Depression Is a Risk Factor for Noncompliance With Medical Treatment

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

M. Robin DiMatteo, PhD; Heidi S. Lepper, PhD; Thomas W. Croghan, MD

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 associations 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.

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MATERIALS AND METHODS

DATA SOURCES AND LITERATURE

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 χ²) 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 χ² 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 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 were analyzed by calculating d effect sizes (for analysis of SD differences) were calculated.45,46

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-

terminate 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
The presence of barriers such as adverse effects and financial constraints, and lack of help and support from family members. 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. This article quantitatively reviews and synthesizes the research assessing the effects of concomitant depression and anxiety on patient adherence to medical treatment recommendations.

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 1. Depression in Medical Patients as a Correlate of Adherence

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Method of Measuring Adherence</th>
<th>Type of Adherence Regimen</th>
<th>Study Definition of Level of Adherence</th>
<th>Measure of Depression</th>
<th>Sample Size</th>
<th>( r ) Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilotcky et al., 1985</td>
<td>Cancer</td>
<td>Medical record</td>
<td>Health behavior regimen</td>
<td>Comparison of consenters and refusers of treatment</td>
<td>Subjective distress</td>
<td>20 Children</td>
<td>–0.48</td>
</tr>
<tr>
<td>Botelho and Dudrak, 1990</td>
<td>General medicine</td>
<td>Pill count</td>
<td>Medication</td>
<td>Pill count (&gt;80% vs ≤80%)</td>
<td>BDI</td>
<td>52 Adults</td>
<td>–0.11</td>
</tr>
<tr>
<td>Brownbridge and Fielding, 1989</td>
<td>ESRD</td>
<td>Patient self-report and physiological assay or test average</td>
<td>Dietary</td>
<td>Care taken and difficulty with treatment and child’s serum urea nitrogen level</td>
<td>Leeds scale for self-assessment of depression in main caregiver and CDI</td>
<td>28 Children</td>
<td>–0.45</td>
</tr>
<tr>
<td>Carney et al., 1998</td>
<td>Angina</td>
<td>Electronic medication monitor</td>
<td>Medication</td>
<td>Days patient removed correct number of pills from electronic monitor, %</td>
<td>BDI</td>
<td>65 Adults</td>
<td>–0.24</td>
</tr>
<tr>
<td>De-Nour and Cozzuk, 1976</td>
<td>ESRD</td>
<td>Physician report</td>
<td>Dietary</td>
<td>Nephrologist’s assessment: good, fair, or poor</td>
<td>Clinical evaluation of depression</td>
<td>32 Adults</td>
<td>–0.45</td>
</tr>
<tr>
<td>Gilbar and DeNour, 1988</td>
<td>Cancer</td>
<td>Medical record</td>
<td>Medication</td>
<td>Continued vs did not continue treatment</td>
<td>BSI: psychosocial distress-depression scale</td>
<td>106 Adults</td>
<td>–0.24</td>
</tr>
<tr>
<td>Katz et al., 1998</td>
<td>ESRD</td>
<td>Physiological assay or test</td>
<td>Dietary</td>
<td>Appropriate levels for serum potassium, serum phosphorus, and IWG</td>
<td>Self-report: depressed in past month</td>
<td>56 Adults</td>
<td>0.00</td>
</tr>
<tr>
<td>Kiley et al., 1993</td>
<td>Renal transplant</td>
<td>Physician report</td>
<td>Health behavior regimen</td>
<td>Physical test of medication levels, IWG, and appointment keeping</td>
<td>CES-D</td>
<td>105 Adults</td>
<td>–0.15</td>
</tr>
<tr>
<td>Lebovits et al., 1990</td>
<td>Breast cancer</td>
<td>Patient self-report</td>
<td>Medication</td>
<td>Doses taken (&gt;90% or ≤90%)</td>
<td>SCL-90: depressive symptom disturbances</td>
<td>37 Adults</td>
<td>–0.32</td>
</tr>
<tr>
<td>Rodríguez et al., 1991</td>
<td>Renal transplant</td>
<td>Medical record</td>
<td>Medication and health behavior regimen</td>
<td>Attend clinic and laboratory, follow diet, take medication, and IWG</td>
<td>Health professional indication of depression in chart review</td>
<td>24 Adults</td>
<td>–0.46</td>
</tr>
<tr>
<td>Schneider et al., 1991</td>
<td>ESRD</td>
<td>Physiological test or assay</td>
<td>Dietary</td>
<td>IWG (&lt;3.0 kg ≥3.0 kg) after fluid restriction</td>
<td>BDI</td>
<td>50 Adults</td>
<td>–0.22</td>
</tr>
<tr>
<td>Taal et al., 1993</td>
<td>Rheumatoid arthritis</td>
<td>Patient self-report</td>
<td>Health behavior regimen</td>
<td>Self-reported adherence problem index</td>
<td>DUTCH-AIMS depression subscale</td>
<td>86 Adults</td>
<td>–0.09</td>
</tr>
</tbody>
</table>

* 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.
adherence 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,46 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.

