Diagnosing and Treating Pain Based on the Underlying Mechanism

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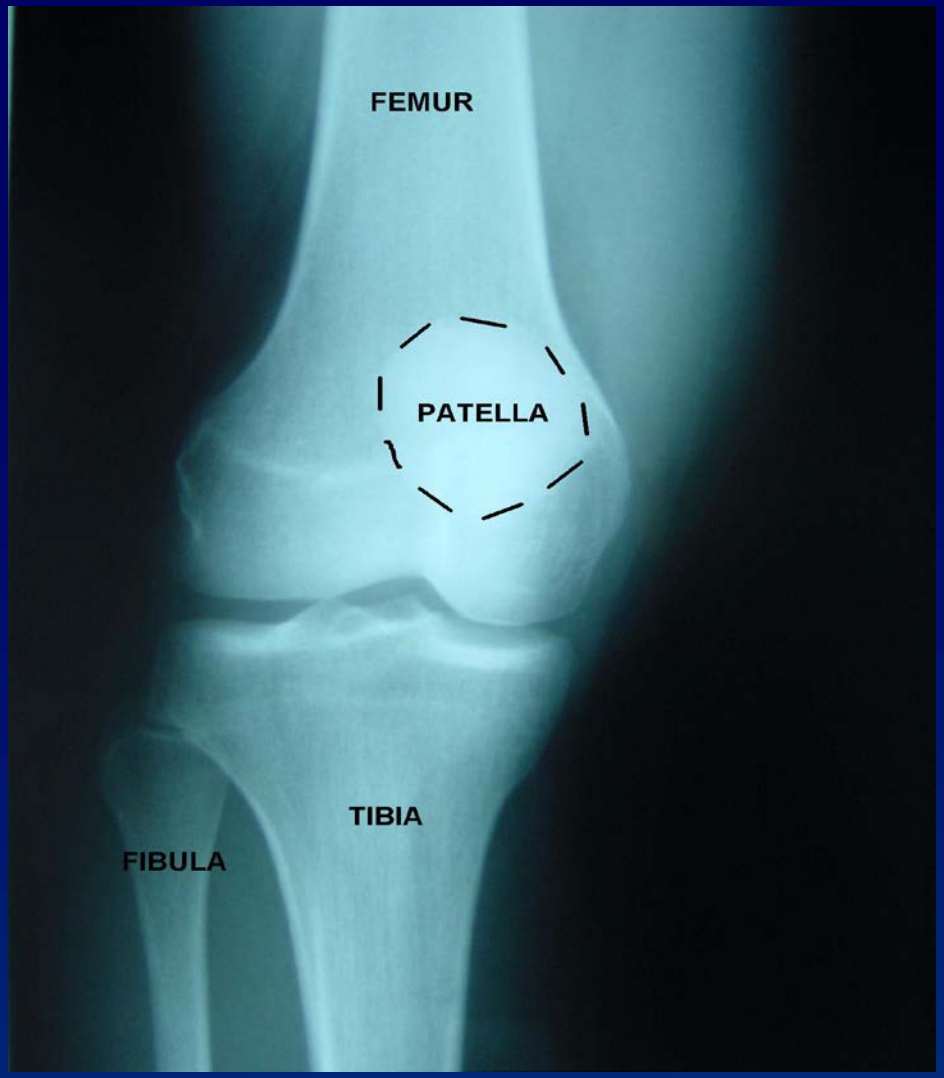
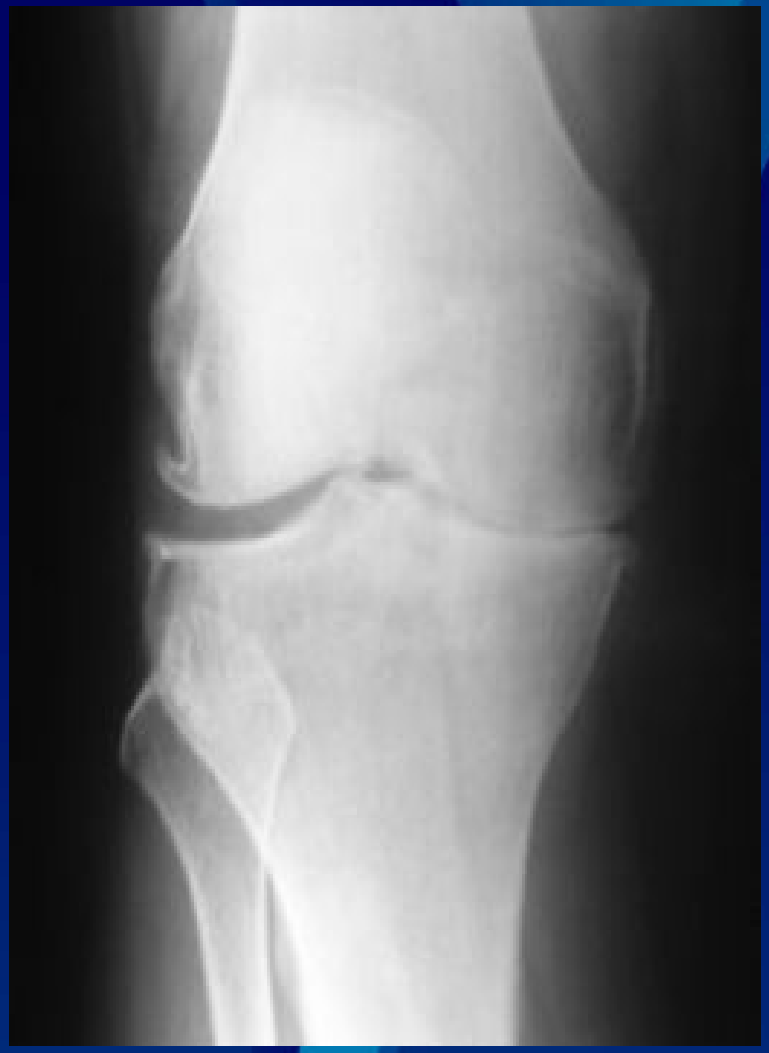
Do you ever look at stuff and wonder how it got there?

Disclosures

- Consulting
  - Pfizer, Pierre Fabre, Abbott, Cerephex, Tonix, Theravance, Zynerba, Samumed, Aptinyx, Daiichi Sankyo
- Research support
  - Pfizer, Cerephex, Aptinyx

Which person has pain?





Osteoarthritis of the knee - I

- Classic “peripheral” pain syndrome
- Poor relationship between structural abnormalities and symptoms[1]. In population-based studies:
  - 30 – 40% of individuals who have grade 3/4 K/L radiographic OA have no symptoms
  - 10% of individuals with severe pain have normal radiographs
- Psychological factors explain very little of the variance between symptoms and structure[2]
- We sometimes delude ourselves into thinking that our current therapies are adequate
  - NSAIDs, acetaminophen, and even opioids have small effect sizes[3,4]
  - Arthroplasty does not predictably relieve pain

(1) Creamer P, et. al. Br J Rheumatol 1997; 36(7):726-8. (2) Creamer P, et. al. Arthritis Care Res 1998; 11(1):60-5. (3) Bjordal JM, et. al. Eur J Pain 2007; 11(2):125-38. (4) Zhang W, et. al. Ann Rheum Dis 2004; 63(8):901-7.

Evolution of Thinking Regarding Fibromyalgia

American College of Rheumatology (ACR) Criteria

- Discrete illness
- Focal areas of tenderness
- Pathophysiology poorly understood and thought to be psychological in nature

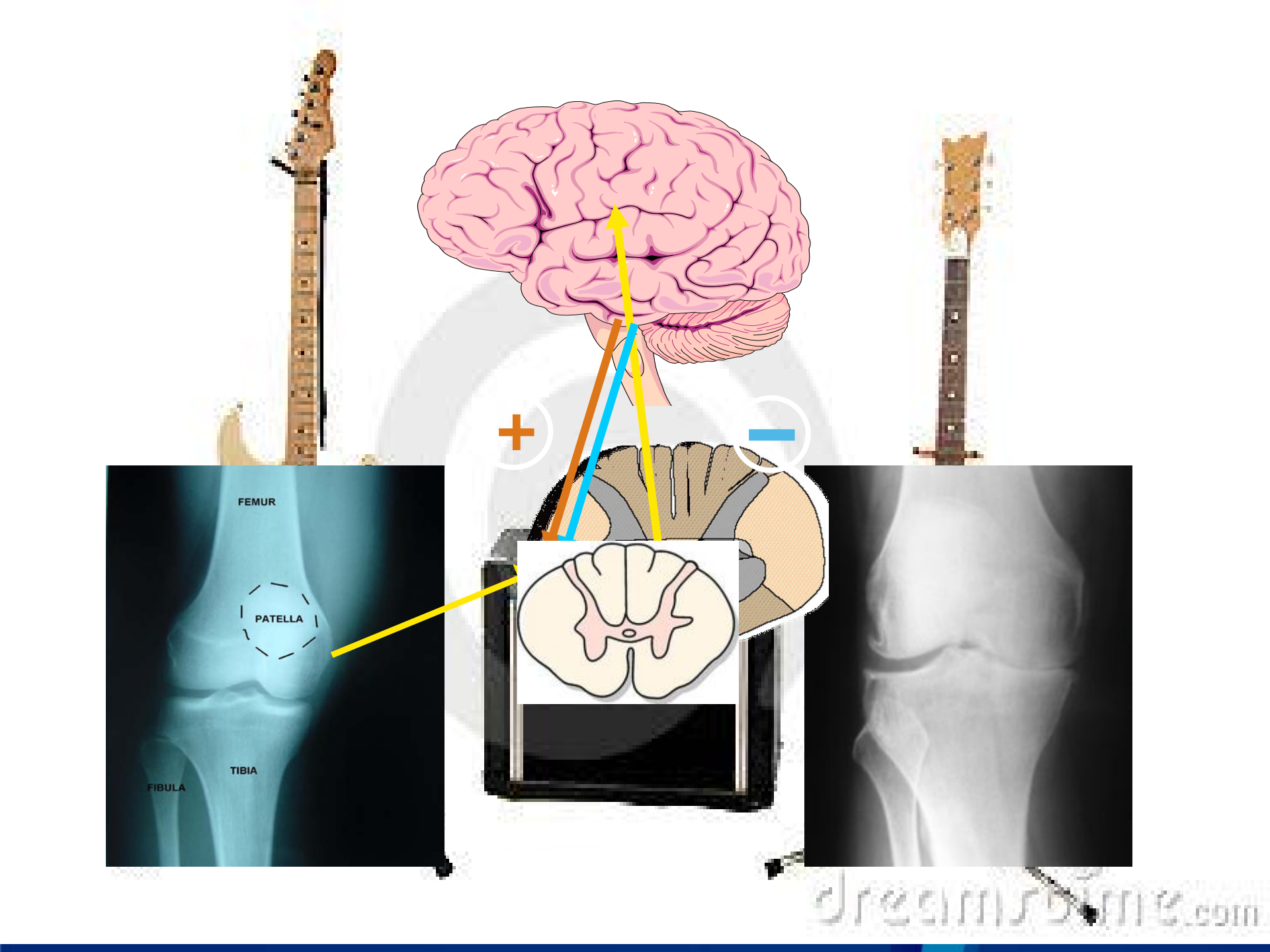
- Chronic widespread pain
- Tenderness in ≥11 of 18 tender points

- Final common pathway (i.e. pain centralization)
- Part of a much larger continuum
- Not just pain
- Pathophysiology fairly well understood and is a CNS process that is independent from classic psychological factors

