ORIGINAL INVESTIGATION

How Can We Improve Adherence to Blood Pressure–Lowering Medication in Ambulatory Care?

Systematic Review of Randomized Controlled Trials

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Background: Lack of adherence to blood pressure–lowering medication is a major reason for poor control of hypertension worldwide. The objective of this study was to determine the effectiveness of interventions to increase adherence to blood pressure–lowering medication.

Methods: We performed a systematic review of randomized controlled trials and searched for all-language publications in the Cochrane Controlled Trials Register, MEDLINE, EMBASE, and CINAHL in April 2002.

Results: We included 38 studies testing 58 different interventions and containing data on 15 519 patients. The studies were conducted in 9 countries between 1975 and 2000. The duration of follow-up ranged from 2 to 60 months. Because of heterogeneity between studies in terms of interventions and the methods used to measure adherence, we did not pool the results. Simplifying dosing regimens increased adherence in 7 of 9 studies, with a relative increase in adherence of 8% to 19.6%. Motivational strategies were partly successful in 10 of 24 studies with generally small increases in adherence up to a maximum of 23%. Complex interventions comparing more than 1 technique increased adherence in 8 of 18 studies, ranging from 5% to a maximum of 41%. Patient education alone seemed largely unsuccessful.

Conclusions: Reducing the number of daily doses appears to be effective in increasing adherence to blood pressure–lowering medication and should be tried as a first-line strategy, although there is so far less evidence of an effect on blood pressure reduction. Some motivational strategies and complex interventions appear promising, but we need more evidence on their effect through carefully designed randomized controlled trials.

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HYPERTENSION IS A MAJOR risk factor in the development of cardiovascular disease and poses a significant public health problem.[1] Randomized trials have demonstrated that treating high blood pressure with medication can substantially reduce the risk of stroke by 30% to 43% and myocardial infarction by 15%.[2] Despite the availability of effective treatments, the control of high blood pressure in the community is far from optimal, with lack of adherence to blood pressure–lowering medication being a major factor.[3-5] Adherence in patients with treated hypertension is estimated between 50% and 70%,[6,7] and the importance of improving adherence to long-term therapies has recently been addressed by the World Health Organization in a major report.[8]

A variety of interventions aiming to improve adherence to antihypertensive medication have been evaluated in randomized controlled trials (RCTs), and 4 systematic reviews have tried to summarize the evidence in this field.[9-12] The searches in 3 of these reviews were limited to studies indexed only in MEDLINE,[9-11] thereby lacking sensitivity and specificity,[13] and included only English-language publications. None of these reviews could recommend any single approaches that increase adherence to blood pressure–lowering medication. The most recent and more general review used a more comprehensive literature search and included 6 studies of hypertension.[12]

Because more trials in this area have emerged recently,[14-16] we carried out a new systematic review of the literature to establish which types of interventions to increase adherence are most effective, using a more comprehensive search strategy and including foreign-language publications. We also aimed to investigate and report the effect of individual interventions used in factorial trials. A version of this review will be available from the Coch-

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rane Hypertension Group for inclusion in the Cochrane Library.

METHODS

LITERATURE SEARCH

We identified original RCTs by an all-language search of articles (any year) in the Cochrane Controlled Trials Register, MEDLINE, EMBASE, and CINAHL (full search strategy available from the authors on request) in February 2002, with the use of an approach advocated by the Cochrane Heart Group. We screened the references of all retrieved articles as well as individual files to identify additional publications. We also contacted study authors and experts in the field about other relevant trials or unpublished material.

STUDY SELECTION

Two of us (K.S. and T.F.) assessed lists of citations and abstracts independently. We were not masked with regard to authors or journal. We selected studies for review if (1) the population of interest was composed of adult patients with essential hypertension in a primary care, outpatient, or community setting; (2) the interventions aimed to increase adherence to blood pressure–lowering medication (eg, education, rewards, improved administration, simplification of drug regimens, use of computers, use of allied health professionals, or self-recording of blood pressure); (3) a reported outcome was adherence to medication; and (4) the type of evidence was limited to RCTs where patient care in the intervention group(s) was compared with either no intervention or usual care. We excluded studies that tested interventions that were not designed to increase adherence or where participants had secondary hypertension. Each reviewer indicated whether a citation was potentially relevant (ie, appearing to meet the inclusion criteria), was clearly not relevant, or gave insufficient information to make a judgment. To be included, a study had to meet all of our inclusion criteria. We resolved differences by discussion and obtained reprints of all potentially relevant citations.

DATA EXTRACTION

Two of us (K.S. and T.F.) independently extracted data in duplicate concerning study design, methods, clinicians and patients, interventions, outcomes, and potential sources of bias, by means of a structured data collection form. A third rater (S.E.) verified the data extraction and made corrections where necessary. Any disagreement was resolved by consensus. We wrote to the corresponding authors of studies to request missing data and clarify study details if required. The included RCTs covered a variety of different interventions, which we divided into 4 categories: (1) simplification of dosing regimens; (2) patient education; (3) patient motivation, support, and reminders; and (4) complex health and organizational interventions or interventions in combination (**Table 1**).

