Sensitivity of Patient Outcomes to Pharmacist Interventions. Part II: Systematic Review and Meta-Analysis in Hypertension Management

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BACKGROUND: Hypertension is a major health concern worldwide due to its deleterious impact. Few studies have quantitatively assessed pharmacists' interventions in hypertensive patients.

OBJECTIVES: To identify and quantify outcomes sensitive to pharmacists' interventions.

METHODS: *International Pharmaceutical Abstracts*, MEDLINE, Cochrane Central, and EMBASE were searched from inception through December 2006. Two independent reviewers identified articles; results were compared and resolved through consensus. Data extracted included intervention type, patient numbers, demographics, study characteristics, instruments used, data compared, and outcomes reported. A random effects meta-analysis was used to combine data. Study quality was assessed using the Downs–Black scale.

RESULTS: Of 203 potential articles identified, 98 were selected and their abstracts were read. Nine of these were reviewed full-text and 19 more were identified from references, resulting in a total of 28 articles. Research designs included 18 randomized controlled trials, 6 single-arm clinical trials, 3 nonrandomized comparative trials, and 1 database study. Average quality score was 66% ± 12% (fair). Medication management (82%) and hypertension education (68%) were the interventions most used. Thirty-nine study results (57% of all outcomes evaluated) were sensitive to pharmacists' interventions. Meta-analysis of 2246 patients in 13 studies found that pharmacists' interventions significantly reduced systolic blood pressure (10.7 ± 11.6 mm Hg; p = 0.002), while controls remained unchanged (3.2 ± 12.1 mm Hg; p = 0.361). Pharmacists' interventions further reduced systolic blood pressure (6.9 ± 12.1 mm Hg; p = 0.047) over controls. Nonsensitive results included further reduction in diastolic blood pressure (3.6 ± 3.7 mm Hg; p = 0.06), quality of life (1 of 8 significant), and adherence (5 of 13 significant).

CONCLUSIONS: Systolic blood pressure is sensitive to pharmacists' interventions. Other outcomes may also be sensitive; however, more high-quality studies are needed for a comprehensive quantitative assessment.

KEY WORDS: hypertension, pharmaceutical care, pharmacist intervention.

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Hypertension is a major health concern worldwide due to its deleterious impact on the population in terms of excessive morbidity and mortality, especially when there is insufficient hypertension control and prevention at the community level.[1] For instance, in the US, blood pressure is controlled only in 34% of people with diagnosed hypertension,[2] and in some countries this percentage can be as low as 20%.[1] Indeed, hypertension alone accounts for greater than 5.8% of the total deaths, 11.9% of the years of life lost, and 1.4% of the disability-adjusted life years worldwide.[1] Therefore, hypertension prevention and control in the community represents a primary challenge.

In most countries, community pharmacists are the most accessible healthcare professionals. Since the late 1980s, pharmacists have been developing and implementing validated methods and services to assist patient needs in the community setting.[3,4] These services, often referred to as pharmaceutical care, aim to prevent, detect, and solve actual or potential drug-related problems in patients.[3] Among these problems are adherence/compliance, lack of efficacy, adverse events, and interactions. In a literature review, Carter and Zillich[5] reported that several studies have found that community pharmacists can improve blood pressure control when they focus on patient management. However, most of the studies evaluating pharmacists' interventions reported in the literature have been criticized for their low quality of study design and analysis.[6] Moreover, to our knowledge, no quantitative review (meta-analysis) of pharmacists' interventions in hypertensive patients has appeared in the literature.

The objective of this study was therefore to identify and evaluate outcomes that can be positively impacted by pharmacists' interventions in the management of patients diagnosed with essential hypertension.

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Methods

To be included, studies must have evaluated pharmacists' interventions in patients with diagnosed hypertension. However, multiprofessional interventions were also accepted, but the pharmacists' role in patient care had to be clearly described. Studies in which the role of the pharmacist could not be isolated were excluded. Additionally, articles dealing with different health conditions and study designs were also excluded. We included all articles in the literature written in any of the major languages (English, French, German, Portuguese, or Spanish). No restriction was placed on study setting.

We searched secondary databases from inception to the end of 2006 to obtain all published studies meeting the inclusion criteria. Databases searched were *International Pharmaceutical Abstracts*, MEDLINE, EMBASE, and The Cochrane Central Register of Controlled Trials, 3rd Quarter. Terms used in the search strategy included hypertension, pharmaceutical services or pharmaceutical care, and patient outcomes (ie, knowledge, compliance, dispensing, satisfaction, quality of life, adverse drug reactions, costs, education). Additionally, reviewers examined the references of retrieved studies and reviews that were identified during the search in an attempt to locate further relevant papers.

Two reviewers independently selected articles by first reading titles, then abstracts, and finally, full texts. They then compared results; disagreements were resolved through consensus. The rationale for decisions was discussed until reviewers agreed on the final decision.

Data extraction was also performed by 2 independent reviewers, and disagreements were resolved through the same consensus process as was used with article selection. The following data were obtained and verified: year of publication, type of study, use of a comparison group, type of pharmacist interventions, study time horizon, study setting, patients' demographic characteristics (eg, number, mean age, proportion of women, concomitant drug use), and outcomes measured. For the present research, the outcomes of particular interest were reductions in diastolic and systolic blood pressure, lipid levels, treatment adherence, medication/disease knowledge, and changes in quality of life.

After data were extracted, we categorized study outcomes as either sensitive or nonsensitive. Sensitive results were those that were influenced positively by the pharmacist's intervention and that had clinical relevance. We defined clinical relevance as a pre/post difference of 10 mm Hg or more in systolic pressure and 5 mm Hg or more difference in diastolic blood pressure. Statistical significance (ie, p value ≤ 0.05 at the endpoint of the study) was needed as well. If either condition (ie, clinical relevance or statistical significance) was not met, we categorized the outcome as nonsensitive.

Initially, simple descriptive statistics (eg, rate, mean, range, standard deviation) were calculated. As well, we prepared a detailed description of study contents (eg, main findings, strengths and weaknesses in the study design). The quality of accepted studies was assessed using the 28-item checklist (addressing study quality of reporting, external and internal validities, bias, confounding, power) of Downs and Black.[7] This validated scoring scale allows for the measurement of quality not only of randomized controlled trials, but also of observational studies. Scores are expressed as percentages, with higher scores being better than lower scores and 100% being the maximum possible score. Scores below 50% were considered weak; those between 50% and 69% were considered fair, 70–79% were good, and 80–100% were very good. We used a Mann–Whitney test to contrast quality scores between outcomes that were sensitive and those that were nonsensitive.