Mechanistic Characterization of Pain

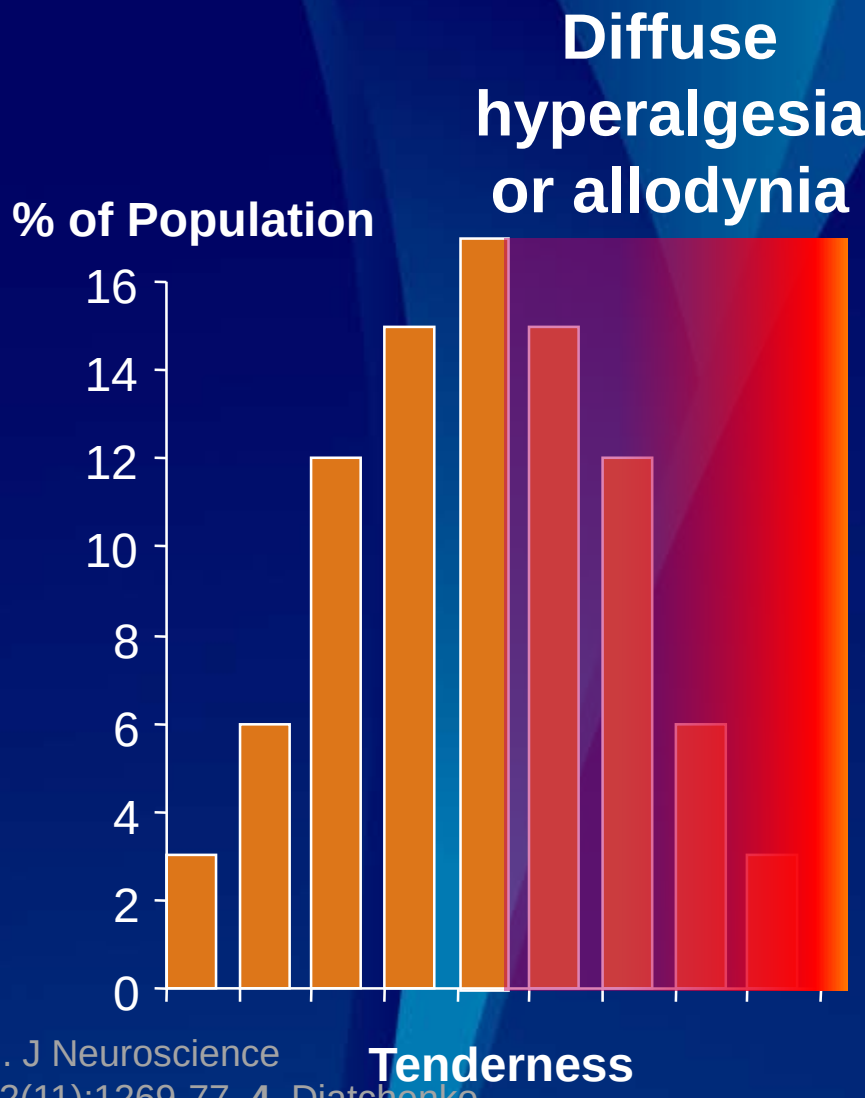
Variable degrees of any mechanism can contribute in any disease

	Nociceptive	Neuropathic	Centralized
Cause	Inflammation or damage	Nerve damage or entrapment	CNS or systemic problem
Clinical features	Pain is well localized, consistent effect of activity on pain	Follows distribution of peripheral nerves (i.e. dermatome or stocking/glove), episodic, lancinating, numbness, tingling	Pain is widespread and accompanied by fatigue, sleep, memory and/or mood difficulties as well as history of previous pain elsewhere in body
Screening tools		PainDETECT	Body map or FM Survey
Treatment	NSAIDs, injections, surgery, ? opioids	Local treatments aimed at nerve (surgery, injections, topical) or CNS-acting drugs	CNS-acting drugs, non-pharmacological therapies
Classic examples	Osteoarthritis Autoimmune disorders Cancer pain	Diabetic painful neuropathy Post-herpetic neuralgia Sciatica, carpal tunnel syndrome	Fibromyalgia Functional GI disorders Temporomandibular disorder Tension headache Interstitial cystitis, bladder pain


FEMUR
PATELLA
TIBIA
FIBULA
+
−

Pain and sensory sensitivity in the population

- Like most other physiological processes, we have a “volume control” setting for how our brain and spinal cord processes pain[1]
- This is likely *set* by the genes that we are born with[2-4], and *modified* by neurohormonal factors and neural plasticity
- The higher the volume control setting, the more pain we will experience, irrespective of peripheral nociceptive input



1. Mogil JS. PNAS, 1999;96(14):7744-51. **2.** Amaya et. al. J Neuroscience 2006;26(50):12852-60. **3.** Tegeder et.al., NatMed. 2006;12(11):1269-77. **4.** Diatchenko et. al. HumMolGenet. 2005;14(1):135-43.

Fibromyalgia-ness

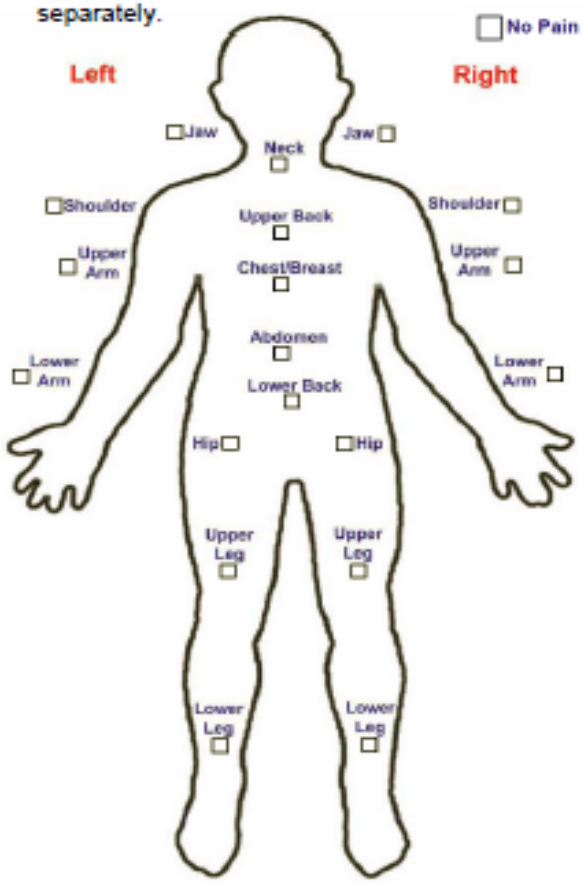
- Term coined by Wolfe to indicate that the symptoms of FM occur as a continuum in the population rather than being present or absent [1]
- In rheumatic disorders such as osteoarthritis, rheumatoid arthritis, lupus, low back pain, etc. this score is more predictive of pain levels and disability than more objective measures of disease [2,3]
- Domain overlaps with somatization in many regards, and there are many questionnaires that collect somatic symptom counts as a surrogate for this construct

1.Wolfe et. al. *Arthritis Rheum.* Jun 15 2009;61(6):715-716. 2. Wolfe et. al. *2.J Rheumatol.* Feb 1 2011. 3. Clauw DJ. JAMA, 2014.

Concept of “Fibromyalgia-ness”

Fibromyalgia Symptoms (Modified ACR 2010 Fibromyalgia Diagnostic Criteria)

1. Please indicate below if you have had pain or tenderness over the past 7 days in each of the areas listed below. Check the boxes in the diagram below for each area in which you have had pain or tenderness. Be sure to mark right and left sides separately.



2. Using the following scale, indicate for each item your severity over the past week by checking the appropriate box.

No problem
Slight or mild problems: generally mild or intermittent
Moderate: considerable problems; often present and/or at a moderate level
Severe: continuous, life-disturbing problems

	No problem	Slight or mild	Moderate	Severe
a. Fatigue	☐	☐	☐	☐
b. Trouble thinking or remembering	☐	☐	☐	☐
c. Waking up tired (unrefreshed)	☐	☐	☐	☐

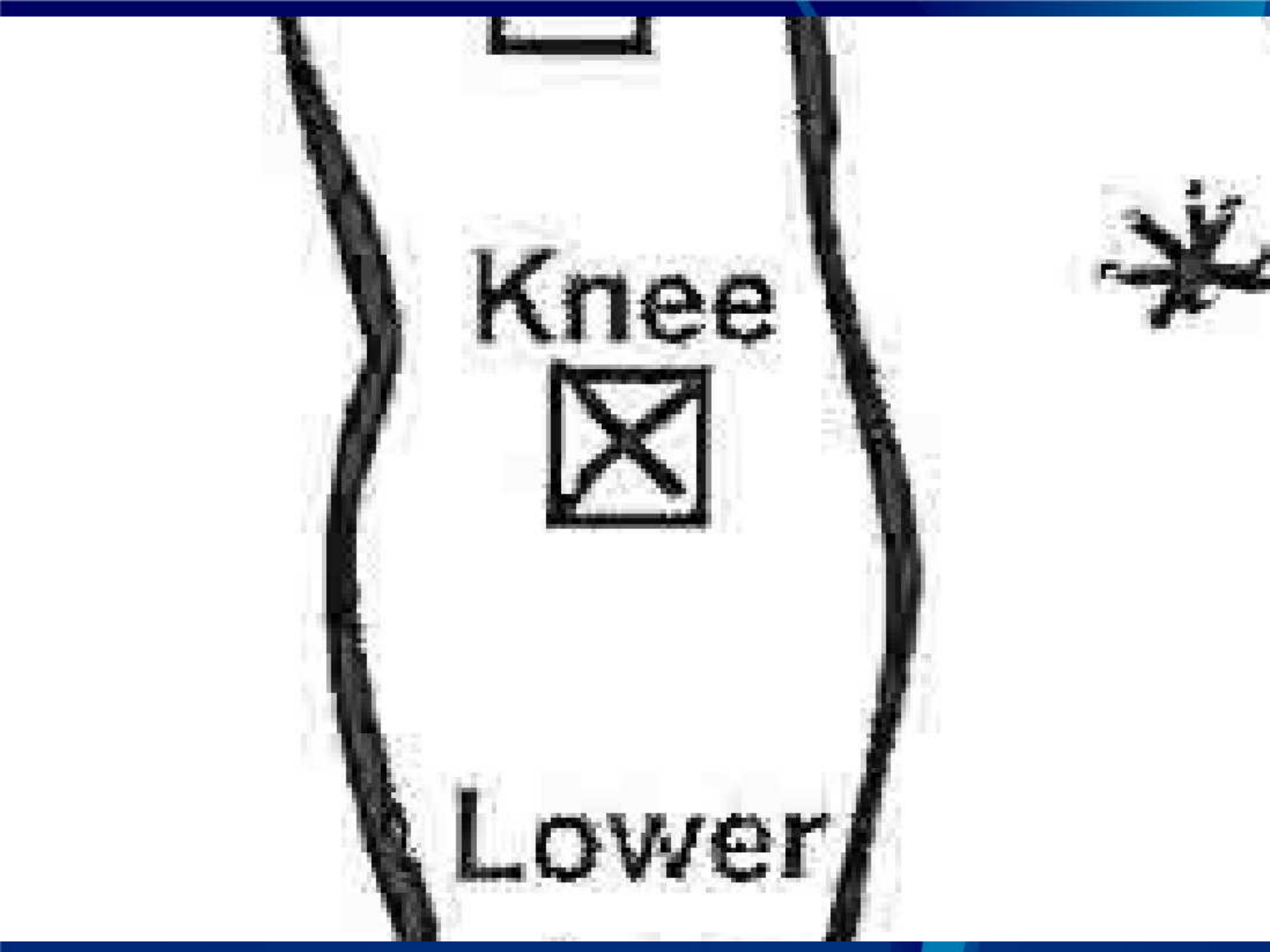
3. During the past 6 months have you had any of the following symptoms?

