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THE IMPACT OF MENTAL DISORDERS AND PSYCHIATRIC TREATMENT ON THE OCCURRENCE AND COURSE OF TAKOTSUBO SYNDROME - REVIEW

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ABSTRACT

The aim of this review was to summarize existing knowledge on pathophysiology and analyze the influence of mental health disorders and psychiatric treatment on the occurrence and course of Takotsubo syndrome (TTS). This review paper was based on resources available in the PubMed database; articles were identified using the following keywords: [takotsubo] + [SNRI; SSRI; ECT; psychotherapy; anxiolytics; neuroleptics]. Additionally, a manual search of the literature cited in the articles was conducted. In order that we could treat TTS properly, we need to know its pathophysiology. The current approach regards a combination of various pathophysiological mechanisms rather than one mechanism alone. Although firstly considered as “stress” or “catecholamine”, Takotsubo cardiomyopathy is more than a simple reaction to stress or catecholamine surge. Novel data indicate a complex interplay between endothelial dysfunction, inflammatory, hormones and neurotransmitters. That leads us to the conclusion that we should treat it interdisciplinary. As there are currently no specific treatments for Takotsubo syndrome, a niche for neurocardiology is emerging. This could lead to developing new management approaches, including broader application of cognitive behavioral therapy and cooperation between cardiologists and psychiatrists.

KEYWORDS

Takotsubo, Psychotherapy, Mental Health Disorders, Antidepressants

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Introduction

“Tako-tsubo-like left ventricular dysfunction” was first described by Hikaru Sato in 1990.

Clinical presentation mimics acute coronary syndrome. Patients frequently present with acute-onset chest pain and dyspnea occurring in association with an acute stressful event. ECG changes may suggest acute ST-segment-elevation myocardial infarction, but invasive coronary angiography shows no abnormalities. Therefore, the diagnosis is often one of exclusion.

For years there was a huge gap in knowledge about TTS. From catecholamine, transient thrombosis, multivessel spasm and microvascular spasm hypotheses to hormonal, metabolic, inflammatory or genetic factors, research developed through the years, but none of them fully captured the nature of TTS.

Along with the development of imaging techniques, like fMRI, PET or SPECT we could better understand the link between heart and nervous system, and with progress of molecular studies we could explore metabolic pathways of TTS. This changed the approach to TTS as a combination of various pathophysiological mechanisms rather than one mechanism alone.

There are certain similarities between heart and brain tissues, including the fact that both organs exhibit electrical activity, as well as their high energy demands and limited capacity for regeneration following cell death (Schnabel et al, 2021).

Mental health disorders (MHD) and cardiovascular diseases (CVD) are common comorbidities, which suggests that these conditions may share common pathophysiological pathways. Lifestyle-related factors, dysfunction of hormonal systems, and an imbalance between pro- and anti-inflammatory factors are taken into account. There are also shared genes involving energy metabolism, stress response pathways, circadian rhythms, inflammatory processes, and neurotransmission, associated with both MHD and CVD. For example, intra-abdominal and epicardial adipose tissue have been observed in patients with depression, however it is not clear whether depression causes it directly or changes lifestyle choices (Schnabel et al, 2021).

Moreover, depression and chronic stress have been linked to decreased hippocampal volume and gray matter loss, and these anatomical alterations in the cerebrum have been connected to changes in the hypothalamic–pituitary–adrenal axis in response to stress (Sethi et al, 2022).

The first to directly prove the brain's involvement in TTS were Suzuki et al. Due to single-photon emission computed tomography they were able to observe changes of cerebral blood flow during the acute phase. It increases in the areas associated with stimulation of the sympathetic nervous system, like hippocampus, brainstem and basal ganglia, and decreases in the prefrontal cortex. These changes, although gradually subsiding, are still present in the chronic phase with full recovery of cardiac wall motion (Suzuki et al, 2014).

In this review, we summarize the current state of knowledge regarding the pathophysiology of Takotsubo syndrome and its associations with psychiatric disorders and psychiatric treatment.

Methodology

A PubMed database search for reviews, meta-analyses and case reports until July 2026 was performed using a combination of keywords: [takotsubo] + [SNRI; SSRI; ECT; psychotherapy; anxiolytics; neuroleptics].

Additionally, a manual search of the literature cited in the articles was conducted.

Results

Pathophysiology

Currently, we could describe Takotsubo pathophysiology on a macro and microscopic level.

There is a brain-heart axis, where the central autonomic network (CAN) regulates the cardiovascular system. CAN consists of the insular cortex, anterior cingulate cortex and the amygdala, and it comprises regions in brain that mediate the cardiac response to stimuli through autonomic nervous system (ANS) and hypothalamus-pituitary-adrenal (HPA) axis (Brazdil et al, 2022).

