Pharmacist interventions to enhance blood pressure control and adherence to antihypertensive therapy: Review and meta-analysis

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Hypertension is a major risk factor for cardiovascular disease and an important public health problem worldwide. The risk of cardiovascular morbidity and mortality is particularly marked when there is insufficient hypertension control and prevention at the community level. Randomized controlled trials (RCTs) have demonstrated that treating high blood pressure (BP) with medication can substantially reduce the risk of stroke by 35–40% and myocardial infarction by 20–25%.[1,2] Although the treatment of hypertension has been shown to reduce the risk of cardiovascular disease and mortality, hypertension remains inadequately managed worldwide, with a lack of adherence to BP-lowering medication playing a major role in poor BP control.[3-7] Hypertensive patients may fail to take their medication because of the symptomless nature of the condition, the long duration of therapy, adverse effects of medi-

Purpose. Pharmacist interventions to enhance blood pressure (BP) control and adherence to antihypertensive therapy in adults with essential hypertension were reviewed.

Methods. A literature search was conducted to identify relevant articles describing pharmacist interventions intended to improve adherence to antihypertensive medications. Studies were included if they described a pharmacist intervention to improve medication adherence and analyzed adherence to therapy and BP control as outcomes. A fixed-effects model was used to combine data from randomized controlled trials.

Results. A total of 15 studies were identified, testing 16 different interventions and containing data on 3280 enrolled patients. Although 87.5% of the interventions resulted in significant improvements in treatment outcomes, only 43.8% of the interventions were associated with significant increases in medication adherence. All interventions that increased antihypertensive medication adherence also significantly reduced BP. Almost all the interventions

that were effective in increasing adherence to medication were complex, including combinations of different strategies. Meta-analysis of 2619 patients in 8 studies found that pharmacist interventions significantly reduced systolic blood pressure (SBP) ($p <$ 0.001) and diastolic blood pressure (DBP) ($p = 0.002$) and that the meta-analytic differences in SBP and DBP changes from baseline to endpoint in intervention and control groups were -4.9 ± 0.9 mm Hg ($p < 0.001$) and -2.6 ± 0.9 mm Hg ($p < 0.001$), respectively.

Conclusion. A literature review and meta-analysis showed that pharmacist interventions can significantly improve medication adherence, SBP, DBP, and BP control in patients with essential hypertension. Interventions were complex and multifaceted and included medication management in all analyzed studies.

Index terms: Blood pressure; Compliance; Hypertension; Hypotensive agents; Interventions; Patients; Pharmacists
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cation, complicated drug regimens, the lack of understanding about hypertension management, costs of medication, and the challenge to individual patients' health beliefs.[8,9] Adherence rates to antihypertensive agents differ depending on the population studied, ranging between 50% and 70%.[5,10,11]

The importance of improving adherence to antihypertensive medication has been addressed by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, emphasizing the role of all health care professionals, including pharmacists, to improve adherence to treatment.[1] In the past two decades, pharmacists have been developing and implementing validated methods and services to improve adherence to antihypertensive medication and the clinical outcomes of this "silent" disease.[12]

One systematic review, which included studies from 1978 to 2006, assessed pharmacist interventions in hypertensive patients in order to enhance patients' adherence to medication and reduce systolic BP (SBP) and diastolic BP (DBP).[13] Since then, several important RCTs[14-17] and non-RCTs[18-20] have been conducted to assess the effect of pharmacist interventions on medication adherence and BP control in hypertensive patients.

While there is strong evidence supporting the benefits of antihypertensive drug therapy,[21] there is little clear evidence as to which types of pharmacist interventions for hypertensive patients are most effective for increasing medication adherence and improving hypertension control. We conducted a systematic review of published data on pharmacist interventions targeting antihypertensive medication adherence in adults with essential hypertension to evaluate the effect of pharmacist interventions on antihypertensive medication adherence and quantify the reductions in SBP and DBP resulting from those interventions.

Methods

A literature search to identify pharmacist interventions intended to improve adherence to antihypertensive medications and BP control was conducted. To be included in the systematic review, studies had to (1) have a population of adults with essential hypertension currently treated with BP-lowering drugs in a primary care, an outpatient, or a community setting, (2) clearly describe and evaluate an intervention delivered by a pharmacist to improve adherence with antihypertensive drugs and BP control, and (3) include both adherence to antihypertensive medication and mean SBP, mean DBP, or BP control as outcomes. Studies describing multidisciplinary interventions were included only if the pharmacist's role in patient care was clearly described. Articles describing different health conditions (e.g., cardiovascular diseases not involving essential hypertension) were excluded, as were studies assessing SBP and DBP or BP control but not antihypertensive medication adherence. The criteria used to assess adherence and treatment outcome were based on the observation that studies showing an increase in adherence without an improvement in clinical outcome provide no practical guidance for practice. Articles were also required to be written in English, French, Spanish, German, Portuguese, or Italian.

We searched the main electronic databases freely available in our research center: MEDLINE, The Cochrane Library, and ISI Web of Knowledge. Each database was independently searched by two reviewers for articles published from January 1999 through June 2009, using the terms *high blood pressure*, *hypertension*, *pharmaceutical services* or *pharmaceutical care or pharmacist*, and *patient outcomes* (i.e., *adherence*, *compliance*, *systolic blood pressure*, *di-* *astolic blood pressure*, and *blood pressure control*). We also hand searched bibliographies of all retrieved articles to identify additional publications of pharmacist interventions on patient medication adherence.

