Development of the AURORA Platform Trial Network to Test Interventions to Reduce Acute Stress Reaction Symptoms, and Illustration of Use Testing Sublingual Cyclobenzaprine TNX-102 SL

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

BACKGROUND

U.S. military personnel exposed to life-threatening traumatic events (e.g., intense firefights with multiple casualties, witnessing death) can experience **acute stress reactions (ASRs)** in the war theater, adversely affecting warfighter performance and safety and predisposing to chronic psychopathological outcomes. Symptoms of ASR include intrusions, dissociation, avoidance, arousal (including poor sleep), pain and other somatic symptoms, and negative mood. When symptoms persists >72 hours after the event, **acute stress disorder (ASD)** may be diagnosed, and when they persist for ≥ 1 month, **posttraumatic stress (PTS) and/or persistent pain, somatic symptoms, cognitive symptoms, and/or depressive symptoms, collectively termed adverse posttraumatic neuropsychiatric sequelae (APNS)** may be diagnosed. **To reduce ASR, PTS, and other acute and chronic APNS symptoms, it may be valuable to intervene in the immediate aftermath of trauma (Fig 1).** Many promising interventions exist to reduce such symptoms and improve warfighter function, but historically there has been no testing platform to rapidly assess candidate interventions for potential efficacy.

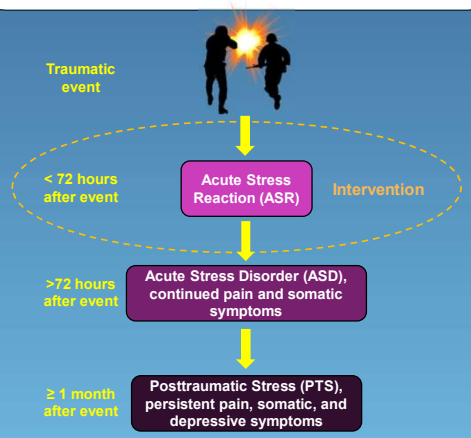

Fig. 1. Early intervention may reduce ASR symptoms and the subsequent development of posttraumatic stress (PTS) and/or persistent pain, somatic symptoms, cognitive symptoms, and/or depressive symptoms, collectively termed adverse posttraumatic neuropsychiatric sequelae (APNS)

The AURORA Research Network is a **US Emergency Department (ED)-based network** of trauma centers that performs prospective longitudinal studies of individuals experiencing traumatic stress. The AURORA Research Network has been in operation for more than 20 years. The Network has recruited more than 6,000 trauma survivors presenting to the ED for care after traumatic stress into observational and intervention studies evaluating the development of APNS and testing interventions to prevent APNS. We are dedicated to process improvement within and across studies, have a unique depth of experience with this work, and have developed screening tools to identify high risk individuals. These assets allow us to achieve high rates of recruitment and follow-up and complete studies successfully. The AURORA Research Network Coordinating Center is based at the University of North Carolina at Chapel Hill.

The AURORA APNS Platform is a standard platform randomized controlled trial (RCT) design. This standardized design and our experienced network sites allow us to rapidly onboard and complete studies testing medications and other early interventions for efficacy in reducing acute or persistent posttraumatic stress (**Fig 2**).

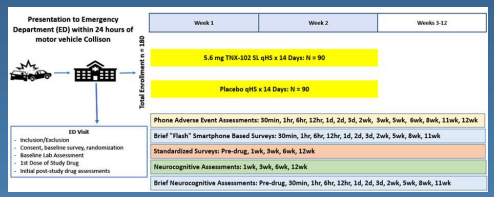

Fig. 2. General AURORA Platform Trial Design, using TNX-102 SL as example. This standard platform randomized controlled trial (RCT) design is being used to rapidly assess interventions, administered in the early aftermath of traumatic stress exposure (motor vehicle collision), for efficacy in reducing acute or chronic Adverse Posttraumatic Neuropsychiatric Sequelae (APNS). Such APNS include ASR/PTS symptoms, pain, somatic symptoms (e.g., dizziness, lightheadness), cognitive symptoms (concentration difficulty, taking longer to think), and depressive symptoms. The platform is currently contracted to test a number of different interventions.

One promising medication intervention to reduce acute and chronic APNS is TNX-102 SL. TNX-102 SL (sublingual cyclobenzaprine HCl) is in development by Tonix Pharmaceuticals Inc., for treating fibromyalgia and PTSD. Cyclobenzaprine **(Fig 3)** is the active ingredient in TNX-102 SL **(Fig. 4)**. This drug was previous evaluated in military PTSD in several randomized, double-blind, placebo-controlled Phase 2 and Phase 3 trials. In these studies, TNX-102 SL reduced PTSD symptom severity (3) and reduced sleep disturbance (a significant factor in stress recovery). TNX-102 SL has favorable tolerability with low rates and low severity of systemic side effects. Local effects, such as numbness/tingling under the tongue and/or awareness of bitter taste are common but generally mild.

