Differential Treatment Effects of a Sublingual Formulation of Cyclobenzaprine (TNX-102 SL*) on Dissociative Symptoms of Derealization and Depersonalization in a Military-Related PTSD

Gregory M. Sullivan[1], Kimmons Wilson[1], R. Michael Gendreau[2], Judy Gendreau[1], Ashild Peters[1], Perry Peters[1], Amy Forst[1], Jean Engels[3], Seth Lederman[1]

[1]Tonix Pharmaceuticals, Inc., New York, NY 10022; [2]Gendreau Consulting, Poway, CA 92064; [3]Engels Statistical Consulting, Minneapolis, MN 55044

*TNX-102 SL is an investigational new drug and has not been approved for any indication

INTRODUCTION

Dissociative phenomena involve the experience of detachment from reality. Symptoms of dissociation are often associated with trauma-related disorders such as posttraumatic stress disorder (PTSD). Prominent in PTSD are symptoms that include depersonalization (DP), a sense of being detached from, or an outside observer of, one's body, and derealization (DR), a sense of the world as unreal, dreamlike, distant, or distorted.

DSM-5 introduced a dissociative subtype of PTSD (D-PTSD) to account for symptoms of DR and/or DP that develop with the disorder, and it is estimated that 15-30% of PTSD patients qualify for D-PTSD.[1,2] Dissociative symptoms are reported to correlate with arousal and reactivity in PTSD,[3] are associated with increased severity of substance abuse,[4] and have been found to be more common in young men.[5] Sleep disturbances appear to worsen dissociation.[6]

DP and DR arise in several psychiatric disorders including PTSD, panic disorder, social anxiety disorder, and generalized anxiety disorder, and treatment of these symptoms has generally focused on treatment of the underlying disorder. Yet, there are some reports of treatment focused specifically on dissociative symptoms, in particular DP; with reports of improvement in symptoms with transcranial magnetic stimulation,[7,8] combination of selective serotonin reuptake inhibitors (SSRIs) and lamotrigine,[9,10] as well as cognitive therapy.[11] In absence of more treatment data from research focused on DP and DR, psychotherapies are currently considered to have the best outcomes when addressing both DP and DR, although pharmacotherapy with desipramine[12] was previously suggested to have a role in the treatment of DP. Current treatments for D-PTSD mostly involve cognitive-behavioral therapies and pharmacotherapy with SSRIs, the same as current guidelines for the treatment of PTSD in general.[13]

Here we report on the effects of pharmacotherapy with TNX-102 SL on dissociative symptoms of DP and DR in participants of a 12-week, Phase 2, randomized clinical trial, the 'AtEase' study, which tested the safety and efficacy of TNX-102 SL in military-related PTSD.

METHODS

The 'AtEase' study was a randomized, double-blind, placebo-controlled, multi-center 12-week safety and efficacy study of TNX-102 SL in military-related PTSD. Participants meeting the diagnosis of PTSD, as assessed by the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), were randomized in a 2:2:1 ratio placebo, TNX-102 SL 2.8 mg, or TNX-102 SL 5.6 mg. Eligible participants had to meet the following criteria: **Inclusions**: males and females; ages 18-65; PTSD DSM-5 Criterion A trauma(s) incurred during military service since 9/11/2001; baseline total CAPS-5 score ≥ 29; free of antidepressants ≥ 2 months; free of or washed off of other psychotropics; not participating in a trauma-focused psychotherapy during study or within one month prior. **Exclusions**: severe suicide risk; substance use disorders within 6 months; lifetime bipolar 1 or 2, psychotic, obsessive-compulsive, or antisocial personality disorders.

Efficacy: The primary efficacy endpoint was mean change from baseline (MCFB) in CAPS-5 score between TNX-102 SL and placebo at Week 12 using mixed model repeated measures (MMRM) analysis. Key secondary endpoints included Clinical Global Impression–Improvement (CGI-I), Sheehan Disability Scale (SDS), PROMIS Sleep Disturbance (SD). Each CAPS-5 evaluation included the first 20 items as well as item 29 (depersonalization, DP) and 30 (derealization, DR). The scores of these two items were independent of the total CAPS-5 severity score, which was the sum of severities from the first 20 items. All analyses of continuous variables used MMRM. Correlations of dissociative symptoms with other variables use Spearman's *rho*.

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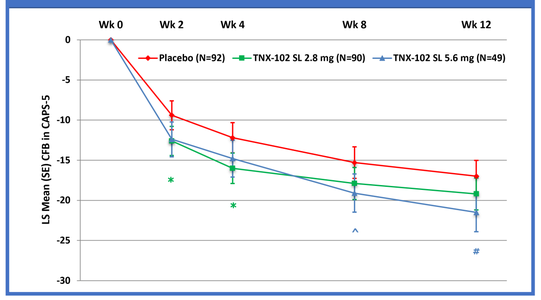
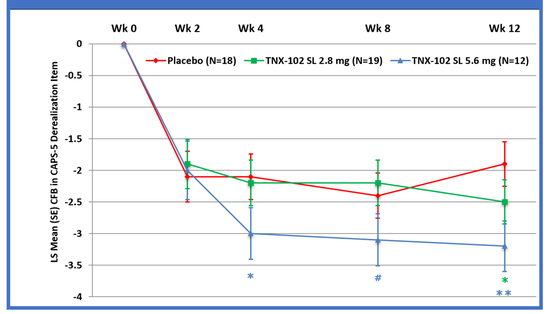
Figure 1. CAPS-5 Least Squares MCFB Over 12 Weeks of Treatment with TNX-102 SL



