Negative Affect and Chronic Pain

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Agenda

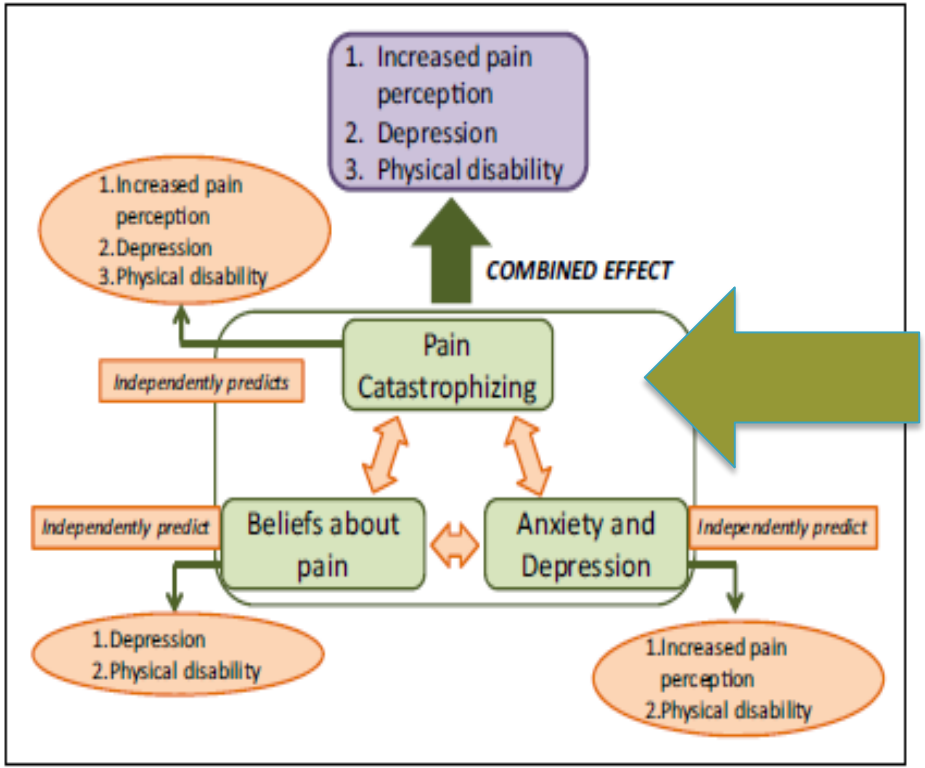
- Concept of Negative Affect
- Epidemiology of NA and Pain
- Brain physiology and pain
- Clinical studies of NA and pain

What is Negative Affect? AKA…Negative Valence Disorders

20% of CLBP patients have a co-morbid depression or anxiety disorder
--Edwards RR, Wasan AD, et. al., *J Pain*, 2016

Affect=Thoughts emotions, and behavior

Pain Catastrophizing= Negative thoughts about pain



NA

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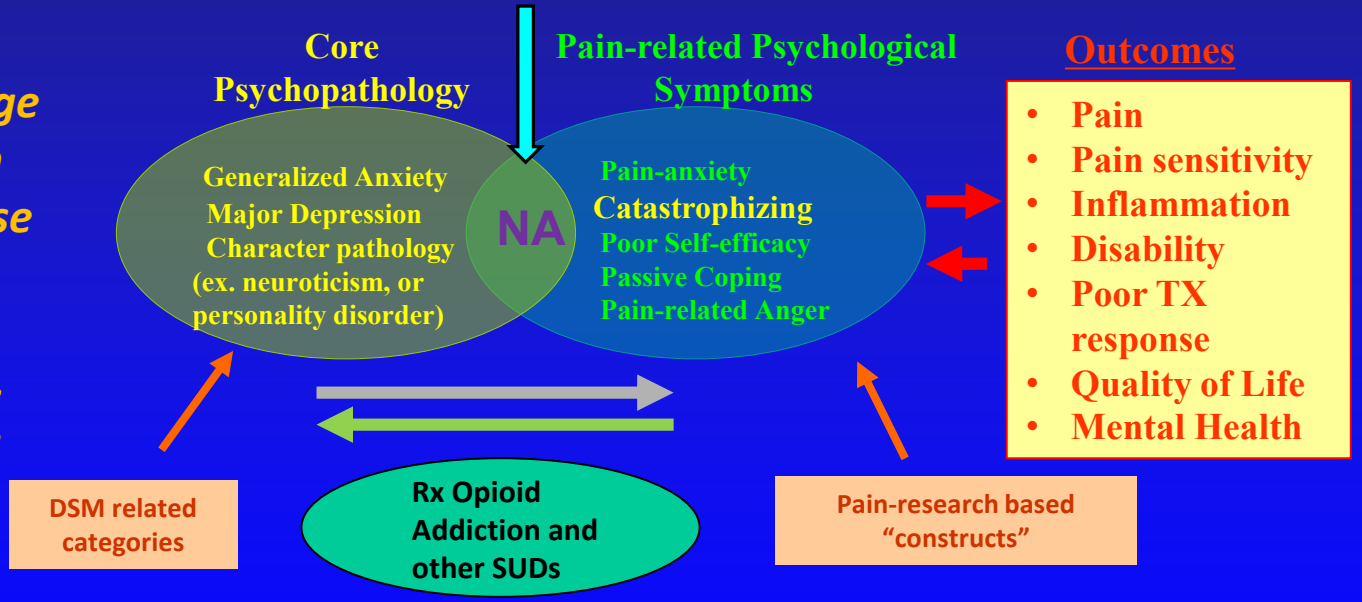
Common Psychiatric Symptoms in Patients with Pain can be Described as Negative Affective Disorders

Correlations of .60-.70 between these categories= Negative Affect, AKA Negative Valence

In a broad range of chronic pain conditions these relationships hold true

Ryan and McGuire, *Brit J Health Psych*, 2016



Redrawn and adapted from Wasan AD and Alpay M, "*Pain and the Psychiatric Comorbidities of Pain*," in Comprehensive Clin. Psychiatry, 2nd Ed., 2016, Elsevier Pub.

Scope of the Psychopathology

- 15-20% of those in the general population who have chronic pain have significant psychopathology.
- 30-40% of those with chronic pain in Primary care have psychopathology
- 50-80% of patients with chronic pain seen in pain clinics have a major psychiatric disorder, by DSM criteria.
- 30-50% of the comorbidity is major depression, followed by anxiety disorders, adjustment disorders, personality vulnerabilities (Neuroticism), somatic symptom d/o (primary), and substance abuse.

Dersh J, JOEM, May 2002

Affective Pain Processing

- Emotional components of pain—sense of unpleasantness, suffering associated with pain, sadness or anxiety that may be evoked by pain.
- Meanings of pain—is pain a nasty sensation that still permits a good quality of life vs. a state of torment and despair, where one's life is ruined?
- Attention to pain—can you notice it less, or does it overwhelm your consciousness?
- Both the emotional and cognitive components of the pain experience form the affective response to **CHRONIC** pain…AKA *Secondary Pain Affect*.

Price, Science, 2000

Who are the patients with psychiatric problems?

- In general, they tend to be the ones with pain complaints and disability out of proportion to their anatomic pathology.
- Little variability of pain day or night
- Poor response to medications or procedures

- Patients with psychiatric problems usually have a combination of psychiatric and physical pathology that amplifies the anatomic basis of their pain.
- Psychiatric problems are the most significant comorbidities of chronic pain and are the **greatest predictor** of poor pain and disability outcome, *regardless* of pain diagnosis!
- Most psychiatric problems are treatable, or at least can get significantly better.

Clark 2002, Psych Clinics N. America 25:March 2002

- Most patients developed psychopathology after the pain began.
- You get optimal relief of pain and improvement in psychopathology with treatment of both simultaneously.
- Psychiatric problems can be contraindications to procedures—spinal cord stim or IT pump.

