MEDICAL CARE
Volume 40, Number 9, pp 794–811

Patient Adherence and Medical Treatment Outcomes

A Meta-Analysis

M. Robin DiMatteo, PhD,* Patrick J. Giordani, MA,* Heidi S. Lepper, PhD,† and Thomas W. Croghan, MD‡

Background. Adherence is a factor in the outcome of medical treatment, but the strength and moderators of the adherence-outcome association have not been systematically assessed.

Objectives. A quantitative review using meta-analysis of three decades of empirical research correlating adherence with objective measures of treatment outcomes.

Method. Sixty-three studies assessing patient adherence and outcomes of medical treatment were found involving medical regimens recommended by a nonpsychiatrist physician, and measuring patient adherence and health outcomes. Studies were analyzed according to disease (acute/chronic, severity), population (adult/child), type of regimen (preventive/treatment, use of medication), and type and sensitivity of adherence and outcomes measurements.

Results. Overall, the outcome difference between high and low adherence is 26%. According to a stringent random effects model, adherence is most strongly related to outcomes in studies of nonmedication regimens, where measures of adherence are continuous, and where the disease is chronic (particularly hypertension, hypercholesterolemia, intestinal disease, and sleep apnea). A less stringent fixed effects model shows a trend for higher adherence-outcome correlations in studies of less serious conditions, of pediatric patients, and in those studies using self-reports of adherence, multiple measures of adherence, and less specific measures of outcomes. Intercorrelations among moderator variables in multiple regression show that the best predictor of the adherence-outcome relationship is methodological—the sensitivity/quality of the adherence assessment.

Key words: Meta-Analysis; patient adherence/compliance; health outcomes. (Med Care 2002;40:794–811)

For the past 30 years, patients' failure to follow advice from their physicians has been proposed as a limiting factor in achievement of the therapeutic goals of medical care.[1] Research in the medical and social sciences has demonstrated that across a wide variety of settings and treatment recommendations, roughly half of all medical patients in the United States do not adhere to, or comply with, their physicians' advice.[1–3] Close to 40% of patients take prescribed medication incorrectly or

*From the Department of Psychology, University of California, Riverside, California.

†From the Department of Psychology, Drake University, Des Moines, Iowa.

‡From the Health Outcomes Evaluation Group, Eli Lilly and Company, and Indiana University, Indianapolis, Indiana.

Supported by grants from Eli Lilly and Company and the University of California, Riverside, Center for Ideas and Society and Academic Senate Committee on Research.

Address correspondence and reprint requests to: M. Robin DiMatteo, Department of Psychology, University of California, Riverside, CA 92521. E-mail: robin@citrus.ucr.edu

Received August 22, 2001; initial review November 5, 2001; accepted February 28, 2002.

DOI: 10.1097/01.MLR.0000024612.61915.2D

not at all,[4] and almost twice that number fail dietary restrictions and prescribed exercise or continue to engage in health compromising habits such as smoking and abusing alcohol.[5–7] Nonadherence increases physician and patient frustration and leads to incorrect diagnoses and unnecessary treatment.[8] In complex regimens requiring precision, deviations from optimal regimens can exacerbate disease and sometimes can even be fatal.[9]

Nonadherence occurs for a variety of reasons including doubt about the expected benefits and efficacy of treatment, real or perceived barriers including side effects and financial constraints, unique demands of the regimen itself, and lack of help and support from family members and peers.[10,11] Clinical depression also accounts for an appreciable amount of nonadherence, probably because of the hopelessness, social isolation, fatigue, and impairments in cognitive focus that accompany depression.[12] Recent qualitative research also points to patients' identity and self-image, and the meaning of medication, as important determinants of adherence to medical advice.[13,14]

Since the first empirical studies of patient adherence in the late 1960s, researchers have attempted to assess, understand, predict, and change patients' responses to medical advice because, it is argued, adherence to treatment improves outcomes.[15,16] The magnitude of the relationship between adherence and treatment outcomes remains to be determined, however, and experts have recently called for its examination and assessment.[17] Fully understanding this relationship, including the factors (such as regimens, diseases, measurements, and methodologies) that moderate it, can be essential to research on determinants of treatment outcomes and on efforts to improve patient adherence.[17] The present study focuses on research correlating patient adherence and treatment outcomes, examining a broad array of disease conditions, regimens, and methodologies in ambulatory care where patients are free to follow, or not follow, treatment advice. We apply the techniques of meta-analysis to assess the adherence-outcome relationship and the factors that influence it.[18]

Materials and Methods

Search Strategy and Inclusion Criteria

PsychLit and Medline (Abbreviated Index Medicus and Cancer subsets) databases were searched from 1968 (when the earliest empirical studies of patient compliance appeared[15,16] through March, 1998 with keywords "patient compliance" and "patient adherence." This yielded 9035 potentially relevant citations (76% from Medline, 24% from PsychLit), comparable with the enumeration by Trostle[19] during a similar time. Approximately 13% of the titles were English language journal articles reporting empirical studies in the included populations described below. (The rest were letters, editorials, reviews, or reports that did not study patient adherence or compliance but included it as an explanation, clinical concern, subject criterion, or clinical application.) These citations were supplemented with potentially relevant titles from article reference sections. Examination of the abstracts narrowed the potential pool of articles to 850. Careful reading yielded 605 empirical studies; most presented overall adherence rates, and some also examined correlates of adherence. Of these, 63 (10.4%) met the inclusion/exclusion criteria of this meta-analysis.