Within this network, the insula seems to play a crucial role in the regulation of the heart-brain axis. Insular abnormalities are associated with adverse cardiovascular outcomes. For instance, strokes involving the insular cortex are correlative with both bradycardia and heart blocks, as well as with supraventricular or ventricular tachyarrhythmias. This could be explained by lateralization of cardiovascular control, where the right insula exhibits sympathetic predomination, while the left insula is related to parasympathetic regulation (Brazdil et al, 2022).

In TTS patients reduced volume and cortical thickness, lower functional connectivity and differences in insular activation were found (Steiger et al, 2022).

Another important part of this system is amygdala, which is a key component of the brain's salience network involved in stress. Tawakol et al. demonstrated that resting metabolic activity within this structure significantly predicts the development of cardiovascular disease, independently of established cardiovascular risk factors. Moreover, they associated amygdalar activity with increased haemopoietic activity and increased arterial inflammation (Tawakol et al, 2017).

In a 2022 study Steiger et al. observed lower brain responses to aversive versus positive visual stimuli in regions involved in affective and cognitive emotional processes in patients in the acute phase of TTS. In contrast, in the recovery phase the brain responses were higher.

Such changes in regions associated with emotional processing may explain why stressful life events can trigger TTS episodes as these regions are co-involved in the regulation of the cardiovascular system. Furthermore, patients with TTS exhibited higher functional connectivity of the inferior frontal gyrus within the resting-state neural network (Steiger et al, 2022).

The ballooning of the heart in Takotsubo syndrome is not accidental. It is related to spatial organization of beta-adrenergic receptors in myocardium, with higher density at the cardiac apex. When concentration of circulating adrenaline is increased the receptors signal via the G α i pathway instead of G α s, which leads to decreased inotropy, chronotropy and lusitropy. The phosphoinositide 3-kinase/protein kinase B (AKT) survival pathway,

which is transiently activated during the acute phase of TTS, regulates metabolism, cell proliferation and apoptosis. The switch from G α s to G α i coupling and activation of the AKT pathway down-regulate myocardial function, which moderate the extent of acute myocardial injury (Sethi et al, 2022).

The role of the sympathetic nervous system has been widely discussed to date, whereas the role of the parasympathetic nervous system has often been overlooked.

It currently appears that the wall motion patterns in TTS are linked to the sympathetic innervation of the heart and correlate with the distribution of the sympathetic nerve endings in the myocardium. Moreover, reduced parasympathetic modulation of heart rate is observed in patients with TTS (Brazdil et al, 2022).

On the other hand, there are researchers, who are sceptical towards catecholamine theory. They point out that dobutamine stress testing only rarely causes TTS and the mean heart rate of approximately 86 beats/min and systolic blood pressure of approximately 131.8 mmHg at clinical presentation do not suggest a credible catecholamine-surge state. They presume that the essential mechanism for TTS is prolonged spasm which leads to the myocardial stunning. They propose ACh testing of endothelial dysfunction in the diagnosis of TTS (Angelini, Uribe & Tobis, 2021)

Due to no significant obstruction during coronary angiography in the acute phase of TTS, for a long time there was a belief that TTS patients are free from any coronary artery disease.

Angelini et al. used acetylcholine to test for spontaneous spasm and cardiac endothelial dysfunction in patients recovering from TTC. They observed a spastic effect on small distal vessels, which were believed to be CAD-free, and on arteries in women. They did not observe this effect on epicardial proximal arteries with coronary artery disease (CAD), especially in men.

Another important conclusion from their study could bring us closer to understanding the gender gap - men with CAD would be protected from TTC manifestation, because CAD would interfere with spasm. Authors believe that even nonobstructive CAD would have a stenting effect resulting from intimal thickening and annexed calcific deposits.

In 2022 Viceconte et al. introduced 'Established Mechanism Underlying TTS' and 'Novel Pathophysiologic Determinants of TTS'. On this basis stressors and predisposing factors activate central and autonomic nervous system, which causes catecholamine surge as well as cardiac sympathetic abnormalities. Circulating catecholamine excess would cause either direct myocardial injury, microvascular spasm, myocardial oxygen consumption or left ventricular contractile gradient. Then, acute dysfunction of left ventricle activates survival pathways and stunning (Viceconte, Petrella, Pelliccia, Tanzilli, & Cicero, 2022)

In study on patient-specific induced pluripotent stem cell-derived endothelial cells Yang et al. determined that epinephrine cause reduced cell migration, lower nitric oxide production, lower Dil-Ac-LDL uptake, reduced mitochondrial membrane potential, reduced ATP production and inhibition of tube formation and wound healing. Catecholamine surges increase the release of vasoconstrictors like endothelin-1 and angiotensin II, while diminishing cardioprotective NO levels. Epinephrine combined with inflammatory stimuli like lipopolysaccharide amplifies pro-inflammatory cytokines such as IL-6 and IL-1 β . Epinephrine affected both types of cells, from healthy and TTS donors, but TTS patient-derived endothelial cells exhibited abnormal functional features even without being exposed to epinephrine. This study highlights the key role of inflammatory signaling pathways in catecholamine-induced endothelial dysfunction in the course of TTS (Yang et al, 2026).