Additionally, we used meta-analysis to combine results from controlled clinical trials. Included in the meta-analysis were studies comparing pharmacists' interventions with standard care in the management of hypertensive adults. No restriction was placed on the use of concomitant drugs, diseases, or follow-up period. The outcomes of interest were reduction in systolic and diastolic blood pressure.

We first calculated the average difference in blood pressure from baseline to endpoint separately for intervention and control groups. We then contrasted results from the intervention and control groups at endpoint. In all cases, outcomes were combined using a random-effects model. We explored the potential for publication bias by using funnel plots and calculating the Begg-Mazumdar statistic.[8] We examined the heterogeneity of outcomes using the χ^2 statistic.[9] We considered p values of 0.05 or less to be indicative of statistical significance for all tests.

Finally, we categorized all outcomes (eg, systolic and diastolic blood pressure, lipid levels, quality of life) into 4 categories of sensitivity: definitely sensitive, possibly sensitive, possibly not sensitive, and definitely not sensitive to pharmacists' interventions. Table 1 presents these categories and describes how they may be identified. To be classified in a specific category, a study must have met both of the corresponding qualitative and quantitative criteria outlined in the 2 columns on the right of Table 1.

Results

STUDY CHARACTERISTICS

Initially, 203 potential articles were identified. We first assessed their titles (excluding those not mentioning any information pertinent to pharmacist intervention studies); 98 were selected and their abstracts were read. A total of 27 articles were retrieved for full-text review; 18 of these were excluded for the following reasons: 6 studied a different disease,[10-15] 4 had data that were not extractable,[16-19] 3 did not include pharmacists in the study interventions,[20-22] 2 presented unacceptable study designs,[23,24] 2 were reviews,[25,26] and 1 appeared

only in abstract form.[27] Finally, 9 studies were included as full-text and an additional 19 were identified from their references, resulting in a total of 28 articles.[28-55]

The majority of studies were conducted in medical clinics (n = 18), followed by 8 in community pharmacies, 1 in a hospital, and 1 in a nuclear-powered aircraft carrier. There were 18 randomized controlled trials, 5 single-arm clinical trials, 4 nonrandomized comparative trials, and 1 database study. Medication management (82%) and hypertension education (68%) were pharmacists' most used interventions.

Table 2 details the characteristics of the included studies. The average sample size was 173 ± 162 (mean ± SD), with a median of 125 and range from 49–629 patients. The correlation between sample size and impact of pharmacists' interventions was –0.37 (p = 0.217) on diastolic blood pressure and –0.53 (p = 0.065) on systolic blood pressure. These observations suggest that larger studies are associated with a smaller impact. This correlation would become significant with the addition of 2 more studies of average size and comparable outcome.

The average follow-up period of the included studies was 7.6 ± 5.5 months. There were 7 studies that specified the length of time of pharmacist–patient interaction, with the average time from these studies being 27 ± 12 minutes. The most common frequency (50% of the studies) of pharmacist–patient interaction was monthly.

The average quality score of study reporting was 66% ± 12% (range 37–85%), which could be considered only fair. The correlation between quality scores and impact of pharmacists' interventions on systolic blood pressure was 0.32 (p = 0.279); correlation on diastolic blood pressure was 0.51 (p = 0.075). The latter value would become significant with the addition of 3 studies of average size and similar outcomes. That finding implies that higher quality studies are associated with a greater impact. As well, quality scores did not increase over time from 1978 to 2006 ($y = 0.0061x - 11.546$, $R^2 = 0.17$; p = 0.364).

In total, 5 different types of outcomes were evaluated in the 28 included studies. Table 3 describes these outcomes, their category of sensitivity, and the quality score from each study included in our review. Fifty-seven percent (39/68) of the outcomes were categorized as sensitive to the pharmacists' interventions, with the remaining 43% being nonsensitive. Studies reporting sensitive outcomes did not have higher quality compared with studies reporting nonsensitive outcomes (66% for studies reporting sensitive outcomes vs 68% for studies reporting nonsensitive outcomes, Mann–Whitney U test, Z = –0.666; p = 0.505).

SYSTOLIC BLOOD PRESSURE

Twenty-six studies included in our review evaluated patients' systolic blood pressure as a clinical outcome. From these studies, 77% reported results sensitive to pharmacists' interventions. These results are detailed in Table 3.

A total of 13 controlled trials were included in the meta-analysis.[34,36,37,40,43,44,48-50,52-55] The remaining 13 studies were not included for the following reasons: 7 for data not being extractable,[28-30,32,38,45,51] 5 for not using a comparison/control group,[31,35,42,46,47] and 1 for being a database study.[41]

The funnel plot (data not shown) did not rule out the possibility of publication bias and also contained one obvious outlier. We therefore applied the trim-and-fill method.[56] When balancing pseudo-values, the impact of the pharmacist on systolic blood pressure fell from 10.7 to 7.6 mm Hg difference, which was nonsignificant (p = 0.08). Removal of the outlier increased the impact to 8.5 mm Hg (p = 0.059). Therefore, there is a potential for publication bias. However, the Begg-Mazumdar statistic was small and nonsignificant ($\tau = -0.21$; p = 0.33). It should be noted that all of these tests are weak and the possibility of bias always exists. Readers need to take this information into consideration when interpreting the results.

The Q-statistic for heterogeneity of effects was not significant ($\chi^2 = 2.84$; p = 0.99); therefore, we considered the study results to be combinable.

Table 1. Outcome Categories of Sensitivity to Pharmacists' Interventions

	Assessment of Study Results	
Outcome Category[a]	**Qualitative**	**Quantitative**
Definitely sensitive	a) difference from baseline is clinically relevant	a) both statistically significant increase over baseline and superior to placebo in meta-analysis
Possibly sensitive	a) clinically relevant difference b) difference that does not reach the threshold for clinical relevance c) too few studies for meta-analysis but results appear positive	a) difference is not significant b) difference is statistically significant c) testing is not possible
Possibly not sensitive	a) difference is not clinically relevant b) too few studies for meta-analysis, but results appear to be negative	a) difference is not significant b) testing is not possible
Definitely not sensitive	a) difference from baseline worse b) difference lower than placebo c) all studies show no change	a) difference is statistically significant b) difference is statistically significant c) difference is not significant

[a]Outcome categorization in terms of sensitivity to pharmacists' interventions.

