

Depression Is a Risk Factor for Noncompliance With Medical Treatment

Meta-analysis of the Effects of Anxiety and Depression on Patient Adherence

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Background: Depression and anxiety are common in medical patients and are associated with diminished health status and increased health care utilization. This article presents a quantitative review and synthesis of studies correlating medical patients' treatment noncompliance with their anxiety and depression.

Methods: Research on patient adherence catalogued on MEDLINE and PsychLit from January 1, 1968, through March 31, 1998, was examined, and studies were included in this review if they measured patient compliance and depression or anxiety (with $n > 10$); involved a medical regimen recommended by a nonpsychiatrist physician to a patient not being treated for anxiety, depression, or a psychiatric illness; and measured the relationship between patient compliance and patient anxiety and/or depression (or provided data to calculate it).

Results: Twelve articles about depression and 13 about anxiety met the inclusion criteria. The associa-

tions between anxiety and noncompliance were variable, and their averages were small and nonsignificant. The relationship between depression and noncompliance, however, was substantial and significant, with an odds ratio of 3.03 (95% confidence interval, 1.96-4.89).

Conclusions: Compared with nondepressed patients, the odds are 3 times greater that depressed patients will be noncompliant with medical treatment recommendations. Recommendations for future research include attention to causal inferences and exploration of mechanisms to explain the effects. Evidence of strong covariation of depression and medical noncompliance suggests the importance of recognizing depression as a risk factor for poor outcomes among patients who might not be adhering to medical advice.

Arch Intern Med. 2000;160:2101-2107

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AFFECTIVE DISORDERS, especially anxiety and depression, are among the most common disorders seen in medical practice. Although estimates of depression in patients undergoing medical treatment vary according to the measurement criteria used, depression of all degrees occurs in at least 25%, with greater likelihood of depression in those who have significant health problems.¹⁻⁵ The coexistence of anxiety with medical disease does not seem to be as common as depression, but it is also prevalent.^{6,7} Anxiety and depression are associated with diminished health status and substantially lower health-related quality of life persisting over time.⁸ Depression is associated with high rates of health care utilization and severe limitations in daily functioning.^{9,10} Anxiety is also associated with increased use of health care services.¹¹⁻¹³

The coexistence of anxiety and depression with medical illness is a topic of considerable clinical and research interest. That anxiety and depression may complicate the treatment of medical conditions is fairly well established, but the extent of and the reasons for these complications are not well understood.^{1,7,14-18} There might be direct effects, with anxiety and depression having adverse physiological manifestations.¹⁹⁻²² It is also likely that indirect effects, particularly behavioral phenomena, are at work, mediating the relationships between anxiety and depression and outcomes.²³ Noncompliance with treatment recommendations (also called nonadherence, here and throughout the research and clinical literature) might be one of these behavioral mediators.

In an effort to understand why depressed and anxious patients have poorer medical care outcomes, we sought to de-

MATERIALS AND METHODS

DATA SOURCES AND LITERATURE SEARCH STRATEGY

We searched the MEDLINE and PsychLit databases from January 1, 1968 (marking the earliest empirical studies of patient compliance⁴²), through March 31, 1998. We used "patient" as a qualifier and chose the broad search terms "patient compliance" and "patient adherence" to avoid citations concerning issues such as compliance of health professionals to guidelines and adherence in the physiology of cells. We focused only on medical recommendations made by a physician, and so we searched the Abbreviated Index Medicus, which does not include allied health journals, and the Cancer subsets of the MEDLINE database; we also culled citations from article reference sections.

CRITERIA FOR STUDY INCLUSION

The initial search yielded 9035 citations, a figure comparable to that found in an enumeration by Trostle⁴³ during a similar, although not identical, period. We found approximately 76% of the citations in the MEDLINE database and 24% in PsychLit. The peak period of publication is January 1993 through December 1998 (28% of articles).

We looked for empirical articles involving patients who were given preventive- or treatment-related medical recommendations by a physician. The adherence of the patient alone, not that of the physician (eg, to treatment guidelines), was examined. Published studies based on samples of special populations including alcoholic, drug-abusing, homeless, or institutionalized patients or military personnel were excluded. Inclusion criteria allowed for adherence to (1) medically prescribed treatments, (2) exercise, (3) diet, (4) medication, (5) health-related behavior, (6) screening, (7) vaccination, and (8) appointments. Because we sought to focus on care in the one-to-one physician-patient relationship, we excluded adherence to anything not prescribed by a physician, including community screening procedures and vaccination programs and commercial weight loss and community-based exercise programs that were not medically prescribed. Other specific criteria for inclusion in the meta-analysis were as follows: (1) the article was published in a peer-reviewed, English-language journal (thus, book chapters, dissertations, non-peer-reviewed journal articles, and conference proceedings were not included); (2) the study defined what constituted adherence or compliance (eg, taking medication correctly or following protein restrictions) and its method of measurement (eg, self-report or physician report); (3) the sample involved patients who were not in psychiatric treatment or in treatment for anxiety or depression; (4) the medical regimen was prescribed or recommended by a nonpsychiatrist physician; (5) the study was not an experiment designed to alter adherence (because we hoped to examine the naturally occurring correlates of

adherence); (6) the total sample size was greater than 10; and (7) a measure of the correlation between anxiety and/or depression and adherence (or the data or a statistic such as t , F , or χ^2 sufficient to calculate the effect size r) was presented. Of the citations that met these criteria, there were 12 articles correlating depression with adherence and 13 articles correlating anxiety with adherence.