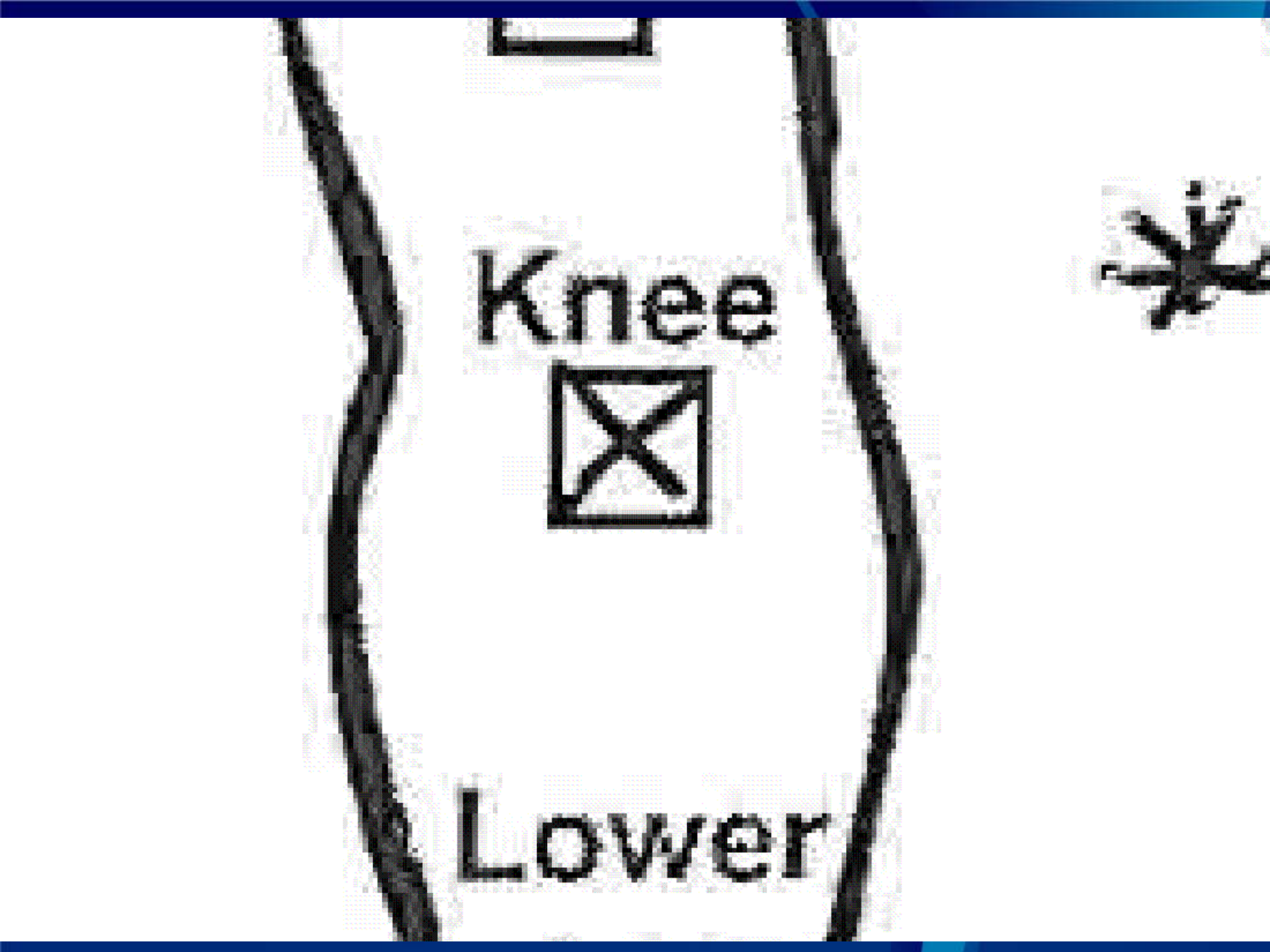
	No	Yes
a. Pain or cramps in lower abdomen	☐	☐
b. Depression	☐	☐
c. Headache	☐	☐

4. Have the symptoms in questions 2-3 and pain been present at a similar level for at least 3 months? **No** ☐ **Yes** ☐

5. Do you have a disorder that would otherwise explain the pain? **No** ☐ **Yes** ☐

1. Wolfe et. al. *Arthritis Rheum.* Jun 15 2009;61(6):715-716. 2. Wolfe et. al.
2. *J Rheumatol.* Feb 1 2011. 3. Clauw DJ. JAMA, 2014.

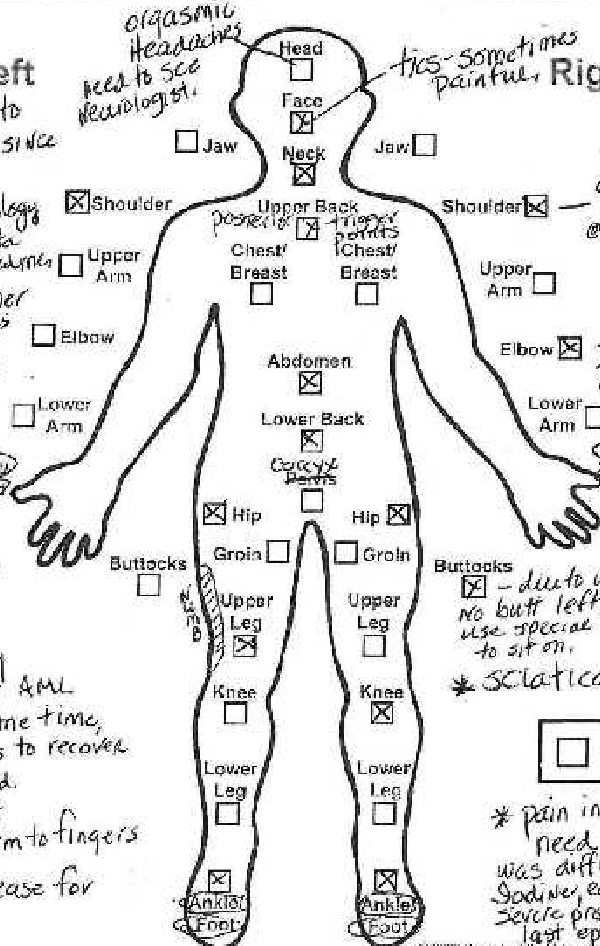

Knee
Lower


Knee
Lower

UNIVERSITY OF MICHIGAN HOSPITALS & HEALTH CENTERS Anesthesiology **New Patient Questionnaire - Back and Pain Center**	NAME REG NO. BIRTHDATE

Michigan Body Map

On the image below, identify **all** the areas of your body where you have felt ***persistent or recurrent pain*** present for the last ***3 months or longer***.



orgasmic Headaches need to see Neurologist.

tics - sometimes painful.

I'm turning into a recliner chair since Dec. 4th

limited Rheumatology in GA, 3 in Atlanta area - Primary helped me

Arthritis ? in other places now

LT carpal tunnel release went bad in GA on ~ 4-26-11. Worse since.

Nerve damage continues with s/s that mimic MS, carpal tunnel ? spasms, twitching etc. very painful.

posterior - trigger points

Coccyx

NUMB

GA plan of tx changed per Dr. Dobson informed @ 1st visit to be done. No PE performed.

- due to using cane from Δ in plan of tx from GA.

surgery for carpal tunnel postponed due to move back home to MI

arthritis or just sore filling out dozens of forms for 3 people.

- due to wt loss No butt left, use special cushion to sit on.

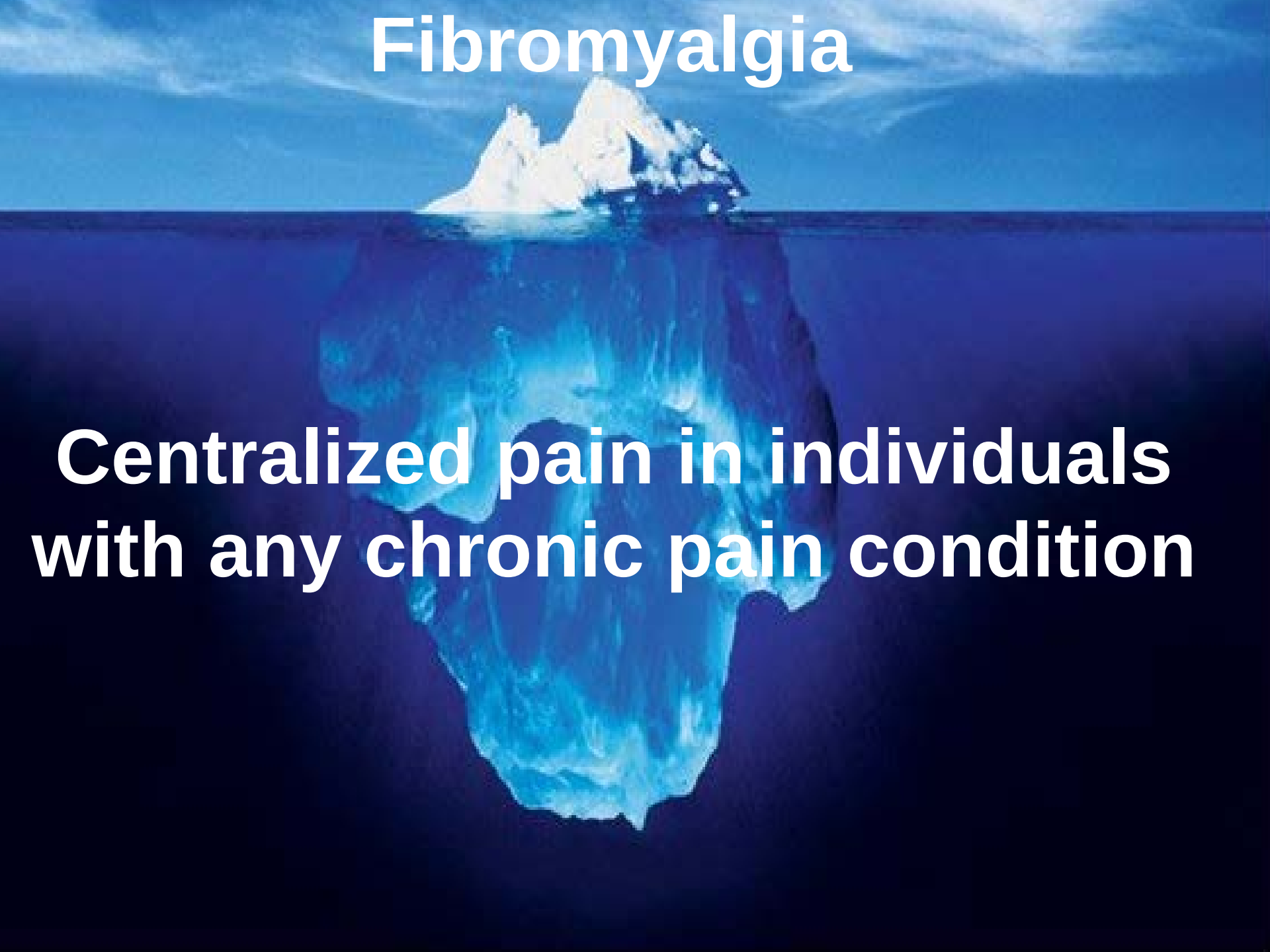
* sciatica - bilaterally.

severe PolyNeuropathy after chemo for AML in 1990. Took some time, months - 1yr - 2yrs to recover to feel the ground.
Mid thigh to feet
Mid upper forearm to fingers

See pt. list please for more info.

