

Whitepaper

Transcutaneous Auricular Neurostimulation
(tAN™) To Aid In The Reduction Of Symptoms
Associated With Opioid Withdrawal

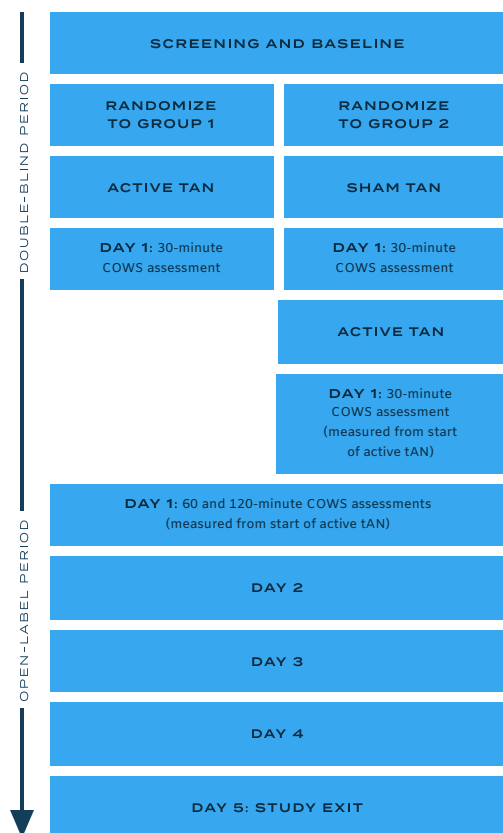


Clinical Trial Results

The product shown is a 2nd generation version of the device used in the clinical study.

Clinical Study Summary

A randomized, sham-controlled, double-blind study, followed by a 5-day open-label period, was designed to assess the effectiveness of the Sparrow Therapy System. The study evaluated transcutaneous nerve stimulation (tAN) as a method to aid in the reduction of symptoms associated with opioid withdrawal.



The patient population included male and female participants, aged 18-65, with a history of dependence on prescriptive or non-prescriptive opioids (n=31). Subjects were enrolled at one U.S. site based on 90% power at alpha 0.05 for detecting a mean (SD) reduction in clinical opiate withdrawal scale (COWS) of 17 (7) points when compared to baseline values.

In brief, study participants were randomized in a 1:1 ratio to one of two groups:

1. Active transcutaneous auricular neurostimulation (tAN) + usual treatment
2. Sham tAN + usual treatment followed by active tAN + usual treatment (during open-label period)

Participants assigned to Group 1 received active tAN in both the double-blind and open-label periods of the study. Subjects assigned to Group 2 received sham tAN (no stimulation) in the double-blind period, followed by active tAN in the open-label period.

All participants were informed of their group assignment at the conclusion of the randomized, double blind period and all continued to receive active tAN throughout the 5-day open-label period.

Blinding

Results of the Patient Blinding Assessment showed that blinding was not able to be maintained despite adherence to all protocol procedures. This result is likely due to the initial perception of electrical stimulation during device programming, which provided a familiar sensation in line with the participant's expectation during active tAN.

Primary Effectiveness Endpoint

The primary effectiveness endpoint of this study was successful mean percent change in COWS score (defined as a $\geq 15\%$ reduction) from baseline to 60 minutes after start of active tAN therapy.

Secondary Endpoint

The secondary endpoints of this study included:

- Comparison of mean percent change in COWS score in active tAN versus sham tAN at the conclusion of the 30-minute double-blind period
- Comparison of the proportion of participants with clinically significant reduction in COWS score (defined as a 15% or greater reduction) in the active tAN versus sham tAN groups at the conclusion of the 30-minute double-blind period
- Mean percent change in COWS score from baseline to 30 minutes after start of active tAN therapy
- Mean percent change in COWS score from baseline to 120 minutes after start of active tAN therapy
- Mean percent change in COWS score from baseline to Days 2 through 5 after start of active tAN therapy

Exploratory Endpoints

The following are exploratory endpoints for this study:

- Mean change in depression symptoms measured by Patient Health Questionnaire (PHQ-9) total score from baseline to Day 5
- Mean change in PTSD symptoms measured by the PTSD Checklist for DSM-5 (PCL-5) total symptom severity score from baseline to Day 5

Safety Endpoints

Safety Endpoints included the prevalence of all adverse events (AEs), serious adverse events (SAEs), adverse device events (ADEs), serious adverse device effects (SADEs), unanticipated serious adverse device effects (USADEs), and device deficiencies.

