Biopsychosocial Science and Medicine Publish Ahead of Print
DOI:10.1097/PSY.0000000000001432

Use of serotonin and catecholamine reuptake inhibitors and onset of Takotsubo syndrome

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Number of tables: 3

Number of supplemental files: 0

Transparency and openness promotion disclosures: This study reports a secondary analysis of existing data and was therefore not pre-registered. Data are available upon reasonable request to the corresponding author.

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Funding: This work was supported by American Heart Association (Dallas, TX) award 13CRP1334001 and by grant R01HL149672 to Dr. Elena Salmoirago-Blotcher.

Conflicts of Interest: None declared

Abstract

Objective: Takotsubo Syndrome (TS), is an acute, transient heart failure primarily affecting older women. Excessive sympathetic stimulation from emotional or physical stressors is assumed to trigger TS through a toxic surge in plasma catecholamines. Case reports have signaled the

onset of TS following treatment with serotonin and catecholamine reuptake inhibitors. This case-control study investigated whether the use of these medications could be associated with TS onset.

Methods: Incident TS cases (n=98) and myocardial infarction (MI; n=32) controls were recruited among women admitted to five emergency departments in New England. Information on psychotropic medications was abstracted from medical records. Logistic regression models were used to examine associations between pre-admission psychotropic medication use and TS onset.

Results: Demographics were similar between groups (98 TS, 32 MI) except for race (92% White in TS vs. 78% in MI). TS women more frequently had a history of any psychiatric disorder (50% vs. 28%, p=0.002); mood disorders, 32% vs. 22% (p=0.41); anxiety disorders, 32% vs. 9% (p =0.024). Logistic regression models adjusting for psychiatric comorbidity showed that women with TS were more likely to have taken any psychotropic medication (OR=4.10; CI 1.42, 5.0); or any catecholamine or serotonin reuptake inhibitor pre-admission (OR=3.39; CI: 1.17, 12.3). Analysis by medication type showed the latter association was driven by associations with SNRI use (11% vs. 0%; p=0.10).

Conclusions: These findings suggest that the use of catecholamine or serotonin reuptake inhibitors may increase the risk of TS. The use of such medications should be carefully considered in TS survivors.

KEYWORDS: Takotsubo Syndrome, Broken Heart Syndrome, Stress-Induced Cardiomyopathy, Myocardial Infarction, Psychotropic medication, Selective serotonin reuptake inhibitor, Catecholamine reuptake inhibitor, Sympathetic activity

ABBREVIATIONS

- ACS - Acute Coronary Artery Syndromes
- BHS-1 - Broken Heart Study 1
- BHS-2 - Broken Heart Study 2
- HADS - Hospital Anxiety and Depression scale
- LSD - Lysergic Acid Diethylamide
- LV - Left Ventricular
- MAOI - Monoamine oxidase inhibitors
- MDMA - Ecstasy
- MI - Myocardial Infarction
- NaSSA - Noradrenergic and specific serotonergic antidepressants
- NDRI - Norepinephrine-dopamine reuptake inhibitor
- NRI - Norepinephrine reuptake inhibitors
- SARI - Serotonin-2 antagonist and reuptake inhibitors
- SNRI - Serotonin-norepinephrine reuptake inhibitor
- SSRI - selective serotonin reuptake inhibitor
- TCA - Tricyclic antidepressant
- TS - Takotsubo Syndrome

INTRODUCTION

Takotsubo Syndrome (TS), also known as Broken Heart Syndrome or stress-induced cardiomyopathy, is an acute, transient form of heart failure characterized by left ventricular (LV) dysfunction and troponin elevation in the absence of significant coronary artery disease (1, 2). Despite its transient nature, this condition is associated with an increased risk of mortality and long-term morbidity following discharge (3-5).

TS is most common in postmenopausal women, who account for up to 90% of cases (4, 6). Although the pathophysiology of TS is not fully understood, emotional or physical stressors play an important role in the onset of LV dysfunction by triggering a toxic surge in plasma catecholamines, causing reversible myocardial damage and apical left ventricular ballooning (7, 8). Indeed, an emotional or physical trigger has been found to precede TS in approximately 40% to 70% of cases (2, 4, 6). The occurrence of TS following the administration of exogenous catecholamines and beta-receptor agonists further implicates the role of an exaggerated sympathetic response in the onset of TS (9, 10).

