Implications of central sensitization and “centralized chronic pain” for the design of chronic pain clinical trials

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“What’s in a name?”
Beg to differ with Shakespeare

- Central Sensitivity Syndrome
- Centralized Chronic Pain
- Overlapping Chronic Pain Conditions
- Chronic Overlying Pain Conditions
- Chronic Widespread Pain
- Chronic Primary Pain
- Fibromyalgia-ness
- Chronic Fatigue Syndrome / Systemic Exertional Intolerance Disease
- Nociplastic Pain
- Somatoform Disorders (DSM-4), Somatic Symptoms & Related disorders (DSM-5)

What have we been discussing?

- **Condition:** An abnormal state of health that interferes with the usual activities or feeling of wellbeing.
- **Disease:** Resulting from a pathophysiological response to external or internal factors.
- **Disorder**: A disruption to the normal or regular functions in the body or a part of the body.
- ***Syndrome*:** A collection or set of signs and symptoms that characterize or suggest a particular disease.

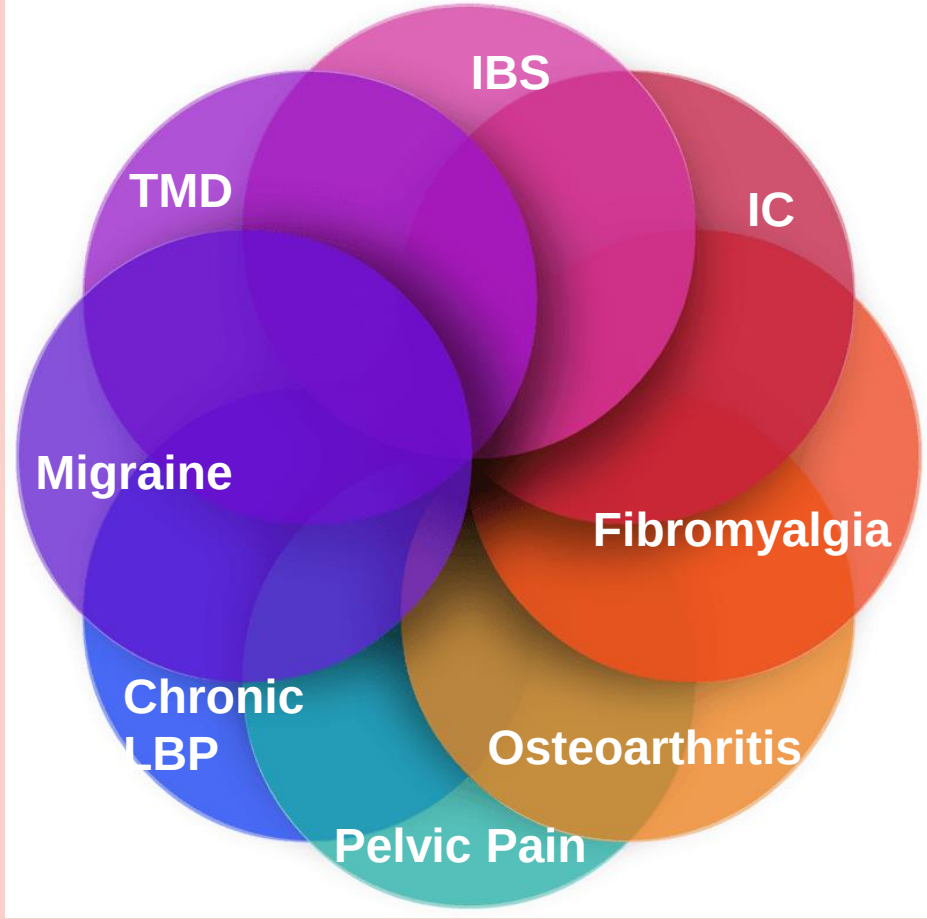
CS, Centralized Pain & Overlapping Pain Conditions

IMMPACT XXIII

Most highly prevalent pain conditions

(2-3 x more prevalent in women vs men)

- Fibromyalgia
- Arthritis- Rheumatoid, Osteo
- Migraine headache
- Irritable bowel syndrome
- Interstitial cystitis
- Temporomandibular disorders
- Chronic pelvic pain



Why do we need IMMPACT-XXIII ?

Do we need a different study design for CSS / COPC?

Research Design Considerations for Chronic Pain Clinical Trials Addressing Central Sensitization/ Somatosensory Amplification and Multiple Comorbidities

- **Hypothesis**: CSS /COPC have a *common* central mechanism that is *different* from other acute or chronic pain conditions, e.g., inflammatory or neuropathic pain (PHN, phantom pain)
  - Twin studies-modest genetic influence for CWP, COPS (Kato 2006, Schur 2007)
- **Inference**: Treatments effective in CSS may be unique & different from other chronic pain conditions and hence research design should be appropriate to identify these therapies

Kato K et al. Arthritis Rheum 2006;54:1682, Schur EA ..J Gen Intern Med 2007;22:818

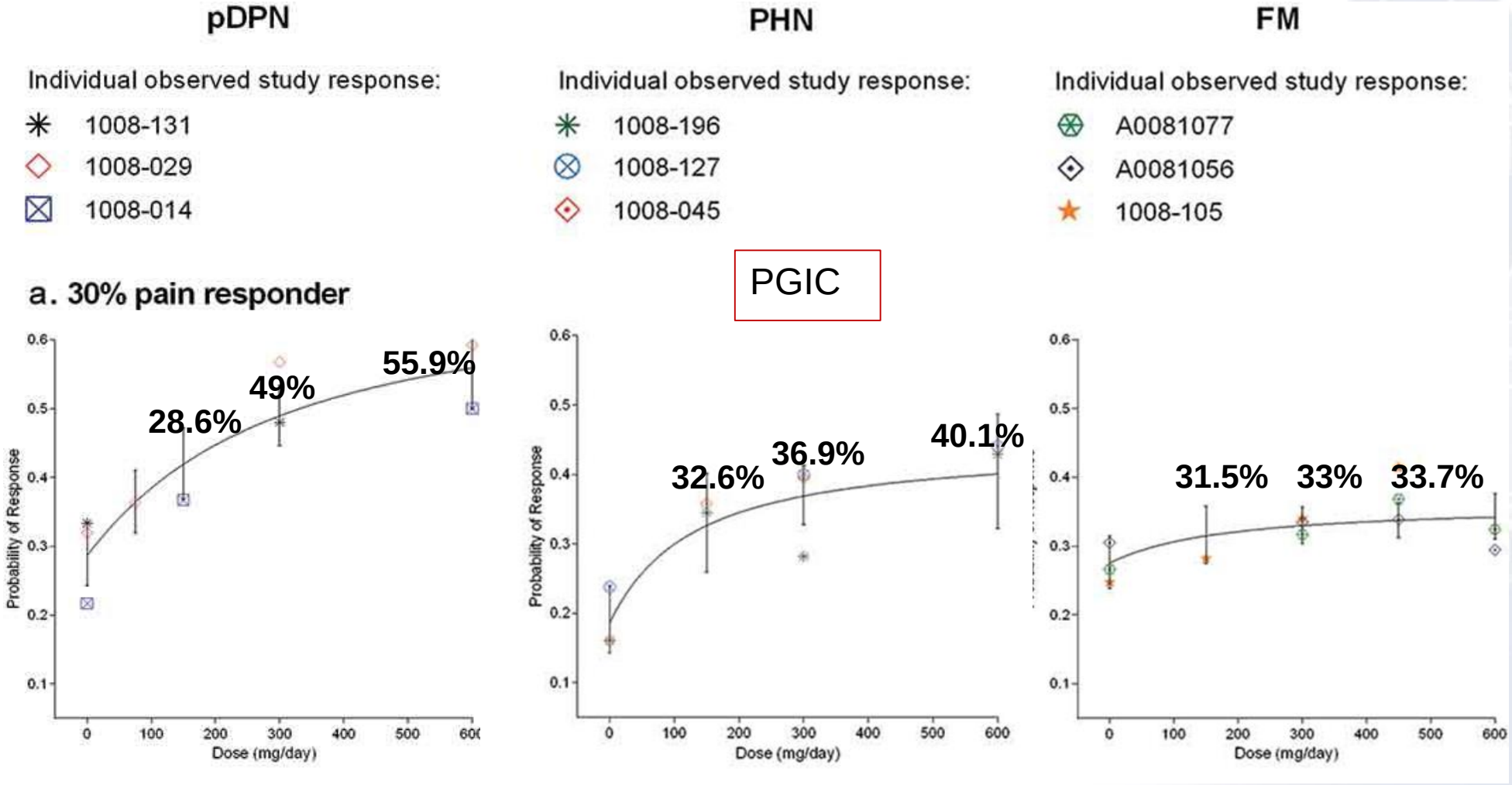
Is Central Sensitization in CSS different from that in Neuropathic Pain? Poster Child- Fibromyalgia (FM)

- FDA approved drugs:
  - Duloxetine- approved for FM, DPNP, chronic M-S pain
  - Pregabalin- approved for FM, NP associated with DPN, PHN, spinal cord injury pain
  - Milnacipran- approved for FM (preclinical studies in NP +)
- Other treatments: ketamine infusion (+ 60% of FM, NP +)
  - CBT- fibromyalgia, NP, OA
- Drugs not effective in NP also not useful in FM
  - NSAIDs: “NSAIDs cannot be regarded as useful for treating fibromyalgia.” Cochrane Aug 31, 2016

Littlejohn G, Guymer E. Biomedicines. 2017; 5(2): 15

Pregabalin in FM vs NP
Is the effect similar?

Arnold LM et al Postgrad Med 2017;129:921



Pregabalin in FM vs NP

Is the effect similar?

Arnold LM et al Postgrad Med 2017;129:921

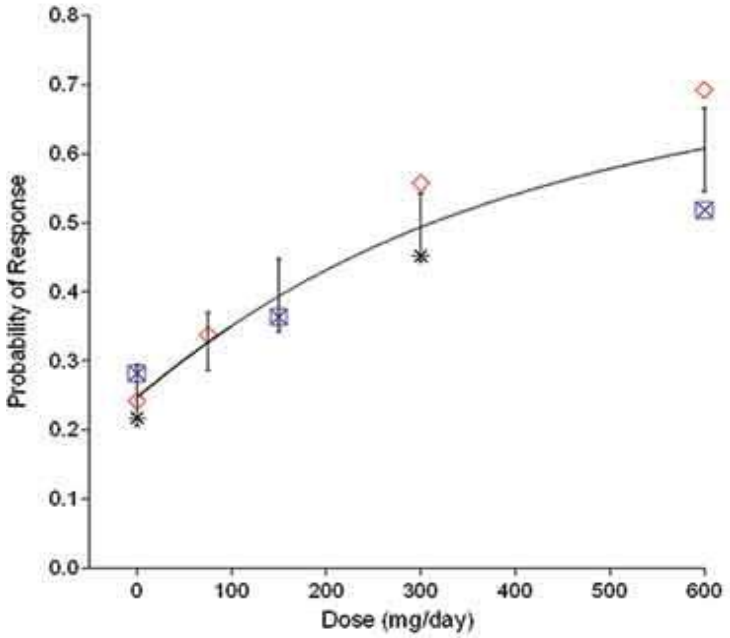
pDPN N = 1438 **PHN** N = 1250 **FM** N = 2022

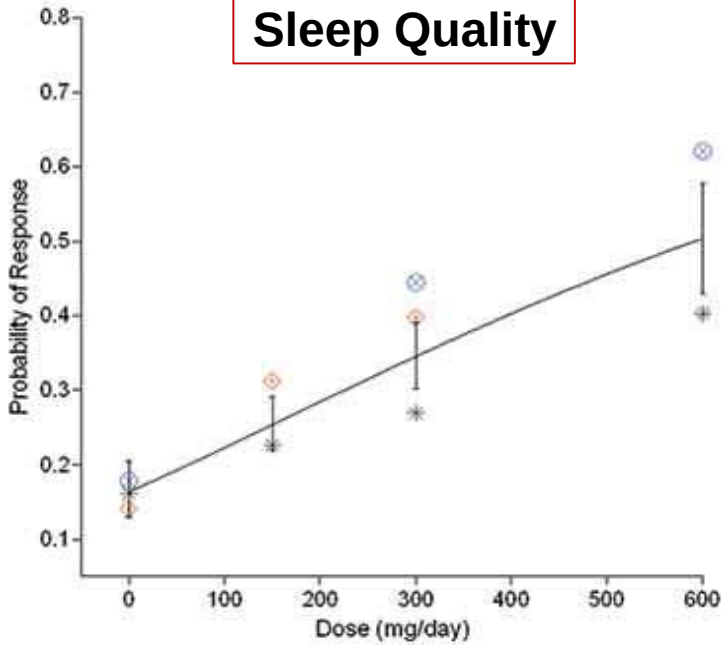
Individual observed study response:

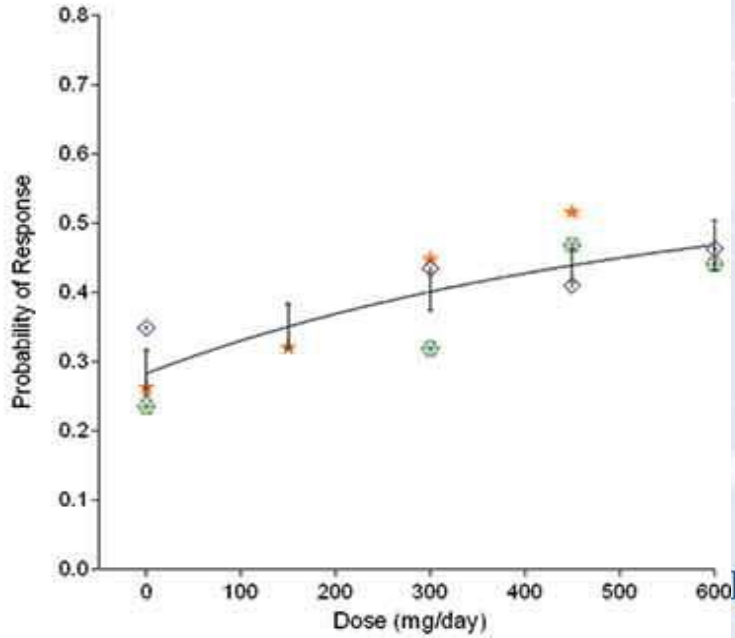
1008-131
1008-029
1008-014

Is it primarily an issue of Assay Sensitivity?
The trial designs are not sensitive enough to differentiate the CS in the two conditions!

