Transcutaneous electrical nerve stimulation (TENS) reduces movement-pain in people with fibromyalgia: Results from FM-TIPS, a cluster randomized pragmatic trial

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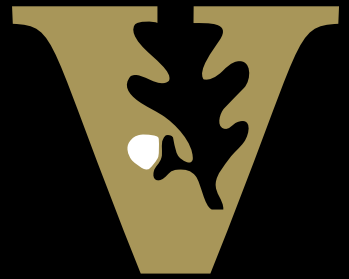


Fibromyalgia/Background

Leslie J. Crofford, MD

Fibromyalgia

- Widespread pain
  - Four quadrants and axial
  - **Pain exacerbated by movement**
- Tenderness
  - No longer required, but characteristic
- Neuropsychiatric symptoms
  - Debilitating fatigue
  - Waking non-refreshed
  - Cognitive symptoms
  - Other syndromes: e.g. depression, headache, abdominal pain

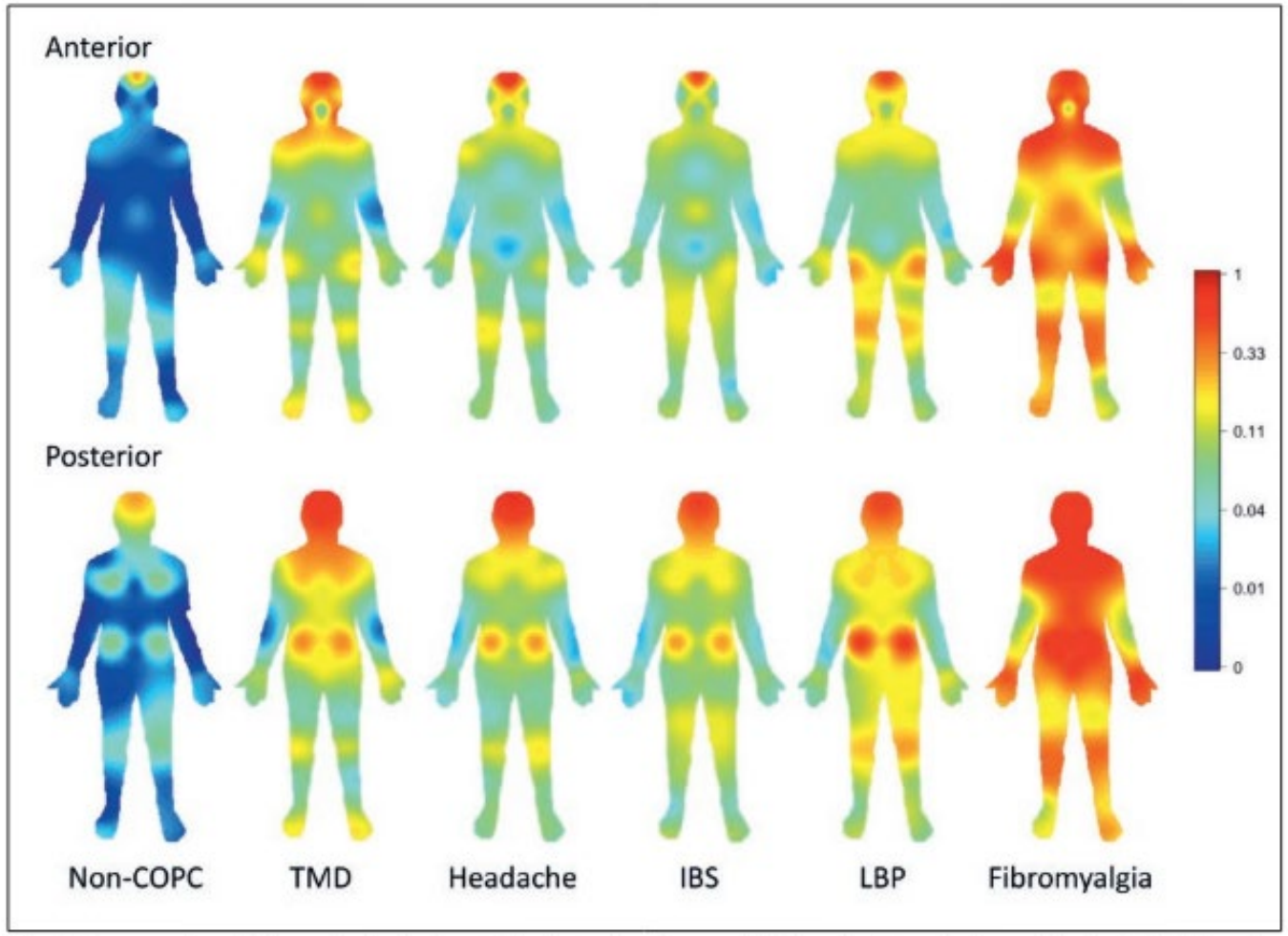


Fig 1 Heat map of manikin-based pain sites for pain lasting 1 day or longer within the prior 3 months for each index COPC. The color spectrum refers to the proportion of individuals with pain reported at the given site on the manikin. The skewed scaling of the color spectrum allows for the detection of body areas reported as painful by relatively few participants, with red color saturation starting at areas reported by approximately one-third of the participants. Non-COPC = individuals not meeting criteria for any of the five listed COPCs.

Distribution of Pain Among Five Chronic Overlapping (or Primary) Pain Conditions

Ohrbach et al. J Oral & Facial Pain and Headache. 34:s29, 2020

Fibromyalgia Mechanisms are Multifactorial

Abnormal pain processing in CNS

- Enhanced Sensitivity in CNS
  - Increased activation of nociceptive pathways
  - Activation of glial cells
  - Increased excitatory neurotransmitters
- Reduced Inhibition in CNS
  - Reduced response to opioid analgesics
  - Reduced serotonin and noradrenaline
  - Reduced conditioned pain modulation
- Other CNS symptoms
  - Cognitive and Physical Fatigue
  - Sleep dysfunction
  - Cognitive symptoms
  - Mood changes (depression/anxiety)

EULAR Revised Recommendations for the Management of Fibromyalgia

Recommendation	Level of evidence	Grade	Strength of recommendation	Agreement (%)
Overarching Principles				
➢ Optimal management requires prompt diagnosis and assessment of pain, function and psychosocial context. Recognition as a complex and heterogeneous condition. Gradual approach.	IV	D		100
➢ Management should aim at improving HRQoL balancing benefit and risk of treatment. **Initial management should focus on non-pharmacologic treatment.**	IV	D		100
Specific recommendations				
➢ Non-pharmacological management				
➢ Aerobic and strengthening exercise	Ia	A	Strong for	100
➢ Cognitive behavioral therapies	Ia	A	Weak for	100
➢ Multicomponent therapies	Ia	A	Weak for	93
➢ Defined physical therapies: acupuncture or hydrotherapy	Ia Ia	A A	Weak for Weak for	93 71-73
➢ Meditative movement therapies (qigong, yoga, tai chi) and mindfulness-based stress reduction				
➢ Pharmacological management	Ia	A	Weak for	100
➢ Amitriptyline (at low dose)	Ia	A	Weak for	100
➢ Duloxetine or milnacipran	Ib	A	Weak for	100
➢ Tramadol	Ia	A	Weak for	94
➢ Pregabalin	Ia	A	Weak for	75
➢ Cyclobenzaprine				

*TENS, A&R 2020

Macfarlane et al. ARD 76:318, 2017

Overall Efficacy of Drugs for FM

Clinical trial data demonstrate modest effect sizes for all drug classes

- Only 30-40% of patients have 40-50% relief[1]

Some treatments may impact concomitant symptoms in different ways; e.g.

- Amitriptyline/pregabalin for sleep
- Sublingual cyclobenzaprine for sleep
- Duloxetine/milnacipran for depression

Combination therapy seen in clinical practice

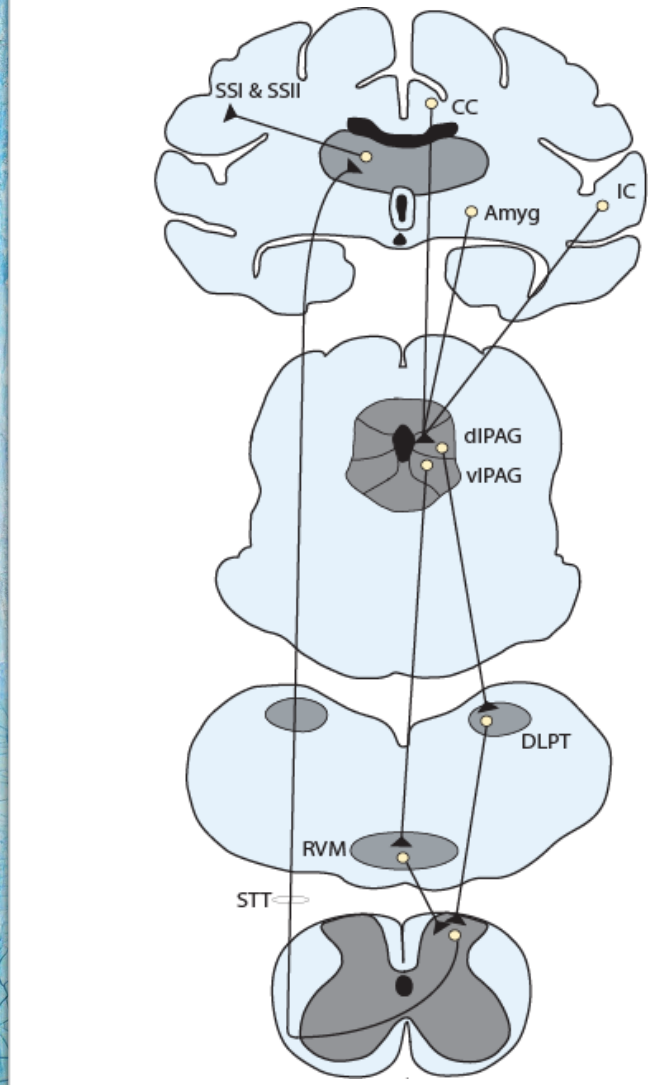
Poor tolerance of centrally acting agents due to adverse effects

