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Depressive symptoms, health-related quality of life, and cardiac event-free survival in patients with heart failure: a mediation analysis

Kyoung Suk Lee · Terry A. Lennie · Jia-Rong Wu · Martha J. Biddle · Debra K. Moser

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Abstract
Purpose Health-related quality of life (HRQOL) and depressive symptoms both are associated with an adverse prognosis in heart failure (HF), although their associations with outcomes have been examined only in isolation. Therefore, it is unknown how HRQOL and depressive symptoms might interact in their associations with outcomes. The present study was conducted to determine whether the association between HRQOL and cardiac event-free survival is mediated by depressive symptoms in HF patients given that depressive symptoms are associated strongly with HRQOL.
Methods A total of 209 HF patients (61 ± 11 years, 24 % female, 49 % NYHA III/IV) participated. The Minnesota Living with HF Questionnaire and the Patient Health Questionnaire-9 were used to measure HRQOL and depressive symptoms, respectively. Patients were followed for a median of 357 days to determine cardiac event-free survival.
Results In Cox regression analysis, HRQOL [hazard ratio (HR) 1.013; 95 % confidence interval (CI) 1.001–1.026] and depressive symptoms (HR 1.075; 95 % CI 1.025–1.127) predicted cardiac event-free survival separately, controlling for demographic and clinical variables. HRQOL independently explained 38.7 % of the variance in depressive symptoms ($p < 0.05$; standardized $\beta = 0.695$) in a multiple regression. When HRQOL and depressive symptoms were entered in the model simultaneously, only depressive symptoms independently predicted cardiac event-free survival (HR 1.068; 95 % CI 1.001–1.139), demonstrating a mediation effect of depressive symptoms.
Conclusions Depressive symptoms mediated the relationship between HRQOL and cardiac event-free survival. Interventions targeting HRQOL to enhance patient outcomes must also address patient depressive symptoms to be fully efficacious.

Keywords Depressive symptoms · Health-related quality of life · Survival · Heart failure

K. S. Lee (✉)
School of Nursing, K6/342 Clinical Sciences Center, University of Wisconsin-Madison, 600 Highland Ave., Madison, WI 53792-2455, USA
e-mail: kslee4@wisc.edu

T. A. Lennie · M. J. Biddle · D. K. Moser
College of Nursing, University of Kentucky, Lexington, KY, USA

J.-R. Wu
University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Introduction

Heart failure (HF) is a prevalent and growing health concern that affects more than 5.1 million adults in the United States [1]. It is expected that the prevalence of HF will increase by 25 % from 2013 to 2030 [1]. Among Medicare beneficiaries from two large HF registries, 3-month and 1-year rehospitalization rates were 40 and 65 %, respectively [2]. In the same study, the 1-year post-discharge mortality rate was 34 % [2]. Despite medical advances, the poor prognosis from HF has not changed substantially [1].

Health-related quality of life (HRQOL) is a multidimensional, subjective construct, illustrating how an illness and its treatment affect not only the physical aspects, but also psychological, social, and economic aspects of a person's life [3, 4]. People with HF experience poorer HRQOL compared to people without HF [5–7]. HRQOL is

an important factor in the prediction of mortality and hospitalization in HF, even after adjusting for disease severity [4, 8–10]. However, little is known about the potential mechanism linking HRQOL with HF prognosis.

Patients who have negative views on the consequences of illness may experience depressed mood [4, 11]. Poor HRQOL is associated with the development of depressive symptoms in patients with HF [11]. Depressive symptoms are associated with an adverse prognosis in HF [12–14]. According to a recent meta-analysis, patients with depressive symptoms have a greater than two times higher risk of death and associated cardiac events (e.g., heart transplantation and new cardiac events) than patients without depressive symptoms [15].

Because many previous researchers have examined the impact of HRQOL and depressive symptoms on prognosis in HF in isolation from each other, little is known how these factors are related to each other in the context of predicting morbidity and mortality. Murberg et al. [16] demonstrated that the prognostic value of the physical aspect of HRQOL on death disappeared in the presence of depressed mood. This suggests that depressive symptoms may be a mediator of the relationship between HRQOL and survival in HF. Therefore, we conducted a study to examine the role that depressive symptoms play in the association of HRQOL with cardiac event-free survival. The specific aim was to determine whether depressive symptoms mediate the relationship between HRQOL and cardiac event-free survival.

