# Use of Transcutaneous Auricular Neurostimulation to Reduce Opioid Withdrawal Symptoms

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# Disclosure

- No relative financial relationships to disclose

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# Transcutaneous Auricular Neurostimulation Device

- FDA-cleared wearable device
- Transcutaneaous Auricular Neurostimulation device (tAN)
- Parameters set by investigator
- Earpiece stimulates 3 regions
  - 1)auricular branch vagus n.
  - 2)auriculotemporal branch of trigeminal n.
  - 3)lesser occipital & post. auricular branch of vagus n.

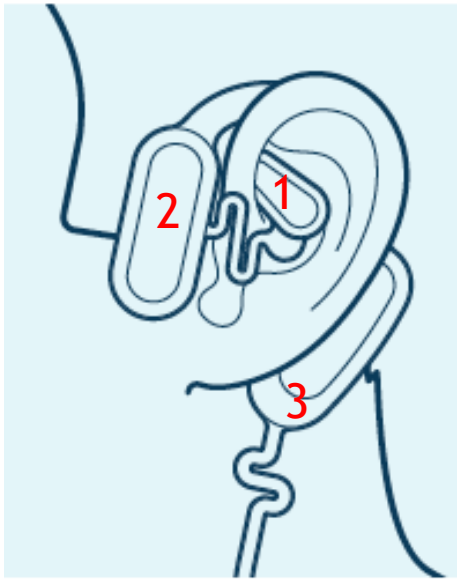
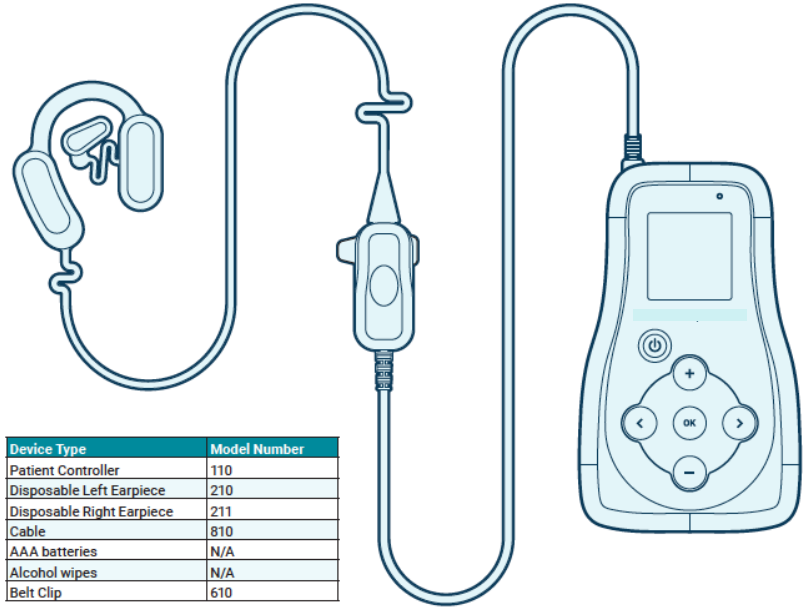



Figure 3: Earpiece placed correctly



| Device Type | Model Number |
|---|---|
| Patient Controller | 110 |
| Disposable Left Earpiece | 210 |
| Disposable Right Earpiece | 211 |
| Cable | 810 |
| AAA batteries | N/A |
| Alcohol wipes | N/A |
| Belt Clip | 610 |

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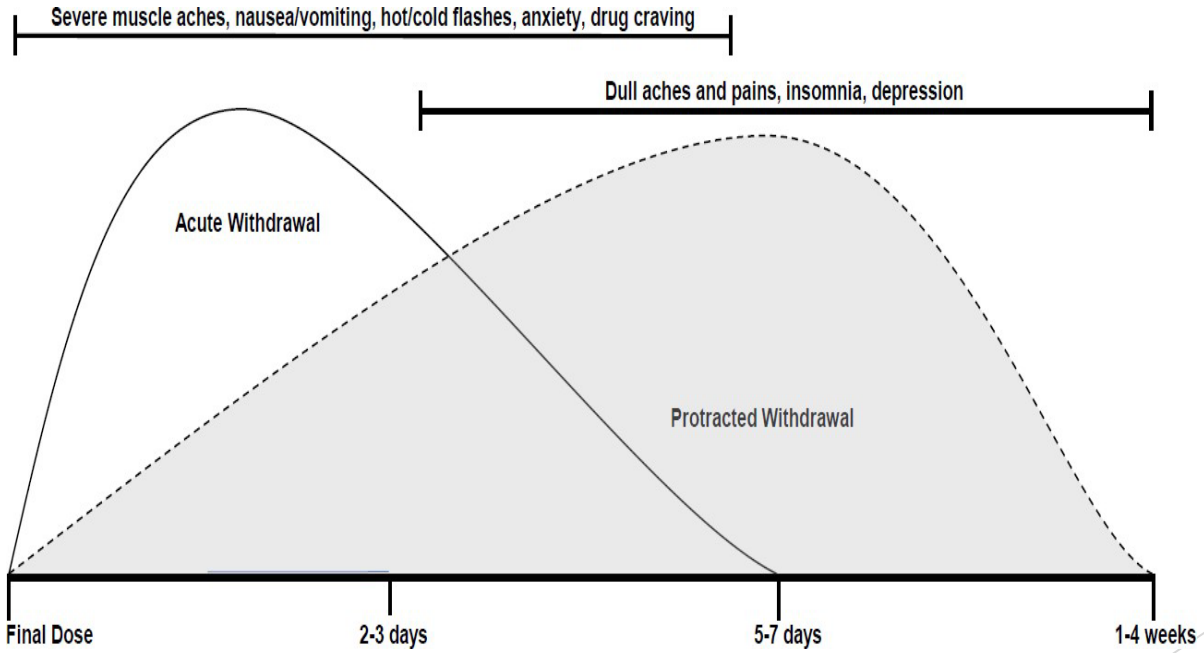
# Opioid Withdrawal Symptoms

- Target Acute withdrawal symptoms
  - Muscle aches
  - Nausea
  - Anxiety
  - Medication craving