CODING OF ARTICLES

Each article was coded according to the following: (1) reference; (2) disease of patient sample (or type of general medical care); (3) method of assessing adherence, including self-report interview or questionnaire, self-report diary, other report (eg, parent, family member, spouse, or researcher), physician or nurse or allied health professional report, pill count, Medication Event Monitoring System (electronic pill monitor), electronic recording (eg, electronic clock on a continuous positive airway pressure device for sleep apnea), pharmacy record, medical record, and physiological marker or test (eg, interdialytic weight gain and serum potassium level in patients undergoing dialysis); (4) type of treatment or recommendation requiring adherence, eg, medication, diet, behavior, exercise, appointments, or diagnostic/screening follow-up; (5) operational definition of adherence used in the research (eg, >80% of medication taken); (6) measure of depression or anxiety used in the research; (7) sample size (including whether adult, pediatric, or both); and (8) correlation effect size (r) between anxiety and/or depression and adherence (reflecting the size [from 0 to 1.00] and the direction [positive or negative] of the association between anxiety or depression and the measure of adherence). The effect size r was used because it represents the strength and direction of the relationship between continuous variables (and in its biserial form, between 2 levels of an independent variable and scores on a continuous dependent variable). Here, r was sometimes computed from statistics t (or means and SDs of 2 groups), F , or χ^2 or from contingency table data (phi coefficient, another form of r).⁴⁴ When studies presented effect sizes that had more than 1 df , we calculated phi if the data were available; if not, we used the probability level to determine the 1-tailed z , then transformed it to r . (For $P < .05$, $z = 1.64$; for $P < .01$, $z = 2.33$; and for $P < .001$, $z = 3.09$.) When results were reported only as "nonsignificant" with no data, a z of 0.00 was assigned. This was a conservative effect estimate, lower than likely was realized.

STATISTICAL ANALYSES AND DATA SYNTHESIS

Each study was a unit of analysis. Median effect sizes and unweighted and weighted (by $n-3$) mean r effect sizes were calculated using Fisher z transformation of r . Confidence intervals (95%) for unweighted mean r were based on a random effects model and for weighted mean r on a fixed effects model. Odds ratios, risk differences, and relative risks as well as d effect sizes (for analysis of SD differences) were calculated.^{45,46}

termine the extent to which anxiety and depression might be linked to poor adherence to treatment recommendations. During the past 3 decades, patient noncompliance has been of concern in attempts to understand limitations in the process of medical care delivery. Research²⁴⁻²⁷

has shown that across a variety of settings, almost half of all medical patients in the United States do not adhere to the recommendations of their physicians for prevention or treatment of acute or chronic conditions. When patients are noncompliant, they do not take their medi-

Table 1. Depression in Medical Patients as a Correlate of Adherence*

Study	Disease	Method of Measuring Adherence	Type of Adherence Regimen	Study Definition of Level of Adherence	Measure of Depression	Sample Size	r Effect Size
Blotcky et al, ⁴⁷ 1985	Cancer	Medical record	Health behavior regimen	Comparison of consenters and refusers of treatment	Subjective distress	20 Children	-0.48
Botelho and Dudrak, ⁴⁸ 1992	General medicine	Pill count	Medication	Pill count (>80% vs ≤80%)	BDI	52 Adults	-0.11
Brownbridge and Fielding, ⁴⁹ 1989	ESRD	Patient self-report and physiological assay or test average	Dietary	Care taken and difficulty with treatment and child's serum urea nitrogen level	Leeds scale for self-assessment of depression in main caregiver and CDI	28 Children	-0.45
Carney et al, ⁵⁰ 1998	Angina	Electronic medication monitor	Medication	Days patient removed correct number of pills from electronic monitor, %	BDI	65 Adults	-0.24
De-Nour and Czaczkes, ⁵¹ 1976	ESRD	Physician report	Dietary	Nephrologist's assessment: good, fair, or poor	Clinical evaluation of depression	32 Adults	-0.45
Gilbar and DeNour, ⁵² 1989	Cancer	Medical record	Medication	Continued vs did not continue treatment	BSI: psychosocial distress-depression scale	106 Adults	-0.24
Katz et al, ⁵³ 1998	ESRD	Physiological assay or test	Dietary	Appropriate levels for serum potassium, serum phosphorus, and IWG	Self-report: depressed in past month	56 Adults	0.00
Kiley et al, ⁵⁴ 1993	Renal transplant	Physician report	Health behavior regimen	Physical test of medication levels, IWG, and appointment keeping	CES-D	105 Adults	-0.15
Lebovits et al, ⁵⁵ 1990	Breast cancer	Patient self-report	Medication	Doses taken (>90% or ≤90%)	SCL-90: depressive symptom disturbances	37 Adults	-0.32
Rodriguez et al, ⁵⁶ 1991	Renal transplant	Medical record	Medication and health behavior regimen	Attend clinic and laboratory, follow diet, take medication, and IWG	Health professional indication of depression in chart review	24 Adults	-0.46
Schneider et al, ⁵⁷ 1991	ESRD	Physiological test or assay	Dietary	IWG (<3.0 kg ≥3.0 kg) after fluid restriction	BDI	50 Adults	-0.22
Taal et al, ⁵⁸ 1993	Rheumatoid arthritis	Patient self-report	Health behavior regimen	Self-reported adherence problem index	DUTCH-AIMS depression subscale	86 Adults	-0.09

