CHAPTER 8

Nurse-Led Interventions to Promote Medication Adherence in Community Care: A Systematic Review

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Abstract: The aim of this systematic review was to describe and assess nurse-led interventions to enhance medication adherence and clinical outcomes among adults in community care. PubMed, Medline, Embase, CINAHL, and CENTRAL were searched for relevant studies. Randomized controlled trials (RCTs) published 2011–2021 that tested nurse-led interventions with community-dwelling patients and quantitatively measured adherence were included. Adherence and clinical outcomes were analyzed descriptively. Seventeen RCTs fulfilled the inclusion criteria and were of acceptable quality. The studies varied in sample size, loss to follow-up rates, study subject ages, medical conditions, and pharmacotherapy. The nurse-led interventions were complex and multifaceted. Four (23.5%) and seven (41.2%) RCTs reported statistically significant effects of nurse-led interventions on medication adherence and clinical outcomes (e.g., blood pressure, quality of life), respectively, when compared with control arms. All studies had methodological quality limitations. In conclusion, low-quality evidence suggests that some nurse-led interventions may improve medication adherence and clinical outcomes in patients living in the community.

Future research should focus on the effective components of interventions identi-fied here, such as motivational interviewing, adherence aids, patient education and eHealth components, and include defined clinical endpoints, for example, hospital admissions, all-cause mortality, and cost-effectiveness.

Keywords: Nurse-led intervention, medication adherence, patient compliance, nursing, intervention studies, systematic review

Optimizing the benefits of pharmacotherapy depends on patients tak-ing medicine as prescribed, a concept defined as medication adherence (hereafter adherence). Adherence involves the patient's agreement to fol-low prescription recommendations from the healthcare provider (Sabaté, 2003), and includes the timing, dosage, and frequency of medication administration. However, many patients are unable to follow the recom-mendations for the administration of their prescribed medicines. Poor adherence is associated with increased morbidity, mortality, and health-care costs, and reduced effectiveness of treatment (Cutler et al., 2018; Sabaté, 2003). Poor adherence is also a risk factor for medication errors (Assiri et al., 2018).

Patient safety in primary care depends on medication management in domiciliary settings, where patients, their caregivers and healthcare providers, like nurses, are the key actors. Adverse drug events and sub-optimal medicine management are important sources of ill-health and hospitalization (Jordan et al., 2021). Nurses increasingly take active responsibility for disease management and health promotion, and are often the professionals closest to patients. They are trained to deliver patient-centred care and liaise between patients and physicians. A review of studies on the impact of nursing on patients' outcomes concludes that deployment of well-trained nurses improves health outcomes for patients in primary care, and nurse-led care promotes patient satisfaction and medication adherence (Coster et al., 2018). A systematic review and meta-analysis including ten randomized controlled trials (RCT) on nurse-led interventions to enhance adherence to long-term medication for HIV, hypertension, depression, or arthritis, indicates that: all interventions improve adherence; counseling is frequently a component of successful interventions; multifaceted, tailored interventions are the most effective;

and patients benefit from continuous follow-up (Van Camp et al., 2013). Another systematic review of 11 RCTs and two controlled clinical trials, reports that, when compared with usual care, nurse-led interventions improve adherence among recently discharged older adults, with statistically significant effect estimates in eight studies (Verloo et al., 2017).

Existing evidence suggests that nurses are well suited to deliver interventions to improve medication adherence, and complex, tailored interventions including counseling are needed (Coster et al., 2018; Van Camp et al., 2013; Verloo et al., 2017). Despite the increasing body of evidence regarding adherence interventions, nurses' contributions in aiding community-dwelling patients to follow pharmacotherapy recommendations have received little attention. This chapter is based on a systematic review, aiming to: 1) describe and assess the impact of nurse-led interventions on medication adherence among adults living in the community; and 2) synthesize the interventions' effects on clinical outcomes.

Method

Study Design

A systematic literature review was conducted, according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Higgins et al., 2021; Moher et al., 2009).

Databases

The databases PubMed, Medline, Embase, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for relevant studies by HS.

Search Terms

The search strategy was determined after team discussions, performing pilot searches, and consultation with a librarian. Key search terms relating to the PICO (Table 1) were combined using Boolean operators: *or* within the PICO elements, *and* between PICO elements.

Limitations

Limitations for the search were: English, Norwegian, Danish or Swedish as the publication language, published in the time period, January 2011 to October 2021, and in a scientific, peer-reviewed journal. The PubMed search included the following additional filters: abstract, full text, clinical study, clinical trial, controlled clinical trial, randomized controlled trial, and Danish, English, Norwegian, or Swedish language.

Inclusion and Exclusion Criteria

The population, intervention, comparison, and outcome (PICO) of the study were defined as in Table 1. An additional inclusion criterion regarding study design was that the studies reported original empirical data from an RCT, including cluster and stepped RCTs. Non-randomized study designs, including non-randomized and pseudo-randomized clinical trials, were excluded.

Table 1. The PICO of the Study, Including Search Terms

Element acronyms	Descriptor	Determinants	Search terms
P	Population	adult (≥18 years old) medication users in community settings, i.e., home health care, long-term care, sheltered housing, residential facilities	community health services (MeSH) or residential facilities (MeSH) or long term care (MeSH) or home health care (MeSH)
I	Intervention	nurse-led interventions, i.e., nurses play a key role in the intervention	nurses (MeSH) or community health nursing (MeSH) or "nurse-led"
C	Comparison	No specific criteria for the comparison	No search terms included
O	Outcome	medication adherence as study outcome, quantified using a subjective or objective medication adherence measure (Lam & Fresco, 2015)	medication adherence (MeSH) or patient compliance (MeSH) or "non-adherence" or "non-compliance"

Search results were exported to EndNote 20.2 software, and duplicates removed. First, the results were screened by reading the article titles and excluding articles that were not relevant, according to PICO and inclusion

criteria. Next, the study abstracts were evaluated, and non-relevant articles were excluded. Subsequently, the full-text articles were assessed for their eligibility. Finally, the reference lists of the identified studies were reviewed to retrieve additional relevant articles, resulting in the identification of one study. One reviewer (HS) performed the identification and screening of studies, and the initial assessment of eligibility based on full-text studies. In cases of uncertainty of relevance and acceptability, three authors read each article in full-text, and consensus on whether to include the article was reached by discussion.