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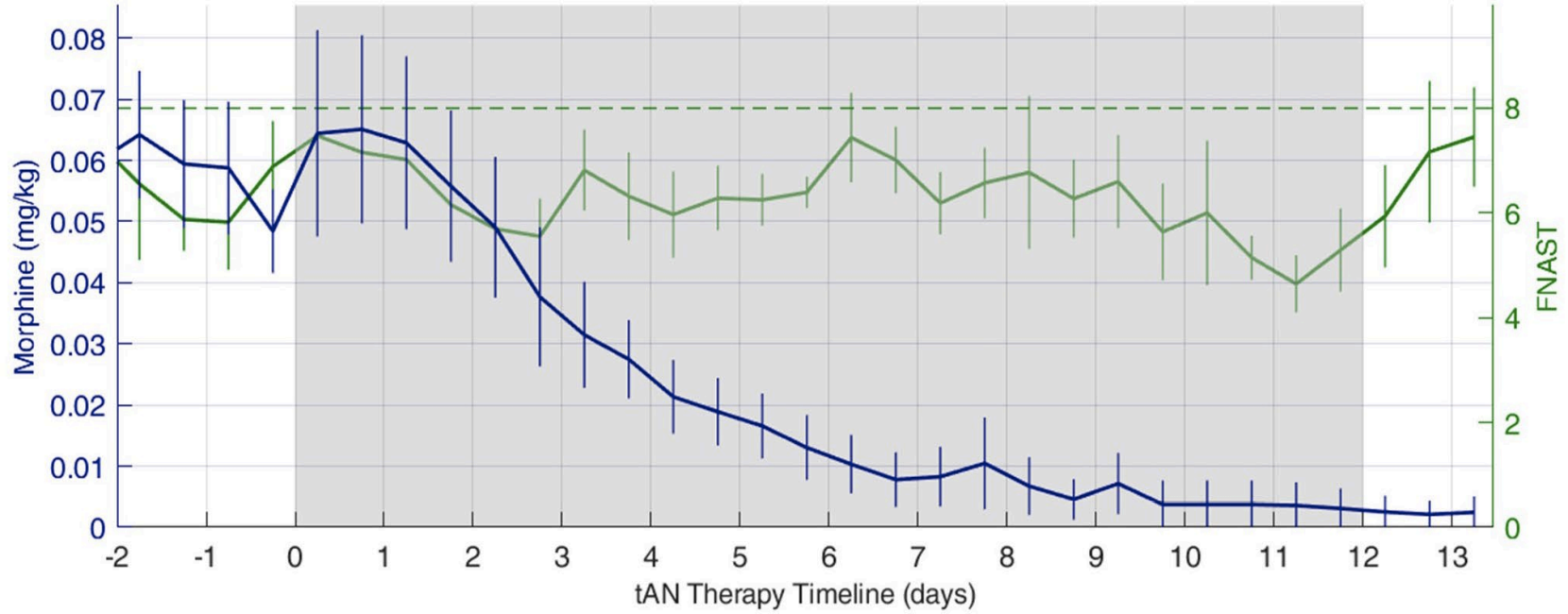
# tAN Reduces Morphine Replacement Therapy in Neonatal Withdrawal

- tAN LOT 13.3 days
- National Ave. 23 days

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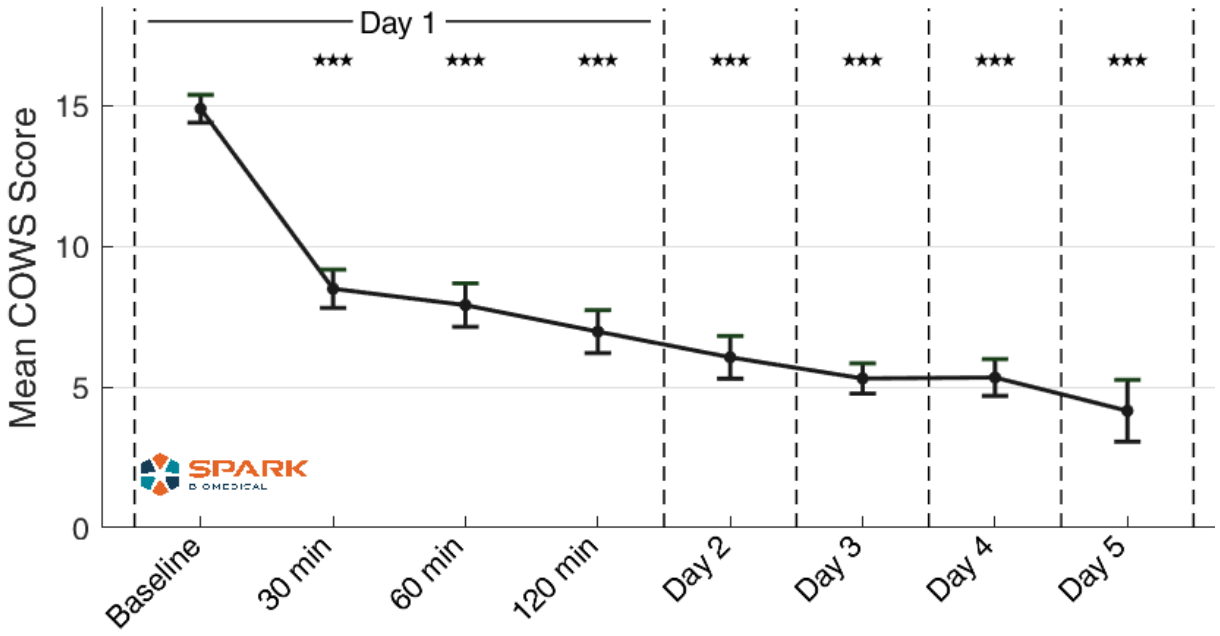
# tAN reduces opioid withdrawal during acute detox




COWS scores were significantly reduced from baseline by **45.9% at 60 minutes and 51.8% at 120 minutes** in patients undergoing acute detox[1]

**Can tAN therapy improve acute and long-term OUD treatment retention?**

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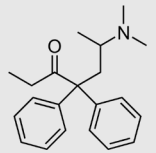
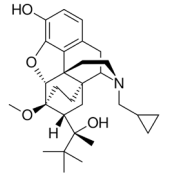
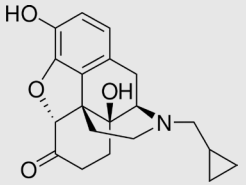
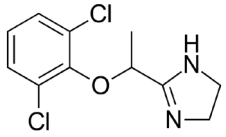
Tirado, Carlos F., et al. "Delivering transcutaneous auricular neurostimulation (tAN) to improve symptoms associated with opioid withdrawal: results from a prospective clinical trial." *Bioelectronic Medicine* 8.1 (2022): 12.