In the 2026 review Madaudo et al. presented pathophysiological mechanisms linking stress to myocardial injury and remodeling in TTS. Psychological or physical stressor activates the sympathetic nervous system and the HPA axis, leading to epinephrine and norepinephrine release. An excess of catecholamines contributes to microvascular dysfunction and epicardial coronary vasospasm, as well as exerts a direct cardiotoxic effect (mediated by intracellular calcium overload and activation of the calcineurin-NFAT signaling pathway), which ultimately results in myocardial stunning and injury.

Myocardial injury activates the following cascade: NLRP3 inflammasome activation leads to release of IL-1 β and IL-18, followed by increased expression of IL-6 and TNF- α , generation of reactive oxygen species (ROS), and macrophage infiltration with M1 to M2 polarization. These inflammatory pathways promote fibrosis, angiogenesis and adverse ventricular remodeling. Oxidative stress and inflammation sustain each other potentially prolonging myocardial dysfunction beyond the period of hemodynamic recovery (Madaudo et al, 2026).

Currently it is unclear whether inflammation is a primary driver of TTS and if modulating inflammatory pathways can influence the course of TTS, although markers of inflammations are being considered for diagnostic and prognostic purposes. In the recent observational study Novo et al. compared blood cell subtypes of patients with TTS and ACS. They observed that TTS patients had higher levels of monocytes and lower lymphocyte monocyte ratio than ACS patients upon admission to the hospital. Additionally neutrophil lymphocyte ratio and lymphocyte monocyte were recognised as ratio independent predictors of long-term mortality in TTS (Novo et al, 2025).

Scientists have not identified any specific genes underlying the disease. However, gene expression could play a role in TTS pathophysiology. MicroRNAs (miRNAs) are molecules that regulate the expression of genes involved in inflammation, oxidative stress, apoptosis, vascular tone and energy metabolism. Moreover, miRNAs could be measured in blood, which makes it a candidate for biomarker (Sousa, Martins, Luís, & Serralheiro, 2025).

The research on miRNAs is still ongoing, but several types of miRNA have been singled out as diagnostic biomarkers or molecules with a potential protective effect.

miR-16 and miR-26a are considered mediators of TTS pathogenesis due to their involvement in stress and depression pathways and their elevated concentration in TTS versus STEMI or healthy controls. Importantly, adrenaline administration alone does not directly stimulate expression of miR-16 or miR-26a, which suggests that chronic psychological stress or underlying neuropsychiatric conditions could create molecular predisposition to acute injury upon subsequent catecholamine surges.

The elevation of miR-16 and miR-26a is consistent with documented psychosocial triggers of TTS and supports the hypothesis of neurocardiogenic mechanisms involving the central nervous system and dysregulation of the stress axis (Sousa, Martins, Luís, & Serralheiro, 2025).

Contrarily, miR-1 and miR-133a, markers of myocardial injury, increase more in STEMI than in TTS, although still elevated in both compared to healthy controls.

Taken together, miR-16, miR-26a, miR-1, and miR-133a, could constitute a panel for differentiation between TTS and STEMI. Authors of this unique signature reported a sensitivity of 96.77% and a specificity of 70.37% (Jaguszewski et al, 2014).

Another interesting observation from Jaguszewski's study was increased plasma concentration of endothelin-1 (ET-1) and decreased (ET-1)-regulating miRNA-125a-5p in patients with TTS (Jaguszewski et al, 2014). Endothelin-1, besides being a strong vasoconstrictor, can also promote the production and release of additional autocrine/paracrine signaling agents in the heart.

Small GTP-binding protein GDP dissociation stimulator, which was recognized as a central mediator of E2-conferred female cardioprotection against ferritinophagy-mediated ferroptosis in TTS in mice (Wang et al, 2023). This could be a potential factor explaining the gender difference in prevalence, however more research is needed to confirm this phenomenon in humans.

Epidemiology

Takotsubo syndrome affects 2–3% of all patients and 5–6% of female patients presenting with acute coronary syndrome, although it may be underrecognized and underdiagnosed, particularly in individuals with coexisting coronary artery disease (Singh et al, 2022).

