TENS in Fibromyalgia: From fundamental neurobiology to pragmatic trial

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DJO, Inc TENS units and electrodes

Presentation Outline

- What is fibromyalgia?
  - Central (nociplastic) pain
  - Basic pain mechanisms
- Why TENS?
  - Mechanisms of TENS
- Randomized controlled trial
  - FAST
- Pragmatic trial
  - FM-TIPS

What is fibromyalgia?

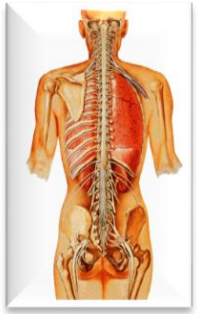
Central (nociplastic) pain syndrome

Diagnosing fibromyalgia

- Symptom of widespread pain
  - "Hurt all over"
  - 1990 ACR Classification Criteria – "Above and below the waist, left and right sides or the body, involving the axial skeleton"
  - 2016 – "Involving 4 of 5 regions from the widespread pain index"
  - Other criteria count number of painful sites
- Symptom/sign of tenderness
  - "Painful with gentle touch"
  - ACR1990 – 11 of 18 tender points (4 kg/cm^2 pressure)
  - Skin roll or BP cuff tenderness
- Pain worsened with physical activity

Diagnosing fibromyalgia

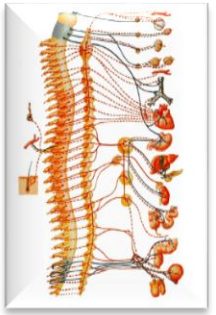
- Chronic fatigue
- Non-refreshing sleep
- Chronic myofascial/visceral pain
  - Irritable bowel syndrome
  - Interstitial cystitis/bladder pain syndrome
  - Temporomandibular pain
  - Chronic headache (tension, migraine)
  - Etc.
- Depression/anxiety



Somatic Pain

Noxious impulses being received and transmitted by normal components of the sensory nervous system

Neuropathic Pain



Noxious impulses originating from an abnormality in neural structures

Central (Nociplastic) Pain

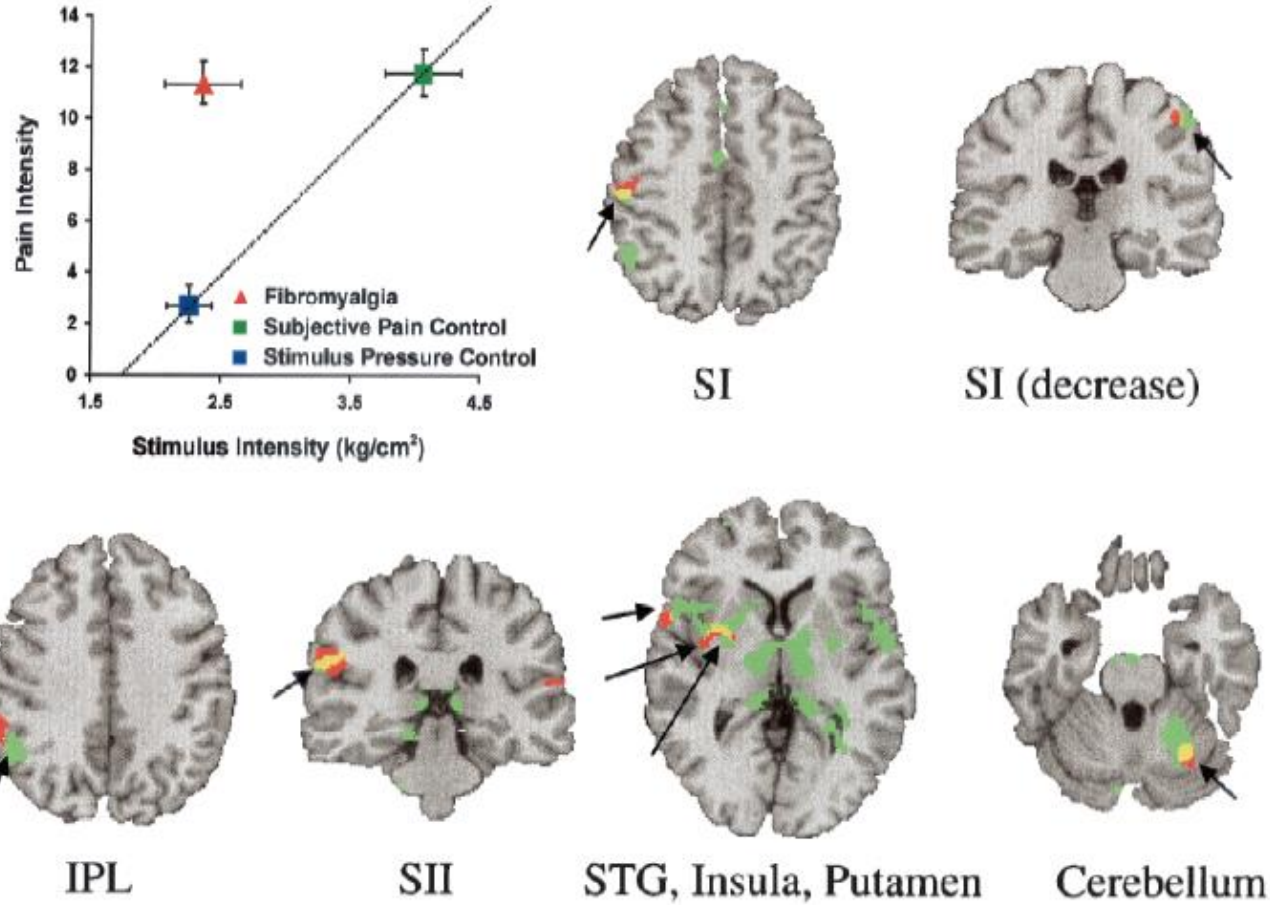
Innocuous impulses perceived as noxious due to physiologic alterations of neural structures

Nociplastic Pain

Pain that arises from **altered nociception** despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.

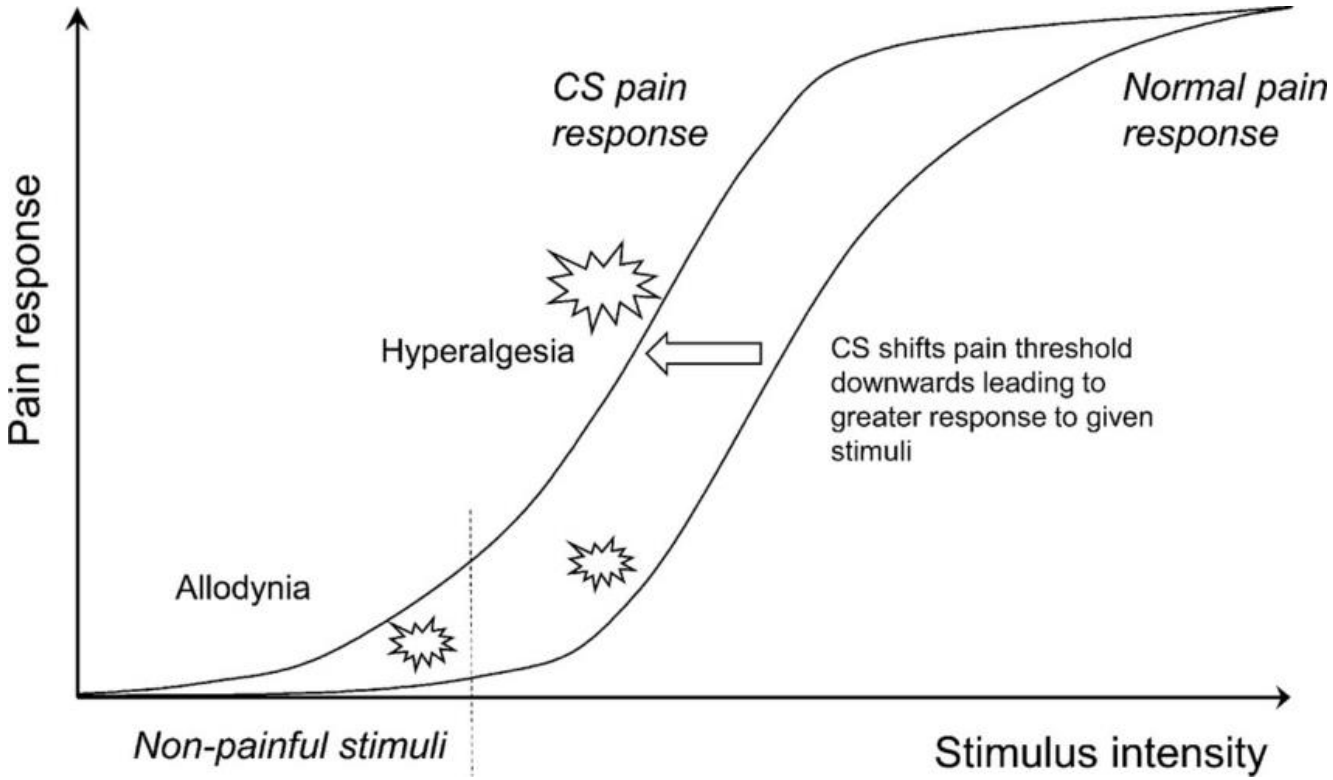
IASP Definition 2017

Is the Pain "Real"?

