Appendix 5. Type of intervention and characteristics of each systematic review and the results of extracted RCTs

Table 1 explains the symbols used in the following tables

Table 1: Description of symbols in result tables

 Statistically significant positive effect in favour of intervention	 Not statistically significant result/no effect of the intervention	 Outcome measured but result not reported	Abbreviations: Odds ratio = OR Mean difference = MD Risk difference = RD Note: All the point estimates had a 95 % CI, unless denoted with*	Statistically significant effect on adherence: ✓ No statistically effect on adherence: ✗ Effect on adherence not reported/ Unknown: ?

Strategies for improving adherence to antiepileptic drug treatment in people with epilepsy (Review)

Table 2: Extracted RCTs from Al-aqeel, Gershuni et al. 2017(56) presenting intervention results on adherence, morbidity and QoL

RCT	**Intervention** **Interventionist** **Effect on adherence**	**Morbidity**	**QoL**
Dash 2015 (57)	EDUCATION Nurse ✓	 Seizure frequency decreased (IG 34.1 % vs CG 18.6% p = 0.043)	
DiIorio 2011 (58)	Web-Based PROGRAM + WEEKLY REMINDERS ✗		 QoL

The first version of this review was published in 2010. The current version from 2017 included 12 RCTs. The objective of this review was to determine the effectiveness of interventions aimed at improving adherence to antiepileptic medication in adults and children with epilepsy. Because of heterogeneity between studies, there was not conducted any meta-analysis(56).

Dash 2015

A one-on-one education intervention in 4 sessions, each lasting at least 30 minutes, was delivered by an epilepsy nurse. Emphasis on compliance was a part of the teaching sessions. After a 6 months follow-up, there were 80 patients in the intervention group and 70 patients in the control group that completed questionnaires. Morisky Medication Adherence Scale (MMAS) was used to measure adherence, and Epilepsy Self-Efficacy Scale (ESES) was used to measure seizure frequency. Before intervention the mean MMAS score was 6.58 for the IG, and after the intervention the mean score was 7.53 (p = 0.001)(56).

Dilorio 2011

148 patients received the WebEase (Web EpilepsyAwareness, Support, and Education) programme that contained 3 modules, each one taking 2 weeks to conduct. Weekly reminders were sent to the participant about taking medication, manage stress and improve sleep quality, in addition to record information about seizures and medication taking. The access to the programme was closed for the patients at the end of 6 weeks. Medication Adherence Scale was used to measure adherence, and humanistic outcome was QoL measured by patient self-report. After 12 weeks, the mean adherence score was 7.33 in IG, and 6.90 in CG(56).

Adherence-enhancing interventions for active antiretroviral therapy in sub-Saharan Africa: A systematic review and meta-analysis

Table 3: Extracted RCTs from Mathes, Antoine et al. 2014 (59) with intervention results and results on mortality, morbidity and QoL

RCT	**Intervention** **Interventionist** **Effect on MA**	**Mortality**	**Morbidity**	**QoL**
Lester 2010 (60)	SMS (and call follow-up) Nurse ✓	 Risk ratio 0.81 [0.49, 1.34] (IG 9 % vs CG 11 %, p = 0.42)		
Mbuagbaw 2012 (61)	MOTIVATIONAL/ REMINDER SMS ✗	 Risk ratio 2.94 [0.31, 27.79]	 Opportunistic infection	 QoL (Mean IG 3.79 vs CG 3.75, p = 0.632)

		(IG 2.9 % vs CG 1.0 %, p = 0.322)	(IG 19.8 % vs. CG 17.2 %, p= 0.632)	
Sarna 2008 (62)	DOT NURSE ✓ (intervention period) ✗ (last follow-up)	 Risk ratio 1.17 [0.70-1.96] (IG 12.9 % vs. GC 10.2 %, p = 0.51)		

Mathes, Antoine et al. 2014 examined the effect of adherence-enhancing interventions among HIV-infected patients using antiretroviral therapy (ART). The systematic review was restricted to six trials conducted in sub-Saharan Africa. There was a low overall risk of bias in the included studies(59).

Lester 2010

Patients in the intervention group (n = 273), received mobile phone short message service (SMS) once a week by a clinic nurse. The patients in the control group (n = 265), received standard care. If the participant in IG responded that there was a problem or failed to respond within 48 hours after receiving the SMS, the patient received a call. Adherence was defined as taking >95 % of the doses and was measured by self-report. The observation period lasted 12 months. IG showed a better adherence, than the CG, 62 % vs. 50 %, respectively (p = 0.006)(59).