* pain in back the priority. need an epidural. Last one was difficult to get in, allergic to Iodine, eat seafood + No problems. Severe problems many hrs. later after last epidural. Pain specialist concerne[d]

51-10004	VER: 6/11 HIM: 07/11	Medical Record	M	New Patient Questionnaire - Back and Pain Center


Fibromyalgia
Centralized pain in individuals with any chronic pain condition

Sub-threshold FM is Highly Predictive of Surgery and Opioid Non-responsiveness in Patients Undergoing Arthroplasty and Hysterectomy

- Primary hypothesis of studies is the measures of centralized pain in OA (FMness) will predict failure to respond to arthroplasty and hysterectomy
- Extensive preoperative phenotype using validated self-report measures of pain, mood, and function
- Two outcomes of interest:
  - Postoperative opioid consumption
  - Pain relief from procedure at 6 months

1. Brummett, C.M., et al., Anesthesiology, 2013. **119**(6): p. 1434-43.
2. Brummett, C.M., et al., Arthritis Rheumatol, 2015. 67(5):1386-94.
3. Janda, A.M., et al., Anesthesiology, 2015. **122**(5): p. 1103-11.

Variables Analyzed

- Age
- Sex
- Surgery (Knee vs Hip)
- Primary anesthetic (GA vs neuraxial)
- Home opioids (IVME)
- Pain severity (BPI)
  - Overall
  - Surgical site
- Neuropathic pain score (PainDETECT)
- Depression (HADS)
- Anxiety (HADS)
- Catastrophizing
- Physical function-WOMAC

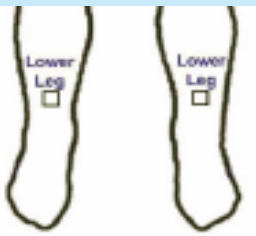
“Fibromyalgia-ness” can be scored 0-31

Fibromyalgia Symptoms (Modified ACR 2010 Fibromyalgia Diagnostic Criteria)

1. Please indicate below if you have had pain or tenderness over the past 7 days in each of the areas listed below. Check the boxes in the diagram below for each area in which you have had pain or tenderness. Be sure to mark right and left sides separately.

☐ No Pain

Left Right



19/31 potential FM score derived from how widespread pain is

2. Using the following scale, indicate for each item your severity over the past week by checking the appropriate box.

No problem
Slight or mild problems: generally mild or intermittent
Moderate: considerable problems; often present and/or at a moderate level
Severe: continuous, life-disturbing problems

Severe

a. Fatigu ☐
b. Troub reme ☐
c. Wakir (unre ☐

3. During th symptoms?

a. Pain
b. Depre
c. Head

4. Have the at a similar level for

5. Do you h n?

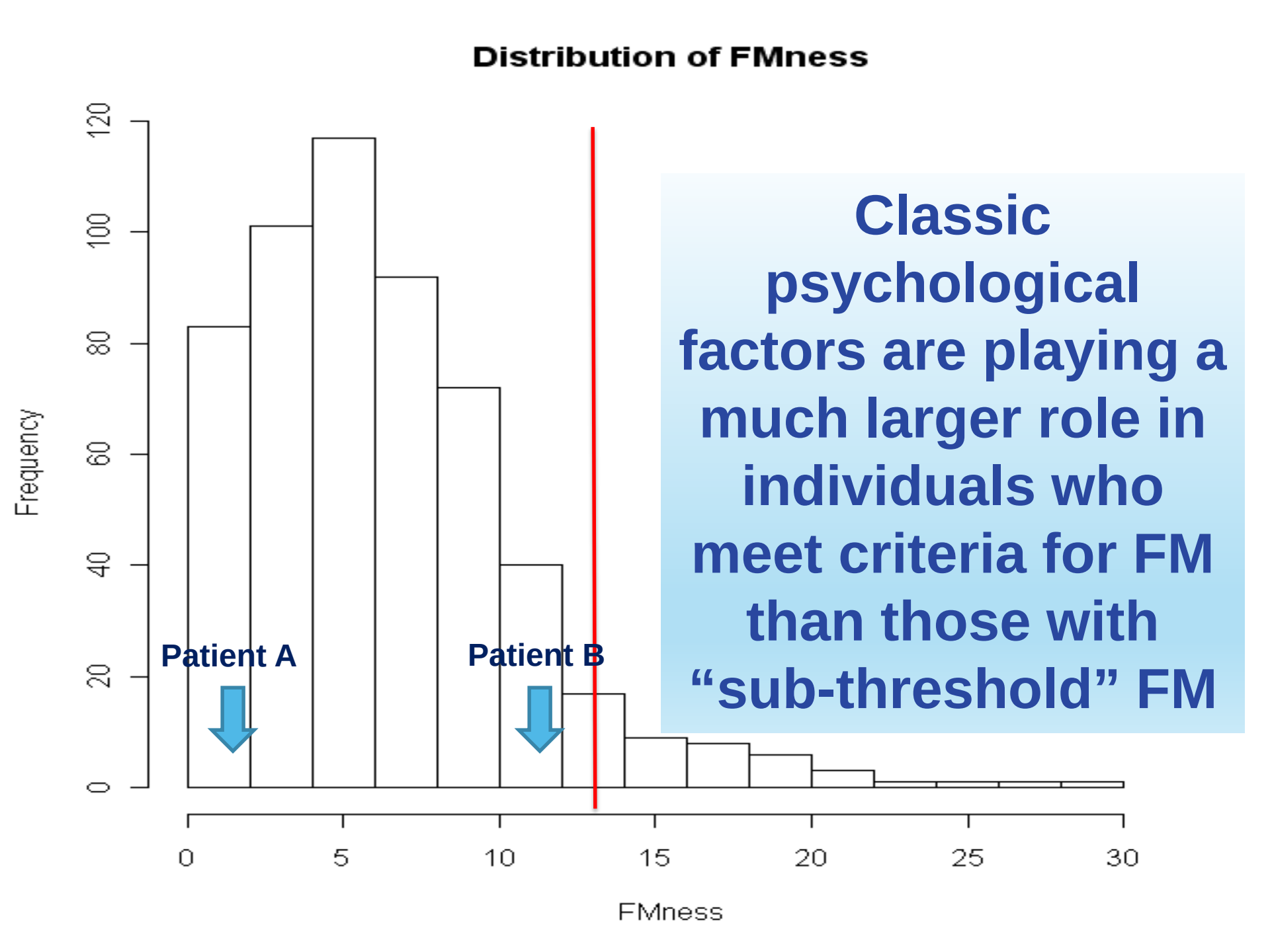
No ☐ Yes ☐

12/31 potential FM score derived from co-morbid CNS-derived symptoms that accompany CNS pain

1. Wolfe et. al. *Arthritis Rheum.* Jun 15 2009;61(6):715-716. 2. Wolfe et. al.
2. *J Rheumatol.* Feb 1 2011. 3. Clauw DJ. JAMA, 2014.

Each one point increase in fibromyalgianess led to:

- 9 mg greater oral morphine requirements during acute hospitalization (8mg greater when all individuals taking opioids as outpatients excluded)
- 20 – 25% greater likelihood of failing to respond to knee or hip arthroplasty (judged by either 50% improvement in pain or much better or very much better on patient global)
- These phenomenon were linear across entire scale up to a score of approximately 18 - and equally strong after individuals who met criteria for FM were excluded
- This phenomenon was much stronger than and largely independent of classic psychological factors



Classic psychological factors are playing a much larger role in individuals who meet criteria for FM than those with "sub-threshold" FM

Mechanistic Characterization of Pain

Variable degrees of any mechanism can contribute in any disease

	Nociceptive	Neuropathic	Centralized
Cause	Inflammation or damage	Nerve damage or entrapment	CNS or systemic problem
Clinical features	Pain is well localized, consistent effect of activity on pain	Follows distribution of peripheral nerves (i.e. dermatome or stocking/glove), episodic, lancinating, numbness, tingling	Pain is widespread and accompanied by fatigue, sleep, memory and/or mood difficulties as well as history of previous pain elsewhere in body
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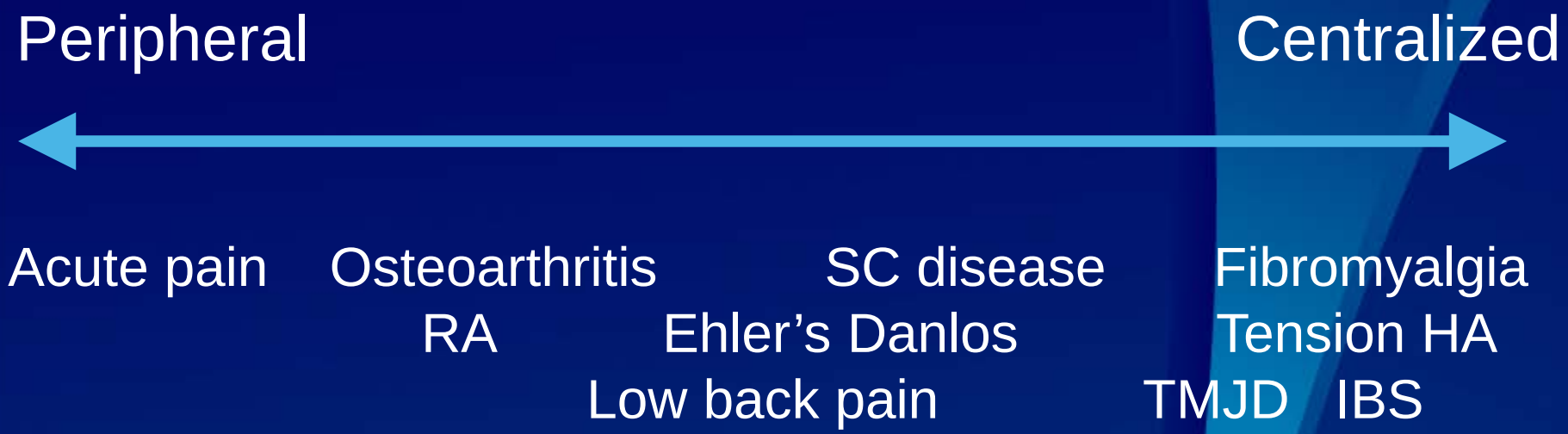
Classic examples	Osteoarthritis Autoimmune disorders Cancer pain	Diabetic painful neuropathy Post-herpetic neuralgia Sciatica, carpal tunnel syndrome	Fibromyalgia Functional GI disorders Temporomandibular disorder Tension headache Interstitial cystitis, bladder pain

Mixed Pain States

Centralization Continuum

Proportion of individuals in chronic pain states that have centralized their pain



The widespreadedness of pain (half of the 2011 FM criteria) predicts increased responsiveness to duloxetine in Low Back Pain

- In LBP, responsiveness to duloxetine was strongly related to number of sites on the Michigan Body Map.
  - Average number of sites of pain in this LBP study was 3 – 4
  - At 14 weeks, using any measure of pain improvement, individuals with more body sites of pain were significantly more likely to respond
  - Relative response rate for responders (30% improvement in pain)
    - MBM pain sites = 1 RR = **1.07**
    - MBM sites = 2 **1.30**
    - MBM sites = 3 **1.34**
    - MBM sites = 4 **1.47**
    - MBM sites > 5 **1.60**

1. Alev et. al. Clinical Journal of Pain, 2017

In RA, the residual pain and fatigue seen despite treatment with biologics can be treated as such

- In a large cohort of RA patients being treated at a US academic medical center, 47.3% continued to report having moderate to high levels of pain and fatigue. Most of these patients had minimal signs of inflammation but high levels of FM or Fmness.[1]
- Using quantitative sensory testing, active inflammation was associated with heightened pain sensitivity at joints (peripheral sensitization), whereas poor sleep was associated with diffuse pain sensitivity as noted in FM (central sensitization or centralized pain).[2]
- In a cross-over trial of six weeks of milnacipran in RA patients, in the overall group there was no statistical improvement, but in the subgroup with the least inflammation (swollen joint count </= 1) milnacipran decrease average pain intensity more than placebo (95% CI -2.26 to -0.01, p = 0.04).[3]

1. Lee YC, et. al. *Arthritis Res Ther.* 2009;11(5):R160. 2. Lee YC, et. al. *Arthritis & rheumatology.* 2014;66(8):2006-2014. 3. Lee YC, et. al. *J Rheumatol.* 2016;43(1):38-45.

