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## Review Article

# Psychiatric Illness in Takotsubo (Stress) Cardiomyopathy: A Review



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**Background:** Takotsubo cardiomyopathy (TC), also known as stress-induced cardiomyopathy, has been increasingly described in relation to psychiatric illness. **Methods:** We performed a literature review to identify the key findings related to psychiatric illness in TC that may be relevant to the practice of mental health and other health care providers. **Results:** The association of psychiatric illness with TC in addition to the spectrum of psychiatric illness found in TC, the role of exacerbation or treatment of psychiatric illness in triggering TC, different modes of presentation, prognostic implications, and long-term management of psychiatric illness

in TC are discussed. Additionally, we review the limitations of the pre-existing literature and suggest areas of future research. **Conclusions:** There is a strong association between pre-existing psychiatric illness, particularly anxiety and mood spectrum disorders, and TC. Acute exacerbation of psychiatric illness, rapid up-titration or overdose of certain psychotropic agents, and electroconvulsive therapy may trigger TC. Further studies are needed to better evaluate the prognostic significance and long-term management of psychiatric illness in TC.

(Psychosomatics 2018; 59:220–226)

**Key words:** Takotsubo, stress cardiomyopathy, psychiatric illness, depression, anxiety.

### INTRODUCTION

Takotsubo cardiomyopathy (TC), also known as stress-induced cardiomyopathy, apical ballooning syndrome, and broken heart syndrome, is an increasingly diagnosed condition.<sup>1</sup> TC is commonly recognized as transient left ventricular dysfunction that may mimic acute coronary syndrome but is without angiographic evidence of obstructive coronary artery disease.<sup>2</sup> Basic demographics of TC are provided in Table 1.<sup>3–5</sup> The condition is typically diagnosed in the setting of an acute emotional or physical stressor (also referred to as triggers) and should resolve with time. However, despite the general conception as a benign disorder, TC is associated with a similar rate of severe in-hospital

complications (including death) as acute coronary syndrome and can recur with time.<sup>3</sup>

In recent years, there has been an ever-increasing number of studies linking psychiatric illness and TC.<sup>3–5</sup> Most of these studies have been retrospective in nature

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**TABLE 1. Baseline Characteristics in TC. Ranges Are Derived From Select Larger-Cohort Studies.<sup>3-5</sup> Typical TC Variant Refers to Apical Predominant Wall Motion Abnormality**

Age, years	60-69
Female (%)	78-92
White (%)	72-84
Medicaid insurance (%)	5-11
Chest pain (%)	47-76
Dyspnea (%)	46-47
Physical trigger (%)	36-72
Typical TC variant (%)	81-86
Pre-existing psychiatric illness (%)	29-37
Pre-existing mood disorder (%)	18-26
Pre-existing anxiety disorder (%)	14-22

and include a large number of case reports/series of patients with pre-existing or active psychiatric illness experiencing TC. In this article, we seek to summarize the key findings of the pre-existing literature on this topic that may be useful for mental health and other health care providers involved in the care of patients with TC. We also attempt to point out the limitations of the pre-existing literature and suggest areas of future research.