There were 2246 patients included in the meta-analysis (1155 patients in the pharmacist intervention group and 1091 in the control group). No significant differences were observed in age between the 2 groups (63.4 ± 4.2 y for the pharmacist intervention group and 62.2 ± 4.6 y for the control group; t = 0.27; p = 0.81). The intervention group had 54% females compared with 57% in the control group (p = 0.669). Little information was obtained from the studies

Table 2. Characteristics of Studies Evaluating Pharmacists' Interventions in Hypertensive Patient Pharmacotherapy

Reference	Design	Setting	Control Group	Interventions	Outcomes Measured
Blenkinsopp (2000)[28]	randomized clinical trial	community pharmacies	yes	drug therapy monitoring, pt. education	blood pressure, adherence
Bogden (1998)[29]	randomized clinical trial	medical clinic	yes	drug therapy monitoring, pt. education	blood pressure
Borenstein (2003)[30]	randomized clinical trial	medical clinic	yes	medication management	blood pressure
Brouker (2000)[31]	single-arm clinical trial	nuclear-powered aircraft carrier	no	medication counseling, information	blood pressure, adherence
Chabot (2003)[32]	nonrandomized clinical trial	community pharmacies	yes	medication management, pt. education	blood pressure, adherence
Côté (2005)[33]	single-arm clinical trial	community pharmacies	no	medication management, pt. education	quality of life
Castro (2006)[34]	randomized clinical trial	medical clinic	yes	medication management, pt. education	blood pressure, adherence
Erhun (2005)[35]	single-arm clinical trial	medical clinic	no	NR	blood pressure
Erickson (1997)[36]	nonrandomized clinical trial	medical clinic	yes	medication management, pt. education	blood pressure, quality of life
Garção (2002)[37]	randomized clinical trial	community pharmacies	yes	medication management, pt. education	blood pressure
Godley (2003)[38]	database analysis	medical clinic	no	medication management, pt. education	blood pressure
Gourley (1998)[39]	randomized clinical trial	medical clinic	yes	medication management, pt. education	knowledge, quality of life
Hawkins (1979)[40]	randomized clinical trial	medical clinic	yes	NR	blood pressure, adherence
Hennessy (2006)[41]	randomized clinical trial	medical clinic	yes	pt. education	blood pressure
McConnell (2006)[42]	single-arm clinical trial	medical clinic	no	medication management	blood pressure
McKenney (1978)[43]	randomized clinical trial	community pharmacies	yes	drug therapy monitoring, pt. education	blood pressure, adherence
McKenney (1985)[44]	nonrandomized clinical trial	hospital	yes	NR	frequency of dosing changes, drug deletions, drug additions, effectiveness of blood pressure control, reported adverse reactions to antihypertensive agents
Mehos (2000)[45]	randomized clinical trial	medical clinic	yes	medication management, pt. education	blood pressure, adherence, quality of life
Menard (1986)[46]	single-arm clinical trial	medical clinic	no	drug therapy monitoring/adjustments, pt. education	adherence, knowledge, blood pressure, biochemical changes
Morse (1986)[47]	nonrandomized clinical trial	medical clinic	no	drug therapy monitoring/adjustments, pt. education	blood pressure
Murray (2004)[48]	randomized clinical trial	medical clinic	yes	medication management	blood pressure, quality of life
Okamoto (2001)[49]	randomized clinical trial	medical clinic	yes	medication management, pt. education	blood pressure, quality of life
Park (1996)[50]	randomized clinical trial	community pharmacies	yes	drug therapy monitoring, pt. education	blood pressure, quality of life, adherence
Reid (2004)[51]	randomized clinical trial	medical clinic	yes	medication management	blood pressure
Solomon (1998)[52]	randomized clinical trial	medical clinic	yes	medication management, pt. education, counseling	blood pressure, adherence
Sookaneknun (2004)[53]	randomized clinical trial	community pharmacies	yes	medication management, pt. education	blood pressure, adherence
Vivian (2002)[54]	randomized clinical trial	medical clinic	yes	changes in prescribed drugs, adjusted dosages, drug counseling	adherence, blood pressure, pt. satisfaction, quality of life
Zillich (2005)[55]	randomized clinical trial	community pharmacies	yes	medication management, pt. education	blood pressure, adherence

NR = not reported.

regarding patients' disease duration, concomitant drug use, or concomitant diseases. Table 4 presents demographics of patients included in the meta-analysis.

The meta-analytic averages in baseline and endpoint of systolic blood pressure in the pharmacist intervention group were 148.5 ± 25.5 mm Hg and 137.2 ± 17.0 mm Hg, respectively, thus producing a clinical and statistical weighted difference of –10.7 ± 11.6 mm Hg (p = 0.002). In the control group, no significant difference was observed in systolic blood pressure from baseline (146.1 ± 21.4 mm Hg) to endpoint (142.1 ± 25.8 mm Hg), where the meta-analytic difference was –3.2 ± 12.1 mm Hg (p = 0.361). Table 5 depicts the

Table 3. Outcome Sensitivity to Pharmacists' Interventions and Article Quality Scores

	Sensitive		Nonsensitive	
Outcome	Reference	Quality Score, %	Reference	Quality Score, %
Systolic blood pressure	Blenkinsopp (2000)[28]	67	Castro (2006)[34]	82
	Bogden (1998)[29]	85	Hawkins (1979)[40]	63
	Borenstein (2003)[30]	74	Hennessy (2006)[41]	59
	Brouker (2000)[31]	56	Mehos (2000)[45]	67
	Chabot (2003)[32]	74	Menard (1986)[46]	48
	Erhun (2005)[35]	59	Murray (2004)[48]	70
	Erickson (1997)[36]	59		
	Garção (2002)[37]	85		
	Godley (2003)[38]	56		
	McConnell (2006)[42]	63		
	McKenney (1978)[43]	59		
	McKenney (1985)[44]	37		
	Morse (1986)[47]	56		
	Okamoto (2001)[49]	70		
	Park (1996)[50]	82		
	Reid (2004)[51]	67		
	Solomon (1998)[52]	78		
	Sookaneknun (2004)[53]	82		
	Vivian (2002)[54]	78		
	Zillich (2005)[55]	59		
Diastolic blood pressure	Erhun (2005)[35]	59	Chabot (2003)[32]	74
	Erickson (1997)[36]	59	Castro (2006)[34]	82
	Garção (2002)[37]	85	Hawkins (1979)[40]	63
	McConnell (2006)[42]	63	Hennessy (2006)[41]	59
	McKenney (1978)[43]	59	Mehos (2000)[45]	67
	McKenney (1985)[44]	37	Menard (1986)[46]	48
	Morse (1986)[47]	56	Murray (2004)[48]	70
	Okamoto (2001)[49]	70	Solomon (1998)[52]	78
	Park (1996)[50]	82		
	Sookaneknun (2004)[53]	82		
	Vivian (2002)[54]	78		
	Zillich (2005)[55]	59		
Adherence	Blenkinsopp (2000)[28]	67	Chabot (2003)[32]	74
	Brouker (2000)[31]	56	Castro (2006)[34]	82
	McKenney (1978)[43]	59	Hawkins (1979)[40]	63
	Solomon (1998)[52]	78	Mehos (2000)[45]	67
	Sookaneknun (2004)[53]	82	Menard (1986)[46]	48
			Park (1996)[50]	82
			Vivian (2002)[54]	78
			Zillich (2005)[55]	59
Knowledge	Gourley (1998)[39]	56		
Quality of life	Gourley (1998)[39]	56	Côté (2005)[33]	67
			Erickson (1997)[36]	59
			Mehos (2000)[45]	67
			Murray (2004)[48]	70
			Okamoto (2001)[49]	70
			Park (1996)[50]	82
			Vivian (2002)[54]	78
Overall (average)[a]		66		68

[a]Mann–Whitney U test (Z = –0.666; p = 0.505).

raw data extracted from the articles and meta-results of systolic blood pressure for the intervention and control groups.