[1]Backonja MM et al. Curr Pain Headache Rep 2006; 10:34

TENS Background

Mechanisms:
TENS Activates Central Inhibition and Reduces Central Excitability

- Activates descending inhibitory mechanisms in central nervous system
- Activates classical pain inhibitory pathways (gate theory)
- Reduces excitability of central pain neurons
- Low and high frequency use different mechanisms
  - Mixed frequency more effective



Open Access Review

Using TENS for Pain Control: Update on the State of the Evidence

by Carol G. T. Vance [1,*,†], Dana L. Dailey [1,2,†], Ruth L. Chimenti [1], Barbara J. Van Gorp [1], Leslie J. Crofford [3] and Kathleen A. Sluka [1]

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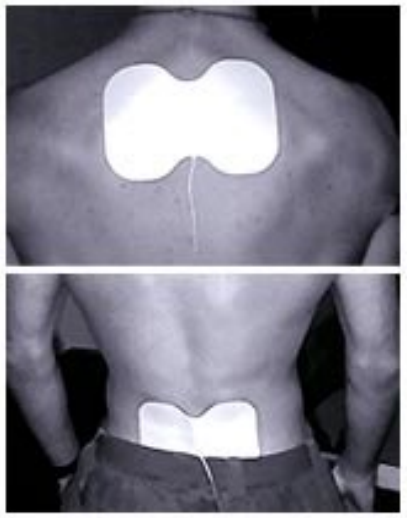
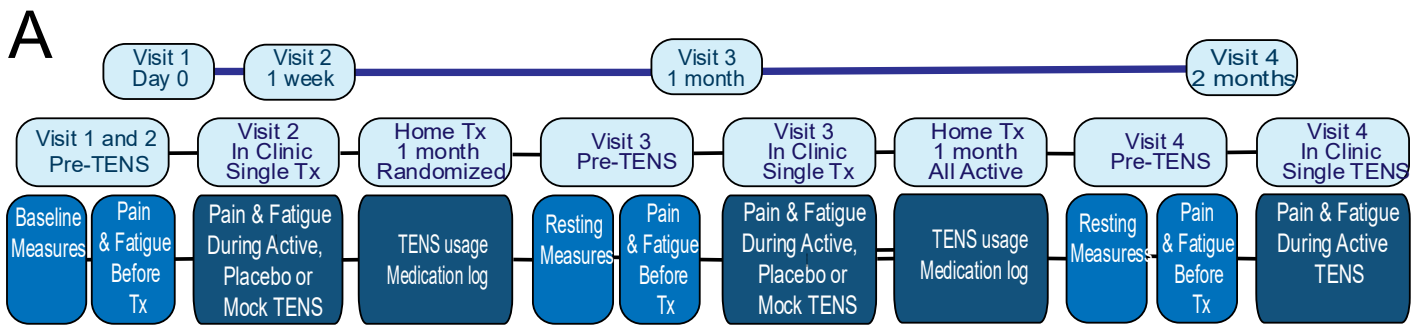
FAST Clinical Trial Design



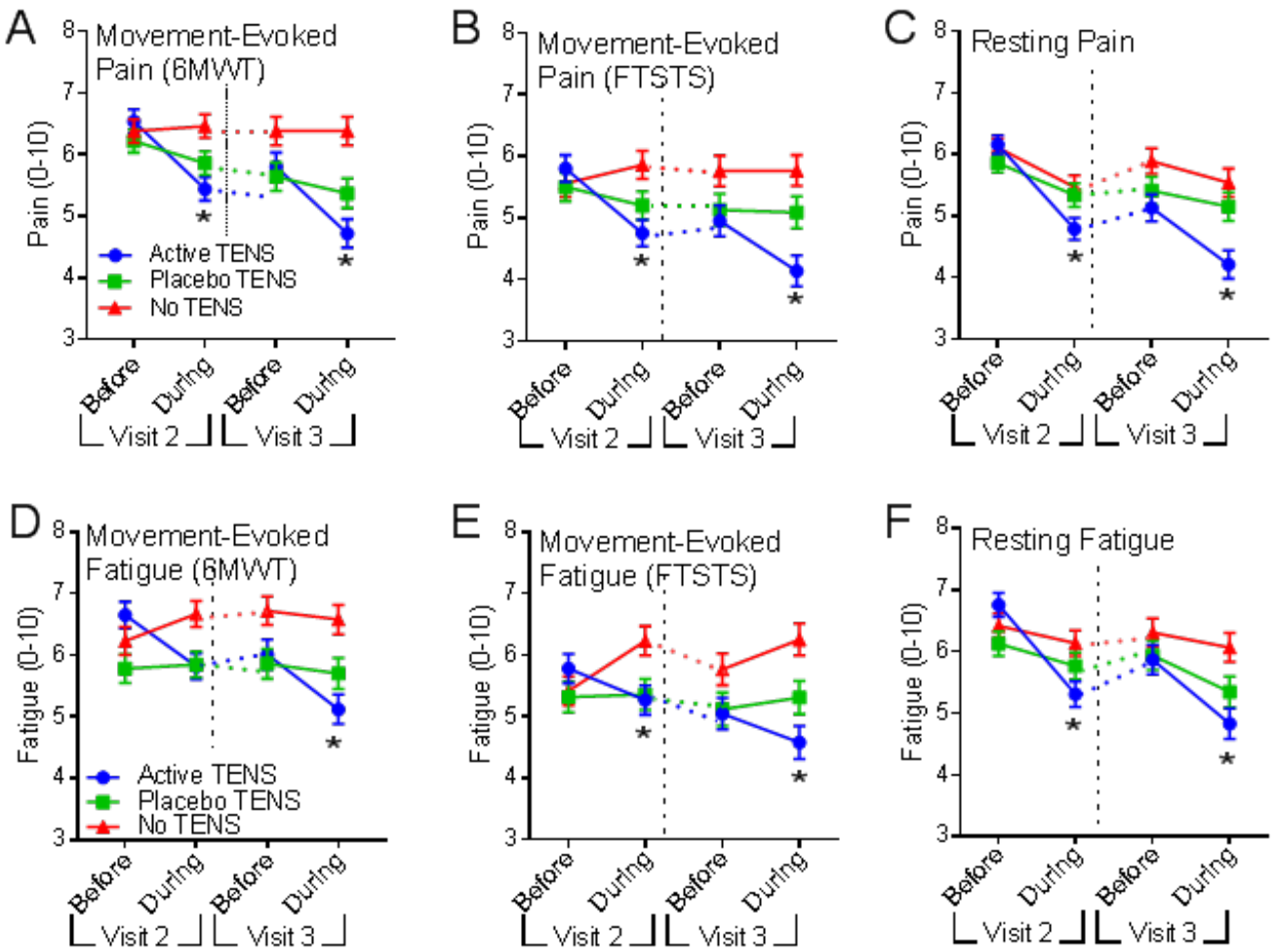


- Randomized placebo-controlled trial design
  - Active (n=103)
  - Placebo (n=99)
  - No TENS (n=99)
- Mixed frequency (4 Hz and 100Hz)
- Applied to upper and lower back
- Subjects used TENS at home
- Primary outcome at 1 month: movement-evoked pain
- Measured outcomes during TENS treatment
- Extension phase to determine persistence of treatment effects at 2 months

Dailey et al., Pain, 2020.

