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SHORT COMMUNICATION

Associations between beta-blocker use and psychological distress in bereaved adults with cardiovascular conditions

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Abstract

The death of a close other is a major life stressor that disrupts mental and physical health. Beta-blocker medications are indicated treatments for cardiovascular conditions that may also mitigate psychological distress in the context of stressors by reducing adrenergic activity. We sought to examine observational links between beta-blocker medication use and psychological distress during bereavement. Using publicly available data from the Midlife in the United States Refresher study, we examined associations between beta-blocker use and general distress, depressive symptoms, and anxiety symptoms (as measured by the Mood and Anxiety Symptom Questionnaire) among bereaved adults with cardiovascular conditions (n = 161) using t-tests and regression models. Beta-blocker users reported lower levels of anxiety-related general distress (b = −2.49, SE = 0.88, p = 0.005) and depression-related general distress than non-users (b = −2.39, SE = 1.14, p = 0.039) in multivariate linear regression models adjusting for demographic characteristics, mental health treatments, time since loss and comorbid health conditions. These observed links between beta-blockers and lower psychological distress in bereavement warrant further investigation in prospective and randomized studies, as beta-blockers could be a scalable intervention for mitigating distress following loss.

KEYWORDS

anxiety, biological mechanisms of stress, cardiovascular disease, cardiovascular reactivity, depression, psychopharmacology, stress

1 | INTRODUCTION

The death of a loved one is a severe, life-altering stressor associated with psychological distress (Holmes & Rahe, 1967). Although most people adapt over time to the loss (Bonanno et al., 2005), a subset of bereaved individuals experiences persistent mental health problems including anxiety (Jacobs et al., 1990), depression (Cole & Dendukuri, 2003) and prolonged grief disorder (Prigerson et al., 2021). Despite effective psychotherapeutic treatments for bereavement-related psychological distress (Shear et al., 2016), several barriers present challenges to receiving mental health services, such as apprehensions about pathologizing the bereavement experience (Dowrick & Frances, 2013), financial concerns or difficulty talking about the loss in psychotherapy (Lichtenthal et al., 2015). Thus, novel strategies targeting psychological symptoms in bereavement are needed.

Beta-blocker medications, which are indicated treatments for cardiovascular conditions, bind to beta-adrenergic receptors and serve as competitive inhibitors for epinephrine and norepinephrine.

By inhibiting sympathetic nervous system activity, a key component of the stress response (Brindle et al., 2014), beta-blockers may influence psychological symptoms. In addition to their essential role in the prevention and treatment of cardiovascular disease (López-Sendó et al., 2004), beta-blockers have been used to reduce short-term psychological distress due to a variety of stressors, including performance anxiety (James & Savage, 1984), diagnosis of cancer (Lindgren et al., 2013), and recall of emotionally arousing stories (Cahill et al., 1994). Consistent with this, it is possible that beta-blockers may also reduce psychological distress in the context of bereavement.

Using publicly available data, we investigated the relationship between beta-blocker use and psychological distress in a sample of bereaved adults with cardiovascular conditions. We hypothesized that beta-blocker users would report lower symptoms of anxiety and depression than non-users.

2 | METHODS

This analysis utilized data from Survey and Biomarker projects of the Midlife in the United States (MIDUS) Refresher observational cohort study, an interdisciplinary study investigating psychosocial factors and health in adults. Participants provided demographic data in an initial structured telephone interview. All participants were then invited to attend an in-person biomedical assessment; bereavement status, medication use, health history, and symptoms of anxiety and depression were assessed at the visit. Documentation regarding recruitment and assessment procedures is available in the MIDUS Refresher datasets (Ryff et al., 2017; Weinstein et al., 2019).

2.1 | Study participants

This analysis included 161 MIDUS Refresher participants who completed both the initial phone interview and in-person Biomarker assessment, reported recent bereavement (i.e., death of a close other that occurred since the initial interview), and endorsed a history of cardiovascular conditions (i.e., hypertension or heart disease). We used these criteria to select those for whom beta-blockers are typically indicated (López-Sendó et al., 2004) and to minimize health differences between those prescribed and not prescribed beta-blockers.