Sleep Quality

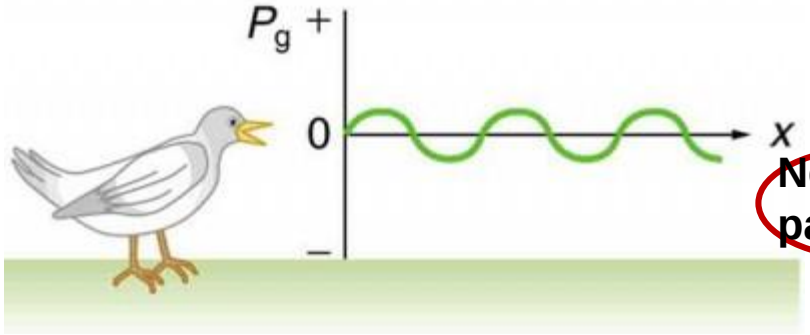






NS

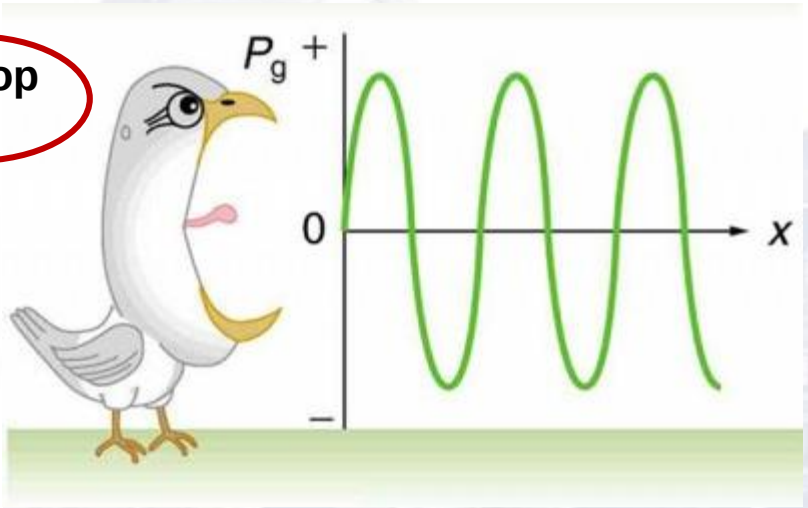
Difference between central amplification in NP & CSS: Magnitude and extent / anatomical sites?



Neuro-pain

FM, COPS

Postop pain



OR

Are the ampl;ification systems different in Neuropathic Pain and Central Sensitization Syndromes?

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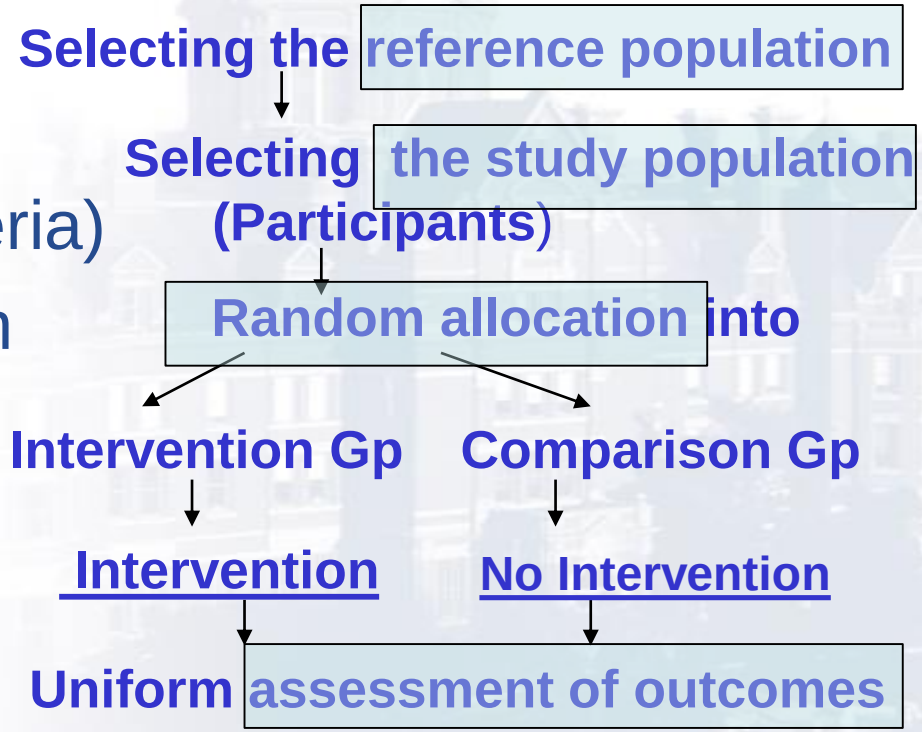
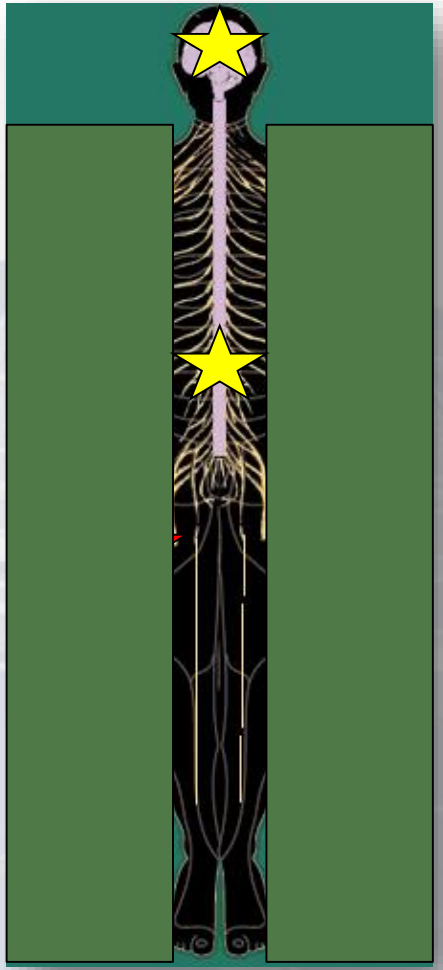
Planning the Optimal Study: 101
From disease concept to execution of Trials

- Defining the population of interest (reference population)
- Objectives- What is the primary question?
- Design of the Study
  - Study population (Inclusion / Exclusion criteria)
  - Eligibility assessment & Baseline evaluation
  - Allocation- randomization method
- Outcome measures
  - Primary and Secondary
  - Biomarkers and Surrogate Response



What is the *Reference Population* for CS and Centralized Pain?

- Patients with central sensitization / somatosensory amplification [*enhanced S-R function*] regardless of clinical presentation (muscular, visceral, joint pains) AND /OR
- 'Centralized Pain' [independent of peripheral afferent drive- autonomous CS]
  - Subset of patients with FM- peripheral input from muscle may play an important role (Staud R, 2009)



Staud R et al. Pain 2009;145:96-104
Buch NS et al. Pain. 2019 Jul;160(7):1622-1633.

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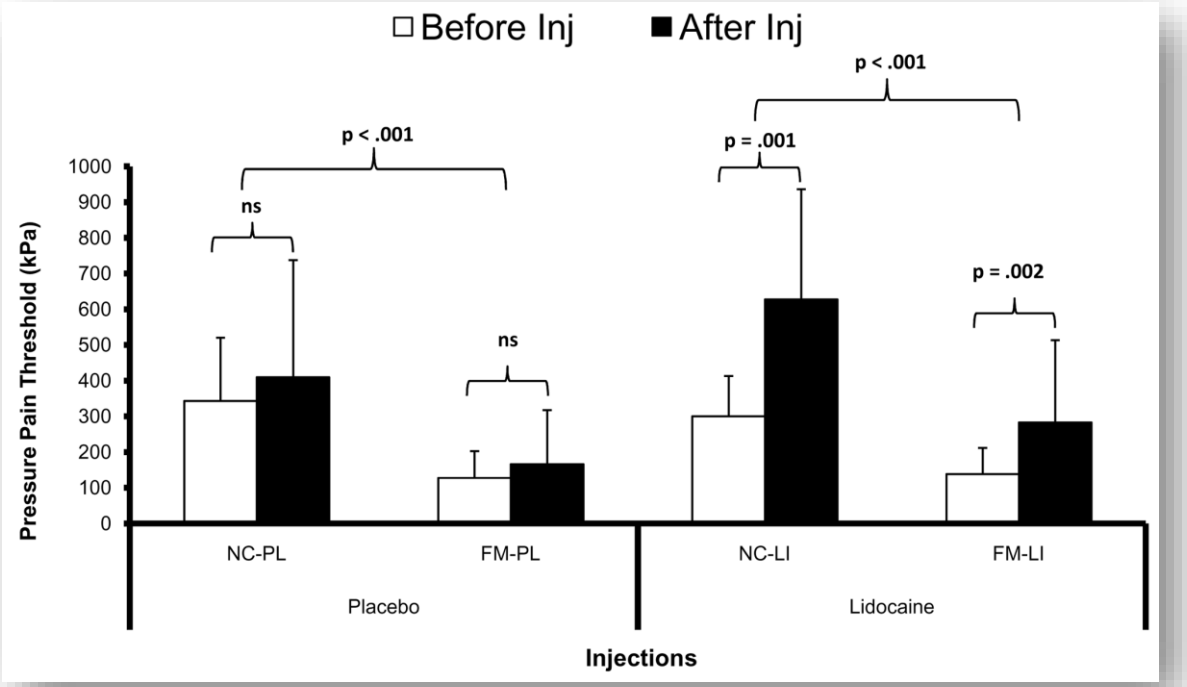
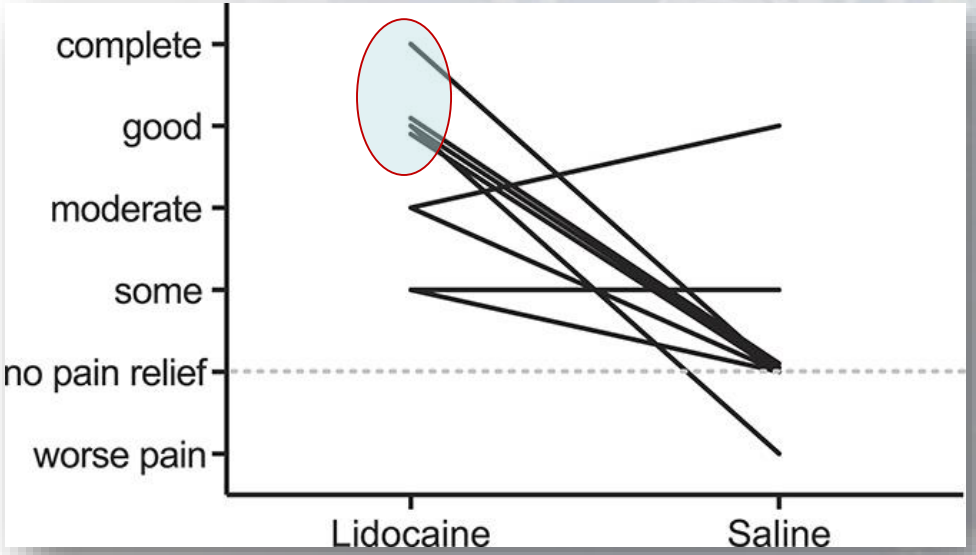
Not all patients with Central Sensitization have "Centralized" Pain: Role of peripheral inputs

I.M. Lidocaine injections increased local pain-thresholds and decreased remote secondary heat hyperalgesia in FM



Staud R et al. Pain 2009;145:96-104

Phantom pain intensity significantly reduced after peripheral nerve block with lidocaine vs saline → Afferent input from the PNS plays an important role