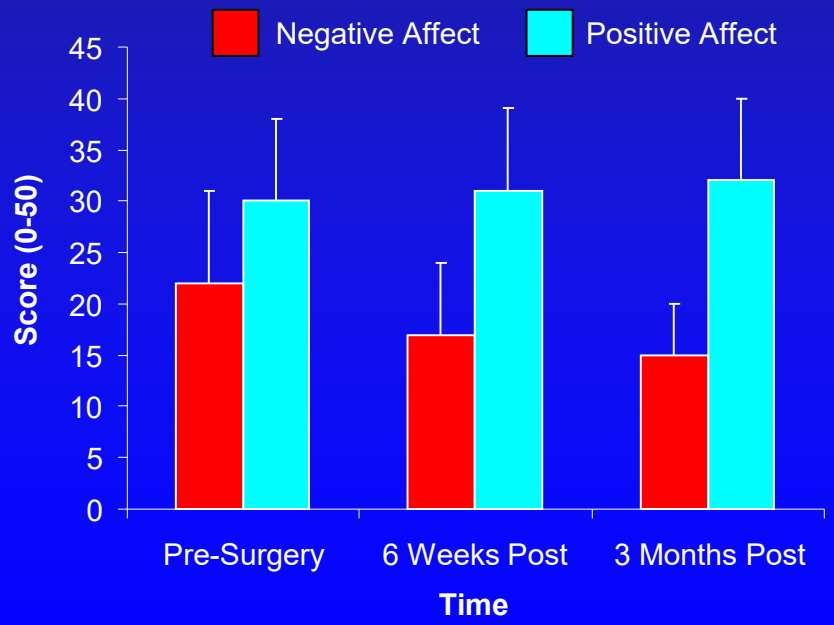
- **Operational definition of HIGH negative affect in our studies:**
  - **High levels of BOTH depression and anxiety symptoms**
  - **Captures the majority of the variance between the different NA constructs (depression, anxiety, catastrophizing, etc)**
  - **Those with high depression more likely to have high anxiety or CAT**

Lin, Jama, 2003

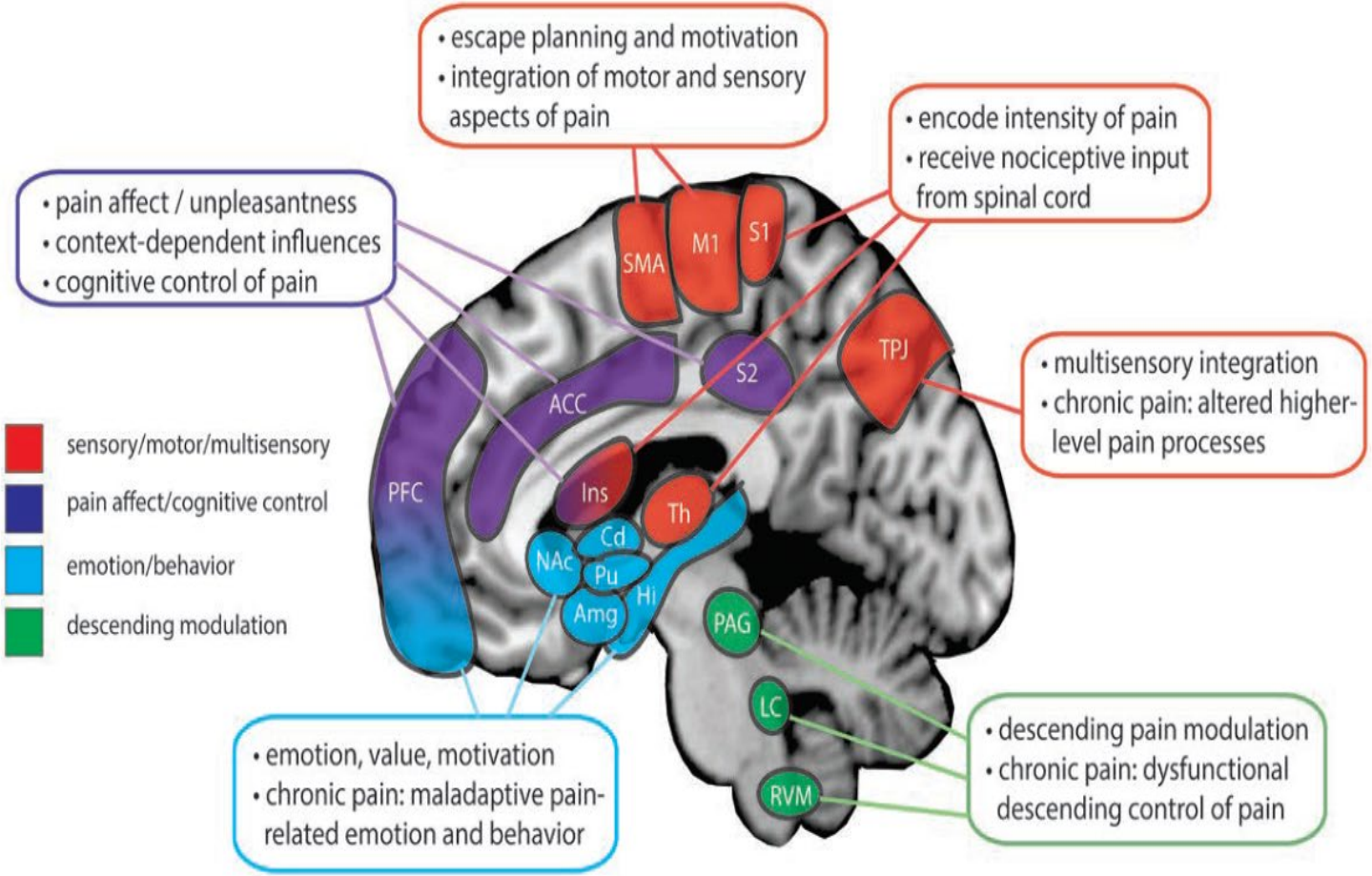
Positive Affect

Examining the role of positive and negative affect in recovery from spine surgery

Caryn L. Seebach [a], Matthew Kirkhart [b], Jeffrey M. Lating [b], Stephen T. Wegener [c], Yanna Song [d], Lee H. Riley III [e], Kristin R. Archer [f,*]



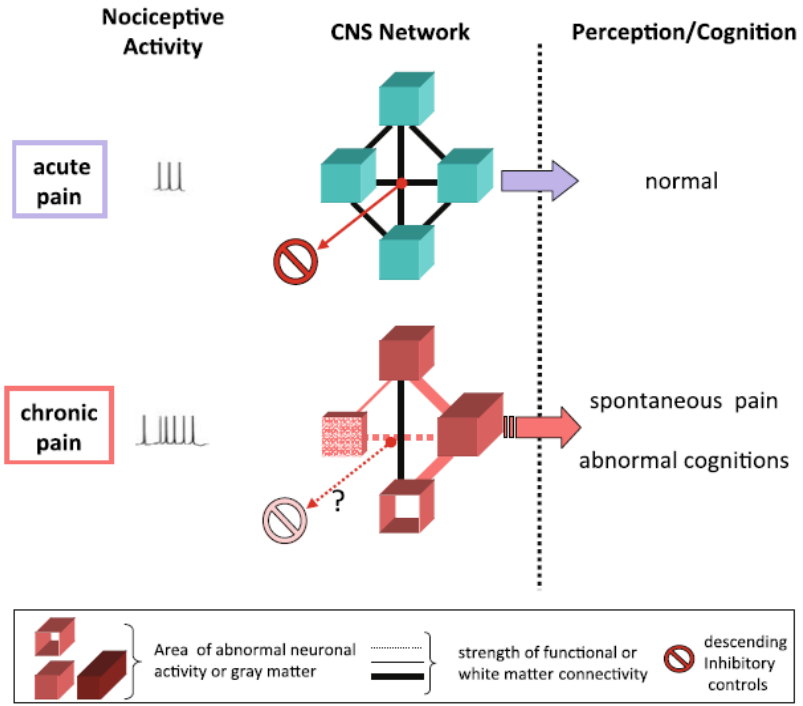
141 patients treated by spine surgery for lumbar or cervical degeneration. Affect was measured with the PANAS. Negative affect decreased post-surgery while positive affect remained constant. Linear regression analyses found that 6-week positive affect predicted functional status at 3 months following surgery.