TENS reduces movement pain

FAST
Fibromyalgia Activity Study with TENS

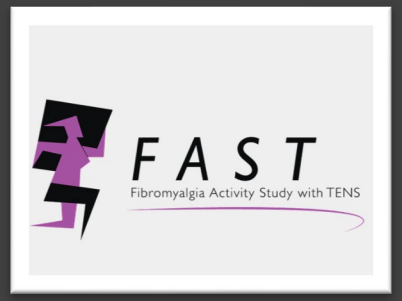


Dailey et al., A&R, 2020

Responder Analysis

	Active TENS n=103	Placebo TENS n=99	No TENS n=99	p-value (adjusted)	
Responder Definitions				**Active vs Placebo**	**Active vs No TENS**
≥30% Reduction pain	44% (34-53)	22% (15-31)	14% (9-22)	**0.004**	**<0.001**
≥20% Reduction fatigue	45% (35-54)	26% (19-36)	23% (16-33)	**0.019**	**0.004**
≥20% Reduction function	38% (29-48)	36% (28-46)	28% (20-38)	0.974	0.319
≥30% Reduction pain + ≥20% fatigue	29% (21-39)	13% (8-21)	13% (8-21)	**0.018**	**0.018**

TENS is safe and effective



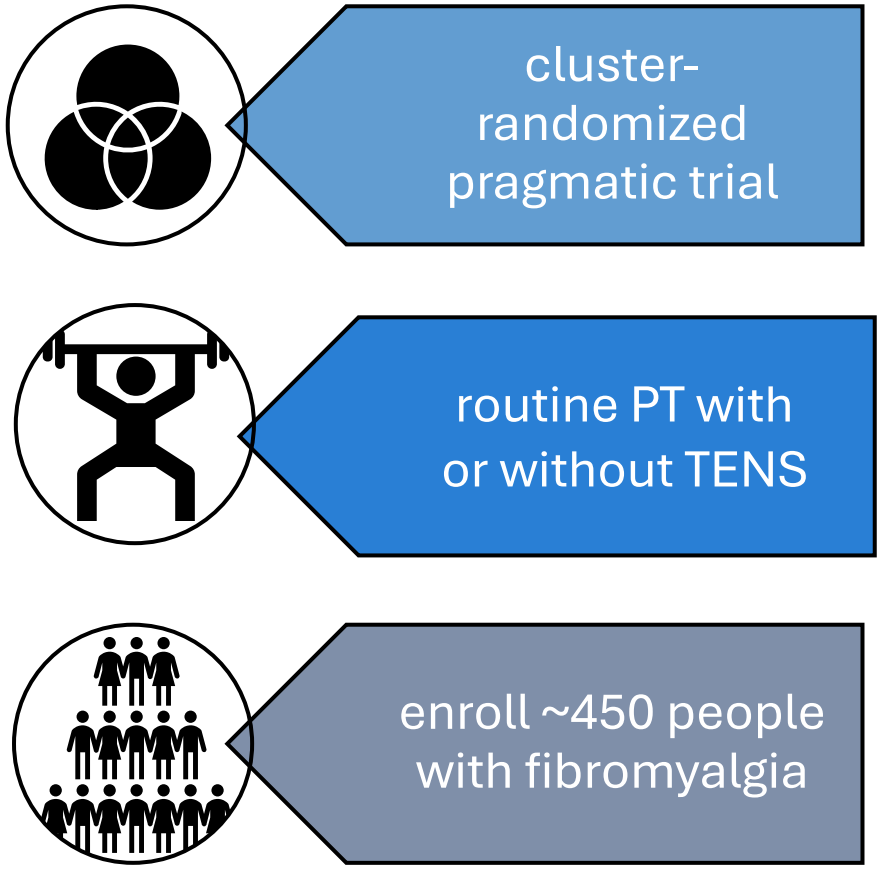
		Compared to placebo-TENS	Compared to no-TENS
NNT	Pain	4.5	3.3
	Fatigue	5.3	4.5
NNH	Serious AE	N/A	N/A
	Itchiness	100	50
	Anxiety	50	50
	Pain with TENS	50	20
	Nausea	33	50
	Skin Irritation	25	20

Vance et al., 2021

FM-TIPS Methods

Dana L. Dailey, PT, PhD

Fibromyalgia TENS in Physical Therapy Study



- Goal of the study
  - Test the feasibility and effectiveness of adding TENS to standard physical therapy (PT) care in a real-world physical therapy setting
- Clinicians and Participants
  - Clinicians (PTs) screened and treated participants
    - Included unless contraindications to TENS
  - Participants
    - 459 enrolled in 28 outpatient physical therapy clinics across 6 healthcare systems across the Midwest
    - 50% were rural

FM-TIPS
Fibromyalgia TENS In Physical Therapy Study

Developed a physical therapy clinic network

1. First step
   - Research PT healthcare systems across the country
     - Focused on those close to the PIs – southern US and Midwest
     - Had to have a stated interest in research
     - Reached out to PT colleagues who had links to healthcare systems for contacts
2. Second Step
   - Called directly to gauge interest
   - Study PIs met with leaders in each system directly
   - Obtained letters of support and willingness to participate from HCS

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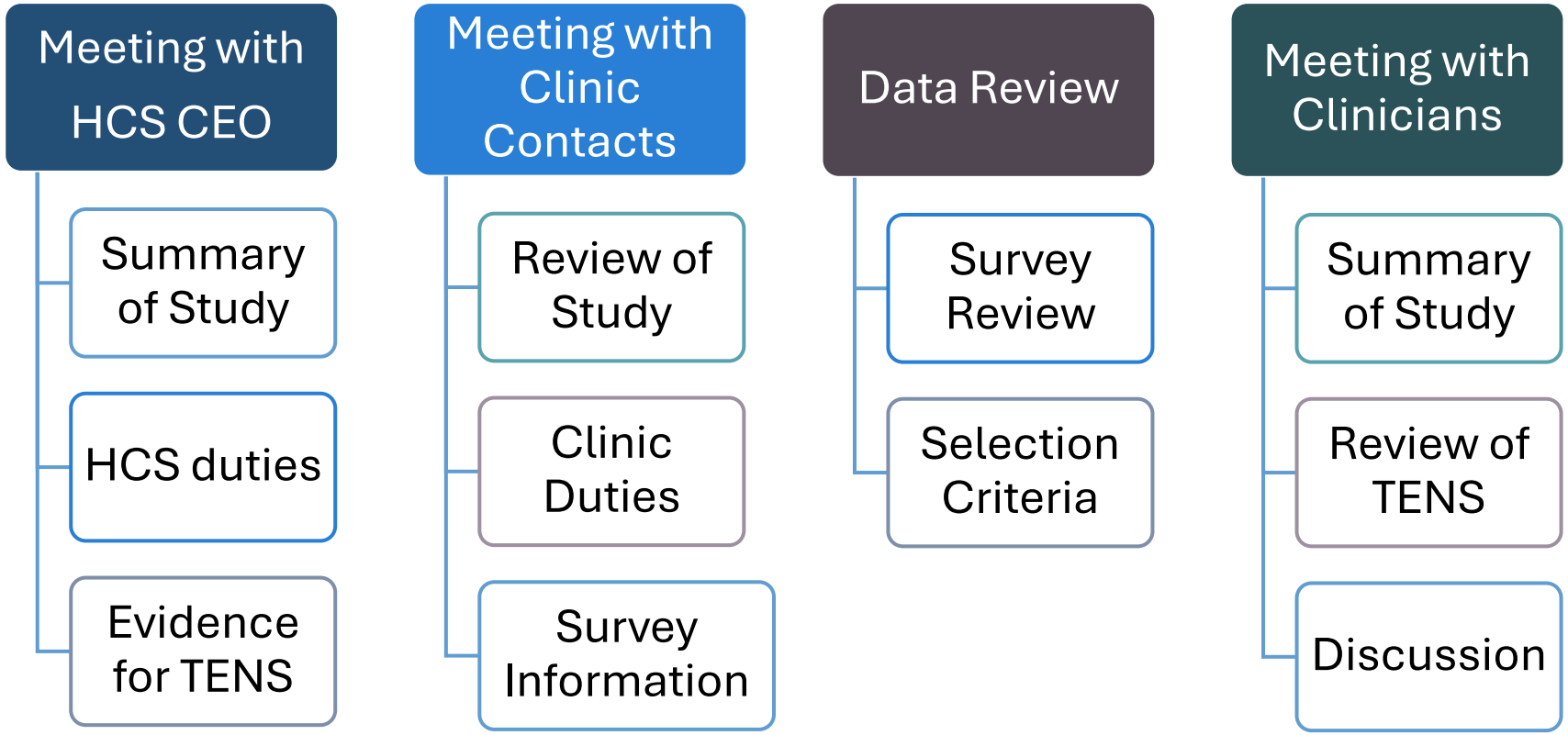
Fibromyalgia TENS In Physical Therapy Study

Study Initiation



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Fibromyalgia TENS In Physical Therapy Study

Clinic Selection Criteria

Healthcare System

- Support from CEO with interest in research
- Complete paperwork and training
  - IRB training, SAMe, invoicing
- Interact with study team
  - Clinic contact, meet with team regularly, extract EHR data

PT Clinic Selection Criteria

- > 50 patients in with chronic pain/year
- Interest in research
- Willing to recruit 25 participants (~1 per month)
- Willing to interact with the team

