Desvenlafaxine as an Alternative Agent in Treating Combat Post Traumatic Stress Disorder in a Case

Idiosyncratic Venlafaxine/Trazodone-Induced Liver Injury: A Case Report

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Background

Psychotropic medications have associated hepatotoxicity as a possible side effect. Venlafaxine and trazodone are agents with documented cases of hepatotoxicity, which may present even at normal therapeutic doses. Herein we report the case of a 28-year-old military service member treated for combat Post Traumatic Stress Disorder (PTSD) and Major Depressive Disorder (MDD) without any previous history of liver disease who developed transaminitis shortly after starting venlafaxine and trazodone therapy, prompting discontinuation of both medications and a switch to desvenlafaxine (DVS) with continued positive response and good tolerability. The objective of this case report is to show that DVS can be an effective agent in treating combat PTSD, especially in cases where venlafaxine and trazodone may produce hepatotoxicity.

Introduction

Venlafaxine and trazodone, two popular psychotropic medications, have documented associated hepatotoxicity as a possible side effect.[1-6] Hepatotoxicity as manifested by chronic and acute hepatitis, hepatic failure, and transaminitis has been reported with the administration of the venlafaxine in monotherapy.[1] Hepatotoxicity as manifested by acute hepatic injury and transaminitis has also been reported with the administration of trazodone.[2-4] A case of fulminant hepatic failure has been described in a patient receiving both venlafaxine and trazodone dual therapy.[5] A case of a patient developing severe acute hepatitis has also been described in a patient receiving lormetazepam, venlafaxine, and trazodone therapy.[6] Herein we report a case of a patient who developed Idiosyncratic Drug-Induced Liver Injury (DILI) after simultaneous administration of venlafaxine and trazodone at normal therapeutic doses.

Case Report

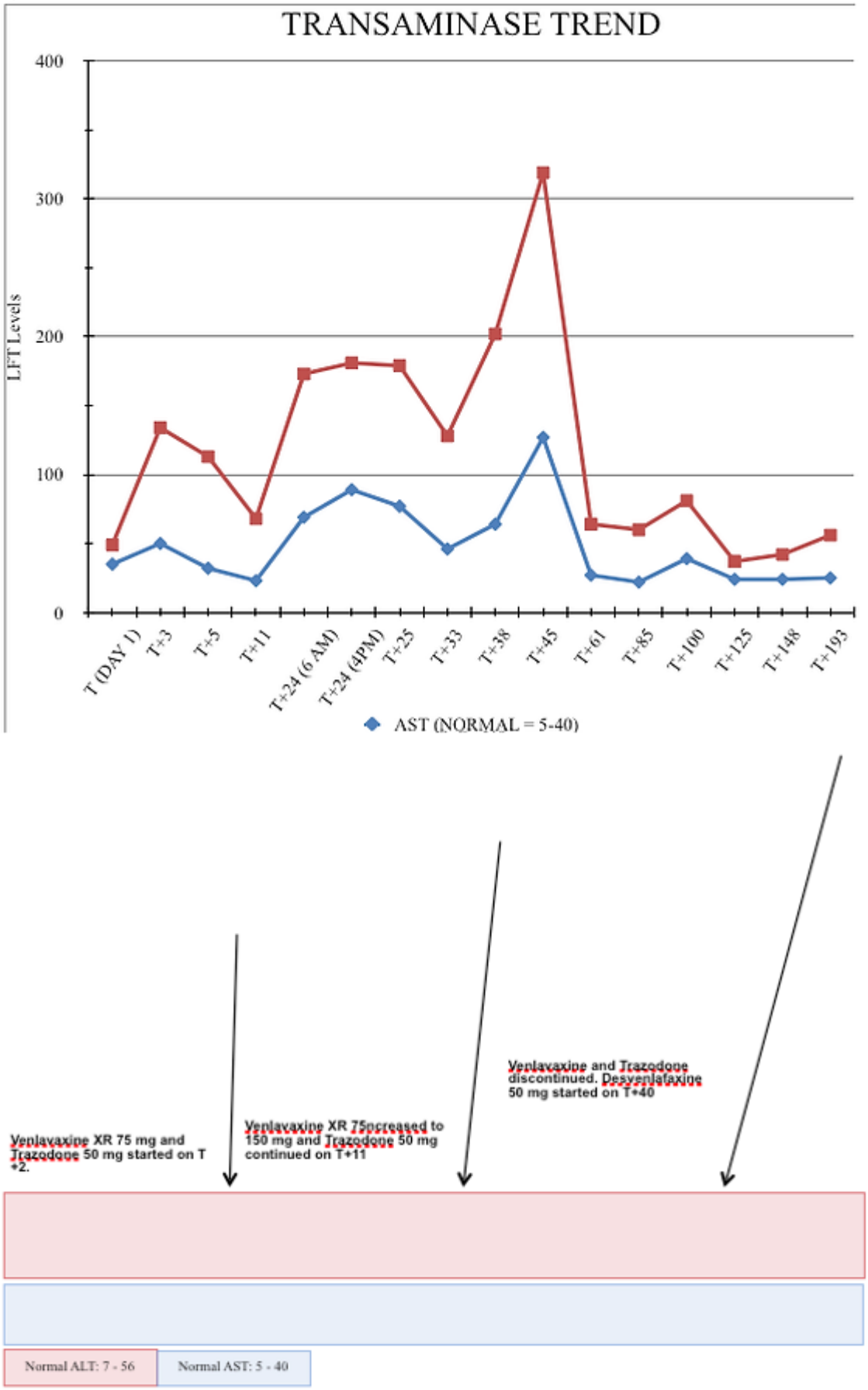
The patient is a 28 year-old Caucasian male with normal baseline liver associated enzymes who had been suffering from chronic MDD and PTSD complicated by suicidal ideations prompting inpatient hospitalization. His history revealed a seven-year history of underlying depression with a 9 month history of worsening mood, 3 suicide attempts with increasing lethality, 2 prior inpatient psychiatric hospitalizations, and worsening interpersonal and occupational stressors. He also had history of alcohol use disorder but had

