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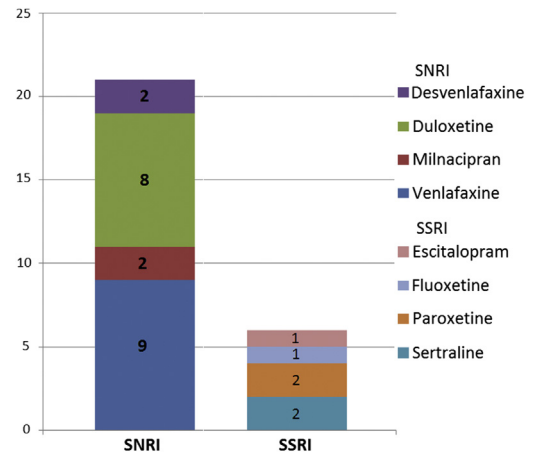
Takotsubo Common Pathways and SNRI Medications

We read with great interest the perspectives of Tavazzi et al. (1) regarding Takotsubo syndrome (TTS), neurogenic stress cardiomyopathy, and the prevailing hypothesis of common catecholamine-mediated pathways. The Division of Pharmacovigilance at the U.S Food and Drug Administration reviewed postmarketing cases of TTS among patients treated with serotonin norepinephrine reuptake inhibitors (SNRIs) compared with selective serotonin reuptake inhibitors (SSRIs) as another possible trigger associated with catecholamine storm and subsequent TTS. We searched the Food and Drug Administration Adverse Event Reporting System database and Medline for all cases of TTS-related adverse events reported with SNRIs or SSRIs submitted through April 11, 2016, meeting Mayo Clinic TTS criteria (2). We identified 21 cases with SNRIs and 6 with SSRIs reporting TTS adverse events (**Figure 1**). TTS developed within the first week of drug initiation or dose escalation in 8 SNRI cases and 1 SSRI case. Case narratives provided information to rule out acute emotional or physical triggers in 10 SNRI cases. Nine SNRI cases reported catecholamine levels, all of which were elevated. None of the SSRI cases reported catecholamine levels. Fourteen SNRI cases developed TTS on doses matching or exceeding the maximum recommended dose, whereas SSRI cases were only reported at doses below the maximum recommended dose. Despite identifying 3.5 times as many SNRI TTS cases relative to SSRI TTS cases, SSRI use has exceeded SNRI use by 4-fold in the National Health and Nutrition Examination Survey database (3). Nonetheless, Food and Drug Administration Adverse Event Reporting System data are subject to under reporting, and total population at risk may be difficult to assess. Confounding by indication remains a concern regarding antidepressants and TTS. Three of our SNRI cases stated only nonpsychiatric reasons for use (fibromyalgia, diabetic neuropathy, urinary incontinence). Additionally, short time to onset, relative absence of emotional or physical triggering events, dose-response relationships, number of cases identified relative to patterns of drug use, and SNRI catecholamine-related mechanism of action are supportive of SNRI-associated TTS, as contrasted with our SSRI cases. The SNRI findings are consistent with the catecholamine storm common pathway noted by Tavazzi et al. (1) SNRI-associated TTS may be a rare event. However, given the seriousness of TTS, practitioners should be aware of the possible association of SNRIs and TTS. SNRI product labels were recently updated to include TTS in adverse reactions (see Section 6.2, Post-Marketing Experience) (4).

FIGURE 1 Food and Drug Administration Adverse Event Reporting System and Medline SNRI and SSRI Cases Associated With Takotsubo Syndrome Adverse Events Through April 11, 2016



There were no citalopram, fluvoxamine, or levomilnacipran cases meeting case series criteria. SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

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REPLY: There Should Not Be Much Doubt That Neurogenic Stress Cardiomyopathy in Cardiac Donors Is a Phenotype of Takotsubo Syndrome, and Takotsubo Common Pathways and SNRI Medications

We appreciate Prof. Madias's insightful comments on our paper and strong endorsement of our hypotheses (1). He suggests additional potential solutions for better management of donors with dysfunctional hearts, including sympathetic activity monitoring, donor heart "nursing" with cardiac mechanical support, and ultimately, donor centralization in dedicated "donor ICUs." These approaches, although stimulating and promising, are likely to pose remarkable logistical, organizational, economic, and resource-allocation challenges; however, we will have to accept these challenges if we aim to determine which transiently dysfunctional hearts are suitable for transplantation. Furthermore, as donor management teams do not currently include professionals specifically trained in the complex and evolving field at the boundary between cardiology and critical care, we believe that the development of a new set of medical skills and competences in "donor cardiology and critical care" would now be required. The increasing awareness of the complexity of this field needs to be matched by a growing specialization in a multimodal diagnostic and therapeutic strategy, aiming at a comprehensive, individually tailored donor approach. This is likely to represent an additional task for the expanding domain of acute cardiac care.

The topic discussed by Dr. Woronow and colleagues is extremely interesting and largely underreported. The interaction between neurohormones/catecholamine (both exogenous and endogenous) on the cardiovascular system and other organs is a matter of daily debate in clinical and scientific settings, and especially in intensive care (2,3).

One thought, which has already been discussed elsewhere (4), is that Takotsubo syndrome is likely a well codified clinical entity, part of a wider "family" of cardiomyopathy that can be caused by an incredibly variety of triggers.

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Solid Organ Transplantation

Recent contributions from the Montreal Heart Institute (Montreal, Quebec, Canada) and Heart Failure and Transplantation Section, Vanderbilt Heart and