Methods

Design, setting, and participants

The investigation was a longitudinal, prospective examination. Patients were enrolled from the outpatient settings of multiple large community hospitals and academic medical centers in the United States. Criteria for eligibility for this study were as follows: (a) confirmed diagnosis of HF from a cardiologist with either preserved or non-preserved systolic function; (b) stable HF medication regimen at the time of study participation; (c) free of obvious cognitive impairment (e.g., inability to provide informed consent or to complete short interviews and questionnaire packets); and (d) adequate English comprehension. Patients were excluded if they had valvular heart disease as an etiology of their HF, had a myocardial infarction within the previous 3 months, were referred for heart transplantation, or had major life-threatening comorbidities, such as end-stage renal or liver disease.

Procedure

This study was approved by the Institutional Review Boards at the each participating institution. Patients with HF were referred by their nurses and physicians to the investigators. Eligible patients were contacted by research nurses who had special expertise in cardiac care. Signed informed consent was obtained by research nurses from patients who agreed to participate after detailed explanation of the study. Sociodemographic and clinical data were collected by medical record review and interview. Data on patients' HRQOL, depressive symptoms, and comorbidity burden were collected using structured questionnaires. Follow-up was conducted over a median of 357 days (interquartile range 161–441 days) to determine patients' outcomes. Cardiac event-free survival was defined as time to first cardiac event that included death, hospitalization, or emergency department (ED) visit for cardiac reasons.

Measures

Health-related quality of life

Health-related quality of life was measured using the Minnesota Living with Heart Failure Questionnaire (MLHFQ), a disease-specific instrument [17]. The MLHFQ consists of 21 items which measure patient perceptions of the impact of HF and treatment on physical (8 items), psychological (5 items), and social (8 items) aspects of their life. Patients rate items with a scale from 0 (no effect) to 5 (great effect). The total scores can range from 0 to 105, with lower scores indicating better HRQOL. The MLHFQ has been extensively used in HF research, and reliability and validity of the instrument have been established [18, 19].

Depressive symptoms

The level of depressive symptoms was measured using the Patient Health Questionnare-9 (PHQ-9), which was developed using criteria for depression from the Diagnostic and Statistical Manual of Mental Disorders (4th ed) [20]. The PHQ-9 includes 9 items rated on a 4-point Likert scale from 0 (not at all) to 3 (nearly every day). The scores are summed and range from 0 to 27; a lower score reflects lower levels of depressive symptoms. Depression severity was categorized into minimal (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), or severe (20 or greater) depressive symptoms. The reliability and validity have been demonstrated in the various populations including patients with cardiovascular disease including HF [20–23].

Cardiac events

The end points evaluated in this study included ED visit due to HF exacerbation, hospitalization for cardiac reasons, or cardiac-related mortality. Patients or their family received monthly telephone follow-up calls in which they were asked to report any ED visits, hospitalizations, or death. Their responses were confirmed by review of medical records and/or death certificates.

Demographic and clinical variables

Age, gender, living arrangement, body mass index (BMI), total comorbidity scores using Charlson Comorbidity Index [24], New York Heart Association (NYHA) functional class, etiology of HF, and prescribed medications were collected through patient interview and medical record review. NYHA functional class was determined by research nurses via a structured patient interview.

Statistical analyses

We analyzed data using SAS 9.3 for Windows (SAS Institute, Inc., Cary, North Carolina). Descriptive statistics were presented as means with standard deviations or frequencies with percentages to describe patient characteristics. Survival curve for cardiac event in the total sample was generated with the Kaplan–Meier method.