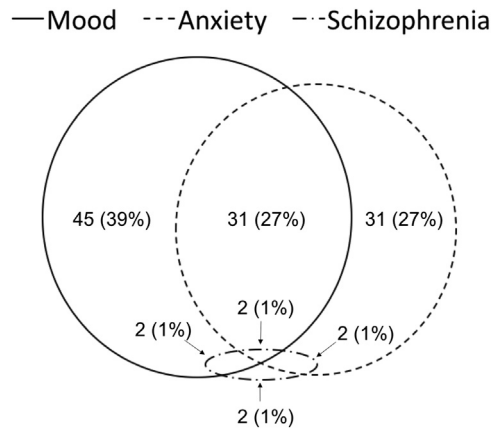
**METHODS**

We conducted a comprehensive search of the pre-existing English language literature using the MEDLINE (U.S. National Library of Medicine) and PubMed (U.S. National Library of Medicine and National Institutes of Health) databases (1966-2017). Search terms included the keywords *takotsubo*, *takot-subo*, *stress cardiomyopathy*, *stress-induced cardiomyopathy*, *apical ballooning syndrome*, and *broken heart syndrome*, in addition to *psychiatric illness*, *mood disorder*, *depression*, *anxiety disorder*, *panic attack*, *panic disorder*, *schizophrenia*, *psychosis*, *antidepressant*, *antipsychotic*, and *electroconvulsive therapy*. The reference lists of the published articles retrieved in the literature search were also reviewed for additional relevant studies. The largest scale studies with sufficient data on pre-existing psychiatric illness were used to provide baseline demographics for the review.<sup>3-5</sup> Figure 1 was borrowed from a prior publication from our group; the data from that publication was used to create Figure 2.<sup>4</sup>

**PRE-EXISTING PSYCHIATRIC ILLNESS AND TAKOTSUBO CARDIOMYOPATHY**

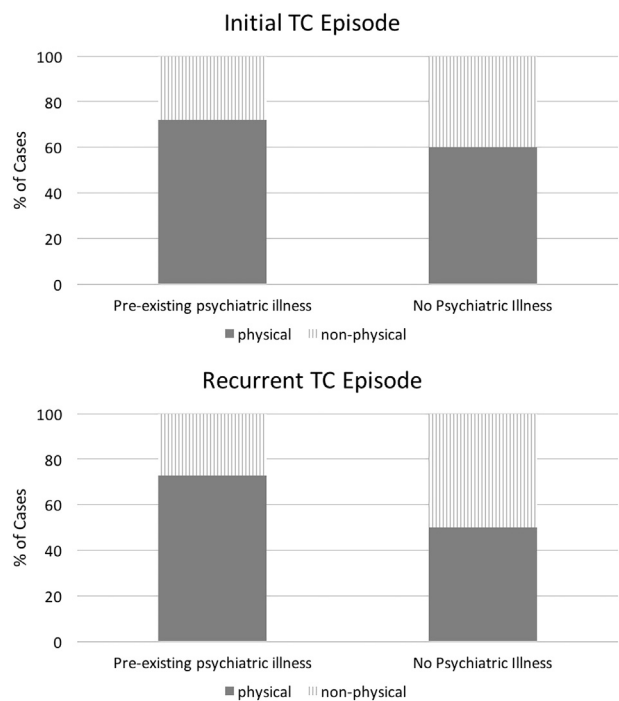
The association of TC with comorbid psychiatric illness has been previously reported.<sup>3,5</sup> Of note, increased age and female sex are known risk factors

**FIGURE 1. Spectrum of Pre-existing Psychiatric Illness in TC (Borrowed, With Permission, From the Original Source)<sup>4</sup>.**



for certain psychiatric illnesses, such as depression, and TC is most classically described among postmenopausal women.<sup>3,6,7</sup> Nevertheless, even when controlling for age and sex, there is a higher burden of pre-existing psychiatric comorbidity in TC patients compared to controls with acute coronary syndrome.<sup>3</sup>

**FIGURE 2. Mode of TC Trigger. Percent of Cases Triggered by Physical vs Nonphysical (Including Emotional) Stressors Are Shown<sup>4</sup>.**



## Psychiatric Illness in TC

The true etiology behind the association of TC and psychiatric illness is largely unknown, and explanations are speculative in nature. The role of the brain-heart axis in the pathophysiology of TC is thought to account for cases of TC secondary to primary neurological processes.<sup>3,8,9</sup> One of the leading postulated mechanisms behind TC is that of catecholamine excess, and patients with pre-existing psychiatric illness have been thought to be at increased risk of TC due to disproportionately high catecholaminergic responses in addition to increased cardiac sympathetic sensitivity.<sup>10</sup> Additionally, as described below, pharmacotherapy for psychiatric illness has also been described as a potential trigger of TC.<sup>11</sup> Overall, the pathophysiology of TC, and hence the cause for its demographic and clinical associations, need further elucidation.