Included were studies that precisely defined adherence (eg, taking medication correctly, following dietary restrictions) and its method and format of measurement (eg, self-report rating scale, electronic monitor reading). Studies were also required to have a sample size greater than 10, and to report the correlation between adherence and a measured outcome of medical treatment (eg, survival, symptoms, cholesterol level, blood pressure, restenosis, visual acuity). If this correlation was not provided, but the data or a statistic such as t, F, or χ^2 sufficient to calculate it were presented, the study was included. Excluded were reports of interventions designed to increase patient adherence, as well as studies that involved psychiatric patients, psychiatric regimens, or treatment provided by psychiatrists. Although psychiatric treatment regimens are widely prescribed and adherence is a relevant issue, the relationship between adherence and outcome within the realm of nonpsychiatric medical treatment was sufficiently multifaceted for the present study. The additional complications from cognitive, emotional, and social dysfunction in mental disorders are best examined in future research. Studies of alcoholic, drug-abusing, homeless, and institutionalized patients were excluded for similar reasons, and military personnel were excluded because of potential institutional controls over adherence. Finally, because the focus of the present research is on recommendations made in the physician-patient

relationship, studies of adherence to community screening procedures and vaccination programs, to commercial weight loss programs, and to community-based exercise programs were not included.

Meta-Analysis Coding

For each of the 63 articles used in the meta-analysis, the following information is presented in Table 1: reference, disease for which care was provided, method for assessing adherence, regimen requiring adherence, measure of adherence and whether it was continuous or dichotomous; outcome assessed; sample size and age group (adult, pediatric, or both); and *r* (correlation) effect size between adherence and outcome measure (provided in the article or computed from t, F, χ^2, summary statistics, or contingency table data (phi).[20]

If a presented effect size had more than one degree of freedom, phi was calculated if the data were available. If not, the exact probability level was used to determine the *z* statistic, which was then transformed to *r*. (Absent the exact probability, these one-tailed *z* values were used: $P < 0.05$ was coded as $z = 1.645$, $P < 0.01$ as $z = 2.326$, and $P < 0.001$ as $z = 3.09$; when results were reported as nonsignificant with no data available, $z = 0.00$ was assigned.) Some studies used several measures of adherence and examined several outcomes, providing multiple data points, which were averaged (a conservative approach).

Statistical Analyses

For each study (unit of analysis) in Table 1,[21–83] the effect size is presented as the correlation coefficient *r* which ranges in size and direction from −1.00 to 1.00. Because it represents the strength and direction of the association between the measure of adherence and the measure of outcome in that study, *r* is preferred to other effect size measures such as *d*.[84,85] In Table 1, positive effect sizes reflect the association of greater adherence with better treatment outcomes. The unweighted mean *r* (equivalent to the "risk difference") was computed for each analysis of interest using Fisher *z* transformation of the *r* effect sizes, and the standardized odds ratio was calculated from this unweighted mean.[86] Confidence intervals (95%) were calculated for each risk difference (unweighted mean *r*) and odds ratio based on a random effects model. Variances among the *r* effects were examined, and the fail-safe n was calculated for each significant effect. (The fail-safe n is the number of new, unpublished, or otherwise unretrieved studies that would need to find, on average, no effect of adherence on outcome to reduce a finding to nonsignificance at the 0.05 level.)[20,87] These statistics were computed for all 63 studies, and separately for the nine diseases for which there were five or more studies (required to insure more stable estimates). To examine the potential role of moderators in the adherence-outcome relationship, each study was further coded according to the following: type of disease (acute/chronic); seriousness of condition (above/at or below the median score on the Seriousness of Illness Rating Scale - Revised [SIRS-r]),[88] condition (prevention/treatment); regimen type (non-medication/medication); number of regimens (one/more than one); age of sample (pediatric/adult); number of adherence measures (one/more than one); self-report of adherence (no/yes); scale of adherence measurement (dichotomous/continuous); outcome measure (specific-"hard"/nonspecific-"soft"). Statistical comparisons of unweighted mean *r* values (risk differences) between the two levels for each of the nine moderators were computed using both *t* (random effects model) and *z* (fixed effects model) statistics. Correlations among the moderators were computed, and multiple regression analysis of the adherence-outcome effect sizes (normalized as the Fisher *z* transformation of *r*[20]) on the moderator variables was computed to examine the independent contributions of the moderators.