# Medications for OUD (MOUD)

## Standard of Care

| Treatment Option | Type | Chemical Structure |
|---|---|---|
| Methadone | Mu opioid receptor full agonist |  |
| Buprenorphine | Mu opioid receptor partial agonist<br>Weak kappa opioid receptor antagonist<br>Delta opioid receptor agonist |  |
| Naltrexone | Mu and kappa opioid receptors antagonist |  |
| Lofexidine | Alpha-2-adrenergic agonist |  |

# The RESTORE Trial

Prospective, randomized, sham-controlled, double-blind, multi-site trial

| | |
|---|---|
| 108 patients with OUD | |
| 7-day in-patient acute detox treatment (Phase I)<br>90-day out-patient treatment (Phase II) | |
| Primary Endpoint | Retention in OUD Treatment |
| Secondary Endpoints | Reduction in cravings, anxiety, PTSD, depression, recovery capital |
| Tertiary Endpoints | Significant reduction in post-acute withdrawal syndrome |

NIH National Institute on Drug Abuse

HEAL NIH · Helping to End Addiction Long-term

Hazelden Betty Ford Foundation

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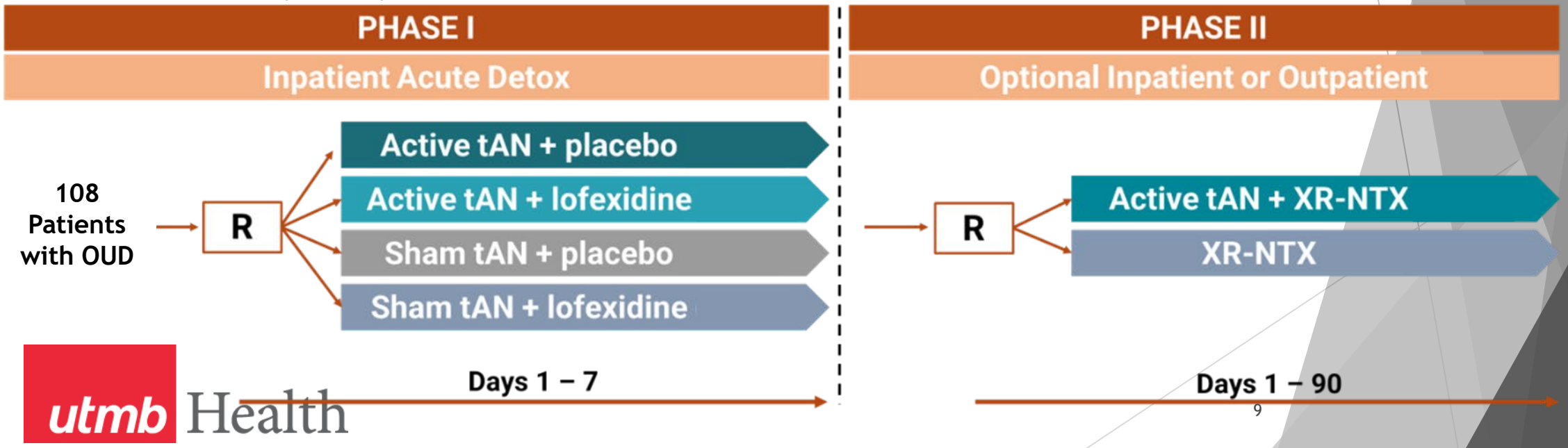
# RESTORE Study Design

- Study Population: Participants with a history of dependence on prescription or non-prescription opioids
  - **Phase I:** 108 Participants were randomized into a 7-day acute detox phase where they are randomized to receive active or sham tAN plus Lofexidine or a placebo.
  - **Phase II:** 44 Participants were then randomized into a 3-month treatment phase to receive active tAN + Extended – release Naltrexone (XR-NTX) or XR-NTX alone.

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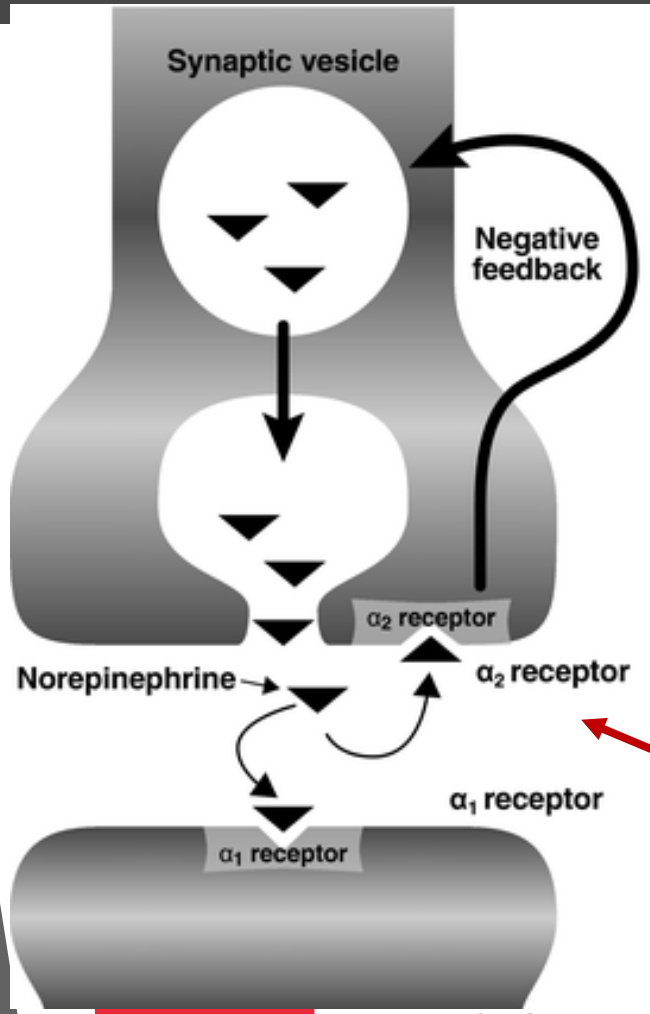
# $\alpha_2$-adrenergic Receptor Agonist




- $\alpha_2$ adrenergic receptors are involved in regulation of norepinephrine
- Activation of presynaptic $\alpha_2$ receptors with $\alpha_2$-adrenergic receptor agonists activates the norepinephrine negative feedback loop
- The negative feedback depresses activating signals, reducing norepinephrine production
- Net effect in a withdrawing patient is to attenuate surging norepinephrine production and return to normal physiological levels

**-Clonidine**
**-Lofexidine**

Activation of this negative feedback loop, either through the binding of NE or $\alpha_2$-adrenergic receptor agonists

- Lowers heart rate and blood pressure
- Lowers stress response
- Increases sedation

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# tAN increases OUD treatment retention

Participants who received **active tAN** during Phase I were

**4.8 times more likely**

to achieve successful acute detox than those who received **sham tAN**

There was a **statistically significant association** between receiving active tAN in Phase I and achieving successful acute detox*.