Mbuagbaw 2012

Patients in the intervention group (n = 101), received a weekly standardized motivational SMS with a reminder component, and a phone number the patient could call if needed. The control group (n = 99), received usual care. The observation period was 6 months, and outcomes were measured at 3 months and at the end of the study. Adherence was measured by prescription refill data from pharmacy (no improvement, p = 0.617), self-report of ≥ 95 % of doses taken (IG 71.3 % vs CG 66.7 %, p = 0.542), and for ≥ 90% of doses taken (IG 90.1 % vs CG 78.8 %, p = 0.027), and self-report of number of missed doses (p = >0.999)(59).

Sarna 2008

The intervention group (n = 116), were assigned to m-DOT. The patients visited a health centre twice weekly for nurse-observed pill intake, adherence support, and medication collection. The intervention lasted 24 weeks, and follow-up continued until week 72. The control group (n = 118),

received standard care that contained three sessions of adherence counselling before therapy was initiated, and thereafter every 4 weeks. Adherence was measured by pill count and self-report (missed doses during last 4 days)(59).

Table 4: Extracted RCTs from Ngwatu, Nsengiyuma et al. 2018 (63) with intervention results and results on mortality and morbidity (see Table 3 for explanation of symbols)

RCT	**Intervention** **Interventionist** **Effect on MA**	**Mortality**	**Morbidity**
Bediang 2014(64)	DAILY SMS REMINDERS ✗		☹ Cure rate Risk ratio 1.06 [0.65-1.73] (IG 64 % vs GC 62 %)
Liu 2015 (65)	TWO-WAY SMS ✗ MEDICATION MONITOR ✓ TWO-WAY SMS and MEDICATION MONITOR ✓	😕 Data was mixed with Treatment failure and loss to follow-up	😕 Data was mixed with Treatment failure and loss to follow-up
Mohammed 2016(66)	SMS REMINDERS ENCOURAGING TO RESPOND ✗		☹ Cure rate Risk ratio 1 [0.90–1.12]

Ngwatu et al examined whether digital technologies were effective at improving adherence to tuberculosis (TB) treatment, and treatment outcomes. This systematic review included both published and unpublished literature (63).

Bediang 2014

Patients with active TB. Patients in the intervention group (n = 137), received daily SMS reminders as adjunct to DOT. Patients in the control group (n = 142), had DOT as standard care. At 5 months the treatment success rate (adherence) was 81 % in IG and 75 % in CG (RR: 1.45 [0.81-2.56])(63).

Liu 2015

Patients with TB. Patients in the intervention group I (n = 1008), received two-way SMS. Intervention group II (n = 997), received medication monitor (MM), and intervention group III (n = 1064), received both two-way SMS and MM. The content was the same for all three groups; reminder to take medicine and to attend follow-up visits. The control group (n = 1104), received DOT and MM without reminders. Non-adherence was defined as months with at least 20 % of the doses missed. IGI had 27 % loss, IGII had 17 % loss, and IGII had 14 % loss, all compared to CG with 30 % loss. Poor treatment outcome as failure, death or loss to follow up was 4 % in IGI, 6 % in IGII and 9 % in IGIII, compared to 9 % loss in GC(63).

Mohammed 2016

Patients with newly diagnosed TB. Patients in the intervention group (n = 1110), received daily automated SMS reminders at prescheduled time. The patients responded via SMS or phone call. Patients in the control group (n = 1097), had DOT as standard care (63)

Interventions for enhancing medication adherence (Review)

Table 5: Extracted RCTs from Nieuwlaat, Wilczynski et al. 2014 (13) with intervention results and results on mortality, morbidity, health care utilization, patient satisfaction and QoL

RCT	Intervention Interventionist Effect on MA	Mortality	Morbidity	Health care utilization	Patient satisfaction/ QoL
Bond 2007 (67)	PHARMACY-LED MEDICINES MANAGEMENT ✕				 QoL  Patient satisfaction
Chung 2011(68)	ALARM DEVICE ✕				