Two authors independently selected articles by first reading titles, then abstracts, and, finally, full texts. The reviewers selected articles based on the predefined inclusion and exclusion criteria and then compared results. Any disagreements were resolved by consensus. The rationale for decisions was discussed until reviewers agreed on the final decision. A third author was called to resolve any remaining discrepancies concerning article eligibility.

Data extraction was also performed by two independent authors, and disagreements were resolved through the same consensus process used with article selection. The following data were obtained in duplicate and verified: year of publication, study design, use of a comparison group, type of pharmacist interventions, extent of follow-up, study setting, sample size of both intervention and control groups, patients lost to follow-up, methods used to measure medication adherence, and outcomes measured. The outcomes of particular interest were medication adherence, SBP, DBP, and BP control. During data extraction, we wrote to corresponding authors of studies to request missing data and clarify study details.

After data were extracted, we classified study outcomes as either sensitive or nonsensitive. Sensitive results were those that were influenced positively by the pharmacist intervention from a clinical point of view and that had statistical significance (i.e., p of ≤ 0.05 at the endpoint of the study). Pharmacist interventions aimed to increase adherence to BP-lowering medication and BP control were classified as (1) medication management (drug therapy monitoring and adjustments; simplification of anti-

hypertensive regimens; optimization of drug regimen in order to solve adverse drug reactions, drug–drug interactions, and food–drug interactions; generic substitution), (2) educational interventions directed at the patient (hypertension education, BP self-monitoring recommendation, lifestyle education and counseling, medication education and counseling), (3) self-monitoring and recording of BP, including education, encouragement, and validatation of BP monitor, (4) medication reminders, including education and counseling tips (adherence aids), and appointment reminders (e.g., telephone or computer-based), (5) improved administration systems (e.g., Medication Event Monitoring System [Aardex Group Ltd., Slon, Valais, Switzerland]), and medications dispensed using an adherence aid (e.g., blister packs), (6) more-frequent follow-up appointments or contacts, (7) educational interventions and alerts directed at the health care professional (personal, telephone- or computer-based), and (8) pharmacist clinical visits in medical, university, hospital, and community-based clinics.

Two reviewers assessed the quality of accepted studies independently and in duplicate, using the quality scale of Downs and Black,[22] which was developed based on epidemiologic principles, reviews of study designs, and existing checklists for assessing RCTs. Disagreements regarding study quality were handled by consensus, and additional information about study design was requested from the authors if necessary. The method of Downs and Black[22] has been validated, and it allows for the scoring of quality of RCTs and observational studies. The instrument consists of a 28-item checklist that addresses a study's quality of reporting (10 items), external validity (3 items), internal validity or bias (7 items), confounding variables (6 items), power (1 item),

and a global score (1 item assessing the rater's overall impression of the quality of a paper) and has a possible total score of 42 (corresponding to the maximum quality score of 100%). Scores below 50% were considered weak, those between 50% and 69% were considered fair, scores of 70–79% were good, and scores of 80–100% were very good. We used a Mann-Whitney *U* test to compare quality scores between sensitive and nonsensitive outcomes, because there may be a relationship between the methodological quality of the included studies and the success of their respective interventions.

Medication adherence was reported in the individual groups of the studies at baseline and end of study. Whenever feasible, the percentage of participants with controlled BP at the end of the study and the corresponding odds ratio were mentioned. In each study, BP was classified as controlled using the national or international guidelines applicable at the time of the study. Because of the substantial differences among selected studies in terms of the various methods that were used to measure adherence (e.g., prescription refill data, pill count, compliance questionnaire, plasma drug level), we believed that pooling of the medication adherence results was inappropriate. A fixed-effects meta-analytic model was used to combine SBP and DBP results. However, only studies with extractable data and that had a contemporary control group were included in the meta-analysis (i.e., subjects allocated to usual care [control group] were treated during the same time period [contemporary] as the intervention group) to ensure that the only difference between the groups was the pharmacist intervention under investigation.

We explored the potential for publication bias by using funnel plots and calculating the Begg–Mazumdar[23] statistic. We examined the heterogeneity of outcomes us-

ing the chi-square test.[24] All analyses were conducted with SPSS, version 17.0 (SPSS Institute, Chicago, IL) and Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ), and the a priori level of significance was 0.05.

Results

Initially, 225 potential articles were identified. After assessing their titles and excluding those not mentioning any information pertinent to hypertension, BP, or medication adherence studies, 130 remained and their abstracts read. Of the 47 articles retrieved for full-text review, 32 were excluded for the following reasons: not an interventional study,[25-27] studied participants with a different disease not relevant to review,[28-32] did not include pharmacists in the study interventions,[33] presented pharmaceutical interventions and outcomes investigating neither adherence nor BP,[34-37] presented pharmaceutical interventions and outcomes investigating BP but not adherence,[38-53] investigated medication adherence outcome in the intervention group only and baseline adherence was not measured,[54] and not studies but reviews.[13,55] A total of 15 articles were included as full-text in our systematic review.[14-20,56-63]

