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Pharmacy Care and Adherence to Primary and Secondary Prevention Cardiovascular Medication- A systematic review of studies:

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Pharmacy care and adherence

pharmacy care, adherence, cardiovascular disease

Abstract

Objective
To determine if pharmacy service intervention can lead to enhanced adherence to primary and secondary cardiovascular medication and to identify features of interventions that have been found to be effective and feasible.

Methods
A systematic search of studies related to pharmacy service interventions on adherence and outcomes of cardiovascular diseases was performed using the following databases: Pubmed central UK, Pubmed, Cochrane Library, CINHAL, PsycINFO, EMBASE, International Pharmaceutical Abstracts and Google Scholar for the period from 01/01/1990 to 19/11/2013. Trials were included if they were (1) randomised control trials (2) studies delivered in hospital or community settings and (3) studies in English language. A hand search of relevant citations was also performed.

Key findings
Forty two studies were identified in which twenty six trials had statistically significant effect on adherence and twenty seven trials had significant effect on clinical outcomes of cardiovascular disease. The interventions included mainly patient education, collaboration between health care professionals, use of electronic devices and combined interventions. The interventions were found to be complex and included multiple components. Patient contact with a pharmacist was frequent and thus the interventions may be difficult to adapt into daily practice. Evidence- based data for pharmacy services remains weak but clearly pharmacists can have an impact through face-to –face patient education and telephone consultations. Further research is needed to evaluate the use of a motivational interview in the counselling session of a pharmacist and also to establish the continuity of pharmacy care in primary/secondary setting. Self reported adherence was the most widely used measure. The acceptable threshold remained 80% among the cardiac population.

Conclusion
Pharmacist interventions have been shown to be successful in enhancing adherence to cardiovascular medication and improving outcomes of cardiovascular diseases. Whilst, pharmacists play a fundamental role in primary and secondary prevention strategies, further RCT combining patient education with behaviour change is likely to reap further benefit in medication adherence.

Background

Adherence has been defined as the "active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behaviour to produce a therapeutic result."[1] Non adherence to medications has been documented to occur in > 60% of cardiovascular patients.[2] Primary non adherence (not initially filling the prescription) leads to a significant increase in one year mortality after hospitalization for myocardial infarction. [3] Secondary non adherence (failure to follow the instructions or to refill the prescription) has been shown to increase mortality, hospitalizations and costs.[2] Therefore, it is crucial to promote adherence to improve outcomes in these groups of patients.

Evidence-based data has demonstrated that pharmacists deliver clinical services that improve cost-effective quality of care in patients with cardiovascular diseases.[4] It is estimated that poor adherence costs 100 billion USD annually in the U.S [5] and the cost of unwanted medications exceeds GBP100 million annually in the UK.[6] Pharmacists have an increasingly important role in improving adherence. This role can be achieved through services in hospitals (for example medicines reconciliation and monitoring) and in community (In the UK Medication Usage Reviews and the New Medicine Service, in the USA Medication Therapy Management and in Australia and Canada MedsCheck program). Moreover, pharmacists have reduced health care costs by minimizing adverse clinical events (hospitalizations, emergency room visits, etc.) and reduced outpatient visits.[4] Advanced patient care services, delivered by pharmacists, decrease drug-related morbidity and mortality.[4] Therefore, it is accepted that pharmacists are well placed to support patients with their medication use. This review aimed to add to existing evidence that illustrate improved health care delivery through the use of pharmacist-delivered patient care with a focus on cardiovascular diseases.

Objectives

- To establish if there is an effect of pharmacy service intervention, on improving adherence to medications and outcomes of cardiovascular diseases.
- To identify types of interventions found to be effective in clinical trials in improving adherence to cardiovascular medication that could be implemented in practice.

Methods

Data resources

A systematic search of articles published in peer-reviewed health-care related journals was performed. Data bases Pubmed central UK, Pubmed, Cochrane Library, CINHAL, PsycINFO, EMBASE, International Pharmaceutical Abstracts and Google Scholar were searched for the period from 01/01/1990 to 19/11/2013.

Search terms and search strategy

The review commenced with three main key words "pharmacy service, adherence and cardiovascular disease"; with search restrictions to randomised control trials. The following key words were used (pharmacy care, adherence, cardiovascular disease or diseases), (pharmacy care, compliance, cardiovascular disease),(pharmaceutical care, adherence, cardiovascular disease), (pharmacists, cardiac disease, adherence), (adherence, pharmacists, cardiovascular disease), (adherence, pharmacist interventions, cardiovascular disease) in addition, search terms related to the type of diseases (hypertension or hyperlipidemia, or diabetes, or coronary heart disease, or heart failure). Following this search other key words were generated from MeSH (medical subject heading) terms in PubMed and term mapping database EMBASE. The reference list of relevant papers was also searched in order to identify any additional studies. Duplicate articles were removed if they were found in the different databases. Two articles published study protocols; therefore, the authors were contacted for results.

Selection criteria

Inclusion criteria: The articles were selected through screening of titles and abstracts. The criteria for relevant studies were: (1) randomised control trials. (2) interventions aiming to enhance adherence to cardiovascular medications. (3) trials evaluating clinical outcomes of cardiovascular diseases in which adherence was the secondary outcome. (4) Studies delivered in hospital or community settings and (5) Studies in English language.

Process of data extraction

A table of details of each intervention was developed and it included a full description of the nature of each intervention and its duration. The interventions were compared for differences and similarities then the main categories were established. They were categorized according to the mode of delivery. A further table was developed for adherence measurements then similar measurements were grouped. Further variables assessed were arranged in tables to enable analysis these included setting, patient groups, outcome measures and study design.

Results

The search yielded a total number of 4095 citations, the titles and/or abstracts of these articles were reviewed, 111 full text articles matched the inclusion criteria and were retrieved electronically and/or paper copy for assessment 39 articles were identified. The reference lists of the relevant 39 articles were also searched and an additional 3 articles were identified thus a total 42 randomised controlled trials were included in this review (Figure-1). All stages; identification, selection and review of papers, data extraction and coding and analysis were undertaken by two independent authors (the first and second author). In regular meetings any discrepancies were discussed and procedures were refined.

