Evaluation of studies investigating the effectiveness of pharmacists' clinical services

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Abstract: A quantitative evaluation of randomized trials of counseling, education, and other clinical services provided by pharmacists was performed.

Data sources were MEDLINE and the bibliographies of published articles. Pharmacists' services were categorized as counseling of patients, counseling of physicians, counseling of both patients and physicians, and patient care. The outcomes extracted were measures of patient behavior, disease, symptoms, and patient knowledge.

Thirty-two trials met the inclusion criteria. The pharmacists were specified as clinical pharmacists in 24 trials and as community pharmacists in 2. In six unblinded trials of patient counseling, the outcomes favored the counseled patients over control patients in every trial, and the effects were statistically significant in five trials (the outcome was medication adherence in these five trials). In seven trials of counseling of both patients and their physicians, patient outcomes were significantly better in the intervention group in six trials, four of which were single blind. Two trials in which patients were randomized to either physician counseling or control groups yielded inconsistent results. In one trial in which physicians were randomized to receive counseling from pharmacists, the proportion of prescriptions meeting guidelines was higher in the counseling group than in the control group. Four trials of patient care by pharmacists were inconclusive.

These trials demonstrated that counseling of patients and their physicians by pharmacists can improve patient outcomes. The evidence that counseling of patients alone improved patient outcomes was good, though weaker because of suboptimal trial design.

Index terms: Clinical pharmacists; Concentration; Education; Outcomes; Patient information; Pharmacists; Pharmacists, community; Physicians

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Pharmacists in ambulatory care and inpatient settings provide education, counseling, drug-use review, and other "cognitive services" to patients as well as to physicians and other health care professionals. The effectiveness of these services has been investigated for decades,[1] but many studies in this field have been of poor quality; for example, only 23 of 104 studies in ambulatory care settings reviewed in 1993 by Hatoum and Akhras[2] incorporated a control group. In recent years, many investigators have performed randomized controlled trials—studies whose design is such that the study hypothesis can be proved. These trials have tested the effects of pharmaceutical services on patient outcomes and have produced evidence of the effectiveness of these services. We conducted a systematic, quantitative evaluation of this evidence.

Methods

Literature search. We attempted to identify all randomized or quasirandomized controlled trials of pharmacists' interventions in which the endpoints were patient outcomes or measures of service. (Quasirandomized trials are those in which group assignment is by alternation, the day of the week, or some other method that is not truly random.) We conducted a MEDLINE search of English-language articles published from 1965 to May 1999, using the MeSH (Medical Subject Heading) terms "pharmaceutical services" *or* "pharmacy services*" *and* "patient education" *and* "comparative study" and then the words "randomized" *and* "control*" in any field *and* "pharmacist*" in the text field. In addition, the bibliographies of review articles identified in a similar search,[1-3] as well as our own literature collection, were screened.

Study inclusion criteria. We included only reports of parallel-group randomized (or quasirandomized) controlled trials of interventions pro-

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vided by pharmacists and published in the peer-reviewed literature. Seventy-four articles were obtained from the MEDLINE and bibliographic searches, of which 32 were included in our analysis. We excluded studies that did not meet our criteria for a parallel-group randomized or quasi-randomized controlled trial[4-13]; studies in which less than 10 subjects (i.e., patients, physicians, or physician groups) were randomized[14,15]; studies in which the intervention was performed by a group of health care professionals, so that the contribution of pharmacists could not be isolated[16-21]; and studies that did not otherwise meet our criteria for a prospective controlled clinical trial. Three articles[22-24] were not included because they duplicated information about studies already collected.[25-27]

Categorization of interventions. The pharmacist interventions were categorized as counseling of patients only, counseling of both patients and their physicians, counseling of physicians only, and patient care by the pharmacist. Counseling was operationally defined as information transferred orally in a face-to-face meeting or by telephone and could include educational information, patient-specific advice, or both. Where the intervention went beyond counseling and the pharmacist prescribed drugs or managed patients, we described the intervention as patient care.

