TSND-201 (Methylone) for the Treatment for PTSD: Improvement in Sleep-Related Outcomes from the Open- Label Portion of the IMPACT-1 Study

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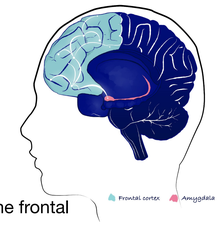
Introduction

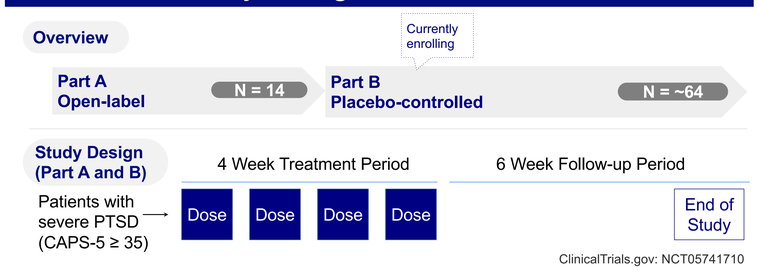
- Post-traumatic stress disorder (PTSD) is a serious debilitating disorder impacting approximately 13M Americans each year.[1] Approved pharmacotherapies for the treatment of PTSD (sertraline and paroxetine) have limited effectiveness. Less than 30% of patients treated with first-line pharmacotherapy achieve remission, which often takes many weeks to achieve.[2]
- Sleep disturbances with PTSD are common and typically include insomnia and nightmares. Nightmares are often resistant to PTSD treatment and have been linked with a five-fold increase in suicidality.[3]
- Poor sleep can worsen PTSD and result in additional health problems such as heart disease, high blood pressure, obesity, substance abuse, and stroke.[4]
- Existing medications have shown mixed results for treating nightmares, highlighting the need for new pharmacological options.[5]
- There is an urgent need for rapid-acting, non-hallucinogenic treatments for PTSD.

About TSND-201 (Methylone)

- **Methylone is a rapid-acting neuroplastogen**
  - Rapidly induces neuroplasticity gene expression (e.g., BDNF) in brain areas underlying pathophysiology of PTSD, depression, and anxiety[6]
- **Well-characterized primary pharmacology**
  - Monoamine transporters are primary site of action
  - No binding at 5HT2A receptor, not hallucinogenic
  - Rapid, robust serotonin and norepinephrine release in the frontal cortex



IMPACT-1 Study Design



ClinicalTrials.gov: NCT05741710

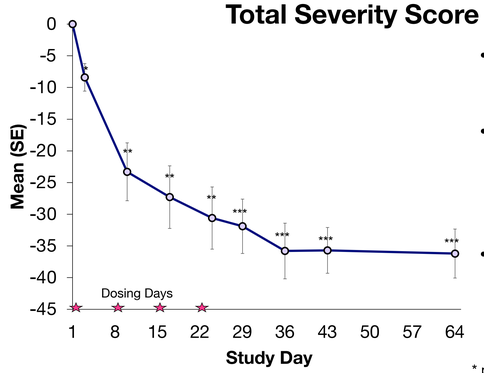
Key Inclusion	Key Exclusion
• Age 18-65 • DSM-5 diagnosis of PTSD • CAPS-5 ≥ 35 • Failed 1 prior PTSD treatment	• Concurrent substance abuse disorder • Use of MDMA or psychedelic <12 months • History of schizophrenia, psychotic disorder, bipolar, personality disorder, etc.

- TSND-201was administered once a week for 4 weeks. Each dose given as an initial dose, followed by a second dose 90 minutes later
- Participants were accompanied by a trained Mentor during the dosing session who provided non-directive support
- After the 4-week treatment period, participants attended follow-up visits at 1, 2, 3, and 6 weeks following the last dose
- Safety was assessed via standard measures including adverse events
- Overall PTSD symptoms were assessed via CAPS-5 total severity score
- Sleep-related improvements were evaluated on the CAPS-5 (distressing dreams [B2] and sleep disturbances [E6]), the reduced sleep item of the MADRS, and the Pittsburg Sleep Quality Index (PSQI; total scores range 0 to 21) and subscales.