*A positive effect indicates that higher depression is associated with higher adherence or compliance. A negative effect indicates that higher depression is associated with lower adherence or compliance. When more than 1 method for assessing adherence was used, or more than 1 type of adherence was assessed, multiple data points were averaged for overall effects and, where possible, used separately for analyses of moderator effects. ESRD indicates end-stage renal disease; IWG, weight gain between dialysis sessions; BDI, Beck Depression Inventory; CDI, Childhood Depression Inventory; BSI, Brief Symptom Inventory; CES-D, Center for Epidemiological Studies Depression Scale; SCL-90, Derogatis Outpatient Psychiatric Rating Scale; and DUTCH-AIMS, Arthritis Impact Management Scale.

cation correctly, forget or refuse to follow a diet, do not engage in prescribed exercise, cancel or do not attend appointments, and persist in lifestyles that endanger their health. Noncompliance can result in exacerbation of illness, incorrect diagnoses, and patient and physician frustration.²⁸⁻³⁰ There is growing evidence³¹⁻³⁴ that noncompliance has a consistently negative effect on treatment outcomes.

Medical patients may be noncompliant for many reasons, including their disbelief in the efficacy of treatment,³⁵ the presence of barriers such as adverse effects and financial constraints,³⁶⁻³⁸ and lack of help and support from family members.³⁹ It is hypothesized that mood disorders such as anxiety and depression that impair cognitive focus, energy, and motivation might also be expected to affect patients' willingness and ability to follow through with treatment. Assessing the extent to which noncompliance might be a concomitant of a treatable condition such as anxiety or depression may be an important step in improving patient adherence, the therapeutic alliance between physicians and patients,

and ultimately the outcomes of medical treatment.^{40,41} This article quantitatively reviews and synthesizes the research assessing the effects of concomitant depression and anxiety on patient adherence to medical treatment recommendations.

RESULTS

Table 1 presents 12 studies that examined the relationship between patients' depression and their adherence to prescribed medical treatment regimens from their physicians. Depression is correlated with enhanced adherence when *r* is positive and with diminished adherence when *r* is negative; the absolute value of *r* is a measure of its magnitude.

Table 2 shows that the 12 effects for depression and adherence are not significantly heterogeneous and that the median and the weighted and unweighted mean effect sizes are negative and of moderate size (with the mean effects achieving statistical significance). The effect size *d* reflects more than a 0.5 SD difference in ad-

Table 2. Summary of Meta-analysis Results*

Independent Variable	Studies, No.	Heterogeneity Test (<i>I</i> ²)	Median <i>r</i>	Mean (95% CI) <i>r</i>		Cohen <i>d</i> [§]
				Unweighted [†]	Weighted [‡]	
Depression						
Total	12	<i>P</i> = .32	-0.24	-0.27 (-0.38 to -0.17) <i>P</i> < .001	-0.21 (-0.29 to -0.13) <i>P</i> < .001	-0.56, -0.43
In ESRD	6	<i>P</i> = .13	-0.34	-0.30 (-0.48 to -0.08) <i>P</i> = .008	-0.22 (-0.33 to -0.11) <i>P</i> < .001	-0.63, -0.45
In non-ESRD	6	<i>P</i> = .54	-0.24	-0.25 (-0.40 to -0.09) <i>P</i> = .005	-0.21 (-0.30 to -0.11) <i>P</i> < .001	-0.52, -0.43
Anxiety	13	<i>P</i> = .007	0.00	-0.04 (-0.21 to 0.12) <i>P</i> = .59	-0.04 (-0.11 to 0.02) <i>P</i> = .20	-0.08, -0.08

*ESRD indicates end-stage renal disease; CI, confidence interval.

[†]Random effects model.

[‡]Each study weighted by *n*-3, fixed effects model.