Data extraction. Structured data were extracted serially from all articles and then double-checked by one of the authors. Proportional data were extracted in preference to continuous data. The study outcomes were extracted according to a predetermined order of preference. When patients were subjects of randomization and several outcomes were reported, the order of preference was as follows: first, patient behavior (e.g., compliance with drugs or correct use of an inhaler); second, physiological measures (e.g., blood pressure or blood sugar); third, other outcomes (e.g., adverse experiences); and last, patient knowledge or perceptions. When physicians were the subjects of randomization, their prescribing behavior was the outcome extracted.

Statistical methods. We adopted a meta-analytic approach and expressed the outcome of each study in terms of a standardized statistic or effect size, generally following the procedures for systematic review of Chalmers et al.[28] For study outcomes expressed as proportions, we calculated an odds ratio and 95% confidence interval (CI) as described.[28] The odds ratio is the ratio of the odds of a particular outcome occurring in the experimental versus the control groups. For example, if 20 patients out of 100 in the experimental group (those receiving pharmacists' services) comply with drug therapy, the odds of compliance are $20/(100 - 20) = 0.25$; if the odds of compliance in the control group, calculated similarly, are 0.125, the odds ratio is $0.25/0.125 = 2.0$, indicating that patients receiving pharmacists' services have twice the odds of complying with drug therapy when compared with patients in the control group. Categorical or proportional data are often preferred in systematic reviews in part because the odds ratio (or the related statistic, relative risk) is regarded as being more easily comprehended than standardized statistics derived for continuous data. For continuous data, we calculated the effect-size estimate Hedges's *g*, which is the difference between the experimental and control group means divided by their pooled standard deviation.[29] Odd ratios and CIs were plotted as a means of visually displaying the data (this does not imply that effect sizes for different outcomes can be strictly quantitatively compared). We did not compute pooled summary statistics for groups of studies; we did not believe that the conceptual criteria for pooling were strictly met, because of heterogeneity in study outcomes and other characteristics. Specifically, even when the same outcome was measured as proportional data (e.g., compliance) in five trials of patient counseling, the endpoint metrics used were different, as were the patients and the reported details of the pharmacist intervention. Our procedure for extracting study outcomes according to a predetermined order was designed to minimize bias in reporting and in data extraction, but it would not be optimal if statistical pooling of endpoints was desired, in which case the same endpoint should be extracted from a group of trials.

For consideration of study quality, the three criteria of Chalmers et al.[28,30] were applied: first, the method of allocating subjects to study treatments; second, whether outcomes were evaluated for all patients allocated to treatment; and, third, blinding of the observers to the subjects' treatment allocation. These criteria were applied as follows. First, for the method of allocating subjects, we accepted only randomization and quasi-randomization—these were requirements for study inclusion. Second, where possible, the numbers of patients with a positive outcome were expressed as a proportion of the numbers allocated to the treatment (as opposed to the number completing the treatment). Patients who do not complete a trial may represent a biased subset, negating the effects of randomization at study entry. For example, patients who are noncompliant with treatment may tend not to finish the trial, which artificially increases the proportion of those remaining who are compliant. Continuous data (mean and standard deviation) are typically presented for patients remaining in the study; this is a reason for preferring proportional data. Third, we noted whether there was blinding of observers to the subjects' treatment assignment; blinding was not used as a study inclusion criterion, however.

Results

Description of trials. The 32 trials meeting our inclusion criteria are summarized in Table 1, which describes the settings, subjects, and in-