Dejesus 2009(69)	SINGLE TABLET REGIMEN ✗		 HIV symptoms		 QoL  Patient satisfaction
Gould 2009 (70)	DISCHARGE INTERVENTION Nurse ✗			 Urgent care	
Holland 2007(71)	PHARMACIST HOME VISIT ✗			 ED visits and admissions	 QoL
Levy 2000 (72)	EDUCATION ON SELF-MANAGEMENT Nurse ✓ (severe attacks) ✗ (mild attacks)		 Asthma symptoms	 Medical services	 QoL
Murray 2007(73)	PHARMACIST INTERVENTION ✓ (MEMS + pharmacy refill records) ✗ (Self-report)		 Heart failure		 QoL
Nazareth 2001(74)	HOME VISIT Pharmacist ✗				

Nieuwkerk 2012(75)	EXTENDED CARE Nurse ✓		 Anxiety		 QoL
Pyne 2011 (76)	TELEPHONE COUNSELLING Nurse, clinical pharmacist, psychiatrist ✗		 Depression severity  Depression free days		 QoL
Sadik 2005 (77)	EDUCATION Pharmacist ✓		 Heart failure		 QoL
Sherrard 2009(78)	INTERACTIVE VOICE RESPONSE (IVR) ✓			 ER visits and hospitalizations	
Udelson 2009(79)	SIMPLIFYING DOSE ✗		 Depressive symptoms	 Hospital and ER service	 QoL  Treatment satisfaction
Vergouwen 2005(80)	DEPRESSION CARE PROGRAM General practitioners ✗		 Depression		
Wu 2006 (81)	INCREASED SUPERVISION Pharmacist ✓	 Relative Risk 0.59 [0.35 to 0.97] (p-value 0.039)		 ER visits and hospitalisation	

		(Decrease from 18 % to 11 %)			

The Cochrane-review from 2014, Interventions for enhancing medication adherence, was an update on previous reviews, first published in 2002. The recent review contained 182 unconfounded RCTs of interventions to improve adherence to prescribed medications, measuring both medication adherence and clinical outcomes. The RCTs were from high-income countries, middle-income countries and low-income countries, and had a great variety of settings, patients, type of interventions, medications, adherence measures and clinical outcomes. Because of heterogeneity among the studies, the authors could not justify a meta-analysis or summarize the findings to general conclusions. Instead they conducted a qualitative analysis, whereas the 15 studies that met the inclusion criteria for this report was extracted from. Results were mostly reported as statistically significant positive effect in favour of intervention, or as no or negative effect(13).

There was not found any common intervention characteristics that were apparent. Effects were inconsistent from study to study, and many of the studies contained complex interventions and multiple outcomes without any statistical corrections. Many studies were underpowered, so the true effect could not be revealed. There was also often an uncertain risk of bias for blinding treatment allocation and outcomes assessment, making generalization about effective and not effective interventions problematic. 17 of the RCTs in the review had low risk of bias, 3 of them were included in this report(13).

Bond 2007

Coronary heart disease. The intervention group (n = 980), had an initial consultation with a community pharmacist to review appropriateness of therapy and compliance among other subjects. Further consultations were given if the pharmacist determined the need according to the medicine management service (MEDMAN). The pharmacists' recommendations were sent to the GP, who returned annotated copies to the pharmacist. The intervention lasted for 12 months. The control group (n = 513), did not receive MEDMAN intervention. Data was collected at base-line and at 12 months(13).

Chung 2011 (low risk of bias)

HIV. The Intervention group (n = 100) was given a digital alarm device to carry during the 6 months study period, that beeped and flashed twice a day at the time convenient for the patient to take the medications. The control group (n = 100), did not receive any alarm device. Results from the

counselling group were left out in/of this report since it was unclear what profession the trained counsellors had(13).

Dejesus 2009

HIV/AIDS. The intervention group (n = 203), was prescribed a single-tablet regimen consisting of 3 ART medications, while the control group (n = 97) was prescribed to regular multi-drug ART. Adherence was measured by self-reported pill count, and visual analogue scale (VAS) was used to measure self-reported adherence. Measures were taken on baseline and 48 weeks, while the patient outcomes measurements were performed at 4, 12, 24, 36, and 48 weeks(13).

Gould 2009

Acute cardiac event. The study included patients between the ages 30 and 80 years treated for an acute cardiac event with percutaneous coronary intervention (PCI), and discharged from the hospital 72 hours after the procedure. The intervention group (n = 64) received written materials in addition to a telephone follow-up by an expert cardiovascular nurse within 24 hours after discharge. The control group (n = 65), received routine discharge materials and usual care. Adherence was measured using the patient self-report collected 1-3 days after discharge later via telephone(13).