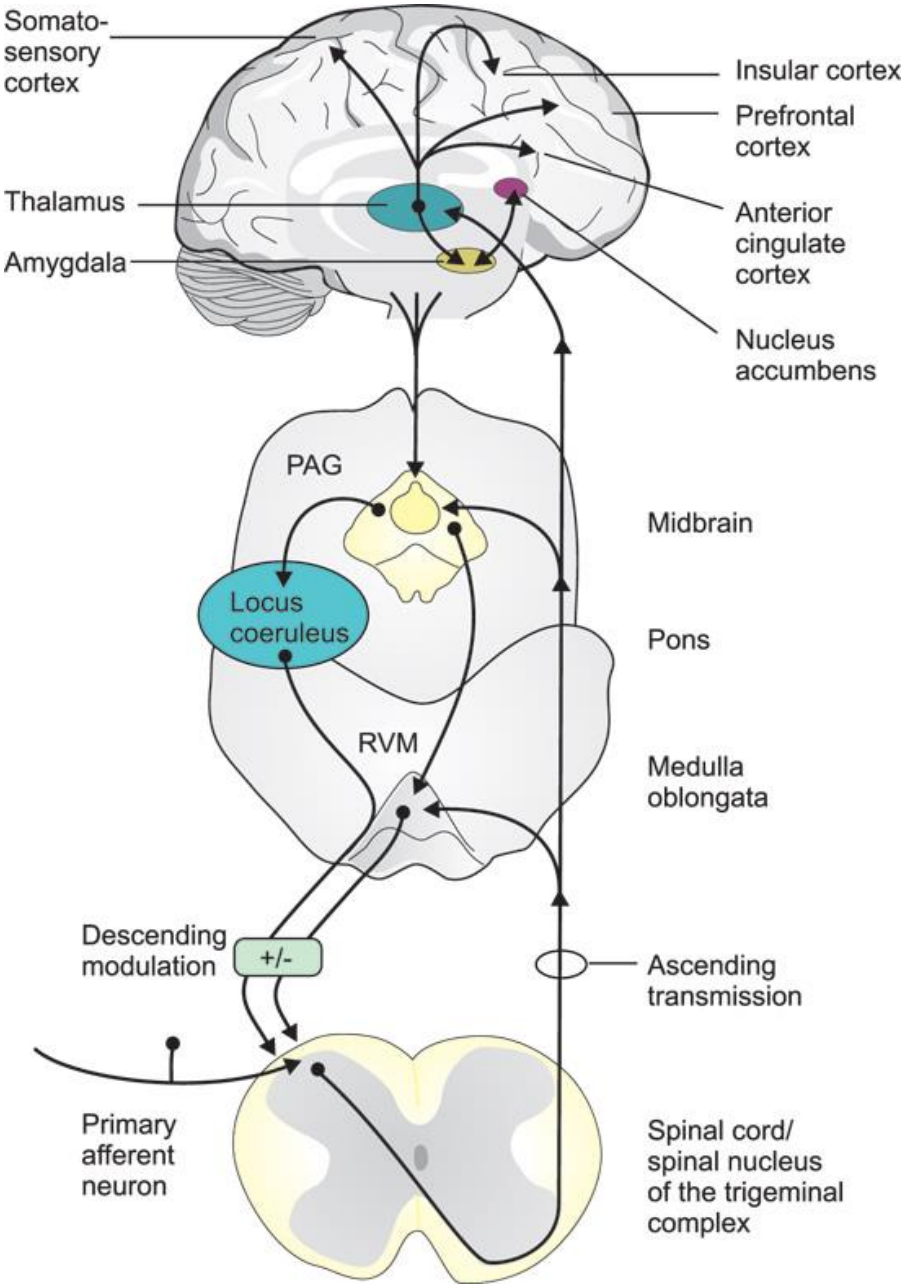


Gracely et al. *Arthritis Rheum* 46:1333-43, 2002

Evoked Pain Testing in Nociplastic Pain



Basic Pain Mechanisms

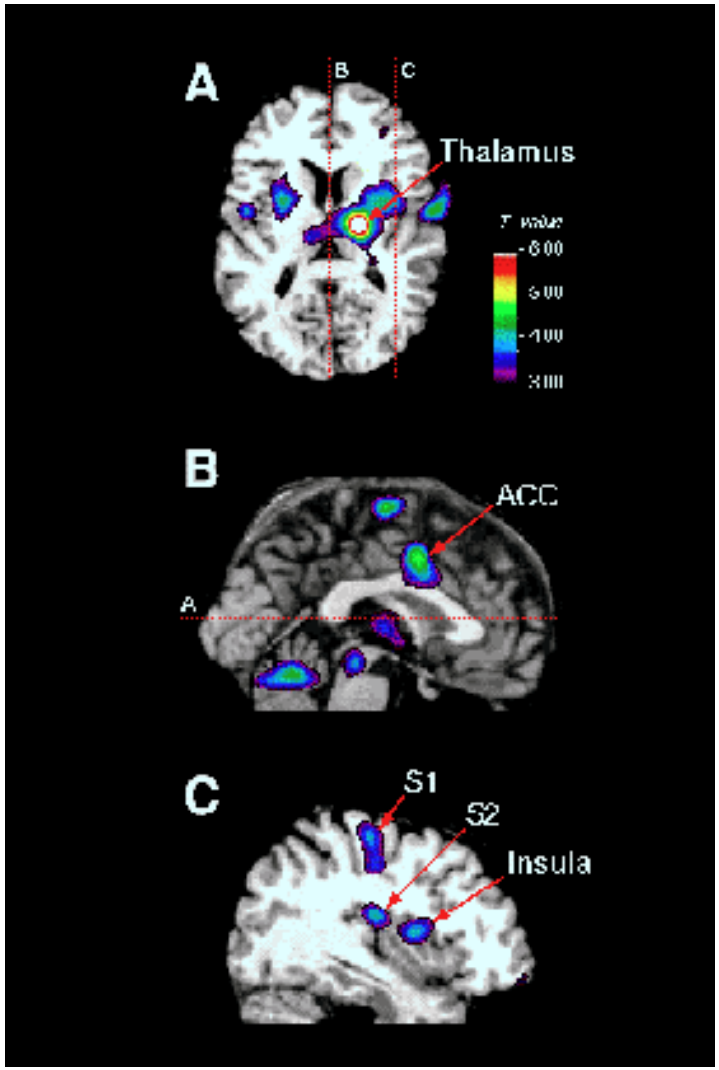


Perception

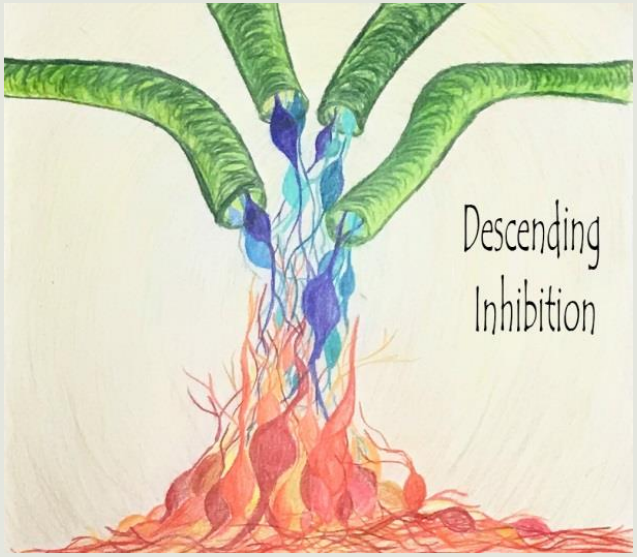
Transmission

Central Pain Pathways

- Sensory discriminative
  - Somatosensory cortex
- Motivational-Affective
  - Cingulate and insular cortex
- Fear-Emotion
  - Amygdala
- Planning, decision-making, social behavior
  - Prefrontal cortex