The subsample was identified as follows: Of the 863 MIDUS Refresher participants who completed the Biomarker sub-project visit, 373 reported recent loss. Of these, 169 also reported heart disease or hypertension, but 8 were missing medication or demographic information. Thus, primary analyses included 161 bereaved adults with cardiovascular conditions.

Compared to the rest of the MIDUS Refresher participants who completed the Biomarker visit ($n = 702$), our analytic subsample was older ($M = 58.3$ years, SD = 10.9 vs. $M = 49.1$ years, SD = 13.4, $p < 0.001$) and had more chronic conditions ($M = 2.1$, SD = 1.4 vs. $M = 1.1$, SD = 1.2, $p < 0.001$). Our analytic subsample also contained a larger proportion of participants who identified as Black (28.0% vs. 16.5%, $p = 0.006$), but did not differ significantly on other demographic variables.

2.2 | Measures

2.2.1 | Demographic characteristics

For the purpose of clarity in interpreting analyses, we coded demographics reported in the initial telephone interview as dichotomous variables for gender (male/female), race (white/non-white), ethnicity (Hispanic/non-Hispanic), marital status (married/other) and education (college graduate/less than college).

2.2.2 | Medication use

Participants were instructed to bring all prescription medication they took over the past 30 days to the in-person Biomarker study visit. Medication use was summarized in the MIDUS dataset by Cerner Multum subclass category (Cerner, 2021). We utilized the available sub-class numbers for beta-adrenergic blocking agents (subclass 47), antidepressants (subclass 249), and anxiolytics, sedatives and hypnotics (subclass 67) to create binary variables indicating any versus no use of these medication classes.

2.2.3 | Anxiety and depressive symptoms

Participants completed the Mood and Anxiety Symptom Questionnaire (MASQ), a valid and reliable measure of anxiety, depression and non-specific distress based on the tripartite model of anxiety and depression (Clark & Watson, 1991). The tripartite model posits that anxiety and depression each have distinct, specific symptoms and also share overlapping features of non-specific general distress. Consistent with the theoretical rationale and validated subscales for the MASQ (Watson et al., 1995), we used the anxious arousal subscale (17 items) to measure distinct symptoms of anxiety and the anhedonic depression subscale (22 items) to measure distinct symptoms of depression. We used the remaining anxiety-related general distress (11 items) and depression-related general distress (12 items) subscales to index non-specific symptoms of general psychological distress. Participants reported the intensity of their symptoms in the past week on a 1–5 Likert-style scale ranging from 'not at all' to 'extremely', with higher scores representing greater symptoms. In the analytic sample, the subscales had acceptable to excellent internal consistency; Cronbach's alpha was 0.89 for depression-related general distress, 0.84 for anxiety-related general distress, 0.79 for anxious arousal and 0.91 for anhedonic depression subscales.

2.2.4 | Chronic conditions

Participants were given a list of chronic health conditions and were asked to indicate whether they had each one as diagnosed by a physician. We calculated the total number of chronic conditions, including diabetes, asthma, emphysema/chronic obstructive pulmonary disease, tuberculosis, thyroid disease, peptic ulcer disease, cancer, colon polyp, arthritis, glaucoma, cirrhosis/liver disease or alcoholism, which was used as a continuous variable in analyses.

2.2.5 | Recent mental health services use

Participants were asked whether they had seen a psychiatrist, general practitioner/other physician, psychologist, counsellor, therapist, social worker or spiritual advisor for their mental health over the past year during the initial telephone interview. We created a binary variable to summarize any versus no recent use of these services.

2.3 | Analysis

Demographic differences between beta-blocker users and non-users were examined using *t*-tests, Fisher's exact test or Chi-square test with continuity correction as appropriate for each variable. To test whether levels of anxiety and depressive symptoms differed between beta-blocker users and non-users, unadjusted analyses utilized Student's *t*-test with the four MASQ subscales as outcomes in separate analyses. Adjusted analyses utilized multiple linear regression models with beta-blocker use as the key predictor of each MASQ subscale as an outcome in separate models. These adjusted models included age, gender, education, marital status, race, ethnicity, time since most recent loss, number of chronic conditions, recent mental health service use, and current anxiolytic or antidepressant use as covariates due to their potential confounding relationships with anxiety and depressive symptoms. Cases with missing data on covariates were excluded listwise, such that four individuals who were missing the date of loss were not included in adjusted analyses. All analyses were performed in R 3.5.1 (R Core Team, 2013).