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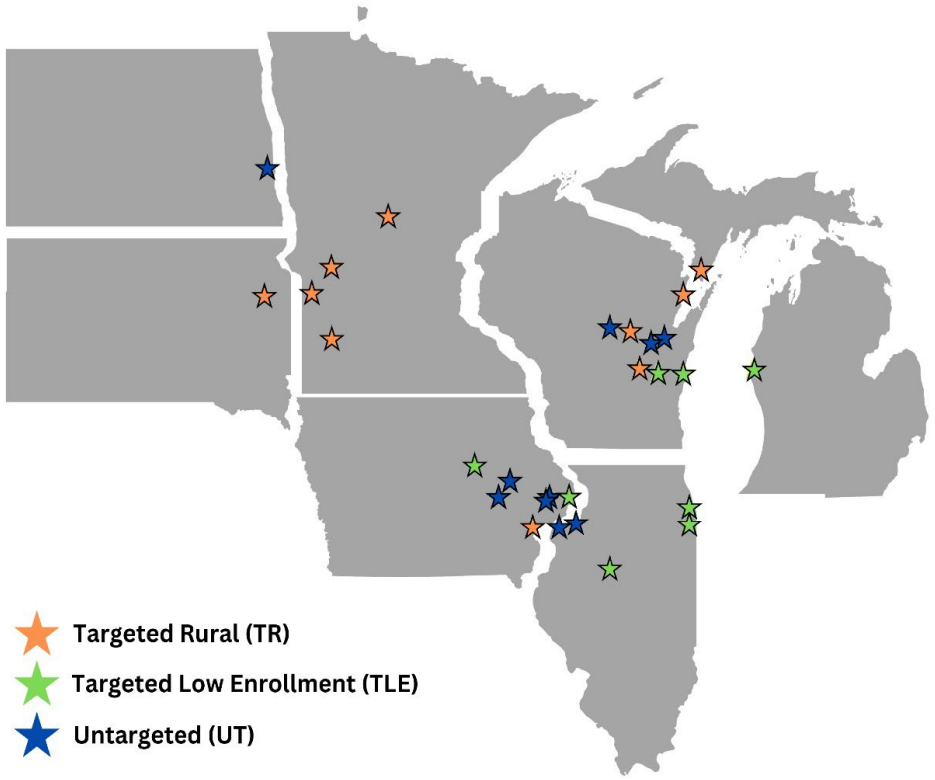
Fibromyalgia TENS In Physical Therapy Study

Physical Therapy Clinics and Communities

- 7 states in the Midwest
- 6 healthcare systems
- 28 physical therapy clinics
  - 13 rural clinics
  - 15 urban clinics
- 100+ physical therapists



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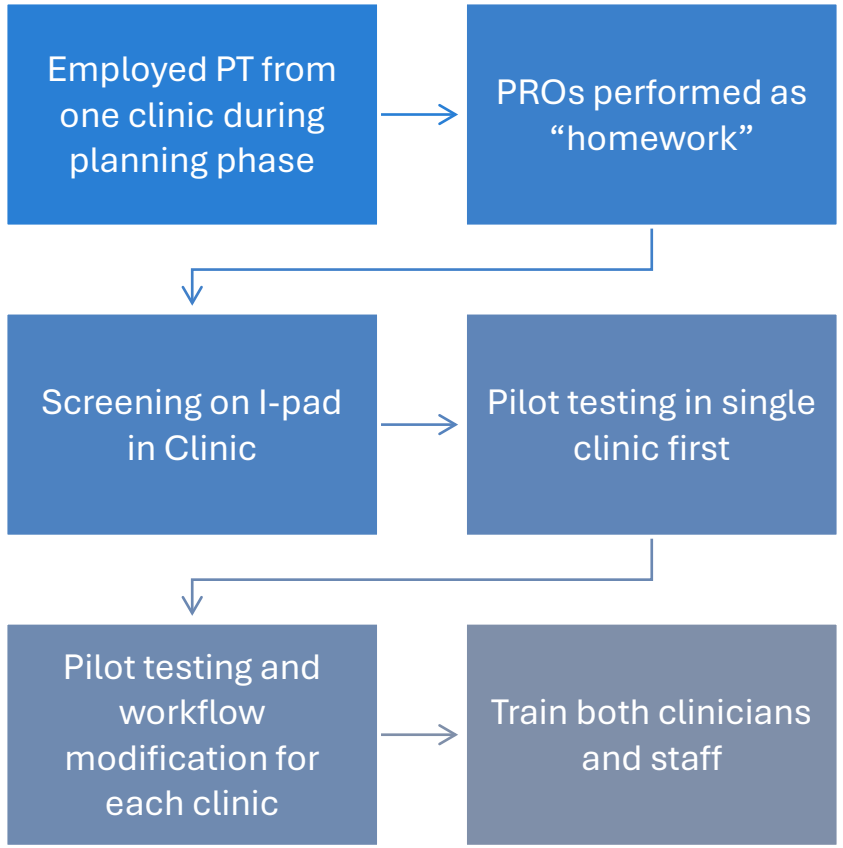
Involvement of Clinicians in Design and Implementation

- **Goal**: Reduce burden on clinicians and integrate into workflow



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Fibromyalgia TENS In Physical Therapy Study

Key take home points for selection, design, and implementation

01

Make sure they have the population you need

02

Get buy-in from HCS *AND* from clinics themselves

03

Ensure company has investment in research and profession

04

Involve clinicians in design/ implementation process

05

Involve and train staff as well as PTs

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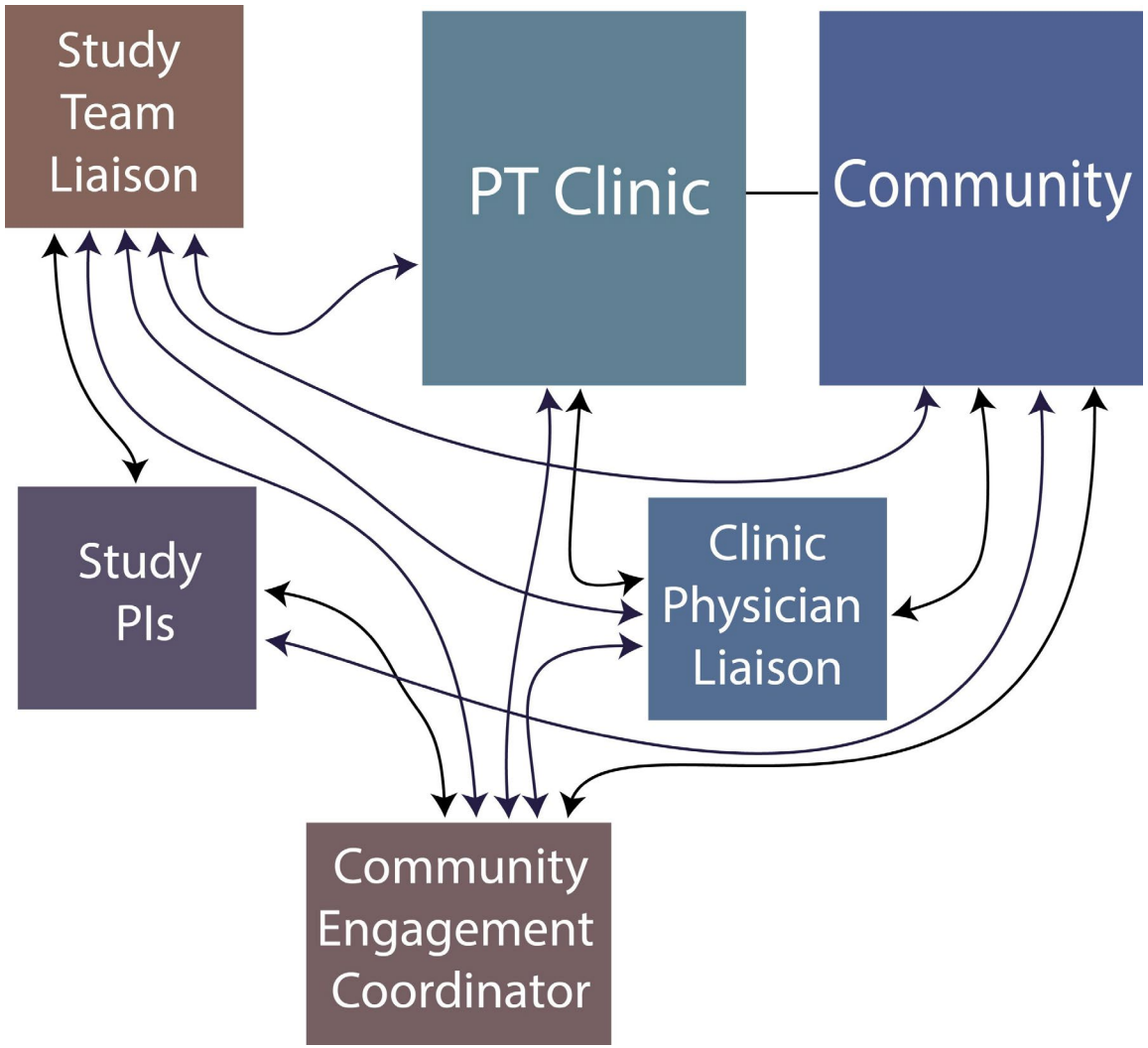

Community and Clinic Engagement

Engagement, Integration and Implementation of CTSA

Dr. Reisinger

University of Iowa

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Fibromyalgia TENS In Physical Therapy Study

