Negative Affect and Chronic Pain

Ajay D. Wasan, MD, MSc
Professor and Vice Chair for Pain Medicine
Departments of Anesthesiology & Perioperative Medicine; and Psychiatry
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

Affect=Thoughts, emotions, and behavior

Pain Catastrophizing=Negative thoughts about pain

20% of CLBP patients have a co-morbid depression or anxiety disorder --Edwards RR, Wasan AD, et. al., J Pain, 2016
In a broad range of chronic pain conditions these relationships hold true. Ryan and McGuire, *Brit J Health Psych*, 2016

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.

• 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*
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.
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
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

Pain sensitivity and catastrophizing

- 31 patients with FM
- Cuff pain stimuli during fMRI scanning
- LPFC activity mediated the relationship btw CAT and cuff pressure

- Pain sensitivity and catastrophizing

- 31 patients with FM
- Cuff pain stimuli during fMRI scanning
- LPFC activity mediated the relationship btw CAT and cuff pressure
Depressed Mood and Pain

N = 20 healthy subjects.
VAS = visual analog scale.


**P<0.05. **P<0.01.
Figure 2. Some pathologic results of microglial cell overactivation.
Brain glial activity and pain

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

In CLBP patients (n=25) Glial cell activation vs. Depression scores
"The Impact of Psychiatric Comorbidity on Opioid Analgesia in Discogenic Low Back Pain"


*a-e=significant pairwise comparisons*

\[ a=0.006 \quad b=0.026 \quad c=0.01 \quad d=0.05 \quad e=0.01 \]
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% improvement


**between group contrast, p=.004**

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

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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>High Psych</th>
<th>Low Psych</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOAPP total score †</td>
<td>10.0 (±6.1)</td>
<td>6.4 (±5.0)</td>
<td>t=4.63***</td>
</tr>
<tr>
<td>COMM total score ‡</td>
<td>12.6 (±7.7)</td>
<td>7.1 (±6.1)</td>
<td>t=5.84***</td>
</tr>
<tr>
<td>POTQ total score (% positive) †</td>
<td>23.7</td>
<td>20.0</td>
<td>ns</td>
</tr>
<tr>
<td>Urine toxicology (% positive)</td>
<td>34.4</td>
<td>18.4</td>
<td>X²=7.26**</td>
</tr>
<tr>
<td>Aberrant Drug Index (% yes) ‡</td>
<td>52.3</td>
<td>22.9</td>
<td>X²=19.34*</td>
</tr>
</tbody>
</table>

**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?

Correlations=

- Preoccupation with next dose
- .07-.10

- Pain now or Avg pain

Correlations:

- .66-.82

Urge

Mood

Craving

Pain now or Avg pain
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

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).
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

N=1193, pain clinic sample
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

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

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 mental health; and medical comorbidities.
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

<table>
<thead>
<tr>
<th>Mental health diagnoses</th>
<th>Adjusted Hazard Ratio (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression disorder</td>
<td>1.38 (1.02, 1.73)</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>1.41 (1.13, 1.77)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>1.32 (0.96, 1.82)</td>
</tr>
<tr>
<td>Stress disorder</td>
<td>1.38 (0.84, 2.27)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>1.14 (0.57, 2.29)</td>
</tr>
<tr>
<td>Any mental health disorder</td>
<td>1.32 (1.08, 1.61)</td>
</tr>
<tr>
<td>No mental health disorder</td>
<td>0.76 (0.62, 0.92)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug and alcohol diagnoses</th>
<th>Adjusted Hazard Ratio (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance use disorder</td>
<td>1.30 (1.09, 1.56)</td>
</tr>
<tr>
<td>Alcohol use disorder</td>
<td>1.52 (1.02, 2.25)</td>
</tr>
</tbody>
</table>
Thank You!

Acknowledgements

• Brigham and Women’s Hospital/Harvard Medical School
  – Robert Edwards
  – Srdj Nedeljkovic
  – Robert Jamison
  – Jeff Katz

• MGH Martinos Center/HMS
  – Marco Loggia
  – Vitaly Napadow
  – Randy Gollub
  – Jian Kong

• University of Pittsburgh
  • Andrea Gillman
  • Jim Ibinson
  • Jeong Jong