### SPECTRUM OF PRE-EXISTING PSYCHIATRIC ILLNESS IN TAKOTSUBO CARDIOMYOPATHY

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As noted in [Table 1](#), roughly one-third of patients with TC have some form of pre-existing psychiatric illness. In prior case reports and retrospective cohort studies, diagnoses of mood disorders, anxiety disorders, schizophrenia-spectrum and other psychotic disorders, adjustment disorders, and neurocognitive disorders have been described in relation to TC.<sup>3,4,12,13</sup> In a previous study, we described the spectrum of psychiatric illness in TC ([Figure 1](#)).<sup>4</sup> There is a high prevalence of mood and anxiety disorders with a significant proportion of patients with multiple diagnoses.<sup>4</sup>

Despite the clear association of TC with psychiatric illness as a broad entity, its independent association with individual disorders remains disputed. The largest point of debate and inconsistency in the literature remains the association of TC with mood vs anxiety disorders. In a few small retrospective case-control studies, only pre-existing anxiety disorders (and not mood disorders) were associated with TC.<sup>14,15</sup> However, in the International Takotsubo Registry, patients with TC had significantly higher rates of depression and anxiety compared to controls.<sup>3</sup> A large observational study with over 24,000 patients from the National Inpatient Sample also found higher prevalence of anxiety and mood disorders in patients with TC compared to controls.<sup>5</sup> Overall, the larger studies on TC have demonstrated a link of TC with

both anxiety and mood disorders, and the confounding data come from largely underpowered studies. The association of other psychiatric illnesses, including schizophrenia-spectrum and other psychotic disorders, with TC remains largely unknown and an area for future research.

### EXACERBATION OF PSYCHIATRIC ILLNESS AS TAKOTSUBO CARDIOMYOPATHY TRIGGER

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In addition to the association of TC with pre-existing psychiatric illness, there is evidence for acute exacerbations of psychiatric disorders as potential triggers of TC. Prior case reports have described exacerbations of anxiety, depression, mania, and psychosis as potential causes of TC episodes.<sup>12,16</sup> In the International Takotsubo Registry, ~10% of patients were diagnosed with “acute psychiatric disorders” with 4% and 1% with mood and anxiety disorders, respectively.<sup>3</sup> However, whether or not acute psychiatric decompensation was the trigger of each TC case was not reported. Currently, the proportion of TC cases clearly triggered by exacerbation of psychiatric illness, remains unknown.

The pathophysiology linking exacerbation of psychiatric illness with TC is largely speculative. As noted above, catecholamine excess is one of the most commonly cited potential mechanisms behind TC.<sup>10</sup> Increased serum catecholamine levels have been demonstrated in patients with mood and anxiety disorders and may explain the association between exacerbations of these disorders and onset of TC.<sup>17,18</sup> These findings invite questions regarding the role of psychiatric treatment in patients with pre-existing psychiatric illness in potentially reducing the risk of TC.

### TREATMENT OF PSYCHIATRIC ILLNESS: POTENTIAL TRIGGER OF TAKOTSUBO CARDIOMYOPATHY?

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In addition to acute exacerbation of psychiatric illness, changes in psychotropic medications have also been shown to trigger TC. Multiple reports have linked both the up-titration and overdose of serotonin-norepinephrine reuptake inhibitors (SNRI) with cases of TC.<sup>19,20</sup> Atomoxetine, a selective norepinephrine reuptake inhibitor (S-NRI), has also been reported

to trigger TC.<sup>21</sup> A recent review of the literature identified 22 cases of TC secondary to SNRI or S-NRI use.<sup>11</sup> Notably, to date, there have been no clear cases of selective serotonin reuptake inhibitors (SSRIs) as a trigger of TC.

Endogenous increase in serum norepinephrine is thought to be the potential trigger of TC in the setting of S-NRI or SNRI use.<sup>11</sup> Lithium has also been linked with increased serum catecholamine levels and has been reported as a trigger of TC.<sup>22,23</sup> Most of the cases of TC trigger secondary to S-NRI, SNRI, or lithium use were in the setting of relatively rapid up-titration or in overdose.<sup>19–21,23</sup> The risk of TC trigger when these medications are appropriately dosed and slowly up-titrated is less clear.