Whether to use a fixed- or random-effects model in meta-analysis is sometimes a source of confusion and controversy in the meta-analysis literature.[89] Conditional inferences from fixed effects apply only to the set of studies observed or to identical ones, whereas generalization beyond the studies sampled requires unconditional inference using the random effects model. Studies in a meta analysis are of greatest interest when they provide insight into population effects (the random effects model) although more limited conditional inferences (from the fixed effects model) can also be informative.[90] In the present research, the determination of whether an average effect size is significantly different from zero is always based on the stringent random effects model, but compari-

TABLE 1. Adherence as a Correlate of Treatment Outcomes*

Reference	Disease	Adherence Assessment Method(s)	Regimen	Adherence Measure† C = continuous D = dichotomous	Measure of Treatment Outcome	Sample Size‡	Effect Size
Arthritis							
21. Ettinger et al., 1997	Knee osteoarthritis	Self-report exercise log	Aerobic exercise	C: Percentage of total exercise sessions attended	Self-reported pain intensity and limitations/disability	144a	0.20
22. De Klerk et al., 1996	Ankylosing spondylitis	Electronic monitor	Medication	C: Scaled combined score of percent of doses taken, timing	Self-reported pain level and duration of morning stiffness	65a	0.14
Cancer							
23. Dekker et al., 1987	Acute leukemia	Self-report and medical record	Medication	C: Adherence judged to be good, moderate, or poor	Clinical signs of infection/Colonization identified in cultures	56a	0.00
24. Fisher et al., 1990	Breast cancer	Medical record	Medication	D: Patient continued or discontinued medication for cancer treatment	Length of disease free survival	254a	0.00
25. Foucar et al., 1991	Acute lymphoid leukemia	Medical record	Medication	D: Any vs. No missed treatment	Survival for 12 months	184p	0.20
26. Pizzo et al., 1983	Cancer	Self-report	Medication	C: Excellent, good, poor adherence	Fever/infection rate	77b	0.39
27. Richardson et al., 1990	Hematologic malignancy	Self-report and serum assay	Medication	C: scaled measure of presence of medication in blood	Survival up to 5 years	90a	0.26
Diabetes							
28. Glasgow et al., 1989	Diabetes	Self-report	Exercise, diet, blood glucose test	C: scaled composite of diet quality, physical activity, and glucose testing	Glycosolated hemoglobin level	108a	−0.05
29. Hadden et al., 1975	Diabetes	Dietician report	Weight loss diet	C: 5 levels from good to poor success at weight loss	Lowered fasting plasma glucose level	57a	0.16
30. Hampson et al., 1990	Diabetes	Self-report	Exercise, diet and glucose testing	C: Index of self-care activities and diet over 7 days	Glycosolated hemoglobin level	46a	0.00
31. Murphy et al., 1997	Diabetes	Electronic glucometer readings	Blood sugar-frequency of checking	C: good (>2/day); adequate (1,2/day) poor (<1/day)	Glycosolated hemoglobin level	29p	0.65
32. Strycher et al., 1998	Diabetes	Self-report and medical record	Diet	C: combined scale of food deviations from Rx diet; and Anderson Gustafson score on lowfat, high carb/fiber diet	Glycosolated hemoglobin level	20a	0.53

(*continued*)

TABLE 1. (Continued)

Reference	Disease	Adherence Assessment Method(s)	Regimen	Adherence Measure† C = continuous D = dichotomous	Measure of Treatment Outcome	Sample Size‡	Effect Size
Eye disorders							
33. Birch et al., 1988	Congenital cataracts	Medical record	Wearing contact lenses and following occlusion therapy	C: Adherence rated good, moderate, or poor in the medical chart	Visual acuity development up to 7 years	19p	0.71
34. Granstrom et al., 1985	Glaucoma	Electronic monitor	Medication (eye drops)	D: greater than or equal to 80% adherence; versus less than 80%	Slower progression of glaucoma visual field defects over 48 months	56a	0.08
35. Kass et al., 1986	Glaucoma	Electronic monitor	Medication (eye drops)	C: weight of medication container indicating amount utilized	Decreased intraocular pressure/pupillary diameter in 1 month	184a	0.01
36. Oliver et al., 1986	Amblyopia	Medical record	Patching of the "good eye"	D: considered adherent only if patching done 100% of the required time	Increased visual acuity in 12 months	350p	0.57
Heart disease							
37. Glynn et al., 1994	Myocardial infarction	Self-report	Medication	C: percent of prescribed aspirin taken (6 levels)	Myocardial infarction or coronary-vascular related death over 5 years	11,004a	0.03
38. Horwitz et al., 1990	Myocardial infarction	Pill count	Medication	D: adherence to propanalol good versus poor	Mortality within 1 year	1081a	0.27
39. Reis et al., 1989	Post angioplasty	Self-report	Medication	D: amount of medication remaining: <25% versus >75%	Plasma phospholipid level after 6 months	124a	0.28
40. Rich et al., 1996	Congestive heart failure	Pill count	Medication	D: greater than or equal to 90%, versus less than 90%	Readmission rate in 1 month	156a	0.11
41. Romm et al., 1976	Congestive heart failure	Self-report, pharmacy records	Medication	D: greater than or equal to 80%, versus less than 80%	Activity level/experience of symptoms over 6 months	122a	0.00
42. Thornton et al., 1984	Post angioplasty	Medical record	Medication	D: Judged excellent or good vs. fair or poor adherence to aspirin and coumadin	Recurrence of stenosis within 9 months	210a	−0.01

TABLE 1. (Continued)