QUALITY ASSESSMENT

Two reviewers (K.S. and T.F.) assessed the quality of the studies independently and in duplicate. We handled disagreements by consensus and requested additional information about study design from the authors if necessary. We extracted data on potential sources of bias, including the method of patient randomization, blinding of the outcome assessor, and differential losses to follow-up, and collated this information in **Table 2**.

QUANTITATIVE DATA ANALYSIS

Because of heterogeneity between studies in terms of interventions and the various methods that were used to measure adherence, we believed that pooling of the results was inappropriate. We grouped and reported the individual arms of factorial trials separately in the respective groups.

RESULTS

STUDY CHARACTERISTICS

We screened 1929 citations and included 38 studies that met all of our predefined criteria, involving a total of 15 519 patients and testing 58 different interventions[14-50] (**Figure**). Table 1 summarizes the characteristics of included RCTs, which were conducted between 1975 and 2000. We chose to report the interventions tested in factorial trials separately and treated these like individual studies. The majority of trials were performed in the United States (n=20) and Canada (n=8), with the remainder located in France (n=3), the United Kingdom (n=2), Australia (n=1), Belgium (n=1), South Africa (n=1), Spain (n=1), and Sweden (n=1). Study participants fell into a number of different categories that included newly diagnosed patients, patients with established hypertension taking medication, patients with controlled or uncontrolled hypertension, patients adherent or nonadherent to medication, and infrequent attendees at clinic. Because there are no generally accepted categories, we grouped studies arbitrarily into the following 4 pragmatic categories: (1) simplification of dosing regimens; (2) patient education; (3) patient motivation, support, and reminders; and (4) complex health and organizational interventions, including interventions in combination. Adherence was measured in different ways, including self-report, direct questioning, pill counts, and the Medication Event Monitoring System (AARDEX Ltd, Zug, Switzerland), and various criteria for adherence were used in the different studies. We treated the different arms of studies by means of a factorial design as separate studies and present the results of these accordingly. All studies examined both men and women in varying proportions, and the duration of follow-up ranged from 2 to 60 months.

QUALITY OF THE PRIMARY STUDIES

The methodologic quality of included studies was generally low (Table 2). The randomization process was reported and provided adequate concealment of allocation in only 10 (26%) of the 38 studies.* The outcome assessors were blind to treatment allocation in 12 studies (32%).† Losses to follow-up were well documented in 33 studies (87%). Only 8 trials (21%) reported a power calculation,[21,25,32,34,39,41,44,45] and most of the remaining trials appeared too small to detect clinically important differences. None of the included studies fulfilled all of the quality criteria.

References 16, 19, 21, 22, 27, 38, 39, 41, 48, 50.
†*References 3, 5, 19, 22, 24, 27, 32, 39-41, 46, 48.*

Table 1. Characteristics of RCTs of Interventions to Improve Adherence to Blood Pressure Medication