Holland 2007

Heart failure. All patients were adults admitted as emergencies with heart failure and prescribed two or more drugs on discharge. The intervention group (n = 149), received home visits by pharmacist within 2 weeks after hospital discharge. The pharmacist provided education about heart failure and drugs and contacted a local pharmacist if any need for drug adherence aid. The control group (n = 144), received usual care. Adherence was measured by a mailed questionnaire at baseline and at 2 years(13).

Levy 2000

Acute asthma. The intervention group (n = 103), had 1-hour structured consultation with a nurse at the beginning of the study, followed by two ½ hour consultations at 6 weekly intervals. The patients' asthma control and management were assessed, and the patient were given education on recognition and how to treat asthma episodes. If the patients recognized uncontrolled asthma using peak expiratory flow (PEF) or having symptoms, they were asked to step-up their medication or referred immediately to the consultant if the asthma symptoms were severe. Patients in the control group (n = 108), had treatment as usual. Compliance was measured by patient self-report on their self-management of mild or severe attacks(13).

Murray 2007

Heart failure. Patients were over 50 years of age and regularly used at least one cardiovascular medication for heart failure and were not using or planning to use a medication container adherence aid. The intervention group (n = 122), received dispensed medication to last approximately 2 months, together with patient-centred verbal instructions and written material about their medications. Each medication category had its own icon on the container label and on the written patient instructions. The pharmacist monitored the patients' medication use and communicated as needed with clinic nurses and primary care physicians. The control group (n = 192), CG received usual care. Medication Event Monitoring System (MEMS) was used to measure adherence in addition to prescription records and self-reported adherence. Duration of intervention was 9 months with an additional 3 months postintervention period(13).

Nazareth 2001 (low risk of bias)

Complex regimens in the elderly (aged 75 years and older on 4 or more medicines who had been discharged). In the intervention group (n = 165), a hospital pharmacist evaluated therapy appropriateness and the patient's ability to manage the medications and provided education on appropriate adherence and how to collaborate with health care providers. The patients were given an individualized discharge plan containing the patient's medication and required adherence support. Copies were given to an assigned community pharmacist, family physician and other involved providers. The community pharmacist visited the patient at home after 7 to 14 days to reassess adherence and scheduled additional follow-up visits if needed. The control group (n = 151), received standard discharge procedures by a hospital pharmacist, and the family physician received a letter(13).

Nieuwkerk 2012

Increased cardiovascular risk. Patients included were adults with indications for statin use. Intervention group (n = 101), received counselling with a nurse focusing on changing modifiable risk factors such as increasing medication adherence, among risk modifying factors. A 10-year risk factor was presented and updated during each follow-up visit. The control group (n = 100), received usual care. All patients received atorvastatin 10 mg unless cholesterol levels demanded more aggressive therapy. Adherence was measured by 2 validated self-report questions. The patients were followed up at 3, 9 and 18 months(13).

Pyne 2011

HIV with depression. The intervention group (n = 138), received a complex intervention delivered by a HIV depression care team (DCM) that consisted of a nurse depression care manager, a clinical pharmacist, and a psychiatrist. The team communicated both with the treating clinicians and the patients (via telephone). The intervention had several components, among them were assessment of treatment barriers and possible resolution, treatment monitoring and self-managements. The NetDSS system identified antidepressant regimen adherence of less than 80 % during the past 14 days and counselling non-adherence of less than 75 % during the past month, in addition to severe adverse effects, increase in depression severity and lack of participant response. The control group (n = 138), received usual care depression treatment provided by HIV or mental health clinicians without involvement of the depression care team. Adherence was measured by self-report including both HIV and depression medication at baseline, 6 months and 12 months by telephone interviewers. There was improvement in treatment response and remission rates at 6 months but not at 12 months(13).

Sadik 2005

Heart failure. The intervention group (n = 109), received booklets and education on heart failure, their prescribed medication and the management of heart failure symptoms, in addition training to a self-monitoring program. Education was given by the research pharmacist. Patients were also given rationalization of drug therapy or simplification of dosage regimen. The control group (n = 112), received usual care. Adherence and clinical outcomes were measured by the patient self-report(13).

Sherrard 2009

Adverse events postcardiac surgery (coronary bypass grafts/valvular surgery). The intervention group (n = 164), received automated telephone calls at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 weeks after discharge. The telephone call contained 11 questions addressing medication compliance among other information. The patients' answers were registered in a database. Depending on the patient's answer a coloured flag appeared in the database next to the question. A nurse called the patient to provide education or counselling. The control group (n = 167), was given standard care and received an IVR call on day 3 and 10 after discharge to screen for common symptoms and was contacted at 6 months with questions about adherence and outcomes(13).