The 42 articles that met the inclusion criteria were conducted in different countries USA (18 articles), UK (3), Australia (3), Canada (4), UAE (2), Netherland (2), Belgium (2), Thailand (2), Northern Ireland (1), Portugal (1), Brazil (1), Spain (1), Jordan (1) and China (1).

Studies design

All the 42 studies included in this review were randomised controlled trials. Follow up for evaluation ranged from 3 months [7] to 36 months [8] however, in the majority of the studies the follow up period was either 6 months or 12 months. Regarding the sample size this ranged from a sample size of 30 [9] to 4100 patients. [10]

Patient/Disease groups

Of the 42 trials that met the inclusion criteria 17 were conducted with patients with hypertension [7,8,11-25], 10 [8,10,18,24-30] in diabetes, 7 [11,18,25,31-34] in dyslipidemia , 7 [35-41] in heart failure and 9 [9,25,42-48] in coronary heart disease (CHD). Five trials were aimed at populations with more than two co- morbidities or risk factors for cardiovascular disease.[8,11,18,24,25] One trial [11] studied patients with hypertension and dyslipidemia, another trial[18] studied patients with hypertension, dyslipidemia, diabetes and patients on anticoagulation therapy. Furthermore, two trials [8,24] included patients with hypertension and diabetes and finally, one trial[25] studied patient populations for both primary and secondary prevention (hypertension, diabetes, dyslipidemia, coronary heart disease).

Overview of goals of interventions and primary/secondary outcomes

In 19 trials[8,9,11,16,19,23,24,32-35,37-39,42,43,46-48] the aim of the intervention was to enhance adherence and adherence was the primary outcome. The remaining interventions measured adherence as a secondary outcome; the primary aims being to improve blood pressure control,[7,10,12-15,17,20-22,24] to improve glycaemic control and quality of care for diabetic patients,[26-30] or improve clinical outcomes in heart failure patients.[36,37,40,41] Other secondary outcomes included reduction in multiple cardiovascular risk factors,[18,25] to improve use of guidelines for secondary prevention medication in patients with CHD [44, 45] and the achievement of target lipid levels and lipid control.[31]

Setting

In fifteen studies the principal setting for the intervention was a community pharmacy[7,15-17,19,21,24,29,31-35,39,44], Fourteen studies the interventions were in hospital[11,12,23,26,27,30,37,38,40-42,45,47,48] and nine [8,10,13,14,18,20,22,25,28] in a clinic or primary care practice setting. In two trials[36,43] the intervention setting was patients' home and in one trial[46] the intervention was delivered from both a hospital and community pharmacist setting.

Details of the intervention

In accordance with eligibility criteria all interventions were conducted by a pharmacist. All interventions were complex and included multiple components. However, they are described here according to the principal component of the intervention:

A. Patient education

Education by a pharmacist was delivered face-to-face, as a telephone contact or by a home visit.

1-Face- to- face patient education

Pharmacists provided education face-to face with a patient in twenty-one trials. It followed a pre-specified structure in seven trials.[11,19,26,34,35,37,40] In addition, the consultation focused on the disease and it's prescribed medications.[11,18,21,24-29,32,37,39,40] The education also included discussions on medication related problems[17,24,28,32], lifestyle changes[12,17,18,21,24,25,27,29,44] and reinforcement of adherence.[12,17,19,34,35,44]

2- Patient education by telephone contact

Telephone counselling was the principal intervention in four trials. Three of which,[9,30,42] had an initial inpatient consultation by a pharmacist regarding their medications, prior to discharge. This was followed by structured pharmacist telephone counselling to reinforce the information. In the fourth trial [47] there was no inpatient consultation prior to the telephone calls. All subjects in the intervention group received education and counselling on medication adherence. The next call took place within 1 to 2 weeks or according to the need to support medication adherence.

3-Home visits by pharmacists

In two trials the intervention was delivered in home visits by a pharmacist. These included education on the disease, life style issues and compliance with therapy. [36,43] Recommendations were also made to the physicians and local pharmacies for adherence aids.

4-Motivational interviews

In one trial [10] adherence counselling and medication management was delivered by clinical pharmacists trained in behavioural counselling approaches (motivational interviewing). Details of training, application and implementation were provided to ensure principles of motivational interviews were followed. A road map was provided for the pharmacists, there was also an

assessment to check fidelity of the technique. Two further trials mentioned motivational interviewing, but gave no details on how this component was implemented as part of the intervention [16, 30] also no assurance of fidelity of the technique.

B. Collaboration between health care professionals

1-Collaborative care

In seven trials [8,13,14,22,31,38,45] the intervention involved collaboration between pharmacists and physicians or nurses, in a multidisciplinary approach. Five[8,13,14,22,31] of these trials, addressed suboptimal regimens and poor adherence to medication through these collaborations. The other two trials [38,45] included joint intensive multidisciplinary team programmes that provided counselling on medications, videos and printed material to promote adherence.

2-Communication between primary and secondary care

One trial [46] evaluated the effect of facilitated communication between hospital and community pharmacists on medication adherence. The intervention group received enhanced in-hospital counselling, communication of discharge medications to community pharmacists and physicians, and ongoing assessment of adherence by community pharmacists.

3- Combined intervention

One trial [48] described as a multifaceted intervention lasted for 1 year following discharge and comprised of: (1) pharmacist-led medication reconciliation 7-10 days after discharge and at one month via an in-person clinic visit or telephone call; (2) Pharmacists' provided the patient's primary care clinician and/or cardiologist with their contact details for questions or clarifications; and (3) 2 types of voice messaging (educational and medication refill reminder calls). The medication refill calls were synchronized to when a medication refill was due.
In a second trial[16] the participants received a number of interventions from the pharmacist which included: (1)Patient education and motivational interviewing; (2)electronic B.P home monitors; (3)home medicine review, dose administration aid and patient medication profile; (4) Refill reminders by SMS, telephone or mail.