Reference	Study Size	Intervention	Control	Method of Measuring Adherence	Net Effect on Adherence Between Intervention and Control Groups, % (*P* Value)
					Simplification of
Asplund et al,[17] 1984	160	Pindolol, 10 mg, and clopamide, 5 mg, once daily (single combination tablet)	Pindolol, 10 mg, and clopamide, 5 mg, once daily (separate tablets)	PC, SR	28.2 (NS)
Baird et al,[18] 1984	389	Once-daily metoprolol tartrate, 200 mg	Twice-daily metoprolol tartrate, 100 mg	PC	8 (.009)
Burris et al,[19] 1991	58	Transdermal clonidine hydrochloride, 0.1 mg/d, plus placebo tablets	Verapamil hydrochloride, 120-mg slow-release tablet plus transdermal placebo	PC, visual assessment	59 (NS)
Detry et al,[20] 1995	320	Once-daily amlodipine besylate, 5 mg	Twice-daily nifedipine, 20 mg	PC, MEMS	17.8 (<.001)
Boissell et al,[21] 1996	7274	Twice-daily nicardipine hydrochloride slow release, 50 mg	Nicardipine hydrochloride, 20 mg 3 times/d	SR	11 (<.001)
Leenen et al,[22] 1997	198	Once-daily amlodipine besylate, 5 mg	Diltiazem hydrochloride slow release, 60 mg twice daily	MEMS	8 (<.01)
Mounier-Vehier et al,[23] 1998	103	Once-daily amlodipine besylate, 5 mg	Twice-daily nifedipine, 20 mg	MEMS	17.7 (<.001)
Girvin et al,[24] 1999	27	Enalapril maleate, 20 mg once daily	Enalapril maleate, 10 mg twice daily	MEMS	19.6 (<.001)
Andrejak et al,[16] 2000	162	Once-daily trandolapril, 2 mg	Twice-daily captopril, 25 mg	MEMS	16 (<.001)
					Patient
Sackett et al,[5] 1975	144	Educational program via slide-audiotape and booklet	Usual care	PC	5 (NS)
Webb,[25] 1980	92	Group education	Regular physician appointments	PC	Compliance score 0.2 points higher (>.10)
Kirscht et al,[26] 1981	343	Written educational material	Usual care	SR	1 (NS)
Pierce et al,[27] 1984	29	Health education in groups, 4 meetings of 90-min duration	Usual care	PC, SR	4% More "good" adherers (NS)
Kerr,[28] 1985	60	Education via visual aids and 10-min lecture, followed by discussion and knowledge test	No intervention apart from paper and pencil tests	SR	12.5 (NS)
Márquez-Contreras et al,[29] 1998	110	Group education in groups of 15 over 90 min and postal information leaflets at 1, 3, and 5 mo	Usual care	PC	24 (<.002)
					Patient Motivation, Support,
Eshelman and Fitzloff,[30] 1976	100	Compliance dispenser	Usual medicine bottle	PC, DQ	2 (NS)
Gabriel et al,[31] 1977	79	Daily drug reminder chart with pharmacist supervision	No chart (ie, usual care)	PC, DQ	12 (.002)
Johnson et al,[32] 1978	68	Self-recording of blood pressure	Usual care	PC	12 (NS)
Johnson et al,[32] 1978	67	Monthly home visits	Usual care	PC, SR	10 (NS)
Nessman et al,[33] 1980	52	Nurse and psychologist teaching self-determination, 8 weekly training sessions lasting 90 min	Nurse- and protocol-run clinic	PC	Intervention group compliant for 1.3 more wk than control group (<.001)
Rehder et al,[45] 1980	50	Counseling (instructions on medication taking, information giving, and discussion of side effects)	Usual care	PC	2 (NS)
Rehder et al,[45] 1980	50	Special medication container	Usual medication vials	PC	6 (NS)
Webb,[25] 1980	86	Counseling (3 sessions with trained social worker, lasting 1 h each at 3-week intervals)	Regular physician appointments	Pill count	0.2-Point difference in adherence score between baseline and follow-up (>.10)
Kirscht et al,[26] 1981	316	Nurse telephone calls	Usual care	SR	5 (<.05)
Kirscht et al,[26] 1981	203	Self-recording of blood pressure	Usual care	SR	0 (NS)
Kirscht et al,[26] 1981	228	Social support	Usual care	SR	5 (<.05)
Pierce et al,[27] 1984	27	Self-monitoring of blood pressure	Usual care	PC, SR	6 (NS)
Kerr,[28] 1985	59	Teaching session on how to take and record own blood pressure	No intervention apart from paper and pencil tests	SR	4 (NS)

Blood Pressure Change, mm Hg (*P* Value)*		Duration of Follow-up, mo	Comments
Systolic	Diastolic		
Dosing Regimens			
2.8 (NS)	3 (NS)	4	Bias possible
1.0 (NS)	0 (NS)	2	Bias possible
5 (<.05)	1 (<.05)	2	Bias possible; compared 2 different drugs
NS, but no data reported	NS	3	Bias possible; compared 2 different drugs
0.2 (NS)	0.3 (NS)	3	Bias possible; compared 2 different drugs
6 (<.01)	1 (NS)	5	Compared 2 different drugs
0.8 (NS)	1.1 (NS)	3	Compared 2 different drugs
5.3 (.07)	1.0 (.09)	3	Potential for selection bias
14% More with normal blood pressure (NS)	N/A	6	Compared different drugs
Education			
24% At goal blood pressure and compliant in intervention group vs 19% in control group (NS)	NR	6	Well-designed study
NR	3.3 (>.1)	3	Randomization process and blinding to outcome assessment not reported
NR	NR	18	Adherence scores unclear and difficult to interpret
16% More patients had blood pressure reduction (<.05, effect size unclear)	N/A	6	Outcomes inadequately reported
NR	4.6 (NS)	3	Large dropouts and inconsistencies between text and tables
NR	NR	6	Unclear how dropouts were treated
and Reminders			
NR	NR	NR	Dropouts at least 33%
NR	NR	3½	Small study, no power calculation reported, unreliable assessment of adherence
2 (NS)	NR	6	Study likely to be underpowered
2 (NS)	NR	6	Power calculation not reported, study likely to be underpowered
6 (<.05)	NR	2	Only 10% of eligible patients took part in the study with potential selection bias; other potential sources of bias poorly reported
NR	9 (NS)	6	High dropout rate, study underpowered; results poorly reported
1 (NS)	NR	6	High dropout rate, study underpowered; results poorly reported
NR	2.3 (>.1)	18	Randomization process and blinding to outcome assessment not reported
NR	NR	18	Adherence scores unclear and difficult to interpret
NR	NR	18	Adherence scores unclear and difficult to interpret
NR	NR	N/A	Adherence scores unclear and difficult to interpret; exact nature of intervention unclear
4% More participants had blood pressure reduction (NS)	NR	6	Randomization procedure prone to bias; reporting of outcomes inadequate
NR	0.4 (NS)	3	Large dropouts and inconsistencies between text and tables

(continued)

Table 1. Characteristics of RCTs of Interventions to Improve Adherence to Blood Pressure Medication (cont)