Buch NS et al. Pain. 2019 Jul;160:1622
Waxman SG Pain 2019; 160:1487

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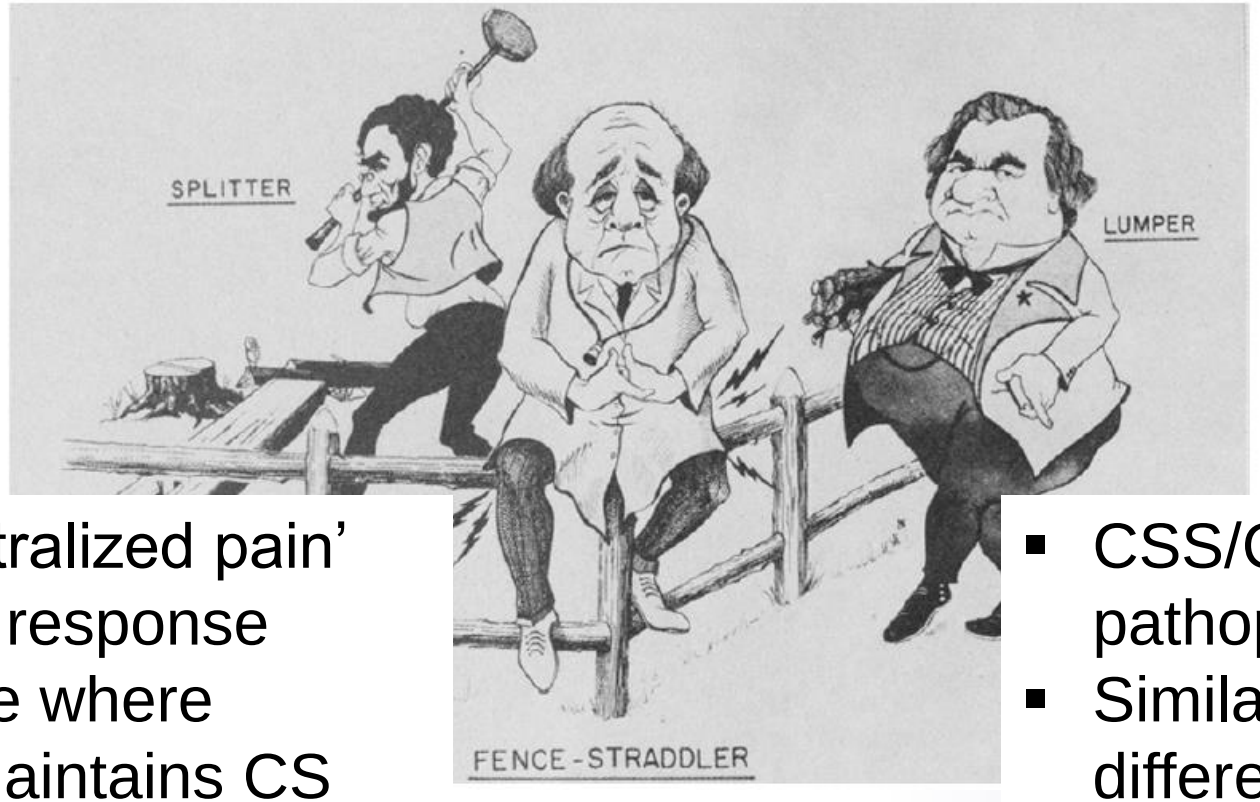
Reference Population of Interest
Lumpers vs Splitters

Splitters focus on
Differences



Lumpers look for
Similarities

- Patients with ‘centralized pain’ differ in their drug response compared to those where peripheral drive maintains CS
- FM phenotypes (top-down/ bottom-up) differ in Rx response

- CSS/COPC share a common pathophysiology/ mechanism
- Similar drug efficacy in different CS conditions

Adapted from V. A. McKusick,

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Study Population: The gold standard diagnostic criteria for 'CS' and centralized pain state ?

Clinical Features

- Widespread pain
- Multi-sensory hypersensitivity
- Fatigue
- affective lability, Δ mood
- Sleep disturbance
- Cognitive problems

How many of these features?
Sensitivity & Specificity ?

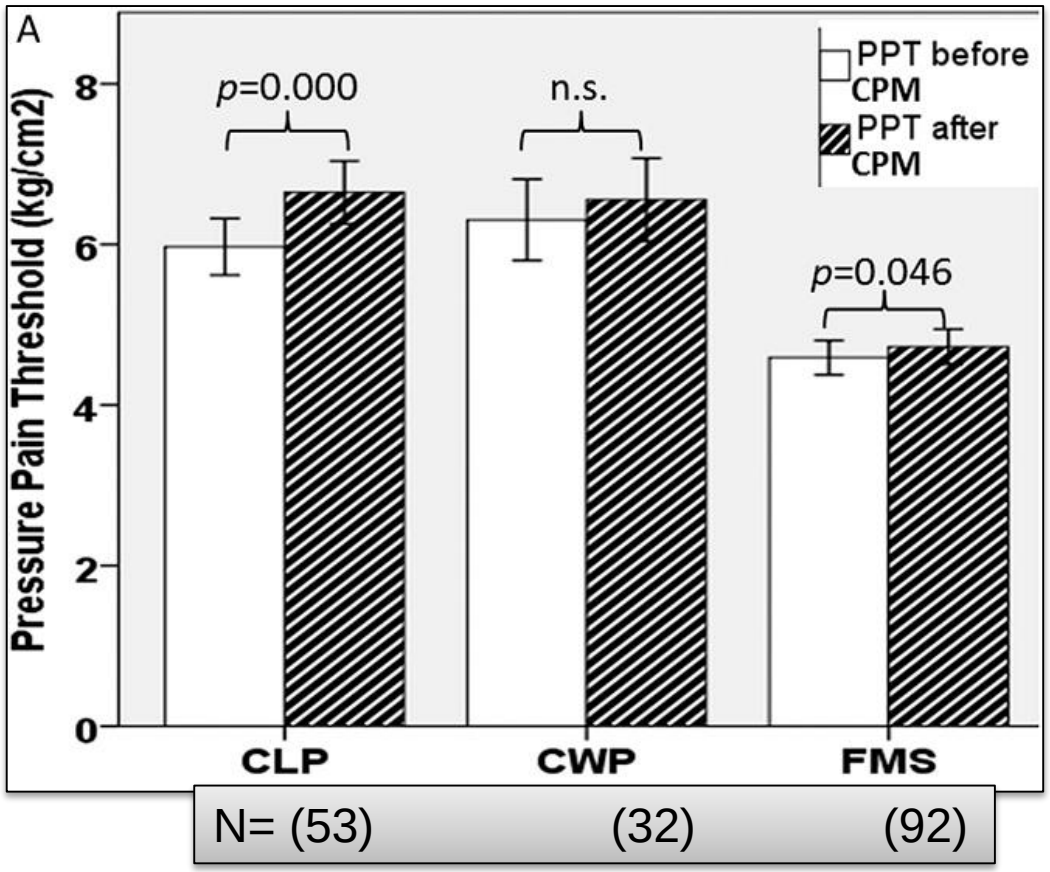
Mechanistic / Neurobiologic Correlates

- *Increased gain of SS system* (QST)
  - Allodynia
  - Hyperalgesia- Mechanical / Thermal
  - Temporal summation / windup
  - Aftersensations
  - Reflex nociceptive threshold
- *Objective Biomarkers*
  - Neuroimaging: altered brain-network connectivity

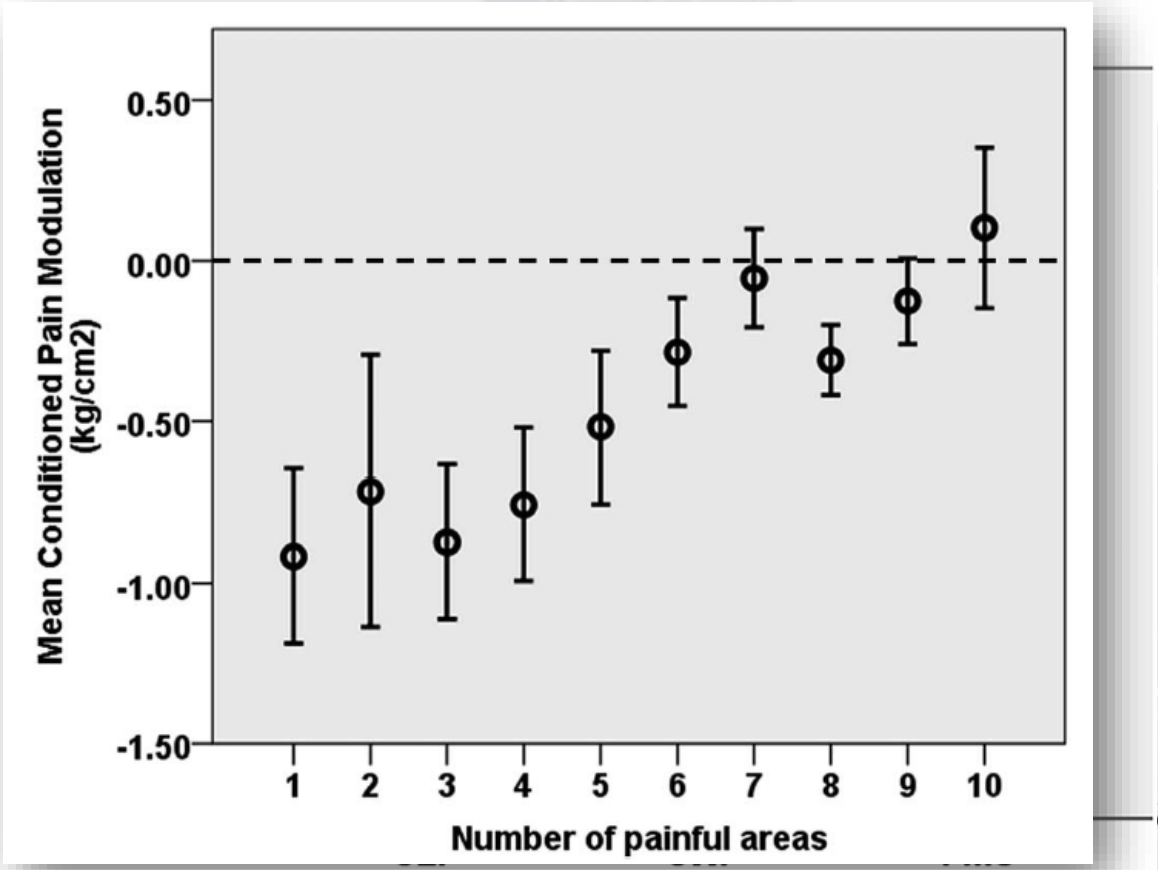
Widespread pain: Dysfunction of Descending Modulation? CPM in Low back pain and FM

Gerhardt A et al.
Pain 2017;158: 430-439

Chronic local back pain (CLP), chronic widespread back pain (CWP), and FM pts.



Association of higher spatial pain extent with lower CPM; CLP but not in FM



Rapid Screening Tools for Fibromyalgia (PROs)
Are these tools useful for other CSS?

- FibroDetect (Baron R. Health Qual Life Outcomes 2014;12:128)
- Fibromyalgia Diagnostic Screen (Arnold LM J Womens Health 2012;21:231)
- Fibromyalgia Rapid Screen Tool (Fan A Rheumatology 2016)

14 questions → 7 scored in Final model

- ≥6 = AUC of 0.74, sensitivity 77%, specificity 61%

Table 3 Final discriminant model based on modified FibroDetect items

	Question	Response choices	Coding
1	At least one body part of upper body ticked (head, neck, shoulders)	Yes	1
		No	0
	At least one body part of upper limb ticked (right and left arms)	Yes	1
		No	0
	At least one body part of lower limb ticked (right and left legs)	Yes	1
		No	0
2	Frequency of the pain	Every day or Almost every day	1
		Some days	0
3	At least 3 kinds of pain ticked*	Yes	1
		No	0
4	Frequency of tiredness	Every day	1
		Some days or Never	0
5	Impact of physical effort on tiredness	Much more tired	1
		Slightly more tired or No difference	0
6	At least 7 symptoms ticked**	Yes	1
		No	0
13	Extent to which patients recognize themselves in the questions being asked	Absolutely	1
		A little or Not at all	0

Fibromyalgia Rapid Screening Tool (FiRST)

Fan A. et al. Rheumatology (Oxford). 2016;55:1746
Perrot S et al. Pain 12010;50:250

- A self-administered questionnaire developed by French researchers, consists of six questions regarding the presence or absence of the various dimensions of fibromyalgia:
- “Yes" or “No" answer, with each "yes" = 1 point. A score of 5 or more has the highest sensitivity and specificity for fibromyalgia

	Sensitivity	Specificity
FiRST vs ACR90	75%	80%
FiRST vs Rheumatologist	76%	85%

NPV is excellent (97%), whereas the PPV is poor (27%)

	Kappa coefficient
1 – Diffuse pain	0.77
2 – Fatigue	0.80
3 – Pain descriptors	0.84
4 – Abnormal sensations	0.80
5 – Associated somatic comorbidities	0.78
6 – Sleep and cognition	0.82

Are these tools too specific for FM and not generic enough to screen for CS and COPC?