Table 1.
Trial Settings, Subjects, and Interventions

Reference	Setting	Patients	Follow-up (mo)[a]	Intervention
Patient Counseling Trials				
31	Outpatient	Elderly patients on cardiovascular drugs	. . .	Oral instruction with or without patient card or calendar packaging or printed information versus no intervention
32	Outpatient	Cardiac and hyperlipoproteinemic outpatients	20 days	Instruction concerning use of medication versus no instruction
33	Outpatient	Adult males with asthma or COPD[b]	. . .	Pharmacist counseling versus no counseling
34	Outpatient	Adult male COPD patients	4.5	Clinical pharmacist counseling versus no pharmacist counseling
35	Outpatient	Prescribed antibiotics	10 days	Oral or written consultation by pharmacist and/or telephone reminder versus control
36	Hospital	Inpatients prescribed one or more of six study drugs	1	Five-minute structured patient counseling by pharmacist versus no counseling
37	Hospital	Elderly patients discharged with medication during 4-wk study	. . .	Counseling from staff pharmacist versus usual care
38	Outpatient	Geriatric dischargees	3	Clinical pharmacist counseling with or without compliance aid versus usual care
39	Hospital pharmacy and patients' homes	Hospital dischargees receiving drugs	10 days	Pharmacist counseling versus routine counseling either with or without patient card
40	Outpatient	Prescribed two or more antihypertensive drugs per day	3	Counseling by pharmacist and/or packaging versus neither
41	Hospital	Inpatients using metered-dose inhalers	8 days	Counseling by pharmacist versus instruction sheet versus neither
42	Outpatient	Diabetics	2	Group counseling versus one-on-one counseling with follow-up versus control
43	Hospital	Hospital dischargees	1.5	Verbal (oral) medication counseling from pharmacist versus no counseling
44	Hospital and patients' homes	Patients of five neurologists newly prescribed listed drug	2	Pharmacist's counseling versus no pharmacist's counseling
Patient and Physician Counseling Trials				
45	Outpatient	Hypercholesterolemia	6	Pharmacist's counseling of patients and physicians versus no pharmacist's counseling
46	Outpatient	Uncontrolled hypertension	6	Pharmacist counseling versus standard care
26	Outpatient	Patients >64 yr old with polypharmacy	3	Clinical pharmacist care versus no clinical pharmacist care
47	Offices	At risk for medication-related problems	6	Pharmacist counseling versus no pharmacist counseling
27	Pharmacist's office or patient's home	Dischargees >65 yr old with drug therapy for chronic condition	3	Clinical pharmacist consultation versus no pharmacist consultation
48	Chain pharmacy	Hypertensives	4	Monthly monitoring and counseling versus no monthly monitoring and minimal counseling
49	Community pharmacy	Elderly patients at high risk for medication problems	11	Home-based education and counseling by pharmacists versus no intervention by pharmacists
25	Outpatient	Hypertension or COPD patients	6	Pharmacist care services versus no pharmacist care services

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Table 1 (*continued*)

Reference	Setting	Patients	Follow-up (mo)[a]	Intervention
Physician Counseling Trials				
50	Offices	NA[c]	9	Face-to-face education by pharmacists versus printed education materials versus no intervention
51	Hospital	Inpatients receiving intravenous antibiotics	1	Pharmacist's advice to patients' physicians versus no advice
52	Hospital	Inpatients receiving aminoglycosides	. . .	Clinical pharmacokinetic service monitoring versus no monitoring
53	Offices	Hypercholesterolemia	22	Pharmacist education of physicians versus no pharmacist education
54	Hospital	Receiving chemotherapy for cancer	2.5	Pharmacist counseling of physicians versus no pharmacist counseling
55	Hospital	Inpatients receiving aminoglycosides for suspected or proven infection	1	Pharmacist-assisted dosing versus physician-directed (customary) dosing
56	Outpatient	. . .	7	Pharmacists' counterdetailing of physicians versus peer-comparison feedback to physicians versus no physician intervention
Patient Care Trials				
57	Outpatient	Hypertensive and diabetic outpatients	29	Clinical pharmacist care versus standard physician care
58	Outpatient	African Americans with non-insulin-dependent diabetes mellitus	4	Pharmacist care versus no pharmacist care
55	Hospital	Inpatients receiving aminoglycosides for suspected or proven infection	1	Pharmacist-directed dosing versus physician-directed (customary) dosing
59	Community pharmacy	Essential hypertension	5	Pharmacist clinical services versus no pharmacist clinical services

[a]Follow-up in months unless stated otherwise.
[b]COPD = chronic obstructive pulmonary disease.
[c]NA = not applicable.

terventions. In 24 of the studies analyzed, the pharmacists were described as clinical pharmacists, in 2 trials the pharmacist was a community pharmacist,[48,59] and in some trials the type of pharmacist was "other" or unspecified.[32,41,42,49,53] The settings were outpatient clinics in 15 trials and community pharmacies in 2 trials; other ambulatory care settings were offices, and in other trials settings were mixed and included patients' homes. Hospitals were the setting in 8 trials. In 12 of the trials no specific disease was studied; when a disease was specified it was most often cardiovascular (10 trials).

