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Depression and Pain in Heart Transplant Recipients: An Observational Study

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Abstract

Characterizing how physical and psychological symptoms interact in heart transplant recipients may lead to advances in therapeutic options. This study examined associations between pain and major depression. **Method:** A cross-sectional study was conducted with adult heart transplant recipients. Pain was measured with the bodily pain domain of the Short Form-36 Health Survey and psychological distress with the Kessler Psychological Distress Scale (K-10). The Mini International Neuropsychiatric Interview, version 6.0, was used to identify participants meeting the criteria for major depression. Hierarchical linear regression was used to determine if there was an association between pain and major depression, controlling for pharmacological treatment of depression, severity of psychological distress, and clinical characteristics including immunosuppression medication which may induce pain as a side effect. **Results:** Average pain score of the 48 heart transplant recipients was 43 ($SD \pm 10$, range 0–100, lower scores indicate worse pain), with moderate pain reported by 39% ($n = 19$). Major depression was associated with worse pain (R^2 change = 36%, $\beta = -16$, 95% confidence interval [CI] = [−30, −4], $p = .012$). Pharmacological treatment for depression was associated with better pain scores (R^2 change = 1.5%, $\beta = 13$, 95% CI [4, 23], $p = .006$). **Conclusions:** Heart transplant recipients with major depression had worse pain after controlling for pharmacological treatment of depression, severity of psychological distress, and clinical characteristics. Thus, it is imperative that clinicians devising a treatment regimen for pain in heart transplant recipients take into account co-occurring depression and vice versa.

Keywords

depression, pain, transplant

Heart transplantation results in better long-term survival than alternative end-stage heart-failure treatments (Daneshmand et al., 2010; Haddad et al., 2004). On average, heart transplantation also markedly improves functional status and overall quality of life (Aravot, Berman, Ben-Gal, Sahar, & Vidne, 2000). However, for many heart transplant recipients, transplantation and other related comorbidities impose a significant and lifelong physical and psychological symptom burden.

Depression, for example, is common after heart transplant (Dew & DiMartini, 2006; McCrystal, Pepe, Esmore, & Rosenfeldt, 2004; Politi et al., 2004; Taylor, Stehlik, & Edwards, 2009). A recent study reported that the estimated frequency of major depression within 5 years after heart transplantation was 41% (Favaro et al., 2011). Posttransplant depression has been associated with increased morbidity and mortality (Dew et al., 1999). Of concern, effective treatments to prevent or alleviate depressive symptoms in heart transplant recipients remain elusive (Conway et al., 2014; Fusar-Poli et al., 2006). Physical symptoms can also be severe and distressing for heart transplant recipients, which arise from the adverse effects of immunosuppression medication as well as comorbidities.

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Better characterization of how physical and psychological symptoms interact in heart transplant recipients may inform therapeutic decisions, as the effectiveness of treatment may be influenced by the impact of other symptoms. For example, it is possible that interventions targeting a physical symptom could simultaneously improve symptoms of co-occurring depression and vice versa.

A previous investigation identified that 46% of a sample of 92 adult outpatient heart transplant recipients reported at least mild pain (Holtzman, Abbey, Stewart, & Ross, 2010). The authors of this study recommended that further research into associations between pain and psychiatric comorbidity in this population be conducted. As a preliminary step toward addressing this gap in knowledge about interactions between physical and psychological symptoms in heart transplant recipients, we aimed in the present study to examine the associations between major depression and pain in heart transplant recipients.

Method

We used a cross-sectional design for this study. The ethics committees of the participating institutions approved the study (HREC13QPCH239; 1300000686). All participants provided informed consent.

Participants

Heart transplant recipients over 18 years of age who attended the outpatient clinic at a major metropolitan hospital in Australia were eligible to participate in the study. A research assistant liaised with clinical staff at the clinic to identify eligible participants and then invited them to participate. We excluded patients who were less than 3 months posttransplant and those who were cognitively impaired (as confirmed by a treating clinician), unable to understand and speak English, and had a diagnosed major psychiatric comorbidity (schizophrenia, bipolar disorder, and dementia) or terminal illness.

Data Collection

We collected data concerning demographics and clinical characteristics from medical records and symptom experience data using self-report questionnaires. Participants completed questionnaires while waiting for their appointment at the outpatient clinic. A research assistant was available to provide clarification about any of the items contained within the questionnaires. A provisional psychologist undertaking a doctor of clinical psychology degree conducted a structured psychological interview.