Mediation analyses were conducted based on the steps proposed by Baron and Kenny [25] in order to examine whether depressive symptoms (mediator) mediated the association between HRQOL (independent variable) and cardiac event-free survival (outcome variable) after controlling for covariates (i.e., age, gender, ethnicity, NYHA class, and etiology of HF). The strategy uses four steps to determine mediation. In the first step, the relationship between HRQOL and cardiac event-free survival was tested using Cox proportional hazards regression. In the second step, the relationship between HRQOL and depressive symptom scores was tested using multiple linear regression. In the third step, the relationship between depressive symptom scores and cardiac event-free survival was tested using Cox proportional hazards regression. In the fourth step, HRQOL and depressive symptom scores were entered simultaneously as independent variables to test their impact on cardiac event-free survival. A mediation effect of depressive symptoms is considered present if: (a) depressive symptoms predicted cardiac event-free survival in the presence of HRQOL and (b) HRQOL was a predictor of cardiac event-free survival in the first step, but not in the fourth step in the presence of depressive symptoms. Assumptions of multiple linear regression (e.g., multicollinearity) and Cox proportional hazard regression were tested, and there were no violations.

Table 1 Sample characteristics ($N = 209$)

Characteristics	Mean ± SD or *N* (%)
Age, years	61 ± 11
Female	51 (24 %)
Caucasian	168 (80 %)
Living arrangement	
Living alone	61 (29 %)
Living with others	148 (71 %)
Highest education achieved	
≤High school	96 (46 %)
Above high school	112 (54 %)
Charlson comorbidity Index	3 ± 2
Ischemic etiology of heart failure	157 (75 %)
Ejection fraction (%) ($n = 198$)	33 ± 13
NYHA class	
I/II	107 (51 %)
III/IV	102 (49 %)
Body mass index (kg/m^2)	31 ± 7
Health-related quality life scores	39 ± 25
Depressive symptom scores	6 ± 6
ACE I or ARB	171 (82 %)
Beta blocker	184 (88 %)

NYHA New York Heart Association functional class, *ACE I* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blocking agents

Results

Sample characteristics

Patients ($N = 209$) were primarily male, Caucasian, and had an ischemic HF etiology (Table 1). The number of patients was evenly distributed between NYHA functional classes I/II and III/IV (51 vs. 49 %). The mean score of the MLHFQ was 39 (SD: 25) with a range of 0–96, which indicates moderately good HRQOL [26]. Scores of depressive symptoms ranged from 0 to 24 with an average of 6 (SD 6). Of the 209 patients, 23.4 % of patients (49/209) were categorized as having moderate to severe levels of depressive symptoms (PHQ-9 scores 10 or greater) (Fig. 1). A total of 56 of 209 patients died for cardiac reasons (4/209) or had at least one cardiac-related admission (47/209) or ED visit due to HF (5/209) (Fig. 2).

Mediation analyses

Cardiac event-free survival and HRQOL (first step)

HRQOL scores were an independent predictor of cardiac event-free survival after controlling for covariates (Fig. 3). Every one point increase in HRQOL, indicating worse

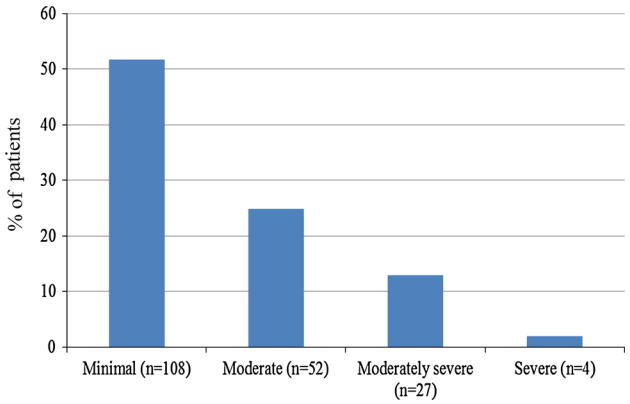

Fig. 1 Levels of depressive symptoms ($N = 209$)

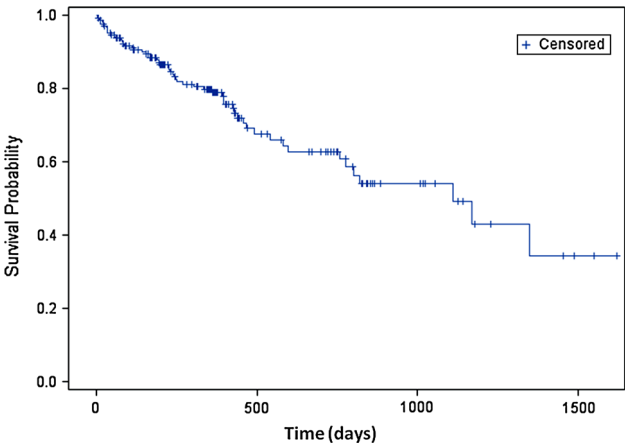

Fig. 2 Kaplan–Meier survival curve for cardiac event ($N = 209$)

HRQOL, was associated with a 1.3 % increase in risk of a cardiac event [hazard ratio (HR) 1.013; 95 % confidence interval (CI) 1.001–1.026].