Descending Inhibition



K. Sluka

- Via RVM and PAG
  - Endogenous opioids
  - Serotonin

Steps in Central Sensitization

- Nociceptive Transmission
  - Requires nociceptive input (peripheral pain generator)
  - Dependent on excitatory amino acids, tachykinins, substance P
- Acute Phase Central Sensitization
  - Release in block of NMDA receptors
  - Activation of kinases via NMDA, NK1, TrkB receptors
- Late Phase Central Sensitization
  - Gene transcription locally and diffusely
  - Activation of microglia
- Disinhibition
  - Altered inhibitory and facilitatory controls from CNS

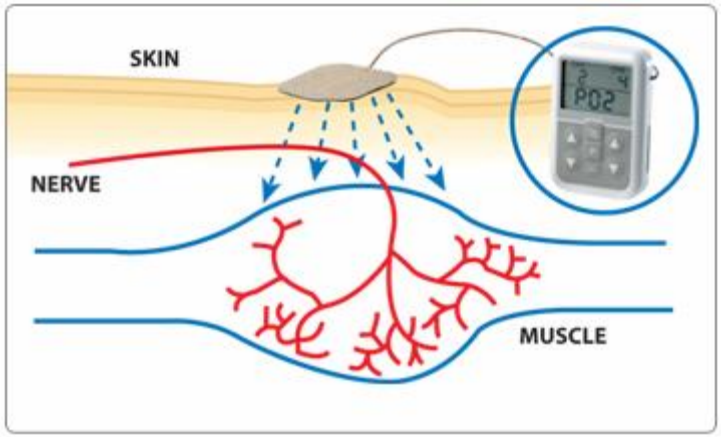
Woolf, C. Ann Intern Med 2004;140:441-451.

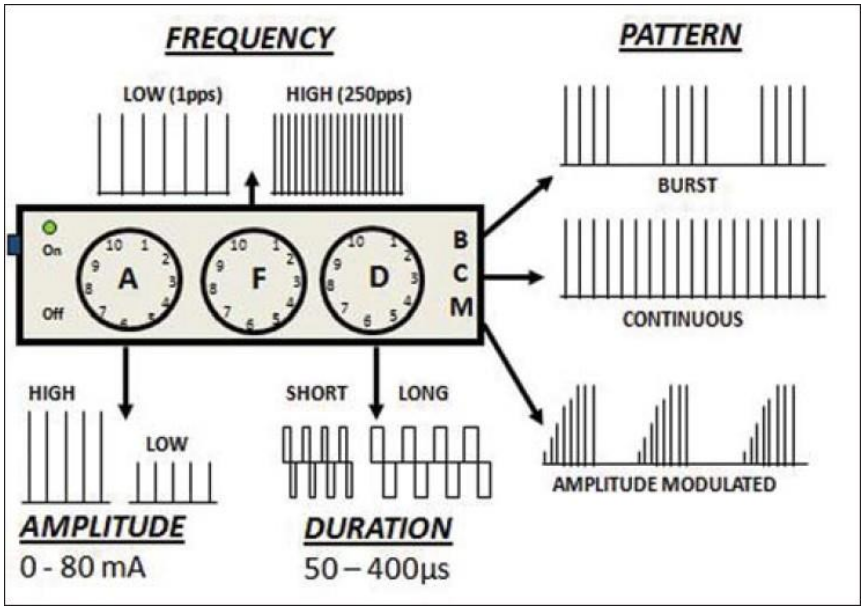
Why TENS?

Mechanisms suggesting potential benefit in central (nociplastic) pain

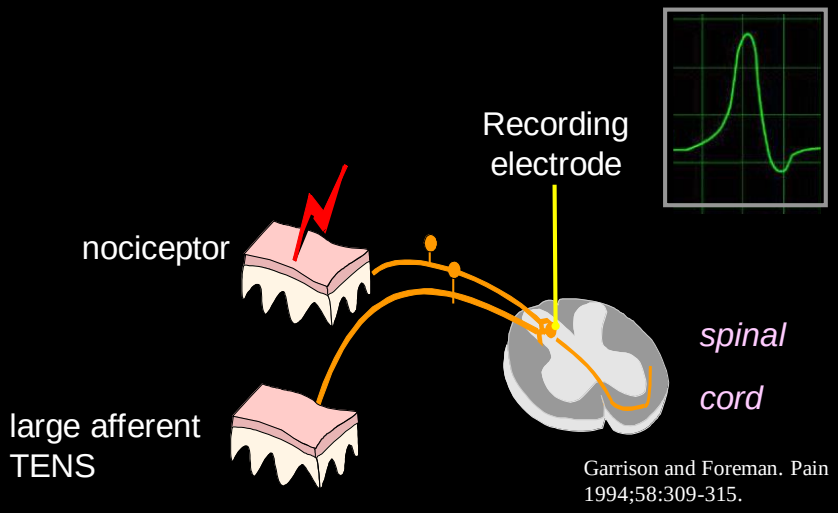
What is TENS?

- Transcutaneous Electrical Nerve Stimulation





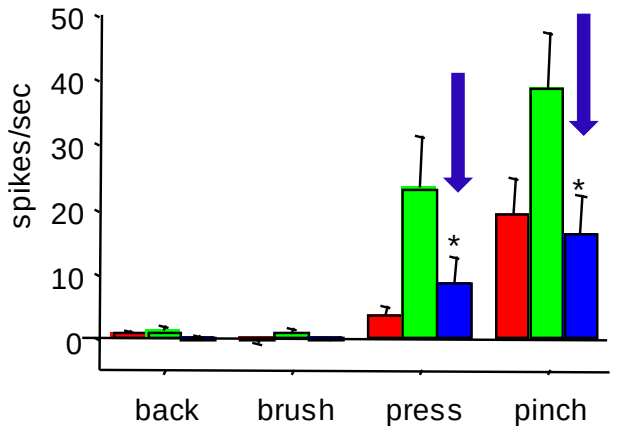
TENS is expected to be effective mainly when the unit is active



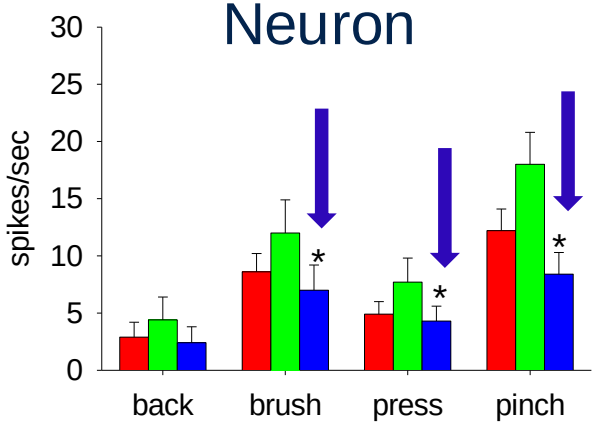
Garrison and Foreman. Pain 1994;58:309-315.