[§]Respectively based on unweighted and weighted mean *r*.

||Standardized and based on unweighted mean *r*: risk difference is difference in risk of noncompliance between depressed (anxious) and nondepressed (nonanxious) patients; relative risk is of noncompliance among depressed (anxious) compared with nondepressed (nonanxious) patients.

herence between the depressed and nondepressed populations, with depressed patients being far less adherent.⁴⁶ The “fail safe *n*” for the unweighted mean *r* in this analysis is 142, meaning that there would need to exist more than 142 new, unpublished, or otherwise unretrieved studies that found, on average, no effect of depression on adherence to reduce this effect to nonsignificance at the .05 level. This is more than twice the “tolerance level” of 70 studies that would be considered acceptable.⁴⁴ As shown in Table 2, this finding represents a risk difference (difference in risk of noncompliance between depressed and nondepressed patients) of 27% and a relative risk of noncompliance of 1.74 among depressed compared with nondepressed patients.⁴⁵ Based on the Binomial Effect Size Display,⁴⁵ this finding means that among every 100 noncompliant patients, on average 63.5 can be expected to be depressed compared with 36.5 not depressed (instead of the 50/50 split that would be expected if there were no relationship between adherence and depression). The standardized odds ratio for the unweighted mean random effects model is 3.03, indicating that the odds are 3 times greater that depressed patients will be noncompliant than that nondepressed patients will be noncompliant.

To examine the possibility that specific disease states and treatments (eg, end-stage renal disease or renal dialysis) may have been overly influential in the significance of this finding, we divided this sample into 2 groups: 6 studies involving end-stage renal disease, renal disease, or renal transplant and 6 studies involving other diseases (including rheumatoid arthritis, cancer, and general medical care). Heterogeneity tests were not significant, and unweighted and weighted mean effect sizes in both groups were significant. In the end-stage renal disease group, the standardized odds ratio is 3.44 (*P* = .008), and in the rheumatoid arthritis, cancer, and general medical group, the standardized odds ratio is 2.77 (*P* = .005). Thus, the relationship between depression and nonadherence seems not to be peculiar to the studies of renal disease (although the overall effect is somewhat stronger, and the individual effects more variable, in the end-stage renal disease subgroup), and the depression-

adherence relationship can be generalized to diseases other than renal failure.

The picture is different for anxiety, however. Its relationship with adherence seems to be minimal on average, and there is considerable variability among the effects. As **Table 3** shows, in 13 studies, 2 effect sizes are zero and 6 are very small; among moderate effects, 2 are positive and 3 are negative. Overall, the median effect size is 0.00, and mean effect sizes are small and nonsignificant. The difference in risk of noncompliance between anxious and nonanxious patients is only 4%. Combining these studies is somewhat problematic, however, because they are variable and significantly heterogeneous. We were unsuccessful in finding moderating variables that could group homogeneous studies.

COMMENT

Meta-analysis was used in this study to summarize the research literature addressing the effects of anxiety and depression on patient adherence to medical treatment regimens. This quantitative approach adds value to qualitative methods for summarizing research domains. It requires thoroughness in finding and carefully analyzing all of the published data on a defined research question and prevents reliance on any one significance test, providing the opportunity for several small effects to contribute to an overall picture of the results of a research enterprise. Certain limitations exist, such as the greater likelihood that significant results will be published (although a statistical method—the fail safe *n*—deals with such bias). Meta-analysis usually includes studies that vary considerably in their sampling units, methods of measuring and operationalizing independent and dependent variables, data-analytic approaches, and statistical findings. Such variation increases the generalizability of results that are clear, such as for depression. When they are not clear, as for anxiety, such variation can be confusing. Meta-analysis systematically assesses only individual zero-order correlations of independent and dependent variables (although for the field of adherence,

Odds Ratio (95% CI)	Risk Difference, %	Relative Risk
3.03 (1.98 to 4.95)	27	1.74
3.44 (1.26 to 8.10)	30	1.85
2.77 (1.43 to 5.44)	25	1.66
1.17 (0.61 to 2.25) P = .59	4	1.08

univariate summary analyses are essential to complete before multidimensional models can be constructed).

In the present quantitative review, the message is clear from the literature on depression and responses to medical treatment. When taking into account the 12 published studies that examined recommendations given by physicians, depressed patients were 3 times as likely as nondepressed patients to be noncompliant. Furthermore, there was considerable consistency in the literature in that 11 of the 12 effects were negative, and in some cases substantially so. Noncompliance is a complicated phenomenon, and decades of research have attempted to establish its clear connection with variables that can be altered and improved in the course of clinical care. Patient depression might be such a variable.

Why might depression increase noncompliance? First, positive expectations and beliefs in the benefits and efficacy of treatment have been shown³⁵ to be essential to patient adherence. Depression often involves an appreciable degree of hopelessness, and compliance might be difficult or impossible for a patient who holds little optimism that any action will be worthwhile. Second, considerable research^{24,25} suggests the importance of support from the family and social network in a patient's attempts to be compliant with medical treatments. Depression is often accompanied by considerable social isolation and withdrawal from the very individuals who would be essential in providing emotional support and assistance. Third, depression might be associated with reductions in the cognitive functioning essential to remembering and following through with treatment recommendations (eg, taking medication). Rigorous testing of multidimensional models would help to choose among these and other possible explanations and to understand more fully the mechanism for depression's effect on adherence. In the meantime, this substantial and significant negative relationship between depression and adherence is worthy of note for future research strategies and for clinical practice.