Udelson 2009

Chronic HF and left ventricular (LV) dysfunction. Patients included in the study were diagnosed with stable heart failure, currently using a twice-daily dose of carvedilol IR. The intervention group (n = 136), was set on once-daily medication. Control group I (n = 133), was set on twice-daily medication, and control group II (n = 133), was set on once-daily medication + placebo as second daily dose.

Adherence was measured using MEMS electronic measurements, and data was collected at 1 and 5 months(13).

Vergouwen 2005

Depression. The intervention targeted both the GPs and their patients. The intervention group (n = 81), was in the Depression Care Program, and the control group (n = 96), was in the Standard Follow-Up Program. In both groups care was delivered by general practitioners. IG had 7 scheduled visits in 26 weeks. Prior to the visits, a newsletter was mailed to the patients regarding depression biology and symptoms, the importance of antidepressant medication and duration of use, and information about effects and side effects of the medication. The patients were asked to fill out a questionnaire the GPs received before each visit, so the GPs and the patients could discuss the self-report via motivational interview. In the CG there were no letters, homework or instructions. The CG had the same frequency of scheduled and structured visits as the IG. Adherence was measured by pill counts at visit week 2, 6, 10, 14, 18, 22, and 26. When the pill containers were not returned, adherence was measured on the patient's self-report(13).

Wu 2006 (low risk of bias)

Chronic illnesses receiving polypharmacy. The patients used 5 or more medications for chronic conditions and were found to be non-compliant upon the first assessment by pharmacist. The intervention group (n = 219), received a 10 to 15-minute telephone call from the pharmacist between clinic visits (usually every 2 to 4 months) under the 2-year study period. The telephone call from the pharmacist contained questions about the patient's current medicine regime, a clarification of misconceptions and concerns, information about side-effects, a reminder about the next clinic visit, an explanation about the importance of compliance to medication and information about medication self-care. The control group (n = 223), received usual care with a follow-up every 2-4 month. Adherence was measured by patient self-report in combination with medication dispensing information. Patients taking 80 % to 120 % of prescribed pills were considered adherent. 236 of the 442 randomized patients became adherent since screening(13).

Interventions to improve adherence to inhaled steroids for asthma (Review)

Table 6: Extracted RCTs from Normansell, Kew el al. 2017 (82) with intervention results and results on morbidity, health care utilization, health care cost and QoL

RCT	Intervention Interventionist Effect on MA	Morbidity	Health care utilization	Health care costs	QoL
Mehuys 2008 (83)	ADHERENCE EDUCATION Pharmacist ✓	 Exacerbations OR 1.11 [0.41, 2.98]  Asthma control OR -0.50 [-1.86, 0.86]	 Unscheduled visits OR 0.16 [0.02, 1.44]		 QoL MD 0.20 [-0.06, 0.46]
NCT00414817 (84-86)	IVR calls ?	 Asthma control	 Acute health care utilization		 QoL
Price 2010(87)	SIMPLIFIED DRUG REGIMEN ✓		 Unscheduled visits OR 1.17 [0.72, 1.90]		 QoL MD 6.00 [-0.76, 12.76]

Normansell et al 2017 examined the effects of interventions to improve adherence to inhaled steroids for asthma. The review included both published and unpublished studies, and most of the trials were conducted in high-income countries. The authors of the review considered about 50 % of the studies to have high risk of attrition bias and selective reporting of outcome(82).

Mehuys 2008

The patients had treatment for asthma for at least 12 moths, carried a prescription for asthma medication, used controller asthma medication and visited the pharmacy regularly. At the first visit a pharmacist provided the participants in the intervention group (n = 107), with personal adherence education, education on inhaler technique, asthma symptoms, and when to use asthma controller and reliever therapy. The pharmacist gave advice based on the patients' asthma control (ACT) score at visit 2 and 3 (1 and 3 months). The control group (n = 94), received usual pharmacy care.

Adherence was measured both by refill rates and self-report scale. Intervention lasted for 6 months(82).

NCT00414817s

The patients in the study had received at least one dispensing of respiratory medication during the last 12 months. The intervention group (n = 3171), received interactive voice recognition (IVR). There were 3 basic IVR calls, with a duration of 2-3 minutes for each call. There were different refill calls based on remaining days' supply due to previous refill date, and if the refill was missed over one month past the refill date. The calls also assessed asthma control, explored barriers to ICS adherence, and provided tailored educational messages. There was an initiator/restart call for those starting for the first time or were lapsed users of ICS. The control group (n = 3260), received usual care. The adherence was measured by the pharmacy as days' supply of ICS available. The intervention lasted for 78 weeks(82).

