




Common Threads: Session 4
**Central Sensitization of Pain in Opioid Use Disorder
AND ALCOHOL USE DISORDER**
Trent Hall, DO
30 Minutes →

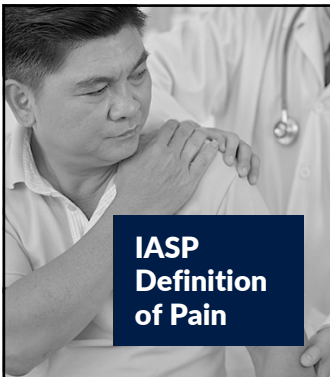


Disclosures

Dr. Hall has provided expert opinion about the overdose crisis for Lumanity on behalf of Emergent BioSolutions and about clinical aspects of Addiction Medicine for AstraZeneca.

Session Learning Objective

01 | Analyze common neurologic mechanisms and central nervous system (CNS) pathways influencing the overlapping etiology and treatment of opioid use disorder (OUD), alcohol use disorder (AUD), and chronic pain.



**IASP
Definition
of Pain**

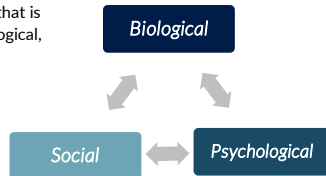
An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.

IASP Definition of Pain, Cont.

Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.

Through their life experiences, individuals learn the concept of pain.

A person's report of an experience as pain should be respected.



When someone with an alcohol or substance use disorder tells you they are in pain...

Please take them seriously.

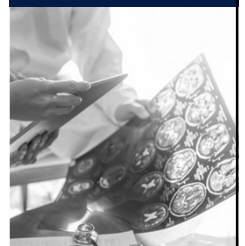
Patients with pain and addictive disorders...

- Have worse physical, psychiatric, and social functioning
- Are more likely to return to use
- Are more likely to overdose
- Are more likely to die by suicide



CNS Pain Sensitization

- Alcohol and substance use can contribute to CNS pain sensitization (aka "Central Sensitization").
- Neural substrates of central sensitization overlap with those of withdrawal/negative affect.
- However, translation of this science has been impeded by the lack of pain phenotyping tools easily deployable for use in addiction treatment settings.



Practical Phenotyping of Central Sensitization

Quantitative Sensory Testing and other phenotyping tools are costly and require special expertise.



Practical Phenotyping of Central Sensitization

- Many addiction treatment providers are not trained to perform a specialized pain history or physical exam.
- How then, can we accomplish phenotyping of central sensitization in addiction treatment settings?



American College of Rheumatology Fibromyalgia Survey

Widespread Pain Index
(1 point per check box, score range: 0-19 points)

1 Please indicate if you have had pain or tenderness during the past 7 days in the areas shown below. Check the boxes in the diagram for each area in which you have had pain or tenderness.

Symptom Severity
(score range: 0-12 points)

2 For each symptom listed below, use the following scale to indicate the severity of the symptom during the past 7 days.

- No problem
- Slight or mild problems: generally mild or intermittent
- Moderate problems: consider able problems, often present and/or at a moderate level
- Severe problems: continuous, life-disrupting problems

	No problem	Slight or mild problem	Moderate problem	Severe problem
Points	0	1	2	3
A. Fatigue	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
B. Trouble thinking or remembering	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
C. Waking up tired (unrefreshed)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

	0	1
Points	0	1
A. Pain or cramps in lower abdomen	<input type="checkbox"/>	<input type="checkbox"/>
B. Depression	<input type="checkbox"/>	<input type="checkbox"/>
C. Headache	<input type="checkbox"/>	<input type="checkbox"/>

Additional criteria (no score)

4 Have the symptoms in questions 2 and 3 and widespread 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

SOURCE: Clauw DJ. Fibromyalgia: a clinical review. JAMA. 2014 Apr 16;311(15):1547-55

Cross-Sectional Survey

General Section
Research Paper

PAIN REPORTS

GREEN

Central sensitization in opioid use disorder: a novel application of the American College of Rheumatology Fibromyalgia Survey Criteria

© Trent Hall¹, Julie Taylor², Peter Ertug², Megan Dunner³, Craig Dwyer⁴, Steven E. Harts⁵, Chelsie M. Kaplan⁶, Khris Luan-Phon⁶, Daniel J. Clauw⁶

Research Paper

PAIN

OPEN

Fibromyalgia predicts increased odds of pain-related addiction exacerbation among individuals with pain and opioid use disorder

© Trent Hall¹, Julie Taylor², Peter Ertug², Megan Dunner³, Craig Dwyer⁴, Steven E. Harts⁵, Chelsie M. Kaplan⁶, Khris Luan-Phon⁶, Daniel J. Clauw⁶

Cross-sectional survey of patients with OUD (n = 141)

Pain was prevalent in this clinical sample of participants with OUD. The sample mean, minimum, and maximum ACR-FMS scores were 9.88 ± 4.91, 0 and 23, respectively.