In contrast to depression, anxiety has an unclear relationship to adherence. Substantial variation in effects (range, -0.64 to 0.39) and lack of any moderator to ac-

count for this variation make combining effect sizes problematic at this point in the accumulated research. The average effect is close to zero, but it is difficult to state that there is no effect of anxiety on adherence. One summary statistic simply does not do justice to the apparent complexity of this literature. As empirical studies accumulate, patterns in effect sizes will likely emerge and moderator variables will be confirmed. Conceptually, further refinement of the construct of anxiety and its relationship to adherence will also be helpful.⁶⁶ Anxiety itself can be heterogeneous and range from panic, which might have no direct effect on compliance, to obsessive-compulsive disorder and generalized anxiety about health, which might actually improve compliance activities. Furthermore, depression tends to co-occur in as many as half of all patients who have certain anxiety disorders.⁶⁶ Sample and measurement characteristics, and the degree of hopelessness and uncontrollability of the diseases studied, might contribute to the existence of shared variance of anxiety and depression in their correlations with adherence. (Six studies are common to the meta-analyses of both depression and anxiety,^{47,49,50,53,57,58} and in 3 cases,^{49,53,58} the effect sizes for anxiety and depression were similar. In the others, depression effects were strongly negative and anxiety effects were near zero, with no apparent moderating factors that distinguish the 2 groups.)

The studies summarized herein are all correlational and cannot determine whether depression causes noncompliance or noncompliance causes depression. Causal conclusions would require experimental assessment of a treatment intervention or causal modeling from longitudinal data. It is possible that a "feedback loop" exists such that depression causes noncompliance with medical treatment and noncompliance further exacerbates depression so that a clinical focus on both might be essential. In addition, it is possible that a third variable (eg, poor health status) causes both depression and noncompliance. Exploration of this would require large, longitudinal samples in which depression, adherence, health status, and other relevant variables are examined at several points in time. As Wells²³ noted, the next research priority across many chronic diseases should be testing specific theoretical and clinical models to examine the direct effects of depression on health outcomes and the indirect effects of depression through patient adherence.

Current limitations in causal inference should not deter awareness by clinicians of depression as a potentially useful marker for their patients' noncompliance. Recognizing that a patient might be depressed could help a physician manage his or her frustration at that patient's noncompliance and thus improve the physician-patient relationship. For patients who are beginning their courses of treatment for chronic disease, screening for depression might prove to be a useful identifier of possible future noncompliance and might suggest closer monitoring and assistance to achieve adherence to treatment. Alternatively, clear noncompliance with a specified treatment regimen should raise suspicion of coexisting depression. Once treatment for known depression, whatever its source, has begun, steps should be taken to enhance adherence because of the possible additional difficulties that depressed

Table 3. Anxiety in Medical Patients as a Correlate of Adherence*

Study	Disease	Method of Measuring Adherence	Type of Adherence Regimen	Study Definition of Level of Adherence	Measure of Anxiety	Sample Size	r Effect Size
Blotchky et al, ⁴⁷ 1985	Cancer	Medical record	Health behavior regimen	Comparison of consenters and refusers of treatment	STAI: state $r = 0.31$; trait $r = -0.56$, averaged for mothers and adolescents	20 Children	0.02
Brownbridge and Fielding, ⁴⁹ 1989	ESRD	Patient self-report	Dietary and medication	Care taken and difficulty with treatment	Child's self reported trait anxiety on the Anxiety Inventory for Children	20 Children	-0.64
Carney et al, ⁵⁰ 1998	Angina	Electronic medication monitor	Medication	Days patient removed correct number of pills from electronic monitor, %	STAI: state $r = -0.21$; trait $r = 0.18$, averaged	65 Adults	0.01
Christensen et al, ⁵⁹ 1997	ESRD	Physiological test or assay	Dietary and medication	Serum potassium, serum phosphorus, IWG	STAI-A Trait Anxiety Scale	51 Adults	0.09
Cockburn et al, ⁶⁰ 1987	Infection	Pill count	Medication	Deviation from prescribed dosage of medication (>20% vs ≤20%)	Self-report on health state scale of "none, some, moderate, or extreme" anxiety	204 Adults	-0.19
Hazzard et al, ⁶¹ 1990	Seizure disorder	Physiological test or assay	Medication	Adherence ratings by pediatric neurologists based on monthly blood assays	Health anxiety of child and parent (averaged)	35 Children	-0.32
Katz et al, ⁵³ 1998	ESRD	Physiological test or assay	Dietary and medication	Appropriate levels for serum potassium, serum phosphorus, IWG	Self-report: anxious in past month	56 Adults	0.00
Kinsman et al, ⁶² 1980	Asthma	Medical record	Medication	Appropriate use vs overuse, underuse and arbitrary use of medications	MMPI: panic/fear	82 Adults	-0.03
Litt et al, ⁶³ 1982	Rheumatoid arthritis	Physiological test or assay	Medication	Average serum salicylate level over 12 mo	Piers-Harris Self-Concept: Anxiety subscale	36 Children	0.39
Mawhinney et al, ⁶⁴ 1993	Asthma	Electronic recording	Medication	Appropriate use vs overuse, underuse, and arbitrary use on asthma medication monitor	MMPI: $r = 0.42$; panic/fear $r = 0$, averaged	Children and adults	0.21
Roter, ⁶⁵ 1977	General medical	Medical record	Appointment	Chart records of appointment keeping	Anxiety of patient rated from audiotapes of medical interaction	100 Adults	0.07
Schneider et al, ⁵⁷ 1991	ESRD	Physiological test or assay	Dietary	IWG <3.0 kg (fluid restriction)	STAI: trait	50 Adults	0.00
Taal et al, ⁵⁸ 1993	Rheumatoid arthritis	Patient self-report	Health behavior regimen	Self-reported adherence problem index	DUTCH-AIMS anxiety subscale	86 Adults	-0.06