Quality Appraisal

The quality of the included studies was assessed using the Cochrane collaboration's tool for assessing risk of bias in randomized trials across seven dimensions (Higgins et al., 2021; Higgins et al., 2011): 1) Random sequence generation (selection bias); 2) Allocation concealment (selection bias); 3) Blinding of participants and personnel (performance bias); 4) Blinding of outcome assessment (detection bias); 5) Incomplete outcome data (attrition bias); 6) Selective reporting (reporting bias); and 7) Other bias. RCTs with a high risk of bias in four or more dimensions were excluded.

Data Extraction and Knowledge Synthesis

Data were extracted using a pre-defined, standardized data extraction table, that included the following study characteristics: study author; year of publication; design; aim; study setting including country; number of study participants; description of the study population (P); intervention (I) and comparison/control (C) group; outcome measurements; results of intervention on medication adherence (O); and results of intervention on clinical outcomes (defined as measurable change in health, function or quality of health). One reviewer (HS) created a preliminary data extraction table with the summary of findings from the included studies. Then, all researchers reviewed the extracted results individually, making comments and corrections to the extracted content. Subsequently, the reviewers discussed the evidence and summarized the findings according to study characteristics.

We focused on synthesizing the nature and content of the interventions, and their impact on adherence and clinical outcome. The diverse nature of the studies with respect to study population, nurse-led interventions, and adherence outcome measurements did not allow meta-analysis. Hence, the results of this review are presented narratively.

Excluded Studies

After full text assessment of eligibility, 39 studies were excluded. Reasons for exclusion were: study design (e.g., pre-post design, non-randomized trial in 10 studies); study setting (e.g., hospital, in 9 studies); not a nurse-led intervention (n = 12); not presenting adherence results (n = 5); and poor study quality (n = 3, with a high risk of bias in ≥4 dimensions).

Results

Figure 1 shows the study flow diagram. The search strategy yielded 715 studies, of which 108 were duplicates. In total, 550 studies were excluded
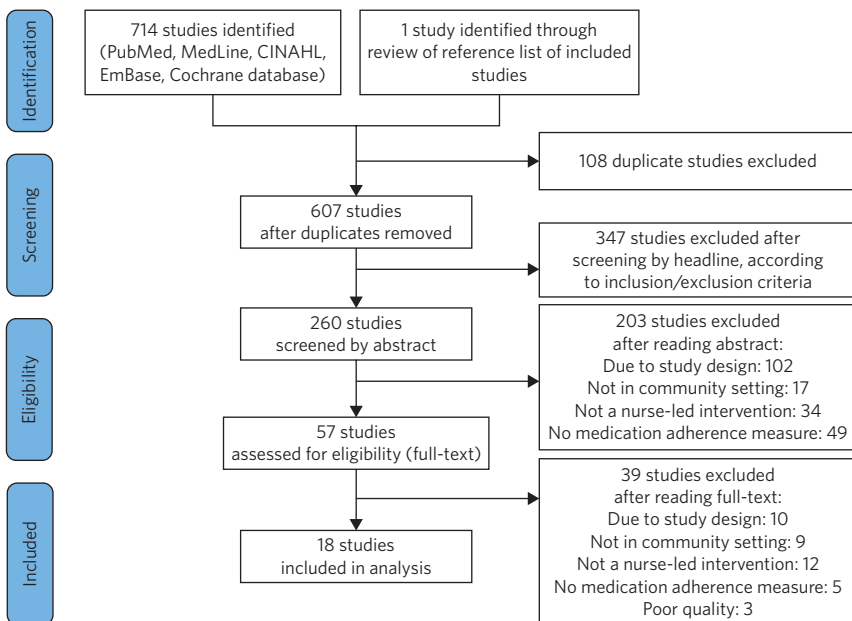

Figure 1. Study Flow Diagram

based on their title or abstract, and 39 studies were excluded following full-text review for eligibility. In total, 18 studies were included for analysis in this review.

Characteristics of Studies

Table 2 shows the characteristics of the included studies and the study sample. Two studies presented results from the same RCT (Blank et al., 2011; Blank et al., 2014), resulting in 17 RCTs to analyze. Study designs included two-armed (n = 14), three-armed (n = 3), cluster (n = 3), and pilot RCTs (n = 4). Clusters were determined by geographical location or health center (Amado Guirado et al., 2011; Lewis et al., 2016; Persell et al., 2018; Shen et al., 2021). The studies were conducted in 13 different countries, predominantly the USA (n = 5), and China (n = 4). Total study sample was 4,654 participants, with an average of 274 study subjects (standard deviation, SD 295) randomized to intervention or control groups. Overall