Meta-analytic differences from baseline to endpoint of both groups were calculated and are presented in Figure 1. Where the systolic blood pressure of patients in the control group declined by 3.2 mm Hg, the pharmacist intervention group was able to reduce it an additional 6.9 ± 12.0 mm Hg (p = 0.047).

DIASTOLIC BLOOD PRESSURE

Sensitive outcomes were reported in 60% (12/20) of all studies evaluating diastolic blood pressure. Included studies for the meta-analysis were the same 13 previously described in the systolic blood pressure evaluation. The resultant patient demographics are also described in Table 4.

The funnel plot was similar to that for systolic blood pressure. Trim-and-fill lowered the impact between intervention and placebo from 3.6 (p = 0.062) to 2.8 (p = 0.138). However, the Begg-Mazumdar statistic did not detect publication bias ($\tau = -0.04$; p = 0.85). Thus, caution must be observed in interpreting results. The Q-statistic found no heterogeneity of effects ($\chi^2 = 3.88$; p = 0.98), so the results were considered combinable.

Significant reductions in diastolic blood pressure from baseline to endpoint were observed in the pharmacist intervention group (–5.8 mm Hg; 95% CI ± 3.8), but not in the control group (–2.4, 95% CI ± 3.7). Table 5 presents the raw data extracted from the included studies and the resultant meta-reduction in diastolic blood pressure in both analyzed groups. No statistically significant result was found (–3.6 mm Hg; 95% CI ± 3.8) when we calculated the meta-analytic difference in diastolic blood pressure changes from baseline to endpoint of intervention and control groups (Figure 1).

LIPID LEVELS IN HYPERTENSIVE PATIENTS

None of the studies included in our review evaluated lipid levels of hypertensive patients.

TREATMENT ADHERENCE

Thirteen studies evaluated treatment adherence of hypertensive patients. Five studies reported sensitive outcomes and

Table 4. Demographics of Patients Included in the Meta-Analysis

				Intervention Group			Control Group		
Reference	Disease Duration, y	Concomitant Drugs	Concomitant Diseases	n	Age, y, mean ± SD	Females (rate)	n	Age, y, mean ± SD	Females (rate)
Castro (2006)[34]	NR	NR	NR	30	63.9 ± 9.0	0.30	34	59.1 ± 10.1	0.34
Erickson (1997)[36]	NR	NR	cardiac, vascular, arthritis, pulmonary, psychiatric disorders	40	66.6 ± 11.2	0.70	40	63.3 ± 14.1	0.67
Garção (2002)[37]	NR	NR	NR	41	66.6 ± 8.2	0.66	41	63.5 ± 12.7	0.78
Hawkins (1979)[40]	NR	NR	diabetes	349	61.0, NR	0.75	280	60.0, NR	0.77
McKenney (1978)[43]	NR	NR	NR	70	NR	0.51	66	NR	0.48
McKenney (1985)[44]	NR	NR	NR	39	NR	NR	39	NR	NR
Murray (2004)[48]	NR	NR	NR	128	54.0 ± 11.0	0.79	124	54.0 ± 11.0	0.75
Okamoto (2001)[49]	15	NR	NR	164	62.0 ± 11.4	0.44	166	61.7 ± 11.3	0.54
Park (1996)[50]	NR	NR	NR	23	57.3, NR	0.52	26	63.0, NR	0.50
Solomon (1998)[52]	NR	NR	NR	63	66.3 ± 10.0	0.02	70	67.3 ± 11.0	0.07
Sookaneknun (2004)[53]	NR	NR	diabetes	118	63.2 ± 9.3	0.64	117	63.2 ± 9.3	0.71
Vivian (2002)[54]	NR	NR	diabetes	26	64.0 ± 10.9	NR	27	65.5 ± 7.8	NR
Zillich (2005)[55]	NR	NR	diabetes, renal disease, heart disease, cerebrovascular disease, dyslipidemia	64	64.0 ± 11.1	0.58	61	66.1 ± 13.8	0.64
Total				**1155**	**63.4 ± 4.17[a]**	**0.37**	**1091**	**62.2 ± 4.62[a]**	**0.68**

NR = not reported.
[a]Inverse variance method for comparison between ages of both intervention and control groups (t = 0.224; p = 0.810).

Table 5. Meta-Analytic Differences from Baseline to Endpoint of Systolic and Diastolic Blood Pressures in the Intervention and Control Groups