Reference	Study Size	Intervention	Control	Method of Measuring Adherence	Net Effect on Adherence Between Intervention and Control Groups, % (*P* Value)
Morisky et al,[43] 1985	66	Family member support through training by health educator	Usual care by physician	SR	13 (<.05)
Morisky et al,[43] 1985	65	Counseling session with health educator directly after doctor appointment (10 min)	Usual care by physician	SR	4 (NS)
Morisky et al,[43] 1985	62	Small training groups	Usual care by physician	SR	0 (NS)
Becker et al,[34] 1986	180	Special unit-dose reminder packaging	No intervention	PC, SR	9 (NS)
McKenney et al,[42] 1992	70	Electronic medication aid cap	Usual drug vial	PC	17 (<.001)
Skaer et al,[48] 1993	151	Postal reminder	Usual care	Prescription record	8 (<.05)
		Special unit-dose reminder packaging	Usual care	Prescription record	11 (<.05)
		Postal reminder combined with special unit-dose reminder packaging	Usual care	Prescription record	23 (<.05)
Friedman et al,[36] 1996	267	Telephone-linked computer counseling	Usual care	PC	6 (.03)
Park et al,[44] 1996	64	Pharmacy-based education and counseling	Traditional pharmacy services	PC	–2.3 (NS)
Zarnke et al,[50] 1997	31	Home blood pressure monitoring and self-management	Usual care	PC (not clearly defined)	0.2 Less dose missed (NS)
				Complex Health and Organizational Interventions,	
Sackett et al,[5] 1975	144	Physician-led work-site care (augmented convenience)	Usual care	PC	3 (NS)
Haynes et al,[39] 1976	39	Self-measurement of blood pressure, medication and blood pressure charting, tailoring to daily routines, and fortnightly review and rewards (financial and praise)	Usual care	PC	23 (<.03)
Johnson et al,[32] 1978	69	Self-recording of blood pressure and monthly home visits	Usual care	PC, SR	10 (NS)
Hawkins et al,[38] 1979	1148	Postdiagnostic management of patients with hypertension and diabetes by clinical pharmacist	Usual physician review	Prescribing record	Diuretic only: 7.6 (<.7); diuretic plus methyldopa: 19.2 (.2)
Logan et al,[40] 1979	457	Work-site management of hypertension by specially trained nurses	Usual care	PC	18 (<.005)
Rehder et al,[45] 1980	50	Counseling and special medication container	Usual medication vials	PC	11 (NS)
Logan et al,[41] 1983	194	Structured hypertension management by occupational health nurses	Usual care	PC	1 (NS)
Pierce et al,[27] 1984	30	Self-monitoring of blood pressure and health education	Usual care	PC, SR	2 (NS)
Kerr,[28] 1985	116	Education through visual aids and 10-min lecture plus self-monitoring	No intervention apart from paper and pencil tests	SR	2 (NS)
Morisky et al,[43] 1985	72	Education, family member support, and small training groups	Usual care by physician	SR	5 (NS)
Burrelle,[35] 1986	16	Home visits, education, and special dosing devices	Usual care	PC, SR	21 (<.001)
Saunders et al,[46] 1991	115	Written reminders, patient-held records, and home visits (newly diagnosed)	Usual care	PC	16 (.19)
Saunders et al,[46] 1991	109	Written reminders, patient-held records, and home visits (infrequent attenders)	Usual care	PC	31 (.009)
Sclar et al,[47] 1991	344	Educational leaflet, telephone reminder, mailed reminder and educational newsletter (previously treated)	Usual care	PC	"Medication possession ratio" 34% higher (<.05)
Sclar et al,[47] 1991	109	Educational leaflet, telephone reminder, and mailed reminder and educational newsletter (newly diagnosed)	Usual care	PC	"Medication possession ratio" 41% higher (<.05)
Hamilton et al,[37] 1993	34	Postcard reminder, nurse-led educational appointment, and follow-up telephone call	Usual care	SR	3-Point difference in adherence score (.12)

EFFECT ON ADHERENCE AND BLOOD PRESSURE

Individual RCTs reported results on adherence in many different ways, making a pooled analysis inappropriate (Table 1). Nineteen studies reported an improvement in adherence alone, 7 found improvement in adherence combined with a reduction in blood pressure, and in 7 studies a reduction in blood