Measures

Medical Outcomes Short Form-36 Health Survey (SF-36). The SF-36 is a widely used generic patient-assessed health outcome measure (Garratt, Schmidt, Mackintosh, & Fitzpatrick, 2002). It yields an 8-scale profile of self-reported functional health and well-being. We included only scores from the ''bodily pain'' domain in this analysis. This domain includes 2 items that measure pain severity (rated as *none, very mild, mild, moderate, severe,* or *very severe*) and pain interference (rated as *not at all* to *extremely* interfering with normal work) over the preceding month. Responses to both items are converted to an overall domain score that ranges from 0 to 100 with lower scores indicating worse pain. The pain-specific patient-reported outcome measure the Brief Pain Inventory exhibited similar relationships to general and condition-specific measures of health as the generic SF-36 pain scale (Keller et al., 2004).

Kessler Psychological Distress Scale (K-10). The K-10 is a brief self-report measure of psychological distress that is used frequently in research and clinical practice to screen for psychological disorders. This 10-item scale measures severity of anxiety and depression symptoms using a 5-point Likert-type scale. It strongly discriminates between community cases and noncases of *Diagnostic and Statistical Manual of Mental Disorders*, Fourth edition (DSM-IV), psychological disorders (Kessler et al., 2002). Higher scores indicate more severe psychological distress.

Mini International Neuropsychiatric Interview, version 6.0 (MINI 6.0). The MINI 6.0 is a short structured diagnostic interview for DSM-IV and *International Statistical Classification of Diseases and Related Health Problems*, 10th edition., psychiatric disorders (Sheehan et al., 1998). It consists of 120 questions and screens 17 Axis I disorders for 24 current and lifetime diagnoses. We used only the major depression (current) module for the present analysis.

Statistical Analysis

We generated descriptive statistics using IBM SPSS Statistics version 21 (IBM Corp., Armonk, NY). We used frequencies, means, and standard deviations (*SD*s) to describe demographic, clinical, and symptom characteristics. To examine associations between pain, major depression and pharmacological treatment for depression, we used hierarchical multiple regression. We defined major depression according to DSM-IV criteria based on the MINI 6.0 structured psychological interview. We entered age (years), gender, time since transplant (years), number of medical comorbidities, presence of chronic allograft vasculopathy, presence of an oncology illness, medications for immunosuppression, and severity of psychological distress measured using the K-10 in the first block, pharmacological treatment for depression in the second block, and major depression in the third block. Regression diagnostics, including checks for normality of residuals, multicollinearity, linearity, heteroscedasticity, and model specification, confirmed that the data met the underlying assumptions for regression analyses.

Table 1. Demographic, Symptom, and Clinical Characteristics.

Variable	Total, $N = 48$	Major Depression, $n = 5$	Pharmacological Treatment for Depression, $n = 9$
Age (years), median (IQR)	63 (55, 67)	54 (35, 63)	65 (54, 71)
Male, *n* (%)	37 (76)	3 (60)	5 (56)
Time since transplant (years), median (IQR)	9 (2.5, 18)	11 (9, 11)	18 (7, 18)
Ischemic etiology of heart failure, *n* (%)	15 (31)	1 (20)	2 (22)
Cancer (including skin cancer), *n* (%)	19 (39)	0 (0)	5 (56)
Current acute rejection, *n* (%)	0 (0)	0 (0)	0 (0)
Number of comorbidities, median (IQR)	7 (4, 8)	7 (7, 8)	8 (7, 10)
Currently taking steroid, *n* (%)	24 (50)	2 (40)	4 (44)
Currently taking antidepressive medications, *n* (%)	9 (18)	2 (40)	9 (100)
K-10 total score, mean (*SD*)	15 (6)	26 (9)	21 (10)
Pain domain score in SF-36, mean (*SD*)	43 (10)	37 (11)	50 (9)

Note. IQR = Interquartile Range; K-10 = Kessler Psychological Distress Scale; SF-36 = Medical Outcomes Short Form-36 Health Survey.

Results

From January to September 2014, 122 of the 126 (97%) heart transplant recipients who were screened at the outpatient clinic met the study eligibility criteria. A total of 48 (40%) chose to participate and completed all measures required for this analysis (MINI and pain domain of the SF-36). The sample consisted mostly of long-term survivors of heart transplantation (median = 9 years posttransplant) and was predominantly male ($n = 37$; 76%). Table 1 presents an overview of demographic and clinical characteristics.