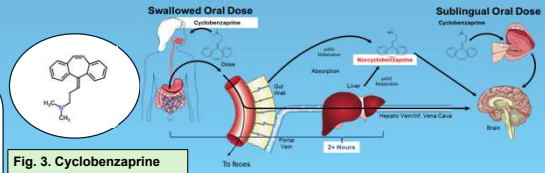

Fig. 3. Cyclobenzaprine

- Potent binding and antagonist activities at postsynaptic receptors:
  - serotonin-5-HT_{2A}
  - α_1-adrenergic
  - histaminergic-H_1
  - muscarinic-M_1
- Improves sleep quality but is not a traditional hypnotic or sedative

Fig. 4. TNX-102 SL (Sublingual Cyclobenzaprine HCl)

Advantages of the sublingual route:

- Faster absorption provides PK that is ideal for bedtime dosing, minimizing morning somnolence
- Bypasses "first-pass" hepatic metabolism.
  - Reduced metabolism of parent CBP to active metabolite norcyclobenzaprine (nCBP); increased CBP to nCBP ratio in blood

METHODS

The OASIS trial (**O**ptimizing **A**cute **S**tress Reaction **I**nterventions with TNX-102 **SL**), will evaluate the efficacy and safety of TNX-102 SL in civilians presenting to the Emergency Department (ED) after a motor vehicle collision (MVC) **(Fig 6)**. MVC is one of the most common traumatic events for which individuals seek ED care. The AURORA study (1) of more than 3,800 civilians showed that in the early aftermath of an MVC, the same ASR/ASD/PTSD symptoms occur as in servicemembers exposed to traumatic events in the war theater. Thus, civilians in a recent MVC are an optimal population to test interventions for evidence of efficacy, which could benefit both service members and civilians.

Fig. 6. Study Design

Emergency Department Visit

- Key inclusion criteria
  - ✓ ≥ 18 years and ≤ 55 years of age
  - ✓ Admitted to ED within 24 hours of MVC
  - ✓ Anticipated to be discharged home
  - ✓ PTSD prediction tool risk score ≥16; pain severity ≥4 (0-10 rating scale) (2)
- Key exclusion criteria
  - ✓ Substantial comorbid injury
  - ✓ Pregnant females
  - ✓ Chronic opioid use prior to MVC
  - ✓ Active psychosis, suicidal ideation, or homicidal ideation
- Consent, baseline surveys, and lab assessments
- Randomization to TNX-102 SL 5.6 mg (n = 90) or placebo (n = 90)
- 1st dose of study drug, and initial post-study drug assessments

Objective

Investigate the potential of TNX-102 SL (cyclobenzaprine HCl sublingual tablets) to reduce the frequency and severity of the adverse effects of traumatic exposure, including ASR, ASD, and PTSD.

Primary Outcome Measure

- Acute Stress Disorder Scale (14-item self report inventory that indexes ASD and predicts PTSD) assessed at 7 and 21 days post MVC

Secondary Outcome Measures

- Posttraumatic stress symptom severity assessed at 6 and 12 weeks post MVC using the PTSD Checklist for DSM-5 (PCL-5)
- Standardized survey instruments of sleep disturbances, anxiety and depression symptoms, general physical and mental health, and clinical global improvement
- Detailed and brief neurocognitive assessments (e.g., generalized cognitive function, psychomotor vigilance, procedural reaction, response inhibition/control, visuospatial processing, and visuospatial attention tasks) performed from baseline to 12 weeks after MVC at specific timepoints throughout study participation period

Safety Assessments

In person or text/email adverse event assessments at 30 minutes, 1 hour, 6 hours, 12 hours, 1 day, 2 days, 3 days, 1 week, 2 weeks, 3 weeks, 5 weeks, 6 weeks, 8 weeks, 11 weeks, and 12 weeks after drug administration. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) will be used to assess AE severity.

CONCLUSIONS

- According to the National Center for PTSD, about 60% of men and 50% of women in the US are exposed to at least one traumatic experience in their lives (4). In the US alone, one-third of ED visits (40-50 million patients per year) are for evaluation after trauma exposure (5). No medications are currently available at or near the point of care to treat patients suffering from acute trauma and support long-term health.
- Previous trials showed that TNX-102 SL reduced military PTS symptoms, in as early as 2 weeks, with favorable tolerability.
- TNX-102 SL is hypothesized to reduce ASR symptoms in the immediate aftermath of an MVC.
- The first participant for the OASIS trial is expected to enroll in Q3 2024.
- The results may ultimately provide military personnel with a new treatment option that, when administered in the early aftermath of a traumatic event to individuals with ASR symptoms, improves warfighter function

ACKNOWLEDGEMENTS

This study is supported by the United States Department of Defense Congressionally Directed Medical Research Program (Award No. W81XWH2220051), National Institutes of Health, Alphabet, and by Tonix Pharmaceuticals, Inc. Siobhan Fogarty (Tonix) contributed significantly to the study protocol and formulation development.

DISCLOSURES

DTH, SL, and GS are employees of Tonix Pharmaceuticals, Inc., and own stock and/or have stock options in the company. CWJ, LG, XA, CM, CB, RS, and SAM declare no conflicts of interest related to this work.

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For information regarding testing medications or device interventions using the AURORA research network/platform, contact Meredith_Bucher@med.unc.edu or Megan_Henderson@med.unc.edu