Blood Pressure Change, mm Hg (*P* Value)*		Duration of Follow-up, mo	Comments
Systolic	Diastolic		
25% More participants controlled ($P<.05$)	NR	60	Randomization method not reported, complex design
4% More participants controlled (NS)	NR	60	Randomization method not reported, complex design
4% More participants with blood pressure controlled (NS)	No	60	Randomization method not reported, complex design
NR	0.2 (NS)	12	Randomization procedure not reported; participating physicians blind to treatment allocation
NR	NR	3	Small sample size, potential sources of bias poorly reported
NR	NR	12	Sources of bias not fully reported
NR	NR	12	Sources of bias not fully reported
NR	NR	12	Sources of bias not fully reported
4.7 (.85)	4.4 (.09)	6	Treatment provided blinded until baseline measurements completed
NR	NR	4	Small sample size, method of randomization not reported
2.9 (Mean arterial blood pressure, $P = .04$)	NR	2	Small sample size
Interventions in Combination			
4% More compliant and at goal blood pressure (NS)	NR	6	Randomization process not reported; outcome assessors blinded to treatment allocation
NR	4 (.12)	6	Potential sources of bias well reported; study underpowered to detect effect on blood pressure
1 (NS)	NR	6	Power calculation not reported, study likely to be underpowered
4 (<.001)	0 (NS)	29	High losses to follow up (45%)
NR	4 (<.001)	6	Randomization process not stated
NR	18 (<.02)	6	High dropout rate, study underpowered; results poorly reported
NR	3 (NS)	12	Randomization process unclear
4% More had blood pressure reduction (NS)	NR	6	Randomization procedure prone to bias; outcome assessor blind to treatment allocation; reporting of outcomes inadequate
1 (NS)	NR	3	Large dropouts and inconsistencies between text and tables
29% More participants had blood pressure controlled (<.01)	NR	60	Randomization method not reported, complex design
7 (>.05)	7 (>.05)	2	Small study; high likelihood of bias
NR	7 (NS)	6	Randomization method not reported; data on adherence only in 40% of participants
4.3 (NS)	NR	6	Randomization method not reported; data on adherence only in 66% of participants
NR	NR	6	Potential sources of bias poorly reported
NR	NR	6	Potential sources of bias poorly reported
17.3 (.03)	4.7 (.22)	6	Small study, randomization method not reported

(continued)

pressure occurred without an increase in adherence. Fifteen (39%) of the included studies did not report a blood pressure outcome, and none of the studies examined major clinical end points. In the following section, the total number of RCTs (ie, interventions) is 58 rather than 38, because some factorial RCTs tested interventions in different categories, which therefore counted more than once.

Table 1. Characteristics of RCTs of Interventions to Improve Adherence to Blood Pressure Medication (cont)

Reference	Study Size	Intervention	Control	Method of Measuring Adherence	Net Effect on Adherence Between Intervention and Control Groups, % (*P* Value)
Solomon et al,[49] 1998	133	Patient-centered pharmaceutical care model by pharmacy residents	Usual care	PC	0.3-Point difference in adherence score (<.05)
Blenkinsopp,[14] 2000	180	Structured, brief questioning protocol on medication problems, including advice, information and referral to general practitioner by pharmacists 3 times at 2-mo intervals	Usual care, delivered 3 times at 2-mo intervals	SR	12 (<.05)
Mehos et al,[15] 2000	41	Home blood pressure monitoring, diary, instruction to measure blood pressure, information on hypertension and risk factors with subsequent evaluation by clinical pharmacist	Usual care	Prescription refill data	7 (.29)

Abbreviations: DQ, direct questioning; MEMS, Medication Event Monitoring System (AARDEX Ltd, Zug, Switzerland); N/A, not available; NR, not reported; NS, not significant (no *P* value reported); PC, pill counts; RCT, randomized controlled trial; SR, self-report.
*Net blood pressure reduction from baseline to follow-up in the intervention group compared with controls or percentage of participants with controlled blood pressure.

SIMPLIFICATION OF DOSING REGIMENS (9 RCTs, 9 STUDY INTERVENTIONS)

Simplifying dosing regimens improved adherence in 7 of 9 studies,[16,18,20-24] with relative improvement in adherence increasing by 8% to 19.6%. All of the studies that used objective outcome measurement (Medication Event Monitoring System) showed an improvement in adherence through the use of once-daily instead of twice-daily dosage regimens,[16,20,22-24] although 4 of these compared 2 different drugs.[16,20,22,23] Only 1 study showed an increase in adherence (90% vs 82%; $P<.01$) together with a reduction in systolic blood pressure of 6 mm Hg ($P<.01$).[22]

PATIENT EDUCATION (6 RCTs, 6 STUDY INTERVENTIONS)

Patient education seemed largely unsuccessful. Only a single small trial improved adherence (93% vs 69%; $P<.002$), with no reported effect on blood pressure.[29] This study used group education in groups of 15 people over 90 minutes and additional postal information leaflets at 1, 3, and 5 months.

PATIENT MOTIVATION, SUPPORT, AND REMINDERS (16 RCTs, 24 STUDY INTERVENTIONS)

Motivational strategies were partly successful in 10 of 24 study interventions, with mostly small increases in adherence up to a maximum of 23%.[26,31,33,36,42,43,48] All of these studies used less reliable methods of measuring adherence, such as pill counts, self-report, direct questioning, and prescription refill records. Successful interventions included daily drug reminder charts (mean adherence score, 82.4% vs 70.4%; $P=.002$),[31] training on self-determination (4.6 of 7 weeks adherent vs 3.3 weeks in the control group; $P<.001$),[33] reminders and packaging (alone and in combination; increase in adherence between 8% for reminders alone and 23% for reminders and packaging in combination; $P<.05$),[48] social support (98% achieved maximum adherence score vs 93%; $P<.05$),[26] nurse telephone calls (96% achieved maximum adherence score vs 91%; $P<.05$),[26] family-member support (53% high adherers vs 40%; $P<.05$),[43] electronic medication aid cap (mean adherence, 95% vs 78%; $P<.001$),[42] and telephone-linked computer counseling (18% adherent vs 12%; $P=.03$).[36]