Depressive symptoms and HRQOL (second step)

HRQOL scores independently predicted depressive symptom scores. HRQOL alone explained 38.7 % of the variance in depressive symptoms ($p < 0.05$; standardized $\beta = 0.695$).

Cardiac event-free survival and depressive symptoms (third step)

Depressive symptom scores were an independent predictor for cardiac event-free survival after controlling for covariates. Each one point increase in depressive symptom scores, indicating higher levels of depressive symptoms, was associated with a 7.5 % increase in risk of a cardiac event (HR 1.075; 95 % CI 1.025–1.127).

Cardiac event-free survival, HRQOL, and depressive symptoms (fourth step)

Depressive symptom scores remained a significant predictor of cardiac event-free survival (HR 1.068; 95 % CI 1.001–1.139) when scores of HRQOL and depressive symptoms were simultaneously entered in the model to predict cardiac event-free survival (Table 2). In contrast, HRQOL scores no longer predicted cardiac event-free survival in the presence of depressive symptom scores. Therefore, the mediation analyses indicated that depressive symptom scores mediated the effect of HRQOL on cardiac event-free survival (Table 2).

Additional analysis

To determine the possibility that HRQOL was a mediator, we treated depressive symptoms as an independent variable. Depressive symptoms independently predicted HRQOL scores ($p < 0.05$; standardized $\beta = 0.633$) after adjusting for the same covariates used in the main mediation analyses. However, HRQOL scores did not predict cardiac event-free survival in the company of depressive symptom scores ($p > 0.05$). Therefore, HRQOL did not mediate the relationship between depressive symptoms and cardiac event-free survival.

Discussion

HF is a chronic condition that influences patient's HRQOL because it has an unpredictable prognosis and high symptom burden [27, 28]. We found that HRQOL predicted cardiac event-free survival. Although similar findings have been reported in previous studies [4, 8–10], the mechanism by which HRQOL may affect cardiac event-free survival is not well understood. In this study, we found that depressive symptoms mediated the relationship between HRQOL and cardiac event-free survival in HF.

HRQOL is an important factor that should be addressed in HF management. Patients must learn how to live with HF given the irreversible and chronic nature of HF. Patients have reported a preference for improved HRQOL as a preferred therapeutic goal rather than longer survival [29]. Although poor HRQOL was consistently observed at the initial assessment in both in- and outpatient settings, HRQOL improves over time [8, 10]. Lupon et al. [20] conducted a longitudinal observational study in which a total of 1,151 patients with HF were followed for 6 years with an annual evaluation of HRQOL. Patients who died in the 1-year follow-up period after any HRQOL assessment reported worse HRQOL than patients who survived [20]. This finding suggests that diminished HRQOL is a warning of worsening prognosis [20].