TENS Reduces Central Excitability

High Threshold Neuron

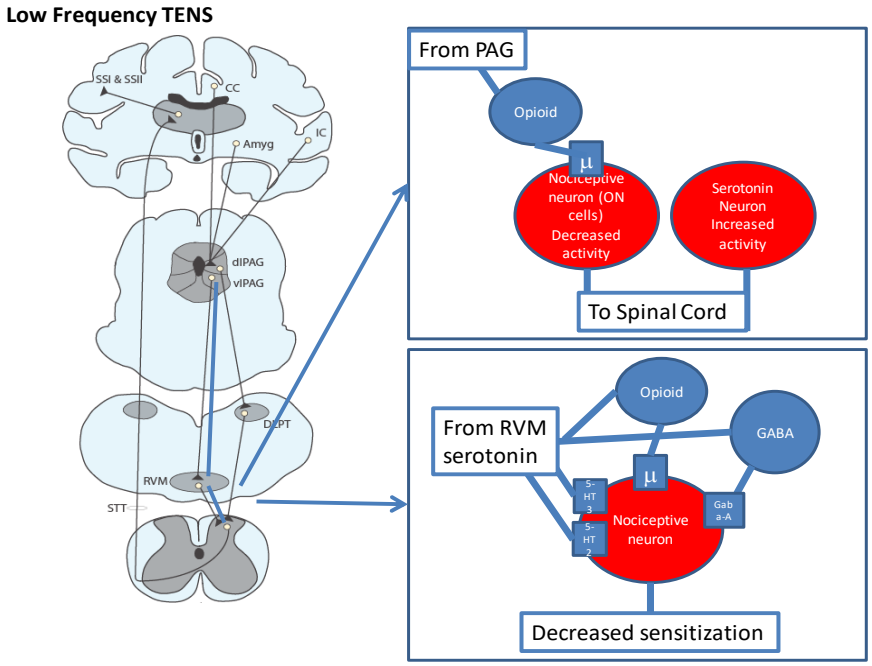


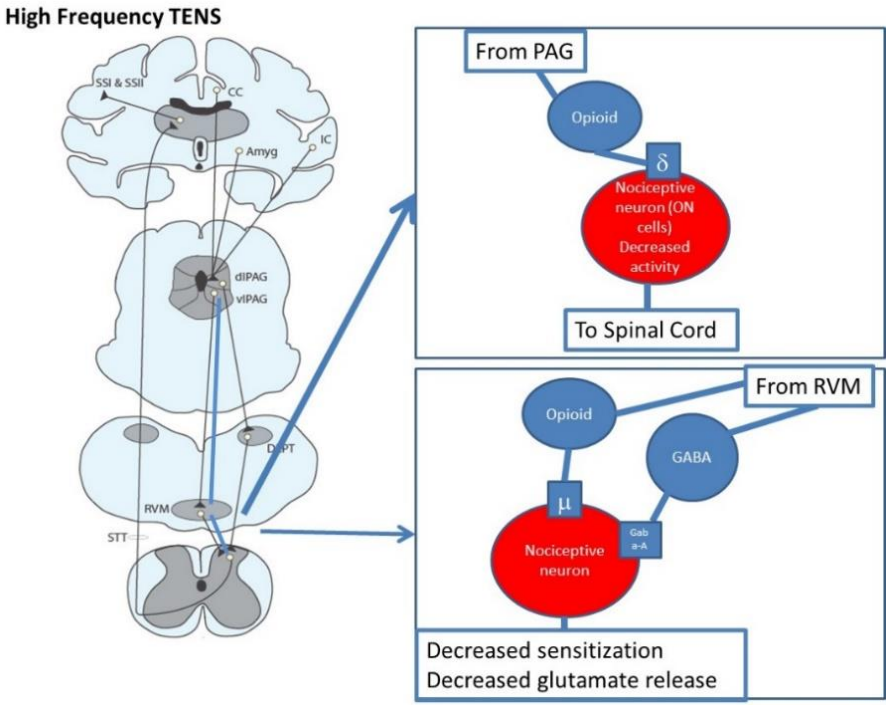
Wide Dynamic Range Neuron



Ma and Sluka, 2001; Sluka et al., 2005; Garrison and Foreman, 1994, 1996

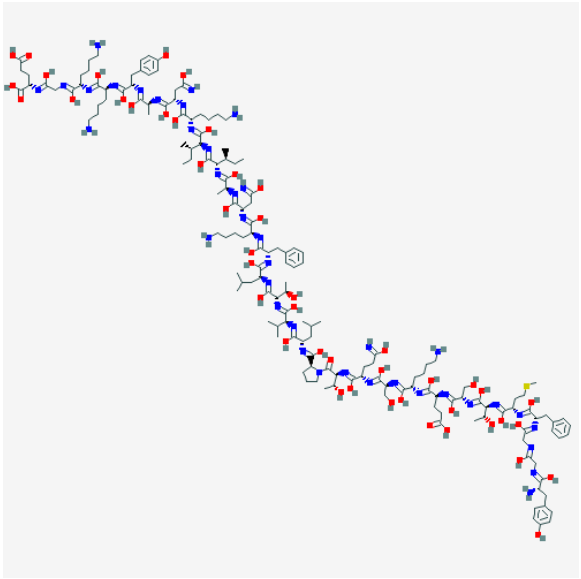
TENS Activates Endogenous Inhibition: Opioids and Serotonin