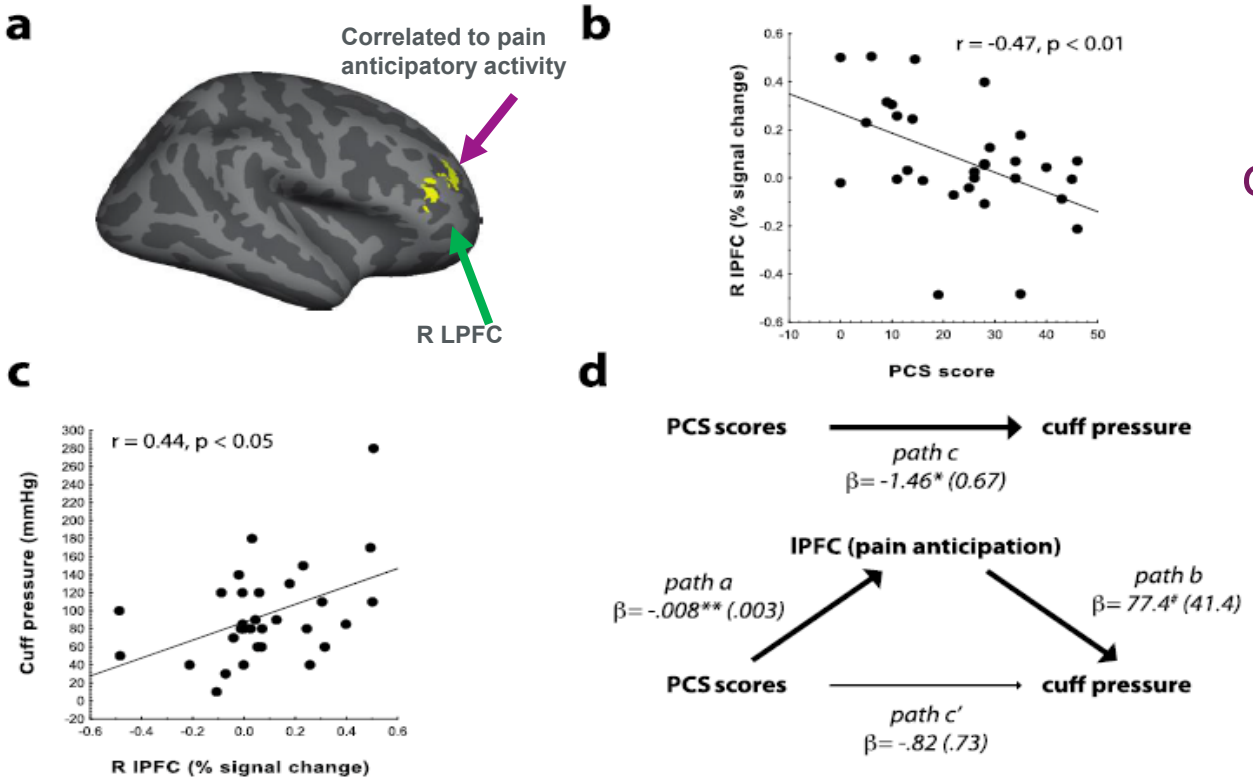
Martucci KT, and Mackey SC, "Neuroimaging of Pain," *Anesthesiology*, 2018 (128) p.1241-54

The Brain as a ‘Dynamic Connectome’

- Underdeveloped area of how chronic pain is processed in the brain and how that processing may change with successful treatment.
- Neuroimaging studies suggest that there are a host of structural and functional abnormalities in the brain that perpetuate and amplify pain processing and pain perception in the brain.
- Davis KD, *J Neuroimmune Pharmacol*, 2013



Pain sensitivity and catastrophizing



- **31 patients with FM**
- **Cuff pain stimuli during fMRI scanning**
- **LPFC activity mediated the relationship btw CAT and cuff pressure**
- **Loggia ML, et, al., *J Pain*, 2015**

- A=R LPFC= right lateral prefrontal cortex; B= Activity in PFC correlated to catastrophizing score; C=PFC activity correlated to cuff pressure; D= PFC activity mediates the effect of catastrophizing on cuff pressure

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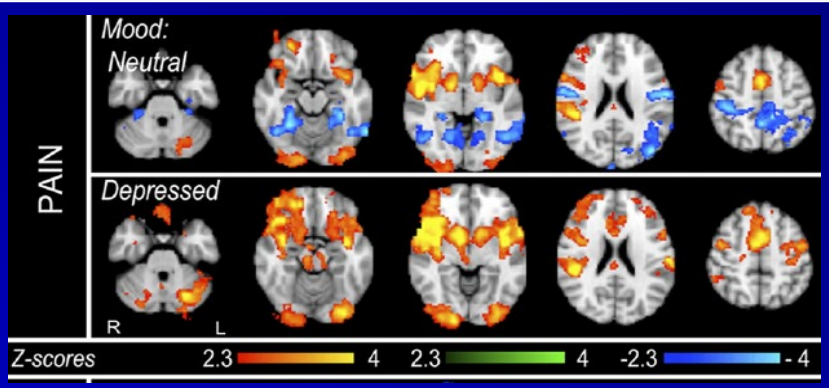
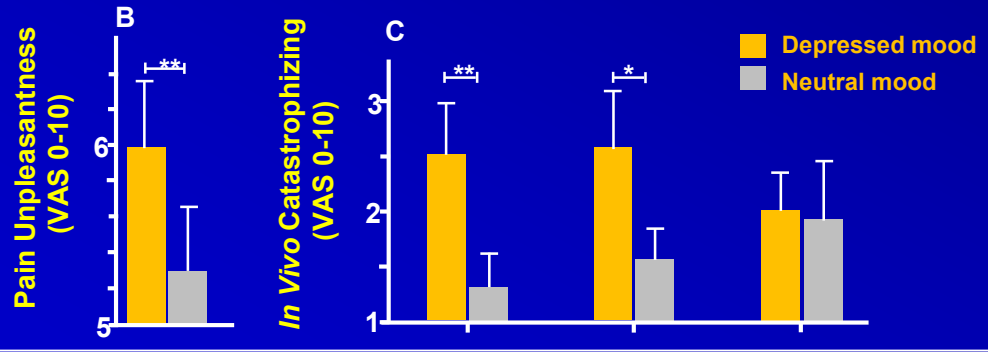
Depressed Mood and Pain



* *P*<0.05. ***P*<0.01.



**P*<0.05. ***P*<0.01.

N = 20 healthy subjects.

VAS = visual analog scale.

Berna C, et. al. *Biol Psychiatry*. 2010;67:1083-1090.

