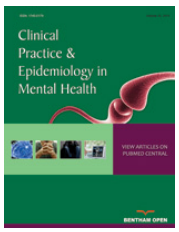

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LETTER

Takotsubo Syndrome and Electroconvulsive Therapy: Time for Rigorous Assessment

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To The Editor,

We followed with interest the recent debate ignited by several commentaries on Takotsubo Syndrome (TTS), adrenergic activation in mood disorder patients, and the associated clinical and public health implications appraised both in the Journal of Clinical Practice and Epidemiology in Mental Health (CPEMH) [1 - 4] and in other peer-reviewed sources [5, 6]. An important issue deals with the putative connection between Electroconvulsive Therapy (ECT) and subsequent TTS.

A burgeoning of case reports [7] published since the year 2009 [8], highlight the not-that infrequent occurrence of TTS soon after the delivery of a course of ECT.

In general, case reports, namely the detailed report of the symptoms, signs, diagnosis, treatment, and follow-up of an individual patient, or (n=1, meaning one unique patient), and case series (up to n=10) represent timely, and essential study design in advancing medical and scientific knowledge, especially of rare diseases in the absence of systematic chart-review [9]. The European Union definition of a rare disease is one that affects fewer than 5 in 10,000 people (https://www.eurordis.org/about-rare-diseases). However, no consensus exists about "how rare" a disease should be considered a "rare" one. This is particularly true for medical fields other than genetics, or whenever the "rare" condition is nonetheless life-threatening.

In recent years, case reports came under scrutiny and disfavor among some in the scientific publishing community, and case studies are frequently relegated to the lowest rank of the hierarchy of study design. Carey documented that 32% of journals do not publish case reports, and another 36% publish them in a modified format [10]. However, prestigious journals, including the New England Medical Journals, the Lancet, or those published by BioMed Central (with ad-hoc editorial destinations), to name a few, continue to publish even case reports [11]. CPEMH likewise does.

Generally speaking, case reports are prone to both "confounding bias" (factors, which we are unaware of may influence the observed outcomes), "chance", and "causation" nexus (inferred in place of mere report of "association" between two events, *e.g.* ECT and subsequent occurrence of TTS).

However, as remarked above, the "rarity" of a condition remains an elusive concept, primarily when it is associated with major or life-threatening outcomes, as is the case with TTS. Also, multiple independent case reports, published consistently over a period of a decade or longer, coming from clinicians based in different geographic regions reasonably deserve attention; especially considering that "more rigorous" controlled clinical trials almost invariably exclude the most severe cases (of mood disorders, in this context) per protocol, thus undermining the chances of occurrence of infrequent events among the most sensitive individuals (read TTS outcome after ECT). Given the self-limiting dissemination of case-reports, and the reluctance of many journals to consider them, especially after previous similar reports on the matter, it cannot be excluded that the "association" (no causal inference made in contrast to "causation") between TTS and ECT is even more frequently observed in clinical settings than appraised in the literature.

Several studies have now established a close association between mood disorders and cardiovascular disorders in general [12, 13], and TTS in particular [4], suggesting a rationale for a possible "vulnerable" condition for TTS, independently of ECT, in people with depressive and bipolar disorders. However, the pathogenetic hypotheses about the role of norepinephrine activation in TTS [2, 14] suggest a causal link between ECT and TTS, given the noradrenergic increase

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following electroconvulsive therapy [15]. Such claims reinforce the suspicion of a possible causal trigger between ECT and TTS that may occur among vulnerable individuals. Given the uneasiness of the diagnosis of TTS [14], it cannot be excluded that, in the absence of careful cardiologic workup, the TTS may have also been misunderstood or underdiagnosed, even among those patients exposed to ECT.

Several factors may inflate the rates of underdiagnosis of previous TTS in patients with severe mood disorders (as those that underwent ECT); especially considering that the consequences of TTS could be better-observed long-term, with rates of long-term mortality among TTS patients exceeding those expected in patients with ST-Elevation Myocardial Infarction (STEMI) [16]. The mortality rates seen among TTS patients are further inflated among those individuals whose severe mood disorders - often requiring intense ECT sessions [17] - already pose a significant mortality risk due to cardiovascular diseases [18].

In conclusion, we congratulate the Editorial Board of the Journal of CPEMH for posing emphasis even on single-patient reports about the intriguing, and clinically burdensome, plausible association between ECT and TTS, and we really hope that further research attention will be given to the topic by implementation of systematic registries and methodologically-rigorous research on the matter.