Price 2010

The intervention group (n = 611), used one-daily dose of ICS (mometasone furoate) in the evening (1 x 400 µg), and the control group (n = 622), used twice-daily ICS (2 x 200 µg). Both groups were instructed in inhaler use and peak flow measurement and were given salbutamol for rescue medication, in addition to a diary card and a formulated asthma action plan. The intervention lasted 12 weeks. Adherence was measured as administered doses from device counter number times 100 divided by number of scheduled doses, in addition to patient self-report. The mean difference in adherence was 3.80 [1.60, 6.00, 95 % CI](82).

Non-medical prescribing versus medical prescribing for acute and chronic disease management in primary and secondary care (Review)

Table 7: Extracted RCTs from Weeks, George et al. 2016 (37) presenting intervention results on adherence, morbidity, health care utilization, health care cost, patient satisfaction and QoL

RCT	Intervention Interventionist Effect on MA	Morbidity	Health care utilization	Health care costs	Patient satisfaction/ QoL
Bruhn 2013 (88)	MEDICATION REVIEW with or without face-to-face pharmacist prescribing	 Chronic Pain Grade improved 47.7 % (p = 0.003) in prescribing arm,			 QoL MD 2.71 [-1.54, 6.96]

	 ("probably little or no difference between groups")	and 38.6 % (p = 0.001) in review arm			 Patient satisfaction
Hunt 2008 (89)	PHARMACIST MANAGEMENT  ("probably little or no difference between groups")		 Clinic visits Physician visits IG had lower number of physician visits but higher number of clinic visit (pharmacist and physician) than CG		 QoL physical: MD 1.00 [-0.43, 2.43], mental: MD -1.00 [-2.43, 0.43]  Patient satisfaction
Magid 2013 (90)	PHARMACIST LED WEB BP MONITORING  ("probably little or no difference between groups")		 ED visits RD -0.02 [-0.06, 0.03]  Hospitalisations RD -0.01 [-0.05, 0.03]		 Patient satisfaction
Margolis 2013(91)	PHARMACIST LED TELEMONITORING  At 6 months  At 12 and 18 months				 QoL Physical MD 0.60 [-2.67, 3.87], mental MD 1.60 [-0.79, 3.99]  Patient satisfaction

The review was an update of the 2014 version, now containing 46 studies. The objective of the review was to assess the clinical, patient-reported, and resource outcomes of non-medical prescribing for managing acute and chronic health conditions in primary and secondary care compared with usual care (medical prescribing). In some countries nurses, pharmacists, allied health professionals, and physician assistants can substitute for doctors in the prescribing role. This can improve access to medicines for consumers where there are shortages of doctors or the health system is overloaded. The findings of this review suggest that non-medical prescribers were as effective as usual care medical prescribers. The outcomes for surrogate outcomes, MA, patient satisfaction, and health-related QoL were comparable between non-medical prescribers and usual care prescribers(37).

Bruhn 2013

Chronic pain. Included patients received two or more prescriptions for an analgesic or a non-steroidal anti-inflammatory drug. The intervention group I (n = 70), received pharmacist medication review with face-to-face prescribing. Intervention group II (n = 63), received pharmacist medication review, where the pharmacist gave feedback to the GP. The control group (n = 63), received usual care. MMAS was used to measure adherence. Compared with baseline, there was significant improvement in the IGs on Chronic Pain Grade, and no improvement in CG. At baseline all patients reported full adherence. 85 % (39/46) patients were totally satisfied with pharmacist prescribing, while 9 % reported that they would have preferred to see their GP, but it was unknown if this result was significant(37).

Hunt 2008

Hypertension and uncontrolled blood pressure. In the intervention group (n = 230) the pharmacists participated in the active management of hypertension in primary care. The control group (n = 233) received usual care. In IG, the pharmacist reviewed the patients' medications and lifestyle habits, assessed adherence barriers among other subjects. The pharmacist optimized the medication regimen by alternating doses, adding new agents, switching medications or consolidating the antihypertensive therapy. The pharmacist could discuss the treatment plan and medical issues with the primary care physician. The intervention lasted for 12 months. MMAS was used to measure adherence. There was an improvement in adherence in the groups from baseline to study end, but not for the subjects reporting high adherence at baseline(37).