Outcome	Group	Reference	Baseline Values, mm Hg		Endpoint Values, mm Hg		Meta-Analytic Difference, Mean ± SD
			Mean ± SD	Pts., n	Mean ± SD	Pts., n	
Systolic blood pressure	intervention	Castro (2006)[34]	140.0 ± 18.0	30	134.0 ± 11.0	30	-6.0 ± 11.1
		Erickson (1997)[36]	156.5 ± 18.6	40	144.5 ± 15.9	40	–12.0 ± 12.3
		Garção (2002)[37]	151.7 ± 23.2	41	128.5 ± 15.1	41	–23.1 ± 14.4
		Hawkins (1979)[40]	145.0 ± 15.0	349	147.0 ± 18.0	349	2.0 ± 11.8
		McKenney (1978)[43]	153.4 ± 18.6	70	148.4 ± 15.9	70	–5.0 ± 12.3
		McKenney (1985)[44]	153.7 ± 20.3	39	142.1 ± 25.5	39	–11.6 ± 16.5
		Murray (2004)[48]	144.0 ± 18.0	128	144.0 ± 21.0	128	0.0 ± 13.9
		Okamoto (2001)[49]	144.2 ± 18.4	164	135.1 ± 15.3	164	–9.1 ± 12.1
		Park (1996)[50]	155.5 ± 21.1	27	143.2 ± 11.5	23	–12.3 ± 12.4
		Solomon (1998)[52]	146.7 ± 16.8	63	138.5 ± 13.9	63	–8.2 ± 11.0
		Sookaneknun (2004)[53]	144.8 ± 19.7	118	121.5 ± 14.9	118	–23.3 ± 12.6
		Vivian (2002)[54]	149.0 ± 15.3	26	130.5 ± 13.2	26	–18.5 ± 10.2
		Zillich (2005)[55]	151.6 ± 18.6	64	138.1 ± 15.9	64	–13.5 ± 12.3
		Overall	**148.5 ± 25.5**	**1159**	**137.2 ± 17.0**	**1155**	**–10.7 ± 11.6**[a]
Systolic blood pressure	control	Castro (2006)[34]	136.0 ± 14.0	34	135.0 ± 15.0	34	–1.0 ± 10.3
		Erickson (1997)[36]	153.7 ± 17.1	40	151.0 ± 19.1	40	–2.7 ± 12.9
		Garção (2002)[37]	147.7 ± 16.0	41	142.9 ± 20.4	41	–4.8 ± 13.1
		Hawkins (1979)[40]	143.0 ± 14.0	280	141.0 ± 13.0	280	–2.0 ± 9.6
		McKenney (1978)[43]	153.1 ± 17.1	66	151.7 ± 19.1	66	–1.4 ± 12.9
		McKenney (1985)[44]	141.3 ± 22.7	39	142.4 ± 25.9	39	1.1 ± 17.3
		Murray (2004)[48]	142.0 ± 16.0	124	143.0 ± 18.0	124	1.0 ± 12.1
		Okamoto (2001)[49]	142.9 ± 18.0	166	141.7 ± 17.9	166	–1.3 ± 12.7
		Park (1996)[50]	147.9 ± 19.6	26	148.6 ± 20.1	26	0.7 ± 14.0
		Solomon (1998)[52]	146.2 ± 17.0	70	144.9 ± 21.3	70	–1.3 ± 13.8
		Sookaneknun (2004)[53]	142.4 ± 19.8	117	124.8 ± 18.0	117	–17.6 ± 13.4
		Vivian (2002)[54]	152.8 ± 14.3	27	148.4 ± 21.0	27	–4.4 ± 13.1
		Zillich (2005)[55]	151.5 ± 17.1	61	142.6 ± 19.1	61	–8.9 ± 12.9
		Overall	**146.1 ± 21.4**	**1091**	**142.1 ± 25.8**	**1091**	**–3.2 ± 12.1**[b]
Diastolic blood pressure	intervention	Castro (2006)[34]	80.0 ± 11.0	30	77.0 ± 10.0	30	–3.0 ± 7.4
		Erickson (1997)[36]	91.6 ± 11.2	40	86.9 ± 9.5	40	–4.7 ± 7.4
		Garção (2002)[37]	85.7 ± 13.2	41	73.3 ± 8.2	41	–12.3 ± 8.1
		Hawkins (1979)[40]	86.0 ± 6.0	349	84.0 ± 6.0	349	–2.0 ± 4.2
		McKenney (1978)[43]	96.1 ± 11.2	70	89.7 ± 9.5	70	–6.4 ± 7.4
		McKenney (1985)[44]	95.3 ± 13.0	39	85.0 ± 11.7	39	–10.3 ± 8.8
		Murray (2004)[48]	78.0 ± 10.0	128	77.0 ± 11.0	128	–1.0 ± 7.4
		Okamoto (2001)[49]	82.8 ± 11.2	164	77.7 ± 8.7	164	–5.1 ± 7.2
		Park (1996)[50]	87.8 ± 9.9	27	83.2 ± 8.0	23	–4.6 ± 6.3
		Solomon (1998)[52]	84.6 ± 13.2	63	80.2 ± 9.6	63	–4.4 ± 8.4
		Sookaneknun (2004)[53]	85.7 ± 13.6	118	71.6 ± 10.8	118	–14.2 ± 8.8
		Vivian (2002)[54]	89.8 ± 10.9	26	77.5 ± 10.7	26	–12.3 ± 7.6
		Zillich (2005)[55]	85.3 ± 11.2	64	76.5 ± 9.5	64	–8.8 ± 7.4
		Overall	**86.5 ± 8.4**	**1159**	**80.4 ± 6.3**	**1155**	**–5.8 ± 3.8**[c]
Diastolic blood pressure	control	Castro (2006)[34]	79.0 ± 10.0	34	78.0 ± 11.0	34	–1.0 ± 7.4
		Erickson (1997)[36]	90.4 ± 10.3	40	87.8 ± 10.2	40	–2.6 ± 7.2
		Garção (2002)[37]	83.9 ± 9.2	41	78.6 ± 8.6	41	–5.3 ± 6.3
		Hawkins (1979)[40]	86.0 ± 6.0	280	84.0 ± 4.0	280	–2.0 ± 3.7
		McKenney (1978)[43]	94.8 ± 10.3	66	94.9 ± 10.2	66	0.1 ± 7.2
		McKenney (1985)[44]	86.9 ± 11.8	39	84.7 ± 11.4	39	–2.2 ± 8.2
		Murray (2004)[48]	78.0 ± 10.0	124	78.0 ± 11.0	124	0.0 ± 7.4
		Okamoto (2001)[49]	82.1 ± 11.4	166	80.7 ± 10.2	166	–1.5 ± 7.7
		Park (1996)[50]	83.3 ± 8.5	26	83.7 ± 10.9	26	0.4 ± 7.0
		Solomon (1998)[52]	87.0 ± 10.9	70	83.2 ± 11.5	70	–3.8 ± 7.9
		Sookaneknun (2004)[53]	86.0 ± 12.9	117	74.2 ± 11.9	117	–11.7 ± 8.8
		Vivian (2002)[54]	77.9 ± 11.9	27	80.4 ± 11.4	27	2.5 ± 8.2
		Zillich (2005)[55]	85.3 ± 10.3	61	79.7 ± 10.2	61	–5.6 ± 7.2
		Overall	**84.8 ± 7.2**	**1091**	**82.8 ± 5.9**	**1091**	**–2.4 ± 3.5**[d]

[a]Pairwise comparison, inverse variance method (Z = –3.15; p = 0.002).
[b]Pairwise comparison, inverse variance method (Z = –0.91; p = 0.361).
[c]Pairwise comparison, inverse variance method (Z = –3.00; p = 0.003).
[d]Pairwise comparison, inverse variance method (Z = –1.26; p = 0.207).

8 reported nonsensitive outcomes. Results are detailed in Table 3.

