Chronic Pain and Depression

Michael R. Clark, MD, MPH, MBA
Director, Chronic Pain Treatment Programs
Vice Chair, Clinical Affairs
Department of Psychiatry & Behavioral Sciences
Johns Hopkins Medical Institutions
Symptoms

- Lifetime prevalence of individual symptoms range from 10-35%.

- 80% of general medical outpatients report at least 1 symptom.

- 50% report improvement 1 year later.

- A specific etiology is discovered in <20%. 
Definition of Pain

- An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.
Depression in patients with chronic pain

- What could it be?
- What do we know?
- What are the associations?
- Which problem comes first?
- Does treatment matter?
Depression and chronic pain

- Disappointment with a way of living
- Dissatisfaction with ineffective choices
- Deficiencies of individual capacities
- Dysphoria of a diseased affect
Top-down treatments

- Descartes is masquerading as multidisciplinary pain treatment (real patients get cured, but psychogenic patients get referred to MPC’s)

- Multidisciplinary pain treatment is an extension of the palliative care, not the rehabilitative, model (everybody gets a little bit of everything)

- Patients are labeled (chronic pain patient) not formulated with individualized medical care
The “depression” of chronic pain

Associations
Relationships
Phenomenology
Depression and chronic pain

- General population: CP-16% vs. no CP-6%
- Increases dramatically in clinical samples
- Varies with patient sample and methodology
- Using rigorous RDC/DSM criteria: 30-54%
Depression and chronic pain

- 60% of patients with depression report pain symptoms at the time of diagnosis
- After 8 years, depression was the best predictor of persistence of chronic pain symptoms in GP
- Patients with depression are at twice the risk of
  - Chronic daily headache
  - Atypical chest pain
  - Musculoskeletal pain
  - Low back pain
Cross-sectional associations

- Patients with chronic pain and depression
  - experience greater pain intensity
  - feel they have less life control
  - use more passive coping strategies
  - report greater interference from pain
  - exhibit more pain behaviors / disability
  - have poorer surgical outcomes
  - utilize more healthcare services
  - retire from work earlier
Longitudinal relationships

- Treatment of depression improves pain and disability
- Majority of the data support the diathesis-stress model (depression is a consequence of chronic pain)
- Specific etiologies remain a mystery
Distinguishing features

- Negative self-attitude
- Anhedonia / loss of interest / pleasure
- Suicidal ideation / hopelessness
- Diminished concentration
- Sleep disturbance / EMA / DMV
Phenomenology: women in CP

Sadness
Guilt
Feeling ugly
No depression

Cannot work
Low libido
Tiredness
Mild depression
Self hate, self blame, life dissatisfaction

Suicidal
Low appetite
Irritable
Severe depression
Phenomenology: men in CP

- Health worry
- Suicidal
- Loss of interest

No depression

Mild depression
- Cannot work
- Low libido

Severe depression
- Cannot cry
- Feel punished

Self hate, guilt, hopelessness
Depression and CP: bottom line

Pain Severity

Treatment

Efficacy

Depression -
Depression +
Opioids

Are the risks worth the benefits?
Pharmacology of chronic pain

Medications for Neuropathic Pain

- Antidepressants
- Anticonvulsants
- Opioids

Adjuvant Medications
- Vanilloids
- α-Adrenergic Agents
- Calcium Channel Blockers
- COX-2 Inhibitors
- Local Anesthetic Agents
- NMDA Receptor Antagonists
Neuropathic pain

- Loss of large diameter myelinated sensory afferent inhibition of nociceptive transmission
- Deafferentation hyperactivity in dorsal horn cells
- Central sensitization (increased gain)
- Ectopic impulse generation
  - sites of injury, demyelination, and regeneration
- SMP → sensitivity of primary afferent nociceptors
- Antidromic release of sensitizing neuromediators
Neuropathic pain

- DPNP
- PHN
- TGN
- PD
- SCI
- PAP
- CA
- EtOH / Toxins
- RSD / CRPS
- LBP / Trauma
- CVA / TBI
- MS / AIDS
- Surgery / XRT
- Medications
Postherpetic neuralgia

- 76 patients with PHN

- Double blind, randomized

- 3-phase crossover
  - LAO (morphine, methadone)
  - TCA (nortriptyline, desipramine)
  - Placebo (inert starch)
Postherpetic neuralgia

- Age: 71 years (32-90)
- Gender: 55% female
- Race: 88% Caucasian
- Duration: 32 months (3-216)
Postherpetic neuralgia

TCA Opioid Placebo

Baseline Maintenance

VAS Pain Intensity Rating

TCA Opioid Placebo
Postherpetic neuralgia

Pain relief...

- Opioids > TCA’s >> Placebo
- Morphine >> Nortriptyline
- Morphine > Methadone
- Nortriptyline = Desipramine
Postherpetic neuralgia

- Patient preference
  - 54% Opioids
  - 30% TCA’s
  - 16% Placebo

- Treatment responders
  - 52% Opioids
  - 34% TCA’s
Postherpetic neuralgia

- No effects on verbal learning
- No effects on activity or pain-related interference
- Sleep improved with both TCA’s and opioids
- Function worsened with TCA’s not opioids
  - Symbol substitution
  - Grooved pegboard
Depression and low back pain: opioids or antidepressants?