been in remission for 6 months. During his recent inpatient hospitalization, there was concern for ingestion of eszopiclone. The quantity of eszopiclone ingested was unclear, but had resulted in sedation and was initially observed in the intensive care unit prior to being transferred to the inpatient psychiatric unit. Following discharge from the medical unit with normal baseline liver enzymes, he was started on venlafaxine XR 75 mg and trazodone 100 mg. The next day, there was a slight increase in both Alanine aminotranferease (ALT) and aspartate aminotransferase (AST). The venlafaxine XR was eventually increased to 150 mg of the trazodone remained at 100 mg, and the subsequent ALT and AST trended upwards significantly to where the ALT was over 5 times normal.[7] He remained clinically asymptomatic during this entire episode. The decision was made to discontinue both the venlafaxine and trazodone due to concern for DILI. Because the patient had made significant clinical gains in reduction of symptoms on venlafaxine and trazodone with the exception of the transaminitis, he was started on DVS given its similar mechanism of action to venlafaxine. Approximately 3 weeks after switching to the desvenlafaxine, his liver enzymes had returned to normal limits, and remained as such over the next 4 months. (see Table 1 and Graph 1).

	AST (NORMAL = 5-40)	ALT (NORMAL = 7-56)
T (DAY 1)	35	49
T+3	50	134
T+5	32	113
T+11	23	68
T+24 (6 AM)	69	173
T+24 (4PM)	89	181
T+25	77	179
T+33	46	128
T+38	64	202
T+45	127	319
T+61	27	64
T+85	22	60
T+100	39	81
T+125	24	37
T+148	24	42
T+193	25	56

TABLE 1: Raw LFT Data – The trend of AST/ALT over time.

GRAPH 1


TRANSAMINASE TREND
LFT Levels
400
300
200
100
0
T (DAY 1)
T+3
T+5
T+11
T+24 (6 AM)
T+24 (4PM)
T+25
T+33
T+38
T+45
T+61
T+85
T+100
T+125
T+148
T+193
AST (NORMAL = 5-40)
Venlavaxine XR 75 mg and Trazodone 50 mg started on T +2.
Venlavaxine XR 75ocreased to 150 mg and Trazodone 50 mg continued on T+11
Venlavaxine and Trazodone discontinued. Desvenlafaxine 50 mg started on T+40
Normal ALT: 7 - 56
Normal AST: 5 - 40