Samumed WNT inhibitor shows differential responsiveness in OA based on pain centralization

- A small molecule, intra-articular, Wnt pathway inhibitor in development for the treatment of knee OA[1,2]
- In preclinical studies, inhibited inflammation, decreased cartilage degradation, and regenerated cartilage[1]
- In preclinical studies, demonstrated sustained local exposure and no observable systemic toxicity[1,2]
- Previous phase 1 study suggested a single intra-articular SM04690 injection appeared well-tolerated and showed potential for improving symptoms and maintaining joint space width in knee OA subjects[2]

1.Hood J. (2016) Abstract. *Ann Rheum Dis.* 2. Yazici Y. (2016) Abstract. *Ann Rheum Dis.*

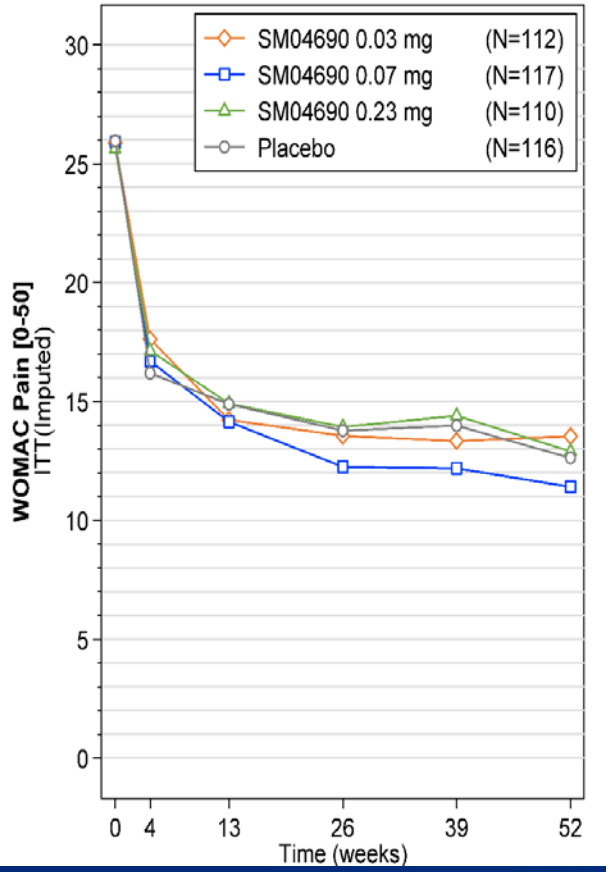
WOMAC Pain [0-50]

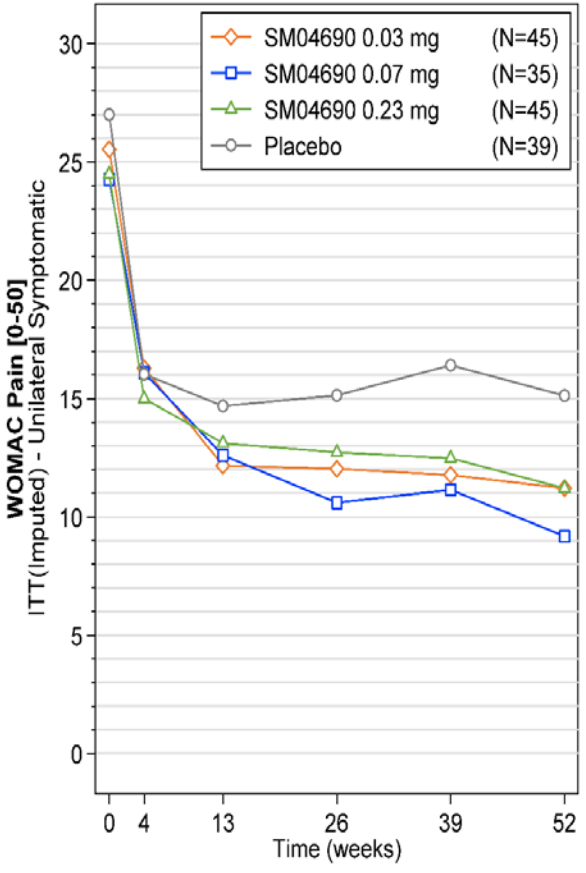
Actual scores (mean)

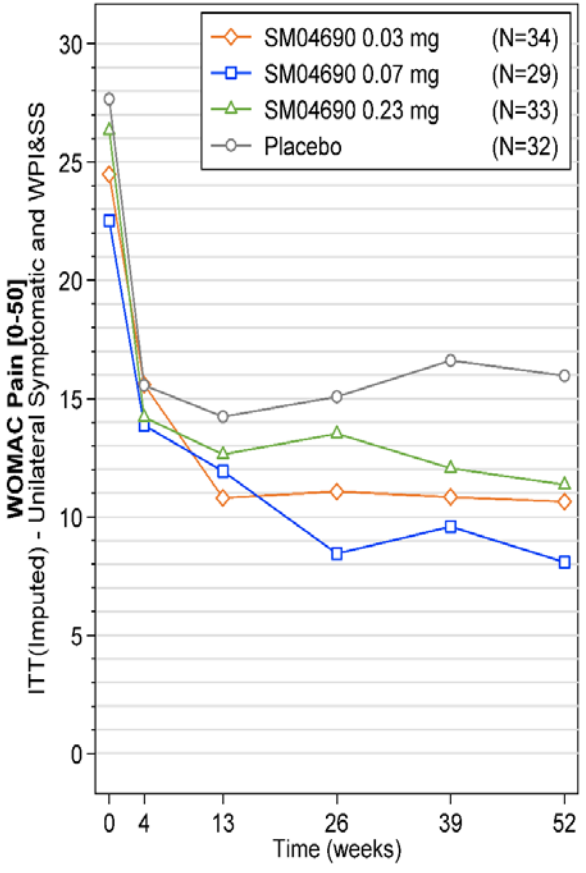
ITT

Unilateral Symptomatic

Unilateral Symptomatic w/o Widespread Pain







Cannabis-derived cannabinoids

More than 80 known, with different strains having different relative concentrations

- **THC** (Synthetic forms include Dronabinol, Marinol, Nabilone)
  - The primary psychoactive cannabinoid in cannabis, and its metabolites are those assayed for in drug tests
  - Although it binds relatively equally to both the CB1 and CB2 receptors, most of its effects are associated with CB1 activity in brain

CB, cannabinoid receptor; THC, Tetrahydrocannabinol

Pertwee RG. Handb Exp Pharmacol. 2005;(168):1-51.

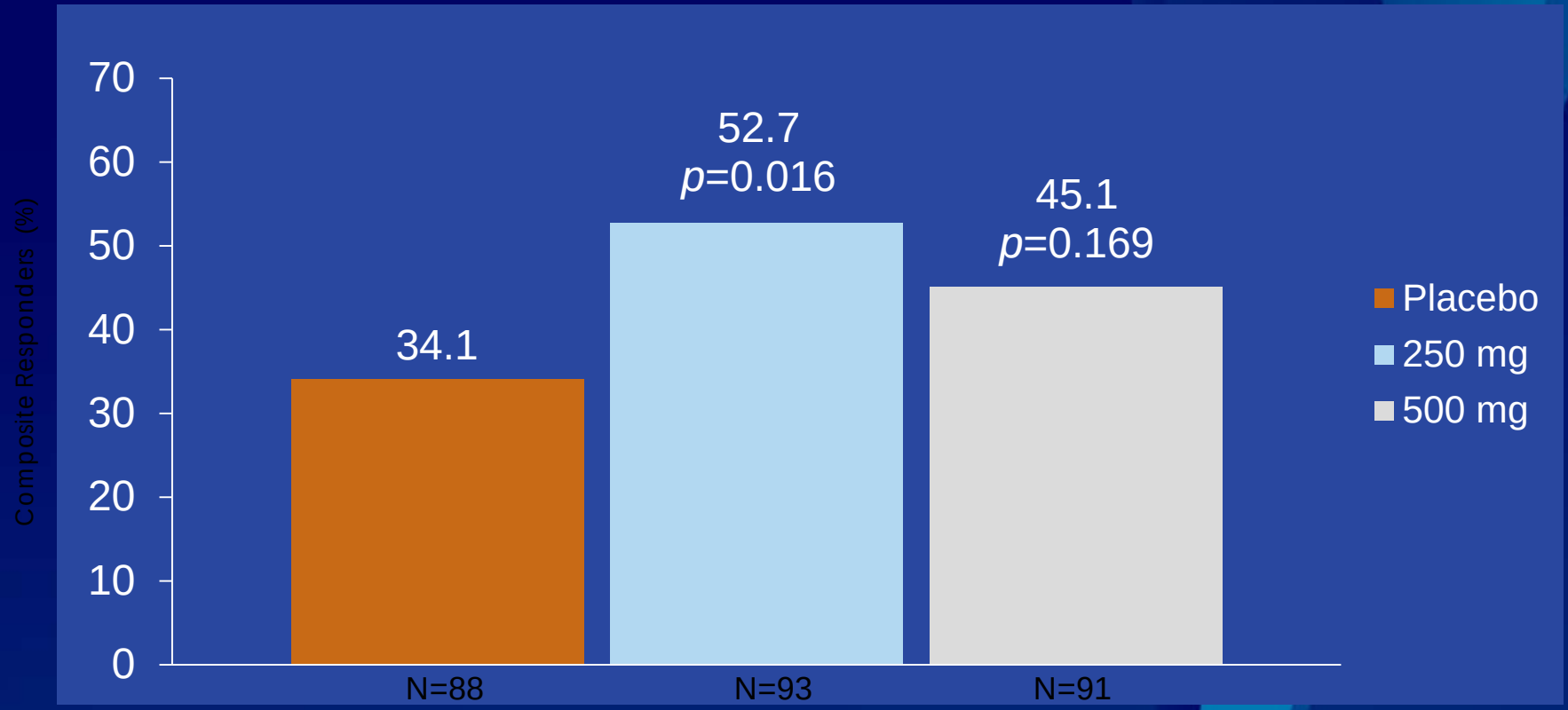
Cannabis-derived cannabinoids

- **Cannabidiol** (CBD)
  - Is not psychoactive and does not bind with any significant affinity to CB receptors, but yet has anticonvulsant and anti-inflammatory effects
  - Is actually thought to potentially protect against psychoactive effects of THC and hypothesized by some to be an effective anti-psychotic (although a recent Cochrane review concluded there was insufficient evidence of this)
  - May act as a indirect antagonist of CB agonists – but it does not seem to reduce activity of THC
  - Also acts as 5HT1a agonist which might be responsible for potential analgesic, antidepressant effects