Electroconvulsive therapy (ECT), an effective treatment option for mood and psychotic disorders, has also been shown to trigger TC.<sup>24–26</sup> ECT is known to transiently and abruptly increase serum catecholamine levels during the induced seizure, which as stated above, is a proposed mechanism behind TC.<sup>27,28</sup> Moreover, primary epileptic seizures have been consistently described as triggers of TC; this may further explain the association of ECT with TC.<sup>29,30</sup> The absolute risk of TC with each ECT therapy remains unknown. Further research is needed to determine whether or not ECT is a safe treatment option for patients with pre-existing psychiatric illness and a history of TC.

#### EMOTIONAL VERSUS PHYSICAL TRIGGERS OF TAKOTSUBO CARDIOMYOPATHY

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Differential modes of triggering TC in patients with pre-existing psychiatric illness have been scarcely studied. In a prior study, we found that somewhat surprisingly, patients with pre-existing psychiatric illness present with TC more often following physical stressors than patients without pre-existing psychiatric illness (Figure 2).<sup>4</sup> Overall, there is no evidence that patients with pre-existing psychiatric diagnoses have initial presentations or recurrences of TC due to emotional triggers at a higher rate than patients with no psychiatric illness.<sup>4</sup> The current evidence seems to suggest that patients with pre-existing psychiatric illness are at increased risk of TC and that the diagnosis should be considered when appropriate even in the absence of clear emotional distress.

#### PROGNOSTIC IMPLICATIONS

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There are scant data on long-term outcome predictors in patients with TC. In a previous study, we demonstrated increased risk of TC recurrence in patients with pre-existing psychiatric illness.<sup>4</sup> As noted above, each episode of TC can be associated with considerable risk of morbidity and mortality.<sup>3</sup> However, psychiatric illness has not been associated with different long-term survival in patients with TC.<sup>3,4</sup> There is concern for insufficient statistical power to detect smaller associations given the relative rarity of TC and the low risk of recurrence (~2% per patient year).<sup>3</sup> Larger scale studies with lengthier follow-up periods are needed to further assess any long-term prognostic significance of acute or chronic psychiatric illness in TC.

#### LONG-TERM MANAGEMENT

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The ideal long-term management in TC, regardless of underlying psychiatric illness, is poorly delineated. In the International Takotsubo Registry, angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs), but not beta blockers, were associated with survival at 1 year of index diagnosis.<sup>3</sup> However, there are no large randomized trials assessing the use of ACEIs, ARBs, or beta blockers following diagnoses of TC.

It is less known about the role of psychotropic medications in the management of patients with TC and psychiatric illness. As mentioned earlier, there is some evidence that rapid up-titration or overdose of SNRIs may trigger TC.<sup>11,19,20</sup> Given the lack of similar reports with SSRIs, it may be reasonable to consider an agent from this class for the treatment of mood or anxiety disorders in patients with TC. Of note, a relatively underpowered retrospective study of 78 patients with TC showed increased mortality and decreased recovery of ventricular function in patients taking SSRIs.<sup>31</sup> However, the findings of this study have not been confirmed in other studies, including those with substantially larger cohorts. Overall, there is no evidence of benefit of psychotropic treatment in patients with TC, and in fact, there is concern for association with trigger of TC or even mortality. Yet, there is evidence that patients with pre-existing psychiatric illness are at increased risk of recurrence; whether or not aggressive management of the

## Psychiatric Illness in TC

underlying psychiatric disorders can reduce the rate of TC recurrence is unknown.<sup>4</sup>

As noted above, ECT can be associated with triggering of TC through several postulated mechanisms.<sup>24–30</sup> Although there is no evidence to suggest that ECT is in some way contraindicated in patients with pre-existing TC, a heightened degree of clinical suspicion may be warranted for such patients.