Reference	Disease	Adherence Assessment Method(s)	Regimen	Adherence Measure† C = continuous D = dichotomous	Measure of Treatment Outcome	Sample Size‡	Effect Size
43. Warner et al., 1995	Myocardial infarction	Medical record	Exercise	C: Percent of attendance at prescribed cardiac rehabilitation sessions	HDL cholesterol level increase over 5 years	74a	0.00
Hypercholesterolemia							
44. Coronary Drug Project, 1980	Coronary heart disease	Pill count	Medication	D: clofibrate intake 80% or greater, versus less than 80%	Mortality in 5 years	1065a	0.12
45. Hoeg et al., 1984	Type II hyperlipoproteinemia	Pill count	Medication	D: neomycin or niacin intake greater than or equal to 85% vs. less than 85%	LDL and total cholesterol level after 3 months	25a	0.07
46. Jacobson et al., 1995	Primary hypercholesterolemia	Pill count	Medication	D: pravastatin intake between 80–120% vs. outside range	LDL cholesterol and triglyceride level after 3 months	214a	0.15
47. Lambert et al., 1996	Familial hypercholesterolemia	Pill count	Medication	C: how much medication taken	Total and LDL cholesterol after 2 months	65p	0.39
48. McCrindle et al., 1997	Familial hypercholesterolemia	Parent report and Pill count	Medication	C: average daily dose taken, measured by self-report log, questionnaire, pill count	LDL cholesterol after 2 months	38p	0.30
49. Malloy et al., 1978	Familial hypercholesterolemia	Parent report, Pill count and Urine assay	Medication	C: mean percentage of doses taken, calculated from three indices of adherence	Total cholesterol level after 6 months	20p	0.36
50. Schectman et al., 1993	Type II hyperlipidemia	Self-report	Medication	C: number of doses of lovastatin taken	LDL cholesterol after 2 months	83a	0.35
Hypertension							
51. Briggs et al., 1975	Hypertension in end stage renal disease	Serum assay	Medication	C: steady state predialysis plasma propranalol concentration	Blood pressure after 2 weeks	35a	0.44
52. Haynes et al., 1980	Hypertension	Pill count	Medication	D: medication intake 80% or greater, versus less than 80%	Blood pressure after 6 months on treatment	134a	0.17

(*continued*)

TABLE 1. (Continued)

Reference	Disease	Adherence Assessment Method(s)	Regimen	Adherence Measure† C = continuous D = dichotomous	Measure of Treatment Outcome	Sample Size‡	Effect Size
53. Morisky et al., 1986	Hypertension	Self-report	Medication	C: four item self-report measure of adherence (reliability 0.61)	Blood pressure measured at 6 and 42 months on treatment	290a	0.50
54. Morrell et al., 1997	Hypertension	Electronic recording	Medication	C: total errors in blood pressure medication	Blood pressure measured after 7 weeks on treatment	48a	0.36
55. Podell et al., 1976	Hypertension	Pharmacy records	Medication	D: medication intake 75% or greater, versus less than 75%	Blood pressure after 12 months on treatment	23a	0.16
56. Widmer et al., 1983	Hypertension	Pharmacy records	Medication	D: Pills taken 1 or 2 times a day vs. 3 or 4 times a day	Blood pressure after 12 months on treatment	284a	0.12
Intestinal disease							
57. Breuer et al., 1997	Ulcerative colitis	Self-report	Medication	C: based on phone interview and patient diary: number of weeks on medication enema regimen and number of enemas retained	Remission of symptomatology	45a	0.63
58. Colaco et al., 1987	Celiac disease	Parent report and health professional rating	Diet	C: Good, moderate, poor adherence to gluten free diet	Weight gain up to 15 years	37p	0.37
59. Congdon et al., 1981	Celiac disease	Dietician rating	Diet	C: strict, moderate, or poor avoidance of gluten free products	Assessment of mucosal abnormalities up to 4 years	32p	0.37
60. Mayer et al., 1991	Celiac disease	Dietician rating	Diet	C: good, moderate, or poor avoidance of gluten free products	Symptomatology up to 10 years	123p	0.28
61. Rappaport et al., 1986	Encopresis	Self-report and Parent report	Medication and Bowel training	C: Percent of time child had to be reminded to do self-care regimen	Symptomatology up to 17 months	42p	0.31
Otitis media							
62. Browning et al., 1988	Recurrentotitis media	Pharmacist judgment of residual volume of medication at end of each week	Medication	D: medication intake 70% or greater, versus less than 70%	Resolution of effusion at 6 weeks	165a	0.01

TABLE 1. (Continued)

Reference	Disease	Adherence Assessment Method(s)	Regimen	Adherence Measure† C = continuous D = dichotomous	Measure of Treatment Outcome	Sample Size‡	Effect Size
63. Kulik & Carlino, 1987	Otitis media	Parent report	Medication	C: Percentage of prescribed doses taken	Resolution of effusion at 1.5–2 weeks	82p	0.51
64. Macknin et al., 1985	Persistent otitis media	Health professional judgment on basis of parent report, pill count	Medication	D: medication intake 90% or greater, versus less than 90%	Resolution of effusion at 2 and 6 weeks	49p	0.00
65. Mattar et al., 1974	Otitis media	Pill count	Medication	D: judgment by health professional that 50% or more of medication was taken, vs. less than 50% based on level of meds remaining	Acute infection, improvement, normal at follow-up 2 weeks	94p	0.02
66. Reed et al., 1984	Otitis media	Urine assay	Medication	C: Urine antibiotic assay level of medication	Days until normal diagnosis, final diagnosis at last visit, recurrence	295p	0.00
67. Schwartz et al., 1982	Otitis media	Urine assay	Medication	C: Response on three urine assays	Recurrence/new infection by 8 weeks	33p	0.59
Sleep apnea							
68. Engleman et al., 1994	Sleep apnea	Electronic recording: time clock	Use of Continuous Positive Airway Pressure device (CPAP)	C: CPAP running time, number of hours CPAP used at night	Multiple sleep latency time improvement	54a	0.13
69. Engleman et al., 1993	Sleep apnea	Electronic recording: time clock	Use of CPAP	C: CPAP running time, number of hours CPAP used at night	Multiple sleep latency time improvement	21a	0.27
70. Loube et al., 1994	Sleep apnea	SR	Use of CPAP	C: CPAP running time, number of hours CPAP used at night	Weight loss	32a	0.45
71. Meurice et al., 1994	Sleep apnea	Electronic recording: time clock	Use of CPAP	C: CPAP running time, number of hours CPAP used at night	Reduction in hypersomnia	44a	0.37
72. Rauscher et al., 1993	Sleep apnea	Electronic recording: time clock	Use of CPAP	C: CPAP running time, number of hours CPAP used at night	Improvement in daytime sleepiness	63a	0.31