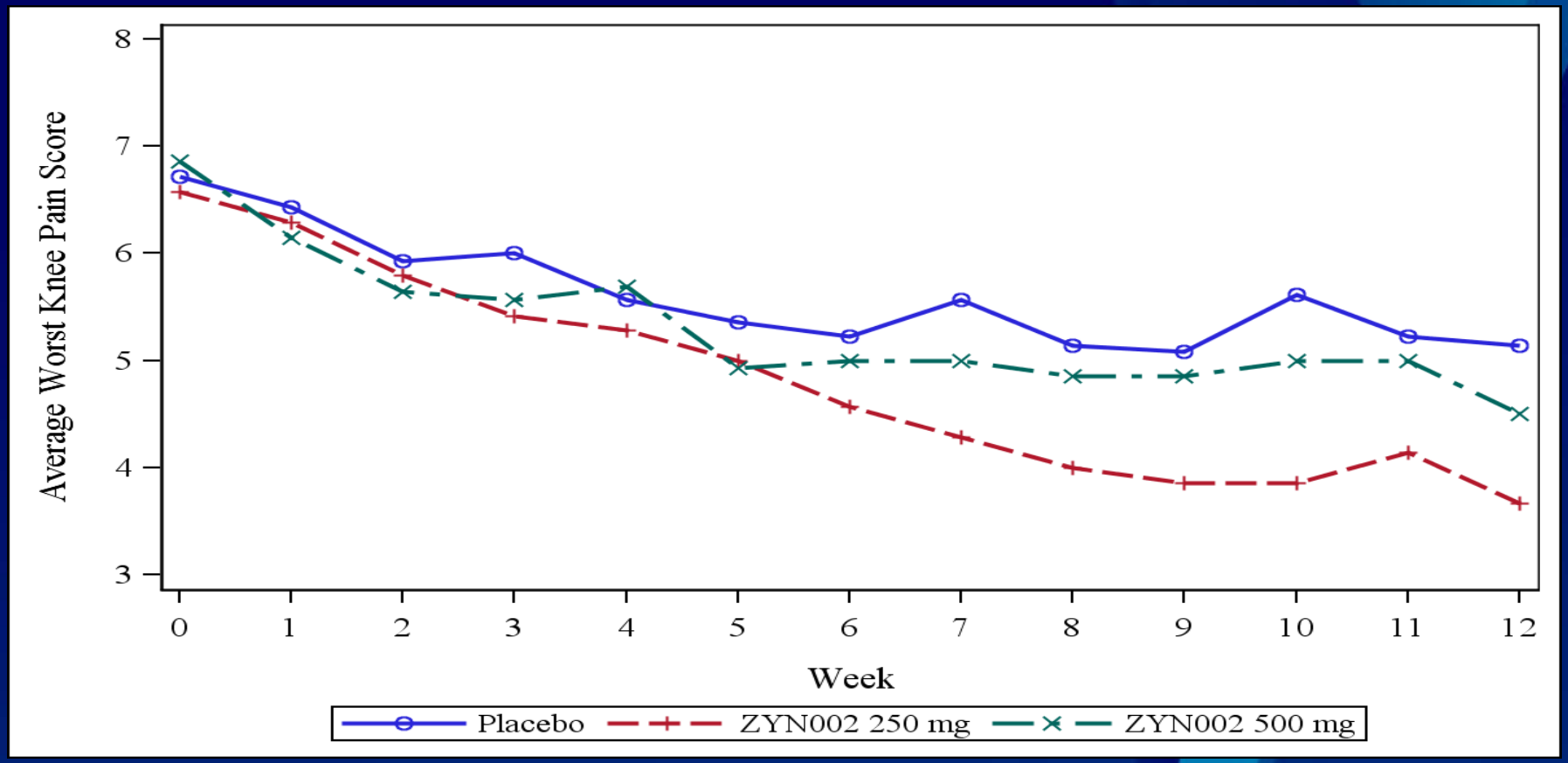
5HT1a, 5-hydroxytriptamine 1A receptor; CB, cannabinoid receptor; THC, tetrahydrocannabinol

Pertwee RG. Handb Exp Pharmacol. 2005;(168):1-51.

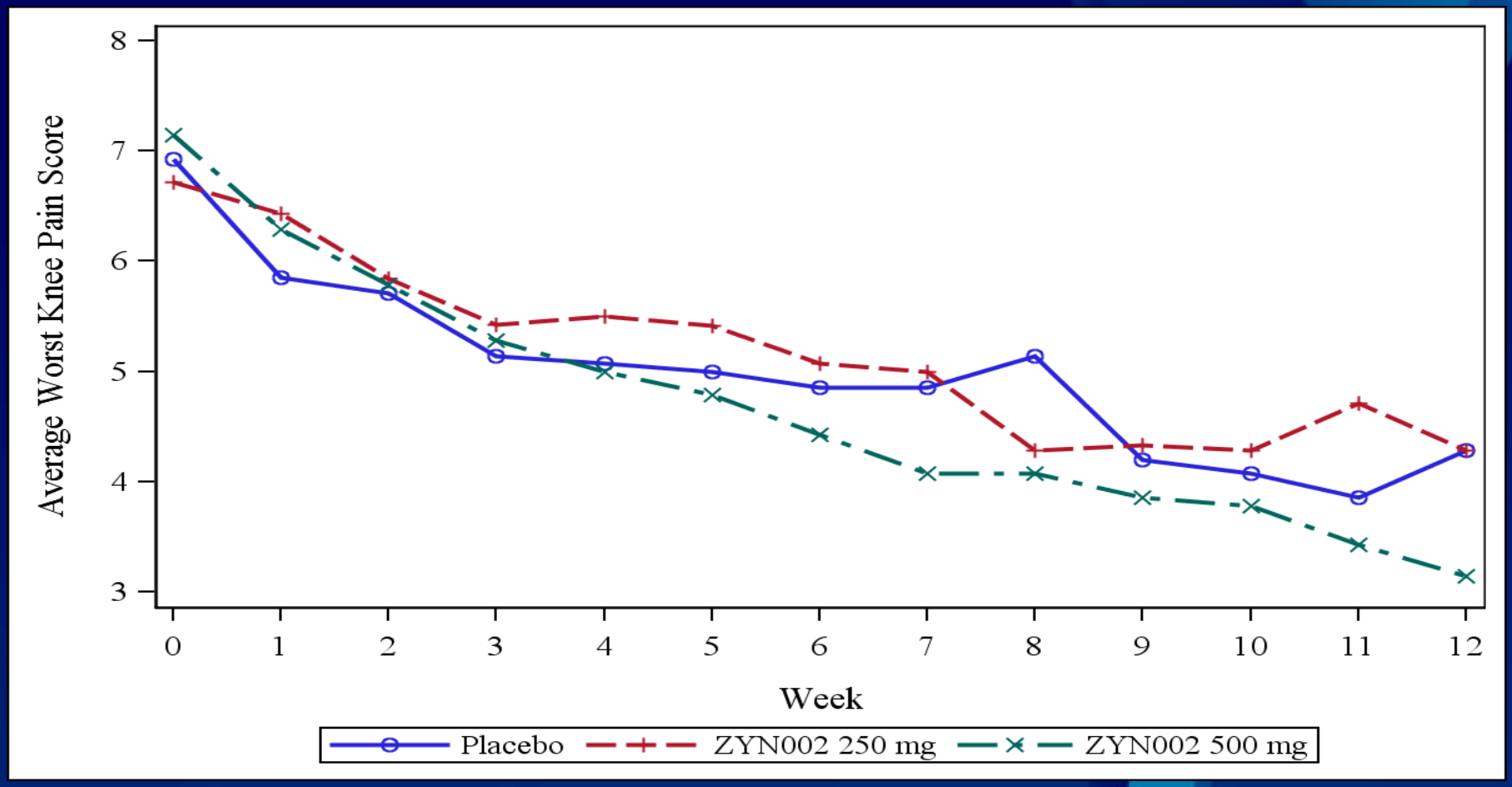
ZYN002 - Composite Responders at LOCF (Composite Responder: ≥30% Reduction Pain + 20% Response in Physical Function WOMAC)



ZYN002 - Median Weekly Average Worst Knee Pain Score over Time - Males



ZYN002 - Median Weekly Average Worst Knee Pain Score over Time – Females



Pathophysiology of centralized pain states

- Most patients display augmented pain and sensory processing on quantitative sensory testing and functional neuroimaging[1,3]
- Manifest by increased connectivity to pro-nociceptive brain regions and decreased connectivity to anti-nociceptive regions[2,3]
- These abnormalities are being driven by imbalances in concentrations of CNS neurotransmitters that control sensory processing, sleep, alertness, affect, memory[3,4]
- Autonomic, HPA, and peripheral abnormalities likely play a prominent role in some individuals

1. Phillips, K. and D.J. Clauw. Arthritis Rheum, 2013. **65**(2): p. 291-302. 2. Napadow, V., et al., Arthritis Rheum, 2012. **64**(7): p. 2398-403. 3. Harris, R.E., et. al. Anesthesiology, 2013. **119**(6): p. 1453-1464. 4.Schmidt-Wilcke, T. and D.J. Clauw, Nature reviews. Rheumatology, 2011. **7**(9): p. 518-27.