Of the 31 subjects enrolled in the study, 15 completed the study. The study results for all subjects, including study completers and non-completers, are listed below. Data from both the active tAN and the delayed-active tAN groups were pooled for the primary effectiveness analysis. The clinical study demonstrated that the subject device met the primary endpoint.

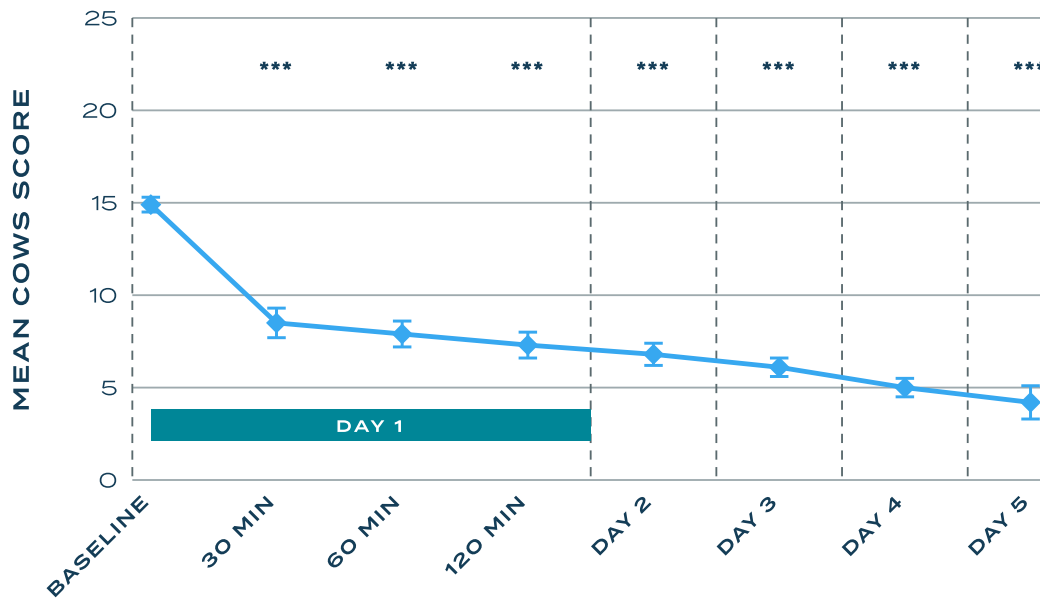
Participant Demographics

	Group 1 (n = 16)	Group 2 (n = 15)	Group 1 (N = 31)
Mean¹ (SD) Age at Enrollment (years) (Range)	34.2 (7.3)	32.5 (7.4)	33.4 (7.3)
	(21–47)	(19–44)	
Mean (SD) Baseline COWS score (Range)	15.3 (2.7)	14.5 (2.7)	14.9 (2.7)
	(10–21)	(9–19)	(9–21)
Mean (SD) Duration of Opioid Use (years) (Range)	12.9 (7.0)	10.8 (6.4)	11.8 (6.7)
	(1–27)	(0.5–24.0)	
Mean (SD) Morphine Milligram Equivalent (Range)	1406.3 (1031.6)	1209.3 (566.5)	1311.0 (831.8)
	(300–4000)	(150–2000)	(150–4000)
Gender: n (n/N%)			
Female	6 (37.5%)	5 (33.3%)	11 (35.5%)
Male	10 (62.5%)	10 (66.7%)	20 (64.5%)
Race: n (n/N%)			
White	14 (87.5%)	12 (80.0%)	26 (83.9%)
Hispanic or Latino	1 (6.3%)	3 (20.0%)	4 (12.9%)
Black or African American	1 (6.3%)	0 (0%)	1 (3.2%)
Psychiatric Co-Morbidities^{2,3}			
Depression	4 (25.0%)	6 (40.0%)	10 (33.3%)
Anxiety	3 (18.8%)	7 (46.7%)	10 (33.3%)
Bipolar Disorder	4 (25.0%)	4 (26.7%)	8 (26.7%)
Opioid Type^{2,4}			
Heroin	14 (93.3%)	13 (86.7%)	27 (90.0%)
Prescription Narcotics	1 (6.7%)	4 (26.7%)	5 (16.7%)
Buprenorphine/Naloxone	1 (6.7%)	0 (0%)	1 (3.3%)
Methadone	0 (0%)	1 (6.7%)	1 (3.3%)