There is a marked disparity in the incidence of TTS, with postmenopausal women accounting for 90% of patients.

However, younger patients are more likely to be male, or have atypical takotsubo, fewer comorbidities, and acute neurological or psychiatric disorders, and to develop in-hospital complications (Singh et al, 2022). In-hospital mortality in young patients is no different from that of other groups (Wittstein, 2020), but mortality rate is higher in men than in women (Krishnamoorthy et al, 2015). In a 2010 study conducted by Kurisu et al, researchers suggested that physical stress might be a more important factor of TTS in males than in females. In the majority of the men studied, the TTS phenomenon was associated with underlying medical conditions (Kurisu et al, 2010). Besides differences in functioning of central and autonomic nervous systems, another explanation could be different stress management in men and women.

Type D personality (Negative Affectivity, Social Inhibition) is associated with an increased risk of adverse events in patients suffering from coronary artery disease (Lodder, 2023). In one study authors linked Type D personality to TTS, emphasizing the role of the social inhibition in increased biological reactivity to acute emotional stress (Compare et al, 2013).

In another study researchers highlighted cluster C personality disorders (Dependent, Avoidant, Obsessive-Compulsive) as significant indicators of vulnerability to TTS. They also stated that, in post-acute phase, TTS should be managed through psychotherapeutic interventions (Müller, Sperling, & Kornhuber, 2017). However, since these studies involved small groups of patients, the results need to be confirmed by further, larger studies.

According to Bagnasco's research, in patients with TTS, depression could occur between 20.5 and 48% of the patients, and anxiety between 25 and 56% (Suárez Bagnasco & Núñez-Gil, 2016). They also claim that anxiety increases the probability of developing Takotsubo syndrome, which was consistent with a later study

by Oliveri et al. In 2020 they analyzed studies about psychiatric disorders and TTS and stated that anxiety, more precisely chronic anxiety disorders, are related to the occurrence of TTS. Moreover, they claimed that depression is not a statistically significant factor in developing TTS (Oliveri et al, 2020). However, in a study from 2025 authors did not confirm that anxiety is a statistically significant factor in TTS. According to them, the conflicting results may arise from differences in tools used to assess anxiety (Obrutu et al, 2025).

Tan et al. analyzed publicly available U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database and noticed that TTS associated with SSRIs and SNRIs prevails in young and middle-aged adults (18-65) in contrary to TTS usually afflicting menopausal women (65 or older), (Tan et al, 2024). However, it has been observed that TTS generally develops at a younger age in patients with pre-existing psychiatric disorders. Moreover, they also have higher risk of recurrence (Nayeri et al, 2017). Interestingly, they are more likely to present with TTS triggered by a physical stressor (Nayeri et al, 2017).

In a large observational study with over 24,000 subjects researchers demonstrated that patients with TTS were less likely to have cardiovascular disease factors but were more likely to have cerebrovascular events, drug abuse, anxiety disorders, mood disorders, malignancy, chronic liver disease and sepsis. Moreover, they were mostly white and lived in wealthier neighbourhoods (El-Sayed, Brinjikji & Salka, 2012).

In 2020 Cattaneo et al. conducted a fMRI study on a group of 50 patients, comprising individuals with microvascular angina, Takotsubo syndrome and previous acute myocardial infarction. They discovered that TTS patients have higher resting state functional activity in specific areas of the central autonomic nervous system involved in interoceptive pain awareness, negative emotional status, and visceral sympathetic activity and parasympathetic regulation (Cattaneo et al, 2020).

In general resting sympathetic nervous activity increases with age. Adult women between puberty and menopause generally present lower HPA axis and autonomic responses compared to men of the same age. Except for the luteal phase, when the response is stronger and may approach the level observed in men. During pregnancy the response is attenuated. An increase in the reactivity of the sympathoadrenal system is observed after menopause. That responsiveness attenuates during oral hormone replacement therapy. It is likely that these sex-related differences in autonomic nervous system function stem from exposure to estrogens, which attenuate the reactivity of the sympathoadrenal system. However, the HPA axis is more complex, and current evidence points to the influence of other modifying factors, such as vasopressin (AVP) and the regulation of circulating cortisol bioavailability by corticosteroid-binding globulin (CBG). These differences in stress responsiveness may stem from evolutionary pressure that led to the emergence of a mechanism protecting the fetus from the adverse effects of maternal stress responses (Kajantie & Phillips, 2006).