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***Successful acute detox is defined as:**

1. Receiving the first shot of vivitrol
2. Completing Phase I and not transition to Phase II but exiting the study with a Day 7 COWS $\leq$ 5 (no to mild withdrawal)
3. Did not complete all 7 days of Phase I, but Subject discontinued to start suboxone and participant had a COWS $\leq$ 5 (no to mild withdrawal)

# Addiction Love Story


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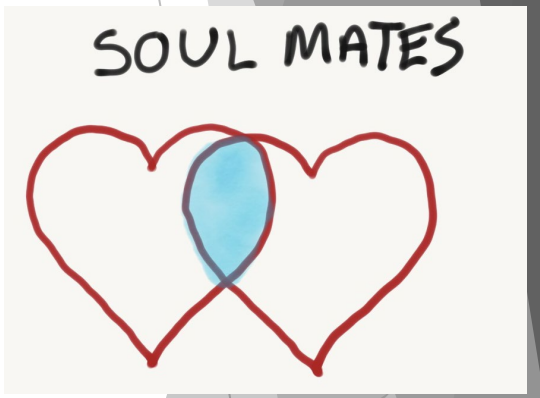


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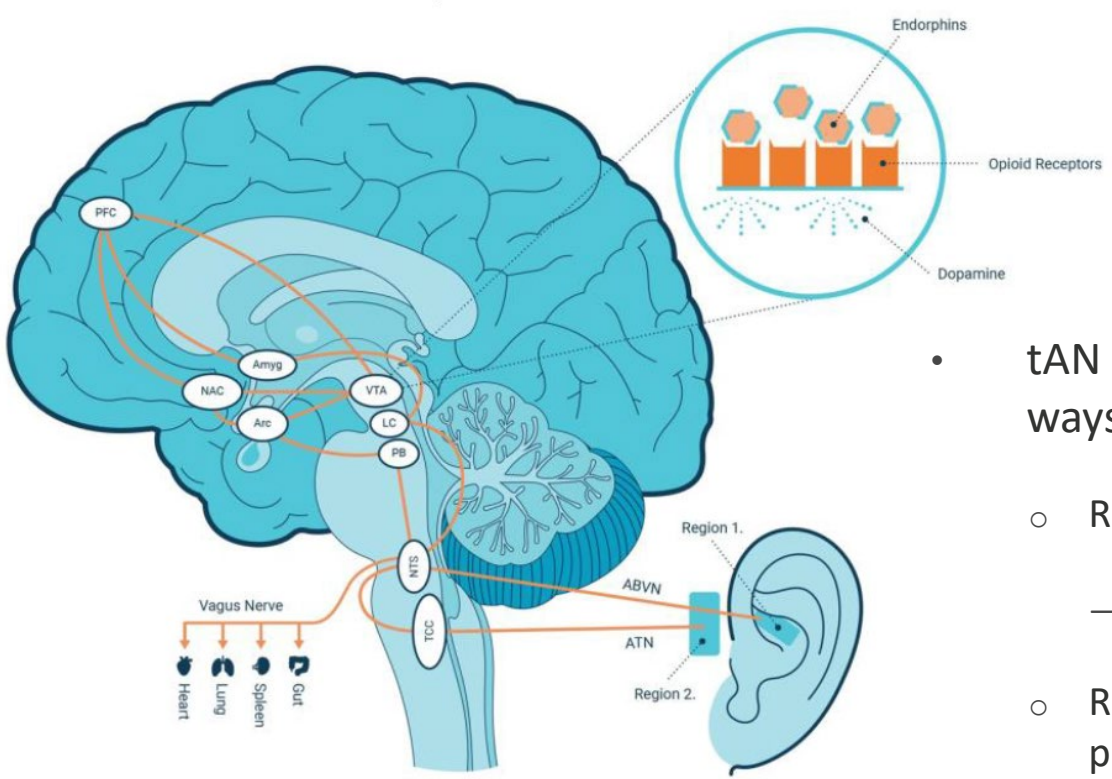
# tAN Alleviates OWS




- tAN improves opioid withdrawal in two ways
  - Release of endogenous opioids
    - Binds to OR in VTA and LC
  - Reduces stress and anxiety by promoting parasympathetic tone

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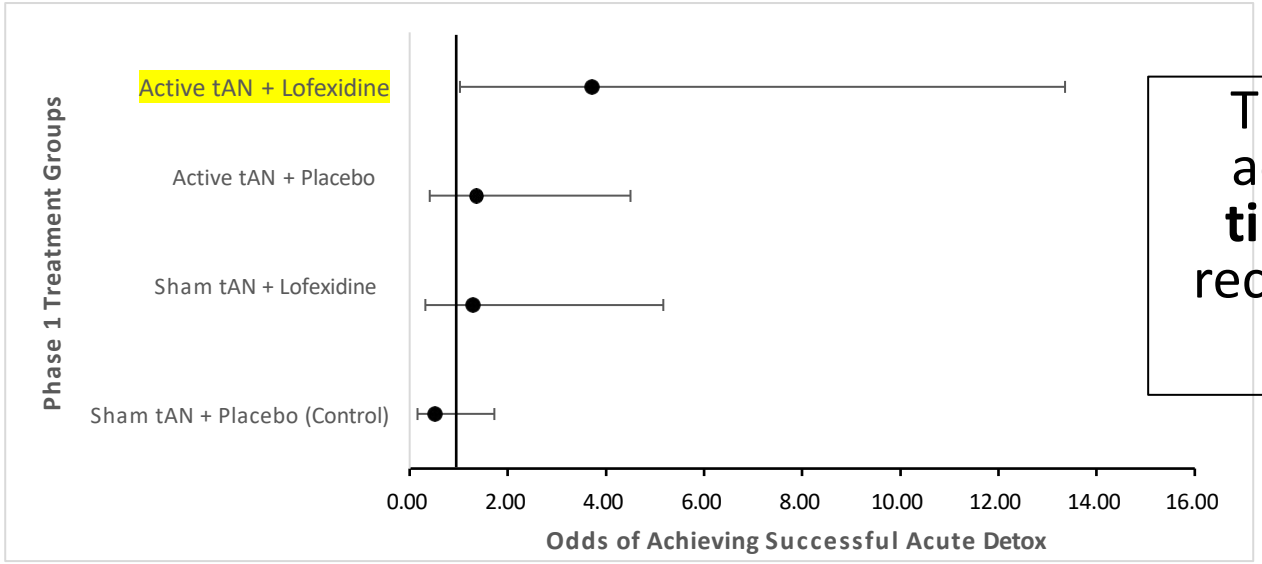
# tAN and Lofexidine Synergistically Improves Treatment Retention




