

The Psychosocial Context Impacts Medication Adherence After Acute Coronary Syndrome

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Abstract

Background Depression is associated with poor adherence to medications and worse prognosis in patients with acute coronary syndrome (ACS).

Purpose To determine whether cognitive, behavioral, and/or psychosocial vulnerabilities for depression explain the association between depression and medication adherence among ACS patients.

Methods One hundred sixty-nine ACS patients who agreed to have their aspirin adherence measured using an electronic pill bottle for 3 months were enrolled within 1 week of hospitalization. Linear regression was used to determine whether depression vulnerabilities predicted aspirin adherence after adjustment for depressive symptoms, demographics, and comorbidity.

Results Of the depression vulnerabilities, only role transitions (beta=-3.32; $P=0.02$) and interpersonal conflict (beta -3.78; $P=0.03$) predicted poor adherence. Depression vulnerabilities did not mediate the association between depressive symptoms and medication adherence.

Conclusions Key elements of the psychosocial context preceding the ACS including major role transitions and conflict with close contacts place ACS patients at increased risk for poor medication adherence independent of depressive symptoms.

Keywords Medication adherence · Depression · Acute coronary syndrome · Interpersonal conflict · Role transitions

Background

Depression after acute coronary syndrome (ACS; unstable angina and myocardial infarction) is an established risk factor for poor prognosis. ACS patients with elevated depressive symptoms have approximately twice the risk of ACS recurrence or mortality [1–3]. One mechanism postulated to mediate the association between depression and prognosis after ACS is poor adherence to cardiovascular medications. There is a strong, consistent relationship between depression and poor medication adherence in cardiovascular [4, 5] and other medical populations [6]. Even patients with mild depressive symptoms are at risk for poor adherence [4]. Poor adherence to cardiovascular medications has been associated with poor prognosis [7, 8], and in one study, we have shown that poor adherence to aspirin appears to partially mediate the association between depression and prognosis after ACS [9]. Despite the strong association between depression and poor adherence, interventions to improve depressive symptoms have not led to reliable improvements in medication adherence, even when these interventions have successfully reduced depressive symptoms [10, 11]. Accordingly, there is still a need to better understand the association between depression and poor adherence to medications.

Depression is a multifaceted psychological disorder that arises from a combination of genetic, biological, and environmental factors in patients with underlying vulnerabilities [12]. These vulnerabilities can be grouped into behavioral, cognitive, and/or psychosocial elements that predispose individuals to developing depression. We have previously explored the intercorrelations and prevalence of these three categories of vulnerability in post-ACS patients. We showed that the intercorrelations between these vulnerabilities were low and that there was

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a higher prevalence of each vulnerability in depressed as compared to non-depressed patients [13]. Each of these more trait-like vulnerabilities has the potential to influence adherence behavior. For example, patients who are not sufficiently behaviorally activated to schedule pleasurable activities may have low overall motivation for self-care activities including medication adherence. Patients with maladaptive cognitive schema may hold dysfunctional attitudes about the risks and benefits of medications that in turn lead them to not adhere to their regimens. Finally, patients who experience vulnerabilities in their psychosocial milieu either in the form of interpersonal conflicts with their partners or major life events may have lower adherence due to limitations in social support or disruptions in habits that support medication adherence. A better understanding as to which of these underlying depression vulnerabilities is associated with adherence and whether they mediate the effect of depressive symptoms on adherence may inform the development of interventions to improve medication adherence among patients with depression.

Accordingly, we tested the association of depression to medication adherence with and without including depression vulnerabilities in a model predicting medication adherence. We hypothesized that when depression vulnerabilities were added to the model, the association between depression and adherence would be mediated, at least in part, by one or more of the depression vulnerabilities.

