Original Research

Safe and effective use of medicines for patients with type 2 diabetes – A randomized controlled trial of two interventions delivered by local pharmacies

Lene Juel Kjeldsen, M.Sc. (Pharm), Ph.D.\textsuperscript{a}, Lars Bjerrum, M.D., Ph.D.\textsuperscript{b}, Pernille Dam, M.Sc. (Public Health)\textsuperscript{c}, Bente Overgaard Larsen, M.Sc. (Pharm)\textsuperscript{d}, Charlotte Rossing, Ph.D. (Pharm)\textsuperscript{c}, Birthe Søndergaard, Ph.D. (Pharm)\textsuperscript{e}, Hanne Herborg, M.Sc. (Pharm)\textsuperscript{c,*}

\textsuperscript{a}The Research Unit for Hospital Pharmacy, Amgros I/S, Copenhagen, Denmark
\textsuperscript{b}Section and Research Unit of General Practice, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
\textsuperscript{c}Pharmakon, Danish College of Pharmacy Practice, Milnersvej 42, Hillerød 3400, Denmark
\textsuperscript{d}Practice Department, Region of Southern Denmark, Vejle, Denmark
\textsuperscript{e}Health Affairs, Association of Danish Pharmacies, Copenhagen, Denmark

Abstract

Background: Poor management of chronic medical treatments may result in severe health consequences for patients as well as costs for society. Non-adherence is common among patients with type 2 diabetes. Interventions by community pharmacists may assist in improving adherence and consequently health outcomes for patients with type 2 diabetes.

Objectives: The study aimed to investigate whether a comprehensive and a brief individually targeted intervention for patients with type 2 diabetes could improve implementation of drug therapy in Danish community pharmacies. The interventions intended to give patients more competence and support to improve adherence and self-management in order to reach treatment goals for diabetes and blood pressure as well as goals for patient perceived outcomes.

Methods: This study was an RCT, comparing two interventions; basic intervention (BI) and extended intervention (EI). The intervention model sought to identify drug-related problems as well as issues experienced by patients in relation to medicines use, and consequently find individually tailored solutions to address the identified problems.

Results: The trial included five pharmacies; five pharmacists and five pharmaconomists, and 205 patients; BI (39 patients), EI (41 patients), Control (125 patients). Patient reported systolic blood pressure improved in both groups and significantly in the EI group compared to the control group ($P = 0.020$). Increase in disease-related knowledge was higher in the EI group compared to the control group ($P = 0.006$), but not in the BI group ($P = 0.139$). Except for quality of life, the EI group reported significantly higher improvement in all aspects of beneficial effects from participating in the trial when compared to the
control group. No significant differences were detected for changes in hospital admissions or in doctor visits. The two intervention groups reported significantly higher satisfaction with all aspects of patient satisfaction with pharmacy staff in the project than control patients.

Conclusions: The study showed improvement in patient health, well-being, knowledge, and satisfaction as a result of the trial, particularly for the EI group. Thus a program comprising patient narratives, problem and resource identification, and multi-dimensional individually tailored patient medication management solutions seems to be an appropriate intervention to ensure outcome improvement of non-adherent patients.

© 2015 Elsevier Inc. All rights reserved.

Keywords: Type 2 diabetes; Randomized controlled trial; Counseling; Self-management; Adherence; Patient empowerment; Pharmacy; Denmark

Background

Type 2 diabetes is one of the most prevalent chronic diseases affecting 350 million patients worldwide in 2011. In Denmark, 5.7% of the population – 320,545 persons – were diagnosed with diabetes in 2012. In 2005, a health technology assessment estimated that 100,000–150,000 were type 2 diabetes patients, but the real number of cases was estimated to be considerably higher (200,000–300,000) with 10,000–20,000 new cases each year. 202,600 patients had a medicine against type 2 diabetes dispensed in 2012. Patients with type 2 diabetes face numerous health risks that have serious consequences for their quality of life and life expectancy. Type 2 diabetes patients have increased cardiovascular risk and risk of long-term micro- or macro-vascular complications. There is strong evidence of benefits from managing type 2 diabetes using lifestyle interventions and/or drug therapy. Treatment of risk factors (elevated glucose, lipids and blood pressure) has been shown to reduce the risk of morbidity and mortality for patients diagnosed with type 2 diabetes. Hence, successful implementation of drug therapy is a key issue for type 2 diabetes patients.

Poor implementation of appropriate medical treatments may result in severe health consequences for patients as well as costs for society. Costs include wastage of medications as well as use of health resources due to lack of treatment effect – potentially leading to illness and death. Problems with use of medicines are common among patients with type 2 diabetes. Reports show that only 50–70% of the patients take their medication as prescribed, and patients with a simple drug regimen (1–2 times per day) seem to have higher adherence. Considering that optimal treatment of type 2 diabetes may include 5–8 medications to ensure effective regulation of blood glucose, blood pressure and lipids, this may pose a risk of non-adherence and problems with self-management. In addition, concomitant treatment with several drugs may result in adverse effects, which could complicate the treatment. According to the World Health Organization (WHO) adherence problems among patients with diabetes are very complex and should consequently not be viewed as a single-factor problem. The most important factors were the complexity of the medication regimen, perception of the disease, poor relationship between the health professional and the patient, depression and psychosocial stress. Research has documented that issues related to behavior are important for adherence, and a number of instruments have been developed to identify patients’ adherence status, motivational status, self-efficacy and desire for information. Concomitantly, surveys of intelligent non-adherence and concordance indicate that high adherence implies a high quality of the drug regimen, accepted by the patient. Furthermore, it implies a good communication between the doctor and the patient, ensuring that the patient is actively involved in decision making about the drug regimen.