(*continued*)

TABLE 1. (Continued)

Reference	Disease	Adherence Assessment Method(s)	Regimen	Adherence Measure† C = continuous D = dichotomous	Measure of Treatment Outcome	Sample Size‡	Effect Size
Transplant							
73. De Geest et al., 1995	Renal transplant	Self-report	Medication	D: judged to be adherent or not by health professional who did interview, asked patient about 'drug holidays" from anti-rejection medication	Graft survival after 1 year	148a	0.15
74. Hilbrands et al., 1995	Renal transplant	Pill count	Medication	C: percentage of prescribed prednisone taken	Acute rejection within 1 year	127a	0.21
75. Phipps et al., 1990	Bone marrow transplant	Medical record	Medication and Various Medical Procedures	D: Judgment by nursing staff in chart (presence or absence of adherence problems)	Relapse	54p	0.00
76. Rovelli et al., 1989	Renal transplant	Self-report and Medical record	Medication and Appointment keeping	C: Scaled multiple measures of visit and lab test appointment keeping, self report of medication use	Rejection or mortality	260a	0.61
77. Sketris et al., 1994	Renal transplant	Self-report	Medication	C: Based on 6 questions: adherent, somewhat adherent, not adherent	Rejection episodes	361a	0.09
Ulcers							
78. Cutler et al., 1993	H. pylori infection, ulcer, and gastritis	Self-report and nurse rating	Medication	D: Nurse interviewed patient and judged adherent vs. not based on medication doses taken	Eradication of H. Pylori after 4 weeks	67a	0.23
79. Dohil et al., 1997	H. pylori infection	Parent report	Medication	D: medication intake 75% or greater, versus less than 75%	Eradication of H. Pylori after 6–8 weeks	15p	−0.07
80. Graham et al., 1992	H. pylori infection	Pill count	Medication	C: percent of medication taken determined by pill count	Eradication of H. Pylori after more than 1 month	75a	0.36
Venous disease							
81. Mayberry et al., 1991	Venous stasis ulceration of low extremity	Health professional report based on patient self-report	Wearing of elastic compression stockings	D: health professional judgment of patient willingness to cooperate with tx	Degree of Ulcer healing after average 5.3 months	113a	0.49

TABLE 1. (Continued)

Reference	Disease	Adherence assessment method(s)	Regimen	Adherence Measure† C = continuous D = dichotomous	Measure of Treatment Outcome	Sample Size‡	Effect Size
82. Samson et al., 1996	Recurrent venous ulcer prevention	Health professional report based on patient self-report	Wearing of elastic compression stockings	C: Adherence good, poor, or absent	Reulceration rate in 1–48 weeks	53a	0.75
83. Wright et al., 1991	Recurrent chronic venous ulcers	Self-Report	Medication and Wearing of elastic compression stockings	D: health professional judgment based on self-report of patient: taking medication and wearing stockings 75% or more of the time, versus less than 75%	Reulceration rate in 18 months	138a	−0.21

*Effect sizes are reported such that a positive effect size "r" indicates association of better adherence with a more positive treatment outcome and a negative effect size "r" indicates association of better adherence with a more negative treatment outcome. In studies assessing the efficacy of medication versus a placebo, effect sizes were obtained or computed if possible only for the relationship between adherence to the medication, not placebo, and the identified outcome.

†A Continuous (C) measure of adherence is one which offers three or more ordered response categories, or is based on multiple adherence criteria, or uses a reliable, validated continuous measure to assess adherence. A Dichotomous (D) measure involves two categories (adherent vs. not adherent), sometimes based on a percentage determined by the researchers.

‡a = adult subjects, p = pediatric subjects, b = both.

sons between levels of the moderator variables examined do use both fixed and random approaches to clarify the relative strength of their influence on the adherence-outcome relationship.

Results

Table 1 presents the 63 studies and details of their diseases, regimens, samples, measurements, and adherence-outcome *r* effect sizes which range from −0.21 to 0.75 (with 4 negative, 8 zero, and 51 positive). Thirteen of the positive effects are substantial (0.40 and above). The median effect size is 0.21, and variability is moderate (SD = 0.22).