COMPLEX HEALTH AND ORGANIZATIONAL INTERVENTIONS INCLUDING INTERVENTIONS IN COMBINATION (17 RCTs, 19 STUDY INTERVENTIONS)

Complex interventions increased adherence in 8 of 18 study interventions,[14,35,40,47,49] ranging from 5% to a maximum of 41%. Work-site care through specially trained nurses improved adherence (67% vs 49%; $P<.005$) and led to a net reduction in blood pressure of 4 mm Hg between intervention and control groups ($P<.001$).[40] A combination of home visits, education, and special dosing devices improved adherence in a small trial of 16 patients (92% vs 71%; $P<.001$).[35] A strategy involving an educational leaflet, a telephone reminder, a mailed reminder, and an educational newsletter was successful in both previously treated hypertensive patients ("medication possession ratio," 82% vs 48%; $P<.05$) and those who were newly diagnosed (93% vs 52%; $P<.05$).[47] Two fairly recent trials reported weak evidence of an effect of a patient-centered pharmaceutical care model (compliance score, 0.23 vs 0.61; $P<.05$)[49] and a combination of structured brief questioning protocol with advice, information, and referral to the family practitioner (62% adherent vs 50%; $P<.05$).[14] In this study, blood pressure was also better controlled in the intervention group (35.7% became controlled vs 17.1%; $P<.05$).

COMMENT

KEY FINDINGS

In this systematic review, we found that simplification of dosing regimens increased adherence in 7 of 9 studies, with improvement in adherence ranging from 8% to 19.6%. Ad-

Blood Pressure Change, mm Hg (*P* Value)*		Duration of Follow-up, mo	Comments
Systolic	Diastolic		
6.9 (<.05)	0.6 (NS)	6	Only results from self-report of adherence reported; high likelihood of bias
18.6% More participants controlled (<.05)	NR	6	Complete data on blood pressure available on only 100 participants; high likelihood of bias
10.1 (.07)	6.7 (.02)	6	Patients randomized by means of a "deck of cards"

herence in these studies was mainly measured with electronic monitors, and these results confirm findings from past research. There was mixed evidence of the effect of motivational and more complex interventions. Education alone appeared largely unsuccessful. A combined effect on adherence and blood pressure was observed in only 7 (12%) of 58 study interventions.

INTERPRETATION OF THE RESULTS IN LIGHT OF PREVIOUS RESEARCH

This review differs from previously published reviews in that we used a more comprehensive search strategy and different methodology. Compared with the latest reviews on adherence-enhancing strategies,[11,12] we found and included considerably more studies (9 and 32 more studies, respectively). The review by Morrison et al[11] extracted categorical data in preference to continuous data and ignored evidence from trials where data could not be converted. This may have been particularly relevant for the results in the group with changes in medication dosing, where we come to the opposite conclusion. This review is also different in that we have reported the results from individual arms of factorial trials separately.

We agree with the review by McDonald et al[12] that, for complex interventions, it is often difficult to estimate the independent effects of individual interventions. It also remains difficult to disentangle specific adherence effects as opposed to nonspecific effects of increased attention. Our findings confirm that even the most effective interventions do not appear to lead to large improvements in adherence and treatment outcomes.

An earlier review of research on adherence reported benefits of educational interventions in improving adherence.[9] However, we were unable to confirm this finding, perhaps because we included only RCTs in our review.

LIMITATIONS OF THIS REVIEW

Comparing the RCTs included in this review was difficult. Many RCTs showed marked heterogeneity in terms of participants, interventions, and outcomes. Study authors also measured and reported adherence inconsistently. Individual RCTs demonstrated variable and often poor methodologic quality, particularly with regard to randomization, blinding of outcome assessment, and losses to follow-up, while the sample sizes of many trials were too small to detect clinically relevant differences. Rather surprisingly, 15 (39%) of the included 38 studies did not report a blood pressure outcome, and none reported major clinical end points.

There are also some difficulties in interpreting the results of this systematic review and meta-analysis. Adherence was measured (eg, self-report, pill counts, direct questioning, electronic monitoring, and drug blood levels) and calculated in different ways (eg, using arbitrary cutoff points, such as 80%, to define adherence), and in addition was usually assessed unblinded to allocation status, which made the comparison of RCTs difficult. Levels of adherence in the control groups of the trials studied ranged from 12% to 94%, which is indicative of the heterogeneity in both criteria for defining adherence and the participants studied. With no agreed-on criteria for how adherence should be measured and defined, it is not surprising that for most interventions the impact on adherence and blood pressure appears to be variable. Because of the different definitions for adherence that have been adopted in individual RCTs, it has not been possible to examine the relationship between adherence to medication and subsequent blood pressure control. Our categorization and grouping of trials was arbitrary, and the group allocation of some trials might be debatable.