The purpose of drug therapy is to benefit patients while keeping patients safe from harm. Adherence is in this respect not a goal in itself, but an important intermediate process measure. Safe and effective use of medicines is the major public health issue and, as documented above, this is in particular a problem for type 2 diabetes patients where successful drug therapy helps reducing diabetes symptoms as well as the risk of microvascular and macrovascular complications. Solutions need to address the complexity of the problem, and reviews confirm that multi-
dimensional models are more likely to be successful.\textsuperscript{7,10,11}

Various recent studies within the community pharmacy setting aimed at patients with type 2 diabetes have been performed. Some studies consisted of group interventions,\textsuperscript{23,24} and some were aimed at individual patients.\textsuperscript{25} A recent systematic review on diabetes and cardiovascular disease interventions by community pharmacists concluded that the reviewed studies were of poor quality, time-intensive, and a lack of clinical significance existed.\textsuperscript{26}

Proactive individual case management in a primary care clinic by a specialized clinical pharmacist has been shown to improve glycemic control and diabetes process-of-care measures.\textsuperscript{27} We found that there is a need for studies investigating the benefit of complex individualized models to support safe and effective use of medicines for type 2 diabetes patients delivered by community pharmacy staff groups in Danish pharmacies.

In the current study, complex problems were addressed using a systems approach based on the WHO model and pharmaceutical care research and individual behavior change in a social context. Hence, we have developed and tested a complex model\textsuperscript{28} which we will implement in a community pharmacy setting and evaluate regarding effect. Additionally, we will test whether the intervention may be delivered in a basic version, even though this intervention is less intensive.

**Objectives**

The aim of the study was to investigate whether a comprehensive and a brief individually targeted intervention for patients with type 2 diabetes could improve implementation of drug therapy in Danish community pharmacies. The intervention intended to give patients more competence and support to improve adherence and self-management in order to reach treatment goals for diabetes and blood pressure as well as goals for patient-perceived outcomes.

**Methods**

This study was designed as an RCT and included a comprehensive process evaluation. The RCT aimed to test two interventions for improving implementation of drug therapy in community pharmacies in the county of Funen in Denmark. In 2006, Funen had a mixed rural and urban population of 478,347 inhabitants, or approximately 9% of the Danish population.\textsuperscript{29}

**Concept of the interventions**

The concept of the interventions consisted of an individualized problem screening and a multidimensional model for designing targeted solutions in collaboration with patients with a potential adherence problem. The model was based on a systems approach using the WHO model for complex problems for patients in long-term therapy\textsuperscript{7} as illustrated in Fig. 1, showing “The individualized systems model,” which was the key tool used for the intervention.\textsuperscript{28} The WHO model operates with five dimensions of adherence: Social and economic factors; Health care team and system related factors; Condition-related factors; Patient-related factors; and Therapy-related factors. In order to design a model for use in the counseling of individual patients, this model was combined with models from pharmaceutical care focusing on monitoring outcomes of drug therapy\textsuperscript{22,27,30} and patient empowerment for self-management and adherence. The current model; “Safe and effective use of medicines,” was developed for implementation in primary care, and has been described in detail elsewhere.\textsuperscript{28} It aimed to support patients in the self-management process regarding choice and implementation of their drug therapy with the purpose of improving patient outcomes. Various strategies were used including review of medication profile and refill compliance, assessing goals for clinical parameters, assessing and distinguishing between different types of non-adherence, use of patient narratives as starting point, use of

![Fig. 1. The individualized systems model.](image)
motivational interviewing strategies and coaching techniques, use of patient information and education, use of adherence-supporting technologies, and collaboration with patient’s GPs. Development of the concept was performed on a different group of chronic patients: users of antihypertensive medications, and subsequently adapted to patients with type 2 diabetes. Hence the overall concept remains the same for the current population: users of oral antidiabetics. We have based our intervention development on the framework for complex interventions published by the British Medical Research Council (MRC). Hence, the development has involved an evidence report, a theoretical work report, and two development projects with blood pressure patients where the model and the individual elements have been evaluated and tested in more explorative and learning-oriented studies focusing on process and feasibility.

**Intervention strategy**

The intervention model sought to identify drug-related problems as well as issues experienced by the patient in relation to medicines use, and consequently find individually tailored solutions to address the identified problems. Despite the potential complexity of the problems, the targeted solutions could be simple, e.g. provision of medication information or introducing a dose administration aid (DAA). Two interventions were created based on this concept of intervention (Table 1):  

1. A Basic Intervention provided by a pharmaconomist (BI)  
2. An Extended Intervention provided by a pharmacist (EI)  

The key elements of both interventions were:  

1. Quick screening for non-adherence and identification of problem types  
2. Patient narratives (story-telling) as the key starting point  
3. Assessment and possibly adjustment of drug therapy  
4. Finding resources in the system around the problem and the patient (the patient’s system)  
5. Dialog based on motivational interview or individual coaching, in order to tailor solutions to individual needs and resources  
6. Offering relevant reminder technology and/or patient instruction  
7. Follow up  
8. Close collaboration with patient’s GP

Quick screening was based on a questionnaire, Quick Screening Instrument (QSI), a check of the patient’s Personal Electronic Medication Profile, a blood sugar measurement and – for patients randomized for the extended intervention group – a blood pressure measurement. Patient narratives were used to individualize, but also to strengthen, the systems approach, and ensure that not only individual factors were addressed, but also factors in the surrounding system. This was in particular important when resources for solutions were investigated.

