Effect of Bedtime Sublingual Cyclobenzaprine (TNX-102 SL) on PTSD Sleep-Dependent Emotional Memory Processing: Retrospective Analysis of Phase 2 and 3 Trial Results in Military-Related and Civilian PTSD

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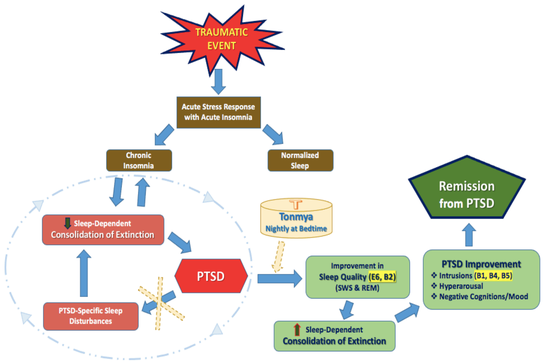
*TNX-102 SL is an investigational drug and has not been approved for any indication

INTRODUCTION

- PTSD is characterized by emotional memory processing deficits, disturbed sleep, and recurrent intrusion symptoms.
- Bedtime TNX-102 SL (sublingual cyclobenzaprine) is a functional antagonist at 5-HT2A-serotonergic, α-1-adrenergic, H1-histaminergic and M1-muscarinic receptors that is proposed to treat PTSD by targeting sleep disturbance that in turn improves sleep-dependent emotional memory consolidation.
- Three randomized, placebo-controlled, double-blind multicenter clinical trials of TNX-102 SL were performed, a Phase 2 (P201) and a Phase 3 (P301) study in military-related PTSD, and a Phase 3 (P302) study in predominantly civilian PTSD.
- All three trials showed encouraging activity of TNX-102 SL on patient- and clinician-rated global PTSD symptoms (Patient Global Impression of Change [PGIC] and Clinician Global Impression [CGI]) but missed significance on the primary endpoints of total Clinician Administered PTSD Scale for DSM-5 (CAPS-5) using the one-week lookback version*.
- The present retrospective analysis examined the activity of TNX-102 SL on select items of the CAPS-5 that reflect its proposed mechanism of action, specifically targeting PTSD sleep disturbance (B2 [trauma nightmares] and E6 [difficulty sleeping]) to ameliorate the sequela of chronic dysfunctional extinction consolidation (B1 [unwanted trauma memories], B4 [emotional upset by trauma triggers] and B5 [physical reactions to trauma triggers]).

*The CAPS-5 was developed as a diagnostic tool and may be problematic for assessment of treatment response

Figure 1. Mechanistic Hypothesis for TNX-102 SL Action in PTSD



Adapted from Fig. 2, Pace-Schott et al. Biology of Mood & Anxiety Disorders 2015; 5:3. PMID: 26034578

METHODS

P201, P301 and P302 were 12-week, multicenter, randomized, double-blind, placebo-controlled, Phase 2 and 3 studies, testing the efficacy and safety of TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) for PTSD. Participants meeting PTSD diagnosis, assessed by CAPS-5, were randomized to TNX-102 SL (TNX) or placebo (PBO) treatment groups. The primary efficacy endpoint for each was mean change from baseline (MCFB) in total CAPS-5 score at Week 12. Demographic information for all three studies is provided in **Table 1**.

Post-hoc analyses included exploratory factor analysis and network analysis on the individual CAPS-5 items to illuminate underlying structures in the data, as well as relationships between items; MCFB analysis was performed via mixed-model repeated measures (MMRM) on five individual CAPS-5 items B1, B2, B4, B5 and E6, and on the "5-item total score" to compare treatment of TNX with placebo in each study.