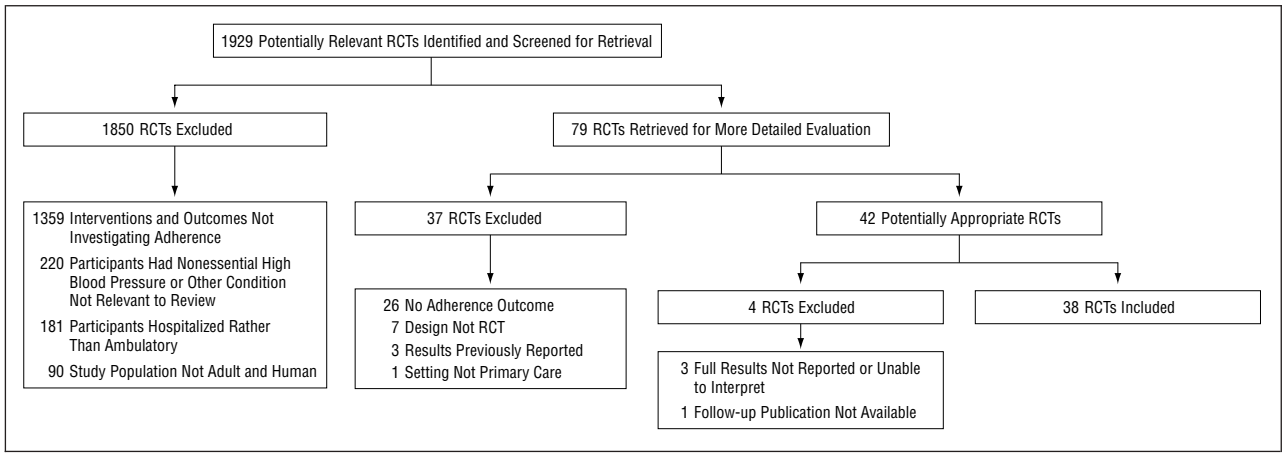
IMPLICATIONS FOR PRACTICE

Our findings suggest that introducing simpler dosing regimens can be effective in improving adherence, but the effect on subsequent blood pressure reduction has not been established and may not be clinically important. The results of various motivational and more complex interventions are promising, although there is insufficient evidence to suggest a single approach. In many countries,