Common for the two interventions was the overall concept of the trial, most of the intervention tools and the importance of recognizing that the patients had to be monitored during a period of time to ensure proper implementation of all identified adherence, medication-related, and patient perceived problems. Thus, the intervention was delivered during a 6 months period from January 2007 to June 2007.

The main differences between the BI and the EI were related to the EI being a more comprehensive and hence time-consuming intervention – and the BI being delivered by pharmaconomists, while the EI was delivered by pharmacists (Table 1). The additional of the EI comprised a medication review, BP measurements, comprehensive interview, coaching and patient education (Table 1). Particularly in the EI group, control of the patient’s diabetes was a key aspect.

Pharmacy staff (pharmacists and pharmaconomists) delivered the interventions in collaboration with the patients, and the patients’ GPs were informed about the program content and contacted whenever necessary. Before commencing the trial, pharmacy staff was trained in delivering all aspects of the respective interventions. In relation to behavior change, both groups were trained in motivational interviewing and given tools to support working with ambivalence toward changing medication use behavior. Pharmacists in the EI group were given additional training and tools for coaching to support establishing and maintaining self-efficacy in relation to behavior change.

---

f Danish pharmaconomists (pharmacy assistants) are educated in pharmacies and at Pharmakon (Danish College of Pharmacy Practice) in a 3-year program. The Ministry of Education regulates the education.
<table>
<thead>
<tr>
<th>Provided by</th>
<th>Basic intervention</th>
<th>Extended intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pharmaconomists</td>
<td>Pharmacists</td>
</tr>
<tr>
<td>Estimated time for</td>
<td>About 65 min distributed over at least 4 sessions and delivered within 6 months</td>
<td>About 130 min distributed over at least 4 sessions and delivered within 6 months</td>
</tr>
<tr>
<td>delivering the intervention</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Medicines use check | Identify potential non-adherence and patient-reported problems using the Quick Screening Instrument | Identify potential non-adherence and patient-reported problems using the Quick Screening Instrument |
| Blood pressure measurement | Not measured | Medication review (therapeutic and economic issues) |
| Blood glucose measurement | Using a manual | Using a manual |
| Interview          | Short basic interview with patient narratives as starting point | Comprehensive interview with focus on patient narratives |
| Knowledge and beliefs | Provide information and counseling | Provide information and counseling |
|                      | Provide pamphlets | Provide pamphlets |
|                      | Patient education in issues regarding the metabolic syndrome including glucose levels, blood pressure, lipid levels, medication, self-management |
| Motivation          | Dialog based on “motivating interview” | Dialog based on “motivating interview” |
|                      | Agreement on shared goals and plans | Using coaching techniques when deemed necessary |
| Behavior            | Support to structuring and remembering medication intake: | Support to structuring and remembering medication intake: |
|                      | ● Individually designed reminder strategies | ● Individually designed reminder strategies |
|                      | ● Dosing aids | ● Dosing aids |
|                      | ● Dose dispensing | ● Dose dispensing |
|                      | ● Medication event monitoring systems (MEMS) and feedback | ● Medication event monitoring systems (MEMS) and feedback |
|                      | ● Blood pressure measurements at home | ● Blood pressure measurements at home |
|                      | ● Paper- or net-based diaries containing own data | ● Paper- or net-based diaries containing own data |
|                      | ● SMS service or e-mail service | ● SMS service or e-mail service |
| Contact with GP     | Feedback to GP concerning dialog and referral of patient if deemed necessary | Feedback to GP concerning dialog and referral of patient if deemed necessary |
| Network and other health professionals | Involving network in support for medicines use | Involving network in support for medicines use |
|                      | Referral to other health services, e.g. smoking cessation | Referral to other health services, e.g. smoking cessation |

The table is updated to the current population from the original description developed for users of antihypertensives as published previously. 29

Participants

Patients were included from five pharmacies in the county of Funen, and we identified from pharmacy records if the patients had purchased oral antidiabetics in the period from 01.01.2006 to 30.09.2006. More than 2000 eligible patients were identified, contacted by mail and invited to participate in the project (Fig. 2). The aim of this broad invitation strategy was to recruit a sample for a questionnaire survey as well as a cohort for the RCT.

Patients were included in the project if they fulfilled the following criteria:

- ≥18 years
- Used oral antidiabetics
- Administered their medication themselves
- Gave written consent to participation in survey and RCT.

All together, 205 patients were eligible to be included in the RCT, and they were randomized to either one of the intervention groups or the control group.

Data collection

Data were collected at baseline by the use of a Quick Screening Instrument (QSI) and an extended questionnaire. The QSI was developed and validated to screen for potential adherence problems among users of oral antidiabetics, and it was also intended as a tool for supporting counseling at the pharmacy as a part of the intervention. The patients filled in the QSI instrument, which they received by mail. The instrument was developed and validated in a previous study that focused on patients treated for hypertension.\textsuperscript{28,32,36,37} The questionnaire consisted partly of self-developed questions, partly of validated questions from international research on adherence. Data from the QSI were collected in December 2006 and contained questions on: Demographics, self-reported clinical measures: Blood sugar (BS) and blood pressure (BP) levels as reported measured by the GP at the most recent visit, GP satisfaction with clinical goals, medication-taking behavior, three adherence measures previously validated\textsuperscript{32}: Behavior-related

Fig. 2. Patient flow regarding inclusion, randomization and analysis of the study.
adherence (non-intentional), Behavior-related adherence (intentional, self-regulation) and Behavior-related adherence (intentional, effect-related), number of medications used, practical problems, e.g. difficulties swallowing the medication. Also HbA1c, LDL, HDL, and triglycerides as reported measured by the GP at the most recent visit were collected, but the response rate for these values was below 50% and consequently considered too low for inclusion in the analyses.