The likelihood of completing acute detox treatment is **3.7 times higher** in patients who received active tAN + lofexidine than any other group

| PHASE 1 TREATMENT GROUP | ODDS RATIO | LOWER 95% CI | HIGHER 95% CI |
|---|---|---|---|
| **SHAM tAN + PLACEBO (CONTROL)** | 0.525 | 0.16 | 1.73 |
| **SHAM tAN + LOFEXIDINE** | 1.286 | 0.320 | 5.169 |
| **ACTIVE tAN + PLACEBO** | 1.357 | 0.409 | 4.500 |
| **ACTIVE tAN + LOFEXIDINE** | 3.714 | 1.025 | 13.356 |

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# Conclusions

- **RESTORE is the first clinical study** to demonstrate how non-invasive neurostimulation can be used as an adjunct to MOUD
- tAN has demonstrated clinically meaningful improvements in acute detox treatment retention
- **tAN + Lofexidine** demonstrate clinically significant improvements in acute detox treatment retention

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# Understanding the Mechanistic, Neurophysiological, and Antinociceptive Effects of Transcutaneous Auricular Neurostimulation for Treatment of Chronic Pain

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# Aim 3: Establish the neurophysiological signature specifically underlying tAN-based analgesia in chronic pain patients during opioid tapering

- Design: Randomized, double-blind, sham controlled mechanistic trial
- Participants: 40 outpatients with chronic non-cancer pain who are on long-term opioid therapy
- Setting: Inpatient clinical research center
- Intervention: Mild opioid taper (20-30% dose reduction) and tAN
- Conditions: Active tAN versus sham tAN
- Primary outcomes: Resting-state brain activity, pain severity and tolerance, opioid withdrawal severity

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# Study Overview

**Aim 3:** Establish the neurophysiological signature specifically underlying tAN-based analgesia in chronic pain patients during opioid tapering

**Design:** Randomized, double-blind, sham controlled mechanistic trial

**Participants:** 40 outpatients with chronic non-cancer pain who are on long-term opioid therapy

**Setting:** Inpatient clinical research center

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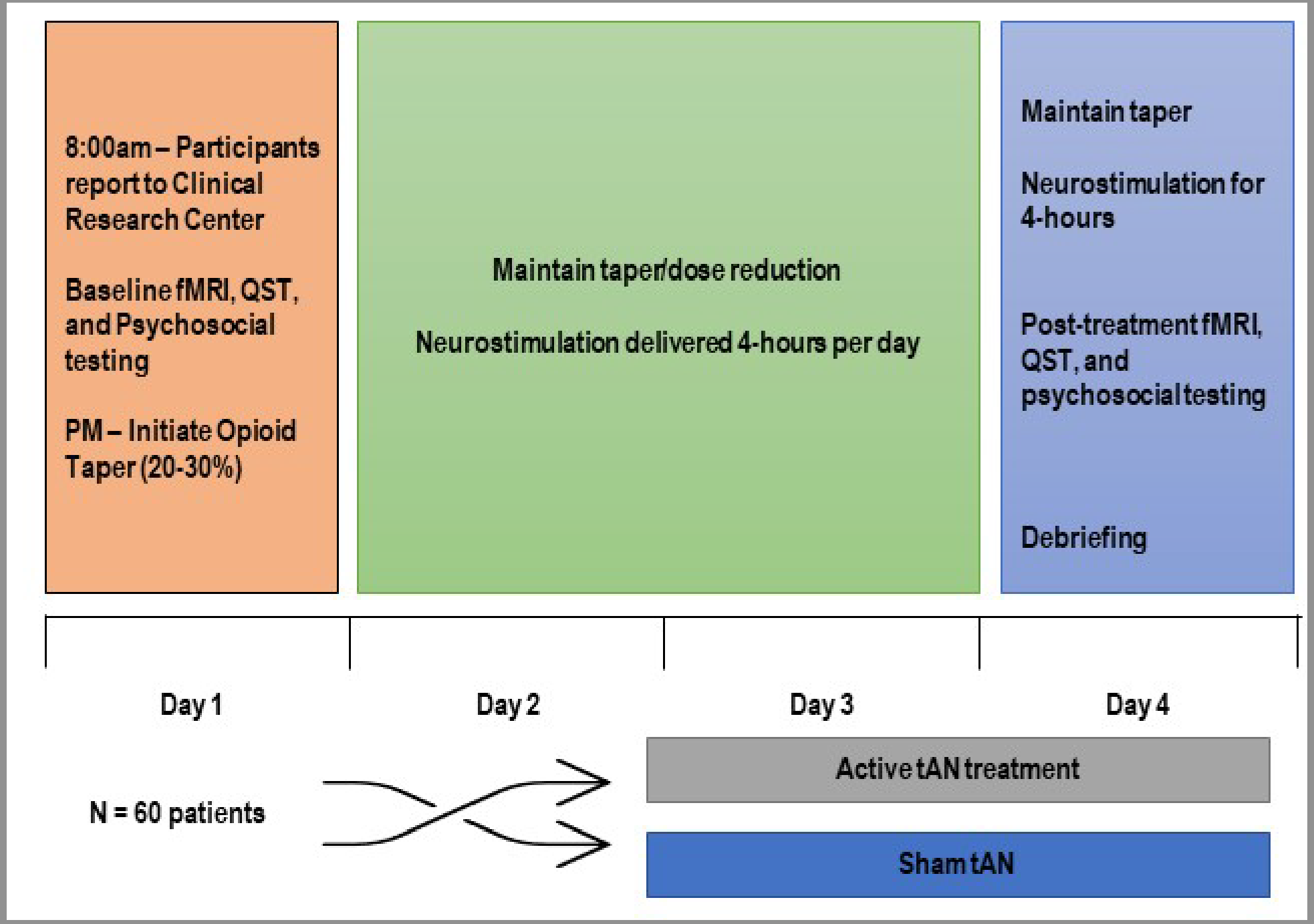
8:00am – Participants report to Clinical Research Center
Baseline fMRI, QST, and Psychosocial testing
PM – Initiate Opioid Taper (20-30%)
Maintain taper/dose reduction
Neurostimulation delivered 4-hours per day
Maintain taper
Neurostimulation for 4-hours
Post-treatment fMRI, QST, and psychosocial testing
Debriefing
Day 1
Day 2
Day 3
Day 4
N = 60 patients
Active tAN treatment
Sham tAN