Recently, TS has been associated with a high prevalence of comorbid psychiatric disorders, with patients with TS showing higher prevalence of neurologic or psychiatric conditions compared to those admitted with acute coronary artery syndromes (ACS) (56% vs 26%) (4). Mood and anxiety disorders, in particular, were found to be more common in patients with TS compared to those with ACS (11, 12). Psychiatric disorders were frequently associated with triggers, which may contribute to heightened emotional distress in response to external stressors (13). Furthermore, patients with pre-existing psychiatric disorders were more likely to experience a recurrent TS episode following discharge (14).

Due to the high prevalence of psychiatric conditions, patients with TS often have a history of psychotropic medication use (11). Because an exaggerated sympathetic response plays a role in the development of this condition (15), the use of psychotropic medications that inhibit the reuptake of catecholamine at the synapse could potentially be harmful. This is especially concerning as patients presenting with psychiatric illnesses already exhibit heightened sympathetic activity (16-18).

Several psychotropic medications have been linked to increased sympathetic activity. For example, tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) were associated with a shorter pre-ejection period in patients with depression and anxiety, suggesting a potential increase in sympathetic nervous system activity (19). Bupropion, a norepinephrine-dopamine reuptake inhibitor (NDRI), was found to decrease heart rate variability in healthy individuals, while reboxetine, a norepinephrine reuptake inhibitor, was found to increase heart rate and blood pressure in healthy controls (20, 21). Several case reports have reported the development of TS during treatment with SNRIs, including Milnacipran, Venlafaxine, Desvenlafaxine, and Duloxetine (22-25), as well as fluoxetine, a selective serotonin reuptake inhibitor (SSRI) (26).

Indeed, it has been suggested that psychotropic drug therapy mediates the association between psychiatric history and TS risk (27). However, the relationship between psychotropic medications and TS risk has primarily been explored through case studies, and there is a paucity of rigorous studies exploring this association. Given the clinical significance of TS, understanding whether psychotropic medication use is related to the pathogenesis of the condition is important to minimize the risk of new or recurrent episodes, especially in patients

presenting with other risk factors. This study sought to determine whether chronic use of SSRI and catecholamine reuptake inhibitors is associated with the onset of TS.

Methods

Study sample

This unmatched case-control study used data previously collected from two different studies: the Broken Heart Study 1 (BHS-1) and the Broken Heart Study 2 (BHS-2). Given that the vast majority of patients with TS are female, and to eliminate confounding by sex, only women were considered for this analysis.

In both studies, incident TS cases (n=98) were prospectively recruited among consecutive women presenting at the emergency departments of 5 large hospitals in New England with a diagnosis of TS. A first TS cohort (n = 45) was recruited between March 2013 and October 2015 from UMass Memorial Medical Center in Worcester, MA, and Hartford Hospital in Hartford, CT. A second TS cohort included the first 53 consecutive patients enrolled in the BHS-2 study who were recruited from the Miriam, Rhode Island, and Newport hospitals in Rhode Island from November 2020 to June 2024 using identical eligibility criteria. Inclusion criteria for both cohorts were age ≥ 21; a first diagnosis of TS fulfilling Mayo Clinic diagnostic criteria (28); English fluency; and access to a telephone. Exclusion criteria were inability or unwillingness to provide informed consent; a history of pheochromocytoma, myocarditis, or hypertrophic cardiomyopathy; dementia or severe cognitive impairment; and clinical instability.

The control group (n=32) comprised women admitted with a confirmed diagnosis of acute non-fatal type 1 myocardial infarction (MI) at UMass Memorial Medical Center in Worcester, MA, and Hartford Hospital in Hartford, CT, from March 2013 to October 2015. Inclusion criteria for MI controls were age ≥ 21; a diagnosis of type 1 MI meeting current

diagnostic criteria (29); English fluency; and access to a telephone. Women were excluded if they had a prior diagnosis of TS, were unable or unwilling to give informed consent, or were clinically unstable.