Table 1. Participant Demographics and Characteristics

	mITT		
Variable	**P201 N=231**	**P301 N=252**	**P302 N=163**
Females, %	6.9%	10.7%	79.1%
White, %	65.8%	67.1%	77.3%
Married, %	41.1%	41.3%	19.6%
Avg. age, years	33.6	35.7	38.9
Employment (current), %	61.9%	59.1%	71.2%
Unable to work due to PTSD symptoms, %	11.3%	14.7%	9.8%
Education, some college or higher, %	83.6%	83.3%	80.4%
Military Service at the time of index trauma, %	97.4%	99.3%	6.1%
# Deployments, mean*	2.0	2.8	3.0
Baseline CAPS-5 Scores, mean	39.5	42.2	42.4

*among participants with military-related PTSD

Statistical Software All MMRM and responder analyses were conducted in SAS, Version 9.4 (SAS Institute Inc., Cary, NC), and the exploratory factor analysis was conducted in Jamovi, Version 1.1 (The Jamovi Project, Sydney, Australia). The network analysis was generated in JASP, Version 0.12.2.0 (The JASP project, Amsterdam, Netherlands), which utilizes the R package 'qgraph'.

RESULTS

TNX-102 SL 5.6 mg treated participants showed a trend towards greater improvement in the 5-item total score at Week 12 as compared to placebo using MMRM in P201 (n = 141; p = 0.12), P301 (n=252; p = 0.09) and P302 (n = 163; p = 0.07). Furthermore, improvement in PTSD symptom severity as measured by the 5-item CAPS-5 is more consistent with patient and clinician-rated global assessments of change than the full, 20-item CAPS-5. Effect size profiles for the CAPS-5, as well as PGIC and CGI-I/S are shown in **Table 2**.

Table 2. Summary of Effect Sizes

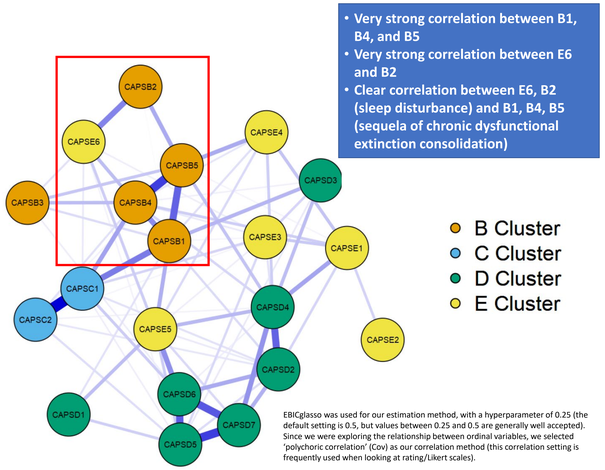
Week 12 Outcome Measures	**P201** PBO N=92 TNX 5.6 mg N=49	**P301** PBO N=127 TNX 5.6 mg N=125	**P302** PBO N= 83 TNX 5.6 mg N=80
Mean CFB CAPS-5	ES	ES	ES
Total Score	0.36#	0.07	0.15
5-items	0.29	0.22#	0.29#
Mean PGIC	0.37*	0.27*	0.43**
Mean CGI-I	0.28	0.08	--
Mean CFB CGI-S	--	--	0.36*

**p<0.01, *p<0.05, #p<0.10

CGI-I= Clinical Global Impression – Improvement scale; CGI-S= Clinical Global Impression – Severity scale; PGIC= Patient Global Impression of Change; CFB= Change from Baseline; ES = Effect size; PBO= placebo

As seen in **Figure 2**, network analysis showed grouping of sleep items (B2 and E6) and intrusion items (B1, B4 and B5).

Figure 2: Network Analysis of P201 and P301 (Military-Related PTSD)



- Very strong correlation between B1, B4, and B5
- Very strong correlation between E6 and B2
- Clear correlation between E6, B2 (sleep disturbance) and B1, B4, B5 (sequela of chronic dysfunctional extinction consolidation)

EBICglasso was used for our estimation method, with a hyperparameter of 0.25 (the default setting is 0.5, but values between 0.25 and 0.5 are generally well accepted). Since we were exploring the relationship between ordinal variables, we selected 'polychoric correlation' (Cow) as our correlation method (this correlation setting is frequently used when looking at rating/Likert scales).

Exploratory factor analysis **(Table 3)** revealed similar CAPS-5 item loadings for military and civilian PTSD. The sleep items (B2 and E6) map onto the same factor as the PGIC and CGI scores and the intrusion items (B1, B4, B5) map onto a separate factor.