Table 2. Characteristics of the Included Studies and Participants

Study reference	RCT design	Country	Setting	N	Loss to follow-up (%)	Mean age (years)[a]	Condition[b]
Adeyemo et al., 2013	Two-arms	Nigeria	Community clinics and patients in own homes	698	154 (22.1)	62.6	Hypertension
Amado Guirado et al., 2011	Two-arms, cluster	Spain	Primary healthcare centres	996	128 (12.9)	63.4	Hypertension
Blank et al., 2011; Blank et al., 2014[c]	Two-arms	USA	Community HIV treatment sites and patients in own homes	238	135 (56.7)	43.6	HIV and mental illness
Chien et al., 2015	Two-arms	China	Community psychiatric nursing service and patients in own homes	114	4 (3.5)	28.7	Schizophrenia
Cicolini et al., 2014	Two-arms	Italy	Primary care centre and patients in own homes	203	5 (2.5)	59.1	Hypertension

(*Continued*)

Table 2. (Continued)

Study reference	RCT design	Country	Setting	N	Loss to follow-up (%)	Mean age (years)[a]	Condition[b]
Del Hoyo et al., 2018	Three-arms, pilot	Spain	Outpatient clinic and patients in own homes	63	3 (4.8)	40.5	Inflammatory bowel disease
Kolcu & Ergun, 2020	Two-arms	Turkey	Nursing homes	74	2 (2.7)	75.6	Hypertension
Liang et al., 2021	Two-arms	Taiwan	Home care	200	33 (16.5)	80.7	Chronic disease (any)
Ma et al., 2014	Two-arms	China	Community health centres and patients in own homes	120	14 (11.7)	58.8	Hypertension
Mayer et al., 2017	Two-arms, pilot	USA	Primary care clinic	50	11 (22.9)	38.2	HIV
McAlister et al., 2019	Two-arms,	Canada	Patients in own homes	361	8 (2.2)	65.2	Upper extremity fragility fracture
Persell et al., 2018	Three-arms, cluster	USA	Community health centres	920	126 (13.7)	52.7	Hypertension
Shen et al., 2021	Two-arms, cluster	China	Community health centres and patients in own homes	82	5 (6.1)	66.2	Coronary heart disease
Simoni et al., 2011	Two-arms, pilot	China	Patients own homes and hospital	70	0 (0)	36.0	HIV
Still et al., 2020	Two-arms, pilot	USA	Community clinics and patients in own homes	60	0 (0)	59.5	Hypertension
Usher et al., 2013	Two-arms	Australia	Community mental health services	101	0 (0)	NA	Mental illness (any)
Wakefield et al., 2011	Three-arms, single centre	USA	Medical centre and patients in own homes	304	58 (19.1)	68.7	Hypertension and diabetes mellitus

Abbreviations: RCT, randomized controlled trial; NA, not available; HIV, human immunodeficiency virus.
[a]Mean age of study participants at baseline in intervention and comparison groups combined.
[b]Health condition of study participants that was an inclusion criterion.
[c]Two articles published on the same intervention.

loss to follow-up was 686 study subjects (14.7%), ranging from 0 to 154 subjects. The mean age of the study subjects at baseline was 56.2 years (SD 14.4), and varied from 28.7 years (Chien et al., 2015) to 80.7 (Liang et al., 2021). The study sample was diverse in terms of health conditions, with hypertension most frequently represented (n = 8), followed by HIV (n = 3). Other health conditions were "mental illness", schizophrenia, inflammatory bowel disease, long-term diseases in general, coronary heart disease, diabetes mellitus, and upper extremity fragility fracture.

Characteristics of Nurse-Led Interventions

Table 3 shows an overview of the nurse-led interventions in the included studies. Overall, the nurse-led interventions were complex, with a variety of components that typically included personalized health or medication information (oral, written and/or digital), education, consultation, counseling and/or motivational interviewing performed by nurses in primary health clinics or home visits. eHealth components, that is information and communication technology in support of health education and/or health and medication management, were used in seven studies (Cicolini et al., 2014; Del Hoyo et al., 2018; Liang et al., 2021; Persell et al., 2018; Shen et al., 2021; Still et al., 2020; Wakefield et al., 2011). The eHealth intervention elements ranged in complexity, from relatively simple e-mail alerts (Cicolini et al., 2014) and apps (Del Hoyo et al., 2018), to a complex integrated tele-homecare program including a smartphone, blood pressure monitor, medication dispenser, glucometer and a necklace emergency call button (Liang et al., 2021). Adherence aids were used in six interventions (Blank et al., 2014; Del Hoyo et al., 2018; Kolcu & Ergun, 2020; Liang et al., 2021; Simoni et al., 2011; Still et al., 2020).

The interventions in 14 of the RCTs included strategies to change behavior, like motivational interviewing (n = 3), counseling sessions (n = 5), habit-based interventions comprising digital alerts and tools (n = 6), or adherence tools like pillbox organizers or reminder alarms (n = 6), and different combinations of these. Additionally, strategies to increase knowledge were used, like patient education on health and medicines, and psychoeducation (n = 13). In two studies, knowledge increasing

Table 3. Characteristics of the Nurse-Led Interventions and Synthesis of Intervention Effects on Adherence and Clinical Outcomes