C. Use of electronic devices

Four trials [7,15,20,33] used electronic devices, as the main intervention. In two trials [7,20] patients were provided with a fully automated Self Blood Pressure Monitor (SBPM) and told to perform 2 B.P measurements each morning. In one trial [15] patients were given a tool kit which included a B.P tracker and a pedometer. In another trial [33] patients were instructed on how to use a Medication Event Monitoring System MEMS (Medication bottles that contain a microelectronic chip that registers the date and time of every bottle opening). Patients' and a pharmacist jointly

reviewed the electronically complied dosing history, educational reminders and a beep card that reminds the patient of the dosing time were also used.

Additional components

Additional components to the above interventions included; written information,[7,9,10,12,15,17-21,25-27,30,36,37,39,40,42,44] providing patients with a diary,[17,37,40] a pocket medication card,[46] educational material, [10,46] education regarding the disease,[7,14,20] educational group activities,[8] recommending life style change,[31] recommendation to physicians, [7,13,15,22,42,45] telephone calls,[19,20,22,25,28,41] home visit,[17] home medicine review,[16] pill box,[7,15,42,46,48] blisters,[11] electronic blood pressure home monitoring[10,16] and visual props and media videos.[38,45]

Intervention duration

The interventions were delivered on a weekly basis,[7,9,10,28,30,36,42,46,47] monthly basis,[8,11-13,17,19-27,31-35,39-41,43,45,48] made at each prescription refill,[15,29,37] or arranged at physician visit,[18,24,27]according to pharmacist –determined patient need [14,44]and at one-time over 2 days.[38]

Measurement of adherence

Diverse indirect measures of adherence were used in the trials these included; prescription refills, Medication Event Monitoring System (MEMS), pill counts and self reported adherence scaled questionnaires MARS and Morisky Scale. Patients' self reported adherence alone or in combination with other methods of measurement were widely used in the 42 trials. Thirty two trials measured adherence by a single approach and ten trials combined two adherence measures (Table 1). To distinguish adherence from non- adherence, consumption or refilling 80% of the prescribed medication doses was the widely accepted threshold among the trials.[8-11,17,18,21,25,31,35,38,40,47,48]

Impact of interventions on adherence

The review aimed to assess the effect of pharmacist service intervention on adherence. Twenty six trials[7-9,11-13,15-19,21,23,26,27,30,33-35,37,39-41,45,46,48] showed a statistically significant improvement on adherence to cardiovascular medication (Table 2) (Supplemental Table 3). Improvement in adherence across the 42 studies ranged from no statistically significant difference to 35% significant absolute change in adherence.

Results indicate that face- to- face patient education by a pharmacist improved adherence in 15/21 studies (Table 2) suggesting education could have a significant effect on adherence. Electronic devices showed success in enhancing adherence in 3/4 studies. These included the integration of home automatic blood pressure monitor, the use of electronic reminders (beep

card) and an electronic blood pressure tracker. In all these trials pharmacists also provided tailored educational services and patient follow up.

One study [10] examined the use of motivational interviews by pharmacists, although it did not show significant results, details on the training of the pharmacists and the delivery and content of motivational interviews were provided. The authors report that high rates of treatment intensification and medication changes occurred in the control group leading to improvements in the studied outcomes among the controls.

Telephone calls with patient education and advice had a success rate on improving adherence in 2/4 trials that examined this type of intervention. Two other trials [16,48] tested a combination of interventions to improve adherence, that also included medication refill reminders by telephone and showed significant results. Three of the seven interventions that evaluated a collaborative care approach to improve adherence had statistically significant results. One trial [46] examined the impact of communication between hospital and community pharmacies and showed significant results on adherence.

Home visits by pharmacists did not have significant results on improving adherence to cardiovascular medication. In one trial [36] some possible reasons were provided by the authors that the intervention was brief and/or may have been too late in the disease course to evoke behaviour change. Also the pharmacists were not specialist in the disease studied.

Effectiveness of interventions on outcomes of cardiovascular diseases

Studied outcomes included; blood pressure control, HbA1c and/or fasting plasma glucose, Lipid profiles and LDL-C. Other outcomes were; reduction in 10 year Framingham risk score, costs and quality of life in addition to rehospitalisation, mortality and patient satisfaction with pharmacy services. Thirty nine trials evaluated the effect of pharmacy service interventions on outcomes of the diseases (Table 2) (Supplemental Table 3). Twenty seven trials had statistically significant results. In primary prevention from the 17 studies that studied hypertension 16/17 [7, 8, 11-24] showed significant results and improvement in cardiovascular risk factors, in diabetes 6/10 [8,18,24,26,29,30] improved glycaemia control for diabetic patients. For dyslipidemia 4/6 [11,18,32,34] studies improved lipid profiles. In secondary prevention 4/7 heart failure trials had significant results [37, 39- 41) on improving clinical outcomes (mortality, rehospitalisation and quality of life) and in coronary heart disease 2/8 trials [9, 43] achieved significant results on clinical outcomes.

Discussion

This review aimed to assess the effect of pharmacist led interventions on adherence to cardiovascular medications. Forty- two studies were identified of which twenty-six had a statistically significant and positive impact on adherence. Interpretation was complex due to the heterogeneity and multiplicity of the components. Results show that face-to-face patient counselling by a pharmacist as well as electronic interventions could be effective in improving

adherence. However, these interventions also involved other components. Evidence in other diseases has revealed that in person pharmacist and electronic interventions significantly improve adherence to medication.[49, 50]

Motivational strategies and behavioural support have been shown to enhance adherence to medication.[51, 52] In addition, Motivational strategies are increasingly used in health care to promote behaviour change, due to the need to focus on addressing the rising prevalence of chronic disease. In this review only one trial studied the use of motivational interviews, by pharmacists, to improve adherence and outcomes and showed no significant results. Furthermore, two trials mentioned the use of motivational interviews in the pharmacist counselling session, but did not give further details on the fidelity of the technique. In their reviews, Thompson *et al*, 2011[53] and Dalem *et al*, 2012[54], have addressed the fact that behavioural interventions are effective in improving adherence. However, they did not focus on pharmacists' role. For this reason, further evidence is needed to establish if and how motivational counselling in the pharmacy setting can lead to improvements on adherence.