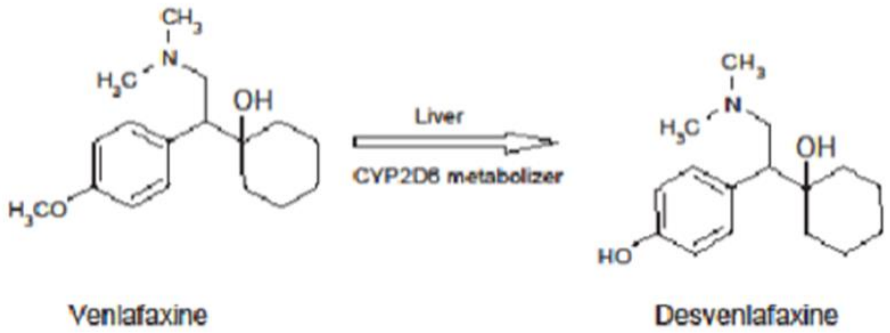
Discussion

First, this case illustrates hepatic injury induced by the co-administration of venlafaxine and trazodone. Venlafaxine and trazodone are well-known antidepressant agents widely used to treat depression.[5] It is of interest to note that there are 2 other reported cases of hepatic injury related to venlafaxine occurring in patient's receiving trazodone.[5,6] These reports, and this reported case highlight that hepatic tests should be routinely monitored in patient's receiving simultaneous venlafaxine and trazodone therapy, as liver toxicity is possible. The responses range from mild laboratory abnormalities such as transaminitis as in this reported case, to symptomatic acute hepatitis,[6] to fulminant hepatic failure.[5] It is further likely that though he has been abstinent from alcohol for 6 months prior to this event, because he was a prior heavy drinker, his risk for hepatic events could have been lowered than had he not been a heavy drinker.

It's important to note, that this case supports a reported case where DVS is used as an alternative agent which corrected transaminitis induced by both venlafaxine and duloxetine.[8] DVS is the major active metabolite of venlafaxine.[9] Data indicates that DVS causes minimal inhibition of the hepatic cytochrome P450 CYP2D6 isoenzyme[9] and is listed as a minor substrate of the hepatic cytochrome P450 CYP3A4[10] indicating a lower risk of drug-drug interaction and lower risk of hepatotoxicity. Comparatively, venlafaxine is a major substrate of both hepatic cytochrome P450 CYP3A4 and CYP2D6.[10] DVS was further supported in a study with having minimal changes in ALT and AST in a sample of 149 patients.[9]

Secondly, this case highlights a possible alternative to venlafaxine when efficacy and tolerability are a concern. Venlafaxine is well supported as efficacious in the treatment of both MDD and PTSD, and is considered first-line by the Department of Defense/Veteran's Affairs clinical practice guidelines.[11] In this reported case, the patient had a significant reduction in both depressive and PTSD symptoms, however because of the aforementioned hepatotoxicity a change was warranted. DVS was chosen primarily for the following reasons: (a) reported safety,[9,1-15] (b) referenced utility as an agent for PTSD,[10,11] and (c) the likeness to venlafaxine in terms of class and mechanism of action in consideration of the patient's positive response to venlafaxine.[10] Venlafaxine is metabolized in the liver through the cytochrome P450 system into three metabolites: O-desmethylvenlafaxine, N-desmethylvenlafaxine, and N, O-desmethylvenlafaxine.[16] DVS is the succinate salt of the isolated major active metabolite of venlafaxine, "O-desmethylvenlafaxine" (Figure 1).[16] Since DVS is almost entirely excreted in urine, patients with renal impairment present a greater clinical concern, then hepatic impairment.[16] As such, there is little need to reduce the starting dose for patients with mild hepatic impairment.[16]

Figure 1: DVS succinate model[16] – exemplifies the chemical similarity to venlafaxine supporting the hypothesis of efficacy for PTSD.



It is further important to note that while there is an abundance of literature to support the efficacy of venlafaxine in PTSD treatment, the only supporting data found on DVS for PTSD was referenced in terms of its class of medication as a serotonin norepinephrine reuptake inhibitor (SNRI), and prescribing reference books under common off label use for the medication[10,11] No bona fide controlled studies were found studying the efficacy specifically of DVS for PTSD. The patient's initial response to venlafaxine had been significantly positive, and his treatment response continued in a positive direction when he was switched to DVS.

Lastly, it is important to note an applicable military correlation for US military prescribing providers working with combat PTSD. It is becoming more acceptable for military service members to deploy on psychotropic medications.[17] Venlafaxine is often chosen over DVS due to cost and availability. However, due to a high prevalence of alcohol use among service members,[18] and the aforementioned increased risk of heavy drinkers of developing hepatic problems, DVS could be a viable alternative with a safer hepatic profile. In addition, there is limited alcohol blood monitoring in the deployed environment, with decreased access to psychiatric services while deployed to combat zones, thus DVS could be a lower risk drug with its lower side effect profile, less drug-drug interaction potential, and decrease chance of adverse effects.

Conclusion

Several important inferences can be made from this case report:

1. DVS can be a viable alternative when there is concern for the safety and tolerability of venlafaxine.

2. This case supports other cases that venlafaxine and trazodone co-administered together have the potential for hepatotoxicity, and should be closely monitored.

3. Because of a lack of placebo controlled studies, no efficacy inference can be made at this time. However, that this combat PTSD patient tolerated DVS with positive results, future research on DVS for PTSD would be warranted.

4. Fourth, patients with significant prior use of alcohol may be at higher risk for hepatotoxicity as an adverse drug event even if alcohol free for period of time.

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