Takotsubo syndrome is extremely rare during pregnancy, with the majority of cases arising in the postpartum period. As in the general population, pregnancy-associated TTS occurred more often in patients with anxiety, depression or bipolar. Considering that most cases happen on the day of childbirth or a few days later, this could be caused by the drugs administered amid cesarean section or physical and emotional changes in the postpartum period (Mogos, Ahn, Muchira, Osmundson & Piano, 2023). TTS that developed during pregnancy has a higher proportion for adverse fetal outcomes than TTS in the postpartum period. Although TTS associated with cesarean section occurs more rapidly than TTS after vaginal delivery, there are no significant differences in the degree of systolic dysfunction or in use of advanced therapies such as ventilator support, intra-aortic balloon pump, and extracorporeal membrane oxygenation (Udemgba et al, 2024).

Treatment

Currently, there is no specific treatment for Takotsubo Syndrome. Medications that are typically administered in myocardial infarction and heart failure are used.

In a meta-regression analysis of beta blockers, ACE-inhibitors and angiotensin receptor blockers and recurrences of TTS researchers confirmed that rates of recurrence of TTS are lower in populations of patients with higher rates of treatment with ACEi/ARB. However, they emphasize that this fact does not prove that ACE inhibitors prevent TTS recurrence, because results may stem from the fact that the groups prescribed with ACEi were under closer monitoring (Brunetti et al, 2016).

Some authors suggest that sodium-glucose cotransporter 2 inhibitors could be beneficial in patients with Takotsubo, however, they also note that the evidence is limited, as most information comes from case reports or animal model studies (Prosperi et al, 2024).

More recently there was a study on 22 patients diagnosed with TTS, who were treated with Sodium-Glucose Cotransporter 2 Inhibitors in acute phase. Authors concluded that dapagliflozin and empagliflozin

could contribute to lowering myocardial edema burden and enhancing LVEF resulting in cardiac magnetic resonance, and therefore precipitate recovery of myocardial function (Arcari et al, 2026).

In the largest real-world TTS cohort, SGLT2Is were associated with lower long-term mortality. These findings support their consideration in TTS management and justify randomized trials to evaluate SGLT2i as adjunctive therapy. In this study mortality was significantly reduced in the SGLT2 inhibitors group compared to RAAS inhibitors with beta-blockers. SGLT2Is were associated with the largest reduction in mortality, followed by angiotensin receptor blockers, ACE inhibitors, and beta-blockers. Sacubitril/valsartan and MRAs showed no significant association with mortality (Rawish et al, 2026).

Of note, there is one case report about canagliflozin causing euglycemic diabetic ketoacidosis (EDKA) and subsequently TTS. However canagliflozin is the most common SGLT2i associated with EDKA and is not registered to treat heart failure, unlike dapagliflozin and empagliflozin (Sabanci, Saaed, Bandi, Das & Wilcox, 2024).

Links between psychiatric treatment and TTS

Currently there are no guidelines for managing psychiatric conditions in TTS, however Nayeri et al in their analysis claimed that there is no evidence that psychiatric illness should be managed differently when coexisting with Takotsubo (Nayeri et al, 2017). The fact that pre-existing psychiatric illness is associated with higher risk of recurrent TTS underline the necessity for treating these conditions.

Antidepressant's influence on cardiovascular diseases is ambiguous. For instance in patients with ST-segment elevation myocardial infarction and major depressive disorder, the use of SSRIs was associated with lower all-cause mortality (Gopal et al, 2026).

There is some evidence that heart failure treatment could cause the remission of depressive symptoms (Angermann et al, 2020). Conversely however, SSRI may increase mortality risk in patients with heart failure (Schnabel et al, 2021).

Data on newer antidepressants is limited, especially when it comes to TTS. Promisingly, agomelatine - melatonin (MT1/MT2) receptor agonist and serotonin (5-HT_{2C}) receptor antagonist - shows antioxidant, antiinflammatory and antiapoptotic activity on cardiac tissue in animal models (Jia, Liu, Wu, Jia, & Sun, 2018), (Asci et al, 2022).

Despite few case reports about exacerbation of psychiatric disorders being potential trigger of TS, currently there is not enough data to be sure if it is meaningful (Nayeri et al, 2018).

Serotonin-norepinephrine reuptake inhibitors

Serotonin-norepinephrine reuptake inhibitors inhibit serotonin transporter and norepinephrine transporter which increases concentration of catecholamines in the neuronal synapses. Therefore, probability and frequency of neurotransmitter binding to postsynaptic receptors rises. In the literature review conducted by Vasudev et al. authors identified eight cases of SNRI-induced TTS, where most patients were taking venlafaxine. In these patients myocardial stunning could be caused by a block of cardiac fast inwards sodium current (Vasudev et al, 2016). Importantly, in the case of TTS caused by doubling the dosage of duloxetine, the patient was, at the same time, taking carvedilol (Selke, Dhar & Cohn, 2011).