After returning the QSI, the patients received a larger questionnaire which served the purpose of elaborating on the potential adherence problems and adherence behavior. Data from this questionnaire were collected in January 2007 and contained validated tools and questions about: Health-Related Quality of Life (HRQoL) measured by EuroQol (EQ-5D), knowledge about diabetes and treatment of the disease, Perceived Competence for Diabetes Scale (PCDS), perceived concordance, self-efficacy, hospital admissions and consultations with doctors. At endpoint (June/July 2007), the questionnaire was distributed again and included patient satisfaction with the service as well. At the same time, pharmacy staff and GPs also received questionnaires about their satisfaction with participation in the project.  

Process data including detailed information on interventions delivered during the trial were collected by the pharmacy staff during the intervention period. This included BS measurements for both groups and BP measurements for the EI group during the trial.

The BP measures from the first and last intervention consultation at the pharmacy were included in the evaluation. In addition, patient-reported problems with reaching clinical goals set by the patient’s GP were recorded during the trial in both groups. The results of this process measure from the first and last intervention consultation at the pharmacy were included in the evaluation.

**Randomization**

If at least one of the following criteria were fulfilled, the patient was considered potentially non-adherent, and was included in the trial:

- Self-reported HbA1c level > 6.1% at the most recent GP visit
- Self-reported blood pressure level > 130/80 mm Hg at the most recent GP visit
- Treatment with 7 or more medications concomitantly
- Indicated non-adherence according to preset questions in QSI questionnaire regarding medication taking behavior.

The potentially non-adherent patients were randomized into the two intervention groups and the control group, respectively. Before commencing the trial, pharmacy staff had announced to how many patients they were willing to deliver the intervention. The goal was to include 80 patients in the interventions, and pharmacists would deliver the extended intervention (EI) to 41 patients, and pharmaconomists the basic intervention (BI) to 39 (Fig. 2). The sample size estimation was based on the assumption that detecting a decrease in systemic blood pressure from 159 mm Hg to 135 mm Hg would require 22 patients in each group, assuming a standard deviation of 15 mm Hg on both values.

**Statistical analyses**

The statistical methods used in the trial were ANOVA and paired t-test for normally distributed continuous variables; Kruskal–Wallis test, Wilcoxon test and Mann–Whitney test for ordinal and non-normally distributed continuous variables; and \( \chi^2 \)-tests and Fisher’s exact tests for categorical variables. A significance level of 0.05 was used, but when the two intervention groups were tested individually against the control group, Bonferroni adjustment was applied, i.e. a significance level of 2.5% was used in those cases. All analyses were performed using SPSS 15.0 for Windows.

**Ethical approval**

The study was approved by the Danish Data Protection Agency, and The National Board of Health, the Association of Danish Pharmacies and the Danish Association of Pharmaconomists granted financial support for the study.

The study was submitted to The National Committee on Health Research Ethics who deemed it unnecessary to assess for approval as it was not of biomedical nature.

The project was overviewed by a steering committee consisting of members representing pharmacies, general practitioners, patient representatives and researchers.

**Results**

Five pharmacies were included in the trial; five pharmacists and five pharmaconomists, and 205 patients met the inclusion criteria and were...
randomly allocated into three groups; 39 to the basic intervention (BI) group, 41 to the extended intervention (EI) group, and 125 to the control (C) group (Fig. 2). The patients were on average 62.6 years of age, 61.0% were males, and they were on average taking 4.7 drugs. No statistically significant differences in demographic or outcome variables were found at baseline (Table 2). The 80 intervention patients visited 56 different GPs.

Problems potentially related to adherence difficulties identified at baseline

The most frequently (44%) reported practical problem was change in names of medicines caused by generic substitution, followed by problems with adverse effects and difficulties opening the medication container.

When exploring the experiences and need for partnership in treatment (concordance), the majority (86%) of the patients reported that they would like to be actively involved in decisions about their treatment, and 85% indicated that they were satisfied with the decisions made (Fig. 3). However, only half of the patients responded that they had been asked sufficiently about their views about their treatment (Fig. 3).

During the initial visit at the pharmacy for intervention patients, problems potentially related to adherence difficulties were identified by the pharmacy staff. According to the intervention registrations based on the QSI instrument, clinical measurements and the patient’s Personal Electronic Medication Profile accessed by the pharmacy staff, potential adherence problems or drug-related problems were identified among 90% of the patients. Problems with lack of knowledge about medication and treatment were reported for more than 60% of the patients (BI: 62%, EI: 54%).