Once the diagnoses of TS and MI were confirmed by a study cardiologist blinded to the study outcomes, participants received a letter inviting them to participate in the study. Interested and eligible participants were invited to complete baseline assessments approximately 12 weeks after hospital discharge. The Broken Heart Study 1 and the Broken Heart Study 2 were both approved by the Institutional Review Board (UMass docket H00000929 and Brown Health docket 1532110). All participants provided informed consent.

Sample size determination

Given that this is a secondary data analysis, no *a priori* power analysis was conducted. The sample size was based on the number of participants enrolled in the parent studies.

Measures

Use of serotonin and catecholamine reuptake inhibitors was defined as ongoing use at hospital admission of any of the following: selective serotonin reuptake inhibitors (SSRI); norepinephrine reuptake inhibitors (NRI); noradrenergic and specific serotonergic antidepressants (NaSSA); serotonin-norepinephrine reuptake inhibitors (SNRI); serotonin-2 antagonist and reuptake inhibitors (SARI); tricyclic antidepressants (TCA); and norepinephrine-dopamine reuptake inhibitors (NDRI). We also collected information on use of other psychotropic medication (e.g., benzodiazepines). The definitions of the different psychiatric conditions in the abstraction form were based on DSM-IV-TR criteria (30). A trained abstractor (blinded to the study outcomes and the case/control status of the participant) collected

information on psychiatric history, including psychotropic medication use, from patients' electronic medical records using ad-hoc abstraction forms designed by a practicing psychiatrist.

Post-discharge anxiety and depression symptoms were self-reported using the Hospital Anxiety and Depression scale (HADS), a 14-item instrument validated in hospital settings with higher scores (range: 0-21) indicating greater anxiety or depression symptoms (31). Scores >7 on each anxiety and depression subscale represent elevated levels of anxiety or depressive symptoms, respectively (31). Both subscales displayed adequate reliability in this sample (depression: α=0.82, anxiety: α=0.86).

Sociodemographic information (e.g., age, race, education) and psychosocial questionnaires were self-reported with direct data entry in electronic study surveys (32).

STATISTICAL ANALYSIS

Baseline characteristics (age, race, education, medical history, and clinical characteristics at admission) were compared between groups using t-tests (or non-parametric tests, as appropriate) for continuous variables and chi-square tests for categorical variables.

Pre-admission prevalence rates of psychiatric conditions and psychotropic medication use were compared using chi-square statistics. Unconditional logistic regression (any serotonin and catecholamine uptake inhibitors vs. none) was used to analyze associations, using the MI group as the reference group. (33) Target covariates/confounders were chosen based on the literature and validated using statistical methods for the definition of confounders, which included age, race, education, and history of anxiety and depression. First, univariate models were generated. Final models adjusted for variables that were associated with both the group status (TS vs MI) and pre-admission use of serotonin and catecholamine reuptake inhibitors. Because race and education were not associated with use of psychotropic medications in univariate models, and

age and prevalence of depression were similar between groups, only pre-admission history of anxiety disorders was included in final models. Model fit statistics suggest that the adjusted model (McFadden's $R^2 = 0.110$) provides a better fit to the data compared to the unadjusted model (McFadden's $R^2 = 0.064$), as shown by the lower Akaike Information Criterion (AIC) ($AIC_{adjusted}$= 153.56 vs $AIC_{unadjusted}$= 155.86) and the likelihood ratio test (p=0.008).

For all estimates, standard errors or confidence intervals were calculated. All analyses were performed using R version 4.3.1.

Results

As detailed in Table 1, women with TS (n=98) and MI (n=32) had similar demographic characteristics at admission except for a higher prevalence of white non-Hispanic women in the TS vs. the MI group. Medical history and clinical characteristics at admission were similar between groups except for a higher prevalence of diabetes mellitus among patients with MI and a lower ejection fraction in women with TS vs. MI (Table 1). Women admitted for TS were more likely to have a history of psychiatric disorders compared to those with MI (50% vs. 28%, p =0.050) and more specifically, anxiety disorders (32% vs. 9%, p =0.024). Post-discharge anxiety symptoms were also higher in TS vs. MI (mean HADS scores 6.3 ± 4.2 vs. 3.5 ± 3.7, p < 0.001), with 39% vs 22% women reporting clinically significant symptoms (HADS anxiety scores > = 7). In contrast, the history of mood disorders (32% vs 22%, p =0.41) and the severity of depressive symptoms post-discharge did not differ between groups (HADS depression scores 4.3 ± 3.5 vs 3.4 ± 3.2, p =0.18) (Table 2).

