VOL. 6, NO. 8, 2018
ISSN 2213-1779/$36.00

Letters

TO THE EDITOR

Catecholamine-Mediated Pathways in Takotsubo Syndrome

Does it Matter If it Is a Serotonin Norepinephrine Reuptake Inhibitor or a Selective Serotonin Reuptake Inhibitor?

We read with great interest the work of Tavazzi et al. (1) about the potential common pathophysiology between Takotsubo syndrome (TTS) and neurogenic stress cardiomyopathy in cardiac donors. Subsequently, Woronow et al. (2) brought to this discussion a very important but frequently overlooked concept: the synergistic effect of neurohormones/catecholamine and its impact on the cardiovascular system.

Several pathophysiological mechanisms have been implicated in the genesis of TTS: microvascular dysfunction, coronary artery spasm, and catecholamine cardiotoxicity. Depression and anxiety disorders have also been associated with increased sympathetic activity and diminished reuptake of norepinephrine (3).

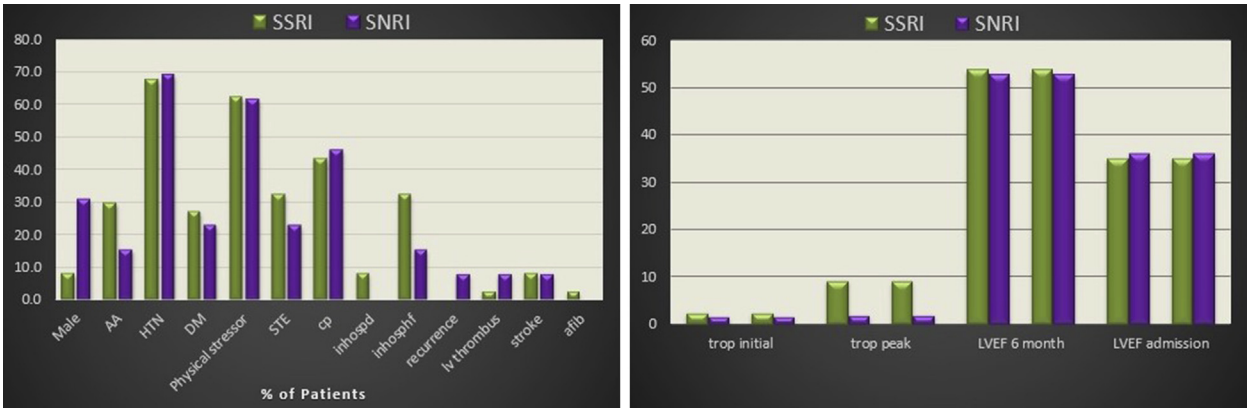
Several studies and case reports (4,5) have linked the use of selective serotonin reuptake inhibitors (SSRIs), in both therapeutic and overdosage scenarios, with TTS. Conceptually, serotonin norepinephrine reuptake inhibitors (SNRIs), by increasing post-synaptic norepinephrine levels in neuronal tissue via reuptake inhibition, could expose susceptible patients to a "catecholamine storm" and TTS.

We reviewed data from our registry of 224 patients with TTS and, in alignment with what was previously reported, SSRI use clearly exceed the number of patients with TTS on SNRIs (a 3:1 ratio). We compare patients with TTS baseline features and 1-year outcomes between SSRI and SNRI users. We have looked at SSRI/SNRI users versus non-SSRI/SNRI users (Online Table 1, **Figure 1**).

Only in 1 isolated case was there solid evidence that it was an SSRI-induced TTS, a suicide attempt with an SSRI overdose, which supports the concept that SNRI-and/or SSRI-induced TTS is a rare event. In theory, and according to the catecholamine-mediated mechanism/common pathway, it would be expected that SNRI users would have a more serious clinical course and worse outcomes in comparison with SSRIs users.

Our findings do not support this concept and, as a matter of fact, outcomes seem to be similar between both groups, except for higher prevalence of

FIGURE 1 Outcomes With a Selective Serotonin Reuptake Inhibitor vs. a Serotonin Norepinephrine Reuptake Inhibitor



AA = African American; afib = atrial fibrillation; cp = chest pain; DM = diabetes mellitus; HTN = hypertension; inhospd = in-hospital mortality; inhosphf = in-hospital heart failure; lv = left ventricle; LVEF = left ventricle ejection fraction; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; STE = ST-segment elevation upon presentation; trop initial = initial troponin; trop peak = peak troponin.

in-hospital heart failure, in-hospital mortality, and peak troponin among SSRI users. These preliminary data need to be validated in larger, multicenter registries.

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https://doi.org/10.1016/j.jchf.2018.04.016

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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APPENDIX For a supplemental table, please see the online version of this paper.

REPLY: Catecholamine-Mediated Pathways in Takotsubo Syndrome

Does it Matter If it Is a Serotonin Norepinephrine Reuptake Inhibitor or a Selective Serotonin Reuptake Inhibitor?

Dr. Dias and colleagues presented some interesting observations about serotonin norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) based on their retrospective descriptive study of Takotsubo syndrome (TTS) that was previously reported (1) in addition to their current update. Because of this relatively small registry, we have concerns about representativeness, generalizability to a larger population, and insufficient information to base a causal assessment.

The investigators reported that 22.3% of TTS patients in their registry were SSRI or SNRI users. This percentage is higher than the 12.8% of patients admitted on antidepressants among the 1,750 TTS patients from the International Takotsubo Registry (2). The National Health and Nutrition Examination Survey (NHANES) showed that from 2011 to 2012 antidepressants were prescribed to 13% of the U.S. adult population, consisting of 8.5% SSRIs, 2% SNRIs, and 2.5% other antidepressant classes (3). The registry used by Dr. Dias and colleagues showed a 3:1 ratio of SSRI to SNRI use, which suggests a larger relative presence of SNRI cases in this registry compared with NHANES data; we could not exclude that SNRIs might be over-represented in the series by Dr. Dias and colleagues because of a possible SNRI increase in the risk of TTS.

Additional information from this registry quantifying the amounts of SSRI or SNRI ingested, duration of use, and catecholamine level information for these patients would have been useful to assess causal associations. The investigators previously reported an 80% stressful trigger for their SSRI patients (1), which suggested that SSRI was not likely to be the TTS trigger in these patients.

The registry's investigators possibly misinterpreted the only 2 case reports that they cited. Both the Christoph et al. (4) and Selke et al. (5) references were case reports of TTS associated with SNRI and catecholamine elevations. These patients in these studies did not ingest SSRI medications. Christoph also cites Johnson et al. (6), stating the SSRI fluvoxamine "does not have significant effects on noradrenergic function." Nonetheless, the possibility of SSRI medications having additional neurotransmitter effects is beyond the scope of this brief reply.

The findings by Dr. Dias and colleagues supported the concept that multiple pathways might influence the pathogenesis of TTS. Furthermore, once TTS occurred, several factors might influence subsequent outcome.

We look forward to additional drug safety information from such registries as they continue to accrue data. We used the Food and Drug Administration Adverse Event Reporting System database in addition to a variety of data sources to conduct our post-marketing pharmacological vigilance activities. Although SNRI-associated TTS might be a rare event, practitioners should be aware of this association for SNRI patients who present with TTS. We encourage submission of suspected adverse drug events to MedWatch (www.fda.gov/medwatch).

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