Trial methods. In all but 4 of the 32 trials analyzed, the patient was the subject of randomization (Table 2); individual physicians were randomized in 3 trials, and physician groups (i.e., health centers) were the subjects of randomization in 1 trial. The interventions were classified as counseling in 25 of the 28 trials in which patients were subjects. Randomization was used to assign subjects, except in 6 quasirandomized trials in which assignment was by rotation,[38] by patient number,[59] or by the last digit of the patient's Social Security number.[33,34,45,46] The observers (nurses, pharmacists, physicians, etc.) of study endpoints were blinded to the patients' treatment assignment in 8 trials, and in 2 trials the subjects of randomization were blinded.[45,54]

Patient counseling. There were 14 trials of patient counseling; 6 of these reported proportional data for patient outcomes. As shown in Figure 1, the outcomes were medication compliance (5 trials) or patient knowledge (1 trial) and the odds ratios for these outcomes ranged from 1.4 to 7.8. All of these results were statistically significant at the 0.05 level or trended toward significance; here, trending means that the α value approached 0.05. Of the remaining 8 trials, 7 presented continuous data and in all of them the reported result favored the counseling group over the control group. We could calculate

Table 2.

Outcomes Measured in Trials

Reference[a]	Outcome Measured	Endpoint Metric
Patient Counseling Trials		
31 (O)	Drug knowledge	Statistical significance of between-group differences in scores on 5-point scale based on self-report[b]
32 (+)	Compliance	Proportion of patients taking correct number of pills
33 (Q, +)	Correct use of inhaler	Mean number of steps missed (of 11)
34 (Q, +)	Compliance	Proportion of patients with actual/predicted theophylline level within 0.1 of unity
35	Compliance	Mean compliance rate (%)[b]
36	Patient knowledge	Proportion of patients scoring >80%
37 (O)	Patient knowledge	Median percentage of critical items correct in questionnaire[b]
38 (Q, +)	Medication errors	Proportion of patients taking medication correctly
39	Compliance	Proportion of patients with compliance rate (pill count) >85%
40 (+)	Compliance	Proportion of patients with compliance rate (pill count) >95%
41 (O)	Correct use of inhaler	Mean number of correct steps[b]
42	Blood sugar	Average weekly blood glucose values[b]
43	Knowledge and compliance	Median score on 4-item survey[b]
44	Patient knowledge	Score on 15-item questionnaire
Patient and Physician Counseling Trials		
45 (Q, S, +)	Blood cholesterol	Proportion of patients reaching National Cholesterol Education Program goal
46 (Q, O, +)	Blood pressure	Proportion of patients reaching JNC-V (Fifth Report of the Joint National Committee, 1994) goal
26 (O)	Adverse experiences	Proportion of patients with adverse experiences during study
47 (O)	Patient understanding and compliance	Score on 12-point scale[b]
27 (O)	Compliance	Proportion of patients with perfect score on 4 dimensions of a compliance scale
48 (+)	Blood pressure	Proportion of patients with blood pressure under control (<140/90 mm Hg) at visit 4
49 (+)	Medication-use patterns	Proportion of patients with improvement in score on 71-item scale
25, HTN	Compliance	Score on 4-item scale at visit 5
25, COPD	Symptoms of dyspnea	Proportion of patients without dyspnea presently at rest at visit 5
Physician Counseling Trials		
50[c]	Prescriptions	Mean number of prescriptions[b]
51 (+)	Discontinuation of i.v. antibiotics	Proportion of patients with discontinuation within 24 hr
52	Time for pyrexia to abate	Mean number of hours
53[d]	Prescriptions	Mean number of prescriptions[b]
54[c] (S)	Prescriptions	Proportion of prescriptions meeting guidelines
55 (O)	Incidence of nephrotoxicity	Proportion of patients with >100% increase in serum creatinine with at least 44-µmol/L increment
56[c]	Prescriptions	Cost per prescription[b]
Patient Care Trials		
57, HTN	Systolic blood pressure	Proportion of patients with improvement (2 categories for blood pressure)
57, DM	Blood sugar	Proportion of patients with improvement (3 categories for blood sugar)
58	Blood sugar	Mean patient fasting plasma glucose concentration
55, Group 3 (O)	Incidence of nephrotoxicity	Proportion of patients with >100% increase in serum creatinine with at least 44-µmol/L increment
59 (Q, +)	Compliance	Proportion of patients compliant (between 90% and 110% of prescribed dose administered) during observation period (after study period)