Several different types of adherence measures were described. Five studies used self-reported adherence,[28,31,32,46,54] 4 used the doses dispensed/percentage of doses prescribed taken,[43,45,50,53] 2 used the 4-item questionnaire developed by Morisky et al.,[52,55] and 1 each used a modified version of Hornes Medication Adherence Report Scale[40] and drug plasma concentrations.[34]

Almost all studies had sample sizes less than 100 in each intervention or control group. Only one study, a randomized clinical trial by Hawkins et al.,[40] had a medium sample size of 349 patients in the pharmacist intervention group and 280 patients in the control group. However, the sample that was used to compare adherent and nonadherent patients was very small (ie, <30 in each group). The study reported a positive, although nonsignificant, benefit in adherence for patients in the intervention group. One study found no differences in adherence in either group,[55] and another study's data could not be extracted.[32] Four studies presenting nonsensitive outcomes showed negative impact of pharmacists' interventions on patients' treatment adherence compared with the control group.[34,45,50,54] Negative results ranged from 2% to 20%. Two other studies, by Brouker et al.,[31] and Menard et al.,[46] reported endpoint adherence rates greater than 80% (increases of 58% and 11% from baseline, respectively) in the intervention group; however, no comparison group was used in either study. From these 2 studies using paired comparisons, only 1 was statistically significant.[31] Differences in adherence rates in endpoint of pharmacist intervention and control groups varied from 8% to 28% from studies reporting positive sensitive outcomes.[28,43,52,53]

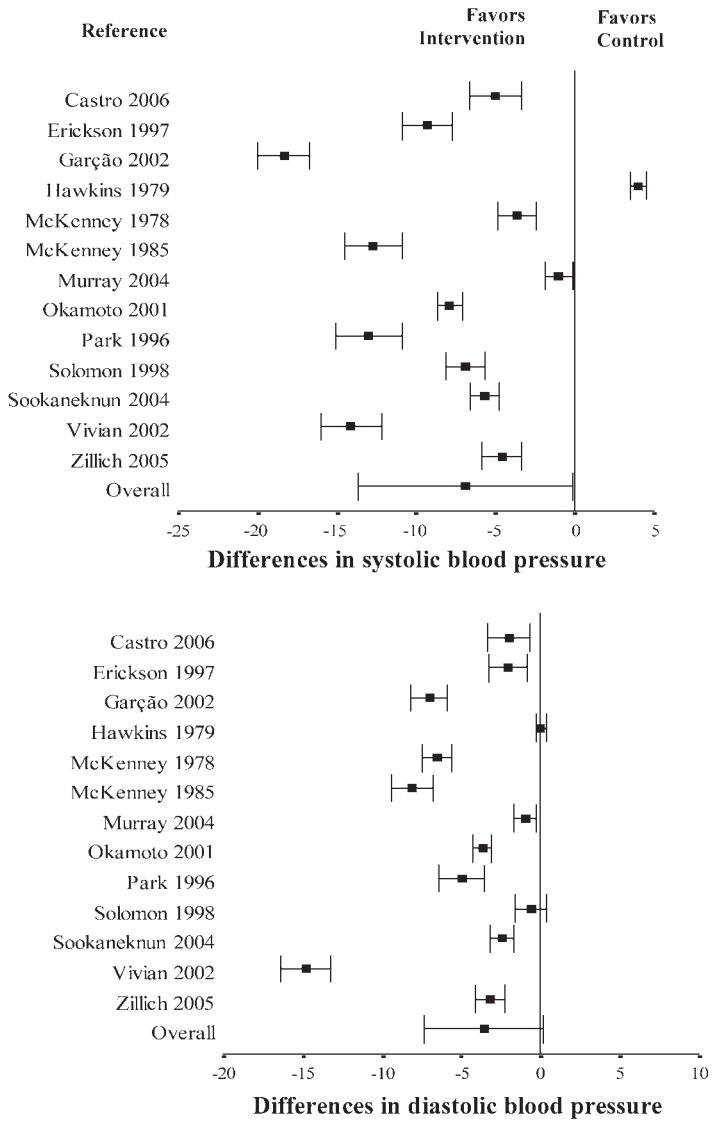

Figure 1. Meta-analytic differences in improvement of systolic and diastolic blood pressures (mm Hg) between patients receiving a pharmacist's intervention and patients in control groups. Negative estimates favor the intervention group over the control group in the reduction of systolic or diastolic blood pressure in hypertensive patients. The squares represent the difference in improvement between groups, with 95% CI.

MEDICATION/DISEASE KNOWLEDGE OF HYPERTENSIVE PATIENTS

Only one study, by Gourley et al.,[39] measured medication/disease management knowledge of hypertensive patients. They used a 17-item true/false test addressing disease symptoms, dietary considerations, exercise, medications, and good health practices. Differences in intervention (n = 63) and control group (n = 68) knowledge scores were significantly higher at endpoint (88.4% for intervention and 84.5% for control) than at baseline (79.9% for intervention and 84.5% for control).

QUALITY OF LIFE IN HYPERTENSIVE PATIENTS

Quality of life was measured in 8 studies evaluating pharmacists' interventions. One study was categorized as sensitive[39] and the remaining 7 were considered nonsensitive to pharmacists' interventions.[33,36,45,48-50,54] Five studies used the Short Form version 36 (SF-36) to measure quality-of-life changes, and 2 studies used the Hypertension/ Lipid Form version 5.1.

The sensitive outcome described by Gourley et al.[39] measured quality of life using the Hypertension/Lipid Form version 5.1. That study was a randomized clinical trial of 130 hypertensive patients. The investigators found that patients in the pharmacist intervention group reported fewer negative symptoms. The main effect for the treatment group was observed for items related to shortness of breath

and dizziness upon standing. All comparisons in this study were carried out using a pairwise approach.

Studies reporting nonsensitive outcomes had sample sizes ranging from 36 to 330 patients. Differences in endpoint in the general health item scores of intervention and control groups from the 5 studies using the SF-36 as quality-of-life measure varied from –5.0 to 7.6 (positive results favor the pharmacist intervention group). The study with the largest sample size (N = 330), a randomized clinical trial by Okamoto and Nakahiro,[49] reported minimal increase in the general health item score from baseline to endpoint in the pharmacist intervention group (0.6 points). However, a decline in the same item score was observed in the control group (–4.3 points).