Study reference	Aim of study	Intervention group (I)	Control group (C)	Outcome measurements[a]	Adherence results	Clinical outcomes
Adeyemo et al., 2013	To expand the evidence base necessary to guide hypertension treatment and control programs in Africa.	I1) Clinic-based nurse-led treatment with free of charge antihypertensive agent(s), facilitation of clinic visits and health education over 6 months. I2) like I1 and additional home visits by nurses	I1 compared with I2	1°: Pill count 2°: Biological assay with a urinary riboflavin tracer (participants instructed to take riboflavin daily combined with antihypertensive medication)	No significant effects on adherence	None measured
Amado Guirado et al., 2011	To evaluate the efficacy of a healthcare education program for patients with hypertension.	Personalized information provided by a trained nurse, and written leaflets, during 4 visits to healthcare centres (average 15 min duration) over 1 year.	Usual care	The Haynes-Sackett and Morisky-Green tests and pill counts measured adherence. BP and BMI.	No significant effects on adherence	No significant effects on BP or BMI.
Blank et al., 2011 Blank et al., 2014 [b]	To test the effectiveness of a community-based advanced practice nurses' intervention to promote adherence to HIV and psychiatric treatment regimens.	The PATH+ I: Preventing AIDS through Health for HIV Positive persons. A practice nurse intervention including weekly in-home consultations (psychoeducation, adherence measurements and tools) and coordinated medical and mental health services over 1 year.	Usual care	1°: Viral load CD4 cell count Pill-counts Health-related QoL	In the I arm 58% (N = 61) were at least 80% adherent at 3 months, 80% (N = 84) from 3 to 6 months, and 70% (N = 74) from 6 to 12 months. No data provided to report on significant effects between groups.	A significantly reduction in log viral load (d = −.361 log 10 copies per ml, p<.001) in I compared with C. No significant difference in CD4 counts or QoL between study groups.

Chien et al., 2015	To test and evaluate the effectiveness of an adherence therapy (AT) for outpatients with schizophrenia spectrum disorders, based on a motivational interviewing approach.	Nurse-led (community psychiatric nurses) motivational interview-based medication adherence therapy (AT) program. The AT (a 4-month program) consisted of 3 phases in which 8 sessions of 2 hours were held in-home every 2 weeks.	Usual care	1°: Adherence Rating Scale (ARS) Symptom severity, insight into treatment, hospitalization rate, functioning	Significant improvements in medication adherence (F = 7.45, P = 0.007) over 6 months follow-up, when compared with usual care.	Significant improvements in insight into illness and/or treatment, psychosocial functioning, symptom severity, number of re-hospitalizations, (F = 5.01 to 7.32, P = 0.008 to 0.030) when compared with usual care.
Cicolini et al., 2014	To test the efficacy of a nurse-led reminder program through email (NRP-e) to improve cardiovascular risk factors among hypertensive adults.	The NRPe I: included self-assessment of medication adherence, and educational programs on a healthy lifestyle. Email alerts (once per week for 6 months) from a nurse care manager. The email required read receipt, and if no response, the nurse phoned to press for reading.	Usual care, including self-assessment of medication adherence and educational program.	One question from the MMAS: "Did you take all your medications yesterday?". BP, glycemia, blood lipids	No significant effects on adherence	Mean systolic BP was 135 ± 8 mmHg in I group vs 143 ± 6 mmHg in C group (p<0.001). Mean total cholesterol was 205 ± 40 mg/dL in I group vs 218 ± 3 2 mg/dL in C group (p = 0.015).
Del Hoyo et al., 2018	To evaluate the impact of remote monitoring using a Web system, compared with standard care and telephone care on health outcomes and health care in patients with complex inflammatory bowel disease (IBD).	TECCU (24 weeks) in two arms: I1) Nurse-assisted telephone care, and written information about IBD and medications. I2) Web-based tele-management system with an app for digital platforms, and included questionnaires, advice, reminders, educational material, preventive measures, and tools for medication management	Usual care, including in-person visits to the outpatient clinic run by nurses	1°: % of patients in clinical remission. 2°: adherence by Morisky-Green index. QoL, adverse effects, satisfaction, social activities.	No significant effects on adherence	No significant effects on clinical outcomes

(Continued)

Table 3. (*Continued*)

Study reference	Aim of study	Intervention group (I)	Control group (C)	Outcome measurements[a]	Adherence results	Clinical outcomes
Kolcu & Ergun, 2020	To evaluate the effects of a nurse-led hypertension management program on QoL, adherence and hypertension management in older adults.	Nurse (who is also the researcher) performed 6 sessions of health education, 4 motivational meetings, institutional actions (e.g., distribution of adherence aids/pillbox organizers), over 20 weeks.	Usual care	1°: BP measurements, MMAS-4 measured at pre-test and post-test (20 weeks) Hypertension therapy knowledge score QoL (SF-36)	Adherence rate was significantly higher in I vs C group (100% vs 64.9%, respectively: $\chi^2 = 15.77$, p = 0,000)	Systolic BP was 118 ± 10 mmHg in I group vs 130 ± 15 mmHg in C group. QoL subscale physical component was 58.4 ± 13.9 in I group vs 44.3 ± 16.7 in C group.
Liang et al., 2021	To evaluate the effectiveness of an integrated nurse-led tele-homecare program for patients with a range of chronic illnesses and a high risk for readmission.	Integrated tele-homecare program (e.g., wireless transmission devices, including a smartphone, BP monitor, medication dispenser, and a necklace emergency call button, glucometer). The smartphone had an alarm for medication reminders. Continuous telemonitoring with nurses assessing patients' conditions. Nurses' home visits (content of care included assessment, patients' education, nutrition and medication consultation, and medication reminders) on discharge day, 3 and 6 months after discharge, and additional visits depending on individual needs.	Patients received discharge planning. Home-visits by nurses (content included assessment, checking vital signs, patient education, nutrition and medication consultation, and medication reminders) at 3 and 6 months after discharge	1°: mortality, readmission, number of ED visits 2°: Chinese version of the Medication Adherence Behavior Scale (C-MABS) Daily living activities Health status QoL	Adherence scores remained stable from initiation and to 3 and 6 months of follow-up. No significant effects on adherence	Mortality and ED visits were significantly reduced in I group compared with C group.