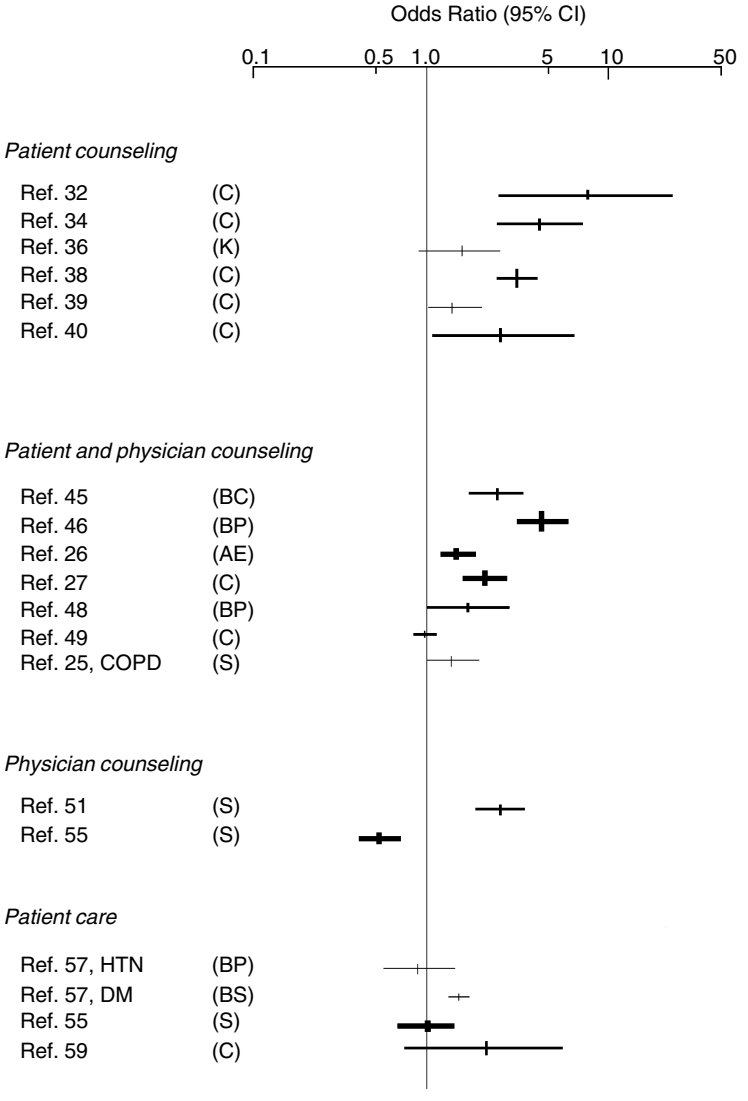
[a]The subjects were patients unless otherwise indicated. Q indicates that group assignment of the subjects was quasirandom; otherwise, it was random. Some studies specified that the observers (O) (who measured outcomes) or subjects (S) (patients or physicians) were blinded to the subjects' group assignment. A + indicates that the outcome was calculated for all patients entering the trial; the absence of a + indicates that outcomes were computed only for those patients remaining in the trial. HTN = hypertension, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus.