A telephone call or a reminder by a pharmacist has been found to be an effective approach to improve medication adherence in other diseases.[55-57] In the review by Cutrona *et al*, 2010 [58], which reviewed studies focusing on cardiovascular diseases, phone calls showed low success (38%). In our review 4/6 trials that evaluated this method had statistically significant results. Therefore, the use of telephone calls and SMS to improve adherence could be an effective approach.

Interventions involving home visits by pharmacists have reported increased adherence to prescribed drugs, in an elderly population.[59, 60] Other studies, in contrast, which included a domiciliary assessment by a community pharmacist have found no effect on adherence,(61) studies in this review were not sufficient to provide evident conclusions.

Although interventions in hospital setting had more significant results, four of these trials were conducted in military hospitals [11,23,26, 48] in which financial barriers to adherence are removed and patients' attendance to appointments is high. Therefore, their results had limited generalisability and external validity. In the review Cutrona *et al*, 2010 [58] the results demonstrate that in-person interventions at hospital discharge were more effective (67%) than clinic interventions (47%) and in-person pharmacist interventions were effective when held in a pharmacy (83%) and less effective in clinics (38%).

Patients' self reported adherence alone or in combination with other methods of measurement were widely used in the 42 trials. This is as recommended by NICE, 2009 guidelines that have identified that whilst other types of measures are useful for clinical trials of new drugs, self report is an appropriate tool for clinical practice.[62] A threshold of 80% to determine adherence from non adherence was accepted among the trials. This finding is similar to other observational studies measuring adherence [63-66]. A study, by Wu *et al*, 2009 [67], showed a positive relationship between level of medication adherence and event-free survival in patients with heart failure. The study found that patients, who take 88% of their prescribed medication doses and on 88% of days take the correct dose, experienced a longer event-free survival than patients who are

less adherent. Moreover, in an article by Ho *et al* , 2009 the authors report an analysis that suggests that there continues to be reductions in clinical outcomes with adherence levels beyond 80% (eg, 80% to 100%), which suggests that the optimal level of adherence may be higher than current cut offs.[68] Whilst 80% is generally accepted, there are few studies which examine levels of adherence against outcomes over a period of time.

"Can the interventions, in the reviewed studies, be adapted to clinical practice?" "What would be features of an intervention to improve adherence?" These questions should be addressed with caution. The interventions were complex and time intensive as concluded in previous reviews [69]. In addition, a wide variety of approaches have been employed in the pharmacy interventions. All the interventions included a range of multiple components underlining a belief that a single focus is less likely to be effective. Electronic devices did improve adherence, however, there could be the possibility of the Hawthorne effect. Face –to-face patient education by a pharmacist and possibly telephone counselling can be effective.

This review has several limitations; there was a marked difference between the studies in their methodology, adherence measurement and duration of follow up. Studies were included from 1990 up to 2013. Definition of adherence was different in the studies conducted in the 1990s than those conducted in 2000s. Moreover, some trials had only their methodology article published therefore; these trials were excluded due to no availability of the results. Descriptive, observational studies and studies published in other languages were not included. Strengths: the review included only randomised control trials, examined interventions in different settings with a focus on pharmacist interventions only.

Conclusions

Evidence- based data for pharmacy services remains weak, but studies have shown that pharmacists can have an impact through patient education and telephone counselling. Behavioural interventions delivered by pharmacists could have a positive effect, but further evidence is needed. Self reported adherence was the most widely used measure. The acceptable threshold remained 80% among the cardiac population.

Recommendations

Personal contact or counselling by a pharmacist can be an effective method in enhancing adherence, but the frequency of contact to make the intervention more adaptable to practice needs to be further examined. Finally, further research is needed to evaluate the continuity of care in both primary and secondary settings and to promote links between hospital, community pharmacists and other health care professionals.

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Table 1- Assessment of outcomes

Adherence

Indirect measures of adherence:
From the 42 trials 32 trials measured adherence by a single adherence measurement 10 trials combined two adherence measures

Single adherence measurement	**Number of trials**
Refill data	10 trials[10,17,20,24,25,31,34,42,47,48]
Self report questionnaires	Seven trials [18,26,28,37,43-45]
Morisky scaled questionnaire	Six trials[7,12,14,22,23,30]
Pill counts	Five trials[11,13,21,27,41]
MEMS (Medication Event Monitoring System)	Two trials[33,35]
The Hornes's Medication Adherence Report Scale (MARS)	Two trials[32,36]
Combination of adherence measurement	
Refill data combined with self reported questionnaires	Four trials[15,29,39,40]
Refill data combined with the Morisky scale	Two trials [8,46]
Refill data combined with MEMS	One trial[38]
Refill data combined with MARS	One trial [19]
Refill data combined with pill counts	One trial [9]
Morisky Scale in addition to two scales originally developed in Australia the Tools for Adherence Behaviour Screening (TABS) and the medication refill data (MedsIndex score).	One trial [16]
For the Morisky scale, Morgado *et al*, 2010, Carter *et al*, 2009 and Calvert *et al*, 2012 used a 5 item scale derived from the 4 item scale. Hunt *et al*, 2008, Zilich *et al*, 2005, Zhao *et al*, 2012, Lau *et al*, 2010 and Jarab *et al*, 2012 all used the 4 item scale. Moreover, Obreli-Neto, 2011 used the 4 item Morisky -Green test translated into Portuguese.	