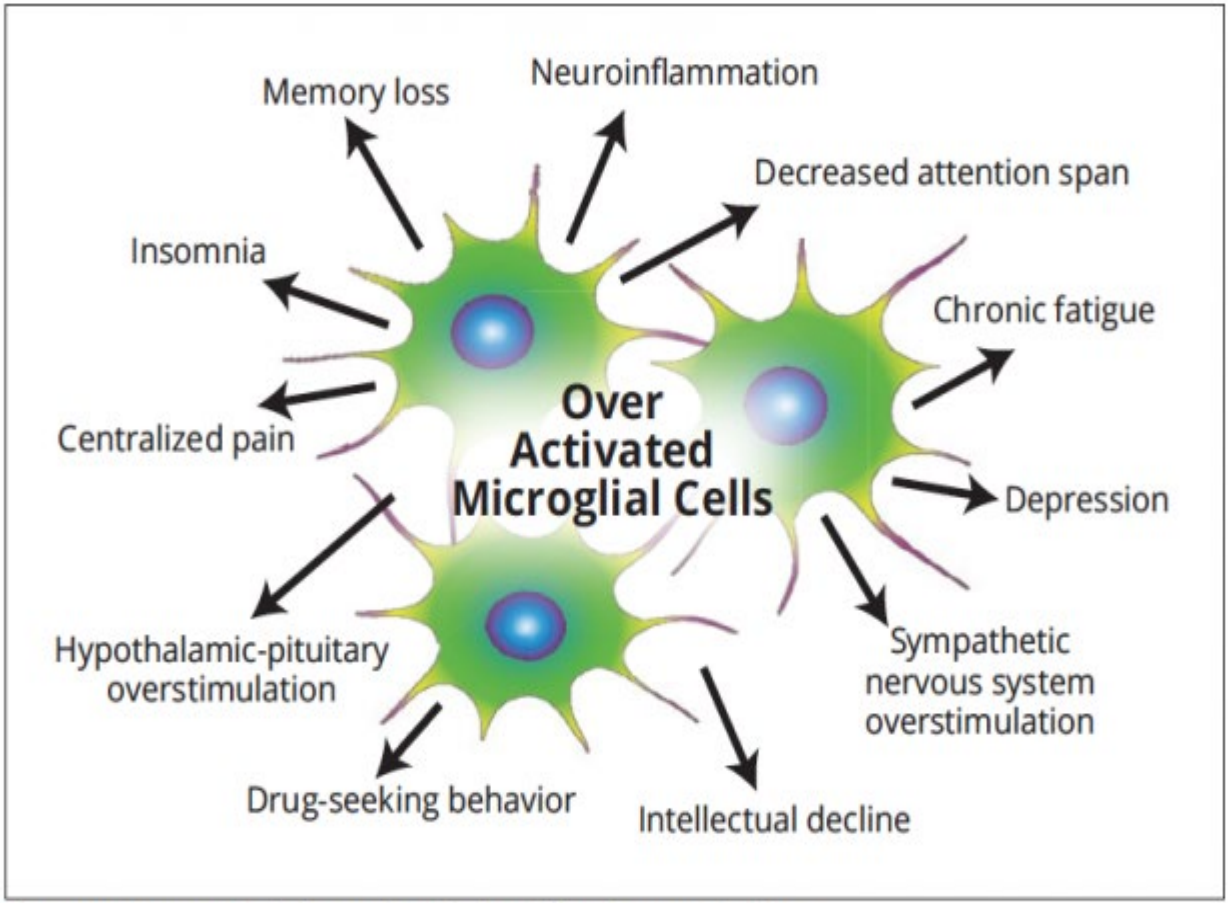
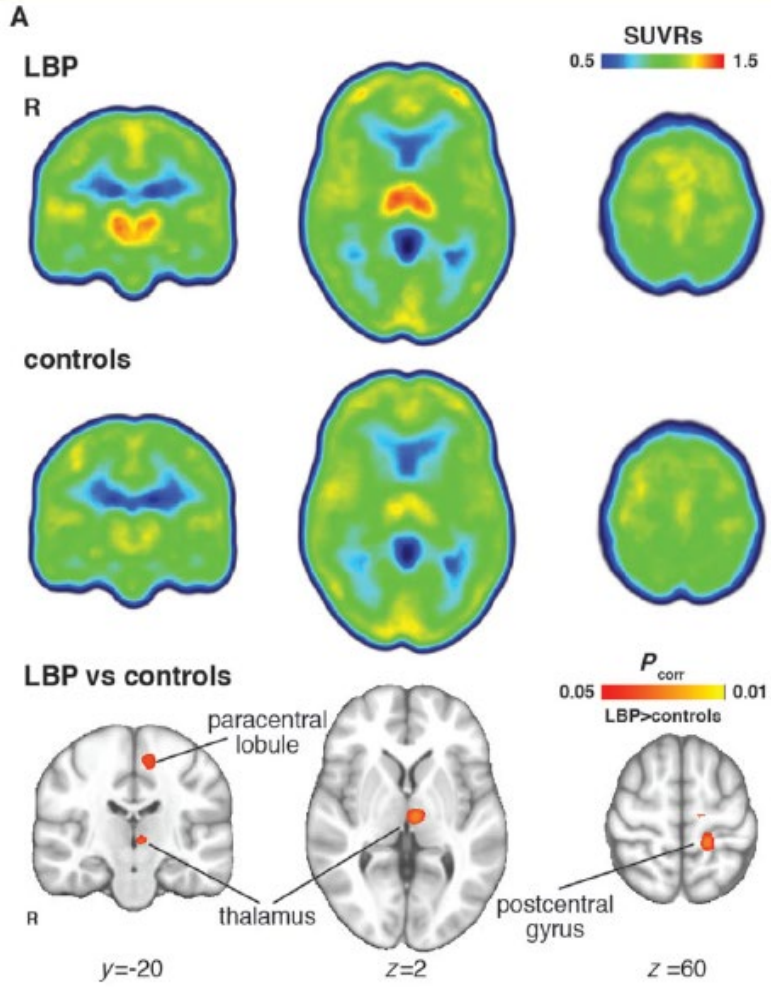


Figure 2. Some pathologic results of microglial cell overactivation.

- Practical Pain Management Centralized Pain Task Force, *PPM*, April, 2015



Brain glial activity and pain

- 10 CLBP patients vs. matched controls
- TSPO ligand has a specificity for glial cells

- Loggia ML, et. al, *Brain*, 2015

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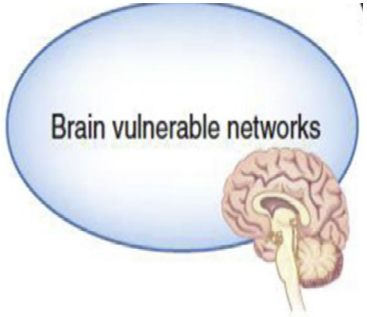
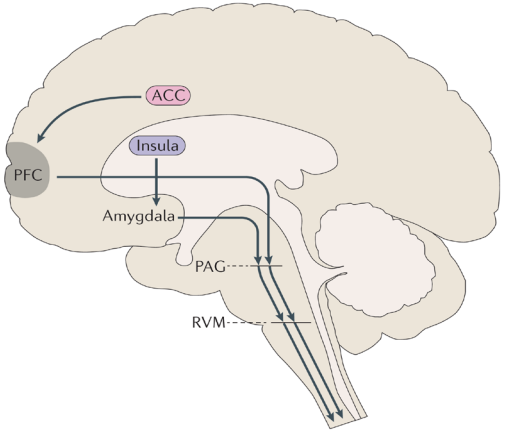
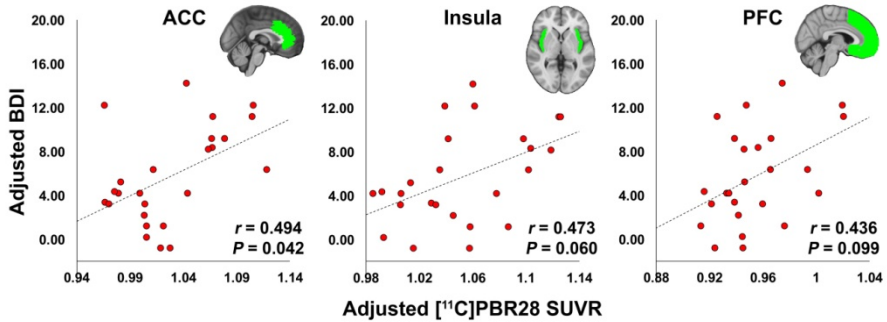