Table 2 presents sample sizes, risk differences, and odds ratios for these effects. There is a robust positive overall effect which translates into more than a half SD difference in average outcomes between adherent and nonadherent subjects (Cohen d = 0.54).[20] According to the fail-safe n, 7650 new, unpublished, or otherwise unretrieved studies averaging null results would be needed to reduce this finding to nonsignificance at the 0.05 level.[20] Adherence (compared with nonadherence) reduces the risk for a null or poor treatment outcome by 26% (standardized risk difference); the odds of a good outcome if the patient is adherent are almost three times higher than the odds of a good outcome if the patient is nonadherent (standardized odds ratio). According to the Binomial Effect Size Display[18] of every 100 adherent patients, on average 63 can be expected to have a good outcome and 37 a null or poor outcome compared with the 50/50 split that would be expected if there were no relationship between adherence and outcome. Table 2 also presents meta-analysis statistics for nine diseases represented by at least five studies each. Under the random effects model, adherence was significantly related to outcome for intestinal disease, hypertension, hypercholesterolemia, and sleep apnea.

The large variation among these effect sizes compels an analysis of moderators of the adherence-outcome relationship. Table 3 presents the differences in unweighted mean effect sizes among studies grouped by eight moderators. Two of these factors produced robust differences, significant under the stringent random effects model, and six revealed trends that were significant (one borderline) under the less rigorous fixed effects model. The adherence-outcome relationship was higher for chronic compared with acute diseases,

TABLE 2. Sample Sizes, Average Effect-Size Risk Differences, and Odds Ratios for All 63 Studies and Separate for Specific Diseases*

Disease/ Condition	No. of Studies	No. of Subjects	Risk Difference (Percent) Based on Unweighted Mean r with 95% Confidence Intervals-Random Effects Model†	Odds Ratio with 95% Confidence Intervals-Random Effects Model‡
Overall	63	19,456	0.26 [0.20, 0.32]‖	2.88 [2.23, 3.73]
Cancer	5	661	0.17 [−0.04, 0.38] ns	2.02 [0.84, 4.89]
Diabetes	5	260	0.29 [−0.16, 0.64] ns	3.26 [0.52, 20.27]
Heart disease	7	12,771	0.10 [−0.02, 0.22] ns	1.49 [0.91, 2.42]
Hypercholesterolemia	7	1510	0.25 [0.13, 0.37]¶	2.81 [1.67, 4.71]
Hypertension	6	814	0.30 [0.12, 0.46]¶	3.44 [1.60, 7.37]
Intestinal disease	5	279	0.40 [0.20, 0.57]¶	5.48 [2.22, 13.54]
Otitis media	6	718	0.21 [−0.12, 0.50] ns	2.33 [0.61, 8.88]
Sleep apnea	5	214	0.31 [0.16, 0.45]¶	3.60 [1.87, 6.93]
Transplant	5	950	0.23 [−0.11, 0.52] ns	2.54 [0.64, 10.07]

*Nine diseases had five or more studies. Four other diseases had fewer than five studies available: arthritis (2), eye disorders (4), ulcers (3) and venous disease (3). These four disease groups are included in the total of 63 studies and in the analysis of moderators in Table 3.

The risk difference is the difference in risk of a null (or poor) treatment outcome after adherence versus nonadherence. The standardized odds ratio is the ratio of the odds of a good outcome if the patient is adherent to the odds of a good outcome if the patient is nonadherent.

†Positive effect sizes reflect the association of greater adherence with better treatment outcomes. Mean effect sizes (risk differences) are presented with 95% confidence intervals, based on a random effects model.

‡Standardized odds ratio, based on unweighted mean r.

§$P < 0.05$.

¶$P < 0.01$.

‖$P < 0.001$.

for less serious compared with more serious conditions, for studies not involving medication compared with those involving medication, and for studies involving pediatric patients compared with those involving adults. Three adherence measurement variables moderated the adherence-outcome effects, which were higher in studies with continuous measures, in studies using more than one method of assessing adherence, and in studies that included self-report. Finally, studies with "softer" or nondisease-specific outcome measures (eg, pain, morning stiffness, hospitalization, weight gain) yielded higher effects than did those with "harder" or disease-specific outcome measures (eg, glycosylated hemoglobin, blood pressure, cholesterol levels, recurrence of stenosis). There were no differences between studies of prevention and those of treatment, or between studies in which patients were asked to adhere to one versus more than one regimen.

Several of the significant moderators were intercorrelated. Phi coefficients (all based on 63 studies, and checked for accuracy where necessary using the Fisher exact probability test) revealed significant relationships among several dichotomous moderators. Studies with more than one adherence measurement were more likely to use self-report (phi = 0.54, $P < 0.001$), and those involving medication were more likely to use hard, disease-specific outcomes (phi = 0.31, $P < 0.05$), to involve acute conditions (phi = 0.42, $P < 0.001$), and to have dichotomous measures of adherence (phi = 0.37, $P < 0.01$). Studies of adult samples were more likely to use hard, disease-specific outcome measures (phi = 0.25, $P < 0.05$) and to involve more serious illnesses (phi = 0.37, $P < 0.01$). Studies of chronic disease were more likely to use continuous measures of adherence (phi = 0.37, $P < 0.01$) and to involve less serious conditions (phi = 0.27, $P < 0.05$).