Table 2-Interventions and their mode of delivery

Intervention	Trials	Result on adherence	Result on outcomes
1-Patient education by pharmacist	Lee *et al* , 2006, Bouvy *et al* , 2003, Morgado *et al* , 2010, Al Mazroui *et al* , 2009, Sadik *et al*, 2005, Alsani *et al* , 2010, Murray *et al*, 2007, Mehuys *et al*, 2011, Taylor *et al* , 2003, Jaffray *et al*, 2007, Blenkinsopp *et al* , 2000, Sookaneknun *et al* , 2004, Phumipamorn *et al*, 2008 , Varma *et al*, 1999, Odegard *et al*, 2005, Park *et al*, 1996, Lopez *et al*, 2006, Zhao *et al* , 2011, Planas *et al*, 2009 , Evans *et al*, 2010, Eussen *et al*, 2010	15(21) significant	16(21) significant
2-Telephone contact	Yunsheng *et al*, 2010, Faulkner *et al*, 2000, Jarab *et al*, 2012, *Alsabbagh *et al,* 2012	2(4) significant	2(3) significant
3-Use of electronic device	Zilich *et al* , 2005 (SMBP), Svarstad *et al* , 2009 (pedometer, blood pressure tracker), *Virijens *et al*, 2006 (Beep card), Mehos *et al*, 2000 (SMBP)	3(4) significant	3(3) significant
4-Home visit	Holland *et al*, 2007, Peterson *et al* , 2004	0 (2) non significant	1(2) significant
5-Collaborative care	Carter *et al* , 2008, Hunt *et al* , 2008, Villeneuve *et al* , 2010, Gwadry-Sridhar *et al* , 2005, Edworthy *et al*, 2007, Obreli Neto *et al*, 2011 , Carter *et al*, 2009.	3(7) significant	4(7) significant
6-Motivational interviews	Heisler *et al*, 2012.	1(1) Non significant	0(1) Non significant
7-Communication between primary and secondary care	*Calvert *et al*, 2012.	1(1) significant	0(0)
8-Combined interventions	Ho et al, 2013, Lau *et al*, 2010.	2(2) significant	1 (2) Significant
	Total	26/42 trials	27/39 trials

*Trials that did not evaluate clinical outcomes
Statistical significance at *p*- value 0.05

Supplemental Table 3- Effect of pharmacy care on adherence and outcomes

Study	Trial length no. of patients	Effect on adherence	Effect on outcomes of the diseases
Lee *et al*, 2006 [11] USA FAME study	14 months 159	35.5% absolute change in adherence p<0.001, persistence was sustained in the pharmacy care group p<0.001	Significant improvements in systolic BP 133.2 mmHg to 129.9mmHg (*P*=.02) and LDL-C 91.7 to 86.8 mg/dl *P*=.001). Significant reductions in systolic BP in the pharmacy care group (−6.9 mm Hg; 95% CI, −10.7 to −3.1 mm Hg) vs the usual care group,(−1.0mmHg; 95%CI, −5.9 to 3.9mmHg; *P*=.04), but no significant between-group differences in LDL-C levels or reductions.
Bouvy *et al*, 2003[35] Netherland	6 months 152	Intervention group did not use diuretics for 140/7656 days, control group 337/6196 days (relative risk 0.33, 95% CI).	There were no significant differences in rehospitalizations, mortality, or disease-specific quality of life between groups.
Morgado *et al* , 2010[12] Portugal	9 months 197	Medication adherence was 57.6% at baseline in the Intervention Group and 74.5% at the end of the study p=0.012. Difference in low adherence 22.3% Intervention Group vs 43.8% Control Group P=0.0017	Significant lower systolic blood pressure -6.8 mmHg (*P* = 0.006) and diastolic blood pressure -2.9 mmHg (*P* = 0.020) levels were observed in the intervention group
Yunsheng *et al* , 2010 [42] USA	Sep 2000-August 2005. 689	No significant effect 0.88 in the Pharmacy Intervention and 0.90 in the Usual Care p=0.51	At one year, 65% in the Pharmacy Intervention condition and 60% in the Usual Care condition achieved an LDL-C level < 100 mg/dL (*P* = .29) the result was not statistically significant.
Carter *et al* , 2008 [13] USA	9 months 179	At baseline medication adherence was significantly better in the control group 89% vs 71% in the Intervention group, after 9 months 92% control and 94% intervention group p=0.396.	The mean adjusted difference in SBP was 8.7 (95% CI: 4.4, 12.9) mm Hg, while the difference in DBP was 5.4 (CI: 2.8, 8.0) mm Hg. BP was controlled in 89.1% of patients in the intervention group and 52.9% in the control group p<0.001 significant result
Al Mazroui *et al* , 2009 [26] UAE	12 months 240	Non adherence was decreased from 48.3% at baseline Intervention Group to 21.4%, 49.1% in the Control group to 32.5% p<0.05	Significant reductions (*P* <0.001) in mean values (baseline *vs.* 12 months of HbA1c [8.5% *vs.* 6.9% systolic 131.4 mmHg *vs.* 127.2 mmHg and diastolic blood pressure 85.2 mmHg *vs.* 76.3 mmHg were observed in the intervention group; no significant changes were noted in the control group.