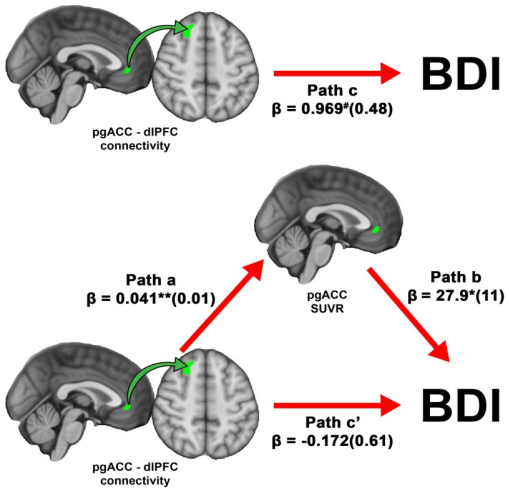


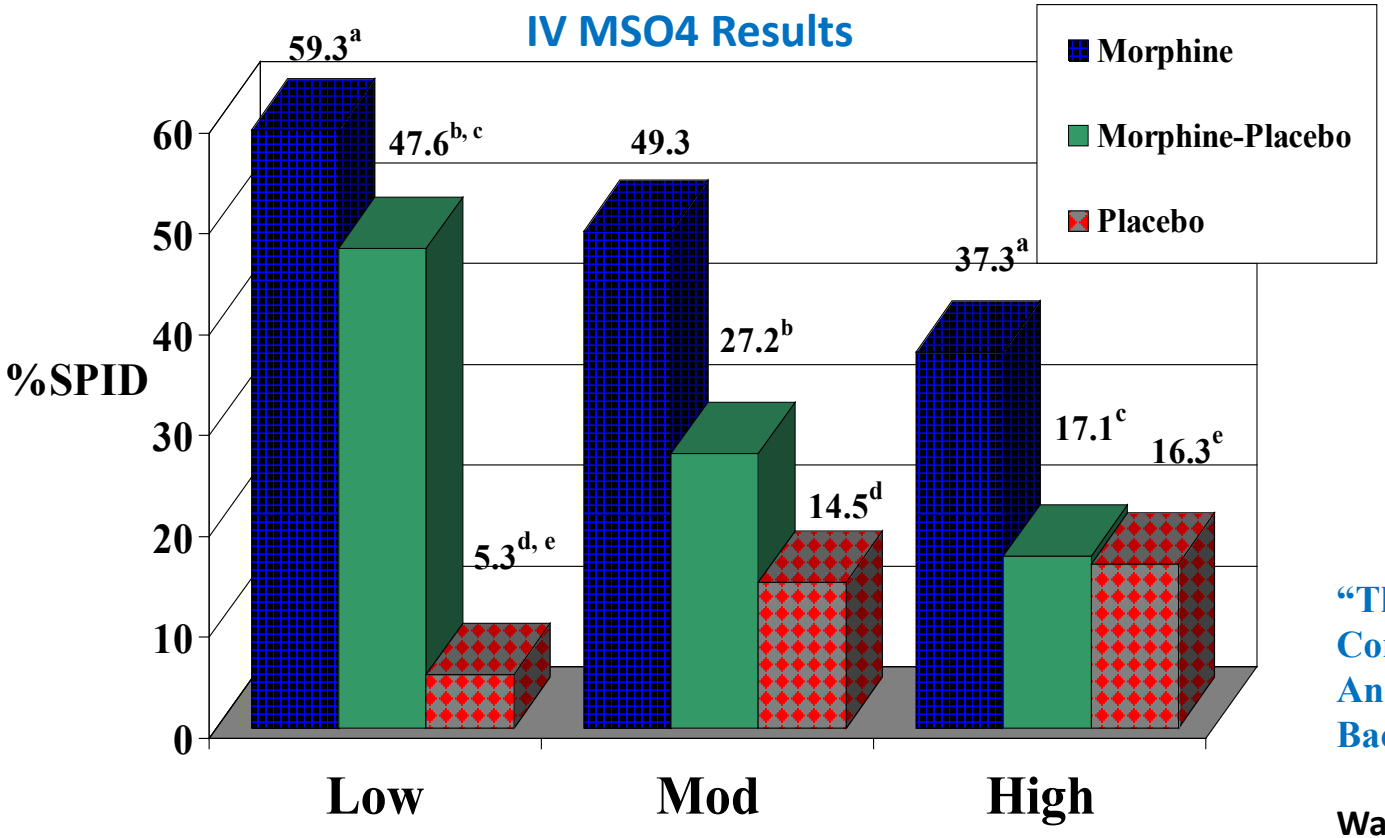
In CLBP patients (n=25) Glial cell activation vs. Depression scores



- Processing of pain and affect overlap in the brain in areas such as the ACC, Insula, and PFC
- Many mechanisms by which limbic areas can amplify the perception of pain and worsen function
- Known as the "dynamic connectome" that describes Salience Networks in the brain related to pain

- Functional connectivity (interactions) between ACC, Insula, and PFC explained a significant portion of BDI scores
- Albrecht DS, Wasan AD, & Loggia ML, et.al, *Molecular Psychiatry*, 2019, "The Neuroinflammatory Component of Negative Affect in Patients with Chronic Pain"





a-e=significant pairwise comparisons

a=.006 b=.026 c=.01 d=.05 e=.01

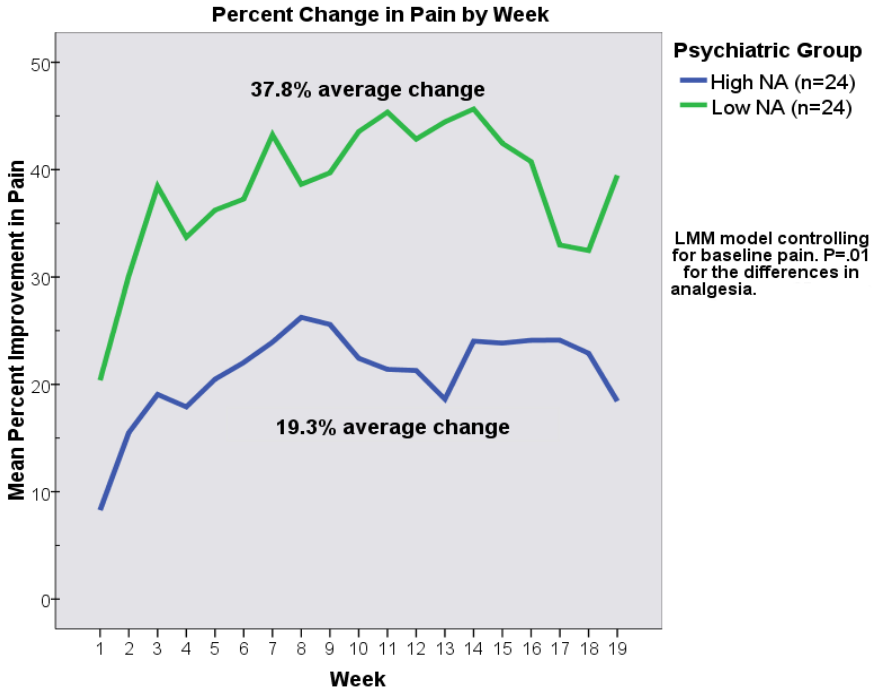
"The Impact of Psychiatric Comorbidity on Opioid Analgesia in Discogenic Low Back Pain"

Wasan AD, Davar G, Jamison RN, *Pain*, 2005

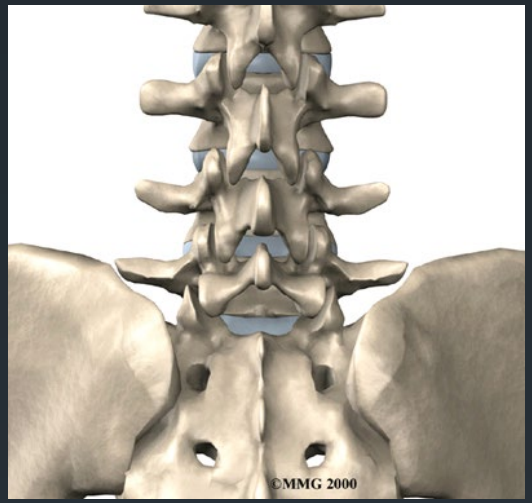
Wasan AD, et. al., "Psychiatric Comorbidity Is Associated Prospectively with Diminished Opioid Analgesia and Increased Opioid Misuse in Patients with Chronic Low Back Pain," *Anesthesiology*, 2015