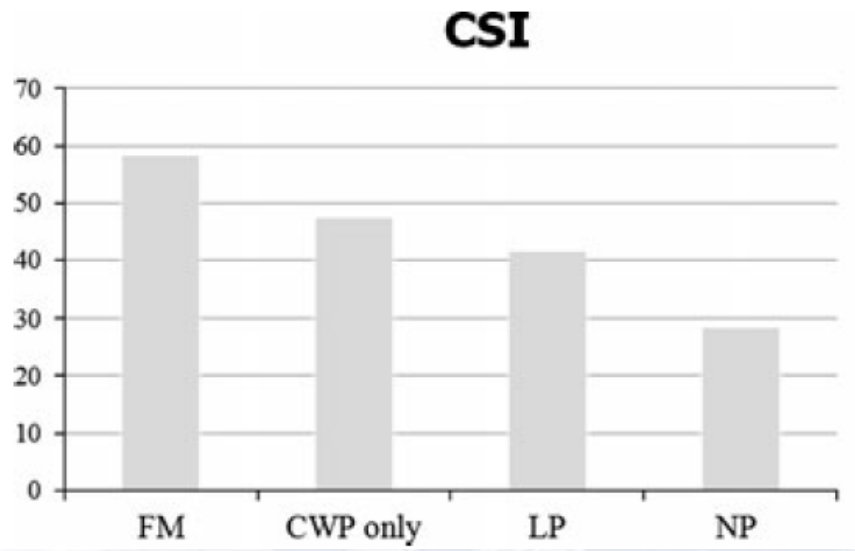
***Study Population*: Screening for Central Sensitization (**Diagnostic Criteria- Scales**)**

- Clinical: widespread ‘unpleasant sensory experiences disproportionate to any observable peripheral cause’
- Pain Sensitivity Questionnaire (Ruscheweyh 2009)
- *Central Sensitization Inventory* (Mayer 2012, Neblett 2013) → **CS**
- Sensory Hypersensitivity Scale (Dixon 2016) → SS Amplification
- Centralized Pain Index (CPI, *‘under-construction’, Clauw D AR070600)*

Williams DA *J Appl Behav Res* 2018;23:e12135; Ruscheweyh R, *Pain* 2009; 146:69
Mayer TG *Pain Pract* 2012;12:276-285; Neblett R, *J Pain* 2013; 14:438-445
Dixon EA et al. J Behavioral Med. 2016; 39:537–550

Central Sensitization Inventory

- Identifies key symptoms associated with CSSs and quantifies the degree of these symptoms
- 25 statements related to current health symptoms, each item measured on a 5-point (0-4) Likert scale, test–retest correlation = 0.817)
- 4 Factors (53.4% of the variance): 1. Physical Symptoms, 2. Emotional Distress, 3. Headache /Jaw Symptoms, 4. Urological Symptoms (5.2%)
- Validated in FM, CWP, CLBP, and normal subjects



Mayer et al.
Pain Practice 2012; 12:276-85

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Sensory Hypersensitivity Scale (SHS)

- 25-item measure of general & modality-specific hypersensitivity
- Useful uni-factorial measure of sensory hypersensitivity
- Modest association with 3 QST measures (heat threshold & tolerance, cold tolerance)
- FM subjects scored higher than LBP, OA, or controls
- SHS scores correlated with symptoms of depression and anxiety

Dixon EA et al. J Behavioral Med. 2016; 39:537–550

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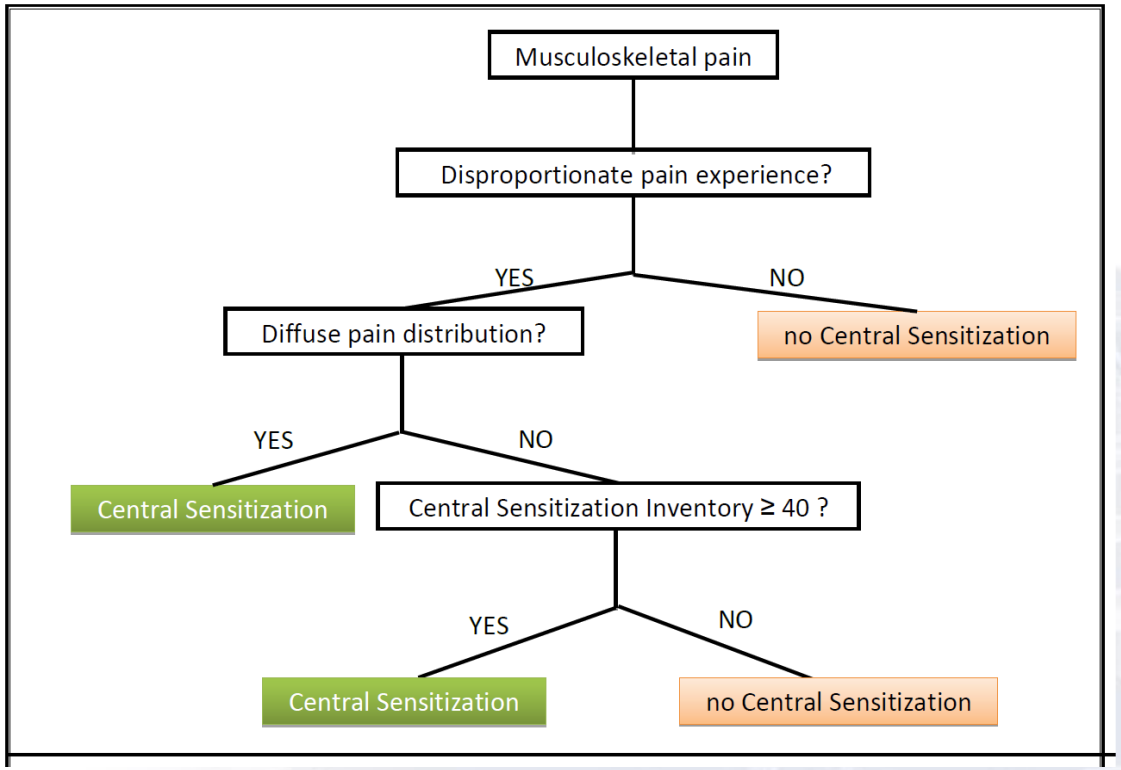
Criteria for Clinical Classification of Central Sensitization Pain- panel recommendation

Steps (1-3 or 1,2, 4 = CS+)

1. Rule out Neuropathic Pain
2. Rule out Nociceptive Pain
3. At least one of the following criteria:

1) Pain experience disproportionate to the nature and extent of injury or pathology 2) Diffuse pain distribution, allodynia, and hyperalgesia

4. General hypersensitivity to sensory stimuli- pressure, cold, heat, odor, light, sounds (CSI >40)



Nijs J et al. Pain Physician 2014; 17:447-57
Williams DA J Appl Behav Res 2018;23:e12135

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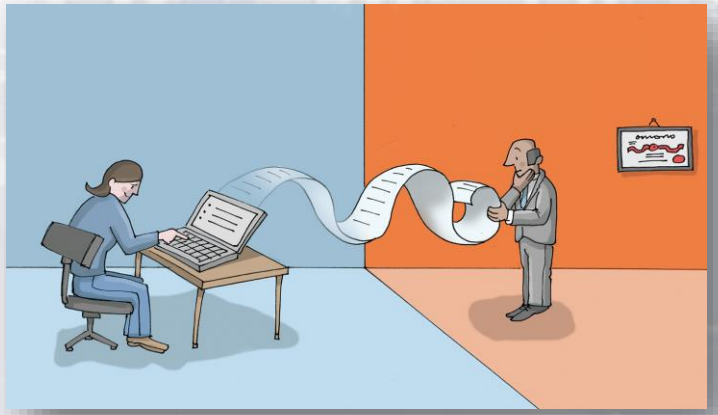
Pros and Cons of Self-assessment Tools

- Practical, easy to administer
- Have been validated for FM/CS clinical syndromes
- Good internal validity, conceptually strong
- Have not been tested carefully for correlation with objective measures/ biomarkers of CS (e.g., TS, CPM, neuroimaging)
- Too specific, not generic for COPC



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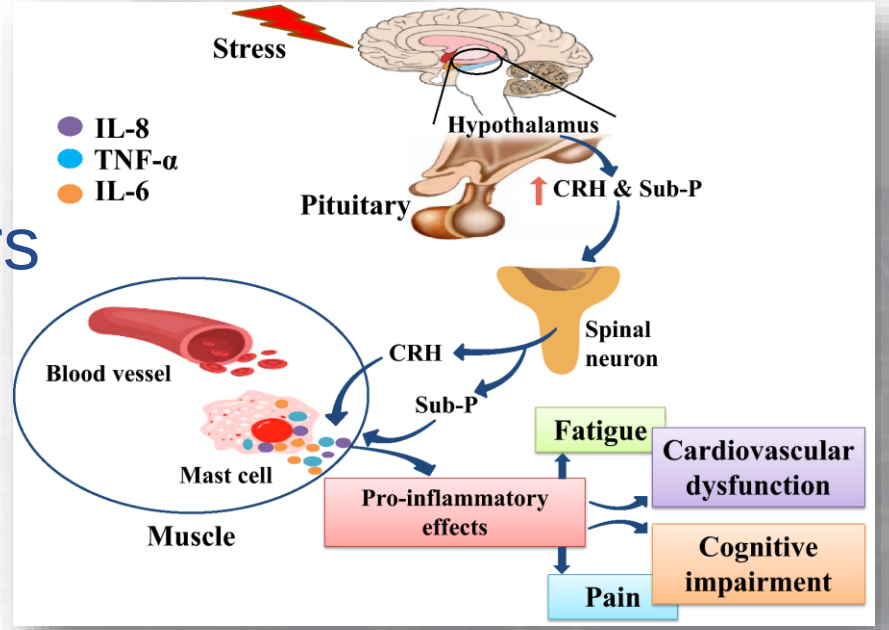
Potential Objective Tests and Biomarkers for Central Sensitization

- QST: Enhanced TS, Decreased CPM
- Imaging: increased activation of pain-related networks
- Increase in pain-facilitating neuro-transmitters (NPY, CRH, subP, BDNF) and inflammatory cytokines (IL-6,8, IL-1β, TNF-α, CSF-fractalkine)?
- Decreased production of pain-inhibiting transmitters (5-HT, dopamine, NE, β–endorphins)?



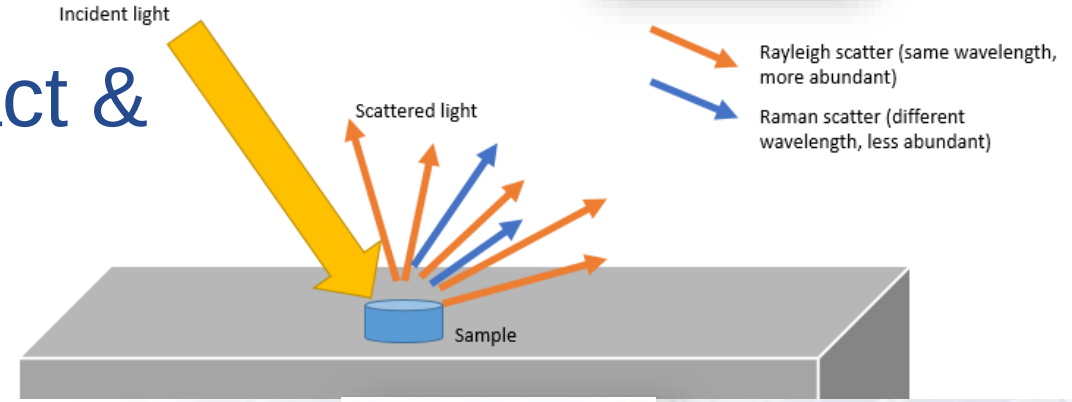
Singh L et al.
J Neurochem Res 2019;44:1517

Sensitivity and Specificity as a Diagnostic Tool in a given patient ?

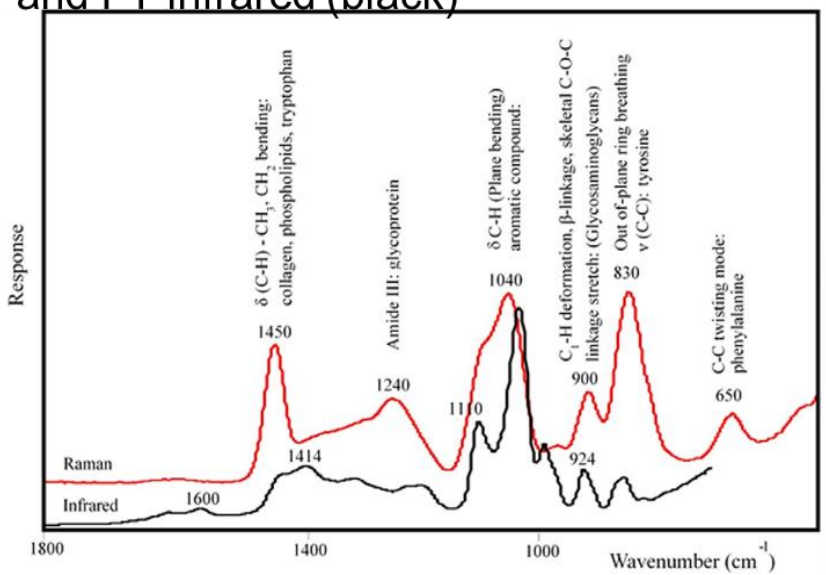
Biomarkers: Metabolomics- "chemical fingerprint"

Vibrational (mid-IR and Raman spectroscopy)

- No sample preparation, non-contact & non-destructive
- Dried blood-spot from finger stick



Microspectroscopy- FT-Raman (red) and FT-infrared (black)