Depression and Pain Scores

Of the 48 participants, 5 (10%) met the criteria for major depression based on a structured psychological interview performed using the MINI 6.0. A total of 9 participants (18%) were currently receiving pharmacological treatment for depression, including 2 (40%) who met the criteria for major depression. Average score on the bodily pain domain of the SF-36 was worse in the major depression group (mean = 37, $SD = 11$) and better in the group that received pharmacological treatment for depression (mean = 50, $SD = 9$) compared with the overall sample (mean = 43, $SD = 10$). At least moderate pain was reported by 39% ($n = 19$) of the sample.

Association Between Pain and Depression

We used hierarchical multivariable linear regression to examine associations between pain and major depression and pharmacological treatment for depression (Table 2). Pharmacological treatment for depression was associated with better pain scores but explained only 1.5% of the variance. Major depression was associated with worse pain, explaining 36.3% of the variance. The final model explained 46.9% of the variance in pain scores.

Discussion

From a clinical perspective, recognition of the physical symptoms that co-occur with major depression in heart transplant recipients is important considering how difficult it is to treat this condition. In our study, heart transplant recipients with major depression had worse pain after controlling for pharmacological treatment of depression, severity of psychological distress, and clinical characteristics including the medications used for immunosuppression, which are known to induce pain as a side effect (Dobbels et al., 2008). A difference in score of 10–20 in the pain domain of the SF-36 corresponds to a small-to-moderate clinically important difference (Wyrwich, Tierney, Babu, Kroenke, & Wolinsky, 2005). Therefore, our findings suggest that the impact of major depression on pain in heart transplant recipients is also clinically significant. We further identified that receiving pharmacological treatment for depression was associated with better pain scores. Our results are consistent with previous research, as both pain and depression are prevalent in other transplant populations (Koller et al., 2010). Research in nontransplant populations has also reported that pain and depression commonly co-occur (Chou, 2007; Doering, Chen, McGuire, Bodán, & Irwin, 2014; Onder et al., 2005).

It is unknown whether pain preceded the onset of major depression in the patients included in our study. However, previous research has identified that pain is a risk factor for depression (Chou, 2007). For this reason, early identification of pain and initiation of interventions to alleviate this symptom may prevent the development of major depression in heart transplant recipients. We also did not investigate the underlying pathology for pain in the present study. Previous research in other transplant populations has likewise identified a high prevalence of pain. For example, Moons et al. (2003) reported that more than half of a cohort of 350 renal transplant recipients experienced pain. Likewise, Koller et al. (2010) found that fatigue and pain were the most frequent and distressing symptoms experienced by 356 renal transplant recipients. These previous studies also did not identify causes of the pain. It is therefore unknown whether pain in this population is related, for example, to adverse effects of immunosuppressive regimens or age-related degenerative musculoskeletal changes (Koller et al., 2010). For this reason, further research focused

Table 2. Associations Between Pain and Depression and Pharmacological Treatment for Depression.[a]

Model		R^2	R^2 Change[a]	*F* Change	Significance
Step 1		0.091			
Step 2		0.107	.015	1.072	.305
Step 3		0.469	.363	18.601	.000
				95% Confidence Interval for β	
Variables in Equation at Step 3	β	*t*	Significance	[Lower, Upper]	
Constant	40.503	1.12	.271	[–33.137, 114.143]	
Age (years)	–0.131	–0.890	.378	[–0.429, 0.167]	
Time since transplant (years)	0.033	0.410	.681	[–.128, .194]	
Gender	–2.200	–0.690	.681	[–8.661, 4.261]	
Steroid	2.929	0.970	.338	[–3.214, 9.073]	
Cyclosporin	4.177	0.830	.412	[–6.065, 14.419]	
Azathropine	–2.383	–0.310	.756	[–17.884, 13.118]	
Sirolimus	4.581	0.880	.384	[–5.990, 15.152]	
Everolimus	–10.539	–1.630	.113	[–23.727, 2.649]	
Tacrolimus	13.072	2.26	.031	[1.299, 24.845]	
Mycophenolate	–10.165	–1.38	.178	[–25.200, 4.869]	
Number of comorbidities	–0.255	–0.390	.698	[–1.586, 1.076]	
Cancer	1.677	0.450	.655	[–5.897, 9.251]	
Severity of psychological distress (K-10 score)	0.342	1.05	.301	[–.320, 1.003]	
Antidepressive medication	13.401	2.96	.006	[4.172, 22.631]	
Major depression (assessed with MINI)	–16.891	–2.66	.012	[–29.844, –3.939]	

Note. K-10 = Kessler Psychological Distress Scale; MINI = Mini International Neuropsychiatric Interview.
[a]Linear regression with score on the pain domain of the Medical Outcomes Short Form-36 as the dependent variable.

on characterizing the underlying causes of pain in transplant recipients, both in general and for heart transplant recipients specifically, may be beneficial in order to inform treatment decisions.