3 | RESULTS

Sample characteristics are displayed in Table 1. Participants had a mean 7.3 months since loss (SD = 7.9). Of the 161 participants included in this analysis, 44 (27.3%) were prescribed beta-blocker medication. Participants were most commonly prescribed metoprolol (n = 22, 50.0%), atenolol (n = 9, 20.5%) and carvedilol (n = 6, 13.6%). The remaining were prescribed labetalol, nebivolol, pindolol, propranolol and sotalol; only two participants had multiple beta-blocker prescriptions. As shown in Table 1, beta-blocker users were older and reported a greater number of chronic health conditions than non-users. Beta-blocker users were also more likely to report co-occurring heart disease and hypertension than non-users.

In unadjusted analyses, participants taking beta-blocker medication reported lower levels of anxiety-related distress and depression-related distress than those who were not taking beta-blockers (Table 2). These associations remained significant in adjusted analyses controlling for demographic characteristics, mental health treatments, time since loss and comorbid health conditions, such that beta-blocker use was associated with anxiety-related distress (b = −2.49, SE = 0.88, p = 0.005) and depression-related distress (b = −2.39, SE = 1.14, p = 0.039) above and beyond these factors (Table 3). There were no statistically significant differences between beta-blocker users and non-users on the anxious arousal or anhedonic depression subscales in either adjusted or unadjusted analyses.

4 | DISCUSSION

In light of the need for treatments to support psychological well-being during bereavement, we investigated whether beta-blocker use was associated with fewer anxiety and depression symptoms among bereaved individuals with cardiovascular conditions in the MIDUS Refresher observational study. Those who used beta-blockers had lower levels of anxiety-related distress and depression-related distress than those who did not use beta-blocker medications. This association remained after adjusting for key demographic characteristics, health-related variables and time since loss. These results are consistent with previously documented effects of beta-blockers on distress in the context of other stressors (Cahill et al., 1994; James & Savage, 1984; Lindgren et al., 2013) and suggest that beta-blocker medications may have mental health benefits in the context of bereavement, a common major stressor.

Surprisingly, beta-blockers were not associated with lower levels of somatic anxiety symptoms, as measured by the anxious arousal subscale. It is possible that differences in somatic anxiety symptoms were more difficult to detect in this sample, given the potential overlap with physical symptoms related to cardiovascular problems and other chronic conditions (i.e., dyspnea, angina, tachycardia). Indeed, those with a greater number of chronic health conditions reported higher anxious arousal than those with fewer chronic conditions in the adjusted model.

In line with recent calls for biobehavioral approaches to bereavement research (Knowles et al., 2019), these findings underscore how examining the interface between physical and mental health has the potential to inform novel intervention strategies. For example, given that autonomic nervous system dysregulation can occur following loss (Fagundes et al., 2018), it is possible that beta-blockers mitigate mental health symptoms by modifying these pathways. Future work to examine the physiological mechanisms linking beta-blockers to psychological benefits, such as disruption of noradrenergic modulation of neural networks that are typically activated during emotional experiences (Hermans et al., 2011), would provide useful insight into these effects.