Sir CV Raman
Nobel-Physics 1930

Hackshaw KV et al.
J Biol Chem. 2019;15;294:2555

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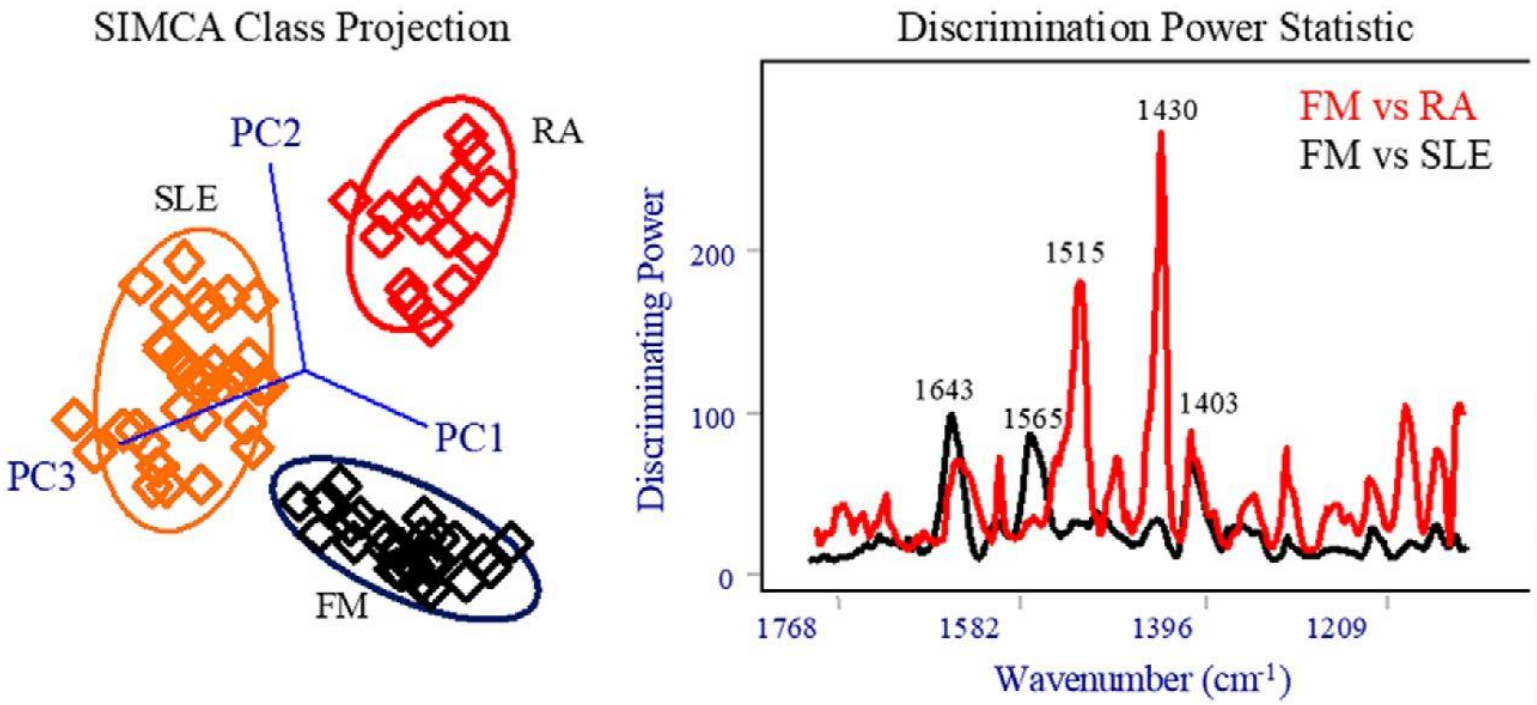
Metabolic fingerprinting for diagnosis of FM



Cluster Patterns: Soft-independent modeling of class analogy (SIMCA) model performance comparing predictions to true categories

Hackshaw KV et al. J Biol Chem2019 Feb 15;294:2555-2568.

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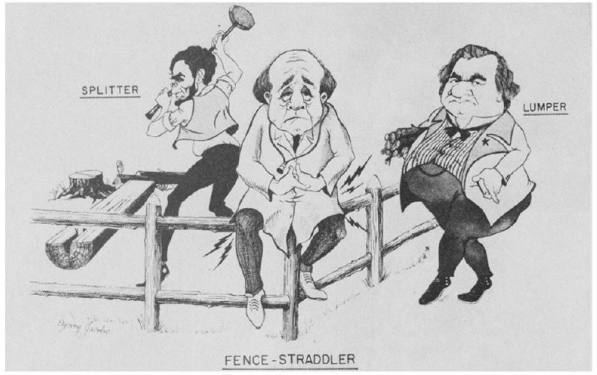
To Include or Not to Include Patients with multiple Comorbidities?



- Widespread pain
  - Allodynia, hyperalgesia
- Muscle, joint, visceral pains
- *Multi-sensory hypersensitivity*
- *Fatigue*
- *Affective lability, Δ mood*
- *Sleep disturbance*
- *Cognitive problems*

PRO (lumper)

- Common shared mechanism?
- A consequence of widespread pain?
  - Pain relief will result in improvement in other features

CON (splitter)

- May confound results and interpretation may be difficult

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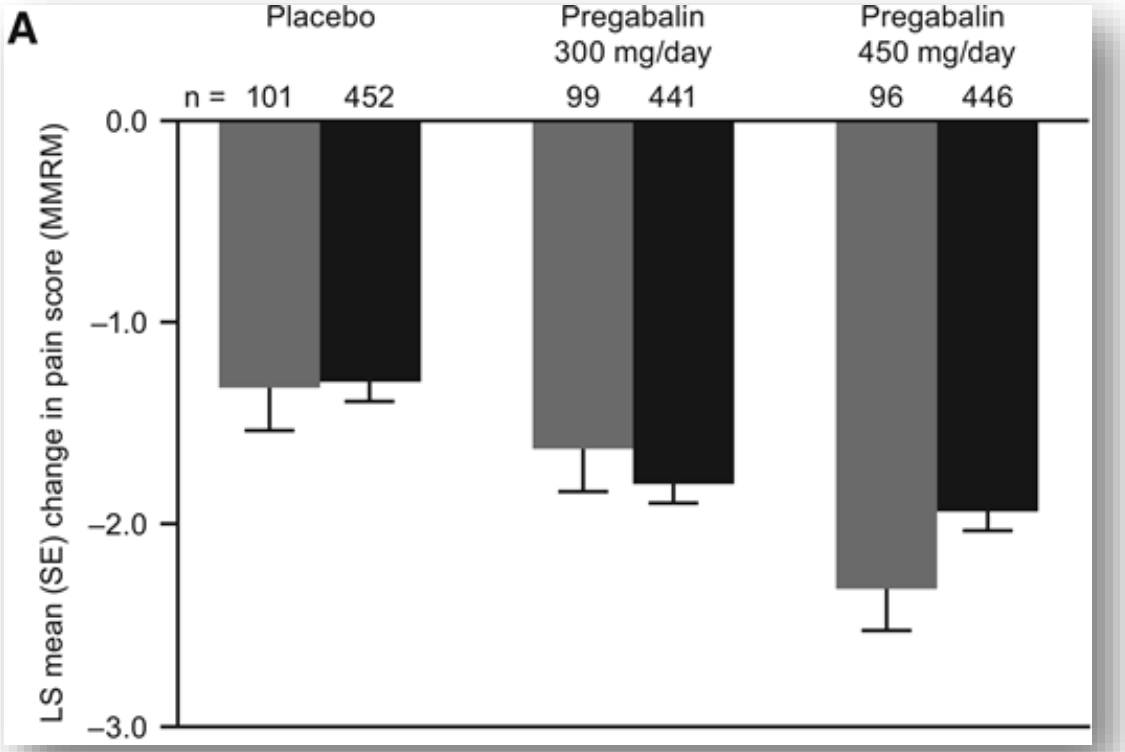
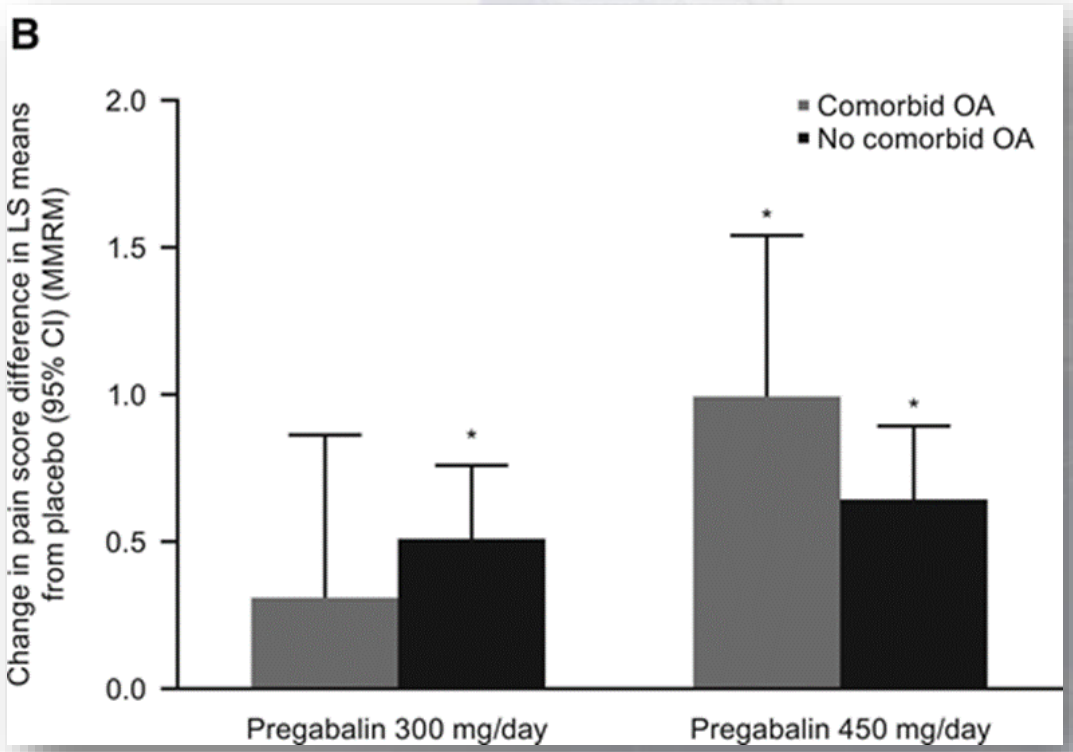
Does Comorbidity influence drug effects?
Pregabalin in FM patients with or without OA

- Pregabalin equally effective in FM patients with or without OA





Argoff CE Pain Med 2016; 17:2100

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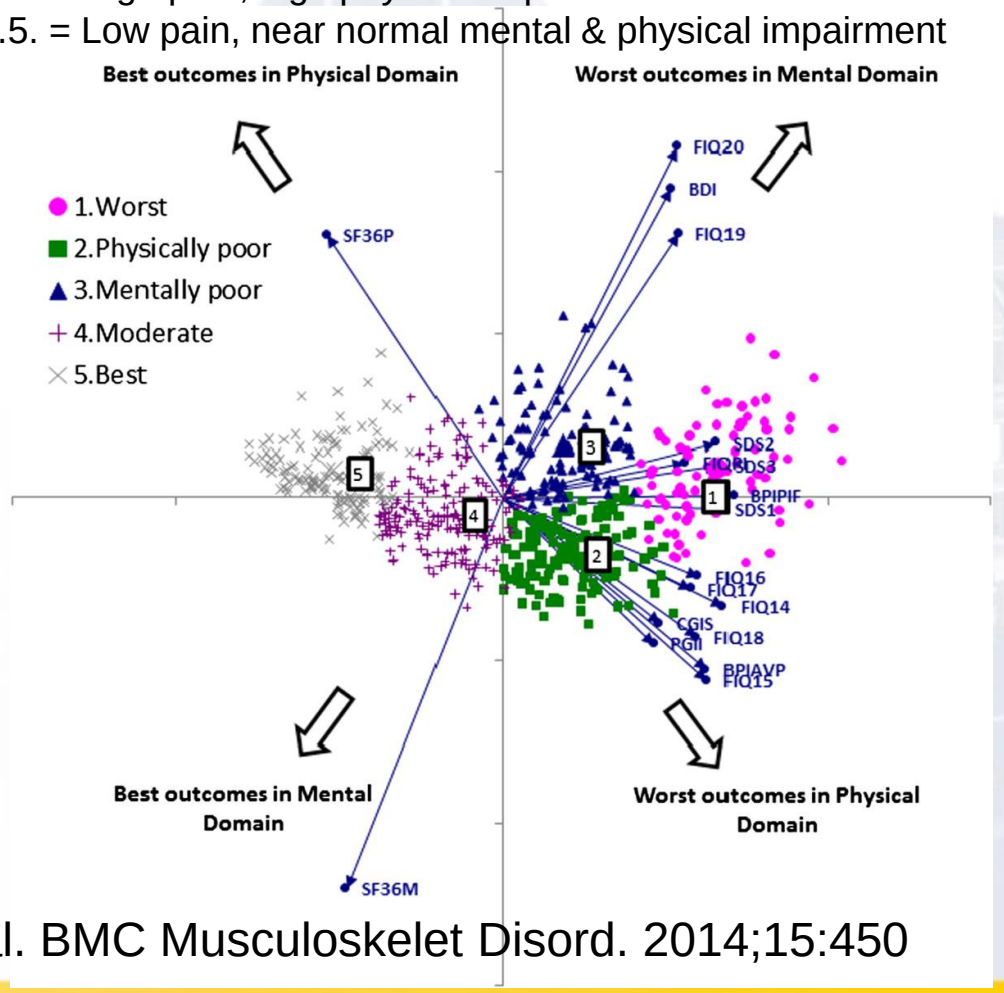
FM patients- a heterogeneous population

Subgroups- Cluster Analysis of Duloxetine study patients

- Pain, mental & physical impairment, global impression, overall functioning
- 1276 pts. (1188 F; 724 D: 464 Pl.)
- Mental impairment most detrimental comorbidity influencing outcome, compared to physical impairment
- Better treatment effect observed in physically impaired group

Cl.1. = High pain, severe mental & physical impairment
Cl.2. = High pain, high physical impairment
Cl.5. = Low pain, near normal mental & physical impairment