Table 1 details some characteristics of the included studies. One study tested different interventions in three distinct intervention groups.[16] In this study the authors attributed the simplest intervention (provider education) to the control group and the remaining interventions ("provider education and alert" and "provider education and alert and patient education") to two intervention groups. Another study included two pharmacist-intervention groups, designated as a high-intensity intervention and a low-intensity intervention. We considered the low-intensity group, in which the only pharmacist intervention was measurement of BP and

Table 1.
Characteristics of Studies Evaluating Pharmacists' Interventions in Hypertension Treatment[a]

Ref.	Study Design[b]	Setting (Country)	Pharmacist Intervention[c]	Frequency of Pharmacist–Patient Interaction in Intervention Group
14	RCT	Community-based primary care clinics (United States)	A, B, C	Mean, 7.2 times in 12 mo[d]
15	RCT	Army medical center (United States)	B, D	Every 2 mo[e]
16	Cluster RCT	Hospital-based clinics (United States)	C	>3 times in 6 mo[f]
		Community-based clinics (United States)	A, C	
17	Cluster RCT	University clinics (United States)	A, B, C, E, F, G	Mean ± S.D., 6.8 ± 1.6 times in 9 mo[g]
18	SGCT	Primary-care clinics and community pharmacies (United States)	A, B, C, E	5 times in 9 mo[h]
19	SGCT	Clinic in university teaching hospital (Brazil)	A, B, C, F	Mean, 10.5 times in 12 mo[h]
20	SGCT	Community pharmacy (Nigeria)	A, B, C, E	Monthly[h]
56	RCT	Community pharmacies (United Kingdom)	A, B	Every 2 mo[i]
57	SGCT	Aircraft carrier (United States)	A	Every 2 wk[h]
58	Non-RCT	Community pharmacies (Canada)	A, B, C, F	Mean, 5.8 times in 9 mo[j]
59	RCT	Medical clinic (Brazil)	A	Monthly[f]
60	RCT	Medical clinic (United States)	A, B, C, E	Monthly[i]
61	RCT	Community pharmacies (Thailand)	A, B	Monthly[i]
62	RCT	Medical clinic (United States)	A, B	Monthly[i]
63	RCT	Community pharmacies (United States)	A, B, C, E	4 times in 3 mo[k]

[a]Medication adherence and blood pressure were measured in all studies. Other measured outcomes included quality of life, self-measurement of blood pressure, alcohol moderation, exercise, salt restriction, smoking cessation, number of antihypertensive drugs, adverse drugs effects, hypertension-related knowledge, patient satisfaction, resource utilization, low-density-lipoprotein cholesterol concentration, and intensification of antihypertensive regimen.

[b]RCT = randomized clinical trial, SGCT = single-group clinical trial.

[c]In all studies, pharmacists' interventions included medication management (e.g., drug therapy monitoring or adjustment, simplification of antihypertensive regimens, resolution of adverse drug reactions). A = educational interventions directed to the patient (e.g., hypertension education, lifestyle education and counseling), B = scheduling more-frequent follow-up appointments or contacts, C = educational interventions and alerts directed to health care professionals, D = providing improved administration systems (e.g., medication event monitoring system, blister packs), E = instituting self-monitoring and recording of blood pressure, including education, encouragement, and validating blood pressure monitor, F = providing medication reminders, including education and counseling tips (adherence aid tools) and appointment reminders (e.g., telephone based, computer based), G = pharmacist clinical visit attendance.

[d]Interaction in the control group occurred a mean of 4.9 times in 12 months.

[e]Interaction in the control group occurred at baseline and at the midpoint and end of the study.

[f]Interaction in the control group occurred with the same frequency as in the intervention group.

[g]Interaction in the control group occurred a mean ± S.D. of 5.5 ± 1.3 times in 9 months.

[h]Patients at baseline served as their own controls.

[i]Interaction in the control group occurred at baseline and at the end of the study.

[j]Interaction in the control group occurred 4 times in 9 months.

[k]Interaction in the control group occurred 3 times in 3 months.

patient counseling to contact their physician whenever BP was above normal, as the control group.

Medication management, educational interventions directed to the patient, and more-frequent follow-up appointments or contacts were the most frequently used pharmacist interventions. The number of pharmacist interventions per study ranged from two to five. After BP values and medication adherence outcomes, which were evaluated in all studies, patient quality of life was the

most evaluated outcome, present in 6 of the 15 included studies.[14,18-20,60,62]

Table 1 also details the pharmacist–patient interaction in control and intervention groups of included studies. The most common frequency of pharmacist–patient interaction in the intervention group was between monthly and every two months, and the purpose of the interaction was to provide pharmacist interventions. The pharmacist–patient interaction in the control group involved mostly baseline,

intermediate, and endpoint assessment of described outcomes.

Article quality scores, sample size, duration of follow-up, losses to follow-up, and outcomes sensitive to pharmacist interventions are shown in Table 2. The mean ± S.D. article quality score was 67.5% ± 10.6% (range, 50–76%), which was considered fair. The mean ± S.D. sample size was 218.7 ± 331.7 patients (median, 111 patients; range, 26–1341 patients). The follow-up period of the studies evaluated ranged from

two weeks to 12 months, with an average duration of 6.7 ± 10.6 months. Losses to follow-up ranged from 3.4% to 48.5% (mean ± S.D., 18.9% ± 15.3%). Article quality scores did not increase from 2000 to 2008 ($y = 596.848 - 0.264x$, $r^2 = 0.006$, $p = 0.790$, where y = article quality score and x = publication year). Sixty-one percent of the outcomes (28/46) were categorized as sensitive to the pharmacist interventions.