Discussion

To our knowledge, this study represents the first published meta-analysis of pharmacist intervention in patients with hypertension. Although other reviews dealing with the same topic are available in the literature,[5,57] no study has provided a synthesis of data from reviewed articles. Additionally, reviews of the methods used in pharmaceutical care and applied specifically to hypertensive patients are also available.[58]

Studies in this systematic review were most frequently carried out in medical clinics and community pharmacies. Medication management and hypertension education were pharmacists' most used interventions. Definitions and methods used in these interventions were provided in 70% (16/23) and 47% (9/19) of the studies, respectively. Drug dosage adjustments were the most commonly used intervention in medication management, and verbal instructions about disease, drug therapy, diet, and exercise were the most used method for educational interventions. The majority of the studies were controlled clinical trials; over 80% of these studies used this research design.

The average quality of the articles was considered to be only fair. Although some of the studies evaluated here were designed using the gold standard (ie, randomized clinical trials) of study designs, it is not possible to blind patients in pharmaceutical care models. The process of blinding is assessed by 2 items of the Downs-Black quality checklist. By removing these items, the average quality of the articles would increase up to more than 70%. However, other issues were poorly reported in the studies, which contributed to the overall fair quality of the articles. The first issue deals with reporting adverse events that may be a consequence of the intervention. In this case, only 3.5% of the articles reported this important issue. The second refers to the reliability of the adherence to the interventions, which was reported by only 4 of 28 (14%) studies.

According to Hepler and Strand,[3] the pharmacist is responsible for identifying, resolving, and preventing patients' drug-related problems, especially adverse events. In our meta-analysis, the majority of the studies evaluated missed the opportunity of demonstrating another positive consequence of pharmacists' interventions in the care of hypertensive patients.

From the 5 outcomes evaluated, almost 60% of the studies reported positive outcomes (ie, either clinically or statistically significant). The quality of these articles did not differ from those presenting negative outcomes. That is, study quality does not predict the sensitivity of outcomes. Therefore, further analysis of other issues is warranted.

Systolic blood pressure was categorized as definitely a pharmacist-sensitive outcome after we classified the 5 outcomes into the 4 predefined sensitivity categories. That is, patients' systolic blood pressure was sensitive to pharmacists' interventions from both clinical and statistical perspectives. We found that baseline-to-endpoint reductions in systolic blood pressure were significantly influenced by pharmacists' interventions compared with the standard care group, with a further reduction of 6.9 ± 12.0 mm Hg ($p = 0.047$). Of the 13 studies included in the meta-analysis, in only 1 was the intervention not exclusively performed by the pharmacist.[53]

To detect the exclusive influence of pharmacist interventions in patient outcomes, we additionally performed a univariate sensitivity analysis by excluding studies with multiprofessional interventions. In this case, the result remained practically unchanged, and pharmacists' interventions alone would still further reduce patients' systolic blood pressure by 7.0 ± 12.9 mm Hg ($p = 0.052$) compared with standard care. Thus, in assessing the impact of pharmacist intervention on patient care in independent or collaborative practices, systolic blood pressure can be assumed to be an outcome that can be attributed to such intervention.

Additionally, studies with the largest effect sizes (ie, reduction in systolic or diastolic blood pressure from baseline to endpoint) were those in which the average baseline values were 150 mm Hg or more or 85 mm Hg or more for systolic and diastolic blood pressure, respectively. In other words, the clinical impact of pharmacists' interventions in patients with hypertension is expected to be more evident in high risk/complex patients.

Knowledge was characterized as being possibly sensitive to pharmacists' interventions. Even though only one study evaluated patients' disease/disease management knowledge, the reported outcome was significant. However, the analysis performed by the authors was based on a paired comparison between baseline and endpoint in the treatment group only and does not reflect differences in the intervention and control groups. Thus, more studies are needed to confirm our definition.

Two other outcomes (adherence and quality of life) were categorized as possibly not sensitive. These outcomes showed, in most cases, that pharmacists' interventions were

unable to produce a significant impact on hypertensive patients. Again, no statistical conclusions could be made. Only 5 of 13 studies evaluating patients' adherence showed sensitive results to pharmacists' interventions. Results were inconsistent, since adherence rate differences in endpoint of pharmacist intervention group and control group varied from –20% to 28% (negative results favor the control group), depending on the type of adherence measure used.

Quality of life was also considered possibly not sensitive to pharmacists' interventions, since only 1 of 8 articles reported sensitive results. The studies presenting nonsensitive results reported minimal changes in quality-of-life scores, and their sample size was not large enough to detect significant changes. Additionally, none of the studies evaluating quality of life of hypertensives used patient preference-based scales (eg, standard gamble, time-trade off, visual analog scale). They used health-status scales (eg, SF-36 and Hypertension/Lipid Form version 5.1) instead, which do not directly reflect patients' quality of life.

Finally, diastolic blood pressure was defined as possibly not sensitive according to our definition. However, pharmacist intervention in patients' diastolic blood pressure was clinically and statistically significant when using paired comparison (reduction of 5.8 ± 3.8 mm Hg from baseline to endpoint) and marginally significant when using unpaired comparison (further reduction of 3.6 ± 3.7 mm Hg; $p = 0.062$, compared with standard care).

Our study contains several limitations. Even though our search criteria intended to capture all published articles evaluating pharmacists' interventions in hypertensive patients, a chance of publication bias could still exist. However, identifying a large number of articles from the references of the elucidated articles suggested potential problems in the original search. Therefore, we expanded our search strategy by including search words such as pharmacist, pharmacy, and blood pressure. As a result, our secondary search found articles that were initially identified via reference search; however, no additional study was found that could have been missed by our primary search strategy. Moreover, some outcomes evaluated here were described in only a small number of published studies. We believe that we have found the majority of the available studies using these outcomes and that, with time, a great number of studies evaluating such outcomes will be available in the literature.

One other limitation is based on the fact that the quality of the provision of pharmacists' interventions could not be assessed in the included studies. Therefore, some degree of variation of results is expected in clinical pharmacy practice. Additionally, the clinical outcome used to assess the impact of pharmacists' interventions on patients' blood pressure (ie, mean changes in blood pressure from baseline to endpoint) was not considered optimal. A more accurate outcome would be the rate of patients achieving targeted blood pressure at endpoint. Such outcome could be used to calculate odds ratios and thus provide a more consistent form of measuring the impact of pharmacists' interventions compared with standard care. However, the rate of patients achieving targeted blood pressure at endpoint was poorly reported in the included studies and could not be included in our meta-analysis.

Future research should continue to assess the impact of pharmacists' interventions on patient outcomes, specifically in other disease areas such as mental and metabolic illnesses. Moreover, clinical studies aiming to measure pharmacists' interventions should be well designed (eg, larger sample size, randomized, more outcome measures) and properly reported (eg, report of adverse events and adherence to the interventions). Additionally, future research should be directed toward high-risk/complex patients, who possibly have little contact with healthcare professionals and require more attention to their disease management.