Hunt *et al*, 2008[14] USA	12 months 463	No difference between the groups 67% IG vs 69% Control Group. A small non significant result increase from baseline 61% to 67%in the Intervention Group.	Significantly lower systolic (p = 0.007) and diastolic (p = 0.002) blood pressures compared to control (137/75 mmHg vs. 143/78 mmHg). In addition, 62% of intervention subjects achieved target blood pressure compared to 44% of control subjects (p = 0.003)
Zilich *et al*, 2005[7] USA HOME study	3 months 125	No significant differences at any time between the groups, p=0.38, significant increase in adherence in the High- Intensity group 61.3% at baseline to 87.7% end of the study p=0.004.	From baseline, SBP declined 13.4mmHg in the High-Intensity group and 9.0mmHg in the Low-Intensity group. At the final visit, the difference in SBP/DBP change between the High-Intensity and Low - Intensity group was -4.5/-3.2mmHg (P=.12 for SBP and P=.03 for DBP). Diastolic B.P significant result
Holland *et al*, 2007 [36] UK	6 months 293	No evident differences, final adherence scores were marginally higher in the intervention group. P=0.68.	134 admissions occurred in the intervention group compared with 112 in the control group (rate ratio=1.15, 95% confidence interval; P=0.28), 30 intervention patients died compared with 24 controls (P=0.54). The difference was statistically non significant.
Sadik *et al* , 2005 [37] UAE	12 months 221	No. of patients with self reported compliance was 85 vs 35 in Intervention Group and Control Group respectively and at baseline was 33 vs 32, P<0.05.	Intervention patients showed significant (P <0.05) improvements in a range of summary outcome measures exercise tolerance, forced vital capacity, health related quality of life.
Peterson *et al*, 2004 [43] Australia	6 months 94	No significant result Self-reported patient compliance with medication did not change over the course of the study, and total cholesterol levels were not significantly related to self-reported patient compliance either at the baseline (P > 0·50) or at follow-up (P > 0·30).	The reduction over the course of the study in cholesterol levels within the intervention group was statistically significant (4·9 ±0·7 to 4·4 ± 0·6, P < 0·005), whereas there was no change within the control group (P = 0·26). The reduction in total cholesterol in the intervention group should translate to an expected 21% reduction in cardiovascular mortality risk and a 16% reduction in total mortality risk – more than twice the risk reduction achieved in the control group.
Villeneuve *et al*, 2010[31] Canada	12 months 108 collaborative care patients (CC). 117 Usual care patients (UC).	Persistence with lipid-lowering medication at 12 months: CC 86%, UC 81%, 1.03 (0.94 to 1.19) Adherence to lipid-lowering medication at 12 months (≥ 80%): CC 72%, UC 68%, 1.04 (0.90 to 1.27)	No significant clinical impact on lipid control in patients with dyslipidemia. At 12 months, patients in the collaborative care group had an additional reduction of 0.2 mmol/L in LDL cholesterol (95% CI −0.3 to −0.1) relative to patients in the usual care group. However, the adjusted difference was not statistically significant (−0.05 mmol/L, 95% CI −0.3 to 0.2). Slight difference in adherence.

Gwadry-Sridhar *et al*, 2005[38] USA	12 months or until death. 134	No statistically significant difference in compliance.	A significant effect on knowledge Health related quality of life The composite end points (mortality, hospital readmission, emergency visits) occurred in 60% control, 67% intervention but was not statistically significant.
Murray *et al*, 2007 [39] USA	12 months 314	During the 9-month intervention period, medication adherence was 67.9% and 78.8% in the usual care and intervention groups, respectively (95% CI). However, these salutary effects dissipated in the 3-month post intervention follow-up period.10.9% difference in adherence between the intervention and the control group adherence became 66.7% and 70.6%difference 3.9%	Emergency department visits and hospital admissions were 19.4% less annual direct health care costs were lower ($–2960) in the intervention group.
Svarstad *et al*, 2009 [15] USA TEAM trial	6 months-one year 576	The intervention group reported lower non adherence (18% vs 29%, p= 0.02).	Had better BP control (55% vs 36%, p 0.001)
Aslani *et al* , 2010[32] Australia	9 months 142	No significant result	Patients significantly lowered their cholesterol levels p<0.01 5.10 mmole/l Intervention Group,4.81 CG end of study 4.63 Intervention Group and 4.80 Control Group
Lau *et al*, 2010[16] Australia HAPPY trial	6 months 395 completed the study Hidden group 178	It cannot be concluded that the intervention improved adherence in comparison to the control group. On the Morisky scale, the proportions of adherent participants in each group increased significantly over six months but the difference between groups was not statistically significant. Significant result in differences between the intervention and the control group in the tabs adherence score p=0.046, and significant results in the intervention between the control and the intervention group in the Medsindex score p=0.046.	Significant reduction in systolic BP occurred in both groups (PCG: 9.97 mmHg, p<0.001; UCG: 4.61 mmHg, p<0.01) and was significantly greater in the PCG (p=0.02) mean reduction in B.P 10mmHg.
Vrijens *et al*, 2006 [33] Belgium	1 year 392	6.5% increase in post baseline adherence p<0.001 and 13% increase in persistence p=0.002	Did not evaluate outcomes
Phumipamorn *et al* , 2008 [27] Thailand	8months 135 diabetic Muslims	The percent pill count was increased in the study group p= 0.004 (+6.8 vs -2.8) but not in the control.	No significant difference in A1c between the study and control group. P=0.56. Total cholesterol and LDL-C improvements were greater in the study group than the control. P=0.002
Sookaneknun *et al*, 2004[17] Thailand	6 months 235	The treatment group showed significantly better adherence p=0.014 Significantly better adherence increased by 58% to 70%	The study group had significant reduction in systolic and diastolic blood pressure p=0.037, 0.027, respectively.
Taylor *et al*, 2003[18] USA	12months 81	The percentage of patients with medication compliance scores of 80%-100% increased by 15% in the intervention group but not in the control, however compliance scores did not differ significantly between the groups.	The percentage of patients responding to hypertension, diabetes, dyslipidemia and anticoagulation therapy increased significantly in the intervention group and declined in the control group.