Effect on medication adherence and BP control. Adherence was measured in different ways, including self-report (through questionnaire or direct questioning), pill counts, analysis of prescription refill data, and plasma levels of hydrochlorothiazide. Various criteria for adherence were used in the studies, making a pooled analysis inappropriate (Table 3). Baseline medication adherence to antihypertensive drugs ranged from 35% to 88.6%, and medication adherence at study end ranged from 50% to 95.8%, which points to an increase in medication adherence due to pharmacist interventions. In fact, 7 of 16 intervention groups demonstrated a significant improvement in medication adherence when compared with the control groups. Differences in adherence rates at study end between pharmacist intervention groups and control groups varied from 8% to 58% in studies with positive sensitive outcomes. Although 5 studies revealed that pharmacist interventions had a negative effect on patients' treatment adherence compared with the control group, which ranged from –1% to –8%, these negative results were not significant. One study found an abnormally high increase in treatment adherence rate (increase of 58% from baseline); however, no comparison group was used in this study, and the follow-up period was only two weeks. The correlation between article quality scores and impact of pharmacist interventions was –0.680 ($p = 0.004$) for medication adherence. This ob-

Table 2.
Article Quality Scores, Sample Size, Duration of Follow-up, and Losses to Follow-Up of Selected Studies[a]

Ref.	Quality Score, %	n	Intervention Group	Control Group	Duration of Follow-up (mo)	No. (%) Pts Lost to Follow-up	Outcomes Sensitive to Pharmacist Interventions
14	76	463	230	233	12	191 (41.3)	SBP
15	69	159	83	76	6	13 (8.2)	Adherence, SBP
16	76	1341	1017	324	6	366 (27.3)	SBP[b]
17	67	179	101	78	9	19 (10.6)	SBP, DBP
18	50	103	103	...[c]	9	50 (48.5)	Adherence, SBP, DBP
19	57	48	48	...[c]	12	4 (8.3)	Adherence, SBP, DBP
20	52	40	40	...[c]	5	16 (40.0)	Adherence, SBP, DBP
56	67	282	167	115	6	102 (36.2)	Adherence, SBP
57	56	26	26	...[c]	0.5 (2 wk)	4 (15.4)	Adherence, SBP
58	74	111	41[d]	59[d]	9	11 (9.9)	SBP
59	82	71	34	37	6	7 (9.9)	None
60	67	41	20	21	6	5 (12.2)	DBP
61	82	235	118	117	6	8 (3.4)	Adherence, SBP, DBP
62	78	56	27	29	6	3 (5.4)	SBP, DBP
63	59	125	64	61	3	8 (6.4)	SBP, DBP

[a]SBP = systolic blood pressure, DBP = diastolic blood pressure.
[b]Provider education and alert and patient education intervention group.
[c]Patients served as their own controls.
[d]Patients at the end of the study (the article does not mention the number of patients enrolled in each group at the beginning of the study).

Table 3.
Medication Adherence Sensitivity to Pharmacist Interventions[a]

Ref.	Method of Measuring Adherence	Baseline Medication Adherence			Endpoint Medication Adherence			Endpoint Medication Adherence	
		% Adherence, Control Group	% Adherence, Intervention Group	p	% Adherence, Control Group	% Adherence, Intervention Group	p	% Difference Between Intervention and Control Groups	p
14	SR[b]	NR	61	NR	69	67	0.52 (control), 0.08 (intervention)	−2	0.77
15	Pill count and PRD	61.1	61.4	0.88	69.1	95.5	NR	26.4	<0.001
16	PRD	86	85[c]	0.13	89	89	NS	0[c]	NS
			83[d]	0.13		88	NS	−1[d]	NS
17	Pill count	88.6	71.1	<0.001	92 (NS)	94 (NR)	NS (control), NR (intervention)	2	0.369
18	PRD	70.6	NA	NA	NA	95.8	NA	25.2	0.02
19	Pill count and SR	63.6	NA	NA	NA	95.5	NA	31.9	<0.05
20	PRD	66.3	NA	NA	NA	83.5	NA	17.2	0.001
56	SR[e]	51.0	52.3	NS	50.0	62.9	NS (control), <0.05 (intervention)	12.9	<0.05
57	SR[f]	35	NA	NA	NA	93	NA	58	0.0001
58	SR[b] and PRD	83 (SR), 93 (PRD)	68 (SR), 98 (PRD)	0.085 (SR), 0.643 (PRD)	80.4 (SR)	74.3 (SR)	NS for both	−6.1	NS
59	Plasma drug level and SR[g]	NR	NR	NR	80	77.8	NR	−2.2	0.904
60	PRD	NR	NR	NR	89	82	NR	7	0.29
61	Pill count	56.5	51.3	0.534	55.6	63.6	NS (control), NR (intervention)	8	0.014
62	PRD and SR[f]	NR	NR	>0.2	93	85	>0.07 (for control and intervention)	−8	>0.42
63	SR[b]	74.1	61.3	NS	84.2	87.7	0.07 (control), 0.004 (intervention)	3.5	0.38