TABLE 1 Demographics

	Total sample		Comparator groups				
	N = 161		Beta-blocker users *N* = 44 (27.3%)		Non-users *N* = 117 (72.7%)		*t*-Test
Variable	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	***p***
Age (years)	58.3	10.9	61.3	10.2	57.1	11.0	0.028
Number of symptoms and conditions	2.1	1.4	2.6	1.3	1.9	1.4	0.006
Time since most recent loss (months)[a]	7.3	7.9	7.1	7.1	7.3	8.1	0.894
Variable	***n***	**%**	***n***	**%**	***n***	**%**	**Chi-square/Fisher's exact *p***
Sex							0.403
Male	81	50.3%	25	56.8%	56	47.9%	
Female	80	49.7%	19	43.2%	61	52.1%	
Race							0.450
White	101	62.7%	28	63.6%	73	62.4%	
Black/African American	45	28.0%	14	31.8%	31	26.5%	
Other	15	9.3%	2	4.5%	13	11.1%	
Ethnicity							0.324
Hispanic	5	3.1%	0	0.0%	5	4.3%	
Non-Hispanic	156	96.9%	44	100.0%	112	95.7%	
Education							0.479
Less than bachelor's degree	86	53.4%	26	59.1%	60	51.3%	
At least bachelor's degree	75	46.6%	18	40.9%	57	48.7%	
Marital status							>0.999
Married	87	54.0%	24	54.5%	63	53.8%	
Other	74	46.0%	20	45.5%	54	46.2%	
Seen mental health professional							>0.999
Yes	56	34.8%	15	34.1%	41	35.0%	
No	105	65.2%	29	65.9%	76	65.0%	
Antidepressants							0.978
Yes	35	21.7%	9	20.5%	26	22.2%	
No	126	78.3%	35	79.5%	91	77.8%	
Anxiolytics, sedatives, hypnotics							0.277
Yes	33	20.5%	12	27.3%	21	17.9%	
No	128	79.5%	32	72.7%	96	82.1%	
Cardiovascular conditions							<0.001
Heart disease	7	4.3%	2	4.5%	5	4.3%	
Hypertension	118	73.3%	19	43.2%	99	84.6%	
Both heart disease and hypertension	36	22.4%	23	52.3%	13	11.1%	

[a]Four cases were missing time since loss data.

TABLE 2 Unadjusted analyses of MASQ anxiety and depression subscales by beta-blocker use

	Total		Comparator groups					
	N = 161		Beta-blocker user *N* = 44 (27.3%		Non-user *N* = 117 (72.7%)		Student's *t*-test	Hedge's *g*
Variable	Mean	SD	Mean	SD	Mean	SD	*p*	*g*
MASQ-General Distress–Anxiety	16.6	5.37	15.1	4.36	17.2	5.62	0.015	−0.39
MASQ-Anxious Arousal	22.5	5.71	22.5	5.68	22.5	5.87	0.954	0.01
MASQ-General Distress–Depression	18.5	6.55	17	5.35	19.1	6.88	0.040	−0.33
MASQ-Anhedonic Depression	53.5	13.03	52.6	13.67	53.9	12.82	0.578	−0.10

Abbreviation: MASQ, Mood and Anxiety Symptom Questionnaire.

TABLE 3 Linear regression of beta-blocker use on MASQ anxiety and depression subscales (*N* = 157)

	General Distress–Anxiety			Anxious Arousal			General Distress–Depression			Anhedonic Depression		
Variable	*b*	Standard error	*p*	*b*	Standard error	*p*	*b*	Standard error	*p*	*b*	Standard Error	p
Beta-blockers	−2.49	0.88	0.005	−0.62	1.00	0.538	−2.39	1.14	0.039	−2.12	2.33	0.366
Age (years)	−0.04	0.04	0.352	−0.07	0.05	0.124	−0.03	0.05	0.608	−0.27	0.11	0.011
Number of chronic conditions	0.21	0.29	0.470	0.70	0.33	0.034	−0.02	0.37	0.966	1.56	0.76	0.041
Time since most recent loss (months)	−0.04	0.05	0.425	−0.07	0.06	0.189	−0.07	0.06	0.289	−0.08	0.13	0.546
Sex (female)	1.46	0.83	0.081	0.27	0.95	0.774	0.15	1.08	0.893	−1.76	2.21	0.429
Education (≥bachelor's degree)	−1.66	0.79	0.037	−2.64	0.90	0.004	−2.73	1.02	0.008	−3.51	2.09	0.095
Marital status (married)	0.83	0.85	0.329	0.51	0.97	0.597	0.17	1.11	0.879	−0.94	2.26	0.679
Race (White)	−0.29	0.87	0.740	−0.48	0.99	0.625	0.81	1.13	0.474	1.37	2.30	0.554
Hispanic ethnicity	−3.20	2.20	0.148	−3.02	2.51	0.230	−3.87	2.87	0.179	−13.39	5.85	0.024
Mental health professional in past year	3.12	0.84	<0.001	1.85	0.96	0.056	3.64	1.10	0.001	1.69	2.24	0.451
Anxiolytics, sedatives, hypnotics	3.70	0.96	<0.001	2.97	1.09	0.007	2.10	1.25	0.095	2.38	2.55	0.353
Antidepressants	1.68	0.98	0.89	1.04	1.12	0.356	1.79	1.28	0.165	5.23	2.61	0.047