Non-intentional non-adherence was more common than intentional non-adherence (BI: 46%, EI: 68%, C: 62%), and intentional self-regulation

Table 2

<table>
<thead>
<tr>
<th>Characteristics of study participants</th>
<th>Basic intervention</th>
<th>Extended intervention</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>22 (57.9%)</td>
<td>25 (59.5%)</td>
<td>78 (62.4%)</td>
<td>0.863&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.1 (8.8)</td>
<td>63.4 (7.8)</td>
<td>62.1 (10.2)</td>
<td>0.897&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Non-adherence measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavior-related non-adherence</td>
<td>17 (45.9)</td>
<td>28 (68.3%)</td>
<td>77 (62.1%)</td>
<td>0.108&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>(non-intentional)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavior-related non-adherence</td>
<td>5 (13.5%)</td>
<td>9 (22.5%)</td>
<td>33 (26.8%)</td>
<td>0.246&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>(intentional, self-regulation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavior-related non-adherence</td>
<td>3 (8.3%)</td>
<td>8 (19.5%)</td>
<td>20 (16.5%)</td>
<td>0.369&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>(intentional, effect-related)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consequences</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital admissions during past 6 months</td>
<td>5 (13.2%)</td>
<td>7 (17.5%)</td>
<td>19 (17.0%)</td>
<td>0.838&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Doctor consultations during last 6 months</td>
<td>36 (94.7%)</td>
<td>39 (97.5%)</td>
<td>106 (95.5%)</td>
<td>0.892&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Experience of one or more practical difficulties with the medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (st.d.)</td>
<td>5.1 (2.6)</td>
<td>4.5 (2.7)</td>
<td>4.6 (2.8)</td>
<td>0.373&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Number of drugs</td>
<td>141 (17.9)</td>
<td>138 (14.1)</td>
<td>139 (14.9)</td>
<td>0.064&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Systolic blood pressure (patient report of latest GP measure) (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td>0.811 (0.201)</td>
<td>0.782 (0.212)</td>
<td>0.812 (0.217)</td>
<td>0.867&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Concordance</td>
<td>13.1 (3.5)</td>
<td>13.3 (3.7)</td>
<td>12.7 (3.8)</td>
<td>0.549&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Knowledge (factual)</td>
<td>4.4 (4.7)</td>
<td>4.1 (4.8)</td>
<td>4.9 (4.4)</td>
<td>0.560&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Self-efficacy (general)</td>
<td>4.4 (0.9)</td>
<td>4.5 (0.5)</td>
<td>4.5 (0.7)</td>
<td>0.912&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Self-efficacy (side-effects)</td>
<td>4.2 (0.9)</td>
<td>4.5 (0.6)</td>
<td>4.4 (0.7)</td>
<td>0.545&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Perceived competence for diabetes scale</td>
<td>3.8 (0.7)</td>
<td>3.9 (0.6)</td>
<td>4.1 (0.6)</td>
<td>0.200&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Pearson’s χ²-test.

<sup>b</sup> Fisher’s Exact Test.

<sup>c</sup> Kruskal–Wallis Test.
was more common that effect-related intentional non-adherence (BI: 8%, EI: 20%, C: 17%). Non-adherence was less common in the BI group, but the difference was not statistically significant.

Adherence and self-management enhancing solutions delivered during the intervention period

For both of the interventions, the most frequently delivered technical adherence and self-management improving interventions were self-monitoring of blood glucose, use of diary, use of individual reminder systems, and introduction of dose administration aids (Table 3). The latter was significantly more frequently delivered in the basic intervention. Also, the use of SMS reminder services was significantly more frequently introduced in the basic intervention. The number of technical adherence improving interventions per patient was 1.1 in the EI group and 2.5 in the BI group. However, when considering more cognitive adherence and self-management improving interventions, provision of patient education and education in how to interpret blood-glucose levels were delivered significantly more frequently to patients receiving the extended intervention (Table 3). The number of counseling services delivered per patient was 10.7 in the EI group and 7.7 in the BI group. Patients who received the extended intervention were also more often recommended to contact their general practitioner, while patients receiving the basic intervention more frequently were referred to lifestyle interventions at the pharmacy (Table 3).

During the trial, blood-glucose levels measured at the pharmacy decreased (however not significantly, paired t-test) in both intervention groups. Another clinical measure, blood pressure, was measured during the trial for patients in the extended intervention group. The systolic blood pressure (first consultation-last consultation at the pharmacy) decreased significantly (paired t-test, \( P < 0.001 \)) in this group during the trial from an average of 152.5 mm Hg (st.d. 18.3) at the first consultation to 138.6 (st.d. 17.6) at the last consultation.

A comprehensive review of the patient’s medication regimen was only required as part of the extended intervention. The most frequently suggested medication changes to the patients’ GPs were medication initiation, change of medication and increase of dose.

Outcome evaluation

The change in systolic blood pressure was significantly different between the three groups.
with both interventions groups experiencing a larger decrease in systolic BP than the control group (Table 4). Pair wise tests between the two intervention groups and the control group showed that the decrease in systolic blood pressure was significantly larger in the extended intervention group ($P = 0.020$, Wilcoxon Test). No significant difference was found between the basic intervention group and the control group ($P = 0.070$, Wilcoxon Test), but the difference is of the same size as for the EI group. Also, change in factual knowledge differed significantly between the three groups (Table 4). Pair wise tests between the two intervention groups and the control group showed that increase in knowledge was significantly higher in the extended intervention group ($P = 0.006$, Wilcoxon Test), but no significant difference was found between the basic intervention group and the control group ($P = 0.139$, Wilcoxon Test). In addition, no significant differences were detected for changes in hospital admissions ($P = 0.905$) or in doctor visits ($P = 0.834$) (Table 5).

No significant differences were found within or between the groups in the three behavior-related non-adherence measures. Only the changes in behavior-related adherence (intentional, self-regulation) showed a trend toward improved adherence in the EI group relative to the control group (change from adherent to non-adherent EI: 2.2%, C: 6.9% and change from non-adherent to adherent EI: 14.3%, C: 12.1%).