As shown in Table 3, 43% of women with TS were receiving psychotropic drugs at the time of their index hospitalization compared to 13% of women with MI (p =0.004) and 38% used any serotonin or catecholamine reuptake inhibitors (p =0.014). Specifically, the prevalence of SSRIs use was 21% vs. 13%; SNRI: 11% vs. 0%; SARI: 6% vs. 0%; TCA: 3% vs. 0%; and

NaSSA: 1% vs. 0%. No women were taking norepinephrine reuptake inhibitors, norepinephrine-dopamine reuptake inhibitors (NDRI), monoamine oxidase inhibitors (MAOI) or mood stabilizers (lithium) at admission (Table 3).

Unadjusted logistic regression models showed that women with TS were significantly more likely to have taken any psychotropic medication prior to admission (OR = 5.25; CI: 1.88; 18.7). A similar association was observed for use of any catecholamine and serotonin reuptake inhibitors (OR = 4.25; CI: 1.52-15.2). These associations remained significant after adjusting for history of anxiety disorders (any psychotropic medication: OR = 4.10; CI: 1.42; 15.0; any catecholamine or serotonin reuptake inhibitor: OR = 3.39; CI: 1.17; 12.3). As shown in Table 3, while associations with pre-admission use of specific medication types did not reach statistical significance due to small cell counts, TS women, compared to MI, were more likely to receive SNRIs (11% vs. 0%; p=0.10).

Discussion

In this rigorous case-control analysis of incident TS cases and MI controls, we sought to evaluate if pre-admission use of catecholamine and serotonin reuptake inhibitors could predispose patients to the occurrence of TS. We found a significant association between the pre-admission use of psychotropic medications, and specifically of any catecholamine and serotonin reuptake inhibitors and the onset of TS. Individual catecholamine and serotonin reuptake inhibitors were not significantly associated with TS onset; however, this may be due to small cell sizes. Analyses by medication type revealed the strongest association for serotonin-norepinephrine reuptake inhibitors with TS. Finally, we found that women with TS have a significantly greater prevalence of pre-admission anxiety disorders and greater anxiety symptoms post-discharge compared to female MI controls.

The literature examining the possible effects of antidepressants and other psychotropic medication on TS risk is sparse and based almost exclusively on case reports. As summarized in a recent review of such studies (34), a number of psychotropic medications, including SNRIs (e.g., venlafaxine, desvenlafaxine, and duloxetine), and SSRIs (e.g., fluoxetine) have been associated with the onset of TS. SNRIs increase the levels of noradrenaline by inhibiting its reuptake in the presynaptic membrane. While SSRIs do not affect reuptake of catecholamines, studies have shown that some SSRIs can indirectly increase noradrenaline and dopamine levels (35, 36).

An alternative explanation for our findings is the possibility of serotonin syndrome. This condition is associated with an excessive activation of both central and peripheral serotonin postsynaptic receptors, which results, among other symptoms, in widespread autonomic activation. A number of drug combinations can result in serotonin syndrome, including co-prescription of SSRIs with other antidepressants (SNRI, TCA, bupropion) as well as commonly prescribed drugs such as migraine medications, illicit drugs (methamphetamine, amphetamine, ecstasy (MDMA), psilocybin, and LSD), and common dietary supplements (37).