Does it really matter?
Antidepressants and CP

- Only 25% of patients in MPC were Rx’d TCA’s
- 75% of treated patients Rx’d Elavil 50 mg or less
- Increased likelihood of response at low doses
- Onset of analgesia more rapid (ongoing, brief)
- 10% Caucasians slow metabolizers (↓CYP2D6)
Antidepressant antinociception

- NE and 5-HT: ↑ diffuse noxious inhibitory control
- Alpha-adrenergic: ↓ NE stimulation of receptors
- NMDA: ↓ neuronal hyperexcitability
- Sodium / calcium channel: ↑ membrane stability
Methods

- Open label, randomized, multi-center, two-way crossover trials with drug titration to optimal effect
- 264 patients with chronic non-malignant pain (70% CLBP) treated with morphine >45 mg/d switched to fentanyl TD or oxycodone-SR
- 229 non-opioid tolerant patients with CLBP started on fentanyl TD or oxycodone-APAP
- Excluded severe medical, psychiatric, and SUD’s
Analyses

- Depressed (SF-36 MH <42, BDI >18) vs. non-depressed on treatment outcome
- Effects of antidepressant use
  - Pain
  - Quality of life
- Effect of opioids on mood
- Intention to treat
Results

- Depressed patients had significantly higher baseline pain intensity and poorer HRQoL
- Opioid therapy did not improve BDI scores
- Pain intensity decreased with treatment but...
- Opioid therapy decreased pain intensity significantly more in the non-depressed group
Outcomes: Pain intensity

![Bar chart showing pain intensity comparison between different conditions and treatments.](chart.png)

- **Baseline vs Final**
- **No Dep** vs **Dep**
- **Fentanyl / Oxy-SR** vs **Fentanyl / Oxy-APAP**
Results

- HRQoL subscales improved significantly more in the non-depressed group.
- HRQoL was higher in depressed patients with chronic pain on antidepressants.
- In depressed patients, treatment outcome:
  - improved for those on antidepressants (AD)
  - worsened for those not on AD’s.
Outcomes: HRQoL change

Depressed Patients (Fentanyl / Oxy-APAP)

- SF-36 MCS
- SF-36 PCS
- TOPS-Pain

No AD's
n=30

AD's
n=10

* p < 0.05
** p < 0.01
Antidepressants and CP

- TCA’s are the old “gold” standard
  - Toxicity, serum level monitoring, metabolic/CV effects

- SSRI’s have been overly relied on
  - Less efficacy in neuropathic pain, MDD still undertreated
  - Fewer side effects improve compliance
  - Disease management benefits (DM, CVD)

- SNRI’s are the current focus
  - Independent efficacy in RCT’s for CP & MDD
  - Norepinephrine a critical “co-factor” for neuropathic pain

- Remission of MDD has the greatest impact on CP
Summary

- In patients with chronic pain, the diagnosis and treatment of depression is a priority.

- Opioids for chronic pain may be harmful for patients with co-morbid depression.

- Opioids are likely to be more effective if depression has been treated to remission.
Data from the PTP at JHH

What are the associations?
Demographics

N=320 patients admitted to the PTP

- Female 67%
- Caucasian 87%
- Age 46.6 +/- 2.7 years
- Education 13.0 +/- 2.7 years
Demographics

- Duration: 8.9 +/- 9.2 years
- Surgeries: 2.6 +/- 3.5
- VAS: 72 mm
- PDI: 4.2 – 8.0
- BDI: 19.5
Demographics

- Most common pain type: neuropathic
- Most common pain location: low back
- Most common pain medicine: opioids
PTP outcomes

- Depression (BDI): $r = 0.573$, $p < 0.0001$
- Interference (MPI): $r = 0.500$, $p = 0.001$
- Pain severity (MPI): $r = 0.842$, $p < 0.0001$

Correlation coefficients and p-values between different outcomes.
PTP outcomes at follow-up

- Relapsers (BDI Worse)
- Non-Relapsers (BDI Better)

Bar chart showing outcomes across all visits and medical visits.

- All Visits
  - Relapsers
  - Non-Relapsers

- Medical Visits
  - Relapsers
  - Non-Relapsers
PTP outcomes at follow-up

Depression (BDI)

\[ r = 0.436 \]
\[ p = 0.014 \]

Healthcare Utilization

Interference (MPI)

Pain severity (MPI)
PTP outcomes at follow-up

- Depression (BDI):
  - $r = 0.573$
  - $p < 0.0001$

- Interference (MPI):
  - $r = 0.500$
  - $p = 0.001$

- Pain severity (MPI):
  - $r = 0.842$
  - $p < 0.0001$

- Healthcare Utilization:
  - $r = 0.436$
  - $p = 0.014$
Healthcare utilization

- Admission to an interdisciplinary PTP provides multiple benefits for patients with chronic pain.

- Data from outcome analyses can prospectively refine the formulation and treatment plan of patients.

- Ongoing follow-up for depression can decrease healthcare utilization and external cost controls.
Conclusions

Pain: the difference between what is and what you want it to be
Treatment basics

- Neuropathic pain responds to medications
- Combination therapy can be synergistic
- Analgesia and function are goals of therapy
- MDD must be treated to achieve success
Chicken or egg?

- Depression and chronic pain co-exist
- Depression should not be “understood”
- Depression and chronic pain interact
- Depression responds well to treatment
- Severe consequences for doing nothing
What is depression in these patients?

- Depression is a latent construct: attributes that are easily described but not directly measurable.

- Current top-down models of depression are collections of facts and their correlations, not a true synthesis of components and relationships.

- Bottom-up investigations allow for natural relationships to emerge from the outcome of research and new experiences (meaningful).
Bottom-up treatment

- Each patient receives more than treatment, that is, a real evaluation and formulation of their case
- Each patient’s problems are described in detail instead of being reduced to standard labels
- Treatments evolve from each problem rather than all treatment being applied to the whole patient
- TCA’s & SNRI’s offer independent benefits for MDD & DPNP based on pharmacological targets