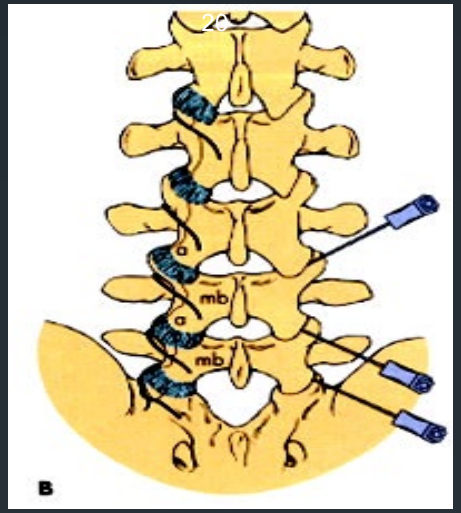
- N=55 patients with CLBP, Hi and Lo negative affect (depression + anxiety symptoms)
- Prescribed opioids over 5 months, with the prescriber blinded to group
- Tracked pain daily

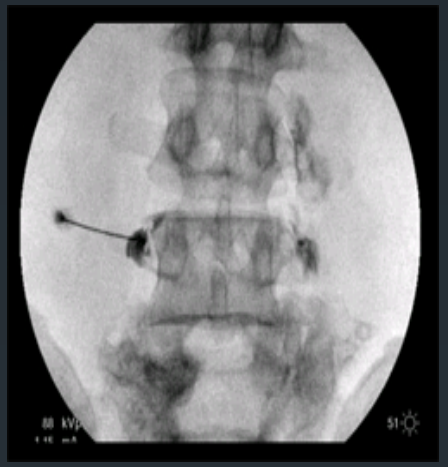
- MISUSE
- 8% rate of opioid misuse in the Low group
- 38% misuse rate in the High group



Facet Syndrome and Therapeutic Medial Branch Blocks



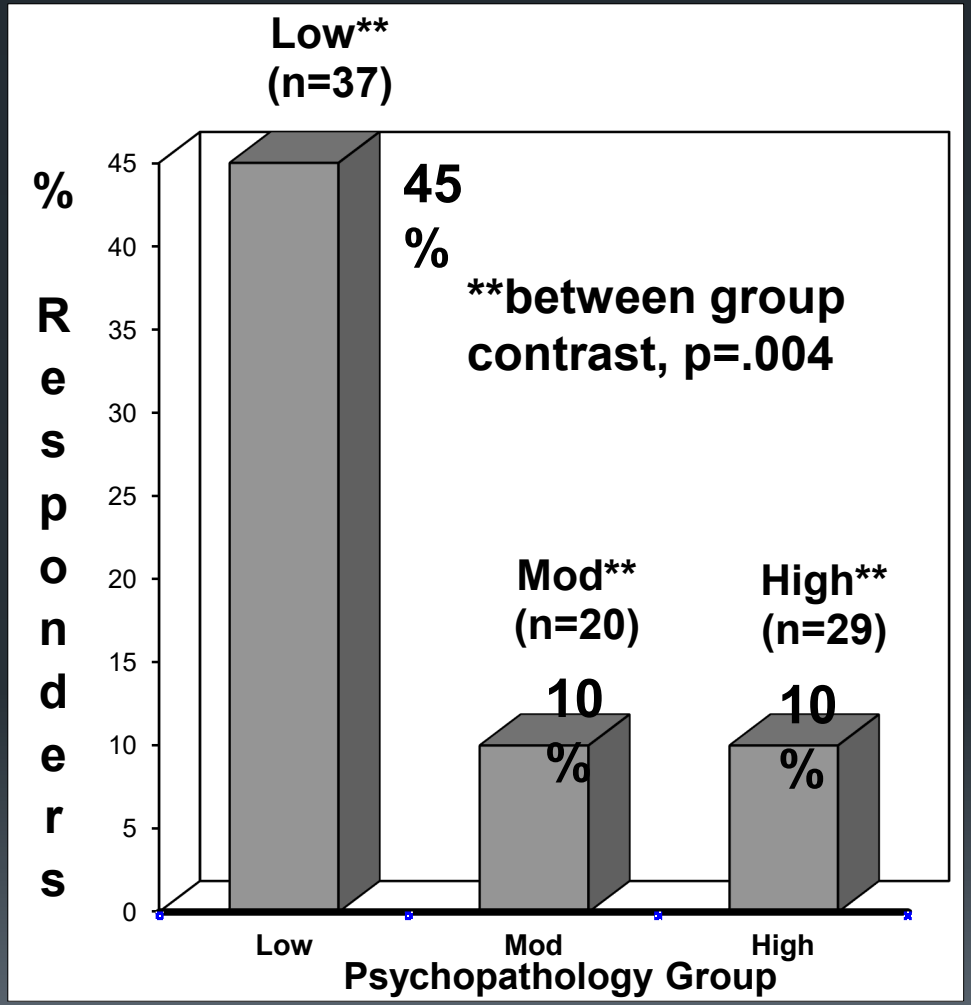




- Axial low back or neck pain—with concordant PE
- MRI or CT findings of facet arthropathy
- Positive bone scan predicts positive response with MBB
- Effectiveness= Improvement in pain and function

Percent of Patients with at least 30% improve-ment

AD Wasan, et. al, *BMC MSK Disorders*, 2009



Similar findings in patients undergoing spine surgery or epidural steroid injections

Psychiatric History and Psychological Adjustment as Risk Factors for Aberrant Drug-Related Behavior among Patients with Chronic Pain

- Multi-center pain clinic study of 229 patients on opioid therapy for non-cancer pain
- Multiple measures of opioid misuse potential at start of study
- Several questions on psych hx or negative affect symptoms
  - **High and Low groups of comorbid psychopathology**
- Followed 6 months
- Completed surveys of opioid use, urine tox screens, and physician ratings of adherence

Wasan AD, and Jamison RN, et al., *Clin J Pain*, 2007: 23 (4), 307-15

TABLE 3. Differences between high and low psychiatric co-morbidity patients on the SOAPP, COMM, POTQ, urine toxicology results, and Aberrant Drug-Related Behavior Index.

Variable	High Psych	Low Psych	p
SOAPP total score[†]	10.0 (±6.1)	6.4 (±5.0)	t=4.63***
COMM total score[‡]	12.6 (±7.7)	7.1 (±6.1)	t=5.84***
POTQ total score (% positive)[+]	23.7	20.0	ns
Urine toxicology (% positive)	34.4	18.4	X^2=7.26**
Aberrant Drug Index (% yes)[¶]	52.3	22.9	X^2=19.34**

**p<0.01 ***p<0.001 ns=nonsignificant

[†]SOAPP scores >7 were positive [‡]COMM scores > 8 were positive [+]POTQ score 2+ is pos

[¶]Aberrant Drug Behavior Index = (+ scores on SOAPP and COMM, or + scores on the POTQ and urine screen)

Does the concept of craving for opioids link NA and opioid misuse?

Does Report of Craving Opioid Medication Predict Aberrant Drug Behavior Among Chronic Pain Patients?