Both our (38) and others' (39) work have shown that patients with TS have greater levels of psychological distress after discharge compared to healthy controls. In our study, we found that women with TS had greater perceived stress and anxiety symptoms, but not depressive symptoms, within 12 weeks of discharge. Others found that patients with TS had higher levels of depressive symptoms and illness-related anxiety, but not of perceived stress, two years after discharge (39). Discrepancies in symptomatology may be related to differences in the time this information was collected (12 weeks vs. several months post discharge), gender differences (females only vs. both sexes), or in sample size. A substantial strength of this study is its novelty,

as previous findings were based on isolated case reports. This case-control study instead prospectively recruited incident TS cases and MI controls, which allowed us to rigorously characterize both groups and to capture detailed information on psychiatric history and psychotropic medications use. Furthermore, because data were abstracted from the medical record vs. self-reported by participants, we were able to avoid recall bias (i.e., patients with either condition may mistakenly report psychotropic medications use, which would bias results toward the null). Finally, cases and controls were remarkably similar in that they had fairly similar baseline characteristics, including, for example, a recent hospital admission. We were also able to adjust for confounding by indication by adjusting for history of anxiety disorders, which are associated with both the likelihood of receiving psychotropic treatment and CV risk. Given the complex association between psychiatric comorbidity, antidepressant use, and CV risk, addressing confounding by indication is critically important.

This study also has important limitations. Because of its observational nature, we cannot exclude residual confounding and the possible effects of changes in prescription patterns over time in the more recently enrolled TS cohort. Second, a diagnosis of psychiatric disorder was abstracted from the medical record vs. conducting a full diagnostic interview, which could have resulted in misclassification of depression or anxiety or simply carrying forward a historical diagnosis. Third, although we adjusted for anxiety, it is difficult to fully disentangle psychiatric morbidity from psychotropic medication use, as it is unlikely that these medications are prescribed to people without a mental disorder. Fourth, findings cannot be generalized to men or racial and ethnic minorities, given the substantial preponderance of white women in our samples. Because this condition overwhelmingly affects women, information on sex and race differences in clinical characteristics and prognosis is limited and should be addressed in future large studies.

Last, future research may consider additional moderating, mediating, and/or confounding factors in the relationship between TS and antidepressant use, such as medication details (e.g., class, dosage, prescribing diagnosis(es), polypharmacy) and the presence of physical or emotional triggers.

In sum, findings from this rigorous case-control study suggest that the pre-admission use of serotonin and catecholamine reuptake inhibitors could increase the risk of TS. Even if we did not explicitly measure associations with TS recurrences, such medication could also potentially increase the risk of recurrences in TS survivors. While associations with SSRIs alone were non-significant, it is possible that their use together with catecholamine reuptake inhibitors may increase TS risk.

These findings could have clinical implications. First, they highlight the importance of obtaining a detailed psychiatric history in patients admitted with TS, including the use of psychotropic medications. The use of psychotropic treatment in these patients is often overlooked and consequently, cases of drug-induced TS might be underestimated. Furthermore, these findings suggest that risks associated with catecholamine or serotonin reuptake inhibitors use in TS survivors should be carefully considered and weighed against use of other psychotropic medications with a different mechanism of action (e.g., paroxetine, sertraline, or non-pharmacological approaches such as CBT depending on the underlying diagnosis).

Acknowledgments – Dr. Elana Rudavsky, M.D. for assisting with the development of psychiatric medication surveys.

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Table 1 – Baseline characteristics of cases and controls

	TS = 98	MI = 32	*p*†
Age (years) (Mean ± SD)	64.0 ± 10.2	64.6 ± 15.3	0.85
Race			0.013
Prefer not to answer	4 (4%)	6 (19%)	
American Indian or Alaskan	0	0	
Asian or Pacific Islander	0	0	
Black or African-American	1 (1%)	1 (3%)	
Hispanic/Latino	3 (3%)	0	
White (non-Hispanic)	90 (92 %)	25 (78%)	
Education			0.22
Prefer not to answer	1 (1%)	0	
≤ High School diploma	31 (32%)	19 (59%)	
College or some college	58 (59%)	13 (41%)	
Post-graduate	8 (8%)	0	
Medical History			
Family history of coronary heart disease	33 (34%)	16 (50%)	0.15
Diabetes mellitus	17 (17%)	14 (44%)	0.005
Hyperlipidemia	41 (42%)	19 (59%)	0.13