[a]SR = self-report, NR = not reported, PRD = prescription refill data, NS = not significant, NA = not applicable.
[b]Morisky questionnaire.
[c]Provider education and alert intervention group.
[d]Provider education and alert and patient education intervention group.
[e]Horne's Medication Adherence Report Scale used in questionnaire and with direct questioning by pharmacist.
[f]Compliance questionnaire.
[g]Dáder method by means of a pharmacotherapy history and using pharmacist's direct questioning.

servation suggests that higher quality scores are associated with a lesser effect on medication adherence. All of the 4 single-group controlled trials evaluated (with no contemporary comparison control group) reported a significant increase in medication adherence. The remaining 3 studies, which were RCTs, that reported a significant increase in medication adherence had more-frequent follow-up with the intervention group. Six other studies also adopted more-frequent follow-up without a significant increase in medication adherence. In 5 of these 6 studies, the endpoint adherence rate was high (>80%) in the control group, possibly making it difficult to achieve a further increase in the intervention group. Indeed, all 7 studies with a high adherence rate at study endpoint (>80%) in the control group

found that pharmacist interventions had a nonsignificant effect on medication adherence. All other studies but 1 revealed that pharmacist interventions had a positive effect on medication adherence, with a mean difference in adherence rates at endpoint between intervention and control groups of 22.2%.

Likewise, various criteria were used to report BP outcome, making it inappropriate to pool data from all included studies, though the range of results from individual studies are presented (Table 4). Of the 15 studies evaluated, 2 did not measure SBP or DBP, 7 studies described a significant improvement in both SBP and DBP, 4 described a significant improvement in SBP alone, and 1 study noted a significant improvement in DBP alone. Significant improvements in SBP and DBP ranged from –5.0 to

–18.6 mm Hg and from –1.0 to –12.2 mm Hg, respectively.

Three of the included studies did not describe the percentage of participants with controlled BP at the end of the study. Seven studies found a significant increase in the percentage of participants with controlled BP at the end of the study when comparing intervention and control groups, which ranged from 17.5% to 51.0%. The authors of each study classified BP as controlled using the national or international guidelines applicable at the time of the study (in most studies, BP was considered controlled when SBP was < 140 mm Hg and DBP was < 90 mm Hg). In 11 studies, we were able to calculate the odds ratio for the rate of patients achieving controlled BP at endpoint in the intervention group compared with the control group, and a range

Table 4.

Effects of Pharmacist Interventions on Blood Pressure (BP) Control[a]

| Ref. | Difference in BP in Intervention vs. Control Group, mm Hg (p) | | % Pts With Controlled BP at End of Study | | p | OR (95% CI) |
	SBP	DBP	Control Group	Intervention Group		
14	5.0 (<0.001)	1.0 (0.235)	44.0	62.0	0.003	2.1 (1.4–3.0)
15	7.3 (0.001)	1.4 (0.216)	NR	NR	NR	NR
16	–0.3 (NS)[b]	1.3 (NS)[b]	42.0	59.5	0.003	2.0 (1.5–2.7)
	6.0 (<0.001)[c]	3.3 (NS)[c]				
17	11.6 (<0.001)	3.3 (0.005)	52.9	89.1	<0.001	7.2 (3.2–15.6)
18	16.7 (0.02)	12.2 (0.04)	NR	NR	NR	NR
19	18.6 (<0.05)	9.1 (<0.05)	0	41.0	<0.05	12.2 (4.6–32.5)
20	14.3 (<0.001)	10.8 (<0.001)	NR	NR	NR	NR
56	NR	NR	17.1	35.7	<0.05	2.7 (1.5–4.7)
57	NR	NR	42.0	73.0	0.02	3.7 (1.2–11.9)
58	HI: 8.3 (0.01)	HI: 2.5 (0.28)	HI: 42.0	HI: 69.0	0.073	3.1 (0.8–12.4)
	LI: –4.4 (NS)	LI: –2.5 (NS)	LI: NS	LI: NS	0.895	NS
59	5.0 (0.063)	2.0 (0.281)	NS	NS	NS	NS
60	10.1 (0.069)	6.7 (0.022)	22.0	44.0	>0.1	2.8 (0.7–10.8)
61	5.7 (0.001)	2.5 (0.029)	57.2	66.1	0.061	1.5 (0.9–2.5)
62	14.1 (<0.001)	14.8 (<0.001)	30.0	81	<0.001	9.8 (2.8–34.1)
			12.0 (diabetic pts)	91.0 (diabetic pts)	<0.001	70.0 (5.6–882.2)
63	4.6 (0.041)	3.2 (0.014)	30.0	42.0	0.45	1.7 (0.8–3.5)

[a]SBP = systolic blood pressure, DBP = diastolic blood pressure, OR = odds ratio, CI = confidence interval, NR = not reported, HI = high income, LI = low income, NS = not significant.

[b]Provider education and alert intervention group.

[c]Provider education and alert and patient education intervention group.

of 1.46–12.18 was obtained, with a mean ± S.D. value of 4.43 ± 3.6.

Of the 7 studies that found a significant improvement in both SBP and DBP, 42.9% were single-group controlled trials (with no contemporary comparison control group). Thus, we analyzed the correlation between article quality scores and the impact of pharmacist interventions on SBP and DBP. This correlation was –0.599 ($p = 0.018$) for SBP and –0.659 ($p = 0.007$) for DBP. These observations suggest that higher quality studies are associated with a lesser effect on BP control.

