**PROTOCOL**

The effect of a pharmaceutical medication review, drug history taking, and follow up on the occurrence of readmissions: A prospective randomized intervention study

**Title in lay terms:** "We let the pharmacist follow you and your medication from the hospital out into your daily life and study what that means to you”

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1. Background

In the literature, the transition between the primary and secondary healthcare sectors is described as being a sensitive area regarding patient medication. (1),(2),(3). Especially the transition from hospital to primary healthcare can be associated with mistakes, which occur during and after discharge and are caused by changes to the patient’s medical treatment during admission. (4),(5). The more drugs the patient takes, the larger the risk of drug related problems. (6) The consequences for the patient can be undertreatment, overtreatment, mistakes in medication, more numerous and also more serious side effects than assumed, low compliance or in worst case readmissions (2),(7).

In order to achieve a continuous and safe drug handling in the transition between the healthcare sectors good communication is required and this is presently described as been insufficient. (1),(2). Description of the patients’ current medication with later changes and reason for changes in the patient’s medication during admission is often incomplete in the discharge summary (8),(9). This makes it difficult for the next doctor, taking over the care of the patient to keep an overview of the current medical treatment.

In Sweden a discharge summary which includes a medication report has been developed, which all patients and the next doctor receive at discharge. This has reduced the number of medication errors (10),(11), drug related clinical risks and administrative corrections (12) at transitions between healthcare sectors.

Empirical studies have shown that 11 to 20 % of hospital admissions are drug related (13),(14),(15). In an evidence report from 2006 on drug related problems it is estimated based on foreign studies, that 69,000 - 162,000 annual hospital admissions are drug related in Denmark (16).

It has been unclear, whether a medication review done by a clinical pharmacist has any effect on the number of admissions. A meta-analysis from 2007 including 32 foreign studies concluded that medication review done by a clinical pharmacist did not make a significant difference to the number of admissions (17). Newer studies however show increasing evidence that medication review reduces the number of drug related admissions and other drug related problems (15),(18) resulting in financial savings (18),(19),(20),(21). In addition follow-up calls to the patients within one week of discharge have resulted in a reduction of the number of side effects, A&E visits, and admissions (22),(23). At time of transition from hospital to primary healthcare it is important to contact to the GP and the primary pharmacy to ensure that any changes to the patient’s medication, made during admission are implemented in the primary healthcare setting(24). This contact is especially important with regard to patients who receive dose dispensed drugs, as dose dispensing also is associated with risks of medication errors at times of transition (3),(25). A study has shown that the number of these errors can be reduced by support from a clinical pharmacist at time of discharge (25).

A patient is classified as non-compliant, if less than 80 % of the prescribed drug doses have been taken as prescribed. (26),(27). It is estimated that approximately 50 % of patients with chronic illnesses do not take their medication as prescribed, which potentially has negative consequences for both the patient and the health care system, in worst case to increased morbidity and mortality (22),(27). Thus, it is important to uncover which patients are non-compliant and need to change their behaviour. The patient dialogue prior to discharge has led to a reduction of discrepancies in the medical treatment, and had a positive effect on compliance (22),(28). Motivational interviewing in health care is an evidence based, communication tool to increase compliance by mobilising the patient’s motivation to change lifestyle (30).

In the literature a number of interventions are described which have been tested to create a safer course during transition between healthcare sectors, i.e. the course, when patients are admitted to hospital and discharged to the general practitioner (24), (31), (32),(33). In spite of this, it has not yet been defined, precisely which intervention(s) secure an efficient communication and knowledge sharing between the primary and secondary healthcare sectors, and thus ensuring a continuous course of medication for the patient.

Clinical pharmacists are presently conducting medication reviews in several Acute Assessment Units (FAM) in Denmark (34). This study will test an approach including medication review, medication discharge dialogue and a follow up telephone call to the patient as well as contact to the primary healthcare sector, the general practitioner and pharmacy respectively in order to improve the continuity of the medical treatment. The clinical pharmacist will take an active part in securing rational pharmacotherapy, increased compliance, and patient safety at time of discharge from the hospital to the GP.
2. Aim
The aim of the study is to investigate the effect of medication review, medication discharge dialogue and follow up calls to the patient, general practitioner and the pharmacy on readmissions and patient compliance at discharge from hospital to general practice. The study will test whether the above combination of pharmaceutical interventions can reduce the number of readmissions and/or time to next admission will be prolonged. The hypothesis, that non-compliant patients are readmitted more often the compliant patients will be tested. The combination of pharmaceutical interventions will be compared to an intervention, including only a focused medication review compared to a control group.