One hundred twenty-five participants (88.7%) reported at least 1 painful body region. Widespread pain was common, with participants averaging 3.27 ± 2.83 painful body regions.

Pain was most often reported in the low back (99.70.2%), neck (45.31.9%), and upper back (43.90.5%). Figure 1 shows the frequency of pain by body region.

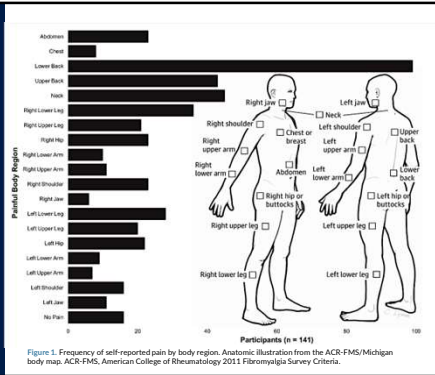


Table 1. Original items about Pain and OUD

Participants were asked:
"To what degree do you agree or disagree with the following statements?"

Responses were scaled as:
strongly disagree (1)
disagree (2)
neutral (3)
agree (4)
strongly agree (5)

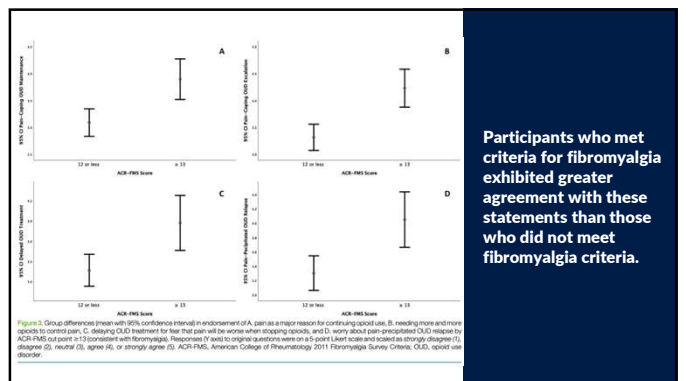
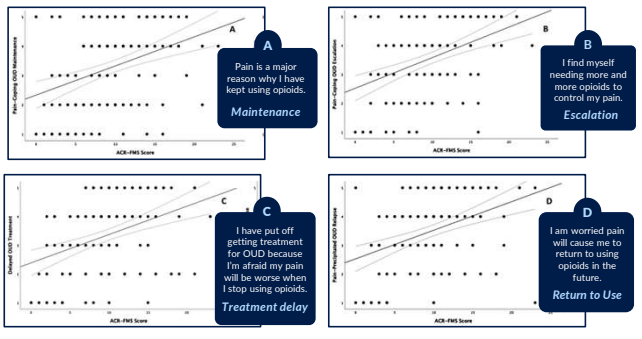
Pain is a major reason why I have kept using opioids.

I find myself needing more and more opioids to control my pain.

I have put off getting treatment for Opioid Use Disorder because I'm afraid my pain will be worse when I stop using opioids.

I am worried pain will cause me to relapse in the future.

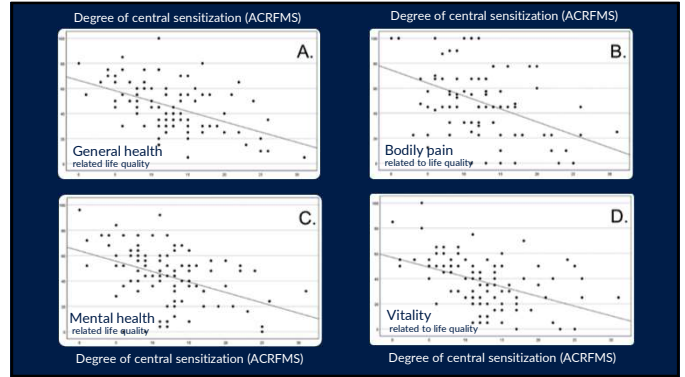
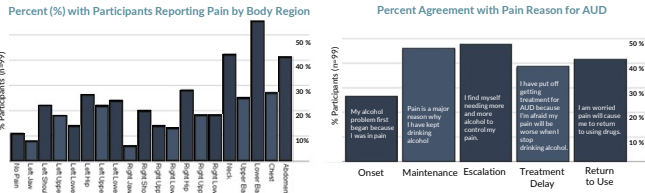
Central sensitization was correlated with agreement with:



Participants who met criteria for fibromyalgia exhibited greater agreement with these statements than those who did not meet fibromyalgia criteria.

Central Sensitization in Alcohol Use Disorder: Correlates of Pain, Addiction and Health-Related Quality of Life

We found similar results among patients with **Alcohol Use Disorder** (n = 138)
Central sensitization was associated with greater agreement with pain as a reason for the onset, maintenance, escalation, treatment delay, and return to use of AUD.



Central Sensitization is Associated with Pain-Motivated Drinking in Alcohol Use Disorder

- Cross-sectional survey of adults with AUD (n = 138)
- Developed a new scale, the *Pain-Motivated Drinking Scale (PMDS)*
- Factor structure
- Internal consistency
- Construct validity
- Then conducted Hierarchical Multiple Linear Regression (MHLR)
 - to determine if central sensitization was associated with frequency of pain-motivated drinking after controlling for: age, gender, race, ethnicity, number of AUD criteria present depression anxiety, and pain severity.

Pain-Motivated Drinking Scale (PMDS)

- Single-factor structure
- Excellent internal consistency reliability Cronbach's $\alpha = .952$

Table 2. Exploratory Factor Analysis: Pain-Motivated Drinking Scale

Questionnaire Item	Mean (SD)	Factor Loading	Communalities
1. To get relief from physical pain.	2.48 (1.3)	.851	.725
2. Because it helps you when you feel physical pain.	2.73 (1.3)	.908	.825
3. To forget your physical pain.	2.84 (1.4)	.905	.819
4. To move better or get things done when you are in physical pain.	2.82 (1.5)	.866	.749
5. Because it makes physical pain more tolerable.	2.75 (1.4)	.940	.884

Note: Questions were prefaced: "Listed below are reasons people might drink alcohol. Decide how often your own drinking is motivated by each of the reasons listed. Physical pain means pain felt anywhere in the body, including headache/head pain."
Responses were scaled: 1) almost never/never, 2) some of the time, 3) half of the time, 4) most of the time, 5) almost always/always.

Pain-Motivated Drinking Scale (PMDS)

Construct validity was demonstrated by Spearman's partial correlations controlling for age, gender, race, and ethnicity.

PMDS was correlated with...

Number of painful body regions (rs (122) = 0.363, p < .00)
Pain severity (rs (122) = 0.575, p < .001)
Pain-related quality of life (SF-36) (rs (122) = -0.619, p < .001)
Worse AUD severity (rs (122) = 0.195, p = .030).
Mental Health (SF-36) (rs (122) = -0.175, p = .052)

There was a *nearly significant correlation with worse anxiety/depression.*



Central Sensitization is Associated with Pain-Motivated Drinking in Alcohol Use Disorder

MHLR was conducted to determine if central sensitization was associated with frequency of pain-motivated drinking after controlling for:

- Age
- Gender
- Race
- Ethnicity
- Number of AUD criteria present,
- Depression,
- Anxiety
- Pain severity

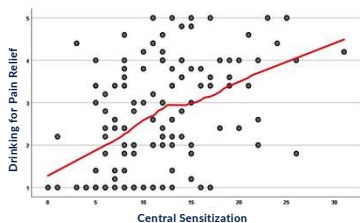
Table 3 - Hierarchical Multiple Regression: Pain-Motivated Drinking Scale

	R	R ²	Adj. R ²	ΔR ²	ΔF	P
Model 1	.009	.000	-.009	.000	.010	.922
Model 2	.124	.015	-.002	.015	1.72	.193
Model 3	.256	.066	.013	.050	1.44	.225
Model 4	.297	.088	.028	.022	2.61	.109
Model 5	.309	.096	.027	.008	.877	.351
Model 6	.526	.277	.214	.181	26.0	<.001
Model 7	.573	.329	.263	.052	7.94	.006

Model 1: age.
 Model 2: age, gender.
 Model 3: age, gender, race, ethnicity.
 Model 4: age, gender, race, ethnicity, Mental Health (RAND-36).
 Model 5: age, gender, race, ethnicity, Mental Health (RAND-36), AUD severity (DSM-5).
 Model 6: age, gender, race, ethnicity, Mental Health (RAND-36), AUD severity (DSM-5), Pain severity (RAND-36).
 Model 7: age, gender, race, ethnicity, Mental Health (RAND-36), AUD severity (DSM-5), Pain severity (RAND-36), Central Sensitization (ACR-FMS).