Methods

Patients

The current analyses utilized data from the Coronary Psychosocial Evaluation Studies (COPES), a series of multi-site observational cohort studies that concern the relationship between depression and prognosis after ACS [14]. To be included in COPES, patients had to be hospitalized for an ACS and have a score on the Beck Depression Inventory (BDI) of <5 or ≥ 10 , ranges selected to delineate not depressed and depressed status at the time of hospitalization for an ACS. Patients were excluded if they lived in a nursing home, exhibited cognitive impairment, or engaged in alcohol or substance abuse. A subset of patients who were prescribed aspirin had their adherence assessed by an electronic pill cap ($N=172$), and these patients are included here. The study was approved by the Institutional Review Boards at each participating hospital and all patients provided informed consent prior to enrollment and data collection.

Procedure

Details regarding enrollment into COPES have been described elsewhere [5]. Briefly, between May 1, 2003 and April 15, 2005, patients were recruited from three academic hospitals

(Yale-New Haven Hospital and Hospital of St. Raphael in New Haven CT; Mount Sinai Hospital in New York City) within 1 week of hospitalization for an ACS, defined as either acute myocardial infarction (MI) or unstable angina using standard criteria [15]. A cardiologist confirmed ACS eligibility for all patients. In addition to depression eligibility being determined by BDI, patients completed questionnaire assessment of depression vulnerabilities and other key study measures. Upon hospital discharge, patients were provided with a 90-day supply of their prescribed aspirin in a Medication Event Monitoring System (MEMS; APREX Corp, Fremont, CA) bottle. At 3 months follow-up, patients returned the MEMS bottle cap.

Measures

Medication Adherence

The MEMS device contains an electronic chip in the bottle cap that records the date and time whenever the bottle cap is opened. MEMS data were collected continuously over the 3 months following discharge for the index ACS event. The percentage of days the bottle cap was opened the correct number of times (once a day) was calculated.

Depression Vulnerabilities

1. *Cognitive vulnerability.* We used the 24-item version of the Dysfunctional Attitudes Scale (DAS-24) to measure attitudes and beliefs that represent a cognitive vulnerability to depression [16, 17]. Sample items include: “If others dislike you, you cannot be happy” and “If a person asks for help, it is a sign of a weak person”. Items are rated on a seven-point scale ranging from 1 (totally agree) to 7 (totally disagree). Scores were recoded so that higher scores indicate higher levels of cognitive dysfunction. No time period for holding these attitudes is specified for this measure. The measure had good internal consistency (Cronbach $\alpha=0.84$).
2. *Behavioral vulnerability.* We used the 20-item short version of the Pleasant Events Schedule for the Elderly (PES-E) to assess behavioral vulnerability to depression [18]. On the PES-E, participants indicate how frequently they engaged in or had experienced each of 20 pleasant events during the past month. Answer options are 0 (not at all), 1 (1–6 times), and 2 (≥ 7 times). Missing items were coded as “0” if at least 50 % of the 20 items had been answered. Items were recoded so that higher scores indicate infrequency of pleasant events. There was good internal consistency with this measure (Cronbach $\alpha=0.84$).
3. *Psychosocial vulnerability.*
 - (a) *Role transitions.* We generated a list of role transitions based on the Interpersonal Problem Area Rating

Scale [19] to assess social vulnerability to depression. Potential role transitions included geographic move, marriage or cohabitation, separation or divorce, graduation or new job, loss of job or retirement, and health problems other than coronary heart disease. Participants were asked to indicate whether they had experienced any of these events within the past year. They were also asked to name any other significant positive or negative events that had occurred within the past year. Items were summed to provide the total number of role transitions, not including heart disease, in the year prior to the ACS.

- (b) *Interpersonal conflict*. We used questions from the Dyadic Adjustment scale to assess interpersonal conflict [20]. Patients are asked to name the one person closest to them and to rate the extent to which they agreed or disagreed with that person on 15 important issues (e.g., handling finances, making major decisions, friends, or philosophy of life). Answers range from 1 (always disagree) to 6 (always agree). Scores were recoded such that higher scores reflected higher disagreement and a mean score was calculated so long as patients had provided responses to at least six items. The measure had good internal consistency (Cronbach $\alpha=0.92$).