**Patient-experienced benefits from trial participation**

Except for quality of life, the EI group reported significantly higher improvement in all aspects of beneficial effects from participating in the trial when compared to the control group (Table 4). Even though there was no difference in quality of life when compared to the control group, the group reported significantly higher improvement than the BI group (Table 4). In fact, improvement in type 2 diabetes, symptoms of type 2 diabetes and sense of security in using medications correctly were significantly higher among EI patients when compared to BI patients. Only knowledge about type 2 diabetes was
improved significantly more among BI patients when compared to the control group (Table 4).

**Patient satisfaction with pharmacy staff**

The two intervention groups reported significantly higher satisfaction with all aspects of patient satisfaction with pharmacy staff in the intervention group than in the control group (Table 4). In addition, the EI group was significantly more satisfied with all aspects of patient satisfaction with pharmacy staff except for one aspect: “My personal contact to the pharmacy staff has improved” (Table 4).

**Collaboration between the pharmacies and the GPs**

While all 10 (100%) pharmacy staff responded regarding their satisfaction with participating in the project, 22 (39.3%) of the GPs returned the

---

**Table 4**

Changes in outcome measures (endpoint-baseline)

<table>
<thead>
<tr>
<th></th>
<th>Extended intervention Mean (st.d.)</th>
<th>Basic intervention Mean (st.d.)</th>
<th>Control Mean (st.d.)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of drugs</td>
<td>0.42 (1.54)</td>
<td>−0.28 (1.67)</td>
<td>−0.16 (2.03)</td>
<td>0.212¹</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>−6.7 (18.7)</td>
<td>−7.5 (15.6)</td>
<td>−1.4 (12.7)</td>
<td>0.033¹</td>
</tr>
<tr>
<td>(patient report of latest GP measure) (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td>0.060 (0.146)</td>
<td>0.050 (0.179)</td>
<td>0.003 (0.144)</td>
<td>0.084¹</td>
</tr>
<tr>
<td>Concordance</td>
<td>−3.1 (3.5)</td>
<td>2.4 (3.8)</td>
<td>−1.9 (3.7)</td>
<td>0.282²</td>
</tr>
<tr>
<td>Knowledge (factual)</td>
<td>1.8 (3.5)</td>
<td>1.0 (3.5)</td>
<td>−0.2 (3.6)</td>
<td>0.016²</td>
</tr>
<tr>
<td>Self-efficacy (general)</td>
<td>0.29 (0.45)</td>
<td>0.29 (0.64)</td>
<td>0.27 (0.65)</td>
<td>0.446²</td>
</tr>
<tr>
<td>Self-efficacy (side-effects)</td>
<td>0.14 (0.51)</td>
<td>0.34 (0.70)</td>
<td>0.20 (0.72)</td>
<td>0.496²</td>
</tr>
<tr>
<td>Perceived competence for Diabetes Scale</td>
<td>−2.1 (1.1)</td>
<td>−2.0 (0.9)</td>
<td>−2.3 (1.0)</td>
<td>0.254²</td>
</tr>
</tbody>
</table>

¹ Kruskal–Wallis Test.
² ANOVA.

---

**Table 5**

Patient perceived outcomes

<table>
<thead>
<tr>
<th>What were your experiences from participating in the trial?</th>
<th>EI (%)</th>
<th>BI (%)</th>
<th>C (%)</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>My type 2 diabetes has improved...</td>
<td>17 (44.7%)</td>
<td>6 (19.4%)</td>
<td>12 (12.2%)</td>
<td>ABC</td>
</tr>
<tr>
<td>My knowledge about type 2 diabetes has improved...</td>
<td>23 (63.9%)</td>
<td>13 (41.9%)</td>
<td>17 (17.3%)</td>
<td>ACD</td>
</tr>
<tr>
<td>My knowledge about the effect of the medicine on type 2 diabetes has improved...</td>
<td>18 (48.6%)</td>
<td>8 (25.8%)</td>
<td>12 (12.4%)</td>
<td>AC</td>
</tr>
<tr>
<td>My knowledge about how my lifestyle affects my type 2 diabetes (e.g. exercise, smoking, diet, weight, stress, alcohol) has improved...</td>
<td>16 (44.4%)</td>
<td>7 (23.3%)</td>
<td>20 (20.4%)</td>
<td>C</td>
</tr>
<tr>
<td>My symptoms of type 2 diabetes has improved...</td>
<td>11 (30.6%)</td>
<td>3 (9.7%)</td>
<td>9 (9.3%)</td>
<td>ABC</td>
</tr>
<tr>
<td>My skills in using my medications correct have improved...</td>
<td>10 (27.8%)</td>
<td>4 (12.9%)</td>
<td>7 (7.2%)</td>
<td>AC</td>
</tr>
<tr>
<td>My sense of security in using my medications correct has improved...</td>
<td>11 (29.7%)</td>
<td>2 (6.5%)</td>
<td>13 (13.4%)</td>
<td>ABC</td>
</tr>
<tr>
<td>My quality of life has improved...</td>
<td>10 (27.0%)</td>
<td>1 (3.2%)</td>
<td>11 (11.2%)</td>
<td>AB</td>
</tr>
<tr>
<td>Satisfaction with the pharmacy staff</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>My personal contact to the pharmacy staff has improved...</td>
<td>24 (64.9%)</td>
<td>15 (50.0%)</td>
<td>8 (8.3%)</td>
<td>ACD</td>
</tr>
<tr>
<td>My view of the professional knowledge of the pharmacy staff has improved...</td>
<td>30 (78.9%)</td>
<td>11 (36.7%)</td>
<td>8 (8.2%)</td>
<td>ABCD</td>
</tr>
<tr>
<td>My view of advice given my the pharmacy staff has improved...</td>
<td>28 (73.7%)</td>
<td>12 (40.0%)</td>
<td>12 (12.2%)</td>
<td>ABCD</td>
</tr>
<tr>
<td>My view of the pharmacy staff’s ability to help me with problems related to my medications has improved...</td>
<td>28 (75.7%)</td>
<td>15 (50.0%)</td>
<td>12 (12.2%)</td>
<td>ABCD</td>
</tr>
<tr>
<td>My confidence in the pharmacy has improved...</td>
<td>28 (73.7%)</td>
<td>13 (41.9%)</td>
<td>10 (10.2%)</td>
<td>ABCD</td>
</tr>
<tr>
<td>My experience of confidentiality at the pharmacy has improved...</td>
<td>25 (67.6%)</td>
<td>12 (38.7%)</td>
<td>8 (8.2%)</td>
<td>ABCD</td>
</tr>
</tbody>
</table>