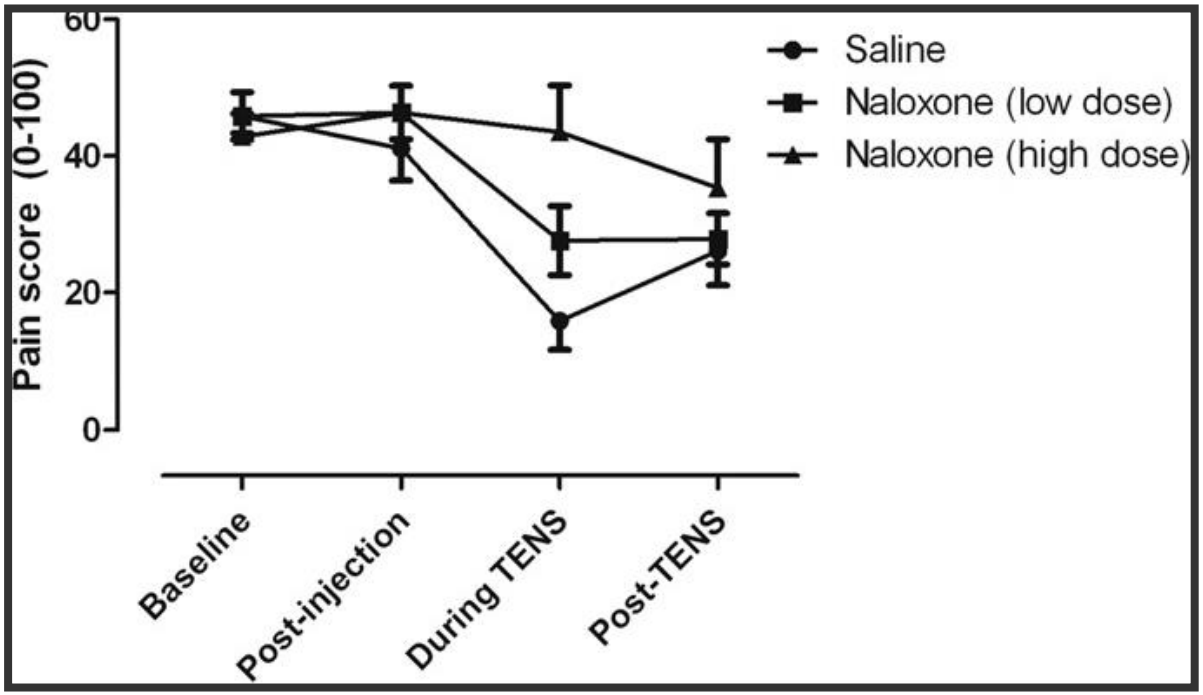




Mixed frequency, low and high, prevents analgesic tolerance

TENS Opioid Effects in Humans

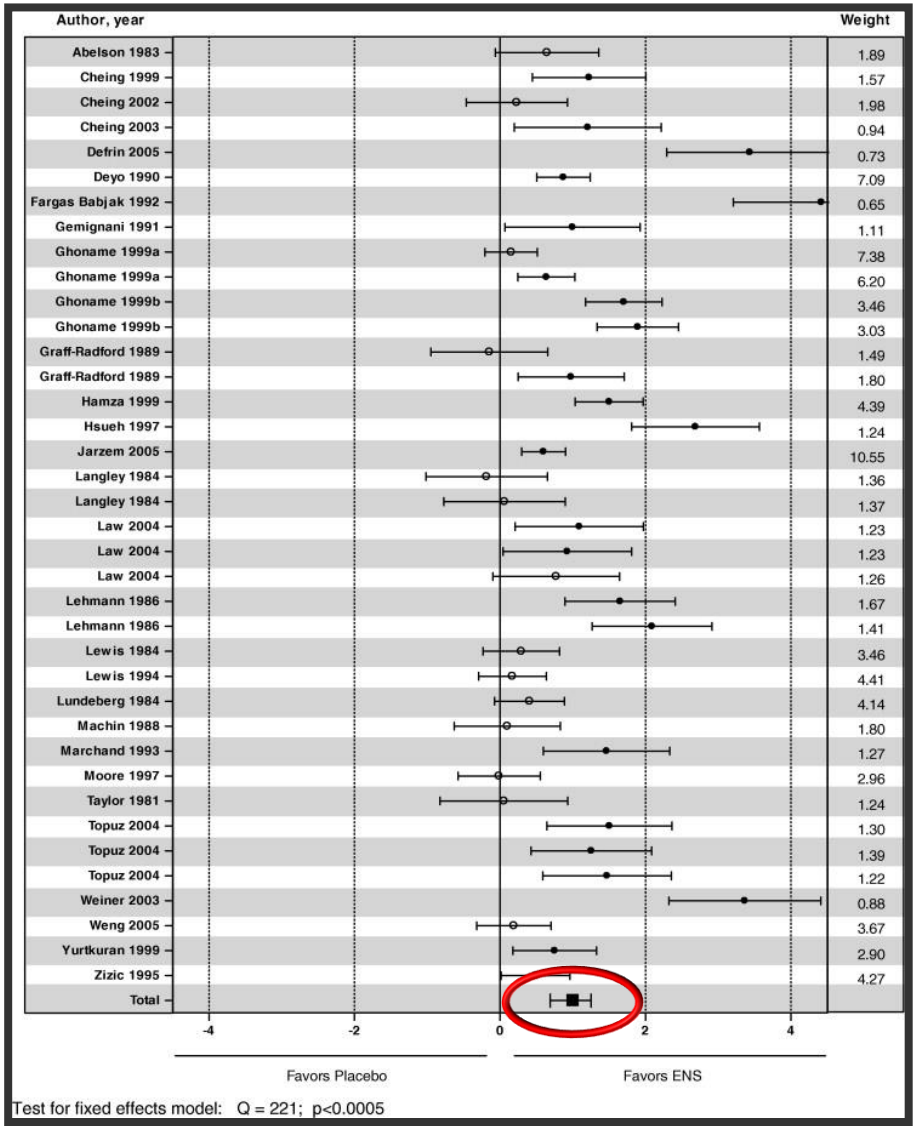




Solomon et al., 1980, Leonard et al., 2010; Sjolund and Eriksson, 1974

TENS for Chronic Musculoskeletal Pain

- Meta-analysis with data from 29 randomized trials
  - Patients had pain from back, hip, neck, and knee
  - 335 placebo, 474 TENS
- TENS had favorable pooled effect vs placebo ($p<0.0005$)
- Out of favor as pain treatment in PT



Why TENS in Fibromyalgia?

- Reduces central excitability at the level of the dorsal horn
  - High threshold neurons **AND** wide dynamic range neurons
  - Reduces neuronal activation to **BOTH** innocuous and noxious stimuli
  - Reduces excitatory amino acid (glutamate) release
- Activates descending inhibitory pathways
  - PAG-RVM-spinal cord
  - Uses endogenous opioids and serotonin

Dana Dailey
PT, PhD

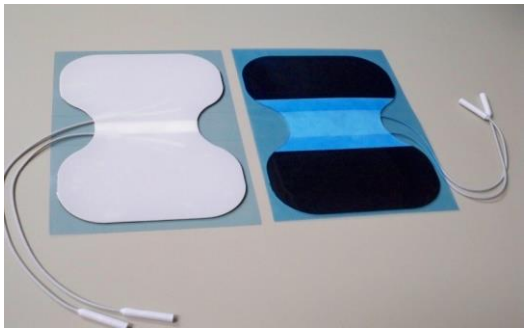
Randomized, Controlled Trial

Fibromyalgia Activity Study with TENS (FAST)

Arthritis Rheumatol. 2020 May;72(5):824-836

Treatment

- Active TENS parameters
  - Butterfly electrodes cervical and lumbar placement
  - Asymmetrical biphasic waveform
  - Modulating frequency 10-125 Hz
  - Variable pulse duration
  - Highest “strong but comfortable” intensity
- Instructed to apply at least 2 hours/day during activities



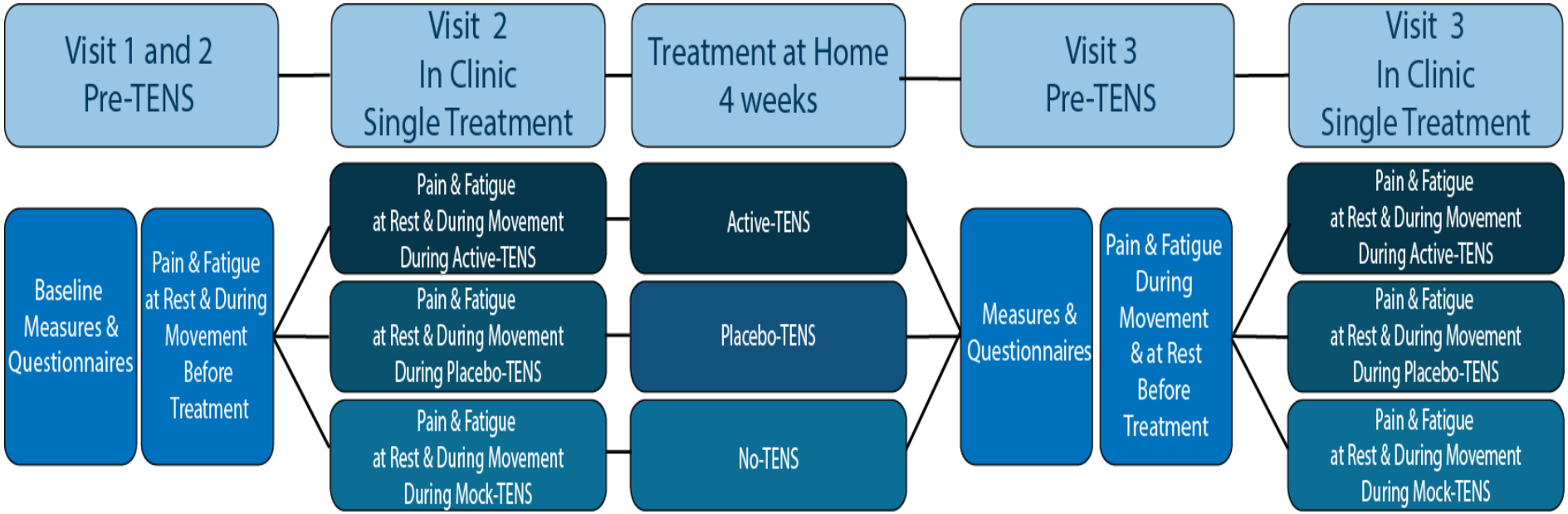
Placebo and Blinding

- Used Placebo TENS
  - Transient unit with short-duration of stimulation of 45s that ramped down over last 15s
  - Blinding script
- Included a No TENS group with Mock TENS during assessments
- Assessors remained blinded to Active TENS (45% correct), Placebo TENS (13% correct), and Mock TENS (20% correct)
- Participants blinded to Placebo TENS (49% correct), but Active TENS correctly identified by 70%

Main Inclusion Exclusion Criteria

- Inclusion
  - Women between 18-70 years old
  - Met 1990 criteria for classification of fibromyalgia
  - Average pain rating ≥ 4 over last 7 days by NRS at Visit 1 **AND** Visit 2
- Exclusion
  - TENS use in last 5 years
  - Contraindications to TENS use