Depressive Symptoms

We measured depressive symptoms using the Beck Depression Inventory (BDI) [21]. The BDI consists of 21 items describing cognitive-affective and somatic depression symptoms. Patients rate the extent to which each symptom had been present in the prior week on a four-point scale (0–3). The BDI has been used in prior studies of depression and ACS, and elevated scores predict shorter post-ACS event-free survival [22]. A score ≥ 10 is consistent with at least mild to moderate depression. The BDI had good internal reliability (Cronbach $\alpha=0.90$) in our sample.

Covariates

Baseline demographics and clinical variables, including the constituents of the Charlson comorbidity index, a validated measure of risk for death in patients with chronic illness [23], were obtained by patient interview and chart abstraction at the time of enrollment.

Analytic Plan

In cases of partial missing data on depression vulnerability scales, total scores were imputed from the subset of answered questions using a regression-based approach so long as the total R -squared of the regression equation predicting the total

score was $>75\%$. This approach led to three participants missing data on the Dyadic Disagreement scale. One of these three participants was also missing data pertinent to role transitions. Only patients with data for all of the vulnerabilities were included in these analyses such that the total sample was comprised of 169 patients.

As per convention in cardiovascular adherence studies, patients were defined as poor adherers if they took their aspirin correctly on fewer than 80 % of days monitored [24]. Patient characteristics were then compared according to adherence status, using chi-squared tests for proportions and t tests for normally distributed continuous variables. Homogeneity of variance was assessed when determining whether data was normally distributed. In cases where continuous variables were not normally distributed, data transformation (e.g., square-root transformation) was applied. Mann–Whitney test was used to compare role transitions, the DAS, and Charlson scores as transforming these data did not fit a normal distribution.

Linear regression was used to determine whether depression vulnerabilities were significantly associated with a continuous measure of adherence. In the first step, sociodemographics (age, gender, race, partner status), comorbidity (Charlson), and depressive symptoms (BDI score) at baseline were entered into the model. Depression vulnerabilities were then entered individually. We also tested a model in which the depression vulnerabilities were entered concurrently. As the distribution of medication adherence was negatively skewed, we performed a sensitivity analysis in which we transformed our measure of adherence to a measure of non-adherence (i.e., 1—adherence) and then applied a square-root transformation such that our dependent variable (adherence) approached a normal distribution. There were no differences in the pattern of association between depressive symptoms and depression vulnerabilities with medication adherence when we transformed the adherence variable. Accordingly, for ease of interpretability, we only present data for the untransformed measure of adherence. We used Preacher and Hayes' bootstrap method with 1,000 bootstrap samples to determine whether the depression vulnerabilities, as a group, mediated the association between depressive symptoms and medication adherence [25]. Two-tailed probability levels are reported for all analyses. All statistical analyses were performed using SPSS 20 (Chicago, Inc.).

Results

The mean age of participants was 59 years, 44 % were women, 86 % were white, and 65 % had a partner or spouse. The majority of participants were hospitalized for a myocardial infarction (26 % ST elevation myocardial infarction; 33 % non-ST elevation myocardial infarction, 41 % unstable angina). Twenty-seven percent of participants had a prior history of MI. Thirty percent had a prior history of depression and 20 %

Table 1 Association between sociodemographics, comorbidities, and depression vulnerabilities with adherence to aspirin

Characteristic	Poor adherence ($<80\%$) $N=38$	Good adherence ($\geq 80\%$) $N=131$	P value
Age, mean (SD), years	58.5 (11.2)	59.5 (12.4)	0.64
Female, %	52.6	41.2	0.21
White, %	78.9	88.5	0.13
Partner, %	63.2	65.6	0.78
Prior myocardial infarction, %	42.1	22.6	0.02
Charlson score, mean (SD)	1.6 (1.4)	1.2 (1.5)	0.05 ^a
Prior history of depression, %	43.6	25.6	0.03
Depressed during ACS hospitalization ($BDI \geq 10$), %	63.2	40.5	0.01
Number of role transitions, mean (SD)	1.3 (1.2)	0.7 (0.9)	0.01 ^a
Interpersonal conflict (Dyadic Adjustment Scale), mean (SD)	2.5 (1.1)	2.1 (0.7)	0.06 ^a
Cognitive vulnerability (Dysfunctional Attitudes Scale), mean (SD)	76.0 (18.5)	78.7 (22.0)	0.48
Behavioral vulnerability (Pleasant Events Scale for the Elderly), mean (SD)	0.3 (0.3)	0.3 (0.2)	0.47 ^b