Table 3. Exploratory Factor Analysis of Week 12 Change from Baseline Scores on the 5-item CAPS, PGIC and CGI

	P201		**P301**		**P302**	
	Factor 1	**Factor 2**	**Factor 1**	**Factor 2**	**Factor 1**	**Factor 2**
B1		0.70		0.53	0.88	
B2	0.60		0.48			0.54
B4		0.61		0.92	0.89	
B5		0.60		0.65	0.62	
E6	0.60		0.65			0.55
PGIC	0.61		0.85			0.77
CGI	0.64	0.33	0.65		0.34	0.60

Note. 'Minimal residual' extraction method was used in combination with a 'promax' rotation. Number of factors based on parallel analysis. Loadings below 0.3 were discarded.

Sleep improvement is defined as at least one point improvement in both E6 and B2. Out of the 206 completers in P301, 32% (n= 66 "improvers", n= 140 "non-improvers") had sleep improvement (E6/B2) at Week 4. Out of the 126 completers in P302, 37% (n= 47 "improvers", n= 79 "non-improvers") had sleep improvement at Week 4. The temporal relationship between items reflecting PTSD sleep disturbance and sleep-dependent emotional memory consolidation is demonstrated in **Table 4**.

Table 4. Evidence of Sleep-dependent Emotional Memory Consolidation

	P301 (N= 206)		**P302 (N= 126)**	
	Sleep Improvers at Week 4 (>1 in both B2 and E6)			
	Sleep Improvers N=66	Non-improvers N=140	Sleep Improvers N=47	Non-improvers N=79
	% of Patients Improved at Week 12 on B1, B4, or B5			
All 3 items	61%	37%	57%	43%
2/3 items	24%	26%	17%	24%
1/3 items	11%	17%	19%	17%
0 items	5%	20%	6%	17%

Safety and Tolerability

- TNX-102 SL was well-tolerated and the adverse events (AEs) reported in P302 were comparable to prior studies with TNX 5.6 mg. There were three participants with serious adverse events (SAEs) reported during the study: two in the placebo group and one in the active group (osteomyelitis of left great toe). None were deemed related to study drug.
- In all three studies, the most common local administration site reaction was oral numbness (hypoaesthesia). Rates of hypoaesthesia were 29.2% in the TNX-102 SL group versus 1.1% on placebo in P302; 37.3% versus 1.5% in P301; and 36.0% versus 2.1% in P201. These oral sensory AEs, oral numbness, oral tingling, and tongue discomfort were rated as mild and transient (<60 min) in the majority of cases.
- Systemic AEs at a rate of ≥ 5% in the TNX- 102 SL group were dry mouth (8.3 v. 3.3%) and upper respiratory tract infections (5.2 v. 4.4%) in P302; somnolence (15.7 v. 9.0%) in P301; and somnolence (16.0 v. 6.4%), dry mouth (16.0 v. 10.6%), headache (12.0 v. 4.3%), insomnia (6.0 v. 8.5%) and sedation (12.0 v. 1.1%) in P201.
- Discontinuations due to AE were at a rate of 6.3% in the TNX-102 SL group versus 2.2% on placebo in P302; 5.7% versus 2.3% in P301; and 2.0% versus 3.2% in P201.
- In P302, the safety population had an overall completion rate of 65.8%, which was numerically higher in the placebo group (70.3%) than in the TNX-102 SL 5.6 mg group (61.5%).

CONCLUSIONS & FUTURE DIRECTIONS

- Drug development can provide biological insights via pharmacological dissection of complex syndromes. For example, three studies of military-related and civilian PTSD revealed that TNX-102 SL impacted select items of the CAPS-5. These five items measure PTSD sleep disturbance and deficient PTSD sleep-dependent emotional memory consolidation, thereby suggesting that TNX-102 may improve daytime PTSD symptoms by facilitating a sleep-dependent healing mechanism.
- Not only does the 5-item CAPS-5 total score appear useful for measuring the clinical response to drugs that promote recovery from PTSD via a pharmacodynamic mechanism of improving sleep-dependent emotional memory processing, but it appears to be sensitive enough for measuring meaningful clinical improvement in a placebo-controlled pharmacological trial.
- In future trials, the one-month lookback version of the CAPS-5 will be employed with the rationale that the extended period of symptom observation could improve its ability to capture response to treatment.

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