# Multidimensional Assessment Battery

- Self- and Clinician-Report
  - Opioid Withdrawal Severity
  - Pain Severity
  - Depression Severity
  - Anxiety Severity
  - Post-traumatic Stress
  - Physical Functioning
  - Sleep Quality
- Quantitative Sensory Testing
  - Thermal
  - Pressure
- Resting-State fMRI
  - Functional, secure data pipeline with MUSC

# Recruitment

| Month | Pre-Screened | Screened | Eligible | Enrolled | Completed |
|---|---|---|---|---|---|
| Combined 2023 | 100 | 18 | 11 | 9 | 7 |
| Combined 2024 | 137 | 26 | 14 | 10 | 10 |
| January 2025 | 129 | 32 | 0 | 2 | 2 |
| February 2025 | 115 | 36 | 2 | 1 | 1 |
| March 2025 | 180 | 25 | 1 | 0 | 0 |
| April 2025 | 49 | 12 | 1 | 2 | 1 |
| May 2025 | 358 | 4 | 0 | 1 | 1 |
| June 2025 | 169 | 4 | 3 | 0 | 0 |
| July 2025 | 0 | 0 | 0 | 3 | 1 |
| August 2025 | 192 | 22 | 1 | 0 | 0 |
| September 2025 | 56 | 7 | TBD | 1 | 1 |
| **Total** | **1237** | **157** | **32** | **28** | **24** |

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# CONSORT Funnel

**TrialFacts Campaign 2:**

**100 referrals received**

- Cancelled phone screen: 4
- Phone screen fails: 60
- Unreachable: 14
- Phone screen passes: 21
- Duplicates: 1
- In progress: 0

**Slicer/Dicer:**

- 224 pre-screen pass
- Failed in-depth screen: 129
  - Incorrect medication: 80
  - Excluded by clinician: 23
  - Out of age range: 3
  - MRI exclusion: 7
  - Unreachable: 3
  - Not interested: 6
  - Duplicates: 7
- In progress: 95

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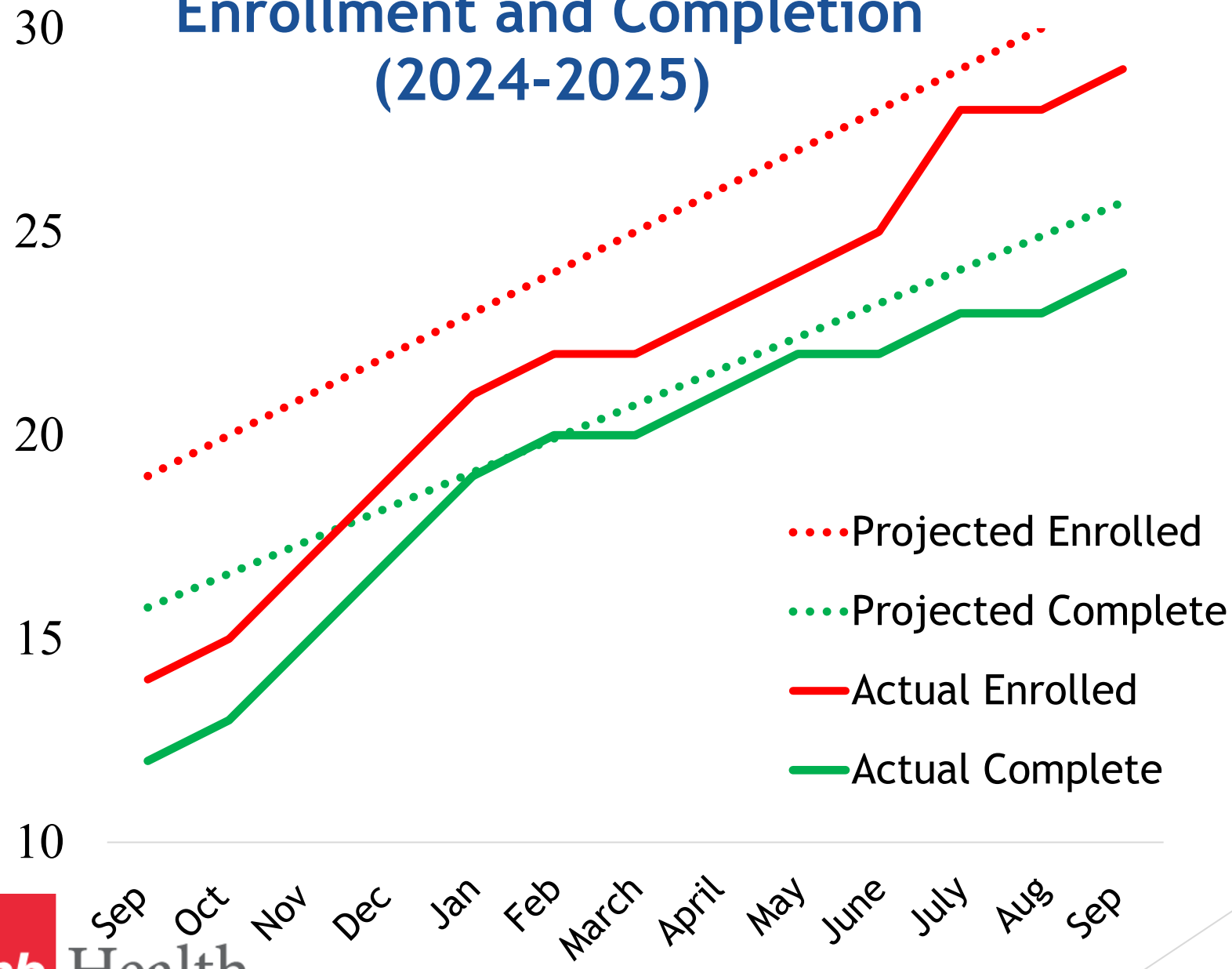
# Enrollment and Completion (2024-2025)

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# Completed Participant Characteristics

| Age | Race | Sex at Birth | Ethnicity |
|---|---|---|---|
| Mean: 57.5 | White: 17 | Male: 5 | Hispanic or Latino: 2 |
| Minimum: 26 | Black: 7 | Female: 19 | Non-Hispanic or Latino: 21 |
| Maximum: 75 | | | Not reported: 1 |

- Currently diverse (n=24)
- Age range is expected
- Working to recruit more males, 1 recently screened

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# Interim Data Check Process

- Imaging analyses performed by Dr. Peng
- Demographics and secondary outcome data exported from RedCap
- Cleaned in Excel and descriptive statistics performed in SAS
- Blinded Group A and B group means and 4-day changes
- Not intended to perform a formal statistical analysis or publish