*A positive effect indicates that higher anxiety is associated with higher adherence or compliance. A negative effect indicates that higher anxiety is associated with lower adherence or compliance. When more than 1 method for assessing adherence was used, or more than 1 type of adherence was assessed, multiple data points were averaged for overall effects and, where possible, used separately for analyses of moderator effects. ESRD indicates end-stage renal disease; IWG, weight gain between dialysis sessions; MMPI, Minnesota Multiphasic Personality Inventory; STAI, State/Trait Anxiety Inventory; and DUTCH-AIMS, Arthritis Impact Management Scale.

patients might encounter. Although it remains to be determined whether treating depression will result in improved patient adherence, the recognition of depression as a significant risk factor for noncompliance with medical treatment carries the potential to improve medical practice, reduce patient disability, enhance patient functioning, and improve health care outcomes.⁶⁷

Accepted for publication January 11, 2000.

This study was funded in part by a grant from Eli Lilly and Co and by research support from the University of California Riverside's Center for Ideas and Society, Center for Social and Behavioral Sciences of the College of Humanities, Arts, and Social Sciences, and Academic Senate Committee on Research (Dr DiMatteo).

We thank Robert Rosenthal, PhD, for advice on meta-analysis, and Patrick Giordani, MA, for research assistance.

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REFERENCES

1. Katon W. Depression: relationship to somatization and chronic medical illness. *J Clin Psychiatry*. 1984;45:4-11.
2. Wells KB, Rogers W, Burnam MA, Greenfield S, Ware JE Jr. How the medical comorbidity of depressed patients differs across health care settings: results from the Medical Outcomes Study. *Am J Psychiatry*. 1991;148:1688-1696.
3. Kessler LG, Cleary PD, Burke JD Jr. Psychiatric disorders in primary care: results of a follow-up study. *Arch Gen Psychiatry*. 1985;42:583-587.
4. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Study. *Arch Gen Psychiatry*. 1994;51:8-19.
5. Croghan TW, Obenchain RL, Crown WE. What does treatment of depression really cost? *Health Aff (Millwood)*. 1998;17:198-208.