Ma et al., 2014	To test the effectiveness of motivational interviewing compared with the usual care for Chinese hypertensive patients.	Motivational interviewing counseling by trained nurses, 8 sessions of 30-40 min over 6 months, performed at-home or health centres.	Usual care, including information on hypertension and recommendations to improve adherence and lifestyle every 6 weeks	1°: Treatment Adherence Questionnaire for Patients with Hypertension (TAQPH) BP QoL	Adherence increased more in I group than C group (29.7 ± 3.5 vs 25.3 ± 3.1, respectively, p = 0.04)	Systolic BP was 141 ± 20 mmHg in I group vs 147 ± 20 mmHg in C group (p = 0.011)
Mayer et al., 2017	To preliminarily test the intervention "Life-Steps for PrEP" compared with an active, time and session-matched comparison condition, among men who have sex with men, initiating HIV pre-exposure prophylaxis (PrEP)	"Life-Steps for PrEP" I: a cognitive behavioral, counseling intervention over 6 months, including 4 nurse-delivered initial sessions and 2 booster sessions of about 50 min, based on Life-Steps, an ART treatment adherence intervention. Overall, the core components focused on medication adherence, sexual behavior, and problem-solving barriers to adherence.	Time and session-matched comparison condition comprised informational and supportive counseling (ISP) by a nurse on the same schedule as I	1°: Wisepill™ (electronic pill storage device, allows for real-time adherence monitoring), calculated a variable for each week that participant had at least 80% adherence. PrEP plasma levels (tenofovir)	No significant difference in adherence between study groups (for those who completed study visits).	None reported
McAlister et al., 2019	To compare the effectiveness of two interventions on long-term oral bisphosphonate adherence after an upper extremity fragility fracture.	C-STOP: Comparing Strategies Targeting Osteoporosis to Prevent fractures after upper extremity fracture. Participants initiating oral bisphosphonate therapy were randomized to two arms over 24 months: I1) A nurse study case manager educated and counseled patients face-to-face or by telephone (minimum 4 times) I2) multi-faceted patient and physician education intervention	I1 compared with I2	1°: adherence to bisphosphonate therapy at 12 months after enrolment. Self-report and pharmacy dispensing records. 2°: health-related QoL	No significant effects on adherence	No differences in QoL between patients who were adherent and those who were not. Any new fractions were not reported.

(*Continued*)

Table 3. (*Continued*)

Study reference	Aim of study	Intervention group (I)	Control group (C)	Outcome measurements[a]	Adherence results	Clinical outcomes
Persell et al., 2018	To test medication management tools delivered through a commercial electronic health record (EHR) with and without a nurse-led education intervention.	I1) EHR-based medication management tools over 12 months; involved medication lists, review sheets at visit check-in, lay medication information sheets printed after visits. I2) EHR+ nurse-led medication management support, involving e.g., medication reconciliation and review, education, and counseling sessions	Usual care	$1°$: Systolic BP $2°$: medication management, including adherence using questions from the Patient Medication Adherence Questionnaire (PMAQ)	No significant effects on adherence	Systolic BP in the I2 group was not significantly lower compared with the C group, but was significantly lower compared with the I1 group (-5.6 mmHg, 95% CI -8.8 to -2.4 mmHg)
Shen et al., 2021	To investigate the effect of a nursing intervention based on Cox's interaction model of client health behavior to improve health outcomes and behaviors for secondary prevention of coronary heart disease.	Nurse-led routine health-education and a 12-week Cox's interaction model of client health behavior and routine health education (6 sessions à 60-90 min). Onsite, telephone and online interaction	Routine health-education	$1°$: self-management, physical activity, anxiety, sexual knowledge, ability to identify sexual health education needs, and adherence, measured by MMAS-8 $2°$: BP, BMI, LDL	The score on adherence in the I group was significantly higher than that in the C group ($t = 3.438$, $p = .001$).	Systolic BP was 128 ± 16 mmHg in I group vs 136 ± 12 mmHg in C group ($p<0.001$). BMI was 21.9 ± 2.3 kg/m^2 in I group vs 24.2 ± 4.0 kg/m^2 in C group ($p = 0.049$) LDL was 2.61 ± 0.4 mmol/L in I group vs 3.12 ± 0.55 mmol/L in C group ($p = 0.03$)

Simoni et al., 2011	To evaluate a nurse-delivered adherence intervention among HIV-positive outpatients initiating antiretroviral therapy.	A 30-min educational session, a pillbox organizer, and a referral to a peer support group. Additionally, participants could choose an electronic reminder device, three sessions of counseling either alone or with a treatment adherence partner, or both reminder and counseling. Counseling sessions delivered by one nurse. I of 13 weeks.	A 30-min educational session, a pillbox, and a referral to a peer support group	1°: Self-reported single-item question. EDM (MEMS®). 2°: CD4 counts and viral load	No significant effects on adherence	No significant effects on CD4 counts or viral load
Still et al., 2020	To explore effects of a community and technology-based intervention for hypertension self-management (COACHMAN) on BP control and health-related QoL in African Americans with hypertension.	COACHMAN I: a technology-based intervention for hypertension self-management. I included web-based education, home BP monitoring, medication management application (MediSafe), and nurse counseling, over 12 weeks. The nurses provided 3–4 sessions of informal counseling focused on medication adherence and BP monitoring.	Usual care, involving printed educational material on hypertension management, and training to use a home BP monitor.	BP The Hill-Bone Compliance to High Blood Pressure Therapy Scale. QoL MediSafe app results.	No significant effects on adherence	No significant effects on BP or QoL
Usher et al., 2013	To test the effect of a nurse-led intervention on weight gain in people with serious mental illness prescribed and taking second generation antipsychotic medication.	Received a 12-week healthy lifestyle booklet, weekly nutrition and exercise education, exercise sessions, and nurse support (nurse also the researcher)	Received a 12-week healthy lifestyle booklet	BMI Medication Compliance Questionnaire Medication side effects Health-related QoL	No significant effects on adherence	No significant effects on BMI or QoL