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# Interim Primary Outcomes (n=20)

- Clinician and subjectively reported opiate withdrawal scales
- Functional connectivity evaluated with fMRI
- Patient reported outcome measures
- Quantitative sensory testing

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# Interim Completed Participants (n=20)

| Age | Race | Sex at Birth |
|---|---|---|
| Mean: 58.3 | White: 13 | Male: 3 |
| Minimum: 26 | Black: 7 | Female: 17 |
| Maximum: 75 | | |

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# Interim Primary Outcomes (n=20)

| Clinician Observed Opiate Withdrawal Scale | Baseline (Mean) | End of Treatment (Mean) | Change (Mean) |
|---|---|---|---|
| Overall (n=20) | 0.6 | 0.75 | 0.15 |
| Group A | 0.6 | 1 | 0.4 |
| Group B | 0.6 | 0.5 | -0.1 |

- Higher COWS represents greater withdrawal severity
- 5-12 is mild, 13-24 is moderate, 25-36 is moderately severe, over 36 is severe

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https://nida.nih.gov/sites/default/files/ClinicalOpiateWithdrawalScale.pdf

# Interim Primary Outcomes (n=20)

| Subjective Opiate Withdrawal Scale | Baseline (Mean) | End of Treatment (Mean) | Change (Mean) |
|---|---|---|---|
| Overall (n=20) | 4.4 | 2.2 | -2.2 |
| Group A | 4.4 | 2.8 | -1.6 |
| Group B | 4.4 | 1.6 | -2.8 |

- Higher SOWS represents greater withdrawal severity
- 1-10 is mild, 11-20 is moderate, 21-30 is severe

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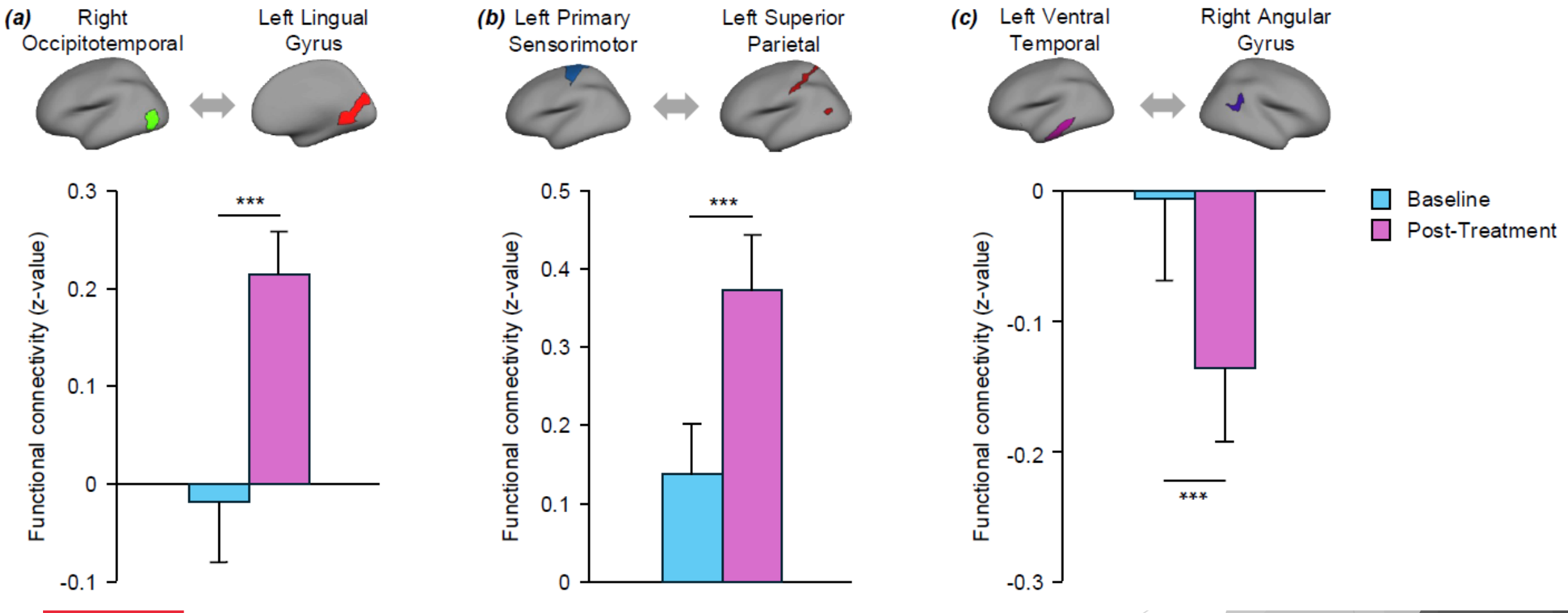
https://www.asam.org/docs/default-source/education-docs/sows_8-28-2017.pdf