Table 2. Quality Assessment of Included Trials and Potential Sources of Bias

Reference	Randomization Procedure Appropriate?	Outcome Assessor Blind to Treatment Allocation?	Losses to Follow-up, No (%)	Power Calculation Reported?	Hypothesis Stated a Priori?	Comments on Validity of Study Results
Sackett et al,[5] 1975	NR	Yes	10/144 (6.9)	NR	Yes	No power calculation as such, but important differences a priori reported
Eshelman and Fitzloff,[30] 1976	NR	NR	33/100 (33.0)	No	No	Dropouts at least 33% with no differential loss to follow-up reported
Haynes et al,[39] 1976	Yes	Yes	5/39 (12.8)	Yes	Yes	Lacked statistical power; power calculation performed, but no exact figures reported
Gabriel et al,[31] 1977	NR	NR	0/79	No	Yes	No power calculation performed
Johnson et al,[32] 1978	NR	Yes	4/140 (2.9)	Yes	Yes	Power calculation not reported in methods, but probability of type II error quantified in discussion
Hawkins et al,[38] 1979	Yes	No	519/1148 (45.2)	No	Yes	High losses to follow-up
Logan et al,[40] 1979	NR	Yes	41/457 (9.0)	No	Yes	Differential loss to follow-up well reported
Nessman et al,[33] 1980	NR	No	NR	No	No	Only 10% of eligible patients took part in study, which may indicate self-selection
Rehder et al,[45] 1980	NR	NR	52/100 (52)	No	No	High dropout rate and small sample size for factorial trial
Webb,[25] 1980	NR	NR	NR	Yes	No	Unclear on what outcome and treatment difference power calculation was based on; unequal numbers due to dropouts after randomization but before start of intervention (no reasons given)
Kirscht et al,[26] 1981	NR	NR	66/417 (15.8)	No	No	Adherence scores unclear and results difficult to interpret
Logan et al,[41] 1983	Yes	Yes	9/194 (4.6)	Yes	Yes	Randomization process unclear
Asplund et al,[17] 1984	NR	NR	30/160 (18.8)	No	Yes	Dropouts not clearly reported
Baird et al,[18] 1984	NR	NR	50/289 (17.3)	No	Yes	Detailed reasons for loss to follow-up reported
Pierce et al,[27] 1984	Yes	Yes	2/115 (1.7)	No	No	Outcomes poorly reported
Kerr,[28] 1985	NR	NR	52/116 (44.8)	No	Yes	Large dropouts in all groups; inconsistencies between denominators in tables and dropouts that vary for blood pressure and adherence outcomes
Morisky et al,[43] 1985	NR	NR	110/400 (27.5)	No	Yes	No significant differences between dropouts and those who continued to receive care
Becker et al,[34] 1986	NR	NR	15/180 (8.3)	Yes	Yes	Physicians blinded to treatment allocation; were aware that compliance study was in progress but unaware of aims of study
Burrelle,[35] 1986	NR	NR	0	No	No	Small study, high likelihood of bias
Burris et al,[19] 1991	Yes	Yes	9/58 (15.5)	No	Yes	No *P* values reported for adherence outcome
Saunders et al,[46] 1991	No	Yes	33/224 (14.7)	Yes	Yes	Dropouts lower in intervention groups but much higher in newly treated group than infrequent attenders
Sclar et al,[47] 1991	NR	NR	NR	No	No	No dropouts reported despite uneven number randomized
McKenney et al,[42] 1992	NR	No	NR	No	Yes	9 Patients required change of medication during second phase, blood pressure measurements not included in analysis
Hamilton et al,[37] 1993	NR	NR	4/34 (11.8)	No	Yes	Small sample size
Skaer et al,[48] 1993	Yes	Yes	NR	No	Yes	Losses to follow-up not reported
Detry et al,[20] 1995	NR	No	18/640 (2.8)	No	No	Crossover RCT, patients double-counted
Boissell et al,[21] 1996	Yes	No	253/7274 (3.5)	Yes	Yes	No differential loss to follow-up reported; high participant numbers due to large number of participating general practitioners
Friedman et al,[36] 1996	NR	Yes	34/267 (12.7)	No	Yes	Treatment provider blinded until baseline measurement completed; randomization by "paired randomization protocol"
Park et al,[44] 1996	NR	No	11/64 (17.2)	Yes	Yes	Small study
Leenen et al,[22] 1997	Yes	Yes	21/198 (10.6)	No	Yes	Compared 2 different drugs; only within-group comparison
Zarnke et al,[50] 1997	Yes	NR	NR	No	Yes	No power calculation but primary and secondary hypotheses stated
Márquez-Contreras et al,[29] 1998	NR	NR	15/110 (13.6)	No	Yes	Differential loss to follow-up in both treatment arms not reported
Mounier-Vehier et al,[23] 1998	NR	No	18/103 (17.5)	No	No	Treatment allocation according to "enrollment order" and "randomization list"
Solomon et al,[49] 1998	NR	No	NR	No	Yes	Multiple sources of bias
Girvin et al,[24] 1999	NR	Yes	2/27 (7.4)	No	Yes	Small study, methods not well reported
Andrejak et al,[16] 2000	Yes	No	29/162 (17.9)	No	Yes	Differential loss to follow-up well reported
Blenkinsopp,[14] 2000	NR	NR	40/282 (14.2)	No	Yes	Randomization at pharmacy level, complete data on blood pressure available on only 100 patients
Mehos et al,[15] 2000	NR	NR	5/41 (12.2)	No	Yes	Inappropriate randomization method, only single family practice setting, high likelihood of bias

Abbreviation: NR, not reported or unclear.



Progress through the stages of the systematic review. RCT indicates randomized controlled trial.

the role of allied health professionals such as nurses or physician assistants is expanding, which may lead to new management opportunities for addressing adherence-related problems in patients with high blood pressure. However, we suggest that innovative approaches should be introduced in the context of further RCTs. It is important that physicians be aware of the various reasons for poor adherence and aim to simplify dosing regimens as far as possible.

IMPLICATIONS FOR FUTURE RESEARCH

The results of this review highlight a number of problem areas in adherence-related research. Many studies used unreliable methods of measuring adherence such as self-report and pill counts. It appears that electronic monitoring provides more objective and reliable results and, in addition, produces data on medication-taking patterns. Although a large number of studies have been conducted in this area, larger trials of higher quality are needed that use reliable methods of measuring adherence and that also investigate the relationship between adherence and blood pressure reduction. We believe this is particularly important in the context of an increasing elderly population of people who often take multiple medications. Hypertensive patients may fail to take their medication because of the long duration of therapy, the symptomless nature of the condition, side effects of medication, complicated drug regimens, lack of understanding about hypertension management, lack of motivation, and the challenge to individual patients' health beliefs.[10,51] It would seem logical that future studies should try to adopt a tailored approach aimed at individual patients and addressing the above-mentioned barriers to adherence. Using combinations of strategies that include simpler dosage regimens, patient motivation, and involvement of other health professionals in a patient-centered approach should be further investigated. In addition, patients' views should be taken into account when interventions are piloted, and the interventions themselves should be based on shared decision making and a true partnership between patient and practitioner.[52-55] Finally, it is of paramount importance that every study that evaluates an intervention to increase adherence to blood pressure–lowering medication should also measure blood pressure as a second outcome to help establish the often unclear relationship between adherence and blood pressure control.

CONCLUSIONS

We conclude that simplification of dosing regimens appears to be the most promising intervention to increase adherence to blood pressure–lowering medication. The evidence of the effect of motivational and more complex interventions is mixed and inconclusive. The results of this review should be interpreted with caution because of the poor methodologic quality and heterogeneity of many trials included in this review. Our findings emphasize the need for further RCTs with sufficient power and rigorous methodology.

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