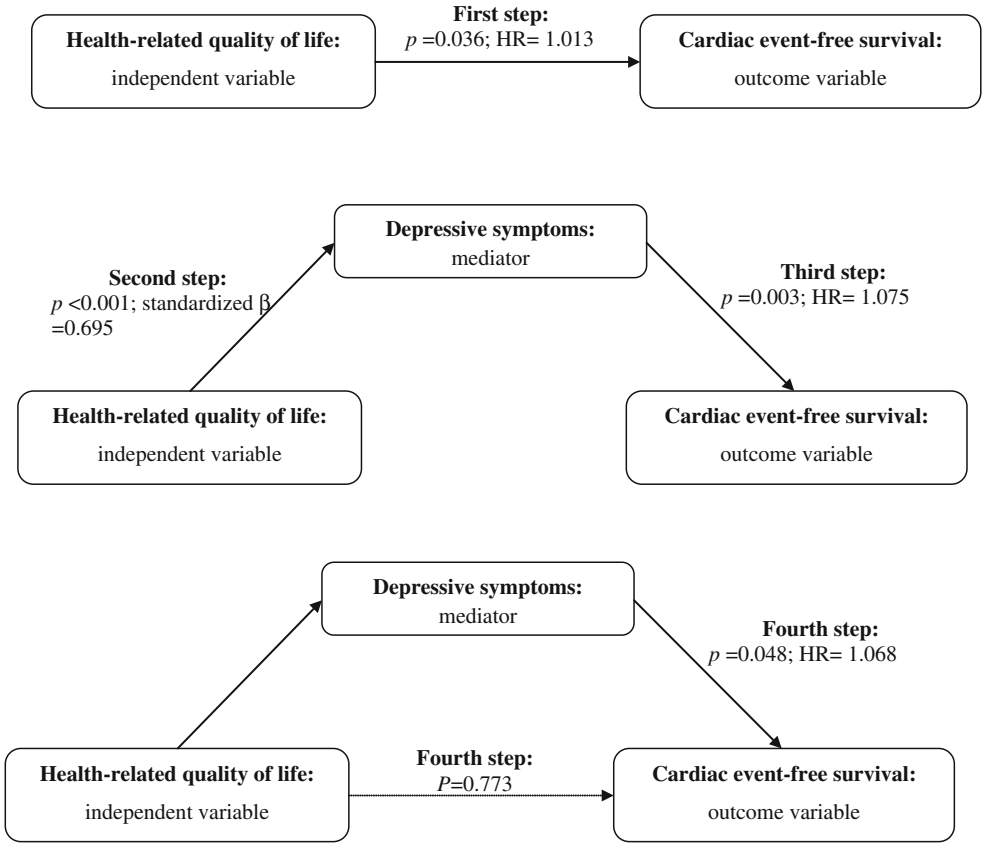

Fig. 3 Mediation analysis ($N = 209$). *Note HR* hazard ratio

Table 2 Mediation effect of depressive symptoms on the relationship between health-related quality of life and cardiac event-free survival ($N = 209$)

	Hazard ratio	*p* value	95 % confidence interval
Age, years	1.003	0.779	0.980–1.028
Female	0.584	0.145	0.283–1.203
Caucasian (vs. minority)	0.394	0.001	0.197–0.788
NYHA class III/IV (vs. I/II)	1.036	0.912	0.552–1.946
Ischemic etiology of heart failure (vs. non-ischemic)	2.001	0.077	0.927–4.367
Health-related quality life scores	1.002	0.773	0.986–1.019
Depressive symptom scores	1.068	0.048	1.001–1.139

Cardiac event = the composite of cardiac death, hospitalization for cardiac reasons, or emergency department visit for heart failure exacerbation

NYHA New York Heart Association functional class

Approximately one-third of HF patients experience clinically significant depressive symptoms [15]. Levels of depressive symptoms decrease over time in patients with HF who were depressed at discharge [30–32]. In the study of Johansson et al. [32], 61 % of the HF patients with depressive symptoms at discharge demonstrated remission of depressive symptoms at 18 months after discharge. In a study in which community-dwelling older adults were followed for up to 4 years, scores of depressive symptoms showed a curvilinear trend; depressive symptom scores decreased for the first 2 years and increased for the next 2 years [33]. The same study also showed that self-rated health status was significantly associated with the trajectory of depressive symptoms in older adults [33].

Depression is associated with functional impairment and mortality as well as poor HRQOL in HF [11–14, 34–36]. Changes in depressive symptom status (e.g., persistent depression and new onset of depression) over 3 or 6 months were associated with 1-year HRQOL in patients with HF [35]. Baseline HRQOL predicted the new onset of depressive symptoms among patients with HF [11]. In qualitative studies, patients with HF report that limited physical ability due to HF symptoms results in changes in their lifestyle and relationships with friends and family, which leads them to feeling depressed [37, 38].