Clinic Engagement

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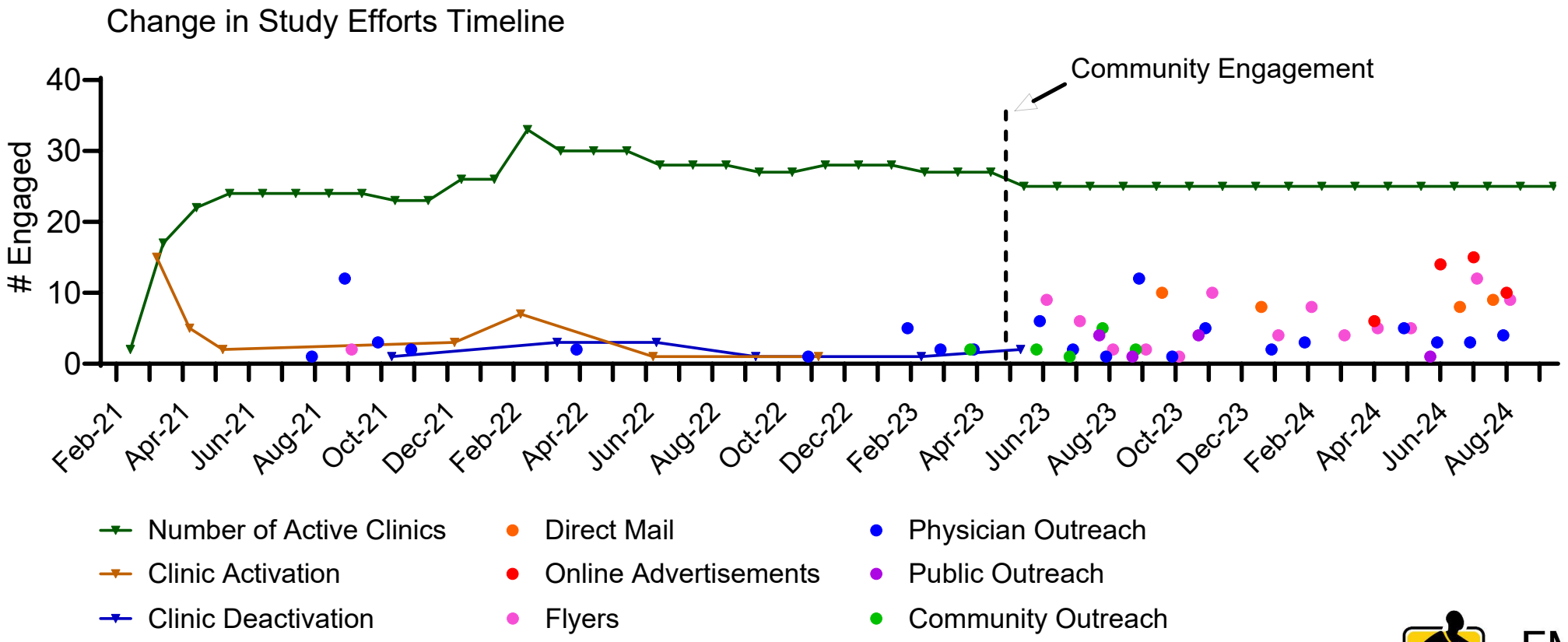
Fibromyalgia TENS In Physical Therapy Study

Community Engagement



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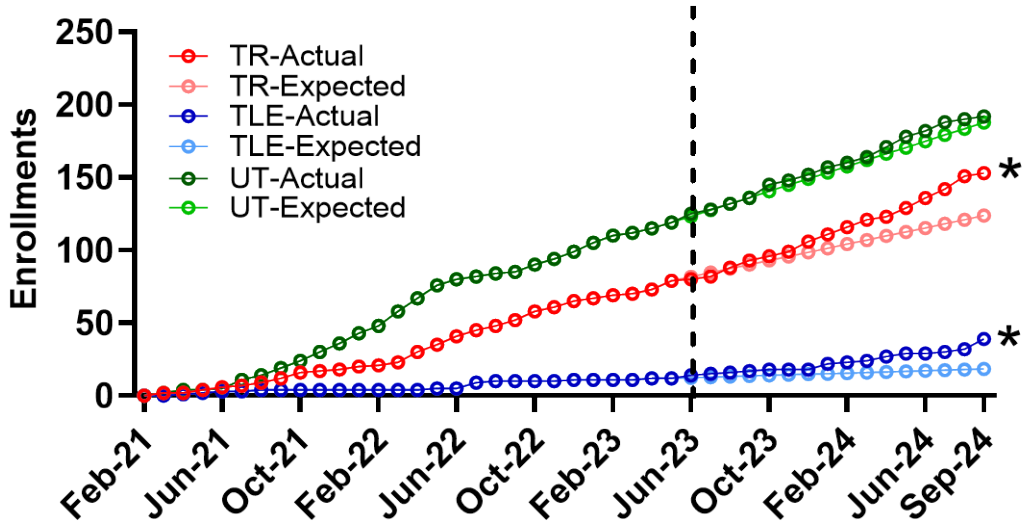
Community Engagement Increased Enrollment



- Targeted Rural Group, n=10
- Targeted Low Enrolling Group, n=6
- Untargeted Group, n=12

- Implemented June 2023

- Total of 82 participants above projection in 16 months

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Fibromyalgia TENS In Physical Therapy Study

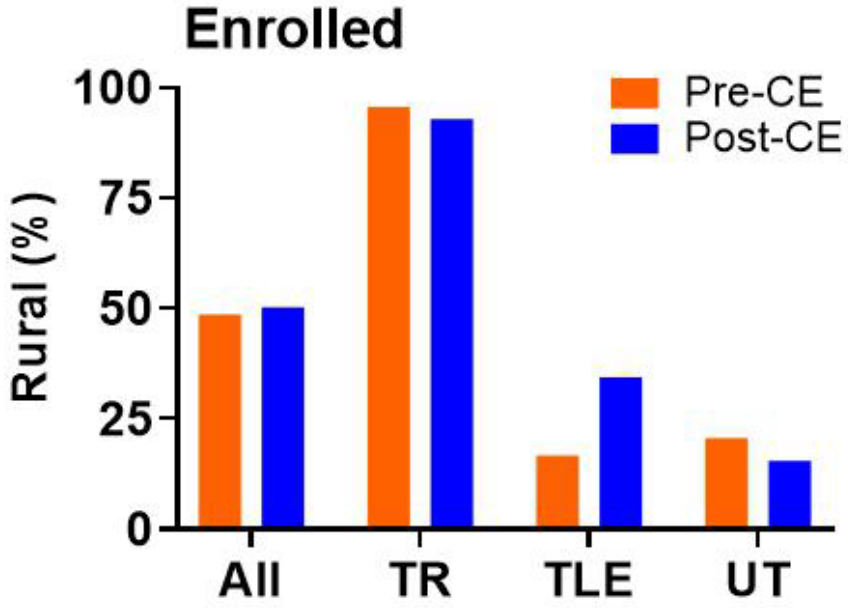
Community Engagement Increased Enrollment of Rural Participants

Rural

99% enrolled if passed screening

Urban

25% enrolled if passed screening



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Fibromyalgia TENS In Physical Therapy Study

Key take home points maintaining network and engagement

01

Regular communication is critical to success

02

Individualize and use multiple methods to engage clinicians

03

Incentives are important motivators to enroll

04

Community engagement enhances enrollment

05

Involve clinicians in community engagement

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FM-TIPS Study Results

Kathleen A. Sluka, PT, PhD, FAPTA

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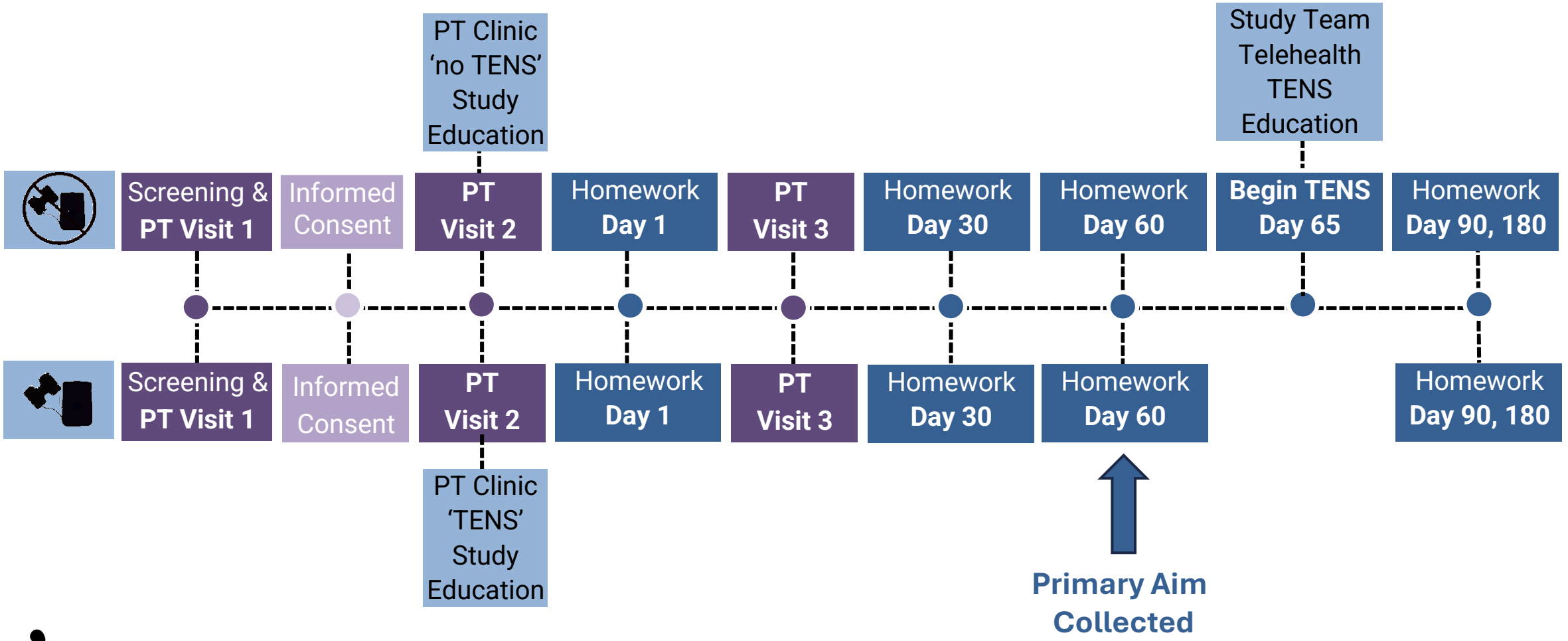
Study Flow