#p=0.053, ^p=0.094, comparing TNX-102 SL 5.6 mg to placebo, MMRM; *p<0.05, comparing TNX-102 SL 2.8 mg to placebo

Figure 2. Derealization Least Squares MCFB Over 12 Weeks of Treatment with TNX-102 SL



**p=0.001, *p=0.026, #p=0.076, comparing TNX-102 SL 5.6 mg to placebo, MMRM; *p=0.046, comparing TNX-102 SL 2.8 mg to placebo, MMRM

RESULTS

As previously reported, the TNX-102 SL 2.8 mg group (N=90) did not separate significantly on MCFB of CAPS-5 total severity score from placebo (N=92) at Week 12 (least squares mean ± standard error, -2.2 ± 1.94 points; p=0.259). But, as shown in **Figure 1**, the 2.8 mg group did separate from placebo at earlier timepoints, at Week 2 (-3.2 ± 1.55 points; p=0.040) and Week 4 (-3.8 ± 1.76 points; p=0.030). Secondary analysis of the TNX-102 SL 5.6 mg group (N=49) showed a strong trend for separation from placebo at Week 12 on MCFB of CAPS-5 (-4.5 ± 2.31 points; p=0.053; effect size of 0.36).

- On the CAPS-5 derealization item (Item 30), 21.2% of the mITT were rated >0 at baseline
  - As shown **in Figure 2**, both doses of TNX-102 SL showed a significant effect for reducing derealization over 12 weeks compared to the placebo (N=18)
    - TNX-102 SL 2.8mg→ -0.6 ± 0.30; N=19; p<0.05
    - TNX-102 SL 5.6mg→ -1.3 ± 0.37; N=12; p=0.001
- On the CAPS-5 depersonalization item (Item 29), 20.4% of the mITT scored >0 at baseline
  - Neither doses decreased depersonalization scores over 12 weeks compared to placebo (N=24)
    - TNX-102 SL 2.8mg→ 0.0 ± 0.33; N=12; p=0.92
    - TNX-102 SL 5.6mg→ 0.5 ± 0.39; N=11; p=0.23
- Participants with the dissociative subtype (DP, DR, or both), 31.2% of the mITT, failed to respond to TNX-102 SL treatment in terms of total CAPS-5 symptom severity reduction compared with the placebo (N=33)
  - TNX-102 SL 2.8mg→ 0.0 ± 4.20 points; N=22; p=0.99
  - TNX-102 SL 5.6mg→ -2.4 ± 4.76 points; N=17; p=0.62
- Baseline depersonalization (Item 29) in participants with >0 depersonalization correlated with baseline:
  - Sleep disturbance (Item 20) score → rho=0.32, p=0.026
  - Arousal and reactivity cluster (Cluster E) score → rho=0.34, p=0.019
  - CAPS-5 total score → rho=0.51, p<0.001
- Baseline derealization (Item 30) in participants with >0 derealization correlated with baseline:
  - Sleep disturbance (Item 20) score → rho=0.29, p=0.046
  - Arousal and reactivity cluster (Cluster E) score → rho=0.42, p=0.002
  - CAPS-5 total score → rho=0.42, p=0.002

Safety

Overall TNX-102 SL was well tolerated. Adverse events occurring at > 5% rate in either TNX-102 SL group are summarized in **Table 1**.

Table 1. Adverse Events at Rate of ≥5% in TNX-102 SL Arms

Systemic Adverse Events	Placebo (N=94)*	TNX-102 SL 2.8 mg (N=93)*	TNX-102 SL 5.6 mg (N=50)*
Somnolence	6.4%	11.8%	16.0%
Dry Mouth	10.6%	4.3%	16.0%
Headache	4.3%	5.4%	12.0%
Insomnia	8.5%	7.5%	6.0%
Sedation	1.1%	2.2%	12.0%
Administration Site Reactions			
Hypoaesthesia oral#	2.1%	38.7%	36.0%
Paraesthesia	3.2%	16.1%	4.0%
Glossodynia	1.1%	3.2%	6.0%

#Oral hypoaesthesia (tongue numbness) was the most common AE, was generally transient (<60 minutes), and rated as mild in 89% and moderate in 11% on TNX-102 SL;
*Safety population (N=237)

CONCLUSIONS

- The finding that 31.2% of this military PTSD population expressed the dissociative subtype (D-PTSD) is consistent with the limited epidemiology of dissociative symptoms in PTSD.
- Both derealization symptoms and depersonalization symptoms were correlated with sleep disturbance and hyperarousal, as reported in the literature
- The D-PTSD subgroup a poorer response to treatment with TNX-102 SL, in terms of improvement in CAPS-5 total score, compared with the mITT population, consistent with literature suggesting D-PTSD is less treatment responsive.
- TNX-102 SL 5.6 mg may be an effective treatment specifically for derealization symptoms but not for depersonalization symptoms
  - Yet caution interpreting this treatment effect is warranted due to the small group numbers with derealization symptoms expressed at baseline, and replication in a larger population is needed
- The differential treatment effect observed suggests derealization and depersonalization may be separate and distinct neurobiological constructs.

ClinicalTrials.gov Identifier: NCT02277704 (P201)

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