Jaffray *et al* , 2007[44] UK The MEDMAN Study.	12 Months 1614	No significant effect on self reported compliance.	No statistical significant differences in outcomes.
Blenkinsopp, 2000[19] UK	6 months 282 180 completed the study	At baseline the percentage of patients who were adherent was very similar in the two groups 52.3% and 51% in the Intervention Group and Control Group respectively post study this increased to 62.9% and 50%, p<0.05.	Patients whose blood pressure was uncontrolled prior to the study were more likely to become controlled in the intervention group (*P*<0.05).
Edworthy *et al*, 2007[45] Canada	19 months 2643	Adherence in the intervention group was greater than in the control group only for beta-blockers (89% versus 80%; P<0.01) and lipid-lowering agents (83% versus 78%; P<0.05).	Total days in hospital per patient were similar (10.9 days in the usual care group versus 10.2 days in the intervention group; P not significant). Crude mortality was 6.2% and 5.5% in the usual care and intervention groups, respectively, with no significant difference (P=0.15) rehospitalization rates results were not significant. Post hoc analysis an important difference in the number of days in hospital might have been achieved by the program with considerable cost savings p<0.05)
Varma *et al*, 1999 [40] Northern Ireland	12months 83	No significant change in adherence from self reports, from computerized patient drug records an increased number of patients in the intervention group were compliant p=0.039.	Group A patients showed improved exercise capacity, significant improved knowledge of their drug therapy, fewer hospital admissions p=0.006.
Odegard *et al* , 2005[28] USA	12months 77	Self report medication adherence was not significantly improved by the intervention.	The mean HbA1c did not differ between groups p=0.61, a reduction in HbA1c was noted for both groups over time compared with baseline (p=0.001).
Mehos *et al* , 2000 [20] USA	6 months 41	Mean compliance with antihypertensive therapy was 89% in the control and 82% in the intervention group p=0.29.	Reductions in systolic and diastolic pressures were significantly reduced from baseline in the intervention group (17.0 and 10.5 mm Hg p<0.0001) but not in the control group (7.0 and 3.8 mmHg, p=0.12 and p=0.09)
Park *et al*, 1996 [21] USA	Oct. 1993-May1994. And Oct.1994-1995. 64	Compliance for visits 2 through 4 showed no difference among the groups , however compliance was greater on visits 2, 3 compared with control 96.7+-4 vs 86.0+- 20.7 p=0.025	Blood pressure control was significantly improved in the study group.
Mehuys *et al*, 2011[29] Belgium	6 months 288	No evident result: prescription refill rates was very high in both study groups (control group: median = 94.7%; intervention group: median = 99.7%). Moreover, a substantial proportion of patients had adherence rates of more than 100%, even up to 200% . Data were considered unsuitable for further analysis. With respect to the self-reported adherence, both study groups declared themselves to be very adherent to their diabetes medication.	The intervention significantly reduced HbA1c (between-group difference 0.5%, P = 0.009).

Obreli-Neto *et al* , 2011[8] Brazil	36 Months 200	Significant improvement 50.5% of adherent patients at baseline vs 83.5% of adherent patients after 36 months p<0.001no significant changes in the control group.	Significant improvements in the number of patients reaching adequate values for their blood pressure (26.8% at baseline vs. 86.6% after 36-months; P< 0.001), fasting glucose (29.9% at baseline vs. 70.1% after, 36 months; P< 0.001), A1C hemoglobin (3.3% at baseline vs. 63.3% after 36 months; P<0.001
Lopez *et al*, 2006[41] Spain	12 months 134	Difference in compliance between the intervention and control group. 88.2% vs 60.5% at 2 months, 91.1% vs 69% at 6 months and 85% vs 73.9%.	32.9% fewer patients in the intervention group were admitted again *vs*. the control group. The mean days of hospital stay per patient in the control group were 9.6 (SD = 18.5) *vs.* 5.9 (SD = 14.1) in the intervention group
Faulkner *et al*, 2000 [9] USA	24 months 30	Compliance was significantly better in the intervention group up to 2 years p<0.05 63% vs 39% and 48% vs 23%.	Lipid profile results were significantly better in the intervention group p<0.05 up to 2 years after start of therapy than in the control group for all parameters except high density lipoprotein.
Calvert *et al* , 2012 [46] USA	6 months 143	Self report adherence no difference between intervention and control. Using Proportion of Days Covered adherence to both statins and beta blocker there was better adherence in the intervention vs control but result not statistically significant(53%-38% p=0.11). Adherence to β-blockers was statistically Significant (p=0.03) in intervention versus control (71% vs 49%, respectively.	Did not evaluate outcomes
Carter *et al* , 2009[22] USA	6 months 402	The percentage of patients with poor self-reported medication adherence declined from 18.7 ± 22.0% to 14.7 ± 20.9 in the control group and from 17.3 ± 27.5 to 14.6 ± 25.4% in the intervention group (p=0.602 and p=0.979, respectively).	Mean BP decreased 6.8/4.5 and 20.7/9.7 mm Hg in the control and intervention groups, respectively, (p<0.05), BP was controlled in 29.9% of patients in the control group and 63.9% in the intervention group p<0.001)
Zhao *et al*, 2012 [23] China	6 months 278	Significant difference in percentage of patients with low adherence 24.8% intervention group vs 41.7% control group p=0.0014	BP was controlled among significant patients more in Intervention Group (76.4%) than in Control Group (50.6%) (P = 0.0000). Significant lower SBP (-8.5 mmHg, P = 0.0001) and DBP (-4.7 mmHg, P = 0.0013) levels were observed in Intervention Group.
Planas *et al* , 2009 [24] USA	9 months 52	Adherence increased by 7% in the intervention group but the result was statistically not significant.	The mean intervention group SBP decreased 17.32 mm Hg, whereas the mean control group SBP level increased 2.73 mm Hg (P = 0.003)
Evans *et al* , 2010 [25] Canada	6 months 176	The proportion of patients exhibiting statin adherence of 80% or greater did not significantly differ between groups at study end (73.1%] and 80.0% respectively, p=0.333). However, 85.2% in the follow-up group continued with statin therapy at the end of the study compared with 67.0% in the single-contact group (p=0.005).	Neither the mean reduction in 10-year risk (-2.68 for the follow-up group and -1.25 for the single-contact group, one-tailed p=0.098) nor individual risk factors were significantly different between groups.