### LIMITATIONS OF THE LITERATURE

As aforementioned, the current understanding of the underlying pathophysiology, clinical associations, and long-term management of TC is very limited. Despite increased recognition and higher rates of diagnosis in recent years, the disorder remains rare, and most published studies are in the form of case reports, case series, or retrospective observational studies based on small cohorts. The resulting limitations in statistical power hinder the study of TC in general, and even more so in the association of other variables, such as psychiatric disorders. Most importantly, in the absence of large-scale randomized controlled trials, the long-term management of TC is often subject to the clinician's gestalt and carried out in the absence of significant evidence.

Regarding the study of psychiatric illness in TC, there is significant limitation in the accurate assessment and analysis of the individual psychiatric diagnoses as reported in the medical record. In most cases, psychiatric diagnoses are obtained from review of the medical record and without real-time assessment of each patient for consistency with Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. This can lead to the under-, over-, or misdiagnosis of psychiatric disorders in such studies. Additionally, insufficient statistical power often limits the ability to analyze different psychiatric illnesses individually, and multiple diagnoses are commonly grouped together in the analyses. Hence, findings from such studies must be interpreted in the context of how "psychiatric illness" was defined with appropriate suspicion for potential confounding.

### FUTURE DIRECTIONS AND CONCLUSIONS

Having established an association between psychiatric disease and TC, further studies are needed to better assess the spectrums of such disease. In particular,

there is very little known regarding any association between nonanxiety and nonmood disorders with TC. Studies looking at such disorders, including schizophrenia, for a potential association with TC could add significant insight to this field. Where an association is already established (that is with mood and anxiety spectrum disorders), we suggest larger scale studies to better evaluate for the prognostic implications of these particular psychiatric illnesses in TC.

Assessment of a patient's emotional state at the time of presentation is often exclusively done per patient report, and there is concern for underreporting of emotional distress due to denial, minimization, and alexithymia.<sup>32</sup> Potential interviews with the significant others of patients with TC may help reveal any underreported degree of emotional distress among patients with or without pre-existing psychiatric illness. Illicit substance abuse which is also often assessed per patient report may be underestimated in patients with TC. Given the known high degree of co-occurrence between psychiatric illness and substance abuse, studies with urine toxicology screens may yield interesting results regarding any potential relationship between substance abuse and TC in patients with psychiatric illness.<sup>33</sup>

**TABLE 2. Key Points Summarizing the Current Knowledge of Psychiatric Illness in TC**

#### Key points

- There is a strong association between psychiatric illness and TC. The pathophysiology behind this association is largely speculative. Postulated mechanisms include the role of the brain-heart axis and catecholamine excess in patients with psychiatric illness.
- The spectrum of psychiatric illness associated with TC likely includes both anxiety and mood spectrum disorders. The association of other psychiatric illnesses, including psychoses, with TC remains largely unknown.
- In patients with psychiatric illness, TC may be triggered by physical or emotional stress.
- There are reports linking up-titration or overdose of SNRIs and S-NRIs with triggering of TC. The long-term safety profiles and ideal choice of psychotropic agents in patients with TC is poorly delineated.
- ECT has been extensively reported as a potential trigger of TC and should be used with caution in patients with a history of TC.
- Pre-existing psychiatric illness may be associated with increased recurrence of TC; however, other long-term prognostic implications are unknown.
- Further studies are needed to better evaluate the management of psychiatric illness in TC, with a focus on the role and safety profile of pharmacotherapy and ECT.

The management of psychiatric illness in TC, as a reflection of TC in general, is in great need of larger scale prospective studies and randomized trials. The safety and utility of treatment of psychiatric illness via pharmacotherapy or ECT in patients with history of TC are largely unknown. In the absence of trials, observational studies comparing outcomes of TC patients based on pharmacological treatment for psychiatric illness may help better evaluate the safety profile of these agents. Here, we suggest careful documentation of drug dosages to further evaluate

the notion that the trigger of TC with these agents is often in the setting of overdose or rapid up-titration. Regarding ECT, a case series of patients with a history of TC who subsequently undergo ECT may provide a starting point to better estimate the safety profile of this treatment modality in this patient population.

A summary of the current knowledge regarding psychiatric illness in TC is provided in [Table 2](#).

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