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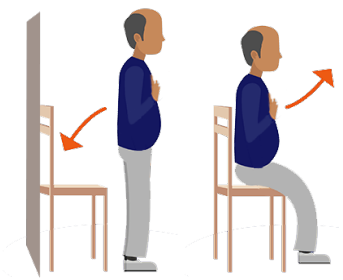
Fibromyalgia TENS In Physical Therapy Study

Outcomes collected at home in REDCap

Primary Outcome

Movement Pain



Secondary Outcomes

Additional Pain Measures

- Resting Pain
- Pain Interference

Secondary Outcomes

Fatigue

- Resting Fatigue
- Movement Fatigue
- Multidimensional Assessment of Fatigue

Secondary Outcomes

Function

- Physical Activity (RAPA)
- Patient Specific Functional Scale

Secondary Outcomes

Other

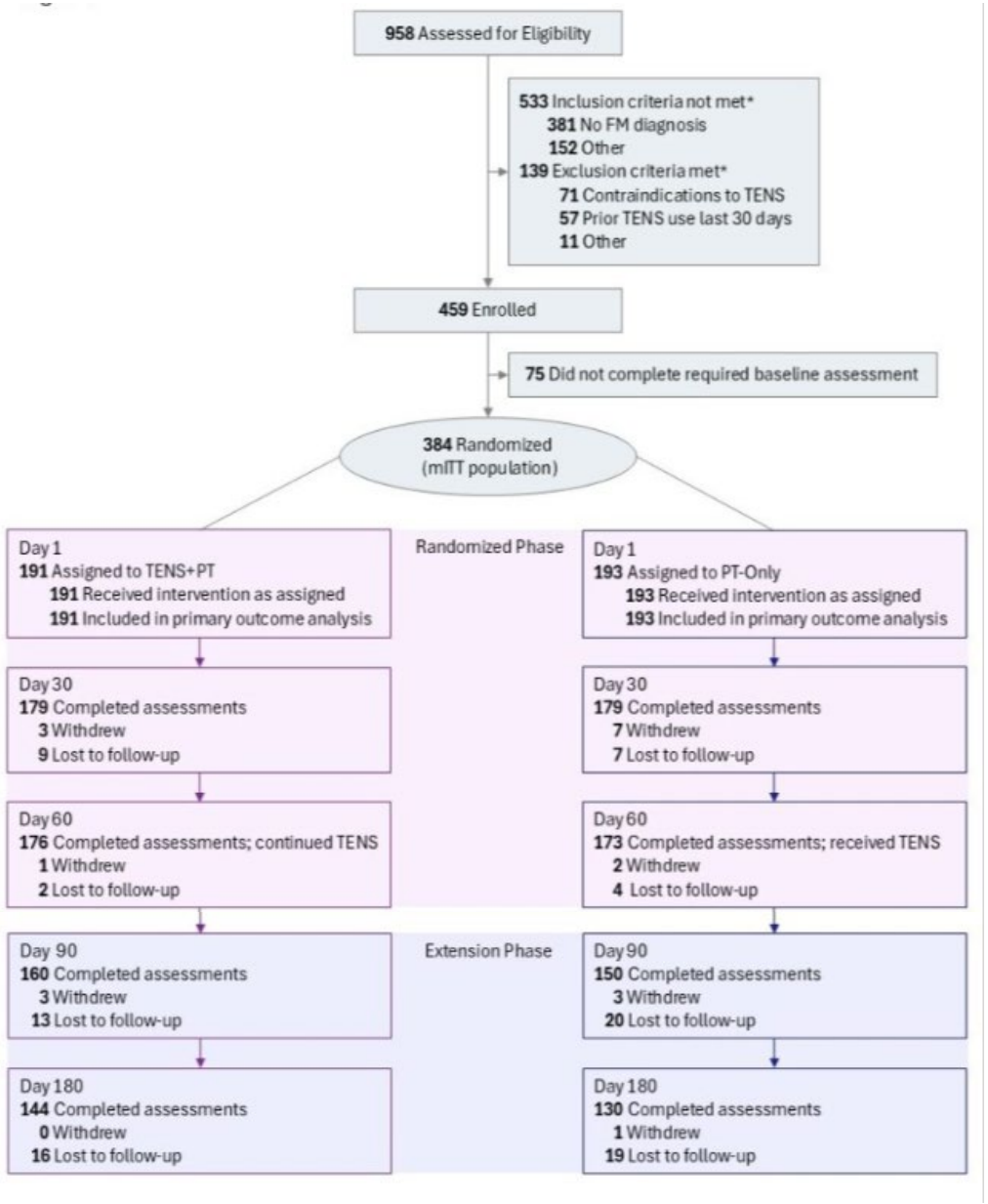
- Fibromyalgia Impact Quest-R
- Patient Global Impression of Change
- HEAL Outcomes

Consort

mITT: 191 TENS+PT
193 PT-Only

Day 60: 179 TENS+PT
173 PT-Only

Day 180: 144 TENS+PT
130 PT-Only



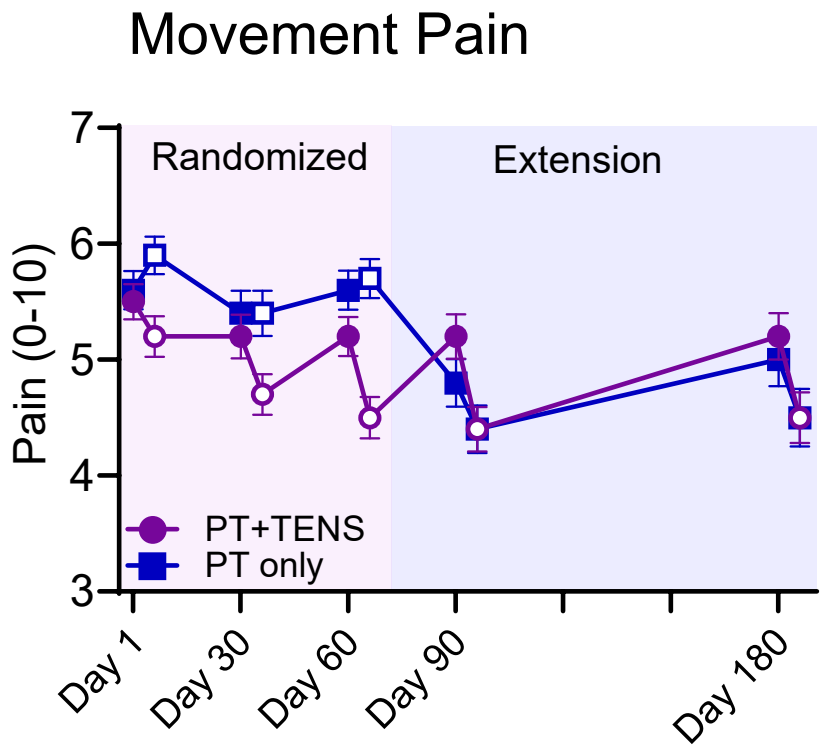
FM-TIPS
Fibromyalgia TENS In Physical Therapy Study