Simultaneous multiple regression determined the relative strength of the eight moderators as they affected the adherence-outcome effect size. Taken together, they resulted in a significant

TABLE 3. Analysis of Moderators of the Adherence-Outcome Relationship

Moderator Variable	N of Studies	Risk Difference (Percent) Based on Unweighted Mean r with 95% Confidence Intervals-Random Effects Model	Random Effects t and Fixed Effects z: Significance of the Difference Between Average r's
Measurement of adherence			
Continuous vs. dichotomous	39	0.34 [0.26, 0.41]	t (61) = 3.65‖
	24	0.13 [0.05, 0.20]	z = 6.49‖
More than one vs. one Method	12	0.35 [0.17, 0.51]	t (61) = 1.53 ns
	51	0.24 [0.17, 0.30]	z = 2.57¶
Self report vs. no self report	28	0.29 [0.18, 0.38]	t (61) = 0.83 ns
	35	0.24 [0.16, 0.31]	z = 1.53‡
Measurement of outcome			
Non-specific (soft) vs. disease specific (hard) outcome	14	0.33 [0.19, 0.46]	t (61) = 1.33 ns
	49	0.24 [0.17, 0.30]	z = 2.11†
Disease, regimen, patients			
Chronic vs. acute disease	33	0.31 [0.22, 0.39]	t (61) = 1.77†
	30	0.20 [0.12, 0.28]	z = 3.29‖
Nonmedication vs. medication	19	0.37 [0.24, 0.49]	t (61) = 2.65¶
	44	0.21 [0.14, 0.27]	z = 4.29‖
Pediatric vs. adult patients	18	0.33 [0.24, 0.49]	t (61) = 1.61 ns
	44	0.23 [0.15, 0.29]	z = 2.64¶
Seriousness of condition lower vs. higher*	34	0.29 [0.20, 0.38]	t (61) = 1.26 ns
	29	0.22 [0.13, 0.30]	z = 2.33¶

*Because the measure of seriousness of condition (the SIRS-r)[88] is continuous, it was first correlated with the (Fisher Z-transformed) adherence-outcome effect (r = −0.15, n = 0.63, ns). Then, in order to provide comparable analysis to the seven dichotomous moderators, a median split (above 95, and equal to or below 95) on the SIRS was used to create two categories of seriousness, as presented in this table.

†$P < 0.082$.
‡$P < 0.063$.
§$P < 0.05$.
¶$P < 0.01$.
‖$P < 0.001$.

model ($F^{8,53} = 2.84$, $P = 0.011$), although they accounted for only 19% of the variance. Scale of Measurement (dichotomous/continuous) was the only significant predictor of the adherence-outcome effect ($t = 2.51$, $P = 0.015$); studies with continuous measures of adherence had higher effects.

Discussion

This study reviews 3 decades of research on patient adherence and the outcomes of treatment using techniques of meta-analysis to combine effects from more than 19,000 patients in 63 studies. On average, 26% more patients experienced a good outcome by adhering than by not adhering—a slightly stronger effect than in a study of the outcomes of adherence-enhancing interventions[17] and similar to a recent focused review on adherence and heart disease outcomes.[91] The strength of these effects suggests that the behavioral phenomenon of adherence may be as important to outcomes as many well-established medical interventions.[92]

The adherence-outcome relationship is not perfect, however, and can be complex. Factors such as the efficacy of recommendations and treatments, genetic variations in response rates, and limitations in current understanding of disease can affect outcomes.[93–95] In some cases, such as when misdiagnosis, adverse drug reactions, or prescribing errors occur, adherence to a recommended

treatment could be harmful. The conceptualization and operationalization of measurement appears to be critical to understanding the adherence-outcome relationship. Reverse causality may also play a role, so that a good outcome may promote subsequent adherence. Finally, it is important to consider the perspectives of patients, many of who may view nonadherence as a rational choice.[96]

Factors that modify the adherence-outcome relationship, particularly those involving the nature of diseases and of patients, appear to be extraordinarily complex. For example, the adherence-outcome relationship is higher in studies of chronic diseases than in studies of acute conditions. One possible explanation is that acute illness might be more self-limiting, making adherence less important than in long term care, although several of the moderators were intercorrelated. Chronic conditions involved more nonmedication regimens, were less serious, and were more likely to use continuous measures of adherence, all factors associated with higher adherence-outcome correlations. The adherence-outcome relationship was also higher in the treatment of pediatric patients compared with adults, possibly because of the less serious medical conditions represented in the pediatric samples or because parental adherence behavior may have been accompanied by additional care taking that promotes better health outcomes. Conversely, the achievement of good outcomes might be more difficult in adults because of comorbid conditions or long-standing poor health habits. This result could also be an artifact of differences between the two groups in their outcome measures. The adherence-outcome relationship was lower in studies of more serious conditions, a finding that could be explained by this variable's correlation with other moderators or by the possibility that patient adherence behavior makes a greater difference under less extreme medical circumstances.