Pharmacological Therapies for Fibromyalgia (i.e. Centralized Pain)

Strong Evidence	▪ Dual reuptake inhibitors such as
	  ▪ Tricyclic compounds (amitriptyline, cyclobenzaprine)
	  ▪ SNRIs and NSRIs (milnacipran, duloxetine, venlafaxine?)
	▪ Gabapentinoids (e.g., pregabalin, gabapentin)

Modest Evidence	▪ Tramadol ▪ Older less selective SSRIs ▪ Gamma hydroxybutyrate ▪ Low dose naltrexone ▪ Cannabinoids
Weak Evidence	▪ Growth hormone, 5-hydroxytryptamine, tropisetron, S-adenosyl-L-methionine (SAMe)
No Evidence	▪ Opioids, corticosteroids, nonsteroidal anti-inflammatory drugs, benzodiazepine and nonbenzodiazepine hypnotics, guanifenesin

Modified from Clauw *JAMA*. 2014

CNS Neurotransmitters Influencing Pain

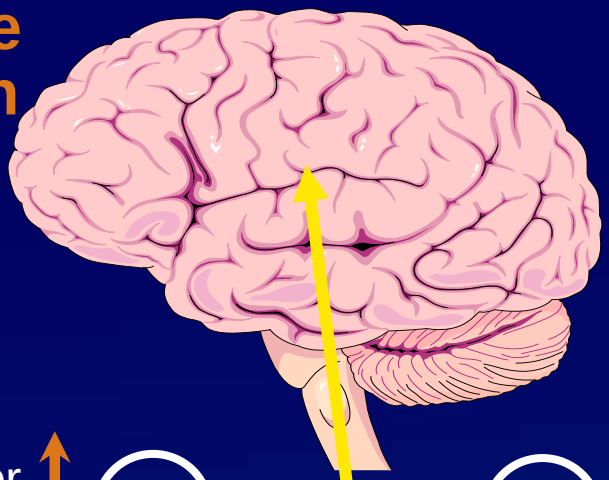
Arrows indicate direction in Fibromyalgia

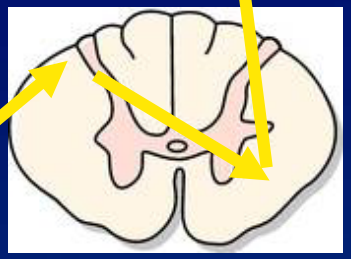
Generally facilitate pain transmission

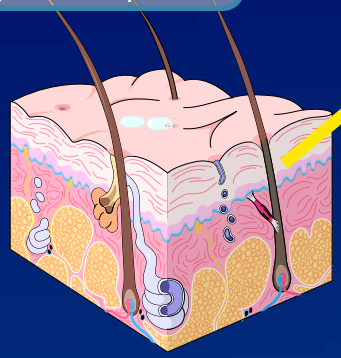
Gabapentinoids, ketamine, memantine

- Glutamate ↑
- Substance P ↑
- Nerve growth factor ↑
- Serotonin ($5HT_{2a, 3a}$)

Anti-migraine drugs (–triptans), cyclobenzaprine







Generally inhibit pain transmission

- Descending anti-nociceptive pathways
  - ↓ Norepinephrine-serotonin ($5HT_{1a,b}$), dopamine
    - Tricyclics, SNRIs. tramadol
  - ↑ Opioids
    - Low dose naltrexone
  - Cannabinoids
  - ↓ GABA
    - Gammahydroxybutyrate moderate alcohol consumption
    - No knowledge of endocannabinoid activity but this class of drugs is effective

1. Schmidt-Wilcke T, Clauw DJ. *Nat Rev Rheumatol.* Jul 19 2011.
2. Clauw DJ. JAMA. 2014.

PAIN

Endogenous opioidergic dysregulation of pain in fibromyalgia: a PET and fMRI study

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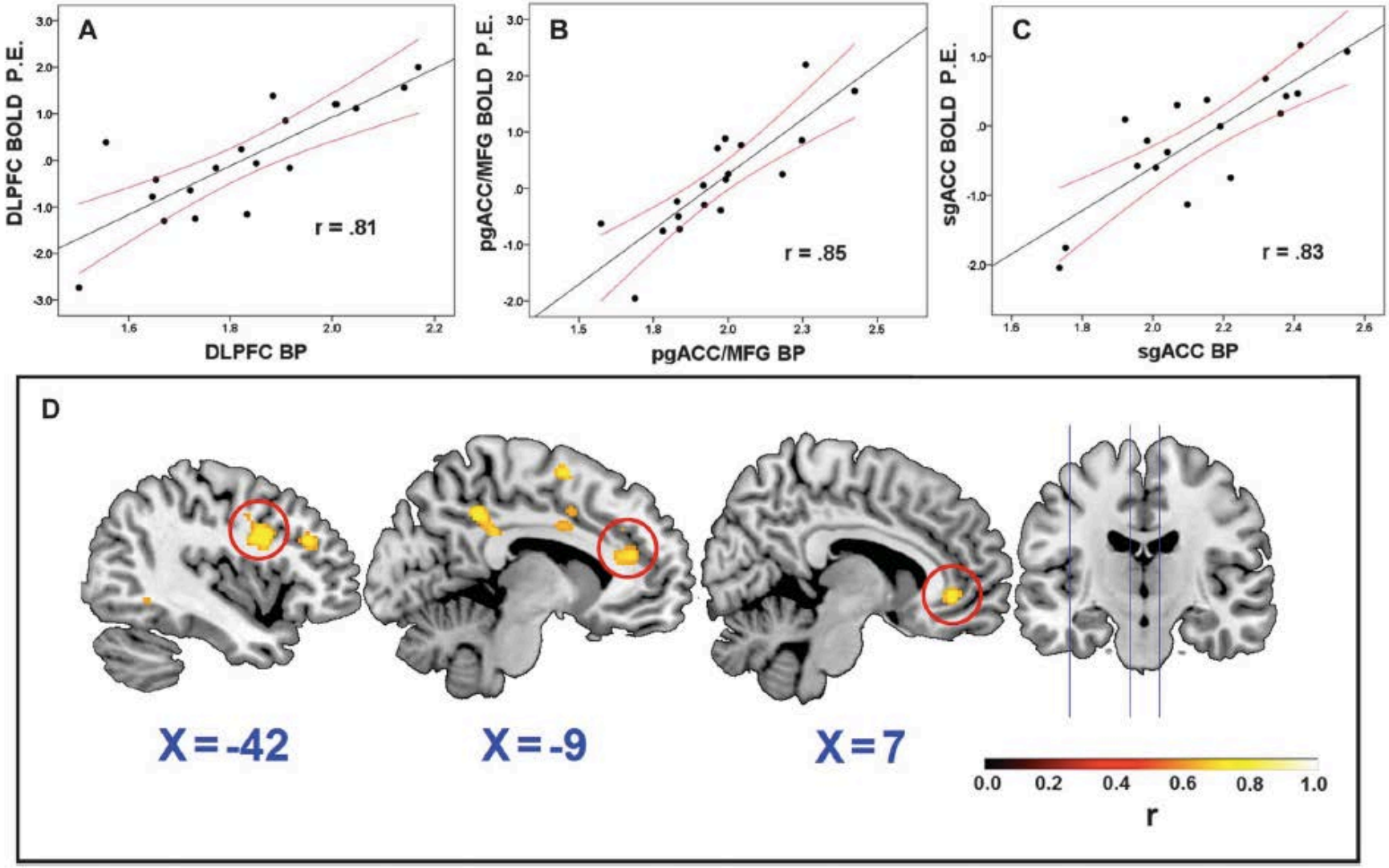

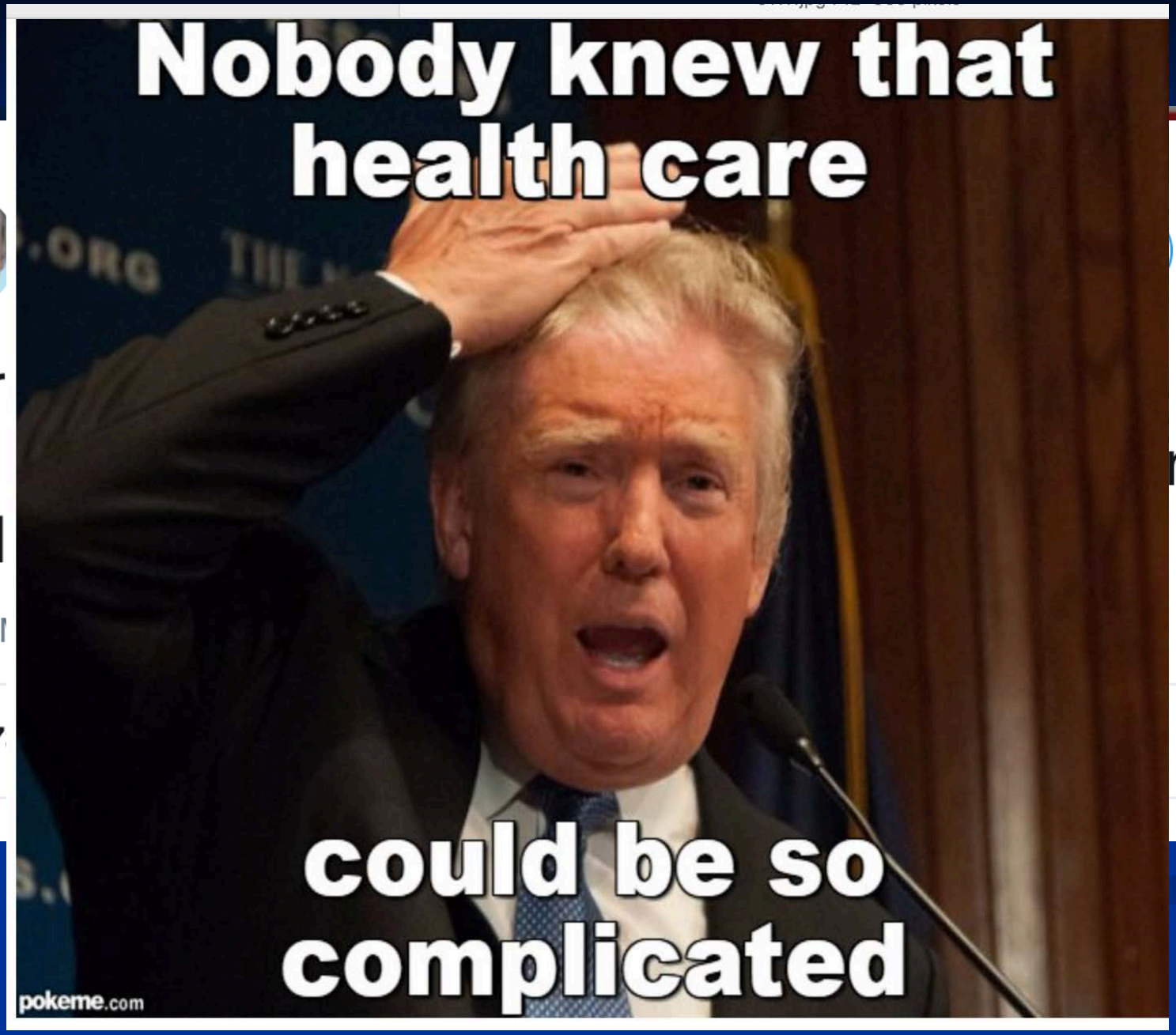
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Commentary

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Hijacking the endogenous opioid system to treat pain: who thought it would be so complicated?

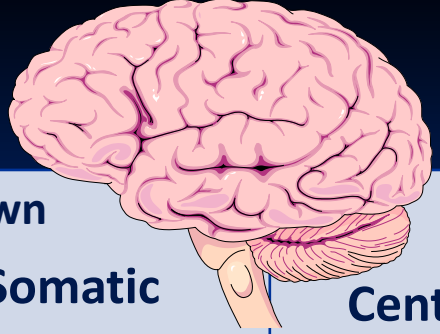
Daniel Clauw

In this issue, there is an especially interesting and important special review by Ballantyne and Sullivan entitled, "The discovery of endogenous opioid systems: what it has meant for the clinician's understanding of pain and its treatment".[1] This review adds to these authors' significant prior contributions to the pain field, as they are now proposing that many of the problems associated with opioid therapy can be understood mechanistically as being off-target effects on the endogenous opioid system. They describe how our emerging understanding of the endogenous opioid system might allow us to better understand how exogenous opioids can "hijack" this system to produce unexpected and undesired consequences, both when they are used for pain relief, and when they are misused or abused. They especially focus on how acute or chronic opioid therapy (COT) may impair some of the nonanalgesic functions of the endoge-

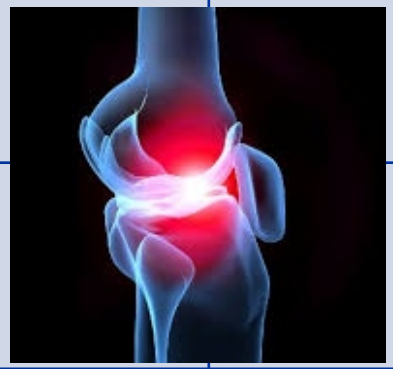
These issues of excess death and addiction, combined with a lack of any evidence of long-term efficacy,[3] have led many of us in the pain field to question whether opioid should ever be used to treat chronic nonmalignant pain. We know of some patients with chronic pain who are on long-term high-dose opioid therapy who are doing well (ie, have good pain control and good functional status), but these patients are exceedingly rare. Instead, we see large numbers of individuals who want to keep taking opioids, although after we assess them, we conclude that the long-term side effects of these drugs far exceed any benefit they are receiving.