6. Lustman PJ. Anxiety disorders in adults with diabetes mellitus. *Psychiatr Clin North Am.* 1988;11:419-432.
7. Wells KB, Golding JM, Burnam MA. Chronic medical conditions in a sample of the general population with anxiety, affective, and substance use disorders. *Am J Psychiatry.* 1989;146:1440-1446.
8. Sherbourne CD, Wells KB, Meredith LS, Jackson CA, Camp P. Comorbid anxiety disorder and the functioning and well-being of chronically ill patients of general medical providers. *Arch Gen Psychiatry.* 1996;53:889-895.
9. Manning W, Wells KB. The effect of psychological distress and psychological well-being on use of medical services. *Med Care.* 1992;30:541-553.
10. Simon G, Ormel J, VonKorff M, et al. Health care costs associated with depressive and anxiety disorders in primary care. *Am J Psychiatry.* 1995;152:352-357.
11. Boyd JH. Use of mental health services for the treatment of panic disorder. *Am J Psychiatry.* 1986;143:1569-1574.
12. Klerman G, Weissman MM, Ouellette R, et al. Panic attacks in the community: social morbidity and health care utilization. *JAMA.* 1991;265:742-746.
13. Shapiro S, Skinner EA, Kessler LG, et al. Utilization of health and mental health services: three epidemiological catchment area sites. *Arch Gen Psychiatry.* 1984;41:971-978.
14. Couleman JL, Schulberg HC, Block MR, Janosky JE, Arena VC. Medical comorbidity of major depressive disorder in a primary medical practice. *Arch Intern Med.* 1990;150:2363-2367.
15. Wells KB, Golding JM, Burnam MA. Psychiatric disorder in a sample of the general population with and without chronic medical conditions. *Am J Psychiatry.* 1988;145:976-981.
16. Katon W. Depression: somatic symptoms and medical disorders in primary care. *Compr Psychiatry.* 1982;23:274-287.
17. LaBruzza A. Physical illness presenting in psychiatric disorder: guidelines for differential diagnosis. *J Operational Psychiatry.* 1981;12:24-31.
18. Verhaak PFM. Variations in the diagnosis of psychosocial disorders: a general practice observational study. *Soc Sci Med.* 1986;23:595-604.
19. Schulberg HC, McClelland M, Burns BJ. Depression and physical illness: the prevalence, causation, and diagnosis of comorbidity. *Clin Psychol Rev.* 1987;7:145-167.
20. Covinsky KE, Fortinsky RH, Palmer RM, Kresevic DM, Landefeld CS. Relation between symptoms of depression and health status outcomes in acutely ill hospitalized older patients. *Ann Intern Med.* 1997;126:417-425.
21. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction: impact on 6-month survival. *JAMA.* 1993;270:1819-1825.
22. Ford DE, Mead LA, Chang PP, Cooper-Patrick L, Wang N-Y, Klag MJ. Depression is a risk factor for coronary artery disease in men: the Precursors Study. *Arch Intern Med.* 1998;158:1422-1426.
23. Wells KB. The role of depression in hypertension-related mortality. *Psychosom Med.* 1995;57:436-438.
24. DiMatteo MR. Enhancing patient adherence to medical recommendations. *JAMA.* 1994;271:79-83.
25. DiMatteo MR, DiNicola DD. *Achieving Patient Compliance.* Elmsford, NY: Pergamon Press Inc; 1982.
26. Epstein LH, Cluss PA. A behavioral medicine perspective on adherence to long-term medical regimens. *J Consult Clin Psychol.* 1982;50:950-971.
27. Lin EHB, Von Korff M, Katon W, et al. The role of the primary care physician in patients' adherence to antidepressant therapy. *Med Care.* 1995;33:67-74.
28. Joshi N, Milfred D. The use and misuse of new antibiotics: a perspective. *Arch Intern Med.* 1995;155:569-577.
29. Sanson-Fisher R, Bowman J, Armstrong S. Factors affecting nonadherence with antibiotics. *Diagn Microbiol Infect Dis.* 1992;15(suppl):103S-109S.
30. Haynes RB, Taylor DW, Sackett DL, eds. *Compliance in Health Care.* Baltimore, Md: Johns Hopkins University Press; 1979.
31. Murphy LMB, Thompson RJ Jr, Morris MA. Adherence behavior among adolescents with type I insulin-dependent diabetes mellitus: the role of cognitive appraisal processes. *J Pediatr Psychol.* 1997;22:811-825.
32. Schectman G, Hiatt J, Hartz A. Evaluation of the effectiveness of lipid-lowering therapy (bile acid sequestrants, niacin, psyllium, and lovastatin) for treating hypercholesterolemia in veterans. *Am J Cardiol.* 1993;71:759-765.
33. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care.* 1986;24:67-74.
34. Rovelli M, Palmeri D, Vossler E, Bartus S, Hull D, Schweizer R. Noncompliance in organ transplant recipients. *Transplant Proc.* 1989;21:833-834.
35. DiMatteo MR, Hays RD, Gritz ER, et al. Patient adherence to cancer control regimens: scale development and initial validation. *Psychol Assess.* 1993;5:102-112.
36. Dolgin MJ, Katz ER, Doctors SR, Siegel SE. Caregivers' perceptions of medical compliance in adolescents with cancer. *J Adolesc Health Care.* 1986;7:22-27.
37. Hoeg JM, Maher MB, Bou E, et al. Normalization of plasma lipoprotein concentrations in patients with type II hyperlipoproteinemia by combined use of neomycin and niacin. *Circulation.* 1984;70:1004-1011.