(*Continued*)

Table 3. (*Continued*)

Study reference	Aim of study	Intervention group (I)	Control group (C)	Outcome measurements[a]	Adherence results	Clinical outcomes
Wakefield et al., 2011	To evaluate the efficacy of a nurse-managed home telehealth intervention to improve outcomes in veterans with comorbid diabetes and critical need to control hypertension.	Nurse-managed home telehealth intervention over 6 months. Participants measured BP and blood glucose, and entered them into the telehealth device, and answered questions. High-intensity I: many questions based on a branching disease management algorithm. Low-intensity I: small subset of questions each day.	Usual care.	1°: systolic BP and HbA1c. 2°: adherence by the Self-Reported Medication Taking scale.	No significant effects on adherence	Results are presented as a change in outcome during I period. HbA1c decreased significantly in both I groups compared with C. Systolic BP decreased significantly for the high-intensity I compared with the other groups

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; BP, blood pressure; C, control; ED, emergency department; EDM, electronic drug monitoring; HbA1c, haemoglobin A1c; HIV, human immunodeficiency virus; I, intervention; LDL, low density lipoprotein; MMAS, the Morisky medication adherence scale; RCT, randomized controlled trial; QoL, quality of life.
[a]Primary (1°) and secondary (2°) outcomes are specified, if defined by the study authors.
[b]Two articles published on the same intervention.

strategies were the main intervention components (Adeyemo et al., 2013; Amado Guirado et al., 2011), and one study used a knowledge strategy involving monitoring key clinical symptoms combined with education and advice (Wakefield et al., 2011).

Interventions appeared to be time-consuming, but time was not reported, and no economic analyses were located.

Effect on Medication Adherence

Table 2 shows an overview of adherence measurements used and the interventions' effects on adherence. Adherence was the primary outcome measure in 13 out of the 17 RCTs (72.2%). Both subjective and objective measures were used, including self-reported adherence scales or questionnaires, pill counts, plasma/urine levels of medication/tracer, medication event monitoring systems (MEMS), and electronic pharmacy refill records. The most commonly used measure was subjective self-reported adherence (n = 14, 82.3%). Two or more adherence measures were used in six studies out of the 17 (35.3%) (Adeyemo et al., 2013; Amado Guirado et al., 2011; Mayer et al., 2017; McAlister et al., 2019; Simoni et al., 2011; Still et al., 2020).

Of the 17 included RCTs, four (23.5%) reported a statistically significant effect of nurse-led interventions on adherence (Chien et al., 2015; Kolcu & Ergun, 2020; Ma et al., 2014; Shen et al., 2021). These interventions targeted behavior and knowledge. The intervention components in these RCTs were: motivational interviewing, pillbox organizers, patient education, and eHealth. Duration of the intervention ranged from 3 to 6 months, and involved antipsychotics, antihypertensive agents, and unspecified agents for treatment of coronary heart disease. A common feature of these four studies was that the nurses' contribution to the intervention was substantial, in terms of scope and time used on repetitive educational and/or behavioral intervention elements. For example, in the study by Shen and co-workers, the nurses provided six sessions over 12 weeks including health education and behavioral/skills, combined with participant interaction onsite (quizzes, seminars, simulation), regular telephone interaction, and continual online interaction via a social media platform (Shen et al., 2021). In the adherence therapy program described in Chien

et al. (2015), nurses provided two hours of in-home motivational interview-based adherence therapy every two weeks for four months.

None of the included RCTs had a negative impact on adherence measures.

Effects on Clinical Outcomes

Seven (41.2%) of the included RCTs reported a statistically significant effect of the intervention on clinical outcomes when compared with control arms (Chien et al., 2015; Cicolini et al., 2014; Kolcu & Ergun, 2020; Liang et al., 2021; Ma et al., 2014; Shen et al., 2021; Wakefield et al., 2011). Table 3 presents an overview of clinical measurements and outcomes of the included studies. The nurse-led interventions on patients living in the community reduced systolic blood pressure (BP) (n = 5) (Cicolini et al., 2014; Kolcu & Ergun, 2020; Ma et al., 2014; Shen et al., 2021; Wakefield et al., 2011), reduced body mass index (BMI) and/or cholesterol concentrations (Cicolini et al., 2014; Shen et al., 2021), and increased quality of life (QoL) (Kolcu & Ergun, 2020), among hypertensive patients. Statistically significant positive effects on symptom severity and reduced numbers of readmissions among outpatients with schizophrenia (Chien et al., 2015), reduction in emergency department (ED) visits among patients with multiple long-term conditions (Liang et al., 2021), and reduction in haemoglobin A1c (HbA1c) among patients with diabetes (Wakefield et al., 2011), were also reported.

Risk of Bias and Quality of Studies

Figure 2 shows the risk of bias (RoB) analysis results of the individual studies. All studies have a high RoB in at least one dimension, most commonly in blinding of participants and/or researchers (15 studies), since the nature of interventions rarely allowed for blinding. Of note, 12 studies gave no information on blinding of outcome assessment and were assessed as unclear RoB. All included studies are defined by the study authors to have an RCT design, however, in one study the randomization was insufficiently described and was assessed to have a high RoB (Amado Guirado et al., 2011). Additionally, the randomization procedure was described vaguely