[b]Insufficient data were reported for effect size and 95% confidence intervals to be computed (because information such as the number of patients evaluated or a measure of variance was not reported).

[c]Subjects were physicians.

[d]Subjects were physician groups.

Figure 1. Outcomes of trials by category of pharmacist intervention. Outcomes for trials of patient counseling, patient and physician counseling, physician counseling, and patient care by pharmacists are presented as odds ratios and 95% confidence intervals (CIs); the horizontal lines represent the CIs and the cross marks represent the mean odds ratios. Odds ratios greater than 1.0 indicate an effect favoring the intervention group, while those less than 1.0 favor the control group. CIs that do not include 1.0 indicate that the pharmacist intervention was significantly different from the control at the 0.05 level. CI lines in bold and in heavy bold represent, respectively, trials in which all patients allocated to the treatment were included in the analysis and trials that incorporated blinding of observers (note that both of these conditions were true in reference 46). Only trials in which patients were the subjects of randomization and in which proportional data were presented are shown. Letters indicat the study outcomes: C = compliance, K = patient knowledge, BC = blood cholesterol, BP = blood pressure, AE = adverse events, S = symptoms, HTN = patients with hypertension, DM = patients with diabetes mellitus, BS = blood sugar.



effect sizes and CIs from only 2 of these trials,[33,44] and in neither case was the result statistically significant. Of the 14 trials, only 3[31,37,41] incorporated blinding of observers (no data were extracted from these trials).

Patient and physician counseling. Of eight trials that tested the effect of pharmacist counseling of both patients and their physicians (Table 1), all but one[47] reported proportional data. The outcomes were blood pressure, blood cholesterol, symptoms, adverse events, and compliance. In six of these trials the odds ratios favored the counseling group, while in one[49] there was null result (Figure 1); the odds ratios ranged from 1.0 to 5.2. The observers were blinded to patient assignment in three of these trials,[26,27,46] and in another patients were blinded.[45] In one trial[47] the mean effect size favored the counseling group but we could not calculate CIs, and for the hypertension patients in another trial[25] the result was null, although again the mean effect size favored the counseling group.

Physician counseling. There were two trials in which patients were randomized either to a control group or to a group in which the patients' physicians received counseling from pharmacists (Table 2).[51,55] Patient outcomes improved in one trial[51] but deteriorated in the other trial of pharmacist-assisted dosing (Figure 1).[55] The results of these two trials are contradictory and no overall conclusion can be drawn. In one further trial,[52] a null result was obtained for the effect of clinical pharmacokinetic service monitoring of patients (Hedges's *g*, 0.41; 95% CI, –6.42 to 7.24).

In four other trials, physicians (or physician groups) were the subjects of randomization either to a group counseled by pharmacists or to a control group (not shown in Figure 1).[50,53,54,56] We could calculate an odds ratio for only one trial[54]; the effect, measured as the proportion of prescriptions meeting guidelines, favored the counseling group (odds ratio, 2.9; 95% CI, 2.2 to 3.8).

Patient care. In four trials with five groups of patients, the services provided by the pharmacist went beyond providing advice to the patient, physician, or both; we categorized them as patient care (Table 1). In one trial,[55] the intervention was pharmacist-directed dosing, in which all orders for aminoglycoside dosing were written by a pharmacist; in two others,[57,59] the pharmacist managed the experimental patients, and in another,[58] the pharmacist managed the experimental patients according to the principles of pharmaceutical care.

There was a null effect of pharmacist care in two patient groups, while the result favored pharmacist care in the other two patient groups (Figure 1). The odds ratio for these four results ranged from 0.9 to 2.2. One study,[58] which presented continuous data, showed an effect size that favored the patient care group but was not statistically significant.