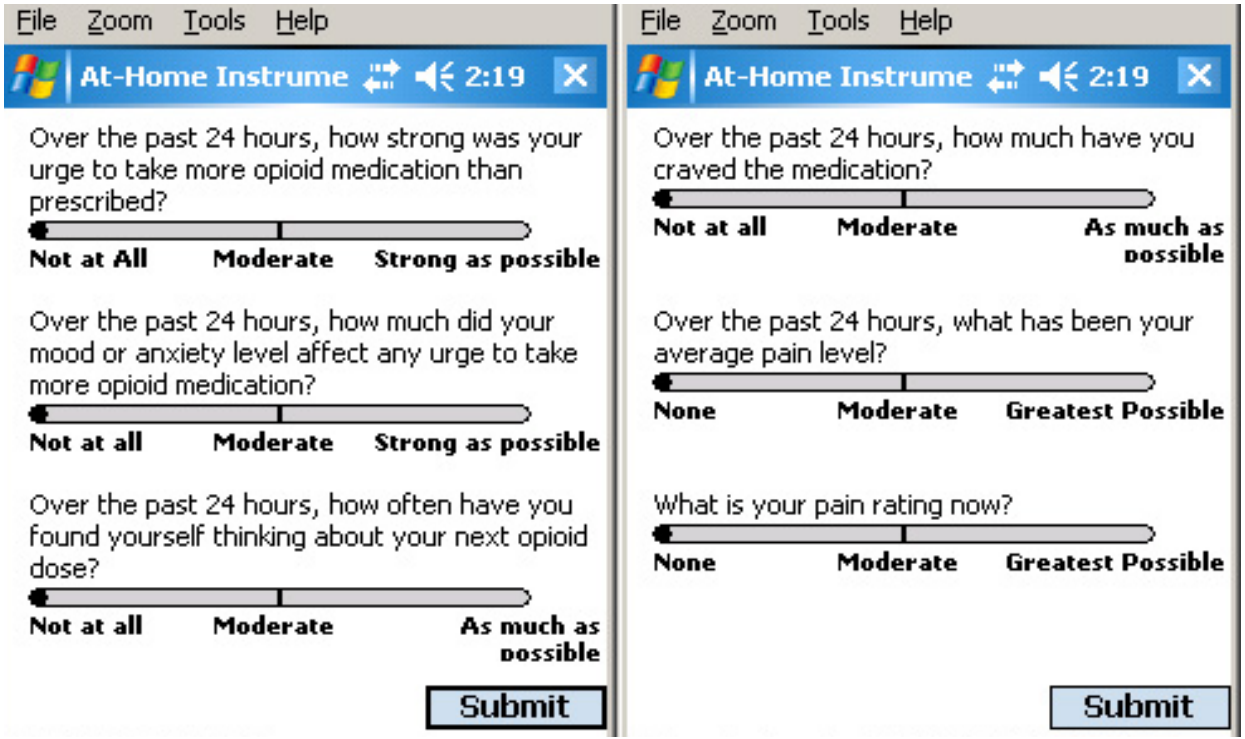
Ajay D. Wasan, MD, MSc, Stephen F. Butler, PhD,† Simon H. Budman, PhD,† Kathrine Fernandez, MBA,† Roger D. Weiss, MD,‡§ Shelly F. Greenfield, MD,‡§ and Robert N. Jamison, PhD**

- Clinical Journal of Pain, 2009

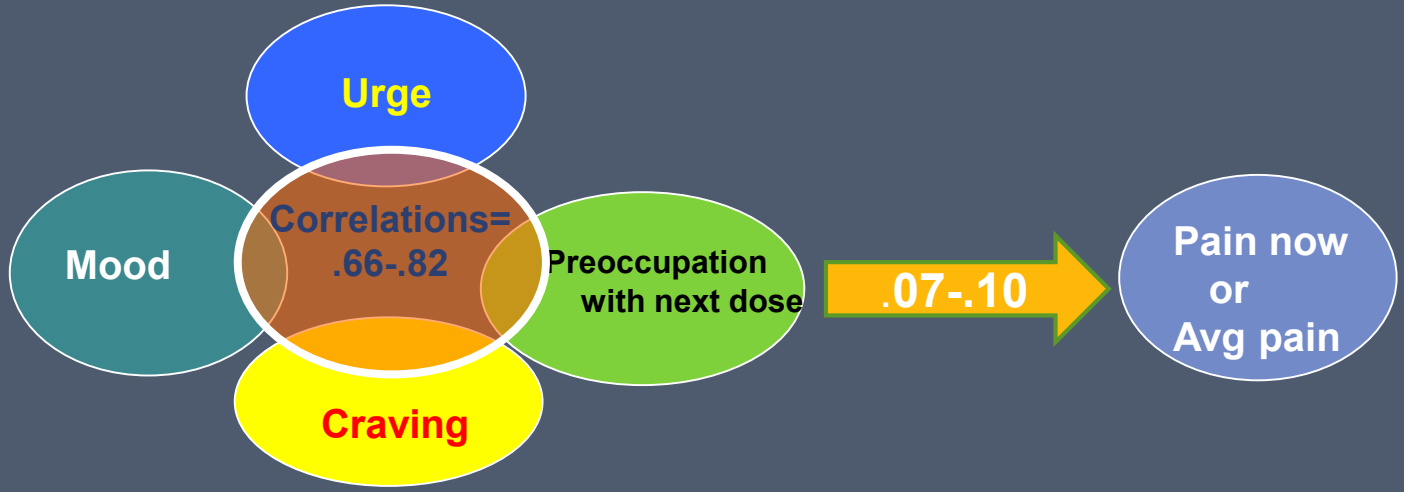
What does craving for prescription opioids mean?

N=60, divided into 3 groups, 2 high risk, 1 low risk, data collected daily for 2 weeks over the 6 month study

Wasan AD, et. al, *J Pain* , 2010



Components of craving for prescription opioids



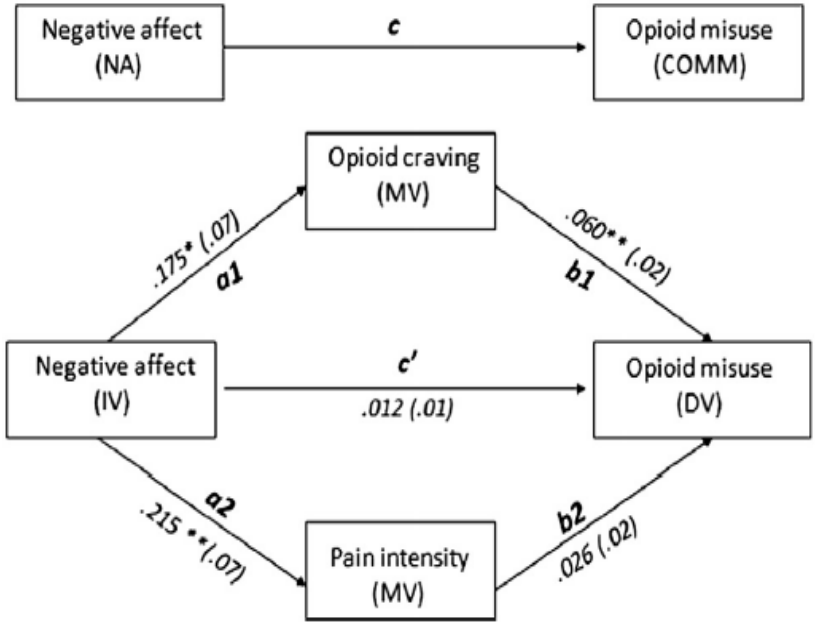
- Levels of craving are a key predictor of relapse in smoking, ETOH, or cocaine use
- Postulated elements of craving—what are these relationships? Would craving predict misuse in an RCT?

Consequences of High Negative Affect in Chronic Pain

RECAP

- Significantly greater pain and disability
- Treatment resistance to opioid medications, nerve blocks, & spine surgery
- Greater rate of opioid misuse

- N=82 patients with chronic pain prescribed opioids and enrolled in an RCT to decrease opioid misuse through individual and group motivational interviewing and adherence education
- Tracked opioid misuse and craving over 6 month period



Martel MO, Wasan AD, et. , al., "The association between negative affect and prescription opioid misuse in patients with chronic pain: The mediating role of opioid craving," *Drug and Alcohol Dependence*, 2013

Mental Health Disorders Associated with More Opioid Prescribing

Trends in Use of Opioids for Chronic Noncancer Pain Among Individuals With Mental Health and Substance Use Disorders: The TROUP Study

Mark J. Edlund, MD, PhD, Bradley C. Martin, PharmD, PhD,† Andrea Devries, PhD,‡ Ming-Yu Fan, PhD,§ Jennifer Brennan Braden, MD, MPH,§ and Mark D. Sullivan, MD, PhD§*

Clin J Pain • Volume 26, Number 1, January 2010

- Examined 950,000 insurance records from commercial and Medicaid claims
- DX of Depression or anxiety 2-3 times as likely to be prescribed an opioid