REFERENCES

[1] Sancassiani F, Giovanni Carta M, Montisci R, Machado S, Marchetti MF, Meloni L. The aim was about the association with psychiatric disorders not on the pathogenesis of Takotsubo:Author's reply. Clin Pract Epidemiol Ment Health 2019; 15: 5-7. [http://dx.doi.org/10.2174/1745017901915010005] [PMID: 30972135]

[2] Finsterer J, Stollberger C. How do depressive mood or antidepressants acutely Increase Serum catecholamines? Clin Pract Epidemiol Ment Health 2019; 15: 1-2. [http://dx.doi.org/10.2174/1745017901915010001] [PMID: 30972133]

[3] Preti A, Sancassiani F. Tako tsubo and treatment of comorbid depression: A reflection is needed: Author's reply. Clin Pract Epidemiol Ment Health 2019; 15: 3-4. [http://dx.doi.org/10.2174/1745017901915010003] [PMID: 30972134]

[4] Sancassiani F, Carta MG, Montisci R, *et al*. Takotsubo syndrome is associated with mood disorders and antidepressants use, not with anxiety and impairment of quality of life due to the psychiatric disorder Clini Pract Epidemiol. 2018; 14: 26-32. [http://dx.doi.org/10.2174/1745017901814010026] [PMID: 29541148]

[5] Zeng JH, Li W, Yao FJ, *et al.* Myocardial contrast echocardiography in the diagnosis of postoperative takotsubo myocardiopathy: Case report and literature review. BMC Cardiovasc Disord 2019; 19(1): 9. [http://dx.doi.org/10.1186/s12872-018-0985-z] [PMID: 30621585]

[6] Finsterer J. Insular cortex lesions are not the only culprit in Takotsubo syndrome. Clin Cardiol 2018; 41(11): 1407-8. [http://dx.doi.org/10.1002/clc.23044] [PMID: 30098032]

[7] Kudling R, Hartmut Schoels W, Kuhn J. Tako-Tsubo Cardiomyopathy during a series of Electroconvulsive Therapy (ECT) applications: A case report, systematic literature research and discussion of specific risk factors. Fortschr Neurol Psychiatr 2018; 86(11): 699-710. [PMID: 30654402]

[8] Chandra PA, Golduber G, Chuprun D, Chandra AB. Tako-tsubo cardiomyopathy following electroconvulsive therapy. J Cardiovasc Med (Hagerstown) 2009; 10(4): 333-5. [http://dx.doi.org/10.2459/JCM.0b013e328324eb0d] [PMID: 19430344]

[9] Tsuang MT, Tohen M, Zahner GE. Textbook in psychiatric epidemiology 2011. [http://dx.doi.org/10.1002/9780470976739]

[10] Carey JC. Significance of case reports in the advancement of medical scientific knowledge. Am J Med Genet A 2006; 140(19): 2131-4. [http://dx.doi.org/10.1002/ajmg.a.31449] [PMID: 16964619]

[11] Carey JC. The importance of case reports in advancing scientific knowledge of rare diseases. Adv Exp Med Biol 2010; 686: 77-86. [http://dx.doi.org/10.1007/978-90-481-9485-8_5] [PMID: 20824440]

[12] Carta MG, Lecca ME, Saba L, *et al.* Patients with carotid atherosclerosis who underwent or did not undergo carotid endarterectomy: Outcome on mood, cognition and quality of life. BMC Psychiatry 2015; 15: 277. [http://dx.doi.org/10.1186/s12888-015-0663-y] [PMID: 26563766]

[13] Lecca M, Saba L, Sanfilippo R, *et al.* Quality of life in Carotid Atherosclerosis: The role of co-morbid mood disorders. Clin Pract Epidemiol Ment Health 2016; 12: 1-8. [http://dx.doi.org/10.2174/1745017901612010001] [PMID: 27346995]

[14] Ghadri JR, Wittstein IS, Prasad A, *et al.* International expert consensus document on takotsubo syndrome (part I): Clinical characteristics, diagnostic criteria, and pathophysiology. Eur Heart J 2018; 7;39(22): 2032-46.

[15] Mongeau R, de Montigny C, Blier P. Effects of long-term alpha-2 adrenergic antagonists and electroconvulsive treatments on the alpha-2 adrenoceptors modulating serotonin neurotransmission. J Pharmacol Exp Ther 1994; 269(3): 1152-9. [PMID: 7912278]

[16] Stiermaier T, Moeller C, Oehler K, *et al.* Long-term excess mortality in Takotsubo cardiomyopathy: predictors, causes and clinical consequences 2016. [http://dx.doi.org/10.1002/ejhf.494]

[17] Medda P, Fornaro M, Fratta S, *et al.* A case of deep venous thrombosis following protracted catatonic immobility recovered with electroconvulsive therapy: the relevance for an early intervention. Gen Hosp Psychiatry 2012; 34(2): 209.e5-7. [http://dx.doi.org/10.1016/j.genhosppsych.2011.08.007] [PMID: 21937119]

[18] Correll CU, Solmi M, Veronese N, *et al.* Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: A large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry 2017; 16(2): 163-80. [http://dx.doi.org/10.1002/wps.20420] [PMID: 28498599]