A, P < 0.05 for all groups; B, P < 0.05 for EI and BI; C, P < 0.05 for EI and C; D, P < 0.05 for BI and C.
evaluation questionnaire, and only 13 (23.2%) reported that they were aware of the project. Pharmacy staff would have liked further involvement in the project from GPs, while GPs were generally neutral or positive about collaborating with the pharmacy staff in the project. Patients receiving the extended intervention (14 (37.8%)) did more frequently report that they felt that the collaboration between their pharmacy and their GP had improved than patients receiving the basic intervention (5 (16.7%)). Patients in both groups experienced neither improvement nor deterioration in their personal relationship with their GPs as a result of the trial compared to the control group.

Satisfaction with participation in the trial among pharmacy staff

No differences were found in project satisfaction between pharmacists and pharmaconomists. They all reported that they were satisfied with their participation in the project, that their competence regarding type 2 diabetes had improved as part of the project, that they were properly professionally trained to deliver the intervention, and that they had appreciated the professional challenges as a result of the project which had given them more variation in their daily work at the pharmacy.

Discussion

The study showed improvement in outcomes of patient health, well-being, knowledge and satisfaction as a result of the interventions – in particular for the EI group patients. Pharmacy staff reported satisfaction with their delivery of the intervention, but wished more involvement from the patients’ GPs. Thus, a program comprising patient narratives, problem and resource identification, and multi-dimensional individually tailored patient medication management solutions seems to be an appropriate intervention to ensure outcome improvement of patients identified to be at risk of non-adherence.

Blood pressure and blood glucose

The outcome analysis showed that all patient groups experienced a decrease in self-reported systolic blood pressure during the trial. However, both intervention groups had improvement in systolic blood pressure when compared with the control group. The improvement was significant for the EI group, but the difference in the BI group is practically of the same size, and the results are probably not clinically different. This result was supported by a significant decrease (−13.9 mm Hg) in systolic blood pressure measured in the EI group during the consultations in the pharmacy. Whether a similar finding would have been evident for the BI group is uncertain since BP measurement was not a part of this intervention.

A change in blood glucose levels could not be detected for any of the intervention groups. However, blood glucose is not an optimal measure of type 2 diabetes status due to the high variability. Other clinical measures of type 2 diabetes (HbA1c, cholesterol, LDL, HDL and triglyceride levels) were sought collected by self-report at baseline and endpoint, but the response rates for these measures were too low (about 50%) to be justified for inclusion in the analyses. The project did not have access to GP records on clinical measures, but was granted access to a regional diabetes database, which unfortunately was incomplete for the time being.

Other outcomes

Knowledge

The outcome analysis showed a significant improvement of factual knowledge in the EI group compared to the control group; however, a similar finding was not evident for the BI group. The finding was supported by reports of improvements experienced by the patients where EI patients reported significant increase in all three types of knowledge; type 2 diabetes, the effect of the type 2 diabetes medicines and lifestyle affecting type 2 diabetes, when compared to the control group. Only improved knowledge about type 2 diabetes was reported significantly more frequently for BI patients when compared to control patients. The interventions delivered during the trial correspond with these findings. The most frequently delivered solutions in the EI group were general patient education and education in how to interpret blood glucose levels, which would be expected to have an effect on patient knowledge about their disease and medication. The most frequently delivered interventions in the BI group were patient information, introduction of DAAs, and SMS reminder services.

Quality of life

Both interventions were associated with a slight improvement in health-related quality of life (EQ-5D), but it was not significantly different
from the improvement in the control group \((P = 0.084)\). However, the EI patients improved significantly more than the BI group. These results show a trend of improved quality of life, in particular for the EI patients, as a consequence of the project. The difference between the two quality of life results may possibly be caused by varying definitions of quality of life between the two measures used. The EQ-5D comprises five aspects of health, which is one way of viewing quality of life, while the direct question to the patient of “quality of life” will require an individual interpretation of what quality of life is. This interpretation may not correspond to the aspects used in EQ-5D.

**Medication taking**

The three behavior-related non-adherence measures did not show significant differences. To detect an effect, a larger sample size would be required. The measures describe if patients intentionally or non-intentionally do not take their medicines as prescribed. The results indicate in accordance with the literature that even though adherence is an important intermediate outcome, safe and effective use of medicines is complex and involves much more than a simple compliance perspective.\(^7,12,28\)

Even though the PCDS, self-efficacy and technical difficulties did not show any significant differences in change between the groups when compared to the control group, the EI group reported improvement in self-reported skills in using medications correctly as well as improvement in sense of security in using my medications correctly. The latter improvement was also significantly better for the EI group when compared to the BI group. The reason for a potential improvement not detected by change in the PCDS and technical difficulties could be ceiling effects for these measures which might have left to little room for improvement, even though the patients had experienced such an effect and reported it in a different part of the questionnaire.