Magid 2013

Hypertension with blood pressure reading above goal. Patients in the study were prescribed ≤ 3 antihypertensive medications. The same educational material was given to both groups, but the intervention group (n = 175), was signed up to a web-based monitoring program. IG patients measured blood pressure at home and uploaded the results to the web-based program 3 times per week. The pharmacist reviewed medication adherence and the blood pressure measurements and made changes or adjustments to the antihypertensive medications when needed, with a notification to the primary care physician. The pharmacist provided counselling to the patients over telephone or secure e-mail. Medication possession ratios was used to measure adherence with little or no difference between groups over the six-month study. Patient satisfaction was reported as probably higher in the intervention group than in the control group (n =173)(37), resulting in not giving any score in this reports table because of uncertainty.

Margolis 2013

Patients with uncontrolled blood pressure. The intervention group (n = 228), received telemonitoring with pharmacist case management. The control group (n = 222), received usual care. For the first 6 months the intervention patients had a telephone meeting with the pharmacist every two weeks until their blood pressure was sustained for 6 weeks, thereafter telephone meetings were reduced to once monthly. Telephone meetings were reduced to every two months from months 7 to 12. In the telephone meetings, the pharmacist emphasized adherence and lifestyle changes, and antihypertensive therapy was adjusted based on the home blood pressure readings in comparison to blood pressure goals. If adverse effects were revealed, the dose was lowered, or the drugs were switched. MMAS was used for measuring adherence. Adherence to antihypertensive medications at six months increased in the IG but decreased in the CG. There were probably no differences between groups at 12 and 18 months. Patients in IG were more satisfied compared to CG at 6 months but not at 12 or 18 months, but it was unclear if the result was significant (37). Utilization and costs were not compared to CG and therefore not given any score in this report.

Providing physicians with feedback on medication adherence for people with chronic diseases taking long-term medication (Review)

Table 8: Extracted RCTs from Zaugg, Korb-Savoldelli et al. 2018 (92) presenting intervention results on adherence, morbidity, health care utilization and health care cost

RCT	Intervention Interventionist	Morbidity	Health care utilization	Health care costs

	Effect on MA			
Pladevall, 2015 (93)	PHYSICIAN INFORMATION ✕	 Major atherosclerosis disease event 18 months: MD 1.49 % (p = 0.091)* 24 months: MD 1.27 % (p = 0.13)* 36 months: MD 1.11 % (p = 0.42)*		
Williams, 2010 (94)	PHYSICIAN INFORMATION ✕		 ER visits Relative rate: 1.13 [0.71 to 1.18, p = 0.61]  Hospitalizations Relative rate: 0.93 [0.34 to 2.56, p = 0.89]	
Willis, 2013 (95)	PHYSICIAN INFORMATION ✕		 Outpatient encounters Relative rate 1.01 (p = 0.42)*  ED encounters Relative rate 0.97 (p = 0.77)*  Hospitalisations Relative. RR 1.11 (p = 0.96)*	

* Data was not confirmed with 95 % CI

The Cochrane review examined if providing physicians with feedback about their patients' medication adherence could improve adherence, patient outcomes, health resource use and processes of care. Due to the review, physicians tend to overestimate their patients' adherence, and therefore miss the opportunities to improve adherence. There was an assumption that when physicians received informed about their patients' adherence, the physicians' behaviour could change and lead to improvement of medication adherence among their patients. The review was restricted to patients having a chronic disease taking long-term medication(92).

The review was published in 2016 and updated in 2018 containing 9 studies from 2003 to 2016. Seven of the studies assessed changes in medication adherence. Because of different definitions of adherence between the studies, and heterogeneity, there was not carried out any meta-analysis but a qualitative assessment of the effects of the studies. There was high risk of bias in eight of the studies, and one study had an unclear risk of bias(92).

The certainty of evidence was low for all outcomes; however, this review was included because of lack of physicians as interventionists in the other included reviews. The authors concluded that there was little or no evidence that provision of feedback to physicians about their patients adherence improved the adherence, patient outcomes or health resource use, but feedback to providers might improve the process of care(92).

Pladevall 2015

Patients with oral diabetes and lipid-lowering prescription drugs. For the intervention group (n = 569), information about the patients' adherence was given to their physicians via the electronic prescribing application, in addition to the latest HbA1C and LDL-C measurements. Physicians also got instructions on how to interpret and discuss adherence with their patients. The control group (n= 567), received usual care without any information provided to the physicians. Adherence was measured by using electronic prescription and fill information(92).