Results

CAPS-5 (PTSD Symptoms)

Change from Baseline in CAPS-5 Total Severity Score

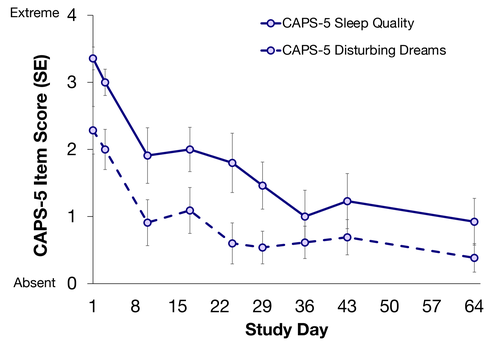


Mean (range) baseline: 47.8 (38 – 59)

- TSND-201 produced rapid and durable improvements
- **Rapid:** On Day 3, scores decreased by 8.4 pts. By Day 10, scores decreased by 23.3 pts
- **Durable:** 6 weeks after the last dose, scores decreased by 36.2 pts

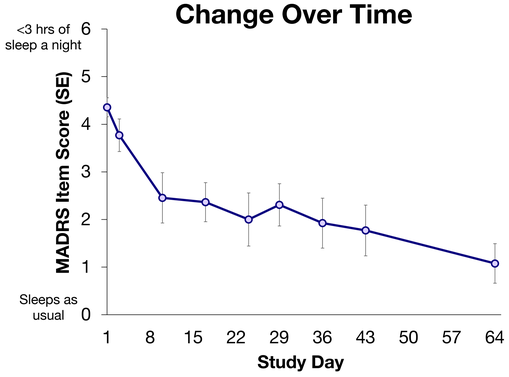
P-values vs. baseline
* p < 0.05; ** p<0.001; *** p<0.0001

CAPS-5 Sleep Items Change Over Time



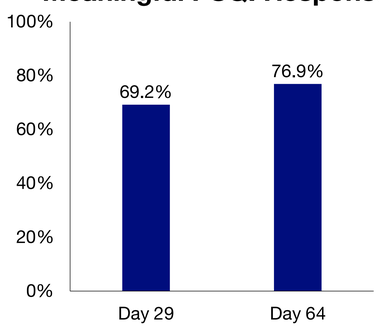
MADRS (Depressive Symptoms)

MADRS Sleep Item Change Over Time



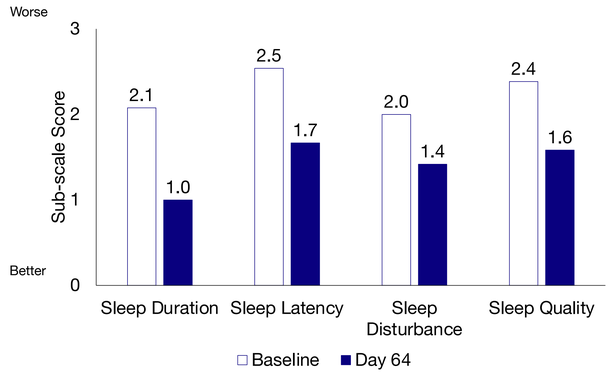
Pittsburg Sleep Quality Index (PSQI)

Patients with a Clinically Meaningful PSQI Response



Response = ≥ 3 point improvement from Baseline

PSQI Subscale Scores



Safety

Treatment-Emergent Adverse Events (> 1 Participant)

Adverse Event	TSND-201 (N=14)
Any AE	**78.6%**
Headache	42.9%
Decreased appetite	28.6%
Non-cardiac chest pain	21.4%
Fatigue	21.4%
Bruxism	14.3%
Dizziness	14.3%
Hyperhidrosis	14.3%
Influenza-like illness	14.3%
Insomnia	14.3%
Nasopharyngitis	14.3%

Conclusions

- TSND-201 demonstrated rapid, robust, and durable effects on PTSD symptoms; including key PTSD-related sleep issues (sleep disturbances and disturbing dreams).
- Overall sleep, measured by MADRS and response on the PSQI, was improved after treatment with TSND-201. Each of the PSQI subscales was consistently improved after treatment with TSND-201 (sleep duration, latency, disturbance, and quality).
- TSND-201 was generally safe and well tolerated, the most common AE was headache.
- Limitations of these results include an open-label design and small sample size.
- This study supports further development of TSND-201 as a treatment for PTSD. Part B of IMPACT-1, a randomized, placebo-controlled study, is currently enrolling.

References

1. NIMH, 2023. 2. Kelmendi et al., *European Journal of Psychotraumatology,* 2016. 3. Martin et al., *J Clin Med*, 2021 4. Colten, *IOM Committee on Sleep Medicine and Research* 2006. 5. Maher et al., *CNS Drugs,* 2006. 6. Warner-Schmidt et al., *Frontiers in Neuroscience*, 2024.

Disclosures

AJ, JW-S, MS, BM, HK are full-time employees with equity in Transcend Therapeutics. BK has equity in Transcend Therapeutics. THWC is a consultant to Transcend Therapeutics.