This review highlights why we may see some of the more insidious problems that occur with COT, which are summarized below.

Individuals on COT may continue to "need" opioids to replicate the functions of endogenous opioids that are no longer being



	Top down Functional Somatic Syndromes	Bottom up Central Sensitization
Resolves when nociceptive input removed	No	Yes
Sex ratio	Female>>Male	Female>Male
Age of onset of pain	Young – typically following puberty	Any age when ongoing nociceptive input occurs
Family history of pain	Yes	No
Psych co-morbidity	High	Moderate
Increased sensitivity to non-pain sensory stimuli	Yes	No
High number of functional somatic syndromes	Yes	No



Clauw DJ. Refresher Courses, 16th World Congress on Pain. 2016.

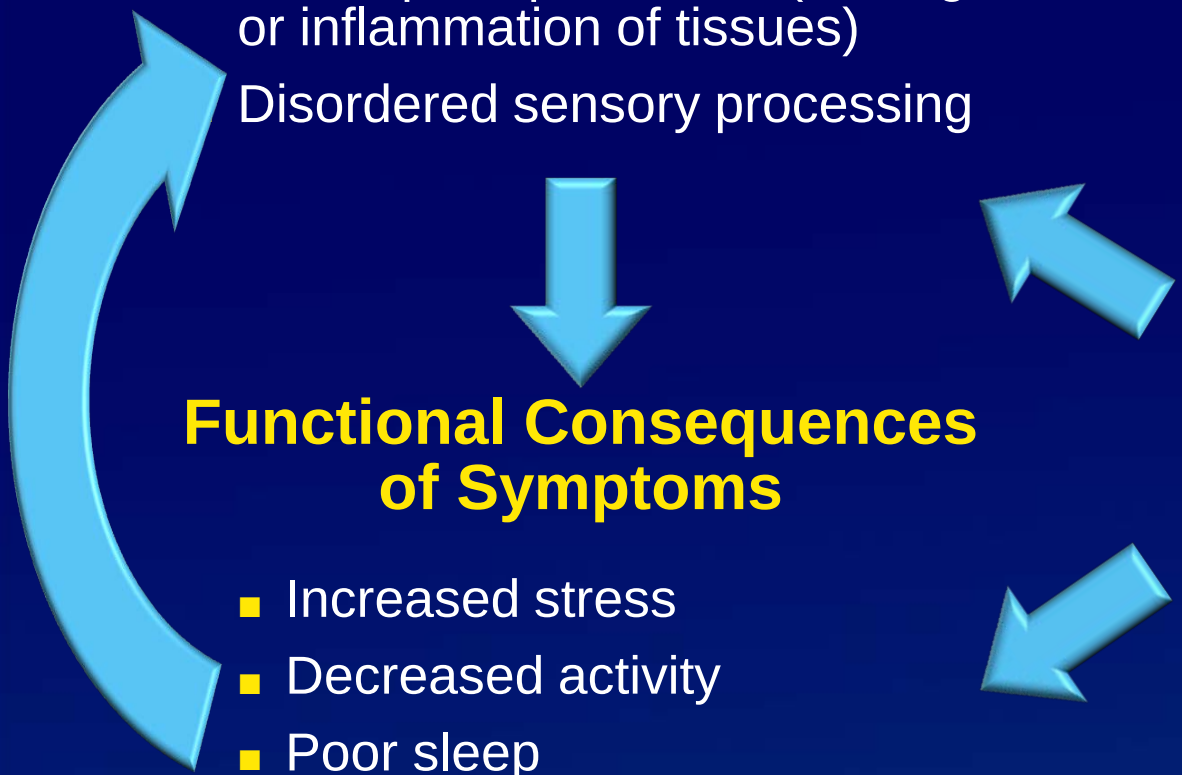
Treating Based on Mechanisms

Any combination may be present

	Peripheral (nociceptive)	Neuropathic	Centralized Pain
NSAIDs	+	-	-
Opioids	+	+	-
Surgery/ Injections	+	+	-
Tricyclics	+	+	+
SNRIs	+	+	+
Gabapentinoid	-	+	+
Cannabinoid	+	+	+

Symptoms of Pain, Fatigue, etc.

- Nociceptive processes (damage or inflammation of tissues)
- Disordered sensory processing



Functional Consequences of Symptoms

- Increased stress
- Decreased activity
- Poor sleep
- Obesity
- Maladaptive illness behaviors

Dually Focused Treatment

- Pharmacological therapies to improve **symptoms**
- Nonpharmacological therapies to address **dysfunction**

Clauw and Crofford. *Best Pract Res Clin Rheumatol*. 2003;17:685-701.

Nonpharmacological Therapies are similar to those for any Chronic Pain State

Strong Evidence	▪ Education ▪ Aerobic exercise ▪ Cognitive behavior therapy
Modest Evidence	▪ Strength training ▪ Hypnotherapy, biofeedback, balneotherapy, yoga, Tai Chi ▪ Neuromodulation
Weak Evidence	▪ Acupuncture, chiropractic, manual and massage therapy, electrotherapy, ultrasound
No Evidence	▪ Tender (trigger) point injections, flexibility exercise

Modified from Clauw *JAMA*. 2014

Summary

- Most practitioners have historically considered chronic pain to be largely from peripheral nociceptive input (i.e. damage or inflammation)
- When thinking about central factors in pain, many focus entirely on psychological factors
- We now understand that non-psychological central nervous system factors can markedly increase (sensitization) or decrease pain sensitivity
- The CNS is now thought of as “setting the volume control” or gain on pain processing and determining what nociception is felt as pain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Summary

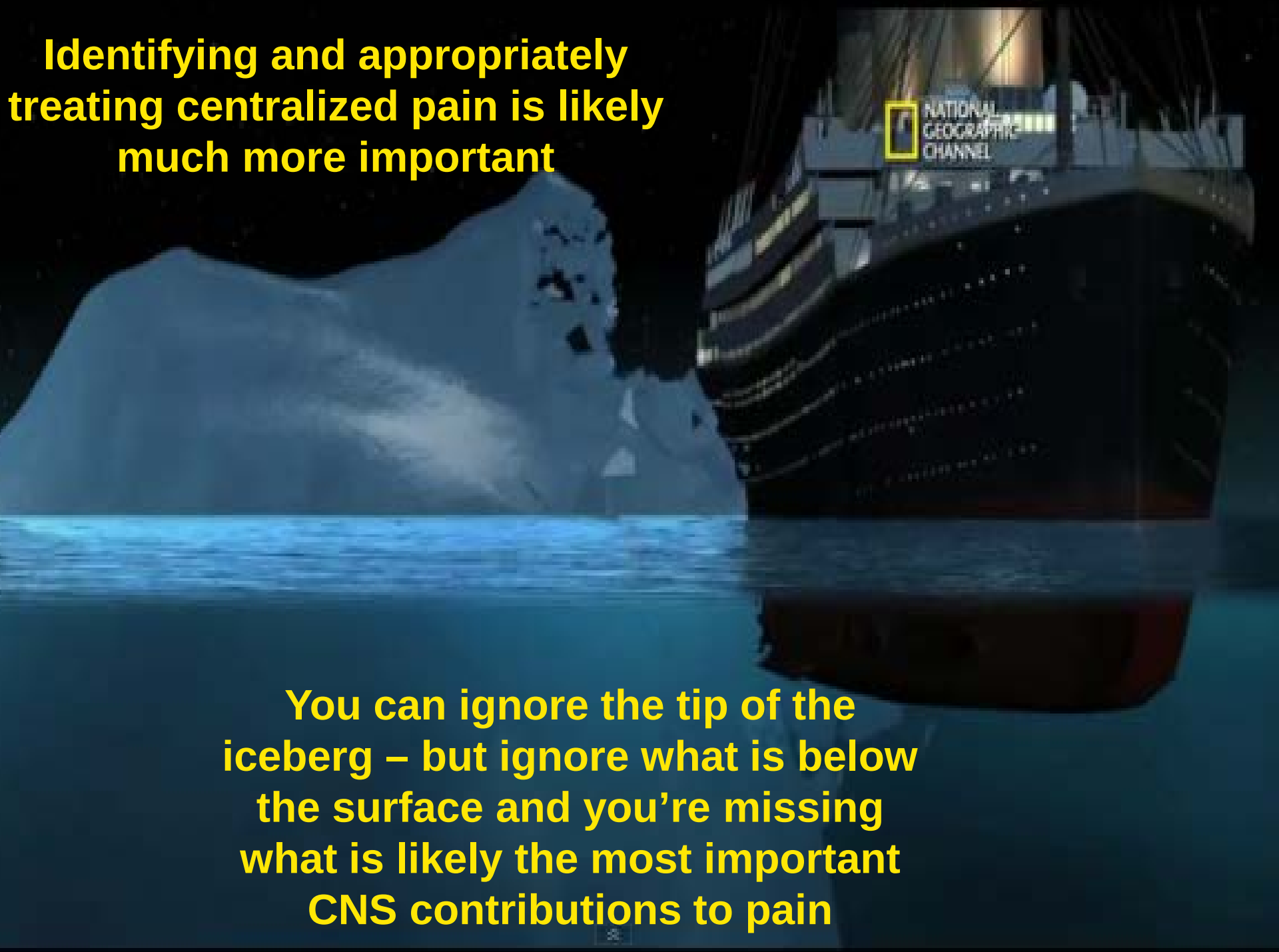
- The most highly prevalent pain conditions in younger individuals are now thought to be more “central” than “peripheral”
- Centralized pain or central sensitization can also be identified in subsets of individuals with any nociceptive or neuropathic pain state
- This is not currently appreciated in clinical practice so there is marked overuse of treatments for acute/nociceptive pain (opioids, injections, surgery, biologics, DMARDs) for treating centralized pain
- **Perhaps moving from considering FM a disease (i.e. the tip of the iceberg) to instead thinking of it as a CNS-driven *pathophysiological process* that can co-exist with any other disease or process would help the field, since current evidence strongly supports this notion**

Future Research Directions

- Does this approach really work?
- Can we predict responsiveness to certain procedures using these measures?
- Incorporating these approaches into prehab programs – especially aimed at high risk or high yield populations (individuals with high FM scores)
  - This a moment in time when individuals are maximally motivated to use behavioral interventions
- Should non-pharmacological therapies be tailored to underlying mechanisms

How do we get there?

- Superimpose light phenotyping with PROs into ongoing clinical care
  - Don’t wait until you can incorporate into EHR – use superimposed research registries and web-based platforms such as Qualtrics to collect data
- Deep phenotyping with more sophisticated research methods on a subset of patients
- Need longitudinal data pre- and post-interventions to match with phenotypic information


Identifying and appropriately treating centralized pain is likely much more important
NATIONAL GEOGRAPHIC CHANNEL
You can ignore the tip of the iceberg – but ignore what is below the surface and you're missing what is likely the most important CNS contributions to pain