Conclusions

Pharmacists' interventions in the care of hypertensive patients can significantly reduce systolic blood pressure. These interventions (mainly medication management and patient education carried out in medical clinics and community pharmacies) are capable of improving patients' systolic blood pressure to a further extent than the standard care. Patients' knowledge about medications or disease was considered possibly sensitive to pharmacists' interventions, while adherence and quality of life were categorized as possibly not sensitive. To date, with the amount of studies evaluated here, diastolic blood pressure was also defined as possibly not sensitive to pharmacists' interventions. However, this scenario is likely to change.

More research with improved quality of design and report is advised to confirm the conclusions drawn here.

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Sensibilidad de los Resultados de Pacientes a las Intervenciones por el Farmacéutico. Parte II: Revisión Sistemática y Análisis Meta en el Manejo de Hipertensión

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EXTRACTO

TRASFONDO: La hipertensión es una preocupación mayor de salud en todo el mundo debido a su impacto perjudicial. Pocos estudios han evaluado cuantitativamente las intervenciones de los farmacéuticos en pacientes hipertensos.

OBJETIVOS: Identificar y cuantificar resultados sensitivos a las intervenciones de los farmacéuticos.

MÉTODOS: Los autores realizaron búsquedas en el *Abstractos Farmacéuticos Internacionales*, MEDLINE, el Registro Cochrane Central, y Embase, desde sus comienzos hasta diciembre 2006, utilizando las palabras de búsqueda en inglés: hypertension, pharmaceutical services o pharmaceutical care y patient outcomes (ie, knowledge, compliance, dispensing, satisfaction, quality of life, adverse drug reactions, costs, y education). Dos críticos/evaluadores independientes identificaron artículos, compararon resultados y resolvieron diferencias a través de consenso. La información extraída incluyó: el tipo de intervención, los números de pacientes, la demografía, las características del estudio, los instrumentos usados, la información comparada, y los resultados reportados. Los datos fueron combinados haciendo uso de un análisis meta de efectos al azar. La calidad del estudio fue evaluada usando la escala de Downs-Black.

RESULTADOS: De 203 artículos potenciales identificados, 98 fueron seleccionados y sus extractos leídos, nueve de los cuales fueron revisados en texto completo más 19 identificados de las referencias, para un total de 28 artículos. Los diseños de investigación incluyeron: 18 estudios controlados aleatorios, 5 estudios clínicos de un solo brazo, 4 estudios comparativos no aleatorios, y 1 estudio de datos de base. El resultado de calidad promedio fue 66% ± 12% (regular). Las intervenciones más utilizadas fueron el manejo de medicamentos (82%) y la educación sobre hipertensión (68%). Treinta y nueve resultados de estudios (57% de todos los resultados evaluados) fueron a las intervenciones de los farmacéuticos. Un análisis meta de 2246 pacientes en 13 estudios encontró que los farmacéuticos redujeron significativamente la presión sanguínea sistólica (10.7 ± 11.6 mm Hg; p = 0.002), mientras que los controles permanecieron inalterados (3.2 ± 12.1 mm Hg; p = 0.361). Las intervenciones de los farmacéuticos redujeron más la presión sanguínea sistólica (6.9 ± 12.1 mm Hg; p = 0.047) que los controles. Los resultados no sensitivos incluyeron: una reducción adicional en la presión sanguínea diastólica (3.6 ± 3.7 mm Hg; p = 0.06), la calidad de vida (1/8 estudios, significativo), y el cumplimiento (5/13 estudios, significativo).

CONCLUSIONES: La presión sanguínea sistólica es sensitiva a las intervenciones de los farmacéuticos. Otros resultados también pueden ser sensitivos, sin embargo, se necesitan más estudios de alta calidad para realizar una evaluación cuantitativa exhaustiva.

Traducido por Brenda R Morand

Effets de l'Intervention du Pharmacien sur les Issues Cliniques. Partie II: Traitement de l'Hypertension.

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RÉSUMÉ

CONTEXTE: L'hypertension artérielle est un problème de santé majeur. Peu d'études ont évalué quantitativement les interventions du pharmacien chez le patient hypertendu.

OBJECTIFS: Identifier et quantifier les issues cliniques sensibles à l'intervention du pharmacien.

MÉTHODOLOGIE: Les bases de données suivantes ont été consultées pour les fins de cet article: *International Pharmaceutique Résumé*, MEDLINE, EMBASE et Cochrane (jusqu'à décembre 2006). Deux réviseurs indépendants ont identifié les articles pertinents; les résultats de leurs recherches ont été comparés et mis en commun par consensus. Les données recueillies incluaient: le type d'interventions, le nombre de patients, les caractéristiques démographiques, les caractéristiques de l'étude, les instruments utilisés, les données comparées et les issues rapportées. Un devis de type méta-analyse a été utilisé pour la combinaison des données. La qualité de l'étude a été évaluée à l'aide de l'échelle Downs-Black.

RÉSULATS: Plus de 203 articles potentiellement pertinents ont été identifiés. Parmi ceux-ci, 98 articles ont été retenus et leurs résumés lus; 9 de ceux-ci ayant fait l'objet d'une lecture approfondie et 19 articles supplémentaires ayant été retracés à partir des bibliographies d'articles pour un total de 28 articles. Les devis de recherche de ces études étaient: études contrôlées à répartition aléatoire (18 études), études cliniques avec un seul groupe (6 études), études comparatives sans répartition aléatoire (3 études) et étude de base de données (1 étude). Le pointage moyen relatif à la qualité des études était de 66% + 12 %. Les interventions portant sur l'ajustement de la médication (82%) et sur l'enseignement en lien avec l'hypertension (68%) étaient celles les plus fréquemment répertoriées. Trente-neuf résultats d'études (57% des toutes les issues évaluées) étaient considérés sensibles aux interventions du pharmacien. Une méta-analyse regroupant 2246 patients issus de 13 études a montré que les interventions du pharmacien ont permis une diminution significative de la tension artérielle systolique (10.7 ± 11.6 mm Hg; p = 0.002) alors que celle des témoins est demeurée inchangée (3.2 ± 12.1 mm Hg; p = 0.361), soit une diminution moyenne supplémentaire de 6.9 ± 12.1 mm Hg; p = 0.047). Les résultats non-sensibles incluaient également la réduction de la tension artérielle diastolique (3.6 ± 3.7 mm Hg; p = 0.06), la qualité de vie et l'observance au traitement.

CONCLUSIONS: La tension artérielle systolique est un paramètre sensible à l'intervention du pharmacien. D'autres issues cliniques peuvent aussi être sensibles; cependant des études de plus grande envergure sont requises pour une évaluation quantitative plus approfondie.

Traduit par Alain Marcotte