**Medication**

The number of medications did not change significantly between the groups during the trial. The number of medications was, however, not a specific target for the evaluation but rather improvement in rational pharmacotherapy. Medication reviews were required as a part of the EI, and these were performed on the basis of national treatment guidelines which recommend polypharmacy for many patients with type 2 diabetes. Even though the most frequent recommendation was medication initiation, there is no guarantee that these were implemented by the GP – or that a similar number of e.g. medication initiations were not implemented for the remaining patients without being a consequence of the trial. However, EI patients had an increase in the number of medications which was not the case for the BI and C groups. Hence, it is still possible that the EI patients’ medication regimen became more rational, but that was not evaluated.

**Health services use**

No differences were found in changes in visits to the general practitioner or hospital admissions. Hospital admissions are rather infrequent, even in this cohort of chronic medication users, and consequently detection of a significant difference – if evident – would require a larger sample size. An increase in visits to the general practitioner could have been expected as a consequence of the interventions, where medication-related problems were identified. This was, however, not the case, and the reason is most likely a ceiling effect in the measurement, since most patients with type 2 diabetes already visit their general practitioners frequently for monitoring of their diabetes.

**Collaboration between pharmacy, general practice and the patient**

One way of measuring the relationship between patient and health professionals is by using the concordance concept. The current study did, however, not show significant changes in concordance between the three groups. This was in spite of the responses of significant improvements in contact, confidence and general relationship with the pharmacy staff, particularly for the EI group, but also for the BI group when compared to control.

While significantly more BI patients were referred to further interventions at the pharmacy, more EI patients were recommended to contact their GPs. This might have led to the result of EI patients reporting significant improvement in collaboration between their pharmacy and GP, even though the patients personally did not experience improved contact with their GPs. Due to the low number of participating pharmacy staff members, it was not possible to establish whether pharmacists felt a significant improvement in collaboration with GPs. In fact, the feedback from pharmacy staff indicated that they would
have preferred further involvement from GPs in the trial, while GPs were generally neutral about collaborating with the pharmacy staff in the project. Pharmacy staff presumably felt an opportunity to establish a close working relationship with the GPs as part of the trial, but did not succeed to the expected extent. GPs, on the contrary, are used to collaborate with a large number of health professionals and might have regarded the contact with pharmacy staff as usual practice. Qualitative feedback from pharmacy staff did show that when they contacted GPs with specific problems, the problems were addressed in most cases. This is likely to reflect the way GPs usually work where specific problems end up getting solved. It is possible that pharmacy staff may need to change their expectations to the collaboration with GPs and focus on problem-solving instead of personal feedback on pharmacy action.

Limitations

The findings of this study are influenced by its limited size. Larger studies from Australia, USA and Brazil of comprehensive pharmacy-based interventions for individual patients with type 2 diabetes have found similar results for patient satisfaction and stronger results in improving adherence and clinical outcomes.37–39 The American Asheville37 project also demonstrated a decline in mean total direct medical costs. This suggests that pharmacy-based models are feasible in many health care systems.

A number of limitations to the current study are evident. First of all, the sample size was small. Even though some results came out significant, it is possible that a larger cohort of patients would show stronger trends in results of outcome measures (type 2 error). The sample size was calculated from a detectable change in systolic blood pressure of 15 mm Hg. However, we followed several other outcomes, and some of those would presumably have required a larger number of participants to demonstrate effect. Additionally, the follow-up period was only half a year. It is possible that a longer follow-up period would have resulted in larger detectable differences between the groups; however, time restraints and funds did not allow for a larger patient population or follow-up period.

The evaluation method also caused some challenges. Even though the interventions were designed using platforms for each of the interventions, all patients were considered as a unique case resulting in individual solutions, which is a challenge to evaluate quantitatively.

Availability of relevant data collection tools was also a limitation to the study. Many of the validated tools used for quantitative analysis in the current study did not show significant changes between the three groups, even though improvements were reported for endpoint evaluation questions, particularly for the EI group, when compared to the other groups. This might be due to lack of sensitivity to change for the data collection tools – or due to the relatively low sample size.

Another limitation to the study was that most of the evaluation measures were self-reported. More objective measures such as e.g. other clinical measures and adherence evaluation using prescription records were proposed initially, but low response rates on the clinical measures and low data quality of the prescription records led to exclusion of those measures.

Finally, the evaluation of GP satisfaction was limited due to a low response rate. Less than half of the GPs responded to the questionnaire in spite of follow-up. This might affect the representativity of the results. Pharmacy staff had contacted all GPs of their intervention patients to let the GPs know that their patients were participating in the trial. It was, however, not necessary to contact all GPs as a part of the interventions as such, which might have caused the GPs to forget the existence of the trial and consequently not respond to the evaluation questionnaire.

Conclusion

The study showed improvement in patient health, well-being, knowledge, and satisfaction as a result of the interventions. This was in particular evident for patients in the EI group. Pharmacy staff reported satisfaction with their delivery of the interventions, but would have liked further involvement from the patients’ GPs.

Thus a program comprising patient narratives, problem and resource identification, and multi-dimensional individually tailored patient medication management solutions seems to be an appropriate intervention to ensure outcome improvement of non-adherent patients.

Acknowledgments

The project was supported financially by the Danish Health and Medicines Authority,
Pharmadanmark, the Danish Association of Pharmaconomists, the Association of Danish Pharmacies and Pharmakon, and the Danish College of Pharmacy Practice.

References