	Adeyemo et al., 2013	Amado Guirado et al., 2011	Blank et al., 2011, 2014	Chien et al., 2015	Cicolini et al., 2014	Del Hoyo et al., 2018	Kolcu & Ergun, 2020	Liang et al., 2021	Ma et al., 2014	Mayer et al., 2017	McAlister et al., 2019	Persell et al., 2018	Shen et al., 2021	Simoni et al., 2011	Still et al., 2020	Usher et al., 2013	Wakefield et al., 2011
Random sequence generation (selection bias)	?	-	+	+	+	+	+	?	+	+	+	?	?	+	+	?	+
Allocation concealment (selection bias)	-	-	+	+	+	+	?	-	-	+	+	+	?	+	+	+	+
Blinding of participants and personnel (performance bias)	-	-	-	-	-	-	-	-	-	-	-	-	-	?	-	-	?
Blinding of outcome assessment (detection bias)	?	?	-	+	?	+	+	?	?	?	+	?	?	?	?	?	?
Incomplete outcome data (attrition bias)	+	+	-	+	+	+	+	?	+	-	+	+	?	-	+	+	-
Selective reporting (reporting bias)	+	+	?	+	+	+	+	+	+	?	+	+	+	?	?	-	-
Other bias	-	?	?	+	?	-	-	+	+	-	+	-	-	-	-	+	-

Figure 2. Risk of Bias (RoB) Analysis of the Included RCTs. +, Low RoB; ?, Unclear RoB; -, High RoB.

in five studies (Adeyemo et al., 2013; Liang et al., 2021; Persell et al., 2018; Shen et al., 2021; Usher et al., 2013), which were therefore assessed to have an unclear RoB. A high risk of attrition bias was detected in four studies (Blank et al., 2011; Mayer et al., 2017; Simoni et al., 2011; Wakefield et al., 2011), mainly due to high attrition (>20%) in combination with unbalanced attrition between intervention and comparison groups. A medium or lower overall attrition (<20%), but unbalanced between groups, was classified as an unknown RoB, concerning two studies (Liang et al., 2021; Shen et al., 2021). Most studies had a low risk of reporting bias (n = 11), and four studies had an unclear risk of reporting bias due to for example, not showing a study flow diagram or not giving detailed data on adherence (Blank et al., 2011; Mayer et al., 2017; Simoni et al., 2011; Still et al., 2020). Two studies had a high risk of reporting bias due to missing data on adherence outcomes, and/or study flow diagrams, and/or study participants' health characteristics (Usher et al., 2013; Wakefield et al., 2011). A high risk of other bias was detected in nine studies, due to low statistical power (small sample sizes, pilot studies), or unbalanced study participant groups likely influencing outcomes.

Figure 3 shows the cumulative risk of bias in the included studies, illustrating the overall quality of evidence in this systematic review. In total, a low RoB was observed in 45% of the dimensions, whereas a high RoB was observed in 30% of the dimensions.
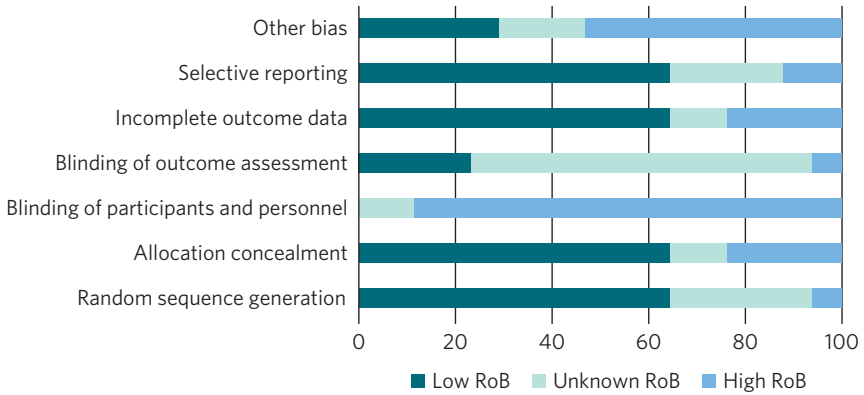
Figure 3. Cumulative Risk of Bias (RoB) Observed in the Studies, Given in Percentage.

Discussion

In this systematic review, we identified and assessed 17 RCTs describing nurses' involvement in aiding adherence and clinical outcomes. Interventions typically targeted adherence through behavior and/or knowledge of health and medicines, with components and combinations of motivational interviewing, counseling, education, adherence tools, and eHealth. Four (23.5%) and seven (41.2%) out of the 17 RCTs reported statistically significant effects on adherence and clinical outcomes, respectively, when compared with control arms. The interventions that improved adherence entailed substantial contributions from nurses, in terms of using several interventional components and the time used in the intervention. Diversity in design and conduct of the RCTs precluded any meta-analysis of the reported nurse-led interventions.

The extent to which patients adhere to the recommendations for prescribed medications, greatly impacts health and healthcare expenditure (Cutler et al., 2018; Sabaté, 2003). Hence, adherence served as a natural primary outcome measure for this review. Additionally, we synthesized nurse-led intervention effects on clinical outcomes, which might serve as an indirect measure of whether patients adhere to treatment. Furthermore, it is important to review existing research evidence on nurses' contributions to patients' health in a community setting, to pinpoint measures

that have been shown to be useful, and to highlight areas of interest and make recommendations for further research.

Of the 17 RCTs in this review, only four (23.5%) reported significant effect estimates on adherence, and concomitantly they reported significant effects on clinical outcomes. However, seven (41.2%) of the RCTs showed significant positive effects on clinical outcomes or surrogate endpoints, such as BP, BMI, HbA1c, and cholesterol-levels. One trial (Liang et al., 2021) demonstrated a reduction in ED visits, and one a reduction in re-hospitalization (Chien et al., 2015). The lack of statistically significant intervention effects might be attributed to insufficient sample sizes in some studies: five had fewer than 100 participants (Del Hoyo et al., 2018; Kolcu & Ergun, 2020; Mayer et al., 2017; Simoni et al., 2011; Still et al., 2020). However, some studies used continuous outcome measures, which can indicate a statistically significant difference with relatively small sample sizes. Adherence was a secondary outcome in four RCTs, hence the interventions were not primarily designed to enhance adherence. Furthermore, there are challenges in measuring adherence as there is no single gold standard measure, and a mixed-method approach is recommended (Lam & Fresco, 2015; Nguyen et al., 2014). Among the RCTs in this review, only six (35.3%) used a mixed-method approach, as recommended (Lam & Fresco, 2015). However, none of these studies detected statistically significant effects. Crucial in detecting intervention effects is quality in study design. This may have affected outcome measures in the RCTs in this review, as all studies had issues regarding risk of bias. Consequently, results should be interpreted with caution.