A total of 8 controlled trials were included in the meta-analysis (Table 5). The remaining 7 studies were not included because the data were not extractable[56,58,60] and a comparison contemporary control group was not used.[18-20,57]

Effects on SBP. Sensitive outcomes were reported in 11 of 13 studies evaluating SBP. It was possible to include only 8 studies for the meta-analysis of SBP outcomes. A funnel plot (data not shown) did not rule out the possibility of publication bias; therefore, we applied the trim-and-fill method,[64] which increased the difference in SBP change between intervention and placebo from 4.9 to 5.6 mm Hg ($p < 0.001$). However, the Begg–Mazumdar[23] statistic was very small and nonsignificant ($t < 0.001$, $p = 1.0$). The Q statistic for heterogeneity of effects was not significant ($\chi^2 = 0.741$, $p = 0.99$); therefore, we considered the study results to be combinable.

The meta-analytic mean ± S.D. baseline and endpoint SBPs in the pharmacist intervention group were 153.0 ± 4.7 and 130.9 ± 4.6 mm Hg, respectively, producing a clinical and statistical weighted difference of –19.4 ± 3.5 mm Hg ($p < 0.001$). A significant difference was also observed in the mean ± S.D. SBP from baseline (151.3 ± 4.9 mm Hg) to endpoint (137.5 ± 6.4 mm Hg) in the control group, with a meta-analytic

difference of –11.3 ± 4.2 ($p = 0.007$). Meta-analytic differences from baseline to endpoint of both groups were calculated and are presented in Figure 1. The meta-analytic mean ± S.D. difference in SBP from baseline to endpoint between intervention and control groups was –4.9 ± 0.9 mm Hg ($p < 0.001$).

Effects on DBP. Sensitive outcomes were reported in 8 of 13 studies evaluating DBP. It was possible to include only 7 studies for the meta-analysis of DBP evaluation. The funnel plot was similar to that for SBP (data not shown). Use of the trim-and-fill method increased the difference between intervention and placebo from 2.6 to 3.3 mm Hg ($p < 0.001$). However, the Begg–Mazumdar[23] statistic did not detect publication bias ($\tau = –0.09$, $p = 0.76$). The Q statistic found no heterogeneity of effects ($\chi^2 = 2.23$, $p = 0.90$), so the results were considered combinable.

The meta-analytic mean ± S.D. baseline and endpoint DBPs in the pharmacist intervention group were 82.6 ± 4.3 and 74.6 ± 3.8 mm Hg, respectively, producing a clinical and statistical weighted difference of –8.8 ± 2.9 mm Hg ($p = 0.002$). However, a nonsignificant difference was observed in DBP from baseline (81.7 ± 4.3 mm Hg) to endpoint (76.9 ± 4.2 mm Hg) in the control group, with a meta-analytic difference of –4.9 ± 3.0 mm Hg ($p = 0.103$). Meta-analytic differences from baseline to endpoint of both groups were calculated and are presented in Figure 1. Pharmacist intervention reduced the DBP of the intervention group an additional 2.6 ± 0.9 mm Hg when compared with the control group ($p < 0.001$).

Discussion

The majority of the studies included in our analysis were RCTs. Although the mean quality of these RCTs was considered good (quality score, 72.3%), the mean quality of all the studies evaluated was fair (quality score, 67.5%). It is not fea-

sible to blind hypertensive patients in pharmaceutical intervention models, as this process of blinding is assessed in one item of the Downs and Black[22] quality checklist. By removing this item, the average quality of all articles included would increase to over 70%. However, 6 studies in which patients were not randomized to intervention groups, which are assessed by two items of the Downs and Black quality checklist, prevented a further increase of the overall quality score.

Although 88% of the interventions tested (14 of 16 in 15 studies) resulted in significant improvements in treatment outcomes (SBP, DBP, or percentage of participants with controlled BP at the end of the study), only 44% of the interventions (7 of 16 in 15 studies) were associated with significant increases in medication adherence. These results were higher than those obtained by Machado et al.,[13] who found that 76.6% and 38.5% of studies analyzed reported improvement in treatment outcomes and in medication adherence, respectively, though they did not address BP control specifically. Differences obtained in the systematic review of Machado et al.[13] and in our review reflect a trend toward improved medication adherence and treatment outcomes obtained with the most recent studies, which included more interventions involving physician–pharmacist collaboration.[14,16-20] In both systematic reviews, all studies that found a significant increase in medication adherence also demonstrated a significant improvement in treatment outcomes, revealing that medication adherence is a key factor (though not the only one) for achieving BP control.