Central Sensitization is Associated with Pain-Motivated Drinking in Alcohol Use Disorder

Among patients with pain **and** AUD (n = 114), those higher in central sensitization reported they drank more often to relieve pain.



This effect was *independent of*:

- pain severity
- AUD severity
- anxiety
- depression
- and other covariates.

Why might clinical pain phenotyping matter in AUD?

Pain phenotype might influence treatment response to MAUD.




Acamprosate
 Modulates glutamate, a key neurotransmitter in excitatory nociception.

Disulfiram
 Works by aversive conditioning. Central sensitization is associated with enhanced reactivity to other non-nociceptive aversive stimuli. It follows that central sensitization might plausibly impact disulfiram acceptance, adherence, and efficacy.

Naltrexone
 Provides temporary blockade of μ-opioid receptors by naltrexone may produce upregulation of β-endorphin and related opioid peptides, as well as opioid receptors, potentially enhancing endogenous analgesia. Early evidence suggests may help with central sensitization.

Why might clinical pain phenotyping matter in OUD?

Pain phenotype might influence treatment response to MOUD.

 Buprenorphine	 Methadone	 Naltrexone
As a partial μ -opioid agonist, buprenorphine has been observed to reduce central sensitization in animal models.	In addition to agonizing μ -opioid receptors, methadone inhibits serotonin and norepinephrine reuptake and antagonizes N-methyl-D-aspartate (NMDA) receptors.	May up-regulate the endogenous opioid system, and early evidence suggests it might improve pain among individuals with central sensitization.

Summary

- 1
When patients with OUD or AUD tell you they are in pain...
Take them seriously.
- 2
Both chronic pain and addiction can sensitize the nociceptive system.
- 3
The ACR-FMS is a surrogate measure for central sensitization.
- 4
Central sensitization might be an underappreciated factor in the clinical presentation of comorbid chronic pain and addiction.

Knowledge Check

Patients with an alcohol or substance use disorder AND chronic pain are at elevated risk of which of the following adverse outcomes? Select all that apply.

A Worse physical, psychiatric, and social functioning	B Overdose
C Return to use	D Death by suicide

Knowledge Check

Patients with an alcohol or substance use disorder AND chronic pain are at elevated risk of which of the following adverse outcomes? Select all that apply.

A Worse physical, psychiatric, and social functioning ✓	B Overdose ✓
C Return to use ✓	D Death by suicide ✓

Knowledge Check

Which of the following is not part of the IASP Definition of Pain?

- A Pain is an unpleasant **sensory and emotional** experience associated with, or resembling that associated with, **actual or potential** tissue damage.
- B Pain is always a personal experience that is **influenced to varying degrees** by **biological, psychological, and social factors**.
- C Through their life experiences, individuals learn the concept of pain.
- D A person's report of an **experience as pain** should be disrespected if they have a history of addiction.

Knowledge Check

Which of the following is not part of the IASP Definition of Pain?

- A Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. **X**
- B Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors. **X**
- C Through their life experiences, individuals learn the concept of pain. **X**
- D A person's report of an **experience as pain** should be disrespected if they have a history of addiction. **✓**

Knowledge Check

Among individuals with AUD or OUD, which of the following was found to be related to Central Sensitization? *Select all that apply.*

- A Health-related quality of life
- B Pain-motivated alcohol use
- C Self-report of pain as a reason for the onset, maintenance, escalation, relapse of their disorder
- D Treatment delay

Knowledge Check

Among individuals with AUD or OUD, which of the following was found to be related to Central Sensitization? *Select all that apply.*

- A Health-related quality of life **✓**
- B Pain-motivated alcohol use **✓**
- C Self-report of pain as a reason for the onset, maintenance, escalation, relapse of their disorder **✓**
- D Treatment delay **✓**

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