Fentanyl	0 (0%)	1 (6.7%)	1 (3.3%)
Non-Opioid Drug Use in Previous 30 Days²			
Alprazolam	5 (33.3%)	4 (26.7%)	9 (30.0%)
THC	3 (20.0%)	5 (33.3%)	8 (26.7%)
Methamphetamine	5 (33.3%)	7 (46.7%)	12 (40.0%)
Alcohol	4 (26.7%)	5 (33.3%)	9 (30.0%)
Cocaine	4 (26.7%)	2 (13.3%)	6 (20.0%)
Other	1 (26.7%)	4 (26.7%)	5 (16.7%)
¹ Means analyzed using unpaired t-test with Welch's correction and Chi Square or Fisher's Exact test used for proportions			
² Data not available for one participant in Group 1; ³ Participants may have more than one co-morbidity; ⁴ Participants may have used more than one opioid			

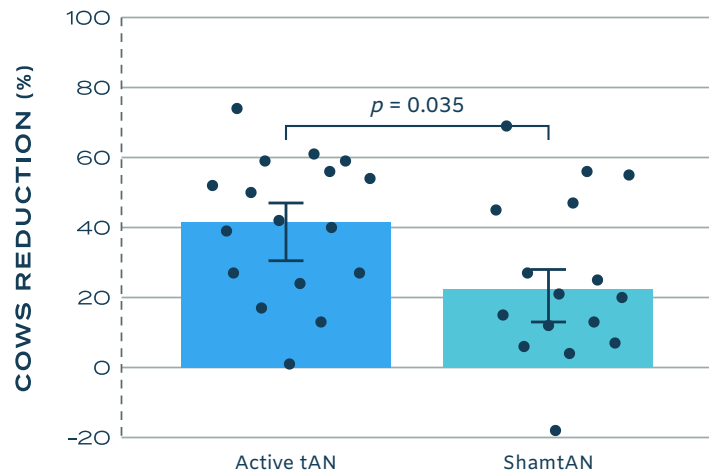
Primary Endpoint: Mean Reduction in COWS Score from Baseline to 60 Minutes after Start of Active tAN Therapy

Timepoint ¹	N	Mean (SD) COWS Reduction	Percent Reduction in COWS Score	p-value ²	95% CI	Percentage of Participants with Clinically Meaningful Reduction (n/N%) ³
30 min	31	6.4 (4.2)	42.0%	< 0.0001	[3.9, 8.9]	24 (77.4%)
60 min	31	7.0 (4.7)	45.9%	< 0.0001	[4.2, 9.7]	26 (83.9%)
120 min	27	7.6 (4.3)	51.8%	< 0.0001	[5.3, 11.0]	25 (92.6%)
Day 2	20	8.1 (4.0)	56.3%	< 0.0001	[6.0, 12.0]	19 (95.0%)
Day 3	20	8.8 (3.4)	61.5%	< 0.0001	[7.2, 12.0]	20 (100%)
Day 4	15	9.9 (3.3)	66.2%	< 0.0001	[7.3, 12.0]	16 (100%)
Day 5	13	10.7 (4.9)	70.4%	< 0.0001	[6.5, 15.0]	12 (92.3%)

¹ Timepoints denote number of minutes after start of active tAN; ² Mixed-effects model (REML); ³ Clinically meaningful reduction defined as a 15% or greater reduction in score