Drug therapy adjustments may have contributed to improvements in BP control in studies where medication adherence rates did not significantly change. Some studies suggested that antihypertensive medications are frequently not intensified when BP remains uncontrolled (clinical in-

Table 5.
Meta-analytic Differences From Baseline to Endpoint of SBP and DBP in the Intervention and Control Groups[a]

Outcome and Ref.	Intervention Group				Control Group			
	n	Mean±S.D. Baseline Value, mm Hg	Mean±S.D. Endpoint Value, mm Hg	Mean±S.D. Meta-Analytic Difference, mm Hg	n	Mean±S.D. Baseline Value, mm Hg	Mean±S.D. Endpoint Value, mm Hg	Mean±S.D. Meta-Analytic Difference, mm Hg
SBP								
14	230	173.0±15.0	142.0±19.0	−31.0±12.3	233	174±15.0	148.0±22.0	−26.0±13.8
15	83	133.4±17.6	124.4±14.0	−9.0±11.4	76	135.0±20.3	133.3±21.5	−1.7±14.8
16[b]	547	158.0±12.4	146.0±19.0	−12.0±11.8	324	157.3±11.9	145.0±19.0	−12.3±11.8
16[c]	470	156.3±11.4	138.0±18.0	−18.3±11.2	...	...	...	...
17	101	153.1±10.0	124.2±9.7	−28.9±7.0	78	150.3±9.0	133.0±14.2	−17.3±8.8
59	30	140.0±18.0	134.0±11.0	−6.0±11.1	34	136±14.0	135.0±15.0	−1.0±10.3
61	118	144.8±19.7	121.5±14.9	−23.3±12.6	117	142.4±19.8	124.8±18.0	−17.6±13.4
62	26	149.0±15.3	130.5±13.2	−18.5±10.2	27	152.8±14.3	148.4±21.0	−4.4±13.1
63	64	151.6±18.6	138.1±15.9	−13.5±12.3	61	151.5±17.1	142.6±19.1	−8.9±12.9
Overall	1669	153.0±4.7	130.9±4.6	−19.4±3.5[d]	950	151.3±4.9	137.5±6.4	−11.3±4.2[e]
DBP								
14	230	90.0±14.0	77.0±10.0	−13.0±8.8	233	92.0±14.0	80.0±12.0	−12.0±9.3
15	83	71.7±9.1	67.5±9.9	−4.2±6.7	76	71.4±10.6	68.6±10.5	−2.8±7.5
17	101	84.9±12.0	74.7±9.6	−10.2±7.8	78	85.4±11.0	78.5±10.9	−6.9±7.7
59	30	80.0±11.0	77.0±10.0	−3.0±7.4	34	79.0±10.0	78.0±11.0	−1.0±7.4
61	118	85.7±13.6	71.6±10.8	−14.2±8.8	117	86.0±12.9	74.2±11.9	−11.7±8.8
62	26	89.8±10.9	77.5±10.7	−12.3±7.6	27	77.9±11.9	80.4±11.4	2.5±8.2
63	64	85.3±11.2	76.5±9.5	−8.8±7.4	61	85.3±10.3	79.7±10.2	−5.6±7.2
Overall	652	82.6±4.3	74.6±3.8	−8.8±2.9[f]	626	81.7±4.3	76.9±4.2	−4.9±3.0[g]

[a]SBP = systolic blood pressure, DBP = diastolic blood pressure.
[b]Provider education and alert intervention group.
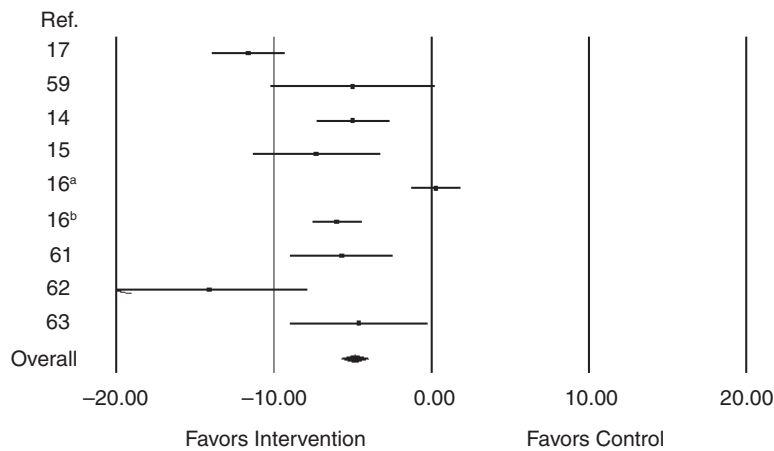[c]Provider education and alert and patient education intervention group.
[d]Pairwise comparison, inverse variance method ($Z = −5.493$, $p < 0.001$).
[e]Pairwise comparison, inverse variance method ($Z = −2.698$, $p = 0.007$).
[f]Pairwise comparison, inverse variance method ($Z = −3.025$, $p = 0.002$).
[g]Pairwise comparison, inverse variance method ($Z = −1.632$, $p = 0.103$).

Figure 1. Meta-analytic differences in improvement of systolic blood pressure (SBP) and diastolic blood pressure (DBP) (mm Hg) between patients receiving a pharmacist intervention and patients in control groups. Negative estimates favor the intervention group over the control group in the reduction of SBP or DBP in hypertensive patients. The squares represent the difference in improvement between groups, with 95% confidence interval (CI).
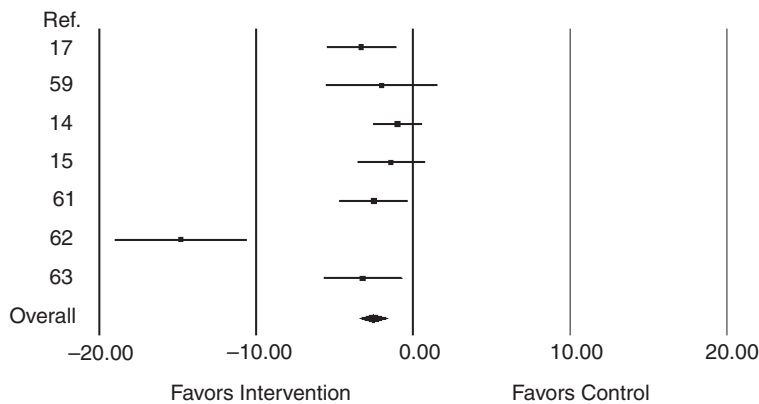
[a]Provider education and alert intervention group.