	All Participants (n=384)	PT + TENS (n=191)	PT Only (n=193)
Demographics			
Age (yrs, mean ± SD)	53.2 ±15.2	52.6 ± 15.5	53.9 ± 14.8
Sex (%, Female)	351 (91%)	175 (92%)	176 (91%)
Ethnicity (%, Not Hispanic or Latino)	326 (85%)	170 (89%)	156 (81%)
Race (%, White)	315 (82%)	156 (82%)	159 (82%)
Education (%, High School or less)	149 (39%)	73 (38%)	76 (39%)
Income (%, <$50,000 per year)	171 (45%)	82 (43%)	89 (46%)
Rurality (% Rural, RUCA Code 4-10)	193 (50%)	79 (41%)	114 (59%)
Employment (% Working)	160 (43%)	84 (45%)	76 (41%)
Relationship (%, Married/Partner)	238 (64%)	117 (64%)	121 (64%)
Fibromyalgia (FM) Measures (n (%) / Mean ± SD)			
FM positive (%)	286 (74%)	139 (73%)	147 (76%)
Fibromyalgia impact (FIQR, 0-100)	57.4 ±17.4	57.5 ± 17.3	57.2 ± 17.5
Baseline Measures (Mean ± SD)			
Movement Evoked Pain (MEP, NRS, 0-10)	5.6 ± 2.2	5.5 ± 2.1	5.6 ± 2.3
Pain at rest (NRS, 0-10)	5.4 ± 2.0	5.5 ± 2.0	5.9 ± 1.7
Pain interference (BPI, 0-10)	6.1 ± 2.1	6.2 ± 2.1	6.0 ± 2.1
Pain severity (BPI, 0-10)	5.9 ± 1.7	5.8 ± 1.8	5.9 ± 1.7
Fatigue (MAF Total, 0-130)	73.0 ± 26.1	74.1 ± 25.4	71.9 ± 26.8
Fatigue at rest (NRS, 0-10)	5.9 ± 2.3	5.8 ± 2.3	5.9 ± 2.3
Fatigue with movement (NRS, 0-10)	6.0 ± 2.3	6.0 ± 2.3	6.0 ± 2.2
Depression (PHQ 8, 0-24)	10.8 ± 5.6	11.0 ± 6.0	10.5 ± 5.2
Anxiety (GAD 7, 0-21)	8.0 ± 5.9	8.1 ± 6.2	7.9 ± 5.6
Physical function (PROMIS, T-score)	32.8 ± 3.9	32.8 ± 4.0	32.9 ± 3.9

Subject Demographics

FM-TIPS
Fibromyalgia TENS In Physical Therapy Study

Primary Aim
TENS significantly reduced movement-evoked pain



- Day 60:
  - *TENS+PT: -1.0 points (CI: -1.4,-0.7)*
  - *PT-Only: 0.0 (CI: -0.3, 0.3)*
  - *Group Difference: -1.2 (CI: -1.6, -0.7)*
- Effect Size:
  - Cohen's d = 0.46
- Day 180:
  - *TENS+PT: -0.9 points (-1.4, -0.5)*
  - *PT-Only: -1.1 (-1.6, -0.7)*

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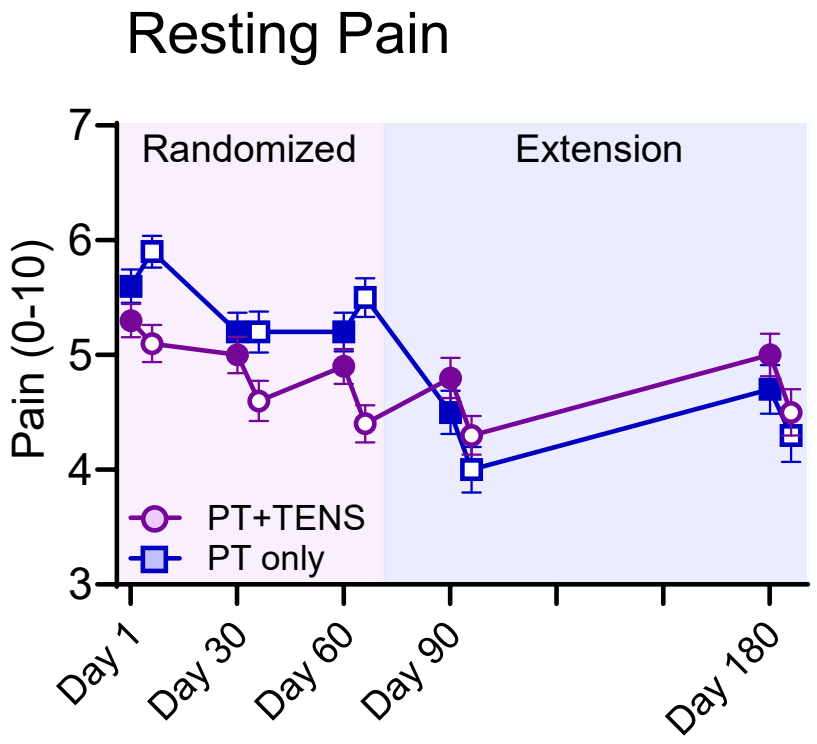
Fibromyalgia TENS In Physical Therapy Study

TENS significantly reduced resting pain



- Day 60:
  - *TENS+PT : -1.0 points (-1.3,-0.7)*
  - *PT-Only: -0.1 (-0.4, 0.2)*
  - *Group Diff: -0.98 (CI: -1.44, -0.52)*
- Effect Size:
  - Cohen's d = 0.44
- Day 180:
  - *TENS+PT : -0.9 points (-1.3, -0.5)*
  - *PT-Only: -1.2 (-1.6, -0,8)*

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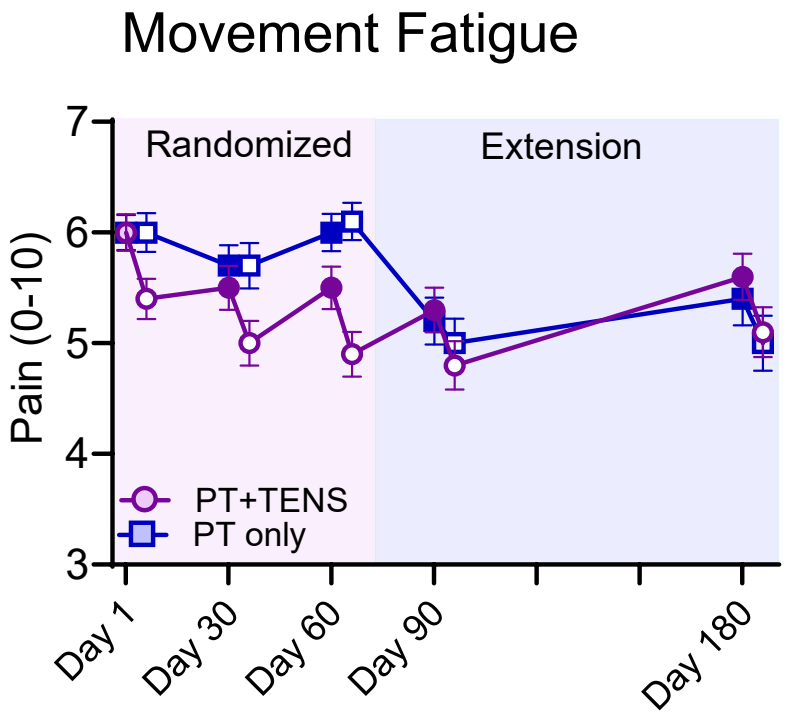
Fibromyalgia TENS In Physical Therapy Study

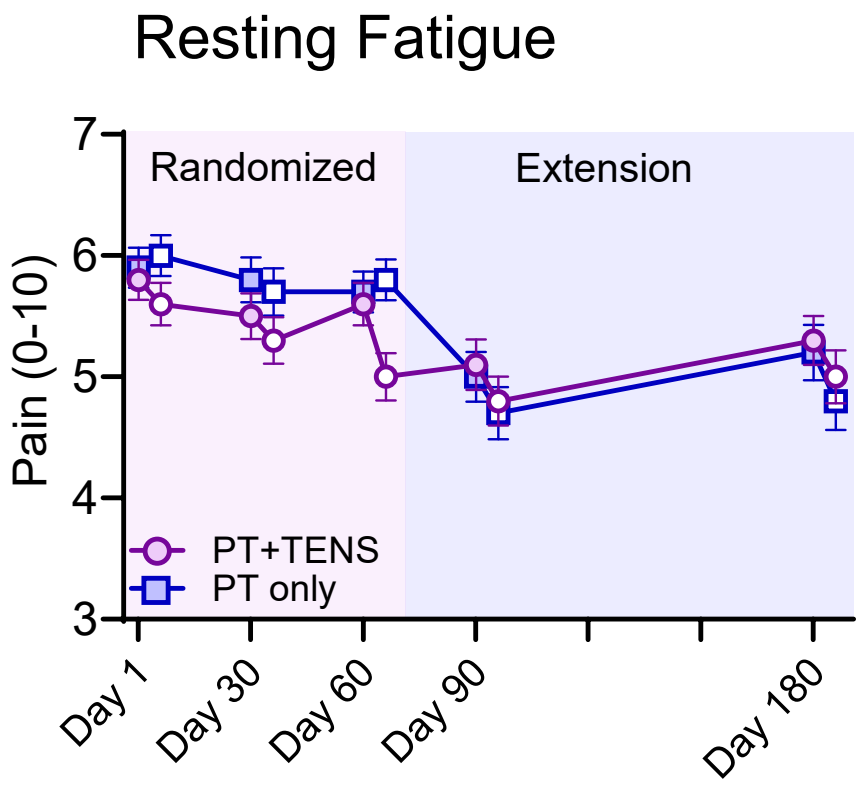
TENS significantly reduced movement-evoked fatigue



- Day 60:
  - *TENS+PT : -1.1 points (-1.5,-0.7)*
  - *PT-Only: 0.0 (-0.3, 0.3)*
  - *Group Diff: -1.19 (-1.7, -0.7)*
- Effect Size:
- Cohen's d = 0.48
- Day 180:
  - *TENS+PT : -1.0 points (-1.4, -0.5)*
  - *PT-Only: -1.1 (-1.5, -0.7)*