For the Pleasant Events Scale for the Elderly scale, scores were recoded so that higher scores indicate infrequency of pleasant events. Higher scores on vulnerability scales indicate increased vulnerability. All displayed descriptive statistics represent values before any transformations were applied to the scales. Chi-squared tests were used to compare proportions and t tests were used to compare differences in continuous measures except where specified otherwise

BDI Beck Depression Inventory, *SD* standard deviation, *ACS* Acute Coronary Syndrome

^a Scores were square-root-transformed prior to performing the t test

^b Mann–Whitney test used for comparison

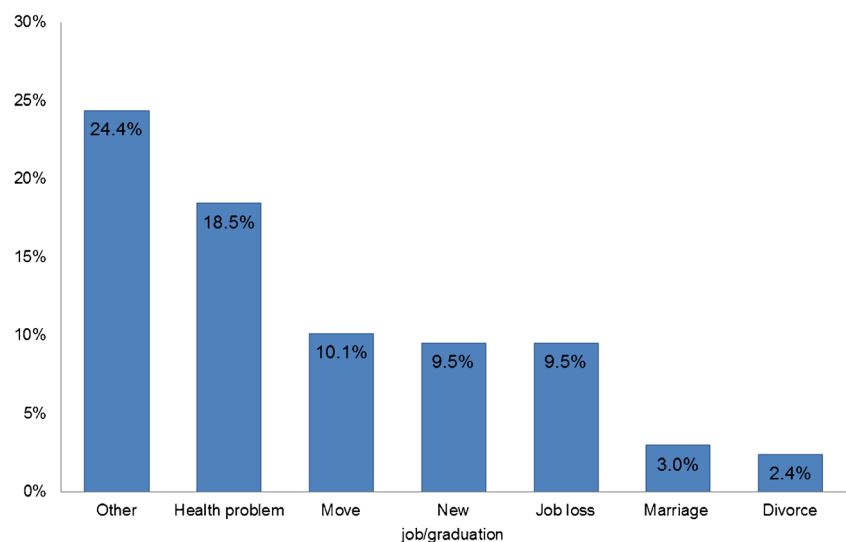
of participants were prescribed antidepressants at discharge. The majority of the sample had minimal depressive symptoms during ACS hospitalization (54 % with $BDI < 5$), 27 % had mild to moderate depressive symptoms ($BDI 10–18$), and 19 % had moderate to severe depressive symptoms ($BDI \geq 19$). Poor adherence to aspirin (took aspirin correctly on $<80\%$ of days) was observed for 23 %. There were no significant differences in sociodemographic characteristics between patients who had poor ($<80\%$) and good ($\geq 80\%$) adherence to aspirin (Table 1). Compared to patients with good adherence, patients with poor adherence had increased comorbidity as measured by the Charlson score (1.6 SD 1.4 versus

1.2 SD 1.5, $P=0.05$) and poor adherers were more likely to be depressed (BDI score ≥ 10 ; 63 % versus 41 %, $P=0.01$).

Depression Vulnerabilities

There was low correlation between our measures of depression vulnerabilities (correlation coefficients ranged from -0.07 to 0.21). In bivariate analyses (Table 1), there was a higher mean number of role transitions in the year prior to the ACS in patients with poor adherence as compared to patients with good adherence (1.3 SD 1.2 versus 0.7 SD 0.9; $P=0.01$).