Williams 2010

Patients were of age 5 to 56 (44 % of the patients under 18 years old) years old, diagnosed with asthma, and had at least one visit to primary care provider within one year prior to the study. Physicians in the intervention group could view their patients' (n = 1335) adherence information in the ePrescribing system. The intervention lasted one year. The control group physicians could not view their patients (n = 1363) adherence via the ePrescribing system. The physicians in both groups received information about the national asthma guidelines and were provided methods for discussing non-adherence with their patients(92).

Willis 2013

The patients had at least one of the following conditions: persistent asthma, diabetes, hypertension, congestive heart failure, ischaemic heart disease or stroke. In the intervention group (n = 744), physicians received a report with a summary list of filled prescription claims, a numeric calculation of adherence and a graphical depiction of “days covered”. In addition, there were provided recommendations about possible faults in drug prescriptions with respect to evidence-based pharmacotherapy guidelines. These reports were reviewed by the physicians during the patient’s encounter. The patients in the control group (n = 739) received usual care, without interventions targeting health care professionals. The outcomes were assessed 6 months after the first contact. 45 % of patients were under 21 years old(92).

Evaluation of pharmacist care for patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis

Table 9: Extracted RCTs from Zhong, Ni et al. 2014 (96) presenting intervention results on adherence, health care cost, health care utilization, patient satisfaction and QoL

RCT	**Intervention** **Interventionist** **Effect on MA**	**Health care costs**	**Health care utilization**	**Patient satisfaction/** **QoL**
Jarab 2012 (97)	EDUCATIONAL AND MOTIVATIONAL INTERVENTION Pharmacist ✓		 Hospital admissions Risk ratio 0.28 [0.08, 0.95]  ED visits Risk ratio 0.85 [0.39, 1.82]	 QoL
Khdour 2009/2011 (98, 99)	EDUCATION Pharmacist ✓	 MD -0,33 [-0.68, 0.02]	 Hospital admissions Risk ratio 0.41 [0.30, 0.57]	 QoL MD -0.34 [-0.67, -0.00]

			 ED visits Risk ratio 0.48 [0.32, 0.73]	
Wei 2013 (100, 101)	COUNCELLING EDUCATION Pharmacist ✓		 ED visits Risk ratio 0.26 [0.12, 0.56]	 QoL MD -0.39 [-0.71, -0.07]
Weinberger 2002(102)	CARE PROGRAM Pharmacist ✗			 QoL  Patient satisfaction

This systematic review examined the impact of pharmacist care for outpatients with obstructive pulmonary disease (COPD). Eight RCTs were included, whereas four of them reported on medication compliance(96).

Jarab 2012

The patients in the intervention group (n = 66), received pharmacist intervention that contained motivation interview, in addition to recording of medications, booklet on breathing techniques and a smoking cessation program. There was no description of the usual care group (n = 64). The IG risk ratio for compliance was 1.39 [1.04, 1.84, 95 % CI](96).

Khdour 2009/2011

The intervention group (n = 67), received education on disease state and medications, and how to handle acute exacerbations from the pharmacist. In addition, they were given a booklet and a customized action plan, and smoking cessation program. The intervention was given on baseline, and at 3, 6, 9 and 12 months. The control group (n = 66), received usual care from medical and nursing staff. The IG risk ratio for compliance was 1.37 [1.10,1.70, 95 % CI](96).

Wei 2013

The intervention group (n = 75), received medication counselling, telephone follow-up, and education on disease, therapy and breathing techniques. In addition, education on diet and nutrition,

and a smoking cessation program was given. The frequency of the intervention was not clear. The control group (n = 75), had normal follow-up as usual care. The IG risk ratio for medication compliance was 1.31 [1.10, 1.56, 95 % CI](96).

Weinberger 2002

The intervention group (n = 185), received a care program provided by pharmacists. The pharmacists reviewed the patients' data. Patients were given PEFR with handout instructions on use, and they were called monthly for their PEFR results. The intervention lasted 12 months. The control group (n = 138), received monthly telephone interviews without PEFR monitoring. The IG risk ratio for medication compliance was 1.07 [0.91, 1.27, 95 % CI] (96) The results on HRQoL and patient satisfaction was not reported in this review, however Niewulaat et al 2014 also included this study, and reported that there was no significant difference between the groups in HRQOL but the patients in IG were significantly more satisfied with their pharmacists compared to CG(13).