Abbreviation: MASQ, Mood and Anxiety Symptom Questionnaire.

Because this analysis was cross-sectional, causal conclusions cannot be drawn about effects of beta-blockers' effects on psychological distress, a primarily limitation. By including relevant sociodemographic and mental health-related covariates, we accounted for potential confounding factors statistically to strengthen the approach; a randomized design would be a stronger method to account for confounders. Furthermore, participants' symptoms of anxiety and depression were subclinical on average; while the level of symptoms was similar to those in other community samples, it is possible that different (and perhaps stronger) effects would be seen in a treatment-seeking sample with clinically elevated distress. In addition, while the overall MIDUS Refresher study employed a national probability sampling strategy, we studied a select subset of participants who completed the Biomarker visit, which limits generalizability.

The findings of this study suggest the need for future prospective research and randomized trials to confirm causal links between beta-blocker usage and reductions in psychological distress during bereavement. Initial results appear promising; in a recent randomized controlled trial, bereaved individuals treated with low-dose metoprolol and aspirin had fewer anxiety and depressive symptoms after 6 weeks compared to those who received a placebo (Tofler et al., 2020). While beta-blocker medications are widely used with established safety profiles, future trials may benefit from approaches to minimize side effects (e.g., in dosing [Tofler et al., 2020]), and to assess side effects in comparison to other medications that may be prescribed for

mental health during bereavement (e.g., anti-depressants [Ornstein et al., 2020]). Testing the impact of beta-blockers on grief-specific symptoms would also be useful, given their relationship with indicators of cardiovascular disease (Fagundes et al., 2018) and distinctness from anxiety and depression symptoms (Prigerson et al., 1996); measures of grief severity were not available in this study.

In summary, effective, low-cost and scalable strategies for supporting mental health are needed to improve quality of life following loss. These results suggest that beta-blockers may have mental health benefits during bereavement beyond their well-known cardiovascular benefits and warrant further investigation in prospective and randomized studies. Because bereaved individuals experience notable cardiovascular and mental health risks (Prigerson et al., 1997; Stroebe et al., 2007), beta-blockers may be an appealing strategy to address both concerns while limiting polypharmacy. If efficacious, beta-blocker medications have the potential to serve as an efficient and accessible care strategy for bereaved individuals with cardiovascular conditions, thus mitigating the mental health impact of this severe stressor.

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CONFLICTS OF INTEREST

Heather Derry reports a financial relationship (spouse employment) with Merck. The other authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Martin Viola made substantial contributions to the conceptualization, analysis and interpretation of data, and drafted the manuscript. Daniel Ouyang made substantial contributions to the conceptualization of the work, interpretation of data, and revised the manuscript for important intellectual content. Jiehui Xu made substantial contributions to the analysis and interpretation of data and revised for important intellectual content. Paul K. Maciejewsk made substantial contributions to the analysis and interpretation of data and revised the manuscript for important intellectual content. Holly G. Prigerson made substantial contributions to the conceptualization of work, interpretation of data, and revised the manuscript for important intellectual content. Heather M. Derry made substantial contributions to the conceptualization of work, interpretation of data, and drafted the manuscript.

DATA AVAILABILITY STATEMENT

All data used in this project are publicly available through the Inter-university Consortium for Political and Social Research (ICPSR) at the following links: Survey data (https://doi.org/10.3886/ICPSR36532.v3), Biomarker data (https://doi.org/10.3886/ICPSR36901.v6) and Milwaukee data (https://doi.org/10.3886/ICPSR36722.v4).

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