The adherence-outcome relationship was higher in studies that did not involve medication than in studies that did, possibly because medication effects can vary (ie, helpful to some patients and harmful to others), or because certain behavior changes (eg, dietary changes, exercise) may have particularly powerful effects on health. The adherence-outcome relationship was lower in studies using disease-specific numerical outcomes (sometimes called "hard outcomes" such as blood pressure and cholesterol) than in studies using outcomes that were nonspecific and patient reported (and often referred to as "softer" outcomes, such as pain and the experience of symptoms). This finding is consistent with research showing a positive effect of adherence on outcomes regardless of whether adherence is to a real treatment or to a placebo.[97] Such research suggests that adherence might improve health through positive expectations and the "placebo effect"[98] which recent work has shown tends to be stronger among "softer," nonspecific outcomes.[99] The importance of these outcomes should not be minimized, however. In many cases, they may actually reflect patient preferences, and can be predictive of underlying physiologic states.[100]

Quality of measurement affects the adherence-outcome relationship, underscoring the importance of effective adherence assessment.[101–103], Three aspects of adherence measurement (scale, number of measures, and use of self-report) moderated the adherence-outcome effect, although the scale of adherence measurement was the only significant predictor in the multiple regression). These findings suggest that, whenever possible, research should use measures that are continuous instead of dichotomous, use more than one measure of adherence, and include self report. The need for multiple and continuous measures of adherence may not be surprising, given their likely greater reliability and power. The use of self-report measures of adherence have long been controversial, although self-report has considerable support both theoretically[101] and empirically.[104] The moderators that could be identified in this meta-analysis accounted for only 19% of the variance, however. Future research should attempt to isolate additional factors that might affect the relationship between adherence and outcomes. It is also important to note that adherence and treatment outcomes, while correlated, are distinctly different conceptually and empirically, and outcomes should never be used as proxies for adherence in adherence research.[103]

The meta-analytic approach is valuable in addressing this and other research questions because it demands thorough and systematic search of the literature and careful analysis of the corpus of published data;[18] it has some limitations, however. First, there is a greater likelihood that significant, rather than nonsignificant results will be published, and despite great care taken to retrieve all the relevant studies in the literature, some may have been missed. In the present case, the fail-safe n provides a correction for the possible existence

of unpublished studies with nonsignificant effects. Conclusions are limited, however, by the availability of only 63 studies that meet the inclusion and exclusion criteria in a large literature on patient adherence. It is not possible to correct for or assess the impact of any potential bias among researchers to conduct studies only on diseases or regimens for which certain adherence-outcome effects are expected. As more empirical data on patient adherence are published, firmer, and more generalizable conclusions will be able to be drawn.

Second, interpretation of the findings must include an analysis of possible biases resulting from sampling. This meta-analysis is limited to medical patients and excludes special groups (eg, drug or alcohol abuse, psychiatric conditions) that are common and particularly challenging in the realm of adherence. These sampling choices limit the scope of the present research, but also focus it more sharply on the already complex problem of adherence uncomplicated by cognitive deficits and emotional reactions that might obscure the adherence-outcome relationship.

Third, the studies summarized here are all correlational. Although we assume that adherence influences treatment outcomes, we acknowledge that outcomes may influence adherence, particularly during a long course of treatment. A third variable (such as positive expectations[105]) might also influence both health outcomes and motivation to adhere. Patients who are more likely to adhere might have personality characteristics (eg, optimism, conscientiousness, personal adjustment) that are positively correlated with better health outcomes.[106] Certain life circumstances (eg, socioeconomic status) might make it easier for patients to adhere and more likely that they will achieve positive health outcomes. Aspects of physician-patient communication might increase the chance of patient adherence and independently improve the outcomes of medical treatment.[1,103] Alternatively, unrecognized clinical depression might bring about poor adherence and poor treatment outcomes, particularly for certain medical conditions (eg, heart disease).[12,107]

Fourth, this study is limited by the general problem of pooling results from observational studies. Effects of confounding variables are implicit in their adherence-outcome correlations. Most studies do not explicitly control for these variables, and the few that do examine a wide array, making comparison of their results inadvisable. Therefore, in the present research, it is possible to account only for moderator variables across studies, not within them.

The present meta-analysis contributes to an extensive research enterprise focused on understanding the immensely complex phenomenon of patient adherence to medical treatment. Empirical studies since the late 1960s have raised many questions, some of which remain unanswered in spite of decades of research and a variety of study designs, including meta-analytic methods and multidimensional models. Both of these methods have contributed important results and usually they tell the same story (although some studies suggest that across many fields, the two methodological approaches disagree 10% to 23% of the time.[108] The present study summarizes the results of a diverse research literature examining one limited realm of the adherence research domain: estimation of the strength and the moderators of the relationship between patient adherence and the outcomes of medical treatment. It is important to recognize that fully understanding the role of adherence in treatment outcomes requires further analysis of the conceptual and methodological factors that affect this relationship, and future research on adherence would do well to provide quantitative data to further this examination. Evidence from the present study complements findings from intervention research to suggest that patient adherence is linked to more positive outcomes than is nonadherence, and, thus, that adherence may be a valuable goal of intervention at the individual as well as the system level.[109] Whether because of improved treatment effects, classical conditioning, positive expectations, or the "inner pharmacy" of neuroendocrine and immune responses mediated by the emotional experience that attends good care,[105] adherence seems to help promote patients' health and recovery.[110] We conclude that efforts to improve patient adherence, particularly in the context of active patient involvement and responsibility in collaboration with their physicians, continue to represent a worthwhile enterprise.[111]

Acknowledgments

The authors thank John Chen and David Payesteh for their research assistance.

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