# Functional Connectivity Changes in Group A

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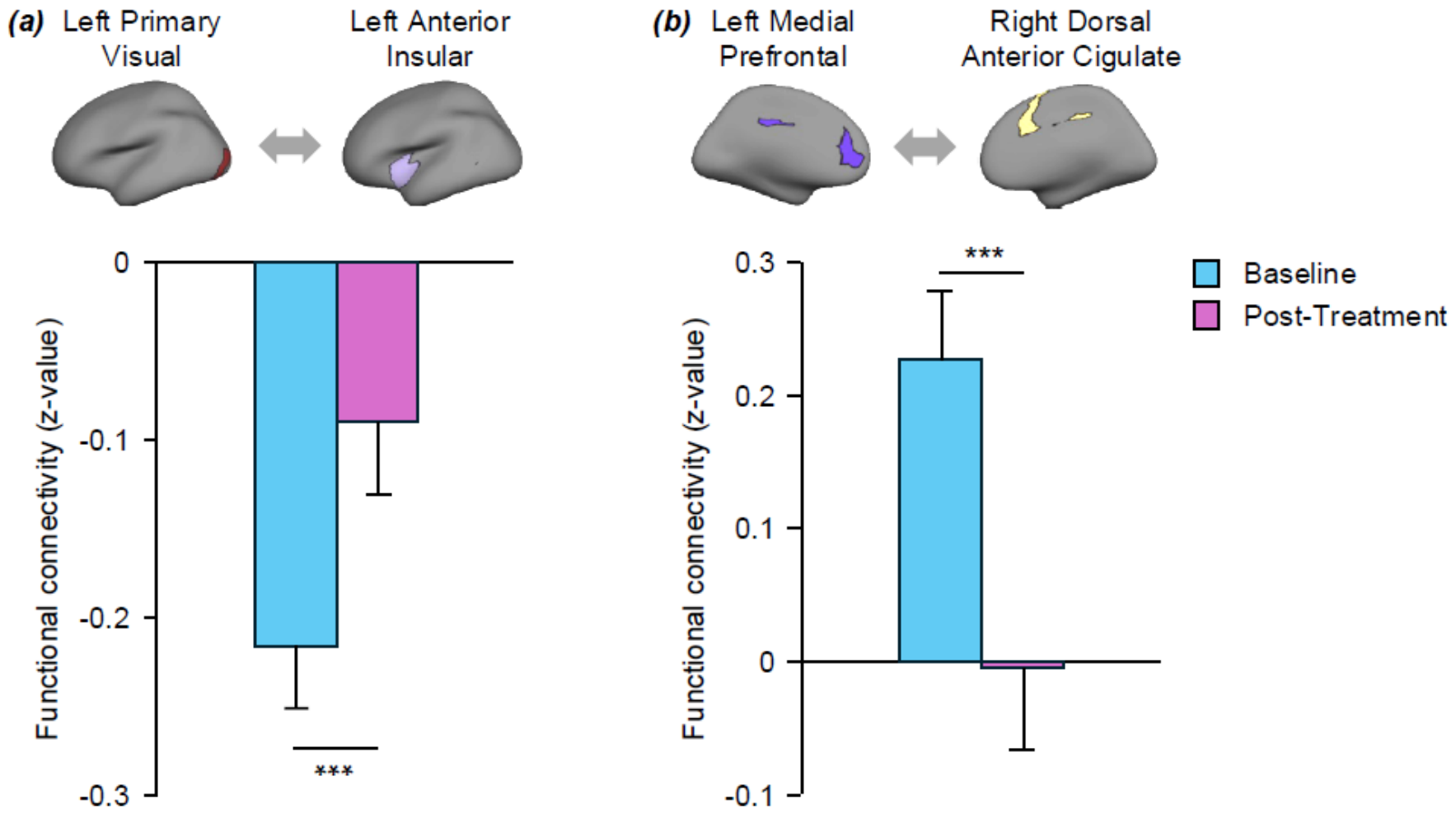
# Functional Connectivity Changes in Group B

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# Interim Secondary Outcomes (n=20)

| PEG-3 Total | Baseline (Mean) | End of Treatment (Mean) | Change (Mean) |
|---|---|---|---|
| Overall (n=20) | 6.1 | 3.6 | -2.1 |
| Group A | 5.6 | 4.3 | -2.1 |
| Group B | 6.75 | 3 | -2.1 |

- Total score is average of Q1-3 (0-10), higher is more severe
  - Q1: Average pain in past week (0-10)
  - Q2: Pain interference with life enjoyment (0-10)
  - Q3: Pain interference with general activity (0-10)

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https://pmc.ncbi.nlm.nih.gov/articles/PMC2686775/

# Interim Secondary Outcomes (n=20)

| PEG-3 Q1: Average pain in past week (0-10) | Baseline (Mean) | End of Treatment (Mean) | Change (Mean) |
|---|---|---|---|
| Overall (n=20) | 6.3 | 4.75 | -1.6 |
| Group A | 6.2 | 4.7 | -1.5 |
| Group B | 6.4 | 4.8 | -1.6 |

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# Interim Secondary Outcomes (n=20)

| PEG-3 Q2: Pain interference with life enjoyment (0-10) | Baseline (Mean) | End of Treatment (Mean) | Change (Mean) |
|---|---|---|---|
| Overall (n=20) | 6.7 | 4.25 | -2.5 |
| Group A | 6.7 | 4.3 | -2.4 |
| Group B | 6.7 | 4.2 | -2.5 |

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# Interim Secondary Outcomes (n=20)

| PEG-3 Q3: Pain interference with general activity (0-10) | Baseline (Mean) | End of Treatment (Mean) | Change (Mean) |
|---|---|---|---|
| Overall (n=20) | 6.25 | 4 | -2.3 |
| Group A | 6.1 | 3.8 | -2.3 |
| Group B | 6.4 | 4.2 | -2.2 |

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# Pressure Pain Threshold

| Pressure Pain Threshold (Avg. of 5) | Baseline (Mean) | End of Treatment (Mean) | Change (Mean) |
|---|---|---|---|
| Overall (n=20) | 351 kPA | 371 kPA | 21 kPA |
| Group A | 337 kPA | 410 kPA | 73 kPA |
| Group B | 364 kPA | 332 kPA | -32 kPA |

- Norm for pain-free older population at the wrist (n=212) is around 418 (±168) kPA.
- Overall change was less sensitive, Group A became less sensitive, Group B became more sensitive
- For context: 21 kPa = 3 PSI

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https://pmc.ncbi.nlm.nih.gov/articles/PMC11559510/

# Heat Pain Threshold

| Heat Pain Threshold (Avg. of 5) | Baseline (Mean) | End of Treatment (Mean) | Change (Mean) |
|---|---|---|---|
| Overall (n=20) | 40.18°C | 40.12° | -0.06° |
| Group A | 40.0° | 39.14° | -0.8° |
| Group B | 40.4° | 41.1° | +0.7° |

- Norm for pain-free population at the wrist (n=20) is around 43.9°C
- Overall change was negligible, Group A became more sensitive, Group B became less sensitive

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https://www.sciencedirect.com/science/article/pii/S1388245708008511

# Summary of Current Impressions

- The goal of this interim analysis was to ensure data integrity
- With this being an interim analysis and no formal statistical tests performed, we are not yet trying to describe group or time differences
- Group or time differences in even one outcome measure are very valuable to understand

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# UTMB Team Members

**MPIs**: Denise Wilkes, MD PhD, Kathryn Cunningham, PhD

**Co-I:** Yong Fang Kuo, PhD

**Postdoctoral Fellow:** Chris Pierson, DPT PhD

**Research Project Manager:** Victoria Korschgen, RN

**Study Coordinator:** Sophia Rodriguez, BS

**MRI Technician:** Rick Pena

**CRC Staff:** Lamonne Crutcher, RN

**RM1 Program Oversight:** Beth Cammarn, CRA

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# The Team

| Medical University of South Carolina | University of Texas Medical Branch | Spark |
|---|---|---|
| Jeff Borckhardt Co-PI | Denise Wilkes Co-PI | Navid Khodaparast Co-PI |
| Bashar Badran Consultant | Kathryn Cunningham Co-PI | Melanie McWade Co-I |
| | Chris Pierson Post-Doc<br>Victoria Korschgen & Sophia Rodriguez, Study Coordinator | |

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# Questions?

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