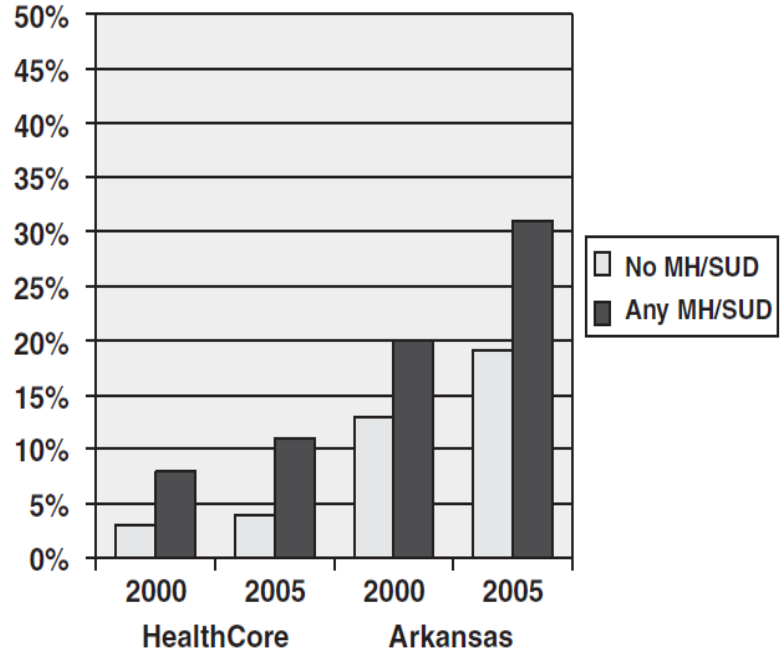


FIGURE 1. Rates of chronic opioid use (90 days per year).

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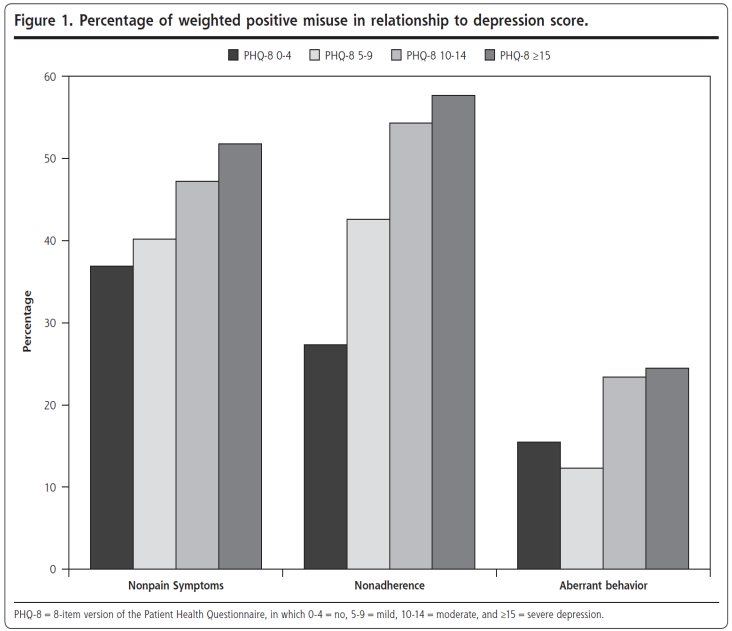
Depression and Prescription Opioid Misuse Among Chronic Opioid Therapy Recipients With No History of Substance Abuse

Alicia Grattan, MD[1]
Mark D. Sullivan, MD, PhD[1]
Kathleen W. Saunders, JD[2]
Cynthia I. Campbell, PhD, MPH[3]
Michael R. Von Korff, ScD[2]

Ann Fam Med 2012;10:304-311.

- Evaluated 1334 chronic pain patients prescribed opioids chronically
- Self report of misuse, such as self-medicating non-pain, increasing doses, or obtaining opioids from others
- Patients with major depression 2X as likely to misuse opioids
- Most commonly by self-increasing their dose



Negative Affect–Related Factors Have the Strongest Association with Prescription Opioid Misuse in a Cross-Sectional Cohort of Patients with Chronic Pain *Pain Medicine*, 21(2), 2020, e127–e138

Gadi Gilam, PhD,* John A. Sturgeon, PhD,† Dokyoung S. You, PhD,* Ajay D. Wasan, MD, MSc,‡ Beth D. Darnall, PhD,* and Sean C. Mackey, MD, PhD*

- N=1193, pain clinic sample

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NA and Rx Opioid OD

Risk Factors for Serious Prescription Opioid-Induced Respiratory Depression or Overdose: Comparison of Commercially Insured and Veterans Health Affairs Populations

Pramit A. Nadpara, PhD, MS, BPharm,* Andrew R. Joyce, PhD,† E. Lenn Murrelle, MSPH, PhD,† Nathan W. Carroll, MHA, PhD,‡ Norman V. Carroll, PhD,* Marie Barnard, PhD,§ and Barbara K. Zedler, MD†

Pain Medicine 2018; 19: 79–96

Results. The strongest associations with serious OIRD in CIP were diagnosed substance use disorder (odds ratio [OR] = 10.20, 95% confidence interval [CI] = 9.06–11.40) and depression (OR= 3.12, 95% CI = 2.84–3.42). Other strongly associated factors included other mental health disorders; impaired

- Analyzed Insurance claims data (VA and commercial) in 18 million patients

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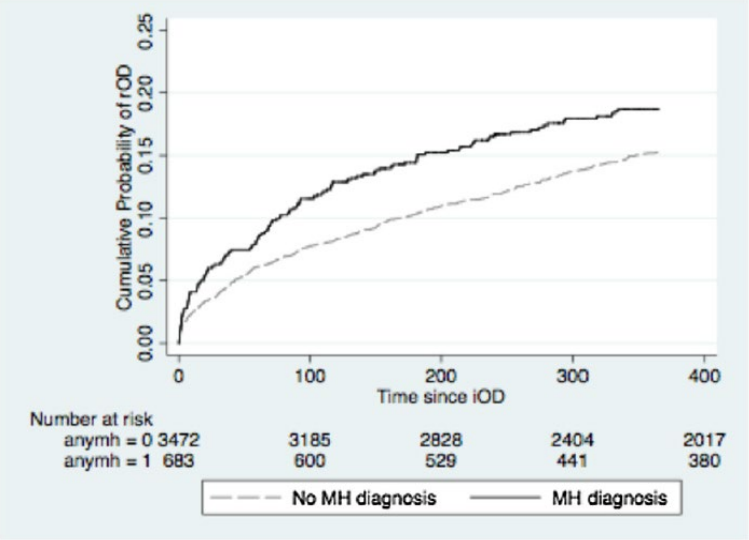
Risk and protective factors for repeated overdose after opioid overdose survival

Drug and Alcohol Dependence 209 (2020) 107890

Brian Suffoletto*, Amy Zeigler

- Retrospective cohort study of 4155 patients presented to a Univ. of Pittsburgh ED with opioid OD
- Rates of repeated OD within 1 year and predictive factors



	Adjusted Hazard Ratio (95 % CI)
Mental health diagnoses	
Depression disorder	1.38 (1.02, 1.73)
Anxiety disorder	1.41 (1.13, 1.77)
Bipolar disorder	1.32 (0.96, 1.82)
Stress disorder	1.38 (0.84, 2.27)
Schizophrenia	1.14 (0.57, 2.29)
Any mental health disorder	1.32 (1.08, 1.61)
No mental health disorder	0.76 (0.62, 0.92)
Drug and alcohol diagnoses	
Substance use disorder	1.30 (1.09, 1.56)
Alcohol use disorder	1.52 (1.02, 2.25)

Thank You!
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  - Srdj Nedeljkovic
  - Robert Jamison
  - Jeff Katz
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  - Vitaly Napadow
  - Randy Gollub
  - Jian Kong
- University of Pittsburgh
  - Andrea Gillman
  - Jim Ibinson
  - Jeong Jong


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