Fig. 1 Prevalence of role transitions in prior year among post-acute coronary syndrome patients ($N=168$) (other major role transitions included events such as death or new major illness in a close family member or friend, arrival of a new child or grandchild, and arrival or departure of someone from the household)



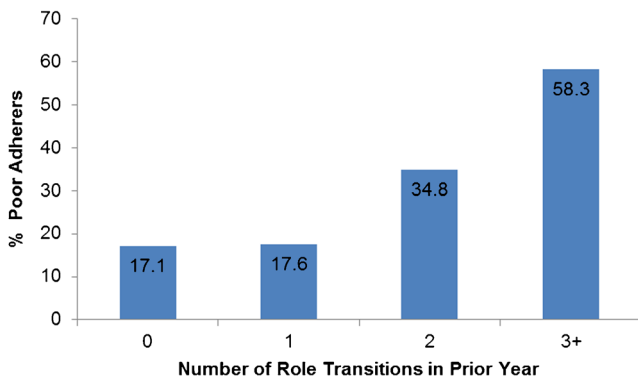


Fig. 2 Graded association between number of role transitions and percentage of patients with poor adherence (<80 %) to aspirin after acute coronary syndrome

There was also a trend toward the measure of interpersonal conflict (Dyadic Adjustment scale) being associated with poor medication adherence ($P=0.06$). In contrast, there were no significant associations between dysfunctional attitudes or infrequency of pleasant events with medication adherence ($P=0.47$ and $P=0.48$, respectively).

The prevalence of different types of role transitions is shown in Fig. 1. The most common role transitions included a new major health problem other than their cardiovascular disease, a geographic move, a new job or graduation, and a job loss or retirement. Overall, there was a higher prevalence of increased role transitions (>1) among patients with poor adherence as compared to patients with good adherence (41.0 versus 16.5 %, $P=0.001$). Further, there was a graded association between the number of role transitions in the prior year and prevalence of poor adherence (Fig. 2).

In a model predicting aspirin adherence that included sociodemographics, comorbidity, and depressive symptoms, only depressive symptoms predicted poor medication adherence (Table 2). When the depression vulnerabilities were individually added to the model, only role transitions and interpersonal conflict significantly predicted medication adherence. In the model that included all the depression vulnerabilities simultaneously, both role transitions (beta coefficient (SE) -3.32 (1.38); $P=0.02$) and interpersonal conflict (beta coefficient (SE) -3.78 (1.74); $P=0.03$) were associated with poor medication adherence, whereas dysfunctional attitudes and infrequency of pleasant events were not. The beta coefficient for the contribution of depressive symptoms to adherence changed little (from -0.40 to -0.42) when all of the depression vulnerabilities were added to the model. A formal test of mediation using Preacher and Hayes’ bootstrap approach confirmed that there was no significant mediation by depression vulnerabilities of the effect of depressive symptoms on aspirin adherence after ACS.

Table 2 Predictors of adherence to aspirin after acute coronary syndromes ($N=169$)

Characteristic	Model 1 beta (SE)	P value	Model 2a odds ratio beta (SE)	P value	Model 2b beta (SE)	P value	Model 2c beta (SE)	P value	Model 2d beta (SE)	P value	Model 3 beta (SE)	P value
Beck Depression Inventory score	-0.40 (0.17)	0.02	-0.38 (0.17)	0.03	-0.32 (0.17)	0.07	-0.49 (0.18)	0.007	-0.41 (0.20)	0.04	-0.42 (0.20)	0.04
Number of role transitions	—	—	-3.43 (1.38)	0.01	—	—	—	—	—	—	-3.32 (1.38)	0.02
Interpersonal conflict	—	—	—	—	-3.65 (1.74)	0.04	—	—	—	—	-3.78 (1.74)	0.03
Dysfunctional attitudes	—	—	—	—	—	—	0.10 (0.07)	0.17	—	—	0.12 (0.07)	0.08
Lack of pleasant events	—	—	—	—	—	—	—	—	0.61 (7.02)	0.93	1.67 (6.91)	0.81