From these previous studies, one may question whether depressed mood is a reflection of impaired HRQOL or, conversely, whether diminished HRQOL is a result of

depressive symptoms. Some investigators suggest a bidirectional relationship between HRQOL and depressive symptoms [39]. Interventions designed to improve HRQOL also influence depressive symptoms [40] or vice versa [41]. Gellis et al. [42] demonstrated that an intervention aimed at improving quality of care effectively enhanced HRQOL and depressive symptoms among homebound older adults with HF or chronic obstructive pulmonary disease. We were not able to determine the directionality of the association between HRQOL and depressive symptoms because we assessed HRQOL and depressive symptoms at baseline simultaneously. However, we did additional analyses that showed HRQOL did not mediate the relationship between depressive symptoms and cardiac event-free survival.

How does a subjective concept of HRQOL impact adverse prognosis in HF? We found a mediational role of depressive symptoms in the relationship between HRQOL and survival. There are two potential pathways to explain how depressive symptoms can mediate the relationship between HRQOL and survival: biological and behavioral pathways. Overexpression of bioactive molecules (e.g., cytokines) is considered to play an important role in the pathogenesis and clinical course of HF. Increased levels of inflammatory markers, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), have been found in patients with HF and are associated with clinical status (e.g., NYHA functional class) and poor survival [43, 44]. Elevated inflammatory activation is observed in patients who have poor HRQOL [9, 30]. Mommersteeg et al. [30] demonstrated that levels of inflammatory markers at 1 year were related to HRQOL at baseline and changes in HRQOL between baseline and 1 year, independent of disease severity. Similarly, previous researchers found that the relationship between depressive symptoms and poor survival was attributed to increased inflammatory response [31, 45]. Therefore, elevated inflammatory activation may be a pathophysiological commonality among HRQOL, depressive symptoms, and prognosis in HF and explain their relationship.

A behavioral mechanism may provide another explanation for the mediation effect of depressive symptoms on the association between HRQOL and survival. The negative view resulting from HF contributes to an increase in emotional distress including depressive symptoms [46]. Havranek et al. [11] demonstrated that compromised HRQOL at baseline was significantly associated with the development of depressive symptoms at 1 year among HF patients who did not have depressive symptoms at baseline. Patients with depressive symptoms are less likely to engage in recommended therapeutic regimens, such as low sodium diet [47, 48], which may attribute to adverse outcomes [49, 50].

Findings of our study consistently highlight the importance of depressive symptom management. In a large randomized controlled trial in which effects of a selective serotonin reuptake inhibitor (i.e., sertraline) on depressives symptoms and prognosis were investigated among HF patients, sertraline therapy did not significantly improve both outcomes compared to placebo [51]. However, positive effects of an exercise training program on depressive symptoms, HRQOL (measured with the Kansas City Cardiomyopathy Questionnaire), and survival have been demonstrated in a large randomized controlled trial (A Controlled Trial Investigating Outcomes of Exercise Training: HF-ACTION) [52–54].

Among covariates included in the model (Table 2), being a non-Caucasian was a risk factor for poor cardiac event-free survival. Non-Caucasian ethnic groups with HF are at a higher risk of rehospitalization compared with their Caucasians counterparts [55, 56]. African Americans had a longer time to seek care for escalating HF symptoms than Caucasians [56]. Evangelista et al. [56] suggested several reasons for racial disparity in HF hospitalization rates, including different etiology of HF, inadequacy of symptom recognition ability, and differences in adherence to recommended regimens.

The current study has several limitations. We measured HRQOL and depressive symptoms in a cross-sectional fashion, which limited our ability to determine directionality of those two variables (e.g., reverse or reciprocal causation). Although our additional analyses indicated that HRQOL did not mediate the relationship between depressive symptoms and cardiac event-free survival, caution is needed in interpretation of the result. We might test associations among the variables instead of causation or medication because HRQOL and depressive symptoms were cross-sectional data. Although mediation analyses based on cross-sectional data are widely used to calculate direct or indirect effects of variables, estimates may be biased [57]. Therefore, longitudinal studies are necessary to determine the directional association between HRQOL and depressive symptoms and to calculate unbiased estimations of direct and indirect effects.

Conclusion

Poor HRQOL predicted cardiac event-free survival over a median follow-up of 357 days in patients with HF. Depressive symptoms mediated the relationship between HRQOL and cardiac event-free survival. The results of this study suggest that close attention needs to be paid to depressive symptoms in patients with HF. It is recommended that interventions targeting HRQOL to enhance

patient outcomes also address patient depressive symptoms in order to be fully effective.

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