Heisler *et al*, 2012 [10] USA	14 months 4100	More effective in increasing medications than improving medication adherence.	The mean SBP decrease from 6 months before to 6 months after the intervention period was approximately 9 mm Hg in both arms. Mean SBPs of eligible intervention patients were 2.4 mm Hg lower (P <0.001) immediately after the intervention than those achieved by control patients.
Eussen *et al*, 2010[34] Netherlands	12 months 1016	Significantly lower rate of discontinuation within 6 months after initiating therapy versus usual care (95% CI). No significant difference between groups was found in discontinuation at 12 months (95% CI). Median Medication Possession Ratio was very high (>99%) in both groups and did not differ between groups.	In the pharmaceutical care patients both mean cholesterol and LDL-C levels declined significantly during the study. A significant negative association between the Medication Possession Ratio and total cholesterol p=0.002
Alsabbagh *et al*, 2012[47] Canada	6 months 95	The mean adherence to all recently initiated cardiovascular medications combined was 88.8% in the intervention group and 89.9% in the usual care group (P = 0 .73).	Did not evaluate outcomes
Jarab *et al*, 2012[30] Jordan	6 months 171	The intervention group compared with the usual care group had small but statistically significant improvements in the secondary measures self-reported medication adherence, and self-care activities.	Patients in the intervention group had a mean reduction of 0.8% in A1c versus a mean increase of 0.1% from baseline in the usual care group (P = 0.019). Between-group differences in changes in the secondary measures of HDL-C and body mass index were not significant.
Ho *et al*, 2013[48] USA	12 months 253	241 (95.3%) completed the study (122 in Intervention and 119 in Usual Care). In the Intervention group, 89.3%of patients were adherent compared with 73.9%in the Usual Care group (P = .003). Mean Proportion of Days Covered was higher in the Intervention group (0.94 vs 0.87; P< .001). A greater proportion of intervention patients were adherent to clopidogrel (86.8%vs 70.7%; P = .03),statins (93.2%vs 71.3%; P < .001), and ACEI/ARB (93.1% vs 81.7%; P = .03) but not β-blockers (88.1%vs 84.8%; P = .59).	There were no statistically significant differences in the proportion of patients who achieved BP and LDL-C level goals.

List of search terms used in the review

Pubmed search terms: ("pharmacy"[MeSH Terms] OR "pharmacy"[All Fields] OR "pharmacies"[MeSH Terms] OR "pharmacies"[All Fields]) AND care[All Fields] AND adherence[All Fields] AND ("cardiovascular diseases"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "diseases"[All Fields]) OR "cardiovascular diseases"[All Fields] OR ("cardiovascular"[All Fields] AND "disease"[All Fields]) OR "cardiovascular disease"[All Fields])) AND (("1990/01/01"[PDAT] : "2012/07/20"[PDAT]) AND Randomised Controlled Trial[ptyp]) adherence[All Fields] AND ("pharmacists"[MeSH Terms] OR "pharmacists"[All Fields]) AND ("hypertension"[MeSH Terms] OR "hypertension"[All Fields])) AND (("1990/01/01"[PDAT] : "2012/07/20"[PDAT]) AND Randomised Controlled Trial[ptyp]) adherence[All Fields] AND ("pharmacists"[MeSH Terms] OR "pharmacists"[All Fields]) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields])) AND (("1990/01/01"[PDAT] : "2012/07/20"[PDAT]) AND Randomised Controlled Trial[ptyp]) (adherence[All Fields] AND ("pharmacists"[MeSH Terms] OR "pharmacists"[All Fields]) AND ("hyperlipidaemia"[All Fields] OR "hyperlipidemias"[MeSH Terms] OR "hyperlipidemias"[All Fields] OR "hyperlipidemia"[All Fields] OR "Hyperlipidemia"[All Fields])) AND (("1990/01/01"[PDAT] : "2012/07/20"[PDAT]) AND Randomised Controlled Trial[ptyp]) (adherence[All Fields] AND ("pharmacists"[MeSH Terms] OR "pharmacists"[All Fields]) AND ("coronary disease"[MeSH Terms] OR ("coronary"[All Fields] AND "disease"[All Fields]) OR "coronary disease"[All Fields] OR ("coronary"[All Fields] AND "heart"[All Fields] AND "disease"[All Fields]) OR "coronary heart disease"[All Fields] OR "coronary artery disease"[MeSH Terms] OR ("coronary"[All Fields] AND "artery"[All Fields] AND "disease"[All Fields]) OR "coronary artery disease"[All Fields] OR ("coronary"[All Fields] AND "heart"[All Fields] AND "disease"[All Fields]))) AND (("1990/01/01"[PDAT] : "2012/07/20"[PDAT]) AND Randomised Controlled Trial[ptyp]) adherence[All Fields] AND ("pharmacists"[MeSH Terms] OR "pharmacists"[All Fields]) AND ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields])) AND (("1990/01/01"[PDAT] : "2012/07/20"[PDAT]) AND Randomised Controlled Trial[ptyp]) (("pharmacy"[MeSH Terms] OR "pharmacy"[All Fields] OR "pharmacies"[MeSH Terms] OR "pharmacies"[All Fields]) AND care[All Fields] AND ("patient compliance"[MeSH Terms] OR ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields] OR "compliance"[All Fields] OR "compliance"[MeSH Terms]) AND ("cardiovascular diseases"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "diseases"[All Fields]) OR "cardiovascular diseases"[All Fields] OR ("cardiovascular"[All Fields] AND "disease"[All Fields]) OR "cardiovascular disease"[All Fields])) AND (("1990/01/01"[PDAT] : "2012/07/20"[PDAT]) AND Randomised Controlled Trial[ptyp]) (("pharmaceutical services"[MeSH Terms] OR ("pharmaceutical"[All Fields] AND "services"[All Fields]) OR "pharmaceutical services"[All Fields] OR ("pharmaceutical"[All Fields] AND "care"[All Fields]) OR "pharmaceutical care"[All Fields]) AND adherence[All Fields] AND ("cardiovascular diseases"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "diseases"[All Fields]) OR "cardiovascular diseases"[All Fields] OR ("cardiovascular"[All Fields] AND "disease"[All Fields]) OR "cardiovascular disease"[All Fields])) AND (("1990/01/01"[PDAT] : "2012/07/20"[PDAT]) AND "humans"[MeSH Terms] AND Randomised Controlled Trial[ptyp]).

EMBASE search terms: Adherence, Cardiovascular, Cardiovascular disease, Care, Disease, Pharmacy, Pharmacy care, Adherence, RCTs. **PsycINFO** search terms: adherence, cardiovascular disease, disorders, care, disease, pharmacy, treatment compliance.