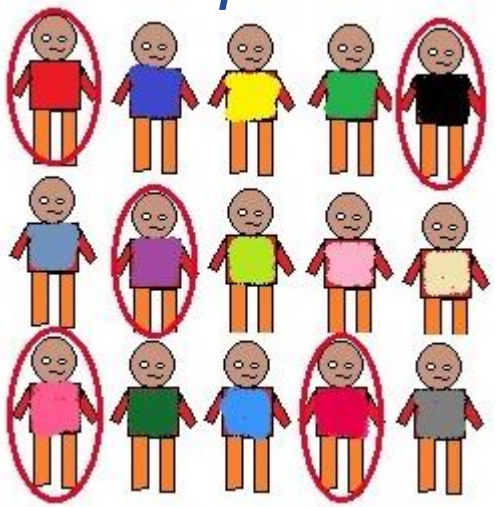


Lipkovich IA et al. BMC Musculoskelet Disord. 2014;15:450

Randomization Sampling Methods

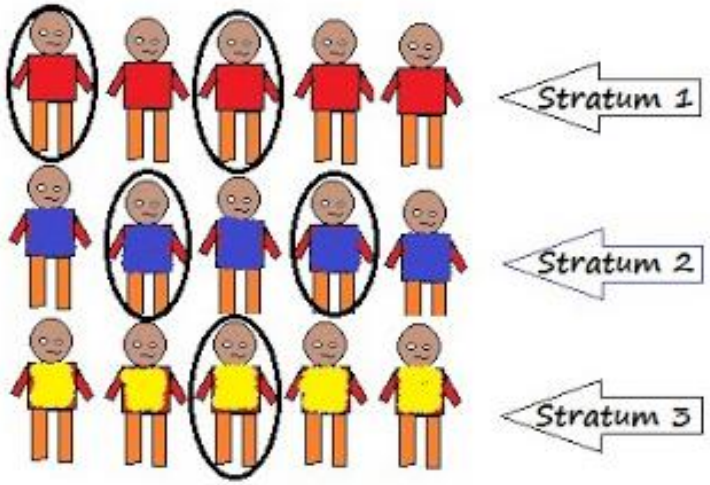
Reference population
↓
Study population
↓
Random allocation

Simple



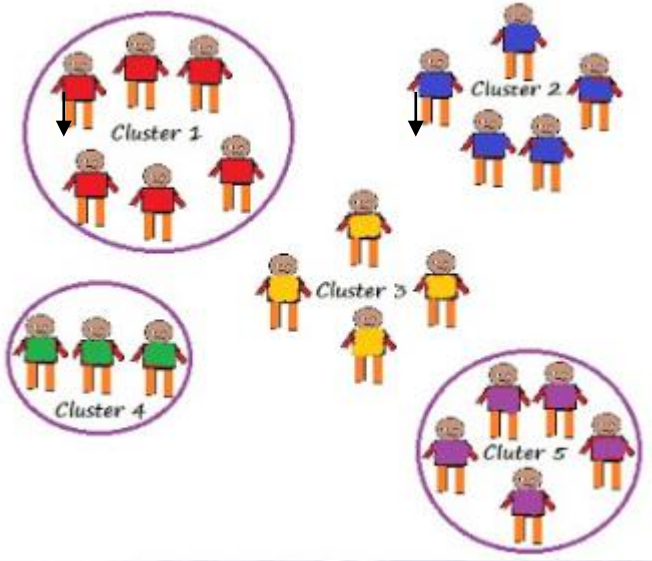
* Total sample size split into equal groups
* Each pt. randomly assigned to one of the groups

Stratified



* Population divided into subgroups
* Randomization and sampling occurs within each subgroup

Cluster



* Population divided into many subgroups
* Random choice of subgroups

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Proportionate Stratified Random Sampling

Pros

- Stratified random sampling accurately reflects/represents the population being studied
- Greater precision, requires a smaller sample, saves money
- Allows subgroup analysis

Cons

- Defining the strata is critical. Requires confidently classifying every member of the population into a subgroup
- More complex to organize and analyze the results compared to simple random sampling

What are the relevant Strata?

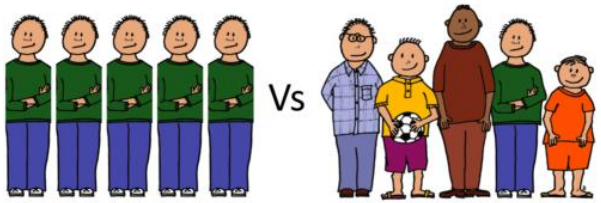
- Single Primary vs Multiple Pain conditions
- “Centralized Pain” vs peripheral + central CS
- Comorbidities: Severity of Physical vs Mental/Psychological features
- Appropriately powered to determine differences across strata

What is the primary clinical question?
Testing a new drug for CSS

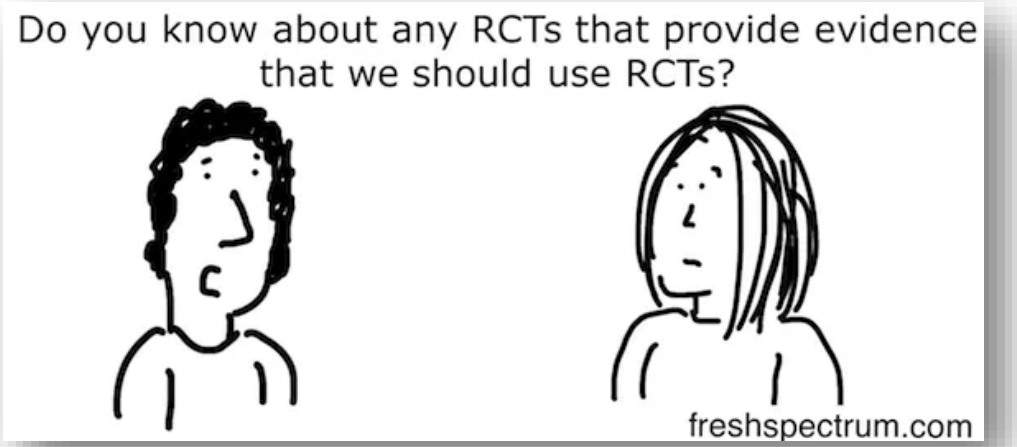
- Q1. Is drug A effective in patients with CSS, regardless of the primary pain presentation?
- Q2. Does drug B help understand the neurobiology of CSS (CS mechanism different from NP)?
- A. Enroll all patients with CSS (regardless of primary pain) and study the efficacy of drug at multiple pain sites
- B. Enroll all patients with central sensitization pain, but stratify based on solitary vs multiple pains and compare with patients with NP

RCTs and clinical decision making!

Efficacy vs Effectiveness in the population



- "Carefully conducted observations studies may provide more evidence than poor RCTs." 1 (Guyatt, G. 2008)
  - Multi-center data from large Registries ?
- "Unfortunately, a perfect trial can only exist in our imagination." 2 (Jadad A. 2007)



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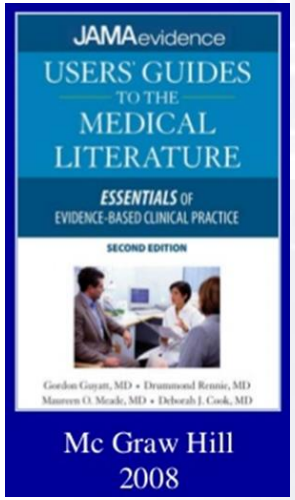

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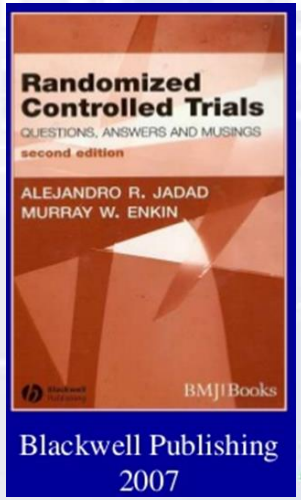

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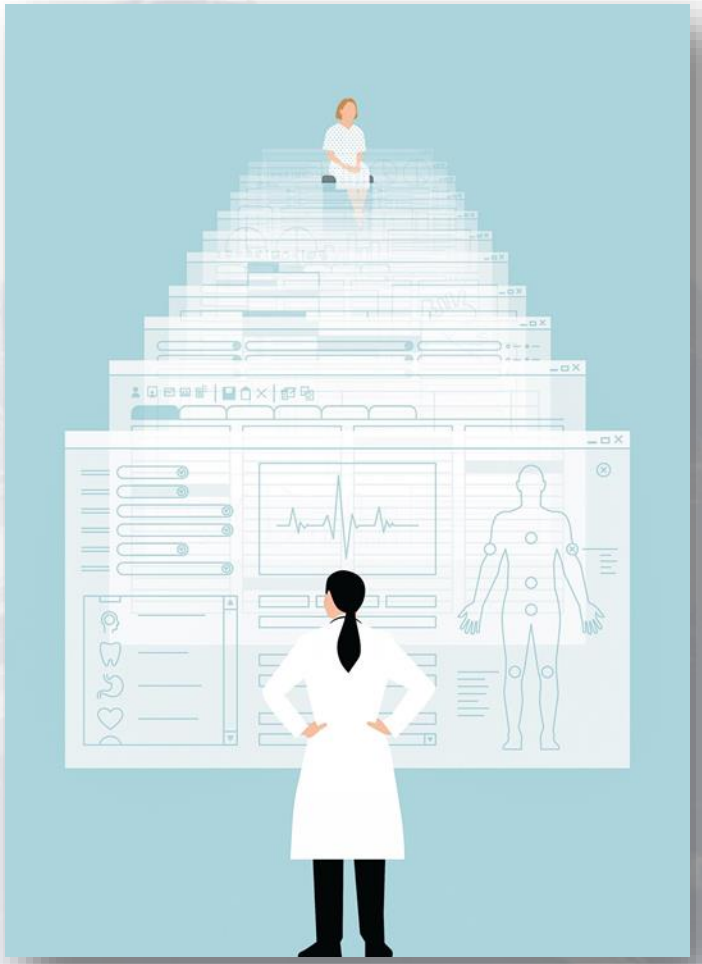
Outcome Measures

- IMMPACT-II Core Outcome Measures
  - Pain; Physical functioning; Emotional functioning; PGIC; Symptoms and adverse events; Participant disposition
- Fibromyalgia Impact Questionnaire revised (FIQR):
- Symptom Clusters
- QST measures: TS, CPM
- Imaging
- Other Biomarkers ?



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Revised Fibromyalgia Impact Questionnaire (FIQR): Validation and Psychometric properties

- 21 items across the 3 domains of Function (n = 9), Overall Impact (n = 2), and Symptoms (n = 10)
- Pt completion time:1.3 min; Scoring time: 1 min
- FIQ total score from 0 to <39 was found to represent a mild effect, >or= 39 to <59 a moderate effect, and >or=59 to 100 a severe effect
- Minimal clinically important differences in the FIQ total score was 14%

Bennett RM et al. Arthritis Res Ther.2009;11:R120

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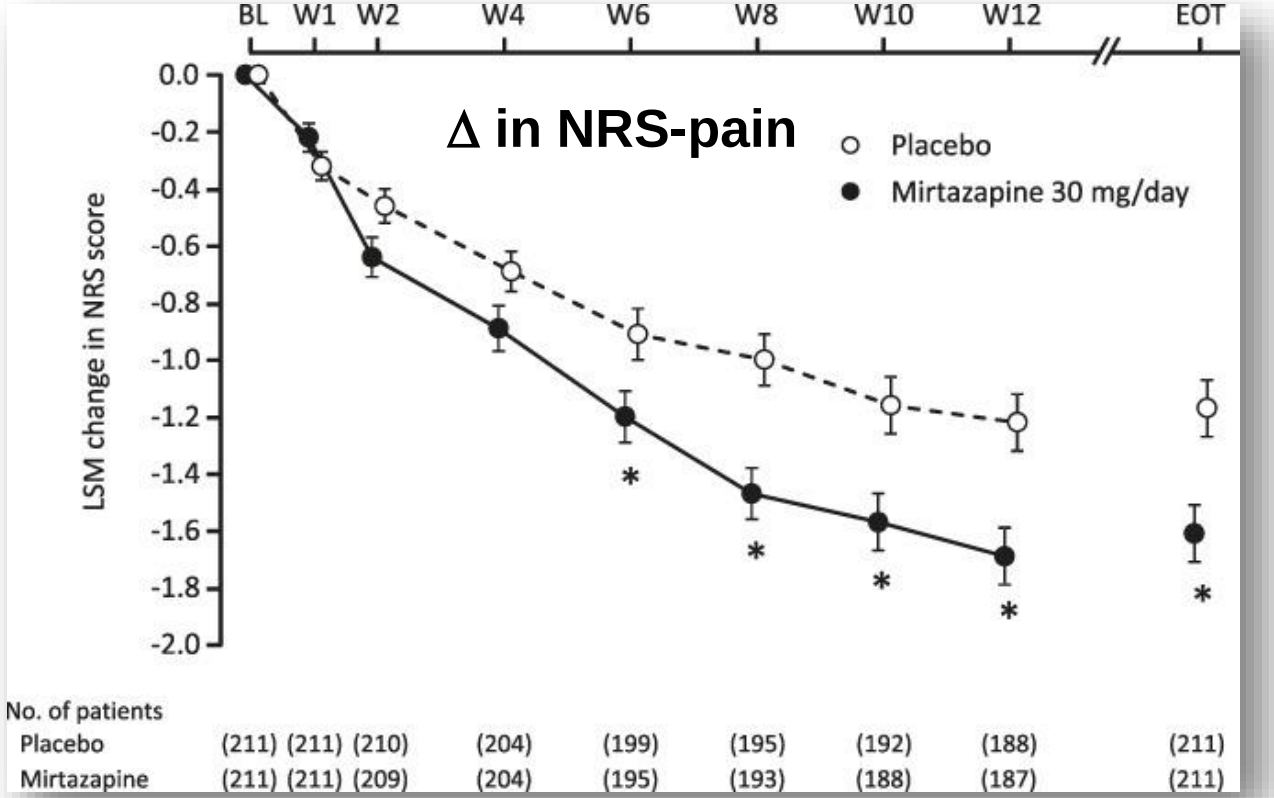
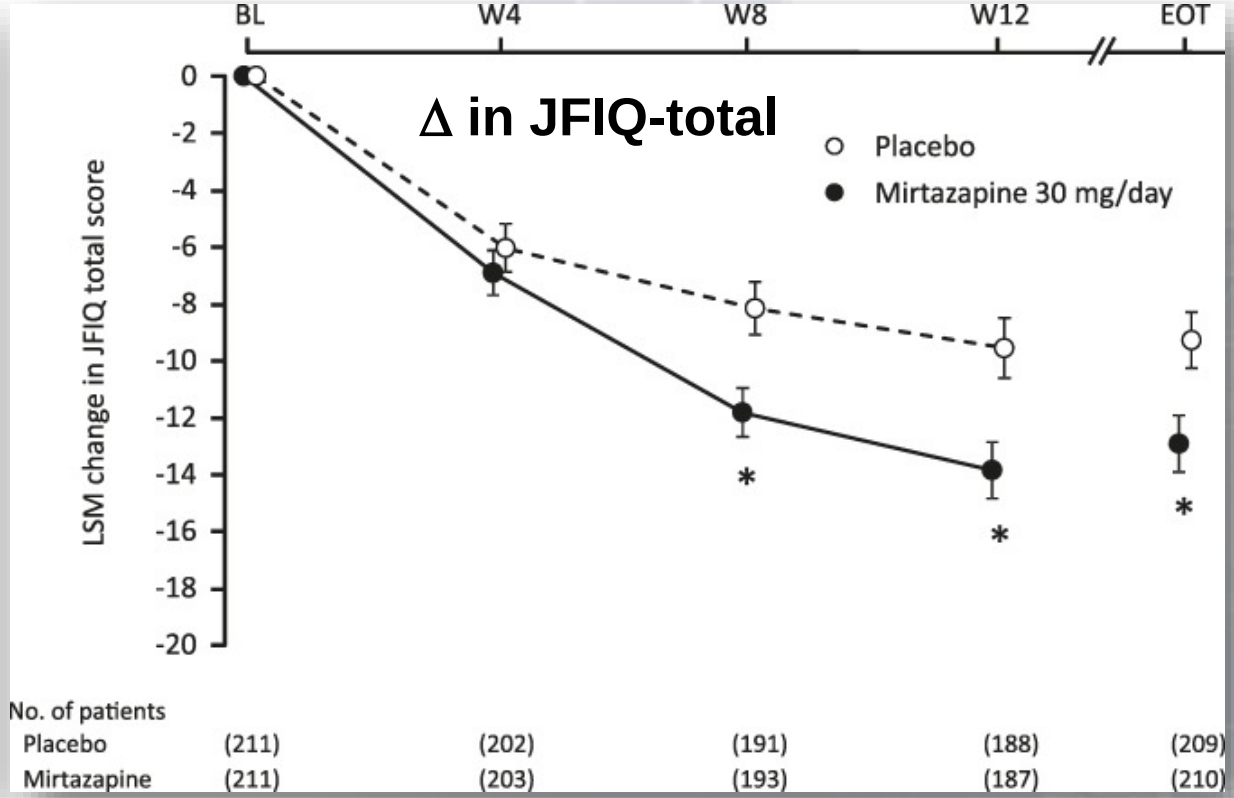
Mirtazapine on FM in Japanese subjects:
Pain and FIQ changes (Japanese version)