We found only one case of possible TTS induced by milnacipran (Forman, Sutej & Jackson, 2011).

Within the group of serotonin-norepinephrine reuptake inhibitors venlafaxine has a 30-fold and duloxetine has a 10-fold selectivity for serotonin, and milnacipran is nonselective in blocking the uptakes of norepinephrine and serotonin. Therefore milnacipran has the best cardiovascular safety profile in this group (Forman, Sutej & Jackson, 2011).

There are also known cases when excessive use of venlafaxine led to cardiogenic shock (Elhami & Engerström, 2021).

On the other hand, in a recent study, patients with TS, then on SNRI, had lower mortality than patients without SNRIs (Shamaki et al, 2025).

Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors block serotonin transporter which increases serotonin activity. This class of antidepressants has little effect on dopamine or norepinephrine, with fluoxetine being an exception. In pharmacovigilance analysis from 2024 fluoxetine was second most common, after venlafaxine, antidepressant associated with TCM risk.

It has been demonstrated that in rats fluoxetine increases extracellular concentration of norepinephrine in the prefrontal cortex and in the hypothalamus (Perry & Fuller, 1997), (Bymaster et al, 2022). Since this

phenomenon was only studied on rats, we do not know whether it occurs in humans. However, in light of statistical data, caution should be exercised when using fluoxetine in at-risk patients, and consideration should be given to using other SSRIs or antidepressants from other classes.

In 2020 Tunzi et al. published a case report about a 64-year-old patient who experienced recurrent takotsubo cardiomyopathy, while receiving guideline-directed medical therapy. They added sertraline and cognitive behavioral therapy to GDMT. In follow-up after 1 month an echocardiogram showed no abnormalities, whereas after 1 year a significant reduction in anxiety symptoms and resolution of heart failure symptoms was observed. Two conclusions can be drawn from this study. Firstly, beta-receptor blockade, which should minimize the effects of excess catecholamine action on the beta-adrenergic receptors in the heart, was insufficient in prevention of recurrence. Secondly, although it is not clear whether SSRI or CBT contributed to prevention of recurrence, it is clear that in this case SSRI did not contribute to TTS. It appears that a tailored combination of pharmacotherapy supported by psychotherapy was beneficial for this patient (Tunzi, Dinkha, Sharp & Gore, 2020).

Of note, about 80% of patients taking SSRIs/SNRIs antidepressants simultaneously use other medications (Tan et al, 2024). Extra caution is advised when using SSRIs/SNRIs concomitantly with other serotonergic medications, because this can lead to serotonergic syndrome, and subsequently TTS (Jang, Nam, Lee & Chang, 2019).

Tricyclic antidepressants

Although the tricyclic antidepressants inhibit serotonin transporters, there are no reports of TCA-induced TCM when used in standard dosage. In literature we found one case report about nortriptyline overdose causing TTS (De Roock et al, 2008). We therefore conclude that the probability of these drugs inducing TTS is low.

Lithium

Lithium inhibits the reuptake of serotonin and norepinephrine, which can cause catecholamine overload. Interestingly there are not so many cases of lithium-induced TTS compared to SNRI-induced TTS. Moreover, dosage were usually excessive in case of lithium, whereas in the case of SNRIs doses were generally standard (Kido & Guglin, 2017).

Vasconcelos et al presented a case report of a woman in her 60s with over 25 years history of taking lithium. At admission her lithium level was barely over the normal range, but in older adults pharmacokinetics change and in chronic use tissue concentration of lithium becomes higher which could not be appropriately reflected in serum levels (Vasconcelos, Mota & Silva, 2024).

There is also a case of a 65-year-old woman with bipolar disorder treated with lithium whose serum lithium concentration was over two times bigger than normal values (Papadopoulos et al, 2024).

Cases of Takotsubo occurring during therapy with other groups of antidepressant drugs were not found.

Anxiolytics

Another rare type of TTS is one occurring after benzodiazepine withdrawal or reduction. This is because abrupt withdrawal of the sedative action of BZDs on GABA causes hyperstimulation of the autonomic nervous system (Edinoff et al, 2021).

In Lafferty's case report a 67-year-old woman showed Takotsubo symptoms three days after decreasing dosage of clonazepam and fluoxetine at the same time, hence cause is not entirely clear (Lafferty et al, 2017). Stronger evidence comes from case of a 40-year-old woman who was hospitalized because of TCM three times, each time while attempting to discontinue lorazepam (Mahmud, Tosanovic, Deep & ElAmm, 2026).

