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Does Venlafaxine Truly Trigger Takotsubo Syndrome?

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Introduction:

In a recent article, Vasudev et al. reported about a 52 years-old Hispanic female who developed Takotsubo syndrome (TTS) four weeks after starting with the selective noradrenaline re-uptake inhibitor (SNRI) venlafaxine (75mg/d) for depression [1]. We have the following comments and concerns.

TTS is usually triggered by physical or psychological stress [2]. How can the authors be sure that the antidepressant triggered the TTS? How were other causes of acute stress excluded in this particular patient? Was the individual history thoroughly taken and any type of stress or anxiety excluded? Was the patient investigated by a psychiatrist or a psychologist? There are also a number of other conditions, neurologic and non-neurologic in nature, which has been reported as triggering factors of TTS. Were all of them excluded? Was a subclinical stroke or a subarachnoid bleeding in stage Hunt-Hess 1 excluded? Did the patient experience extensive back pain from disc bulging when TTS occurred? Had she discontinued oxicodone shortly before onset of TTS? We should be informed if the presented patient was taking drugs other than venlafaxine, which could have contributed to the pathogenesis of TTS. Which was the cause of depression in this female?

In case the pathomechanism of TTS is based on increased levels of catecholamines, is it conceivable that the trigger in Vasudev's case was overdosing of venlafaxine? Were there any indications for a suicide attempt with venlafaxine or venlafaxine poisoning in this patient?

An argument against the SNRI to be causative is that the number of patients taking SNRI is high but only a few of them developed TTS (table 1). A further argument against the SNRI as a trigger of TTS is that animals in dose-finding studies during the admission process were not reported to have developed heart failure or TTS. If catecholamines are the culprit, all patients with a

pheochromocytoma or a noradrenaline producing tumour should have TTS, which is definitively not the case. Cardiac side effects of venlafaxine listed in the leaflet include blood-pressure elevation, QT-prolongation, Torsades des pointes, and fatal ventricular tachycardia, but not TTS [3].

The authors themselves mention that enhanced sympathetic activity could play an important role in the pathogenesis of TTS [1]. Which was the cause of increased sympathetic activity in the presented patient? Was there imbalance between parasympathetic and sympathetic activity? Was the parasympathetic tone reduced?

Not only 9 patients, as presented in Vasudev's case report, have been reported who developed TTS triggered by a SSRI, SNRI, or SARI (table 1). At least 20 more patients have been published who experienced SSRI-, SNRI-, or SARI-triggered TTS (table 1). Also the 16 cases reported by Dias et al. and by others have to be mentioned (table 1).

Table 1: Reports about serotonine / noradrenaline reuptke inhibitors triggering TTS

SSRI/S/NRI	NOP	sex	age (y)	Outcome	Reference
Venlafaxin	1	f	52	FR	[1]
Fluoxetine	1	f	51	FR	[5]
SSRI	15	nm	nm	nm	[6]
SNRI	1	nm	nm	nm	[6]
SARI	1	nm	nm	nm	[6]
Venlafaxine	1	f	82	FR	[7]
Venlafaxine	1	m	73	nm	[7]
Venlafaxine	1	f	37	nm	[7]
Venlafaxine	1	f	61	nm	[7]
Desvenlafaxine	1	f	58	nm	[7]
Venlafaxine	1	f	50	nm	[7]
Milnacipran	1	f	42	FR	[8]
Duloxetine	1	f	59	FR	[9]
Duloxetine	1	f	68	FR	[10]
Venlafaxine	1	f	43	FR	[11]
Venlafaxine	1	f	43	FR	[12]

SSRI: selective serotonine reuptake-inhibitor, SNRI: selective noradrenaline reuptake inhibitor, SARI: serotonine antagonist/reuptake inhibitor, FR: full recovery, nm: not mentioned

We do not agree with the notion that TTS is a temporary condition [1]. TTS of any subtype may be permanent and may lead to intractable heart failure, and death.

The authors recommend prescribing antidepressants other than SSRI, SNRI, SARI in case someone develops TTS under these drugs? Which alternative antidepressants do the authors recommend? Tricyclic antidepressants have a number of other, particularly cardiac, side effects.

ECG abnormalities usually recover within 10 weeks after onset of TTS and echocardiographic abnormalities recover within 6 weeks after onset [4]. We should be informed about the time after which ECG respectively echocardiography normalised again in the presented patient.

Overall, this interesting case requires evidence that the sole intake of venlafaxine triggered TTS in the absence of additional stressors. As long as a causative relation between SSRI and TTS remains unproven, alternative causes of TTS should be considered.

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