FM-TIPS
Fibromyalgia TENS In Physical Therapy Study

TENS significantly reduced resting fatigue



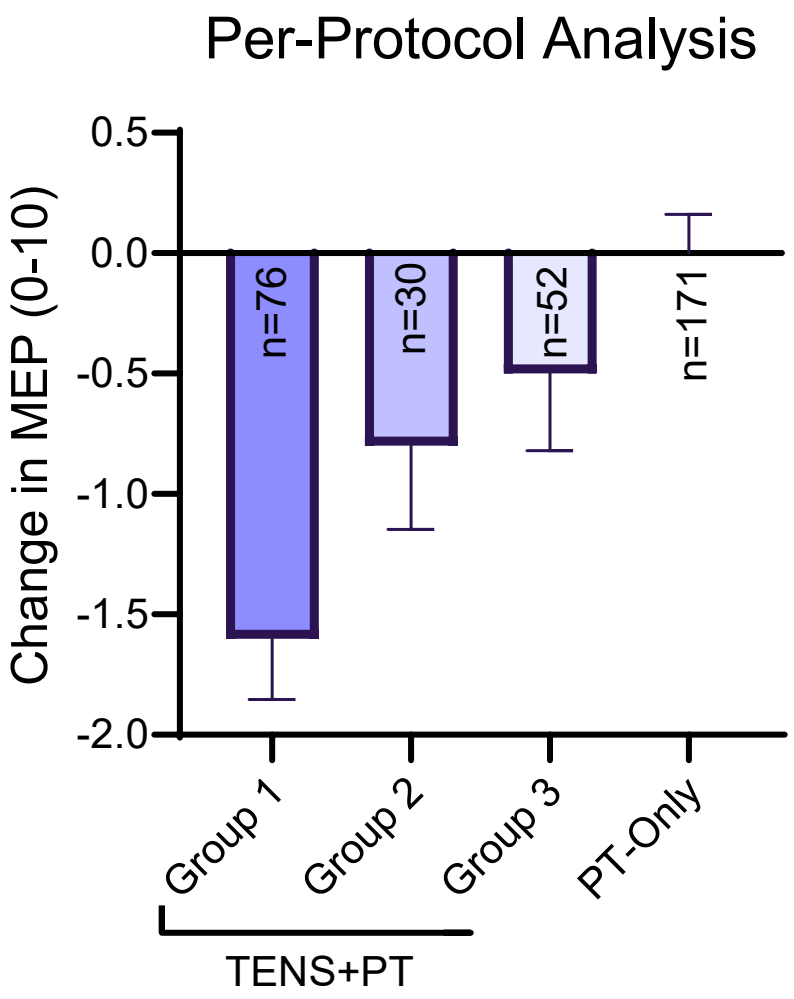
- Day 60:
  - *TENS+PT : -0.8 points (-1.2,-0.5)*
  - *PT-Only: -0.1 (-0.4, 0.2)*
  - *Group Diff: -0.75 (-1.3, -0.2)*
- Effect Size:
- Cohen's d =0.32
- Day 180:
  - *TENS+PT : -0.9 points (-1.3, -0.5)*
  - *PT-Only: -1.1 (-1.5, -0.7)*

FM-TIPS
Fibromyalgia TENS In Physical Therapy Study

TENS effects are dose-dependent

Adequate Monthly Dose:
2x/week (8x/month) AND
2h/day (total: 1800 min/month)

Group 1: Adequate dose for Day 1-30 AND Day 31-60
Group 2: Adequate dose for Day 1-30
Group 3: Inadequate dose



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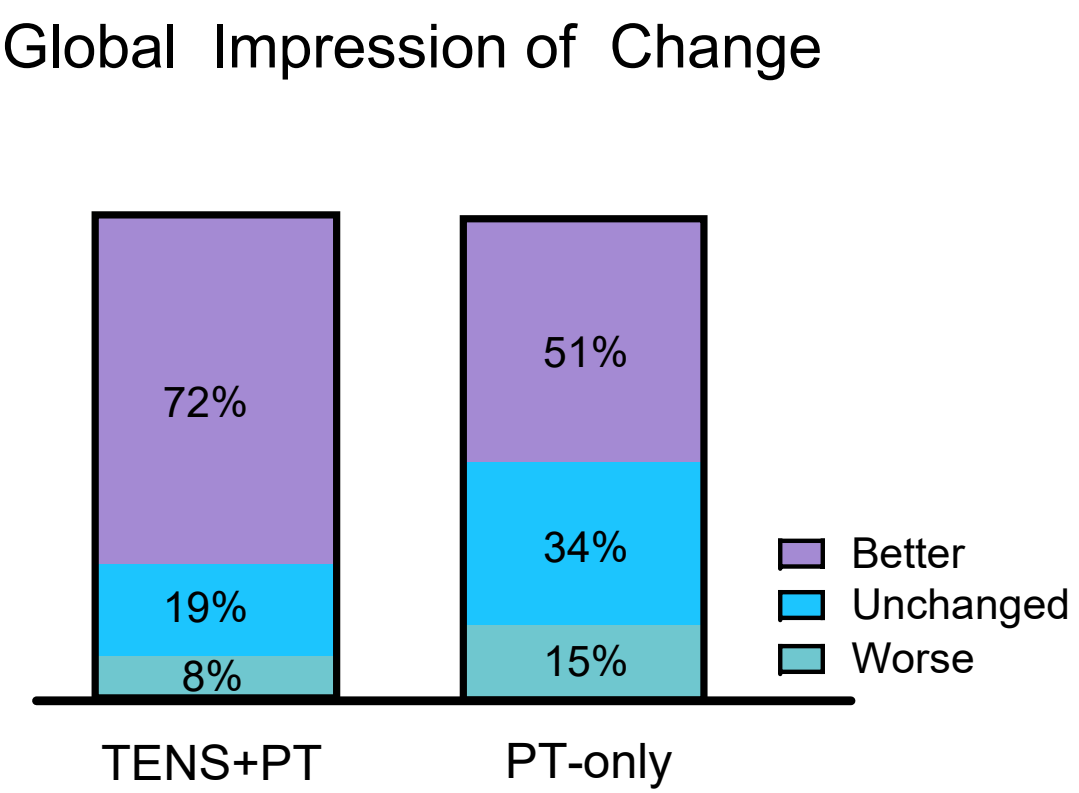
Fibromyalgia TENS In Physical Therapy Study

The majority of patients reported improvement in the TENS+PT group



FM-TIPS
Fibromyalgia TENS In Physical Therapy Study

Greater number of responders in the PT+TENS group

(≥30% reduction)

	MOVEMENT PAIN (30%)	RESTING PAIN (30%)
PT-only	13% (n=22/169)	22% (37/172)
PT+TENS	41% (n=66/161)	39% (65/166)
	χ^2=33, P<0.0001	χ^2=12.5, P=0.0004

FM-TIPS
Fibromyalgia TENS In Physical Therapy Study

The majority of people continue to use TENS at 6 months

	All	TENS+PT	PT-Only
Did you find TENS helpful?			
Yes	217 (81%)	111 (78%)	106 (84%)
No	51 (19%)	31 (22%)	20 (16%)
How often are you using your TENS unit now?			
Daily (at least 4x/wk)	147 (55%)	81 (57%)	66 (52%)
At least once/week	66 (25%)	34 (24%)	32 (25%)
At least once/month	25 (9%)	10 (7%)	15 (12%)
Other	31 (12%)	18 (13%)	13 (10%)

FM-TIPS
Fibromyalgia TENS In Physical Therapy Study

Minimal adverse events with repeated use over 4-6 months

Experience (n=358)	Cumulative Number of Experiences (Total)	Number of Safety Participants with Experiences (# part.)	% (#/358)
Anxiety with TENS	22	15	4.2%
Itchiness with TENS	31	22	6.1%
Nausea with TENS	5	4	1.1%
Skin irritation (electrodes)	36	24	6.7%
Pain with TENS	35	27	7.5%
Other	107	72	20.1%
Serious AE-TENS related	0	0	0

FM-TIPS
Fibromyalgia TENS In Physical Therapy Study

Multiple lines of evidence support that TENS produces a clinically meaningful effect

- Difference of 1.2 in movement-evoked pain (1.1 MCID for MEP)
- Significant improvements in other measures during randomized phase
  - Resting pain, pain interference, movement-evoked fatigue, FIQR
- Similar reduction in pain and fatigue for PT-Only group after TENS
- TENS effects occurred within 30 days and sustained for 6 months
- Dose-response effect for TENS
- 41% of PT+TENS group achieved $\geq$30% decrease in MEP
- Majority of individuals in TENS group reported improvement (PGIC)
- Most participants (~80%) found TENS helpful and still used weekly

Summary

- Applying TENS at an optimal dose is *clinically* effective for reduction of movement-evoked pain in a real-world setting

- TENS is a safe, inexpensive, and readily available treatment for fibromyalgia

FM-TIPS
Fibromyalgia TENS In Physical Therapy Study

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