Miki K et al. Pain. 2016; 157:2089–2096.

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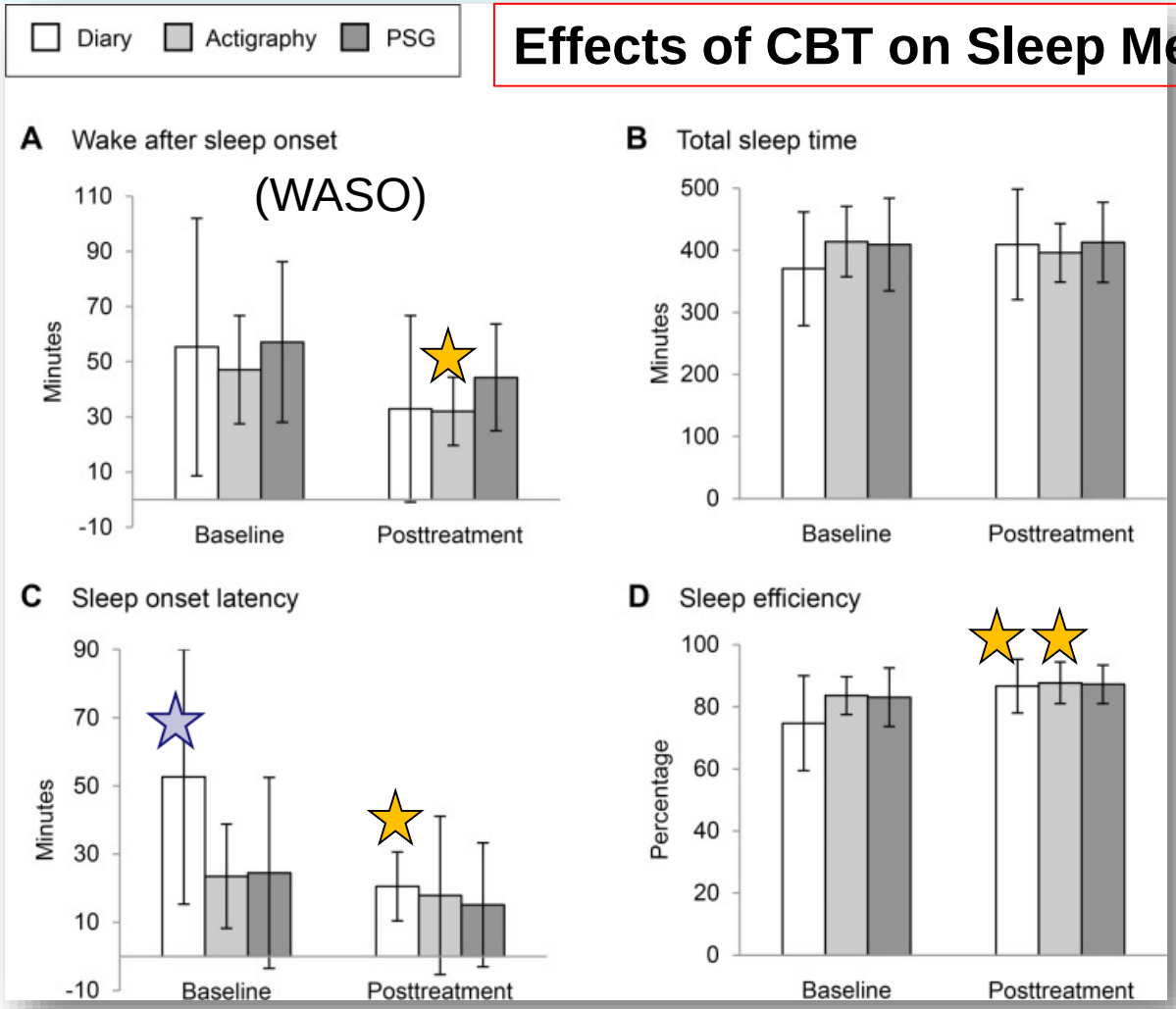
Symptom Clusters
Are these features unique to CSS?

- SPADE: Sleep disturbance, Pain, Anxiety, Depression, low Energy/fatigue (Davis 2016- musculoskeletal pain)
- PSF: Oncology patients (Dodd 2001)
- SPACE: Sleep disturbance, Pain, Affective perturbation, Cognitive disturbance, Energy deficit
- Worth considering, but need additional validation

Davis LL et al. Clin J Pain 2016;32:388
Williams DA J Appl Behav Res 2018;23:e12135

Measuring Sleep in FM: Diaries vs Objective measures (Actigraphy, Polysomnography (PSG))



Effects of CBT on Sleep Measures in FM

- Actigraphy was generally more concordant with PSG than with diaries
- Actigraphy showed greater sensitivity to treatment-related changes than PSG
- Actigraphy demonstrated changes in WASO and SE, which were also found with diaries.
- Sleep diaries captured the greatest improvements in all parameters

Mundt JM et al.J Clin Sleep Med. 2016;12:215

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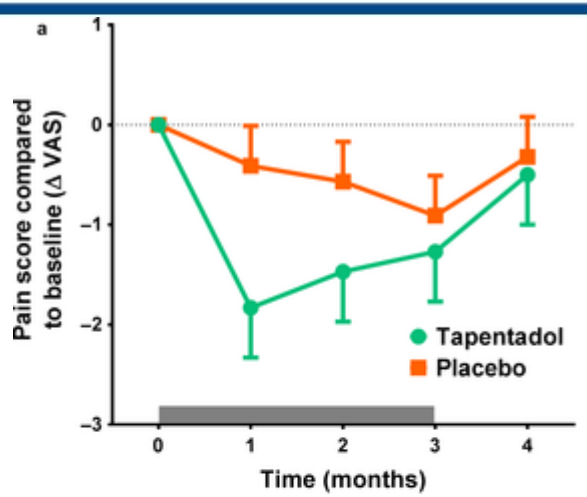
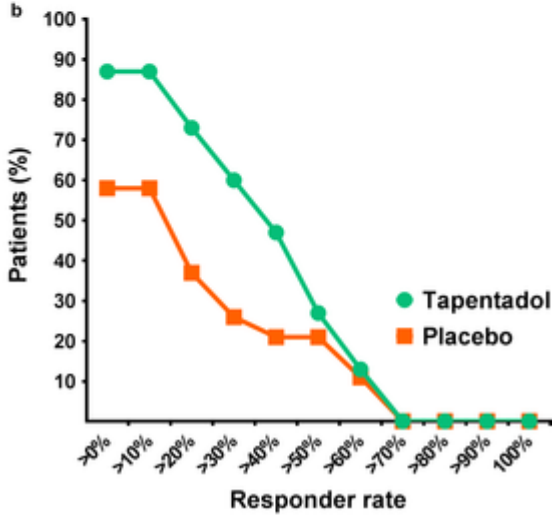
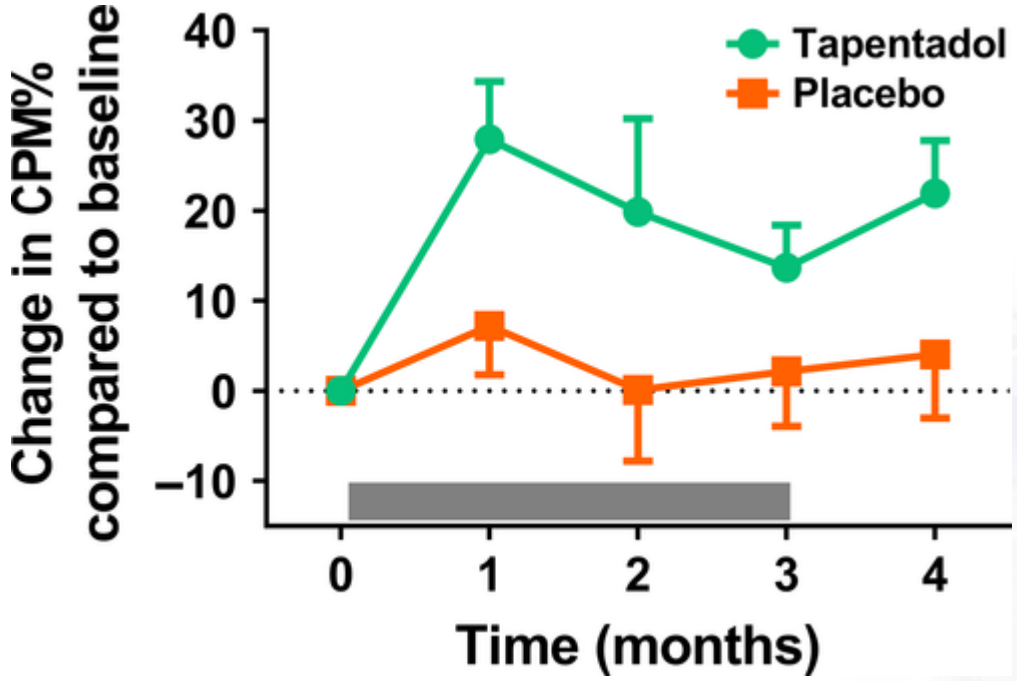
Effects of Tapentadol on CPM in FM

Tapentadol increased CPM efficacy







Tapentadol in contrast to placebo significantly increased the efficacy of the descending inhibitory pain pathway (CPM)

Cornea confocal microscopy

Quantification of Cornea:

Nerve fibre length (CNFL)

Nerve fibre density(CNFD)

Nerve branching density (CNBD)