3. Method

3.1. Design
A prospective, blinded, randomised controlled multi-centre study on patients admitted to the Acute Assessment Unit (FAM) at Odense University Hospital, Svendborg and Odense, the Regional Hospital in Viborg, and the Acute Admissions Unit at Holbæk Hospital. From March 2014 patients are included only from Odense University hospital, Svendborg and Odense.

3.2. Study population

3.2.1. Inclusion criteria
- Patient ≥ 18 years of age
- Present medication must consist of at least five drugs according to the admission notes, possibly supplemented by the Personal Electronic Medication profile (PEM)/The Shared Medical Card (FMK)\(^6\)
- The patient can speak and understand Danish
- The patient is admitted to the Acute Assessment Unit (FAM) or an acute admissions unit and referred to FAM, a medical admissions unit or another medical department.
- Must be able to give informed consent or have a next of kin, who is able to give informed consent on behalf of the patient. Informed consent is obtained at an actual contact based on adequate information from a clinical pharmacist.

3.2.2. Exclusion criteria
- The patient has participated in one or more similar intervention studies.
- The patient is declared terminally ill.
- The patient is poisoned with suicidal intent
- The patient requires constant supervision/is suicidal
- The patient has impressive and/or expressive aphasia
- The patient has severe dementia
- The patient is detained
- The patient is isolated

3.3. Information and collaboration between primary and secondary healthcare sector
Written information for patients and information material for doctors and nurses at the hospital is provided prior to starting the study. Corresponding information material is provided for doctors and pharmacies in the primary care sector. Information material for all primary pharmacies in Denmark is distributed via the

\(^6\) FMK (the Shared Medical Card) is found at [www.fmk-online.dk](http://www.fmk-online.dk) and requires log-in with digital signature. FMK is a central database at The National Board of Health, which contains information on all Danish citizens’ purchase of prescription medication within the past two years. FMK also contains an updated record of present medication lists of all current drug prescriptions for each citizen.
Association of Danish Pharmacies and information material is provided for general practitioners through regional newsletters.

3.4. Patient selection, randomization and data collection.
Based on a power calculation it is decided to include 1500 patients in the study. The patients are randomized into one of three groups: basic intervention group, advanced intervention group, and control group. 500 patients are included into each group. The patients are randomized first to the intervention group or the control group respectively. Everyone in the intervention group undergoes a medication review, after which the patients in the intervention group are re-randomized. To minimize the risk of bias both the clinical pharmacist and the patient are blinded as to whether the patient belongs to the basic intervention group or the advanced intervention group, until the medication review is completed. The civil registration numbers of all the patients, who have been included in or have rejected the study, are registered. At each new admission the register will be checked to see if the patient is registered, so that the same patient is included only once. The patient flow is illustrated in the diagram in figure 1.

**Figure 1. Patient flow diagram.**

The patient lists are checked for new admission at FAM every day during the study. All patients’ admission notes are examined in order to determine the number of usual drugs, meaning drugs used on a regular basis. (Additionally it is possible to look up the patient’s Shared Medical Card (FMK)/PEM). Patients, who meet the inclusion criteria are informed of the study and asked to participate in the study. All approached patients are registered. The patients not wishing to participate are registered including the reason for refusal. Upon acceptance the patient or next of kin fill out a consent form.
3.5. **Patient groups**

Patients in all three groups are examined for compliance, where compliance is defined as an expression of the level of concordance between the patient’s actual drug intake and the treatment chosen by the doctor. Patients are classified as non-compliant if prescriptions for less than 80% of the prescribed doses are redeemed.

3.5.1. **Control group**

The purpose of the control group is to have the same starting point for all three groups, providing a base for comparison of data between the groups. These patients do not receive a medication review, discharge dialogue and follow up from a clinical pharmacist.

3.5.2. **Basic intervention group**

A clinical pharmacist does a medication review once during the admission. As a minimum the admission notes are required to be completed and available. Any intervention proposals are noted in the patient’s electronic patient records, EPJ. The medication review is done systematically from a defined guideline. Any intervention proposals are entered into the electronic database. The clinical pharmacist does a medication review with the medical records as a primary source but also interviews the patient and uses the Shared Medical Card (FMK) if further information is necessary for clarification.

3.5.3. **Advanced intervention group**

The patients undergo a medication review as described for the basic intervention group, where the same registrations are made. Once a doctor from FAM has adjusted the medication upon discharge\textsuperscript{7}, possibly with the assistance of a clinical pharmacist, the clinical pharmacist delivers an actual medication list and holds a medication discharge dialogue, including a motivational interview. If the patient is transferred to a different medical ward during the admission, the motivational interview can be held before the transfer to a different ward.

After the patient is discharged the clinical pharmacist sends a list of suggested interventions, which have not been decided upon during admission, to the patient’s GP.

