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4d) Falls der Patient privat betreut wird, sind die Betreuenden arbeitsfähig[1]?

☐ Ja ☐ Nein ☐ Ich weiss nicht

5a) Was ist der gelernte Beruf Ihres Patienten? ..... ☐ Ich weiss nicht

5b) Geht ihr Patient einer bezahlten Tätigkeit ausserhalb von zu Hause nach (erster Arbeitsmarkt)?

☐ Ja ☐ Nein ☐ Ich weiss nicht

5c) Falls Ja → Wie viel Prozent? (10% = ein halber Arbeitstag/Woche) ..... ☐ Ich weiss nicht

5d) Falls Nein → Ist der Patient arbeitsfähig[1]? ☐ Nein ☐ Ja ☐ Ich weiss nicht

5e) Bezieht ihr Patient...

☐ Invalidenrente ☐ Arbeitslosengeld ☐ Sozialhilfe ☐ Ich weiss nicht

Bitte fügen Sie jedem Fragebogen die folgenden Dokumente des Patienten bei:

- Medikationsliste ☐ ausgedruckt und angeheftet
- Diagnoseliste ☐ ausgedruckt und angeheftet

Vielen Dank für Ihre Teilnahme!

[1] Arbeitsfähig = Jünger als 65 Jahre und in der Lage, eine Arbeit zu verrichten

A.5. Project D2

A.5.1. Criteria for the coding of determinants in inclusion criteria

- Age was considered a determinant when specifically vulnerable groups (e.g., children or elderly patients) were included
- Duration of treatment was considered when explicitly stated
- Illness chronicity was considered when explicitly stated
- Change of therapy included new therapy
- Gender was considered a determinant when explicitly stated as determinant of non-adherence
- Pill burden was considered a determinant when patients had to take >2 daily medications
- Cognitive impairment was considered a determinant when explicitly stated
- Language was considered a determinant when explicitly non-native patients with language barriers were included
- Adverse events were considered a determinant when explicitly patients with current adverse events were included

A.5.2. Behaviour theories – frequencies overview

66 studies identified a model or theory (41 update + 25 from 2009 review).
33 Theories or models were identified:

- Behaviour Family Therapy Model (2)
- Behavioural Model of Health Care Utilization (2)
- Chronic Care Model/Collaborative Care Model (3)
- Cognitive Behaviour Model/Theory (3)
- Common Sense Model of illness representation (1)
- Community Based Rehabilitation Model (1)
- Conflict Theory of Decision Making (1)
- Frith's notion of apathy versus disinhibition (1)
- Health Belief Model (5)
- Health Collaboration Model (1)
- Information-motivation-behavioural skills model (IMB model) (5)
- Integrative Health Coaching Model (1)
- Lay Health Mentoring Model (1)
- Multisystemic Therapy Model (2)
- Peer Support Model (1)
- PRECEDE Model (2)
- Protection Motivation Theory (1)
- Rationality Model (1)
- Self-Determination Theory (1)
- Self-Efficacy Theory (8)
- Self-Regulation Model of Health & Illness/Theory (4)
- Shared Decision Making Model (2)
- Social Identity Theory (1)
- Transtheoretical Model (Stages of Change Model)
- Social Action Theory (1)
- Social Cognitive Theory (7)
- Social Learning Theory (5)
- Social Support Model (1)
- Stress and Coping Theory (1)
- Symptom Management Conceptual Model (1)
- Theory of Learned Helplessness/Health Belief Model (1)
- Theory of Planned behavior (1)
- Theory of Reasoned Action (1)
- Transtheoretical Model (Stages of Change Model) (2)

14 studies identified more than one theory or model on which the intervention was founded.

Curriculum vitae and publication list

Current version available from the author on request.