Likewise, we did not examine the antecedents of major depression in the present study. The development of this condition was likely influenced by the unique experience of end-stage heart failure and subsequent transplantation, which is highly traumatic. Trauma is associated with the subsequent development of major depression as well as worse cardiovascular health (Felitti et al., 1998). Competing senses of hope and gratitude mixed with guilt and grief regarding the acceptance of a heart from a deceased donor may contribute to psychopathology in this population (Conway et al., 2013). More research into how depression manifests after heart transplantation is required in order to determine the most effective supportive strategies.

Several biological and behavioral mechanisms might explain the co-occurrence of pain and major depression that we observed (Bair, Robinson, Katon, & Kroenke, 2003; Williams, Jacka, Pasco, Dodd, & Berk, 2006). For example, deficiencies in the neurotransmitters serotonin and norepinephrine associated with depression may result in a reduced ability of these neurotransmitters to dampen peripheral pain signals (Bair et al., 2003). A potential mechanism for the development of depression in people who experience pain over a prolonged period of time is that it triggers stress responses that lead to dysregulation of the hypothalamus–pituitary–adrenal axis resulting in depression (Williams et al., 2006). Other hypotheses about the etiology of the pain and depression comorbidity focus more on the behavioral implications of these conditions. For example, greater levels of life interference caused by symptoms of pain were associated with higher levels of depression in a prior study (Endler, Corace, Summerfeldt, Johnson, & Rothbart, 2003). As results from our study are consistent with this broader literature about the physical experience of depression, it would suggest that the core symptoms within the identified cluster could result from interactive psychological, physiological, or behavioral mechanisms.

Pharmacological treatment for depression was associated with better pain scores in the present study, suggesting a potential additional benefit of this form of therapy. However, the potential for a responder bias should be noted. We did not examine whether or not those patients who had major depression had previously been prescribed antidepressive pharmacological therapies and had since stopped taking this medication due to ineffectiveness. It is also unknown whether nonpharmacological treatments for depression, such as cognitive behavioral therapy, influence pain in the heart transplant population. This area could be considered for investigation in the future.

Despite being recommended in clinical guidelines for caring for heart transplant recipients, regular screening for depression is not currently standard practice in all institutions (Costanzo et al., 2010). Our findings in the present study suggest that, at institutions that do not routinely screen for depression, it may be beneficial for clinicians to conduct a more formal evaluation for psychopathology in transplant recipients who report pain.

A limitation of this study is the potential for selection bias arising from the nonrandomized design and low response rate. Also, due to the sample comprising predominantly long-term survivors of heart transplantation, results should not be

generalized outside of this context. Further research with a larger sample size is required to increase confidence in the results. Moreover, a longitudinal design would be preferable in any future studies, so that the relationship between major depression and pain could be determined over time. A longitudinal design would permit analyses to determine whether the co-occurrence of major depression and pain exerts a synergistically negative impact on clinical outcomes for heart transplant recipients by tracking morbidity and mortality. We should also note that the pain domain of the SF-36 provides a composite measure of pain severity and its interference with normal daily activities. It may be that, although experienced frequently, pain may not have been distressing for all participants. Furthermore, those participants who were more able to cope with symptoms of pain (i.e., rated them as causing less interference) may also have been less likely to have depressive symptoms. Further research investigating these potential interactions with depression may be beneficial.

In conclusion, our results are consistent with the broader literature about the physical experience of depression. It is imperative that clinicians devising a treatment regimen for pain in heart transplant recipients take into account co-occurring depression and vice versa.

Author Contributions

A. Conway contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. J. Sheridan contributed to conception and design; contributed to acquisition, analysis, and interpretation; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. J. Maddicks-Law contributed to conception and design; contributed to acquisition; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. P. Fulbrook contributed to conception and design; contributed to acquisition, analysis, and interpretation; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. C. F. Ski contributed to conception and design; contributed to analysis and interpretation; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. D. R. Thompson contributed to conception and design; contributed to analysis and interpretation; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. R. Clark contributed to conception and design, contributed to analysis and interpretation, critically revised the manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. L. V. Doering contributed to conception and design, contributed to analysis and interpretation, critically revised the manuscript; gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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