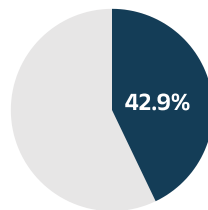


Comparison of COWS Scores: Active and Sham tAN at the End of the Double-Blind Period



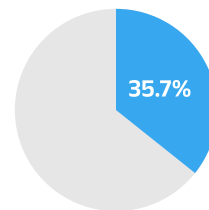
PHQ-9 (Depression) and PCL-5 (PTSD) Results

PHQ-9 TOTAL SCORE



42.9% of participants had clinically meaningful reduction in PHQ-9 scores at Day 5.

PCL-5 SCORE



35.7% of participants had clinically meaningful reduction in PCL-5 scores at Day 5.

Questionnaire (Domain)	Mean (SD) Reduction in Score from Baseline to Day 5 (N=13 ¹)	Percent Change in Score from Baseline to Day 5 (N=13 ¹)	p value	Percentage of Participants with Clinically Meaningful Reduction ^{1,2}
PHQ-9 (Depression)	5.4 (6.1)	31.4 (35.7)%	0.015	6/13 (46.2%)
PCL-5 (PTSD)	10.2 (9.1)	31.4 (33.4)%	0.001	5/13 (38.5%)

¹ Defined as at least a 5-point change for PHQ-9 (Kroenke K, Spitzer RL, Williams JB, et al. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. Gen Hosp Psychiatry 2010;32:345–59) and at least a 10-point change for PCL-5 (National Center for PTSD. (2016). Using the PTSD Checklist for DSM-5 (PCL-5). Retrieved from <https://www.ptsd.va.gov/professional/assessment/documents/using-PCL5.pdf> on June 17, 2020.

² Excludes one participant with score over 2 standard deviations above the mean

Safety Results

Only two device-related adverse events have occurred. Both were mild in severity and required no intervention to resolve.

Event	Device-Related	Severity	SAE	Action Taken	Outcome
Precipitated withdrawal due to naloxone challenge ¹	No	Moderate	No	Comfort medication given	Resolved without sequelae
Irregular heartbeat due to withdrawal (pre-existing, known condition)	No	Mild	No	Participant taken to ER but no treatment administered	Resolved without sequelae
Ear discomfort due to inner cymba arm ²	Yes	Mild	No	None	Resolved without sequelae
Ear discomfort due to inner cymba arm ²	Yes	Mild	No	None	Resolved without sequelae
¹ This event occurred in the first participant and the event categorized as the adverse event was a direct result of a naloxone challenge being administered when the participant had tested positive for opiates/morphine on Day 3. ² Not reported directly by participant but discovered when participant completed device usability questionnaire.					



Published results from this clinical trial can be reviewed in Bioelectric Medicine, Delivering transcutaneous auricular neurostimulation (tAN) to improve symptoms associated with opioid withdrawal: results from a prospective clinical trial.

We're Dedicated to the Science

We built upon a solid history of neurostimulation therapy, then applied over 150 years of our own combined neuroscience and medical device expertise to develop a scientifically proven solution that can significantly enhance the management of opioid withdrawal. We believe in an evidence-based approach, and are committed to making ongoing investments in engineering and clinical neuroscience to advance the therapy even further — beyond opioid withdrawal.

At Spark Biomedical, we want to provide an easy, safe, and effective path forward so more patients can overcome withdrawal, heal, and achieve a better quality of life, free of opioid dependence.

Tirado, C.F., Washburn, S.N., Covalin, A., Hedenberg, C., Vanderpool, H., Benner, C., Powell, D.P., McWade, M.A. and Khodaparast, N., 2022. Delivering transcutaneous auricular neurostimulation (tAN) to improve symptoms associated with opioid withdrawal: results from a prospective clinical trial. *Bioelectronic Medicine*, 8(1), pp.1-13.

Indication for Use

The Sparrow is a transcutaneous nerve field stimulator that is intended to be used in patients experiencing opioid withdrawal in conjunction with standard symptomatic medications and other therapies for opioid withdrawal symptoms under the supervision of trained clinical personnel.