The patient is contacted 3-5 days after discharge in order to follow up on the discharge dialogue. The home care services, GP and primary pharmacy are contacted by telephone also within 3-5 days of discharge as required.

\textsuperscript{7} Process, whereby the drug list on admission, discharge and/or transfer is adjusted/checked by a drug history on admission and drugs prescribed during admission. (the Danish Healthcare Quality Programme, DDKM)
Figure 2. Intervention overview.

The clinical pharmaceutical interventions shown in figure 2 are done by selected clinical pharmacists from Hospital Pharmacy of Funen, Hospital Pharmacy of Region Zealand and The Regional Hospital Pharmacy, Viborg. The clinical pharmacists are trained prior to study start in order to minimise the risk of cultural differences and variations in work procedures between the regions influencing the data.

3.6. Outcome measures

Primary outcome measures:

- Number of admissions, readmissions\(^8\) and A&E visits within six months of discharge

\(^8\) Admission within 30 days of discharge
Secondary outcome measures:
- Number of drug related admissions
- Number of drug related readmissions
- Time until next admission
- Number of days admitted
- Mortality
- Drug related mortality
- Number of unscheduled visits to the GP
- Compliance
- Acceptance rate

3.7. Data analysis

Data are analysed both for all hospitals in total and for each hospital separately, in order to identify any local differences. Furthermore, data are analysed from the information continuously being registered in patient protocols.

3.7.1. Drug related admissions and readmissions.

Each hospital administration are able to access data for all admissions regarding number of inpatient days, number of A&E visits, number of readmissions, and mortality. An impartial clinical pharmacologist is manually reviewing patient records to estimate the share of drug related admissions, readmissions, and drug related deaths out of all readmissions and deaths. The inventory of unscheduled visits to the GP is based on The National Health Insurance Service Register administrated by the National Board of Health, which again is based on reimbursement codes.

In case of doubt the respective medical practices are contacted to ascertain whether the visit was scheduled. As it is important to know the range of the interventions made during the admission, the effect of the primary sector's acceptance rate of interventions made by the secondary sector is evaluated. The Shared Medical Card (FMK) is used for this purpose and the GP is also contacted. Thus it can be measured whether there will be a knock-on effect from the secondary to the primary sector. The acceptance rate during the admission is calculated using an extract of data from the Excel sheet where interventions and suggestions are registered.

3.7.2. Compliance

After six months calculation as to whether the patient is compliant or non-compliant is made based on the assumption that a patient is non-compliant if prescriptions are redeemed for less than 80% of the prescribed doses. This calculation is based on the Shared Medical Card (FMK).

3.8. Statistical analysis

3.8.1. Drug related admissions and readmissions

Time until new contact to the health service, death, number of admissions and readmissions are analysed using survival statistics (Kaplan-Meier graphs and Cox-regression). Likewise, the persistence of completed and accepted interventions after discharge are described by survival statistics, i.e. as an analysis of waiting time until the patient receives the medication in use prior to the intervention.

3.8.2. Compliance

The survival statistics, as described above, are used for analysis of non-persistence as a measure of non-compliance, as the patient is assumed to be persistent at discharge but may become non-persistent at a variable time point after discharge.

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9 Defined as number of interventions completed by the clinical pharmacist and the suggestions for interventions accepted by hospital doctors and the GP’s respectively in relation to the total number of suggestions for interventions
Another measure of compliance is the proportion of days covered, which describes a ratio between dispensed drug quantity within a given period and the drug quantity, having been dispensed in case of perfect compliance. Parametrical analyses are used in analyses of this measure.

3.9. Power calculation
Based on an estimated risk of readmission at 20 % in the control group, a two-sided level of significance at 5%, and 80% power, the study will require 354 patients in each intervention group and in the control group in order to show a reduction in the prevalence of admissions to 12 %. Thus, 1062 patients will be needed in total. In order to account for possible withdrawals it is decided to include 500 patients in each group, 1500 patients in total. In cases of withdrawal the patient is included until the time of withdrawal, corresponding to a per protocol analyses.

4. Ethics
The Danish Data Protection Agency and the Regional Ethics Committee have both been notified of the study. The Heads of Departments have given permission to access the department’s electronic records system. Written informed consent is required, whereby the patients accept that we gain access to the electronic records and Shared Medical Card (FMK), contact patient’s general practitioner and authorise that we deactivate and thus invalidate outdated prescriptions at the primary pharmacy, which according to the National Health-IT is in accordance with current legislation. Identifiable personal data will be anonymised when registered/published.
5. References


8. Ilsøe-Kristensen S. Cross-sectorial communication and drug management after hospital discharge: an observational study of heart failure patients: Faculty of Pharmaceutical Sciences, Department of Pharmaceutics and Analytical Chemistry, University of Copenhagen; 2010.