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,
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 Wells 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

univariate summary analyses are essential to complete before multidimensional models can be constructed).
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.\(^{67}\)

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REFERENCES


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<tr>
<th>Study</th>
<th>Disease</th>
<th>Method of Measuring Adherence</th>
<th>Type of Adherence Regimen</th>
<th>Study Definition of Level of Adherence</th>
<th>Measure of Anxiety</th>
<th>Sample Size</th>
<th>r Effect</th>
<th>Size</th>
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<tbody>
<tr>
<td>Blotckyk et al,(^{47}) 1985</td>
<td>Cancer</td>
<td>Medical record</td>
<td>Health behavior regimen</td>
<td>Comparison of consenters and refusers of treatment</td>
<td>STAI: trait $r = 0.31$; trait $r = -0.56$, averaged for mothers and adolescents</td>
<td>20 Children</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Brownbridge and Fielding,(^{48}) 1989</td>
<td>ESRD</td>
<td>Patient self-report</td>
<td>Dietary and medication</td>
<td>Care taken and difficulty with treatment</td>
<td>Child’s self reported trait anxiety on the Anxiety Inventory for Children</td>
<td>20 Children</td>
<td>-0.64</td>
<td></td>
</tr>
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<td>Carney et al,(^{59}) 1998</td>
<td>Angina</td>
<td>Electronic medication monitor</td>
<td>Medication</td>
<td>Days patient removed correct number of pills from</td>
<td>STAI: state $r = -0.21$; trait $r = 0.18$, averaged</td>
<td>65 Adults</td>
<td>0.01</td>
<td></td>
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<tr>
<td>Christensen et al,(^{58}) 1997</td>
<td>ESRD</td>
<td>Physiological test or assay</td>
<td>Dietary and medication</td>
<td>Serum potassium, serum phosphorus, IWG</td>
<td>STAI-A Trait Anxiety Scale</td>
<td>51 Adults</td>
<td>0.09</td>
<td></td>
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<td>Cockburn et al,(^{60}) 1987</td>
<td>Infection</td>
<td>Pill count</td>
<td>Medication</td>
<td>Deviation from prescribed dosage of medication ($&gt;20%$ vs $\leq 20%$)</td>
<td>Self-report on health state scale of “none, some, moderate, or extreme” anxiety</td>
<td>204 Adults</td>
<td>-0.19</td>
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<td>Hazzard et al,(^{61}) 1990</td>
<td>Seizure disorder</td>
<td>Physiological test or assay</td>
<td>Medication</td>
<td>Adherence ratings by pediatric neurologists based on monthly blood assays</td>
<td>Health anxiety of child and parent (averaged)</td>
<td>35 Children</td>
<td>-0.32</td>
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<tr>
<td>Katz et al,(^{62}) 1998</td>
<td>ESRD</td>
<td>Physiological test or assay</td>
<td>Dietary and medication</td>
<td>Appropriate levels for serum potassium, serum phosphorus, IWG</td>
<td>Self-report: anxious in past month</td>
<td>56 Adults</td>
<td>0.00</td>
<td></td>
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<tr>
<td>Kinman et al,(^{63}) 1980</td>
<td>Asthma</td>
<td>Medical record</td>
<td>Medication</td>
<td>Appropriate use vs overuse, underuse and arbitrary use of medications</td>
<td>MMPI: panic/fear</td>
<td>82 Adults</td>
<td>-0.03</td>
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<tr>
<td>Litt et al,(^{64}) 1982</td>
<td>Rheumatoid arthritis</td>
<td>Physiological test or assay</td>
<td>Medication</td>
<td>Average serum salicylate level over 12 mo</td>
<td>Piers-Harris Self-Concept: Anxiety subscale</td>
<td>36 Children</td>
<td>0.39</td>
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<tr>
<td>Mawhinney et al,(^{65}) 1993</td>
<td>Asthma</td>
<td>Electronic recording</td>
<td>Medication</td>
<td>Appropriate use vs overuse, underuse, and arbitrary use on asthma medication monitor</td>
<td>MMPI: $r = 0.42$; panic/fear $r = 0$, averaged</td>
<td>Children and adults</td>
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<tr>
<td>Roter, 1977</td>
<td>General medical</td>
<td>Medical record</td>
<td>Appointment</td>
<td>Chart records of appointment keeping</td>
<td>Anxiety of patient rated from audiotapes of medical interaction</td>
<td>100 Adults</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Schneider et al,(^{67}) 1991</td>
<td>ESRD</td>
<td>Physiological test or assay</td>
<td>Dietary</td>
<td>IWG $&lt;3.0$ kg (fluid restriction)</td>
<td>STAI: trait</td>
<td>50 Adults</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Taal et al,(^{68}) 1993</td>
<td>Rheumatoid arthritis</td>
<td>Patient self-report</td>
<td>Health behavior regimen</td>
<td>Self-reported adherence problem index</td>
<td>DUTCH-AIMS anxiety subscale</td>
<td>86 Adults</td>
<td>-0.06</td>
<td></td>
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\(^{*}\)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.