Discussion

Pharmacists' provision of clinical services, including patient care and physician education, is common. According to the 1997 ASHP survey of the ambulatory care responsibilities of pharmacists in integrated health systems, pharmacists spent about 30% of their time on clinical functions and the rest on distributive or administrative functions.[60] The clinical functions of tracking adverse drug reactions, monitoring medication adherence, drug-use review, and patient counseling were routinely provided by pharmacists at 75% or more of the surveyed health systems. The health systems evaluated pharmacists' services by using a number of different performance measures, most often patient satisfaction (used in 87% of health systems) and financial performance (85%), while clinical outcome was used less often (56%). According to the American College of Clinical Pharmacy's 1995 national survey, 85% of U.S. hospitals surveyed reported that their clinical pharmacy services included patient care and 73% included education of health care professionals.[61]

The pharmacists' clinical services in the trials reviewed here most often included some form of patient counseling. Patient counseling typically included information about the patient's drug and its administration and potential adverse effects[25-27,32,34,38-40,48,49] and was frequently interactive in that the patient was able to ask the pharmacist questions.[25,34,38-40,45,46,48] Counseling often included encouragement to comply with the prescribed medications[26,34,45,46,48]; characteristics specified less frequently were information about the patient's disease,[25,40,49] a structured format,[36,39] individualized information,[26,32,49] and a counseling duration of more than five minutes.[27,38,45,46] Physician counseling most often consisted of the pharmacist contacting the patient's physician by telephone to make recommendations regarding drug therapy.[26,27,48,49,51] In some cases, the pharmacist provided written recommendations to the patient's physician[26,45,46,55]; only in a few cases did the pharmacist meet face-to-face with the physician and collaboratively review the patient's data.[25,45,46]

The most robust results were seen for counseling of both patients and physicians. The outcomes summarized in Figure 1 were patient signs,[45,46,48] adverse events or symptoms,[25,26] and medication compliance[27,49]; thus, the outcomes reflected the patient's disease or behavior in six of these trials. The improvements in blood pressure and blood cholesterol were not just statistically but also clinically significant according to national guidelines.[45,46,48] The results for counseling of patients only were less robust, because we were able to extract proportional data from only half of the trials, none of which employed blinding, and some of the trials had short durations of 10 days or less.[35,39,41] Nevertheless, of the six trials of counseling of patients only, five yielded statistically significant effects and one trended toward statistical significance.

While counseling of patients, with or without counseling of their physicians, was effective, it is difficult to specify which elements of these mixed and varied interventions were responsible for the effects. It is not clear that adding physician counseling to patient counseling improved patient outcomes over what was observed with patient counseling alone, because trials of physician counseling alone produced contradictory results. Most of the pharmacists' clinical services were provided in ambulatory care settings, typically outpatient clinics. The mean effect sizes in the two trials in a community setting[48,59] were similar to those for trials of comparable interventions performed in outpatient clinics,[25,26,34,38,40,45,46] while trials performed in hospitals produced mixed results.[36]

The quality of the study methods in the trials reviewed was fair overall. Group assignment was by a random or quasirandom method in all of the trials (this was a criterion for study inclusion). Our analyses of proportional outcomes were based on all patients entering the trials rather than on those remaining in the trial for the majority of trials in the patient counseling[32,34,38,40] and patient and physician counseling groups[45,46,48,49] (Figure 1), although some trials did not report the number of patients randomized.[24,25,36,39,51,55,57] Only 8 of the 32 trials incorporated blinding of the observers. However, there is no indication that the results were biased because of this, and the effect sizes of trials of better methodological quality—trials in which all patients assigned to treatment were included in the analysis or trials in which observers were blinded, shown in bold or double bold in Figure 1—were about the same as in other trials.

In our data set of 32 studies, 4 were published in the 1970s, 10 in the 1980s, and 18 in the 1990s (13 from 1995 to 1999), indicating that the value of pharmacists' clinical services continues to be the subject of intensive experimental study. At least in the case of counseling of patients and their physicians, the evidence has proven that these interventions can improve patients' outcomes. It is less clear which elements of these interventions were responsible for the effects, and there are relatively few measurements of the economic benefits, although in some of the trials drug costs[47,51,56] or total direct costs[52] were reduced.

Conclusion

An evaluation of pharmacists' clinical services showed that counsel-

ing of patients and their physicians by pharmacists can improve patient outcomes. The evidence that counseling of patients alone improved patient outcomes was good, though weaker because of suboptimal trial design.

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