38. Jamison RN, Lewis S, Burish TG. Cooperation with treatment in adolescent cancer patients. *J Adolesc Health Care.* 1986;7:162-167.
39. Glasgow RE, Toobert DJ, Riddle M, Donnelly J, Mitchell DL, Calder D. Diabetes-specific social learning variables and self-care behaviors among persons with type II diabetes. *Health Psychol.* 1989;8:285-303.
40. VonKorff M, Ormel J, Katon W, et al. Disability and depression among high utilizers of health care: a longitudinal analysis. *Arch Gen Psychiatry.* 1992;49:91-100.
41. Simonsick EM, Wallace RB, Blazer DG, et al. Depressive symptomatology and hypertension associated morbidity and mortality in older adults. *Psychosom Med.* 1995;57:427-435.
42. Davis MS. Variations in patients' compliance with doctors' advice: an empirical analysis of patterns of communication. *Am J Public Health.* 1968;58:274-288.
43. Trostle JA. Patient compliance as an ideology. In: Gochman DS, ed. *Handbook of Health Behavior Research, II: Provider Determinants.* New York, NY: Plenum Publishing Corp; 1997:109-122.
44. Rosenthal R. *Meta-analytic Procedures for Social Research.* Beverly Hills, Calif: Sage; 1984.
45. Rosenthal R, Rosnow RL, Rubin DB. *Contrasts and Effect Sizes in Behavioral Research: A Correlational Approach.* New York, NY: Cambridge University Press; 1999.
46. Cohen J. *Statistical Power Analysis for the Behavioral Sciences.* 2nd ed. Hillsdale, NJ: Lawrence A Erlbaum Associates; 1988.
47. Blotcky AD, Cohen DG, Conaster C, Klopovich P. Psychosocial characteristics of adolescents who refuse cancer treatment. *J Consult Clin Psychol.* 1985;53:729-731.
48. Botelho RJ, Dudrak R. Home assessment of adherence to long-term medication in the elderly. *J Fam Pract.* 1992;35:61-65.
49. Brownbridge B, Fielding D. An investigation of psychological factors influencing adherence to medical regime in children and adolescents undergoing hemodialysis and CAPD. *Int J Adolesc Med Health.* 1989;4:7-18.
50. Carney RM, Freedland KE, Eisen SA, Rich MW, Skala JA, Jaffe AS. Adherence to a prophylactic medication regimen in patients with symptomatic versus asymptomatic ischemic heart disease. *Behav Med.* 1998;24:35-39.
51. De-Nour AK, Czaczkes JW. The influence of patient's personality on adjustment to chronic dialysis. *J Nerv Ment Dis.* 1976;162:323-333.
52. Gilbar O, DeNour AK. Adjustment to illness and dropout of chemotherapy. *J Psychosom Res.* 1989;33:1-5.
53. Katz RC, Ashmore J, Barboa E, Trueblood K, McLaughlin V, Mathews L. Knowledge of disease and dietary compliance in patients with end-stage renal disease. *Psychol Rep.* 1998;82:331-336.
54. Kiley DJ, Lam CS, Pollak R. A study of treatment compliance following kidney transplantation. *Transplantation.* 1993;55:51-56.
55. Lebovits AH, Strain JJ, Schleifer SJ, Tanaka JS, Bhardwaj S, Messe MR. Patient noncompliance with self-administered chemotherapy. *Cancer.* 1990;65:17-22.
56. Rodriguez A, Diaz M, Colon A, Santiago-Delpin EA. Psychosocial profile of non-compliant transplant patients. *Transplant Proc.* 1991;23:1807-1809.
57. Schneider MS, Friend R, Whitaker P, Wadhwa NK. Fluid noncompliance and symptomatology in end-stage renal disease: cognitive and emotional variables. *Health Psychol.* 1991;10:209-215.
58. Taal E, Rasker JJ, Seydel ER, Wiegman O. Health status, adherence with health recommendations, self-efficacy and social support in patients with rheumatoid arthritis. *Patient Educ Counsel.* 1993;20:63-76.
59. Christensen AJ, Moran PJ, Lawton WJ, Stallman D, Voigts AL. Monitoring attentional style and medical regimen adherence in hemodialysis patients. *Health Psychol.* 1997;16:256-262.
60. Cockburn J, Gibberd RW, Reid AL, Sanson-Fisher RW. Determinants of non-compliance with short term antibiotic regimens. *BMJ.* 1987;295:814-818.
61. Hazzard A, Hutchinson SJ, Kraviecki N. Factors related to adherence to medication regimens in pediatric seizure patients. *J Pediatr Psychol.* 1990;15:543-555.
62. Kinsman RA, Dirks JF, Dahlem NW. Noncompliance to prescribed-as-needed medication use in asthma: usage patterns and patient characteristics. *J Psychosom Res.* 1980;24:97-107.
63. Litt IF, Cuskey WR, Rosenberg A. Role of self-esteem and autonomy in determining medication compliance among adolescents with juvenile rheumatoid arthritis. *Pediatrics.* 1982;69:15-17.
64. Mawhinney H, Spector SL, Heitjan D, Kinsman RA, Dirks JF, Pines I. As-needed medication use in asthma usage patterns and patient characteristics. *J Asthma.* 1993;30:61-71.
65. Roter DL. Patient participation in the patient-provider interaction: the effects of patient question asking on the quality of interaction, satisfaction and compliance. *Health Educ Monogr.* 1977;5:281-315.
66. Mineka S, Watson D, Clark LA. Comorbidity of anxiety and unipolar mood disorders. *Annu Rev Psychol.* 1998;49:377-412.
67. Sturm R, Wells KB. How can care for depression become more cost-effective? *JAMA.* 1995;273:51-58.