Two previous systematic reviews have investigated nurse-led interventions on improving adherence, focusing on discharged older adults (Verloo et al., 2017), and long-term medications (Van Camp et al., 2013). The latter review identified ten studies published from 2006 to 2011, where five studies reported significant effects on short and/or long-term adherence to long-term medications. In contrast to our review, Van Camp and co-authors reported odds ratios and pooled mean differences in adherence between intervention and control arms, revealing that nurses can enhance adherence in this population. However, the generalizability is

limited, since seven of the ten studies involved only HIV-positive patients (Van Camp et al., 2013). Furthermore, the review states that nursing interventions for tackling non-adherence must be multifaceted and tailored, with continuous efforts and follow-up of patients (Van Camp et al., 2013), a conclusion that is supported by the results of this review. This review endorses these conclusions: to ensure the correct and safe use of medicines, several strategies – multifaceted and multitargeted – are needed (Cross et al., 2020; Jordan et al., 2021; Khalil et al., 2017; Ryan et al., 2014; World Health Organization (WHO), 2017).

Verloo and co-authors reviewed 14 studies published between 1989–2015 that included nurse-led (n = 7) or nurse-collaborative (n = 7) interventions. The population primarily consisted of discharged older inpatients with cardiovascular diseases (n = 8), and post-surgical patients from hospital geriatric and internal medicine units (n = 4) (Verloo et al., 2017). Hence, the patients and contexts differed from this review. In further contrast, Verloo et al. detected a relatively high proportion of interventions that significantly increased adherence (57.1%, 8 of 14 studies) (Verloo et al., 2017). In line with our results, Verloo et al. describes heterogeneity between studies regarding design and type of intervention, and relative low quality of evidence (Verloo et al., 2017). Low quality of evidence in studies investigating adherence interventions has been described previously in several reviews, due to heterogeneity and the methodological limitations of the studies (Conn & Ruppar, 2017; Cross et al., 2020; Sletvold et al., 2020).

The overall effect of nursing on health outcomes in the community is of interest, and this review found that nurses can play an important role in patients' clinical outcomes, particularly surrogate markers, such as BP. To make an impact on patient-focused outcomes of pharmacotherapy, increased engagement among healthcare professionals, including nurses, is necessary, and may be facilitated by nurse-led approaches (Jordan et al., 2021). An overview of research evidence by Coster et al., indicates moderate evidence for nurses being able to produce health outcomes that are equivalent to those of doctors, for patients with long-term conditions, particularly in primary care (Coster et al., 2018). Furthermore, a meta-analysis found that modest but significant improvements in patient-centered

outcomes (knowledge of medications, QoL, physical functioning and symptoms) followed adherence interventions (Conn et al., 2016). This review adds to this evidence: in some trials, nursing-led adherence interventions contributed to improvement in patients' BP, BMI, HbA1c, and cholesterol-levels, when compared with controls in the community. In two trials, adherence interventions in primary care reduced the demands on secondary healthcare (Chien et al., 2015; Liang et al., 2021). Both these interventions were high intensity. Further research might consider investigating if intensity of interventions is associated with effectiveness of outcomes.

Strengths and Limitations

The major strength of this review is the systematic approach in all parts of the study, from search strategy, study selection, results extraction, to assessment of quality. Furthermore, we included studies covering adult patients with a wide age range, a variety of health conditions, and studies were performed in diverse community settings. Both adherence and clinical outcomes are reported, which might enhance the transferability of findings.

The main limitation of this review is publication bias, since we did not search for grey literature or unpublished reports. Furthermore, the evidence is limited to articles published between 2011 and 2021 and includes only adults (≥18 years old). This review is solely based on the results presented in the published articles, hence there was no contact with corresponding authors to provide additional information that could have improved the result synthesis.

In the study selection process, the exclusion of irrelevant studies through perusal of the titles and abstracts was done by one researcher only, which may have resulted in missing studies. However, the reviewer has substantial experience in relevance screening for systematic reviews (three peer-reviewed systematic reviews published in scientific journals the last four years), which is suggested to be an acceptable approach (Waffenschmidt et al., 2019). Single researcher evaluation of study quality may pose a risk of misclassification, and is a study limitation.

The diverse nature of the studies precluded a numerical analysis, and studies are reported narratively. The time spent on these interventions was not costed, and no economic analysis could be attempted. No studies indicated whether any nursing tasks were delegated or omitted to allow nurses to complete these interventions. Given the global shortages in the nursing workforce, the impact of interventions on all aspects of nursing care warrants attention.

Conclusion

This systematic review provides updated and expanded knowledge on the impact of nurses on the correct use of medications among community-based patients. Low-quality evidence, as assessed in line with GRADE criteria (Schünemann, 2013), suggests that nurse-led interventions may improve medication adherence and clinical outcomes in community care. Interventions are typically multifaceted, targeting adherence through behavior and knowledge strategies, and nurses may play a significant role. However, to increase confidence in the effectiveness of these interventions, further high-quality studies reporting clinical outcomes and cost-effectiveness are needed.

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