[b]Provider education and alert and patient education intervention group.

ertia).[65,66] By addressing suboptimal medication regimens, pharmacists may have contributed to changing unsuccessful regimens, searching for those regimens that would be more likely to succeed. However, it is also possible that the several methods used to measure adherence, some of which were unreliable, may have contributed to the inconsistency in adherence-rate differences between control and intervention groups. Large high-quality trials that use reliable methods of measuring adherence are needed to investigate the relationship between adherence and BP reduction.

SBP and DBP were definitely sensitive to pharmacist interventions, as we found that baseline to endpoint reductions in these outcomes were significantly influenced in intervention groups compared with control groups. These results also differ from those obtained by Machado et al.,[13] whose review showed that only SBP was sensitive to pharmacist interventions.

Almost all the interventions that were effective for medication adherence or BP control improvements were complex, including combinations of medication management, educational programs directed at the patient, scheduling of more-frequent follow-up appointments, medication reminders, counseling, self-monitoring of BP, and other forms of additional supervision or attention. We were not able to find a pattern of types or numbers of interventions that predicted success. Methods for improving antihypertensive adherence and BP control were generally labor-intensive (and therefore expensive) and not predictably effective. However, many intervention programs did lead to improved adherence or treatment outcomes. In 10 studies, we were able to calculate the odds ratio for the rate of patients achieving targeted BP at endpoint in the intervention group when compared with the control group, and a range of 1.46–12.18 was obtained, with a mean ± S.D. value of 4.43 ± 3.6. These values imply that achieving controlled BP at the end of the study was more likely in the intervention group and are in accordance with the values obtained by Carter et al.[67] In addition, studies with the largest effect sizes (i.e., the largest reductions in SBP or DBP from baseline to endpoint) had higher mean baseline SBP and DBP values (Table 5). Thus, the clinical impact of pharmacist interventions in hypertensive patients is expected to be more pronounced in high-risk patients. Moreover, it is possible that some pharmacist intervention programs put more emphasis on better communication and empathetic reinforcement, as these actions build trust, are potent motivators, and tend

to improve outcomes.[1] Motivation improves when patients have positive experiences with and trust in their health care staff. More studies are needed to assess the role of communication and empathetic reinforcement skills of pharmacists and other health care personnel on patient motivation and outcomes improvement.

Our study had several limitations. Comparing the different studies included in this review was difficult due to marked heterogeneity in terms of research designs, interventions, duration of follow-up, methods to measure medication adherence, and reporting of clinical outcomes. Some studies demonstrated poor methodological quality, particularly with regard to the presence of a contemporary comparison control group, randomization, blinding of outcomes assessment, and losses to follow-up. In two studies, the duration of follow-up was too short (three months or less), which is considered inadequate to classify adherence rates accurately[25,68] and to demonstrate persistent positive clinical findings.[69]

Adherence was measured and calculated in various ways, which made a pooled analysis inappropriate. For example, in one study,[58] the baseline adherence measured by the Morisky et al.[70] questionnaire was 83% and 68% in the control and intervention groups, respectively. When using refill-data analysis, the baseline adherence of the same patients was 93% and 98% in the control and intervention groups, respectively. Medication adherence was usually assessed unblinded to allocation status, which constitutes a potential source of bias. Without an agreement on criteria to measure and define medication adherence, it is not surprising that the effect of most interventions on adherence and BP was variable, making it difficult to examine the relationship between medication adherence and subsequent BP control.

We were not able to include several studies in our meta-analysis of SBP and DBP in the intervention and control groups, because some studies either did not report these data or did not use a comparison or control group. One other limitation is based on the quality of pharmacist interventions made. It is possible that the same pharmacist intervention led to different results, depending on the empathetic reinforcement and motivation provided by the health care personnel that have contact with hypertensive patients. Therefore, some degree of variation of results is expected in clinical pharmacy practice. Another limitation is our literature search was conducted using the main electronic databases freely available in our research center, leaving out important databases like International Pharmaceutical Abstracts and EMBASE. We tried to circumvent this limitation by hand searching bibliographies of all retrieved articles to identify additional publications of pharmacist interventions on patient medication adherence. Finally, a chance of publication bias cannot be ruled out based on funnel plot analyses and the trim-and-fill method, though our search criteria were intended to capture all published articles evaluating pharmacist interventions on both antihypertensive medication adherence and BP control. Publication bias occurs when authors are more likely to submit, or editors accept, positive rather than null (negative or inconclusive) results. A search performed for unpublished data would have helped to minimize the occurrence of publication bias.

Conclusion

A literature review and meta-analysis showed that pharmacist interventions can significantly improve medication adherence, SBP, DBP, and BP control in patients with essential hypertension. Interventions were complex and multifaceted and included medication management in all analyzed studies.

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