Evidence is limited, but occurrence of TTS after withdrawal or reduction of anxiolytic agents, might suggest that this group of medications could be used in treatment or prevention of TCM. Another argument could be the link between TTS and anxiety. However, benzodiazepines, especially short-acting, should not be used chronically, because of the phenomenon of tolerance and severe potential for dependence.

Therefore we should search for more secure medication. Buspirone is nonbenzodiazepine anxiolytic with efficacy comparable to benzodiazepines without abuse, dependence and withdrawal symptoms of benzodiazepines (Jann, 1988). However, on the molecular level buspirone is believed to interact with dopamine and serotonin receptors (Taylor, Eison, Riblet & Vandermaelen, 1985). There is no clear evidence whether it could affect adrenergic receptors in the heart, therefore whether it could be safe and effective in Takotsubo. Hydroxyzine is used in treating anxiety and blocks histamine H1 receptors. However, patients tend to develop tolerance to antihistamines over time, and there are concerns regarding a high risk of bias in existing studies;

consequently, hydroxyzine is not currently recommended as a first-line treatment for generalized anxiety disorder (Garakani et al, 2020). Another promising medication could be pregabalin which showed effectiveness and good tolerance when compared to SSRIs, SNRIs and benzodiazepines in treating generalized anxiety disorder (Cardoner et al, 2025).

In Zvonarev's review there is a statement that not only psychiatric drugs, but the beta-blockers are used to fight anxiety, especially in postmenopausal women, and can be prescribed for longer periods to control the production of the stress hormones (Zvonarev, 2019).

In the 2020 review Garakani et al. present novel treatments for anxiety disorders, including neuropeptides, neurosteroids and natural remedies (Garakani et al, 2020). Perhaps, with the development of medications for anxiety disorders, a drug substance helpful in treating TTS will emerge.

Neuroleptics

No cases of TTS induced by the use of neuroleptics at standard doses were identified in the searched databases.

However, a case of TTS was reported following neuroleptic malignant syndrome (NMS), which is a potentially fatal neurological disorder resulting from the use of antipsychotic drugs. In patients presenting with rigidity and fever, as well as symptoms of acute myocardial infarction, NMS associated TTS should be suspected. The authors emphasize the importance of avoiding dantrolene due to the potential for worsening of cardiomyopathy (Ullah et al, 2020).

Newer antipsychotics like risperidone, olanzapine or clozapine have been linked to adverse metabolic effects, such as changes in adiposity and insulin sensitivity or, in experimental models, reduced endothelial nitric oxide levels and increased oxidative stress. Ergo, these medications appear to have the potential to cause complications contributing to an increased cardiovascular risk (Schnabel et al, 2021).

Electroconvulsive therapy

Besides psychiatric pharmacotherapy, there are some cases where electroconvulsive therapy were considered as a main cause of TTS, though it is an extremely rare complication. The most recent review identifies only 24 cases of ECT-induced TTS in history (Kinoshita et al, 2023), whereas there are approximately 1.4 million courses of ECT delivered worldwide annually (Antosik-Wójcińska et al, 2021). A plausible mechanism is a catecholamine surge caused by ECT. As in most cases, TTS following ECT in large part affects post-menopausal women. The vast majority of patients recover from ECT-induced TTS. We found only one case report about a woman with schizophrenia who died 3 weeks after ECT because of TTS, but she had suffered from pneumonia and malnutrition, which could contribute to a fatal outcome (Muto, & Kyono, 2024).

On the other hand, there are cases of successful electroconvulsive therapy in patients who underwent TTS (Roy, Soufi & Greenway, 2024), even those who developed TTS following previous ECT treatment (Clifford, Chaudhry, Muscat, Connors & Whitesell, 2019), (Kent, Weston, Heyer, Sherman, & Prudic, 2009). The most common preventive measure during ECT retreatment was use of beta blockers. However, the type, dose and route of administration varied (Kinoshita et al, 2023).

In Kent's case report doctors administered esmolol - an intravenous cardioselective beta blocker with a very rapid onset and offset of action, and labetalol which has selective, competitive alpha1-adrenergic blocking and nonselective, competitive beta-adrenergic blocking activity, around the procedure, and metoprolol, selective beta-1-adrenergic receptors inhibitor, was used on a more long-term basis (Kent et al, 2009).

In Clifford's case report doctors used metoprolol 4 weeks before first post-ECT TCM and esmolol during the procedure (Clifford et al, 2019).

In Kezuka's case report they used bisoprolol fumarate patch before, during and after the procedure (Kezuka, Haruyama, Suzuki & Sakuma, 2024).