Table 1 – Baseline characteristics of cases and controls

	TS = 98	MI = 32	*p*†
Hypertension	53 (54%)	22 (69%)	0.21
Anemia	5 (5%)	0	0.33
Asthma	7 (7%)	0	0.19
Cancer	15 (15%)	2 (7%)	0.24
COPD	14 (14%)	4 (13%)	>0.99
MI	9 (9%)	6 (20%)	0.20
Coronary bypass	1 (1%)	2 (6%)	0.15
Ever a smoker	31 (32%)	7 (22%)	0.41
Percutaneous coronary intervention	1 (1%)	0	>0.99
Stroke	1 (1%)	0	>0.99
Pre-admission beta-blockers	12 (12%)	16 (50%)	<0.001
Admission Systolic blood pressure (mmHg) (Mean ± SD)	125 ± 25	130 ± 23	0.30
Admission Diastolic blood pressure (mmHg) (Mean ± SD)	75 ± 18	75 ± 19	0.93
Heart rate (bpm) (Mean ± SD)	85 ± 20	85 ± 17	>0.99
Admission ejection fraction (%) (Mean ± SD)	40 ± 14	48 ± 12	0.025
Peak troponin (ng/ml) (Mean ± SD)	3428 ± 3621	6761 ± 7774	0.39

* Values are n (%) unless otherwise indicated

† *T-test* or chi-square

TS = takotsubo syndrome; MI = Type 1 myocardial infarction

Table 2 – Psychiatric history and psychologic symptoms, by group

	TS = 98	MI = 32	*p*†
Pervasive developmental disorder (autism, Asperger's)	0	0	n/a
Attention-deficit and disruptive behavior disorder (ADHD)	4 (4%)	0	0.57
Delirium, dementia, amnesia, and other cognitive disorders	0	0	n/a
Substance-related disorder	4 (4%)	0	0.57
Schizophrenia and other psychotic disorders	0	0	n/a
Mood disorders (depressive disorder, bipolar disorder)	31 (32%)	7 (22%)	0.41
Anxiety disorders (generalized anxiety disorder, social anxiety disorder)	31 (32%)	3 (9%)	0.024
Panic disorder, phobias, obsessive-compulsive disorder, post-traumatic stress disorder	6 (6%)	1 (3%)	0.84
Eating disorders (anorexia nervosa, bulimia nervosa)	1 (1%)	0	>0.99
Sleep disorder	11 (11%)	1 (3%)	0.31
Personality disorder	1 (1%)	0	>0.99
Any psychiatric condition	49 (50%)	9 (28%)	0.050
Post-discharge HADS anxiety scores	6.3 ± 4.2	3.5 ± 3.7	<0.001
Post-discharge HADS depression scores	4.3 ± 3.5	3.4 ± 3.2	0.18

TS = takotsubo syndrome; MI = Type 1 myocardial infarction

Table 3 – Use of psychotropic medications prior to admission, by group

	TS = 98	MI = 32	*p*†
Any psychotropic medication	42 (43%)*	4 (13%)	0.004
SSRI	20 (21%)	4 (13%)	0.46
NaSSA	1 (1%)	0	>0.99
SNRI	11 (11%)	0	0.10
SARI	6 (6%)	0	0.34
TCA	3 (3%)	0	0.75
Any SSRI, NaSSA, SNRI, SARI, or TCA	37 (38%)*	4 (13%)	0.014
Psychostimulants	3 (3%)	0	0.75
Benzodiazepines	9 (9%)	0	0.17
Antipsychotics (1st, 2nd, and 3rd generation)	7 (7%)	0	0.27

*Totals do not match because some participants took multiple categories of medications.

TS = takotsubo syndrome; MI = Type 1 myocardial infarction
SSRI = Selective serotonin reuptake inhibitors
NaSSA = Noradrenergic and specific serotonergic antidepressants
SNRI = Serotonin-norepinephrine reuptake inhibitors (SNRI)
SARI = Serotonin-2 antagonist and reuptake inhibitors (SARI)
TCA – tricyclic antidepressants
No women in either group were taking norepinephrine reuptake inhibitors, norepinephrine-dopamine reuptake inhibitors (NDRI), monoamine oxidase inhibitors (MAOI) or mood stabilizers (lithium) at admission.