SE standard error

All models were additionally adjusted for age, gender, race, partner status, and Charlson score; none of these covariates were significantly associated with aspirin adherence (all $P>0.1$)

Model 1 tests the extent to which depressive symptoms predicted aspirin adherence in the 3 months after hospitalization for an acute coronary syndrome; adjusted $R^2=0.03$

Models 2a–2d test the extent to which depressive symptoms predicted aspirin adherence in the 3 months after hospitalization for an acute coronary syndrome after accounting for each depression vulnerability, individually

Model 3 tests the extent to which depressive symptoms predicted aspirin adherence in the 3 months after hospitalization for an acute coronary syndrome after accounting for all of the depression vulnerabilities concurrently; adjusted $R^2=0.08$

Discussion

The psychosocial context up to 1 year prior to an ACS—as measured by interpersonal conflict and the number of major role transitions—was associated with lower adherence to aspirin after ACS even after accounting for depressive symptoms, sociodemographics, and comorbidity characteristics. These findings expand upon prior literature showing that psychosocial factors play an important role in the way patients take their cardiovascular medications [26]. Prior studies have found an association between major life events and adherence to medications prescribed for medical illnesses including hypertension and human immunodeficiency virus [27–29]. Furthermore, when considered alongside the finding that a measure of interpersonal conflict also predicted worse adherence, the current study demonstrates that among the potential depression vulnerabilities, psychosocial factors may be the most impactful on medication adherence.

According to interpersonal theory, the psychosocial factors we measured—major role transitions and interpersonal conflict—have the potential to cause emotional distress, and this distress compromises a patients' ability to handle social roles, which puts them at even more risk for further negative events [30, 31]. The mechanism(s) by which these interpersonal factors place patients at risk of poor medication adherence remains unknown, but we speculate that this cycle of distress leads to deficits in social support and an inability to maintain healthy habits such as medication adherence. Both social support and habit strength have been associated with medication adherence in prior studies [32–36].

Interestingly, adding depression vulnerabilities to the model predicting medication adherence did not significantly reduce the association between depressive symptoms and medication adherence and our formal test of mediation confirmed that there was no mediation by these factors. This finding suggests that the measured psychosocial depression vulnerabilities (interpersonal conflict and major role transitions) impact medication adherence independent of depressive symptoms. Holt and colleagues similarly found that major life events, a measure of psychosocial depression vulnerability similar to our measure of role transitions, were associated with lower adherence to antihypertensive medications independent of depression [27].

In contrast with psychosocial factors, demographic factors were not associated with medication adherence. This result is consistent with multiple studies that have shown demographic factors to have little role in predicting who will be adherent to medications [37, 38].

A major strength of this study includes its use of the gold-standard measure of medication adherence—electronic measurement—and the careful collection of detailed information regarding psychological characteristics among patients with cardiovascular disease. There were also several limitations

including a small sample size and the abbreviated range in depression symptoms for study participants (BDI scores of 5–9 excluded). Furthermore, the study only measured adherence to aspirin—hence the impact of these depression vulnerabilities on adherence to the full post-ACS medication regimen remains unknown.

Implications

The current findings highlight the potential importance for clinicians to assess the psychosocial milieu among post-ACS patients as a means of ascertaining risk of poor adherence to medications. Clinicians taking care of ACS patients should be mindful of obtaining histories about the psychosocial context that preceded the ACS event. A particular focus on recent major life transitions and interpersonal conflict with key members of the patient's social network may alert clinicians to the potential for adherence problems. Future studies should seek to clarify the mechanisms through which role transitions and interpersonal conflict impact medication adherence. Interventions that focus on the resolution of interpersonal conflict and on the promotion of positive adjustment to role transitions should be formally evaluated to determine whether they can improve adherence to medications in the post-ACS setting. Approaches that seek to increase the automaticity of medication-taking behaviors may also be worth testing as they may help patients become more resilient to challenges from the psychosocial environment [39].

Conflict of Interest Statement The authors have no conflicts of interest to disclose.

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