Despite receiving beta-blockers a patient could still develop TTS after ECT. Kinoshita et al. identified eight such cases (Kinoshita et al, 2023). Moreover, there were some concerns about lipophilic beta blockers, which cross the blood-brain barrier, and their influence on the central nervous system. But meta-analyses showed no evidence for the risk of new-onset depression after starting beta blocker treatment (Andrade, 2021). In the cases of successful ECT retreatments cited above, beta blockers with moderate to low lipophilicity were used.

Overall, beta-blockers are not flawless. In fact, in the GEIST registry, over 50% of patients who developed TTS have already been taking a beta-blocker, an ACE inhibitor, or an AT-II receptor antagonist, and in case of combination of a beta blocker and ACE inhibitor or AT-II antagonist, the recurrence rate was 28% (Tunzi et al, 2020).

In conclusion, we should consider the advantages and disadvantages of ETC, especially in postmenopausal women, as a predominant group of TTS. The use of beta-blockers around the procedure could be beneficial for some patients, however researchers emphasize the importance of seeking other cardioprotective agents (Kent et al, 2019). Further research is needed, as well as cooperation between the cardiology, anesthesiology and psychiatry teams to determine some guidelines for this group of patients.

Psychotherapy

As described above, structural changes in the brain are present in TTS. There is evidence that psychotherapy could alter brain structure as well (Malhotra & Sahoo, 2017). Hence, we can indirectly infer that this type of intervention would be beneficial for this group of patients.

Leissner et al. conducted a parallel, multicenter, randomized controlled trial with a wait-list control group on patients with myocardial infarction with nonobstructive coronary arteries (MINOCA) or Takotsubo syndrome with elevated symptoms of stress or anxiety. The aim of the study was to assess the patient-tailored internet-delivered cognitive behavioral therapy's effects on stress and anxiety in this group. Their analysis showed that especially patients who suffered from TTS could benefit from this type of intervention (Leissner et al, 2026).

In 2026 randomized controlled trial Gamble et al. purport that physical exercise or cognitive behavioral therapy improved left ventricular myocardial energetics compared with standard care (Gamble et al, 2026).

Unfortunately, research on psychotherapy in treating or preventing TTS is very limited.

As demonstrated in patients with anxiety disorders, cognitive-behavioral therapy normalizes excessive neural reactivity in the amygdala (Månsson et al, 2016).

At the same time, individuals with TTS have a higher baseline metabolic rate of amygdala activity relative to the activity of regulatory regions (ventromedial prefrontal cortex) compared to healthy individuals (Radfar et al, 2021).

The response to stressors such as those that could trigger TTS is governed by an ensemble of neural structures within the limbic system, which notably includes the amygdala

In this first longitudinal study to link regional brain activity to subsequent cardiovascular disease, heightened amygdalar activity independently and robustly predicted cardiovascular disease events. Amygdalar activity is involved partly via a path that includes arterial inflammation (Brazdil et al, 2022).

Discussion

It cannot be ruled out that brain changes are a consequence rather than a cause of cardiovascular dysfunction. However, existing studies tend to indicate that cardiovascular dysfunction is caused by autonomic nervous system dysfunction (Brazdil et al, 2022).

Influence of personality type or personality disorders is currently unclear.

Data on psychiatric medications in Takotsubo syndrome are incomplete. Whether TTS in psychiatric patients is the consequence of administered treatment or the disease itself remains unclear.

In men and postmenopausal women there is an increased reactivity of the sympathoadrenal system. Oral hormone replacement therapy may offer potential benefits to postmenopausal women.

It appears that the use of beta-blockers alone does not constitute a sufficient precaution for preventing recurrence. ACE inhibitors and angiotensin receptor blockers are probably more effective. There are also new potential therapeutic agents acting upon different steps of inflammation cascade, for instance anakinra, TNF- α inhibitors, colchicine or antioxidants.

Researchers propose measuring microRNA and markers of inflammation to establish diagnosis and prognosis. An advantage of these markers is the ease with which they can be detected and measured in the blood.

Combination of cardiac and psychiatric medications would be most beneficial for this group of patients. Moreover, considering the interplay between the cardiovascular and nervous systems the initiation of psychiatric treatment should be considered for all patients with TTS. This could lead to the development of new therapeutic approaches, including the wider use of cognitive-behavioral therapy.

Conclusions

Takotsubo syndrome is the result of the interplay between the nervous and cardiovascular systems. It seems that the most beneficial for patients would be a combination of cardiological and psychiatric treatment. With new psychiatric medications, there is hope of finding a treatment for Takotsubo patients that does not stimulate the adrenergic system. However, psychotherapy appears to be the most promising path, free from at least some of the side effects associated with pharmacotherapy. Psychotherapy is also the primary method for treating personality disorders, the link between which and Takotsubo syndrome requires investigation. Further research and collaboration between cardiologists and psychiatrists are indicated.

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