Study Design



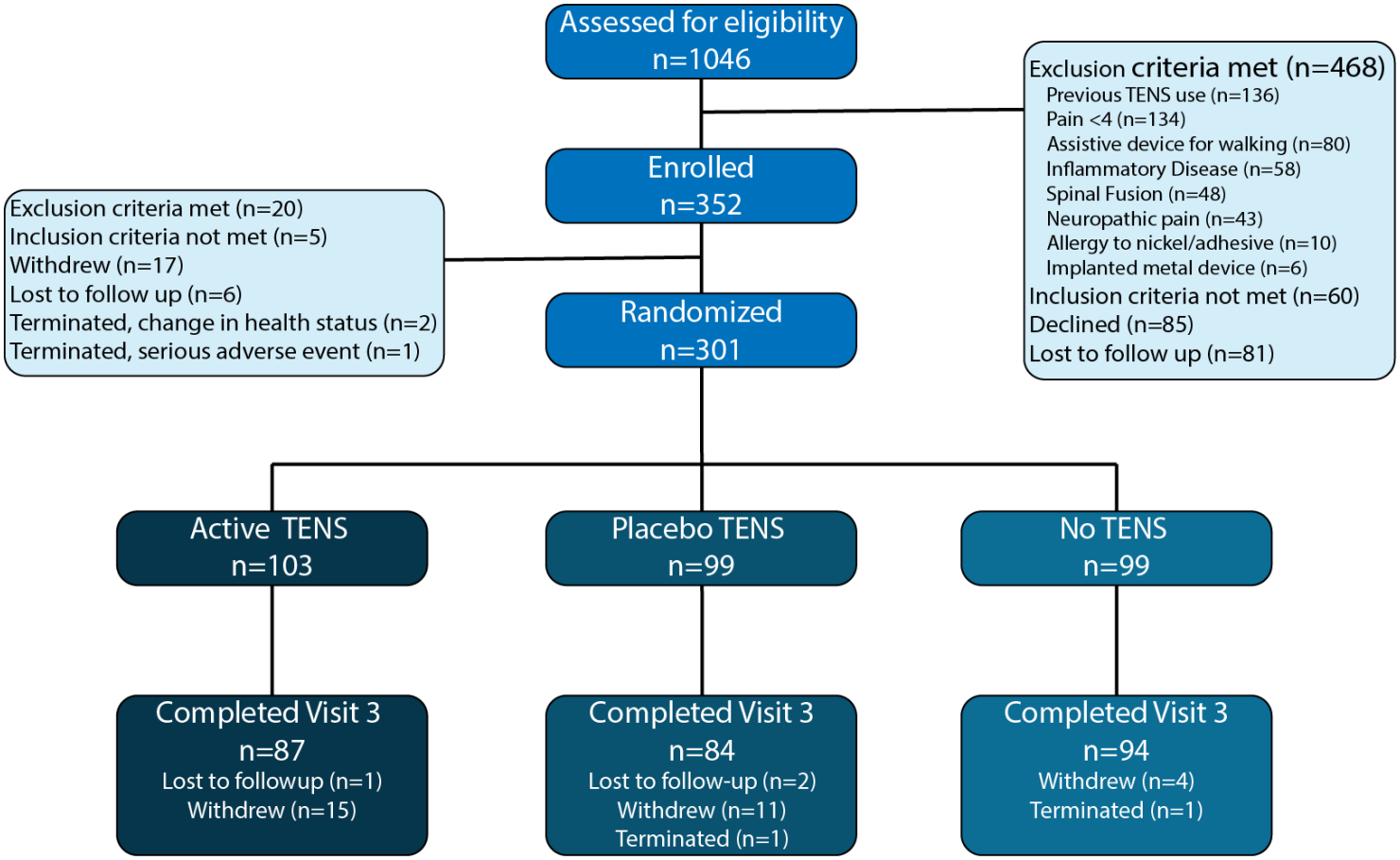
All participants received 4 weeks of Active TENS between Visit 3 and Visit 4

Outcome Measures

- **Primary**
  Pain during movement measured by NRS during 6-minute walk test (6MWT) of the ITT population
  - Comparing before/during TENS at study visits

- **Secondary**
  - Resting pain pre/post TENS during visits
  - Disease activity/impact (FIQR)
  - Pain intensity/interference (BPI: Brief Pain Inventory)
  - Pain self-efficacy (PSEQ)
  - Pain catastrophizing (PCS)
  - Fatigue during movement and at rest
  - Multidimensional fatigue (MAF)
  - Sleep (PSQI)
  - Fear of movement (TSK)
  - PROMIS-Anxiety
  - PROMIS-Depression
  - Quality of life (SF-36)
  - Self-report physical function (FIQR-function)
  - Performance based physical function (6WMT, 5TSTS)
  - Patient global rating of change

Participants

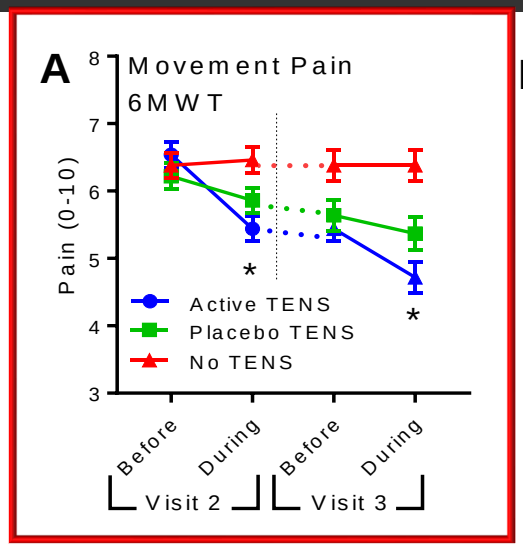


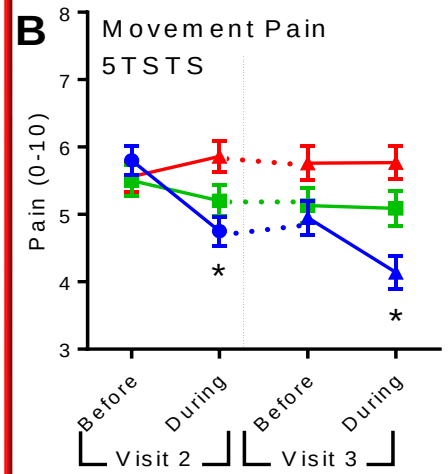
Completed Visit 4: Active TENS (n=75), Placebo TENS (n= 73), No TENS (n=84)

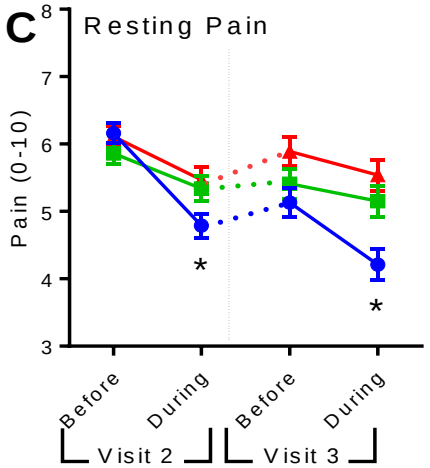
	Active TENS n=103	Placebo TENS n=99	No TENS n=99	p-value
Demographic Variables*				
Age, mean (SD)	44.7 (14.3)	47.2 (12.6)	48.6 (11.8)	0.10
Race, White	92%	92%	92%	0.99
Ethnicity, Not Hispanic	95%	95%	95%	0.99
Married / Living with partner	33%	51%	52%	**0.01**
Less than college graduate	61%	61%	64%	0.48
Working	55%	45%	58%	0.42
Health Variables				
Never smoked	82%	80%	70%	0.16
Body mass index (kg/m2)	34.8 (8.7)	33.7 (8.8)	34.0 (8.9)	0.65
Duration of fibromyalgia (yrs)	7 (3-12)	7 (2-14)	7 (4-15)	0.47
Opioids for pain^	27 (26%)	26 (26%)	26 (26%)	--
Baseline Measures				
Pain at rest (NRS)	6.2 (1.5)	5.9 (1.4)	6.1 (1.6)	0.33
Fatigue at rest (NRS)	6.8^{a} (2.0)	6.1^{b} (1.8)	6.4^{ab} (2.0)	0.08
FIQ-R 7-day pain	6.7 (1.8)	6.0 (1.6)	6.15 (1.8)	**0.02**
FIQ-R	59.2^{a} (16.8)	53.7^{b} (15.9)	55.6^{ab} (16.0)	**0.05**
SF-36 MCS	38.7 (10.0)	40.2 (10.2)	39.5 (10.6)	0.57
SF-36 PCS	32.7 (6.4)	33.3 (6.2)	32.7 (6.6)	0.72
PSQI, z-score	12.6 (3.8)	12.0 (3.8)	11.9 (3.4)	0.38
PCS	23.1 (13.0)	20.4 (12.5)	20.8 (12.1)	0.26
PSEQ	28.2 (13.3)	29.9 (13.1)	29.0 (13.2)	0.67
TSK	36.5 (7.7)	37.1 (8.0)	37.4 (8.3)	0.68

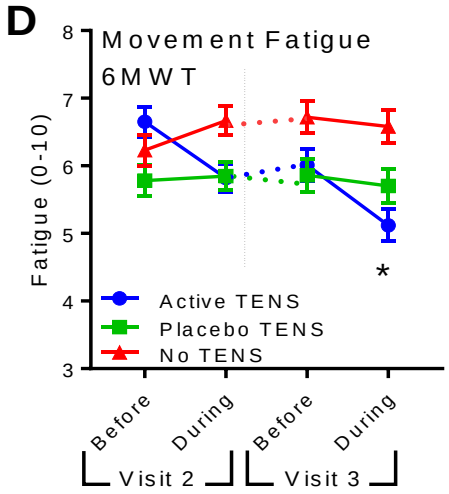
^Enrollment stratified by site and by opioid use