2/3 parameters abnormal = Abnormal fiber state

Van de Donk T et al. Eur J Pain. 2019 Jun 4. Epub, in press

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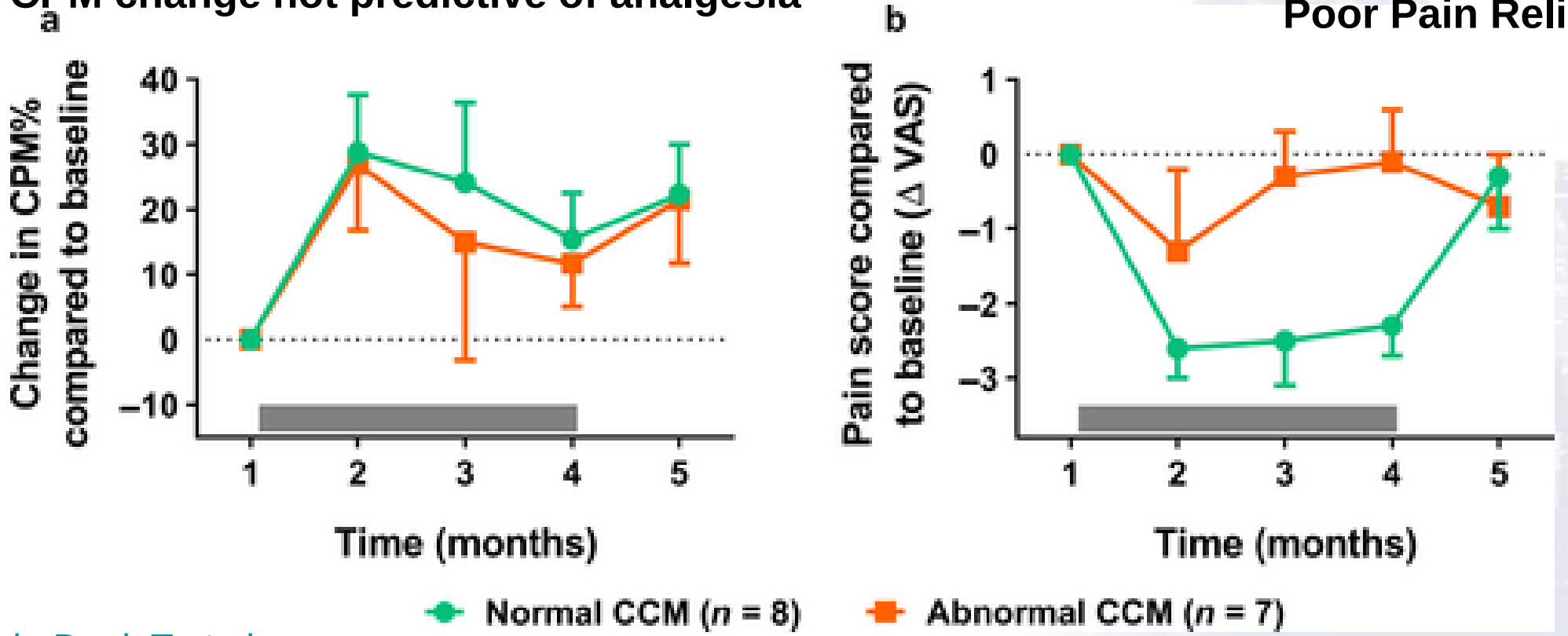
Effects of Tapentadol in FM:

Corneal confocal microscopy state predicts drug response

Drug enhances CPM in all patients
CPM change not predicted of analgesia

Abnormal Cornea fiber state =
Poor Pain Relief



Van de Donk T et al.
Eur J Pain. 2019 Epub, in press

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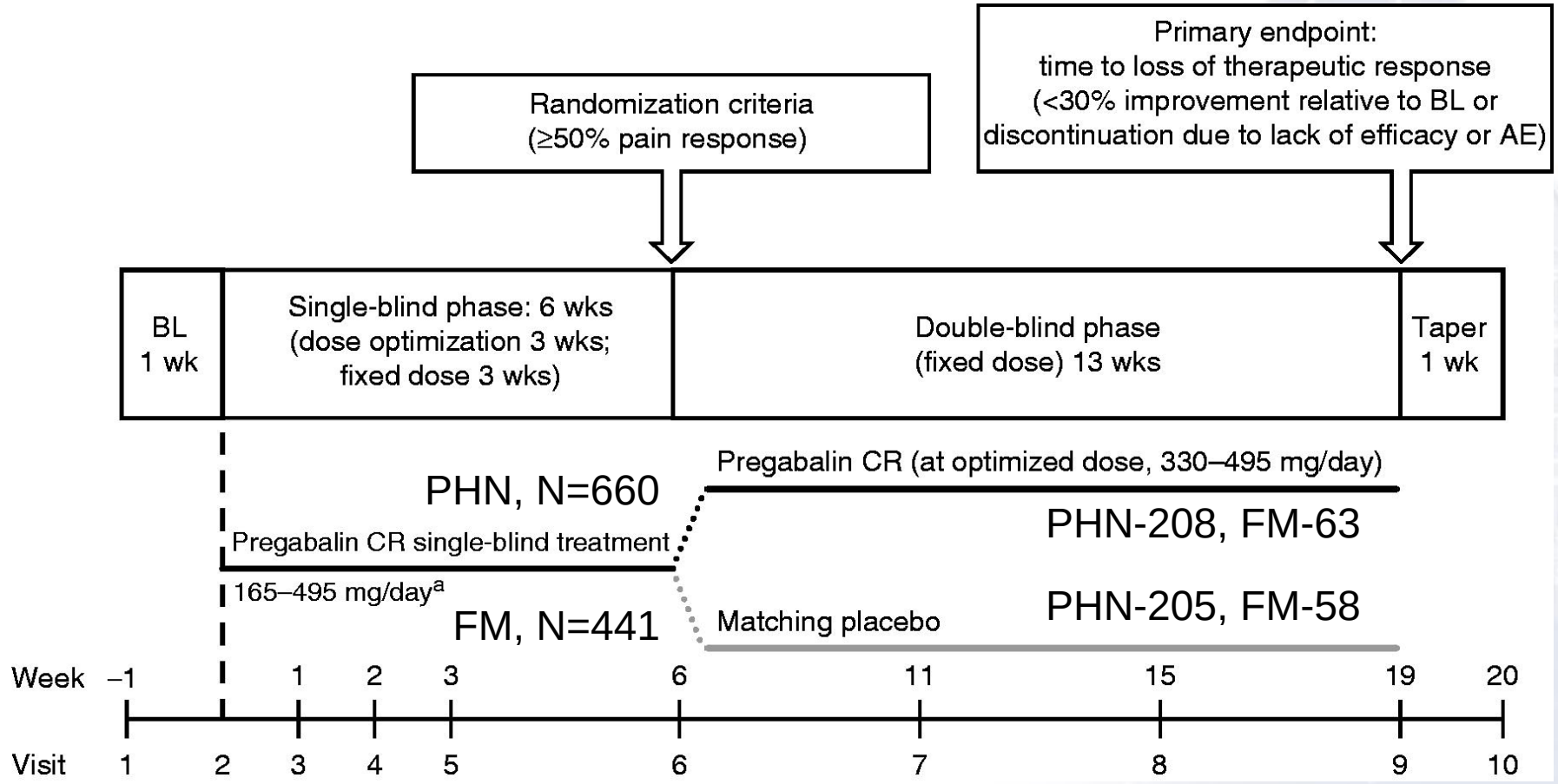
Phase III study of controlled release pregabalin for PHN and FM- Randomized withdrawal RCT



Huffman CL.. Cl J Pain 2017;33:569; Arnold LM et al. Curr Med Res Opin. 2014;30:2069

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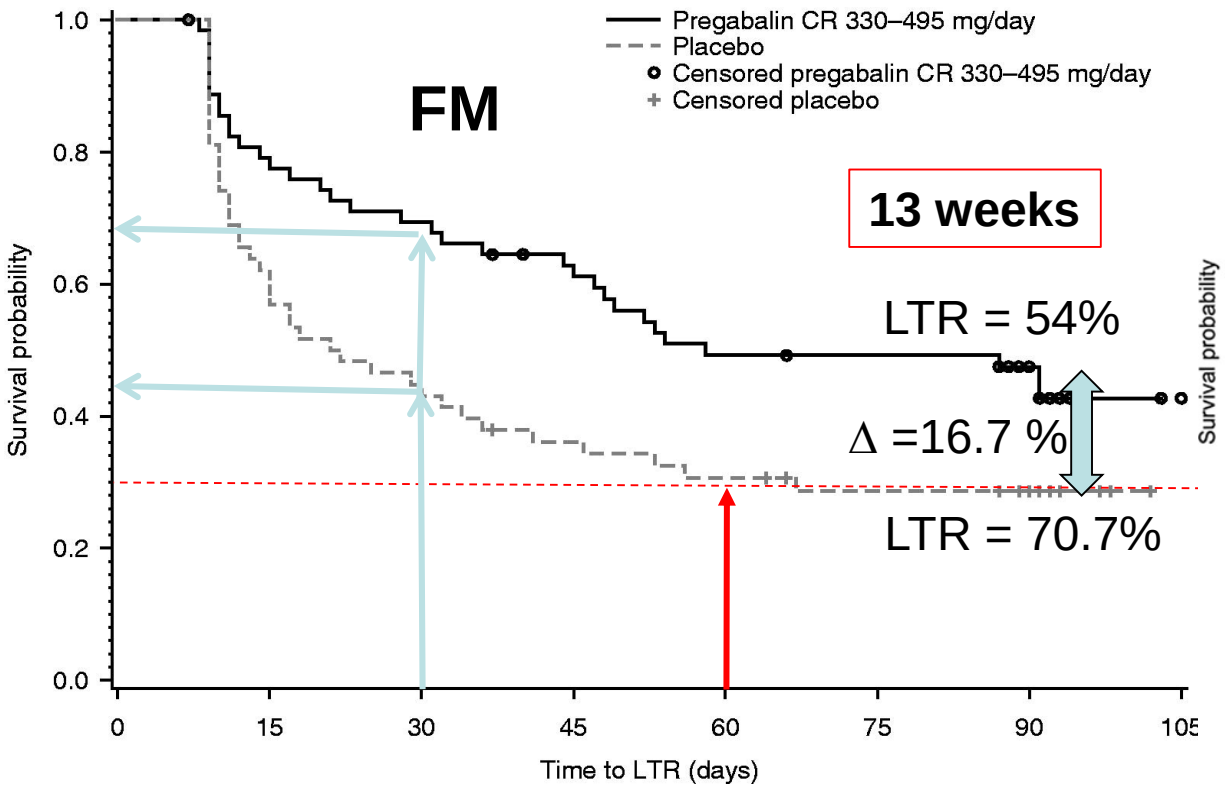
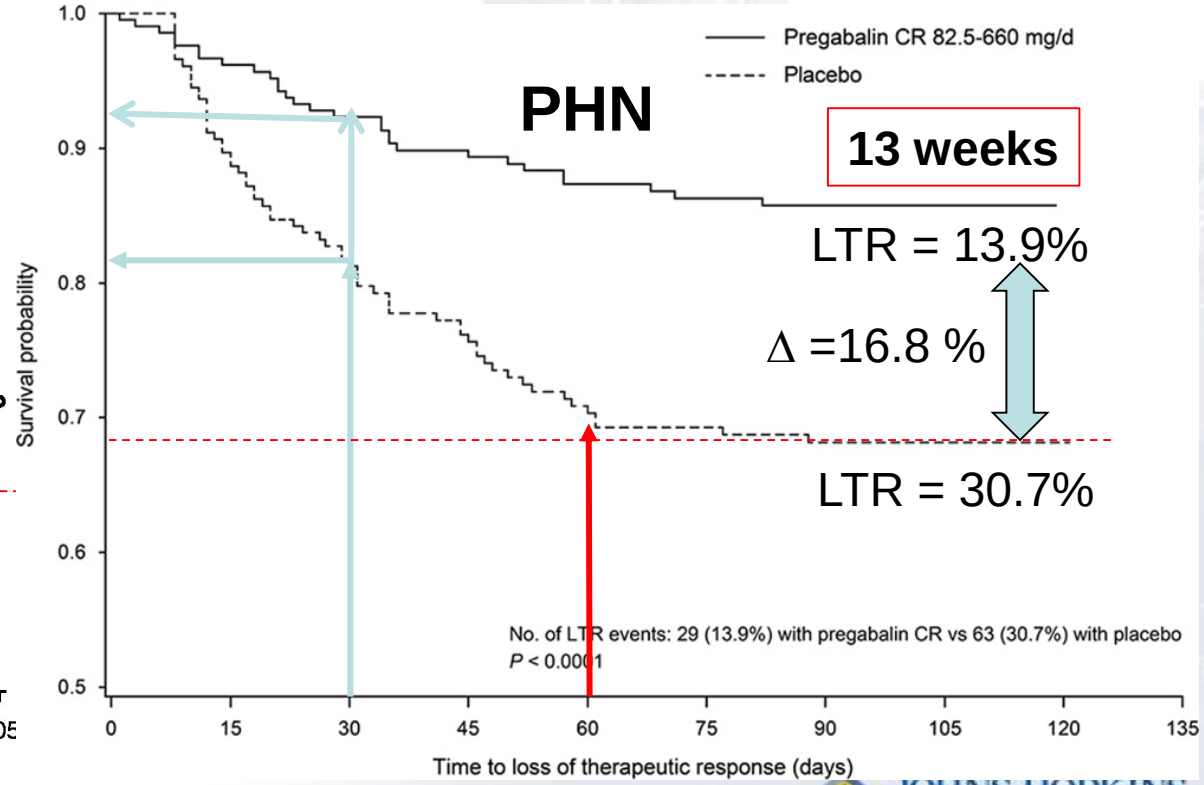
CR-Pregabalin for PHN and FM
D-B, randomized withdrawal, placebo-controlled

Median time to Loss of Therapeutic Response (LTR)- Kaplan–Meier analysis)

LTR= <30% pain reduction relative to single-blind baseline or discontinuation owing to lack of efficacy or adverse event (AE)





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SUMMARY:
Study Design Considerations in CSS

- Consensus on name and diagnostic criteria
- *Defining the Study population:* Self-assessment tools, CSI &SHI Objective measures of CS; Spectroscopic fingerprints ?
- Lum*ping vs Splitting*: What is the study question of interest? Neurobiology vs treatment efficacy in a heterogeneous population- Efficacy vs Effectiveness
- *Study Design & Stratification* for better understanding of shared mechanism and drug effectiveness across CS, COPS
- *Outcome measures*: Additional to IMMPACT-II; FIQR, Challenges and confounding effects of comorbidity

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