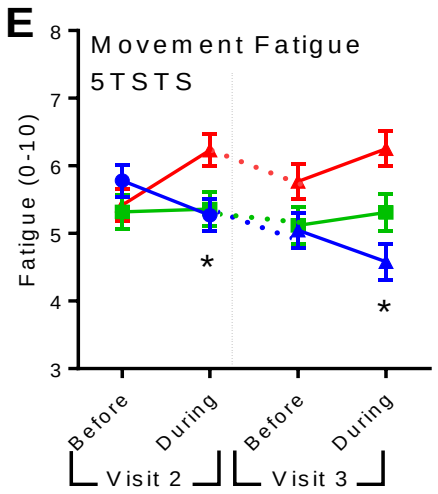
Movement and Resting Pain/Fatigue

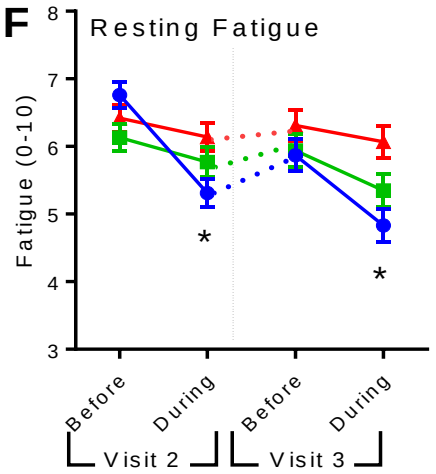








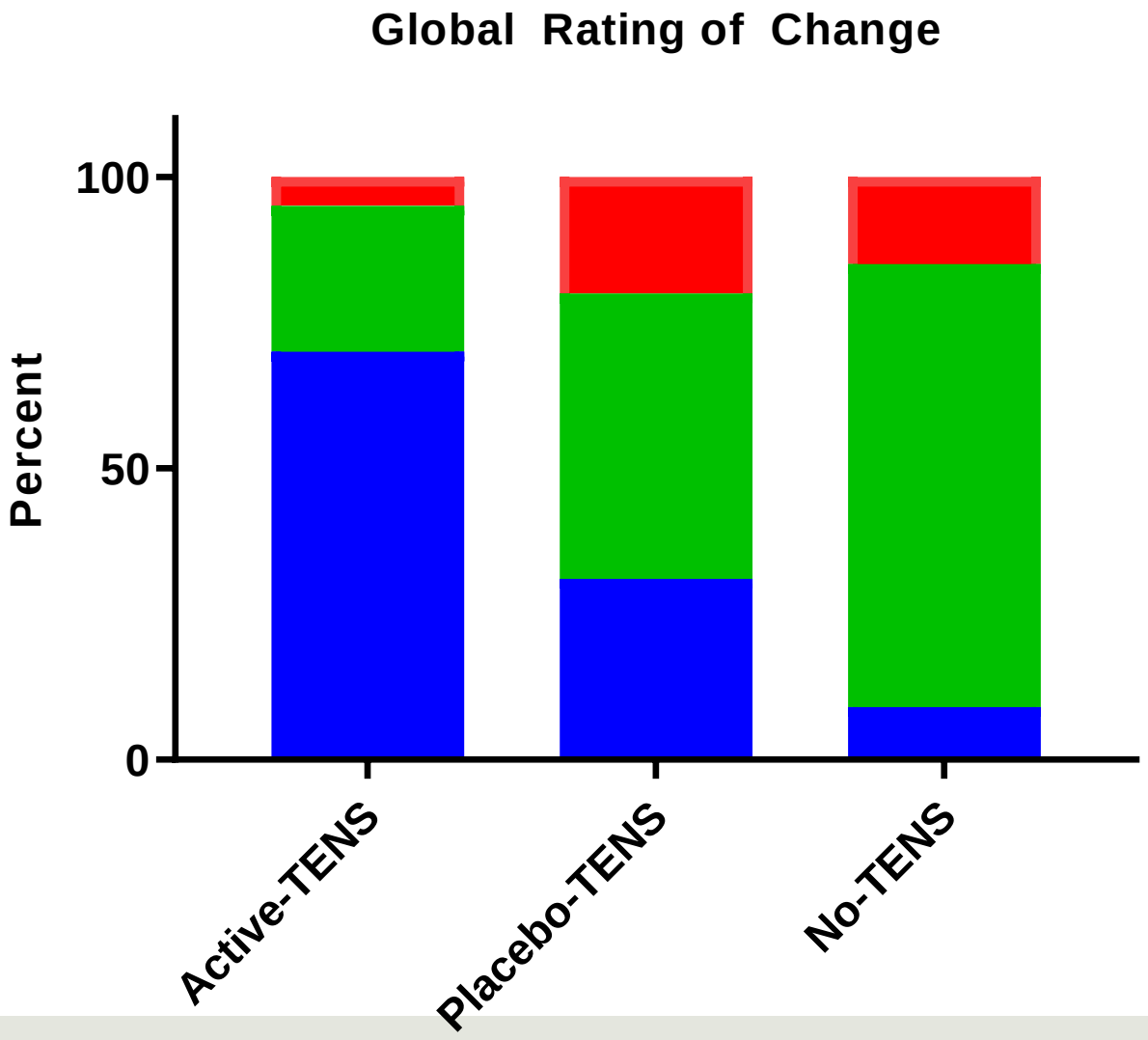




Patient-reported outcomes	Active TENS n=103	Placebo TENS n=99	No TENS n=99	Group Mean Difference (95% CI) P-value	
				Active vs PLACEBO	Active vs No TENS
FIQ-R	-8.48 (-12.92, -4.04)^^	-3.42 (-6.54, -0.30)^	-1.39 (-4.40, 1.62)	-5.06 (-10.44, 0.32) 0.073	-7.09 (-12.42, -1.77) **0.005**
FIQ-R Pain	-1.3 (-1.8, -0.7)^^	-0.4 (-0.9, 0.2)	-0.1 (-0.6, 0.4)	-0.9 (-1.7, -0.1) **0.018**	-1.2 (-1.9, -0.4) **0.0006**
BPI-Interference	-0.94 (-1.40, -0.48)^^	-0.26 (-0.73, 0.21)	-0.29 (-0.74, 0.16)	-0.68 (-1.33, -0.01) **0.044**	-0.65 (-1.29, -0.01) **0.047**
BPI-Intensity	-0.75 (-1.08, -0.43)^^	-0.26 (-0.59, 0.07)	0.15 (-0.17, 0.46)	-0.49 (-0.96, -0.02) **0.035**	-0.90 (-1.35, -0.44) **<0.0001**
MAF GFI	-4.63 (-6.42, -2.84)^^	-1.46 (-3.29, 0.37)	-0.26 (-1.98, 1.47)	-3.17 (-5.73, -0.61) **0.009**	-4.37 (-6.85, -1.88) **<0.0001**
PSQI (z-score)	-0.88 (-1.67, -0.10)^	-0.87 (-1,68, -0.09)^	-0.07 (-1.03, 0.49)	-0.01 (-1.11, 1.12) >0.99	-0.61 (-1.70, 0.48) 0.538
PSEQ#	3.16 (0.75, 5.57)^^	1.51 (-0.94, 3.96)	0.82 (-1.5, 3.15)	1.65 (-1.79, 5.09) 0.745	2.34 (-1.01, 5.69) 0.281
PCS	-3.38 (-5.32, -1.45)^^	-3.12 (-5.09, -1.15)^^	-1.39 (-3.26, 0.48)	-0.26 (-3.03, 2.50) >0.99	-1.99 (-4.69, 0.70) 0.226
TSK	-0.73 (-2.04, 0.59)	-0.34 (-1.68, 1.00)	-0.18 (-1.45, 1.09)	-0.39 (-2.26, 1.49) >0.99	-0.55 (-2.38, 1.28) >0.99
SF-36 MCS#	2.32 (0.21, 4.43)^	1.24 (-0.91, 3.39)	-0.04 (-2.08, 2.00)	1.08 (-1.94, 4.09) >0.99	2.36 (-0.58, 5.30) 0.164
SF-36 PCS#	2.37 (1.05, 3.70)^^	1.15 (-0.20, 2.50)	1.37 (0.09, 2.65)	1.22 (-0.67, 3.12) 0.359	1.00 (-0.84, 2.84) 0.574
PROMIS-Anxiety	-1.07 (-2.59, 0.46)	-0.57 (-2.12, 0.98)	-0.66 (-2.14, 0.82)	-0.05 (-2.68, 1.68) >0.99	-0.41 (-2.53, 1.72) >0.99
PROMIS-Depression	-2.84 (-4.18, -1.49) ^^	-0.09 (-1.47, 1.28)	0.38 (-0.92, 1.68)	-2.71 (-4.66, -0.82) **0.002**	-3.22 (-5.09, -1.35) **0.0001**

	Active TENS n=103	Placebo TENS n=99	No TENS n=99	Group Mean Difference (95% CI) P-value	
				Active vs PLACEBO	Active vs No TENS
Self-report function outcomes					
FIQ-R Function	-2.71 (-4.00, -1.42)^^	-1.38 (-2.70, -0.06)^	-0.56 (-1.81, 0.68)	-1.33 (-3.18, 0.51) 0.073	-2.15 (-3.94, -0.36) **0.005**
SF-36 Physical Function	1.39 (0.10, 2.69)^	0.53 (-1.79, 1.84)	0.75 (-0.50, 2.00)	0.86 (-0.98, 2.71) >0.99	0.65 (-1.15, 2.44) >0.99
Performance-based function outcomes					
6MWT	0.06 (-0.49, 0.61)	-0.11 (-0.66, 0.44)	-0.34 (-0.87, 0.19)	0.17 (-0.61, 0.95) >0.99	0.40 (-0.36, 1.17) >0.99
Functional reach	0.16 (-0.42, 0.74)	0.04 (-0.55, 0.63)	-0.13 (-0.69, 0.44)	0.29 (-0.60, 1.18) >0.99	0.29 (-0.60, 1.18) >0.99

TENS improves global rating of change



NNT=3

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**

Strongest predictor of pain response was reduction of MEP during first TENS treatment

Other Results

- No difference in ITT compared with per protocol analysis
  - PP: At least 30 min/d for 8 sessions over 4 weeks
- Placebo TENS and No TENS groups had similar beneficial results after 4 weeks open-label Active TENS
- Active TENS group had sustained/improved outcome after an additional 4 weeks open-label treatment
- No significant reduction in effectiveness of TENS in opioid versus non-opioid strata
- TENS-related adverse effects
  - Skin irritation from electrodes
  - Anxiety, nausea
  - Pain (muscle spasm, unspecified)
  - NNH between 20 and 100

Summary

- Active TENS improves resting and movement-evoked pain and fatigue acutely
  - No TENS tolerance develops over 4-8 weeks of treatment
- After 4 weeks of treatment, there was evidence of a chronic TENS effect with a reduction in baseline pain and fatigue
- Active TENS resulted in global improvement of disease impact
- There was improvement in one measure of depression, but no significant effect of TENS on measures of function, sleep, or other clinical domains
- There were minimal adverse effects associated with TENS treatment

Pragmatic Trial

Fibromyalgia – TENS in Physical Therapy Study (FM-TIPS)

Study Team

CT DMC
Clinical Trials Statistical and Data Management Center

University of Iowa Carver College of Medicine
University of Iowa Health Care

Study Overview

- **Goal**:
  - Demonstrate the feasibility of adding TENS to treatment of patients with FM in a real-world *Physical Therapy* practice setting **and**
  - Determine if addition of TENS to standard *Physical Therapy* for FM reduces pain, increases adherence to PT and allows patients with FM to reach their specific functional goals with less drug use.

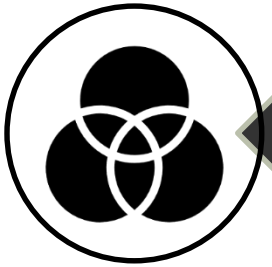
- **Hypothesis**
  - Using TENS in a *Physical Therapy* setting is feasible and that FM patients using TENS are more likely to reach their therapeutic goals.

Specific Aims

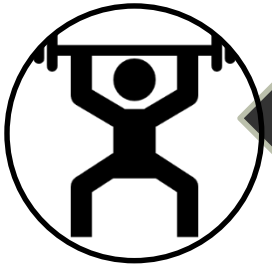
Aim 1: *Determine if addition of TENS to routine PT improves movement-evoked pain*

Aim 2: *Determine if addition of TENS to routine PT improves 1) disease activity, 2) likelihood of meeting patient-specific functional goals, 3) adherence to PT, and 4) medication use*

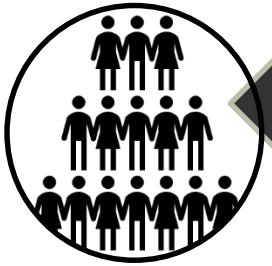
Aim 3: *Examine feasibility of implementing TENS into routine PT care for FM using semi-structured exit interviews of patients and PTs*



cluster-randomized pragmatic trial



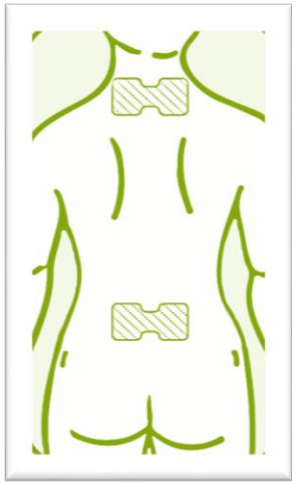
routine PT with or without TENS for FM



enroll ~600 people with FM

Study Design

- Physical therapy setting
  - PT are familiar with TENS
  - TENS may be most helpful when used during movement
  - More frequent "touches" with patients may facilitate compliance
- Cluster randomized
  - Five PT health systems – Iowa, Illinois, Tennessee
  - Twenty-four PT sites
  - Each site randomized to TENS + PT or PT only
  - Stratified randomization by health system and site size
    - Versus constrained randomization
- Pragmatic design
  - Inclusion/exclusion criteria
  - Minimal interference with usual care
  - Emphasis on PRO
- Intervention
  - TENS (Quell) x 2 applied to cervical/low back regions recommended for 2h daily during activity
  - Mixed frequency, strong but comfortable intensity



Visit Schedule

PT V1	Home	PT V2	Home	PT V3-PT completed	Home Days 30, 60, 90, 180
• Identify eligible participants • Provide study materials and REDCap access • Develop treatment plan	• Review study materials • Sign e-Consent	• Check that consent is signed • Provide TENS	• Collect baseline pre-TENS data • First TENS treatment • Collect baseline post-TENS data	• Check that baseline data entered • Provide treatment	• Primary endpoint Day 60 • TENS provided to no-TENS randomized participants if data completed

Pre-Resting NRS pain/fatigue, Pre-MEPT with NRS mvmt pain/fatigue, TENS applied for 1st full treatment (or not) x 30 min, Demographic data, 2016 FM criteria, FIQR, MAF, BPI, PROMIS PhysFunct, PROMIS Sleep, Sleep Duration, PCS, PHQ-8, GAD-7, TAPS1, Medications, RAPA, Post Resting NRS pain/fatigue, Post MEPT with NRS mvmt pain/fatigue, Adverse event, Barriers to TENS

Outcome measures

- Primary outcome: Movement evoked pain
  - Baseline: Five times sit-to-stand pre-TENS
  - Primary endpoint: 5TSTS after 30-min TENS at day 60
  - TENS + PT vs PT only
  - Power analysis → 600 participants
- Secondary outcomes
  - Other PRO
  - PT adherence
- Descriptive comparisons
  - Baseline vs days 90, 180: TENS + PT (long-term use) and PT-only followed by TENS started at home

Challenges

- PT sites not used to conducting embedded research
- Multiple different EHR
  - Data collection limited
- COVID impact on free-standing PT practices
  - Changes in volumes, financial issues
  - Rolling starts of PT systems

Conclusions

- TENS can be safely used in addition to other treatments to improve pain and fatigue in women with fibromyalgia in the setting of an RCT
- Practicality of using TENS for patients with fibromyalgia referred for PT needs to be determined
  - Is TENS uptake improved if applied during PT treatment?
- Effectiveness of TENS in a real-world type setting remains to be determined

Comments or Questions?